THE ASSOCIATION BETWEEN HIP MORPHOLOGY PARAMETERS AND 19-YEAR RISK OF END-STAGE OSTEOARTHRITIS OF THE HIP IN CAUCASIAN FEMALES: A CASE-CONTROL STUDY

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ALEXANDER STUART NICHOLLS
GREEN TEMPLETON COLLEGE
OXFORD



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SUPERVISORS: PROFESSOR ANDY CARR & PROFESSOR NIGEL ARDEN

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
University of Oxford

ABSTRACT

Alexander Stuart Nicholls **Master of Science**
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Over the past decade, measures of hip morphology have been recognised as biomechanical risk factors for the development of osteoarthritis (OA) in the hip. Few studies have examined the relationship between pelvic morphology and OA in a cohort of healthy volunteers with prolonged follow-up. The present study validates a new method for quantifying morphological parameters of the hip and pelvis and looks for relationships between these parameters and 19-year risk of total hip arthroplasty (THA) due to OA.

In order to conduct this investigation, we developed and validated a new software program specifically designed for measuring 23 selected morphological parameters in the pelvis, acetabulum and proximal femur. We tested inter-user reproducibility using 6 investigators, each of whom measured the same group of 10 blinded radiographs. Intra-user reproducibility was measured by the primary investigator measuring 10 blinded radiographs on three separate occasions.

Following validation of the new software, a nested case-control study was used with individuals from a well-described cohort of 1003 caucasian women who were recruited in 1989 and followed up for 20 years. A group of 157 individuals (31 THAs & 126 randomly-selected controls) were selected for morphological analysis. Pelvis radiographs taken at study-year two were analyzed for variations in hip morphology using the software. Morphological measurements were then compared between the THA case group and the control group in search of significant associations. THA was used as the clinical outcome measure for severe OA.

Most morphological measures were reproducible, with the exception of horizontal toit externe (HTE) and joint space width. The alpha-angle was significantly greater in the THA cases than in the controls (60.7 degrees vs 48.1 degrees; $p < 0.001$). The lateral centre edge angle (LCE) was significantly smaller in the cases than the controls (30.0 degrees vs 33.4 degrees; $p = 0.002$). The Extrusion Index (Ext Ind) was significantly greater in the THA cases than in the controls (30% vs 20%; $p < 0.001$). Significant morphological measures were then adjusted for epidemiological covariates (baseline age, height, weight & radiographic osteoarthritis) using a multivariate logistic regression analysis. Alpha angle (Odds ratio 1.040, degrees; $p = 0.01$), LCE (Odds ratio 0.871, degrees: $p < 0.001$) and Ext Ind (Odds ratio 1.079, percent; $p < 0.001$) each remained significantly associated with THA.

This investigation demonstrates measurements that provide a useful tool in predicting a woman's risk of THA before she develops radiographic hip OA. These measurements can be made on an AP pelvis radiograph which is cheap, accessible and commonly used as a clinical investigation tool.

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List Of Abbreviations

ACE Ratio	Acetabular depth:width ratio
ACE Tilt	Acetabular Tilt
AP	Anterior posterior
CI	Confidence interval
CV	Coefficient of variation
Ext Ind	Extrusion Index
DDH	Developmental dysplasia of the hip
FAI	Femoroacetabular impingement
FNSA	Femoral neck-shaft angle
GDP	Gross Domestic Product
HTE	Horizontal toit externe
JSN	Joint space narrowing
JSW	Joint space width
LCE	Lateral centre edge angle
MPFA	Modified proximal femoral angle
MTIH	Modified triangular index height
OA	Osteoarthritis
OP	Osteophyte
OR	Odds ratio
PDG	Pistol grip deformity
ROA	Radiographic osteoarthritis
THA	Total hip arthroplasty
TJA	Total joint arthroplasty
XR	X-ray

CHAPTER 1

INTRODUCTION & BACKGROUND

CHAPTER 1 – INTRODUCTION & BACKGROUND

1.1 - Osteoarthritis: Burden of Disease

Osteoarthritis (OA) represents a large and expanding burden of disease in our society[2-4]. 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[3,4].

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[2]. This expenditure figure represents approximately 3% of that country's entire Gross Domestic Product (GDP) which gives some perspective of its scale[2].

Consequently, there is a paramount 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 progression of OA.

1.2 – Classifying Osteoarthritis

Many epidemiological risk factors for hip OA have previously been identified. Age, sex, body mass index (BMI), previous hip 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[3,5,6]. Using these factors to select high-risk populations for future studies is important. Equally, defining what we classify as osteoarthritis affects how results are subsequently interpreted. The diagnosis of OA is difficult and consequently there are several potential classifications in use, each of which has its limitations. OA can be defined by (i) clinical, (ii) radiological, (iii) pathological and (iv) surgical characteristics.

1.2.1 – Clinical Classifications

Typically, patients with OA present with joint pain that is exacerbated by activity and relieved by rest. 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

Tenderness over the joint line
Crepitus
Bony enlargement of the joint
Reduced range of movement
Angulation deformity (varus/valgus)
Pain on passive range of movement
Instability of joint
Altered antalgic gait
Muscle atrophy & weakness
Joint effusion

Thorough clinical history taking and examination of the joints can form a reliable diagnostic pathway in the hands of an experienced physician but can lack objectivity. However, the American College of Rheumatologists (ACR) criteria are often used for clinical research, especially as an entry criteria for clinical trials. ACR criteria are demonstrated in **Table 1.2**.

Table 1. 2 American College Of Rheumatology (ACR) criteria for classification of hip & knee osteoarthritis

Knee	**Hip**
Clinical and radiographic knee pain	Combined clinical and radiographic hip pain
AND at least 1 of 3:	*AND*
Age >50 years	Femoral *AND/OR* acetabular osteophytes of radiograph
Stiffness <30 min	*OR*
Crepitus	ESR < 20 mm/1st hour
Osteophytes	*AND*
	Axial joint space narrowing on radiograph

ESR: erythrocyte sedimentation rate

There are several validated scoring systems for quantifying patients' disease severity using both pain and disability with activities of daily living (ADLs). Examples of these scoring protocols include the Western Ontario And McMaster Universities Osteoarthritis Index (WOMAC)[7] and the Oxford Hip & Knee Scores[8,9]. Such questionnaires are often used by healthcare practitioners and researchers in order to stratify severity of OA and to quantify joint function before and after arthroplasty.

1.2.2 – Radiological Classifications

In practice, clinical scoring is seldom used in isolation. Radiological diagnosis and grading of OA has long been held as the "gold standard" in epidemiological studies[10]. Conventional scoring systems such as those described by Kellgren & Lawrence[10] and

Altman[11] are based on awarding points for the presence and severity of individual radiographic features of OA on plain film x-rays. Radiographic features 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 easy 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[12-14]. While both have been used to investigate structural progression of OA and links to symptomatic severity[12,13], neither of these forms of imaging are currently used in the diagnosis of OA or classification of OA for research.

1.2.3 – Pathological Definitions

A definitive diagnostic test for OA is a histological tissue specimen which can only be taken during the TJA procedure or at post mortem investigation. This is never used as a diagnostic tool in clinical practice, however, understanding the histological pattern of OA is useful in gaining insight into the radiographic features that are regularly seen. The initial phases begin with excessive wear and micro damage to the articular cartilage. This process releases cytokines and enzymes which slowly alter the biomechanical nature of the cartilage making it less spongy and more brittle. With further wear the cartilage becomes thinner and cracks begin to appear on the articular surface. As these cracks deepen they eventually expose sub-chondral bone to the synovial fluid. 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 cause the fibrous joint capsule to progressively become thicker. Finally, sub-chondral bone begins

remodeling to become more sclerotic and bone at the joint margins begins sprouting new outgrowths known as osteophytes.

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 promising results[15,16]. Biomarkers for OA have a strong potential future in early diagnosis, however, at present few studies have been able to reliably link them to OA progression in longitudinal studies.

1.2.4 – Surgical Classifications

The combination of clinical OA severity and radiographic OA severity leads patients in developed nations towards the surgical treatment pathway. The most common and effective interventional therapy for severe OA in the large joints of the hip and knee is total joint arthroplasty (TJA). A patient who has undergone a TJA is an individual who has had a combination of both clinical OA severity and radiographic OA severity to a level that warrants the risks and expense of the procedure. Subsequently, validated history of TJA is commonly used as a measure of severe OA in longitudinal studies. Clearly this measure of OA is affected by the level of patient access to the surgical treatment, however, access in the United Kingdom has improved dramatically over recent years. Furthermore, employment status, income and level of education have also been shown to have some effect on the likelihood of patients requesting TJA[17]. The Osteoarthritis Research Society International (OARSI) Committee and the Outcome Measures in Rheumatoid Arthritis Clinical Trials Conference (OMERACT) Committee are in the process of producing a set of criteria for a virtual THA to overcome these issues and more accurately identify individuals with severe OA[18]. In

nations with state-funded health systems, where access to arthroplasty has improved, THA is still the best tool for measuring severe hip OA.

1.3 – Osteoarthritis Of The Hip

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[19]. 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 epidemiological traits, high impact activities and other hip pathologies. Increased age, caucasian race, female gender and elevated body mass index (BMI) represent the epidemiological profile. Previous peri-articular or intra-articular trauma (usually fracture) and 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-Calfe-Perthe's 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 included conditions such as developmental dysplasia of the hip (DDH) and femoroacetabular dysplasia (FAI).

However, despite these risk factors being listed in many medical textbooks, OA continues to be a very difficult disease to predict[20-23]. At present, few single tests exist for accurately identifying healthy individuals who are at high risk of developing future hip OA[24].

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 variants within the hip joint. These factors are present from the age of skeletal maturity and can be measured using a variety of radiographic techniques. This study aims to investigate these morphological variants in order to identify a correlation to OA that may become useful in predicting its onset.

Biomechanical risk factors for OA encompass a wide spectrum of hip morphology variation ranging from acetabular deformities to proximal femoral deformities, and quite commonly a combination of the two. The additive effects of constituent morphological deformities concentrate elevated forces over smaller contact areas causing abnormally high focal stress points and subsequent premature joint dysfunction. In order to illustrate this concept two examples of morphological hip pathologies are discussed in further detail.

1.3.1 – Developmental Dysplasia Of The Hip (DDH)

DDH is a common cause of secondary OA in young adults and is responsible for up to 29% of THA's in people aged below 60 and 9% of all THA's[25]. Risk factors for DDH include (in order) breech positioning, positive family history, female gender, first born child, Down's syndrome and congenital muscular torticollis[26].

DDH involves a spectrum of morphological derangements. The mildly affected hip has a partially shallow acetabulum, centrally located femoral head and is stable. The severely affected hip has an extremely shallow acetabulum and dislocates spontaneously. Mild DDH is commonly subclinical, occasionally presenting with

symptoms in adult life, whereas severe DDH usually presents in infancy or early childhood.

Several grading systems exist for quantifying severity on AP pelvis radiograph. The Crowe[27] classification is one such system that classifies hips on the basis of acetabular depth and femoral head location. This categorizes 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). In addition to grading systems, there are also a series of well-described morphological measurements which are used not only to diagnose DDH but also to quantify severity. Lateral centre edge (LCE) angle[28], Sharp's angle[29] and Horizontal toit externe (HTE)[30] are examples of such measurements and are demonstrated in **Figures 1.1, 1.2** and **1.3** respectively. Surgical therapies for DDH are discussed in **Chapter 1.4**.

Figure 1. 1 Lateral Centre Edge Angle (LCE).

Point 1 is the centre of the congruent circle placed over the femoral head. Point 2 is the superior lateral edge of the acetabulum. LCE is marked as the angle between the vertical axis and the line joining point 1 and point 2. The vertical axis is calculated as the line perpendicular to the inter-teardrop line (horizontal).

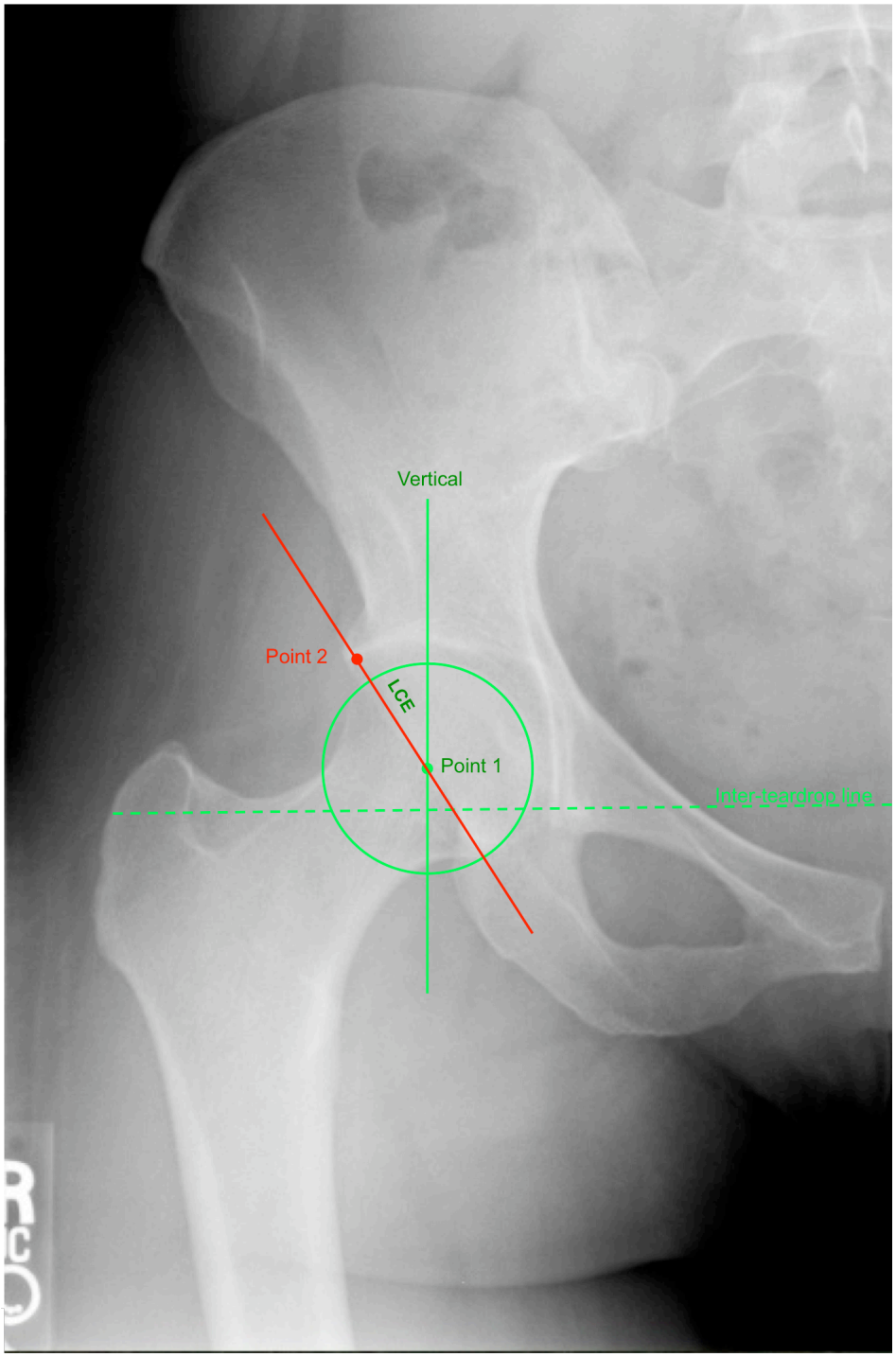


Figure 1. 2 Sharp's Angle.

Point 1 is the right teardrop. Point 2 is the superior lateral edge of the acetabulum. Sharpe's angle is marked as the angle between the inter-teardrop line (horizontal) and the line joining Point 1 and Point 2.

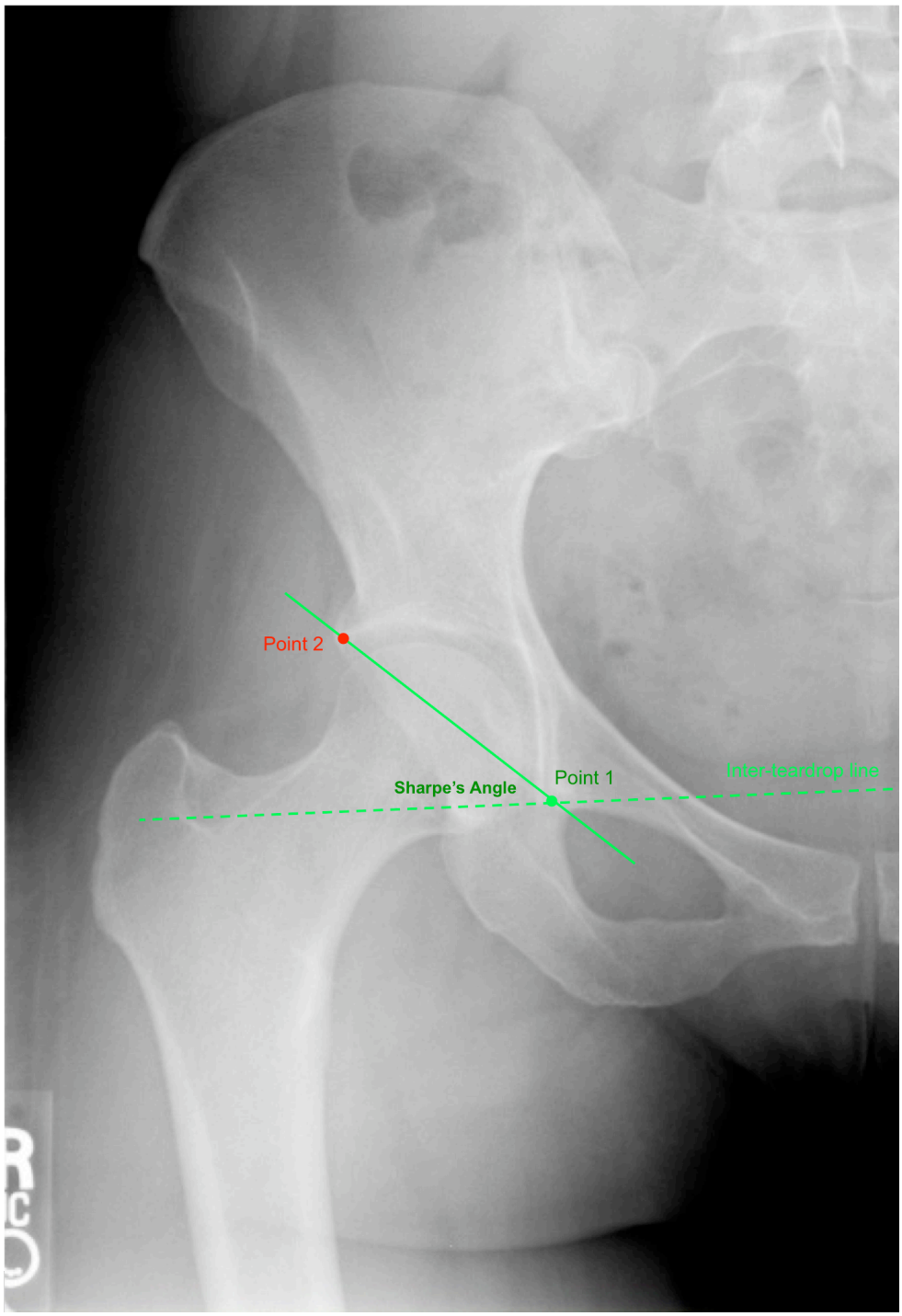
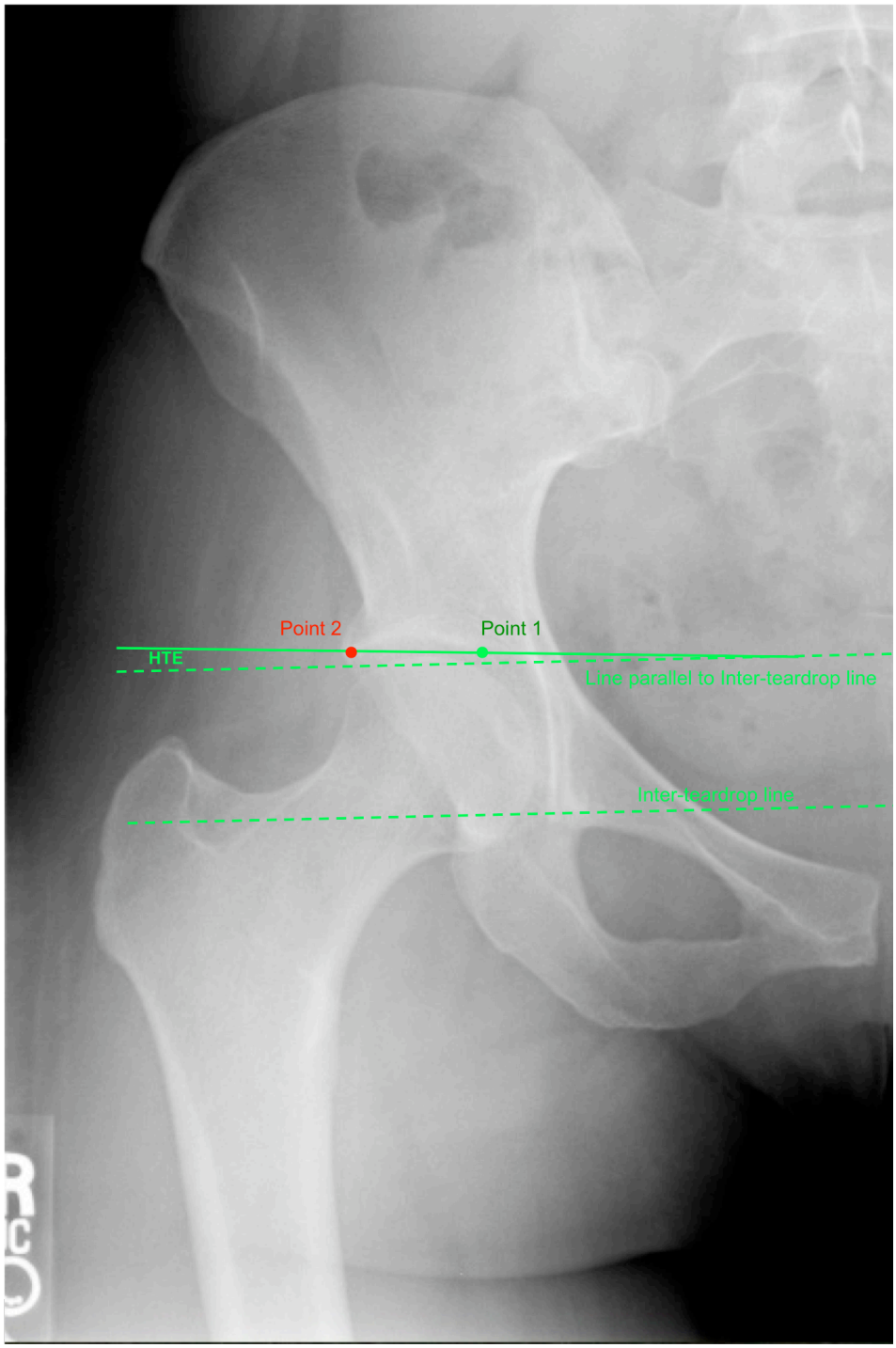


Figure 1. 3 Horizontal Toit Externe (HTE).

Point 1 is the medial edge of the acetabular weight bearing sourcil. Point 2 is the superior lateral edge of the acetabulum. HTE is marked as the angle between the inter-teardrop line (horizontal) and the line joining Point 1 and Point 2.



1.3.2 - Femoroacetabular Impingement (FAI)

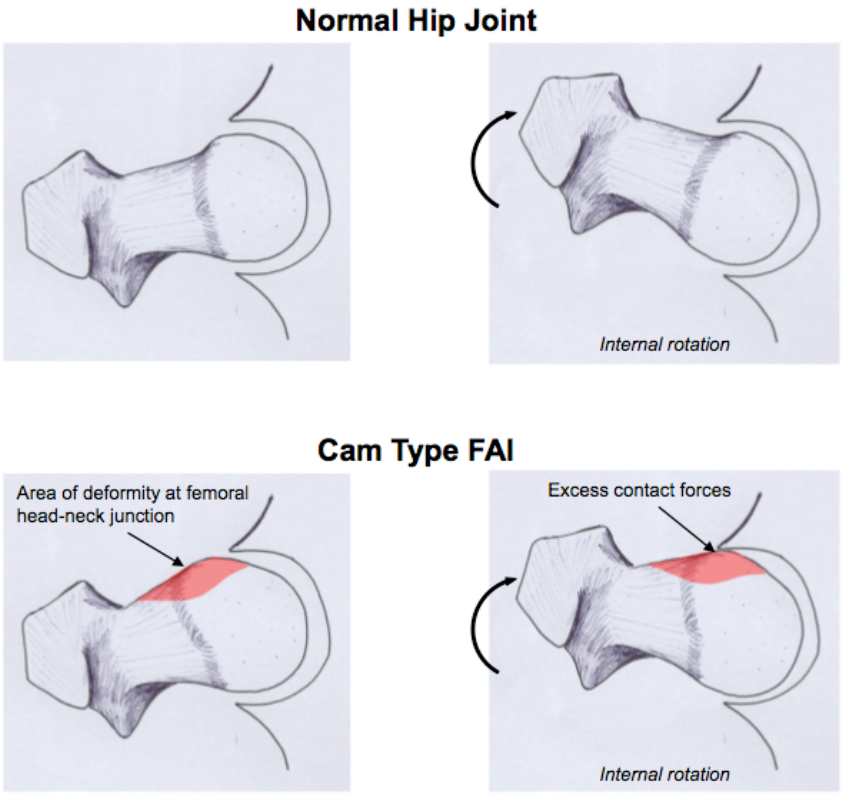
FAI is a more recently described articular mechanism responsible for causing abnormal contact stresses[31,32]. Several studies have suggested that it is responsible for degenerative changes leading to idiopathic hip OA in later life[33-36]. Individuals usually present with anterior hip pain that is exacerbated by physical activity and by long periods of sitting. There is little or no history of precipitating trauma. On examination, pain is reproduced by flexing, adducting and internally rotating the affected hip joint.

FAI consists of cam type impingement, pincer type impingement and permutations of the two. Similar to DDH, 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. Minor FAI deformities may also lead to severe OA if subject to supra-physiological range of motion and activity levels[33].

Cam impingement is more common in young men and consists of femoral asphericity at the head-neck junction. This area undergoes increased shearing forces and abutment against the superior lateral acetabular rim, particularly when the hip is flexed and internally rotated[36] (**Figure 1.4**).

Figure 1. 4 Cam Type Femoroacetabular Impingement

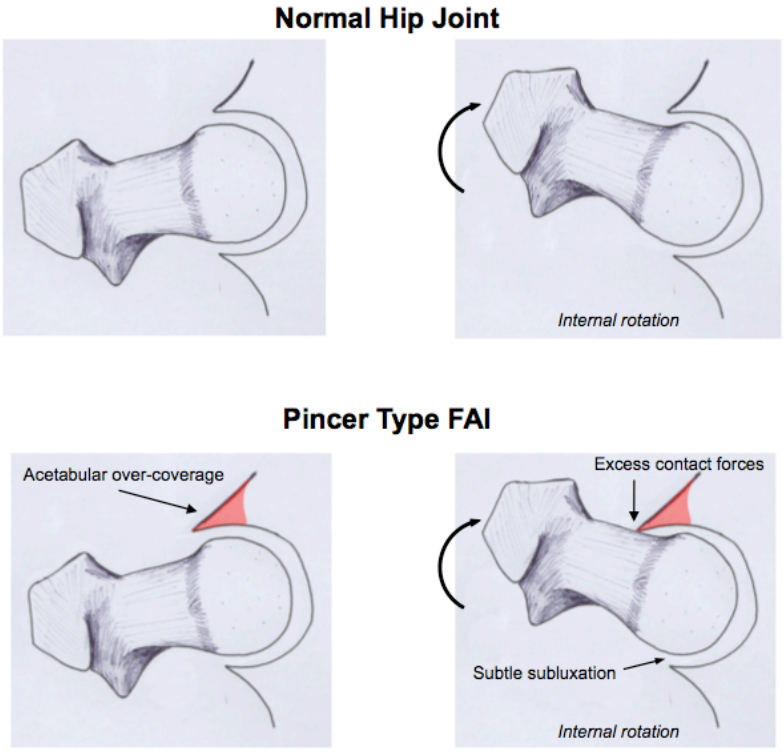
This diagram shows an axial cross-section of the right hip joint. The top two diagrams demonstrate a normal hip joint at rest and in internal rotation. The bottom two diagrams demonstrate an acetabulum with cam type FAI. The area of asphericity at the femoral head-neck junction is shaded in red and represents the cam deformity. As the femur internally rotates the cam deformity makes contact with the acetabular rim causing focal stressors. (*figure adapted from Tannast et al, 2007*[37]*)*



Pincer impingement is more common in middle-aged women and consists of acetabular over-coverage of the femoral head. The protruding shelf of the acetabular rim causes increased circumferential shearing forces, especially along the anterior superior labrum[34,36] (**Figure 1.5**). Subsequent forces may also lead to subtle joint subluxation, which contributes to global joint inflammation and deterioration.

Figure 1. 5 Pincer Type Femoroacetabular Impingement.

This diagram shows an axial cross-section of the right hip joint. The top two diagrams demonstrate a normal hip joint at rest, and in internal rotation. The bottom two diagrams demonstrate an acetabulum with pincer type FAI. The area of acetabular over-coverage is shaded in red and represents the pincer deformity. As the femur internally rotates the pincer deformity makes contact with the femoral neck causing circumferential stressors and subtle joint subluxation. *(figure adapted from Tannast et el, 2007[37])*



FAI is a relatively recent concept and consequently 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[38].

Whilst there are no commonly used radiological classification systems for FAI there are several constituent morphological measurements which have been used in literature to quantify the severity. Alpha (α) angle[39] (**Figures 1.6**), pistol-grip deformity (PGD) (calculated via femoral head:neck ratio)[40,41] and Gosvig Triangular index[1] (**Figure 1.7**) are examples of three such measurements.

Figure 1. 6 Alpha (α) Angle.

Point 1 is the centre of the congruent circle placed over the femoral head. Point 2 is placed on the superior cortex of the femoral neck as it passes out of the circle placed over the femoral head. Alpha angle (α) is marked as the angle between the femoral neck axis and the line joining Point 1 and Point 2.

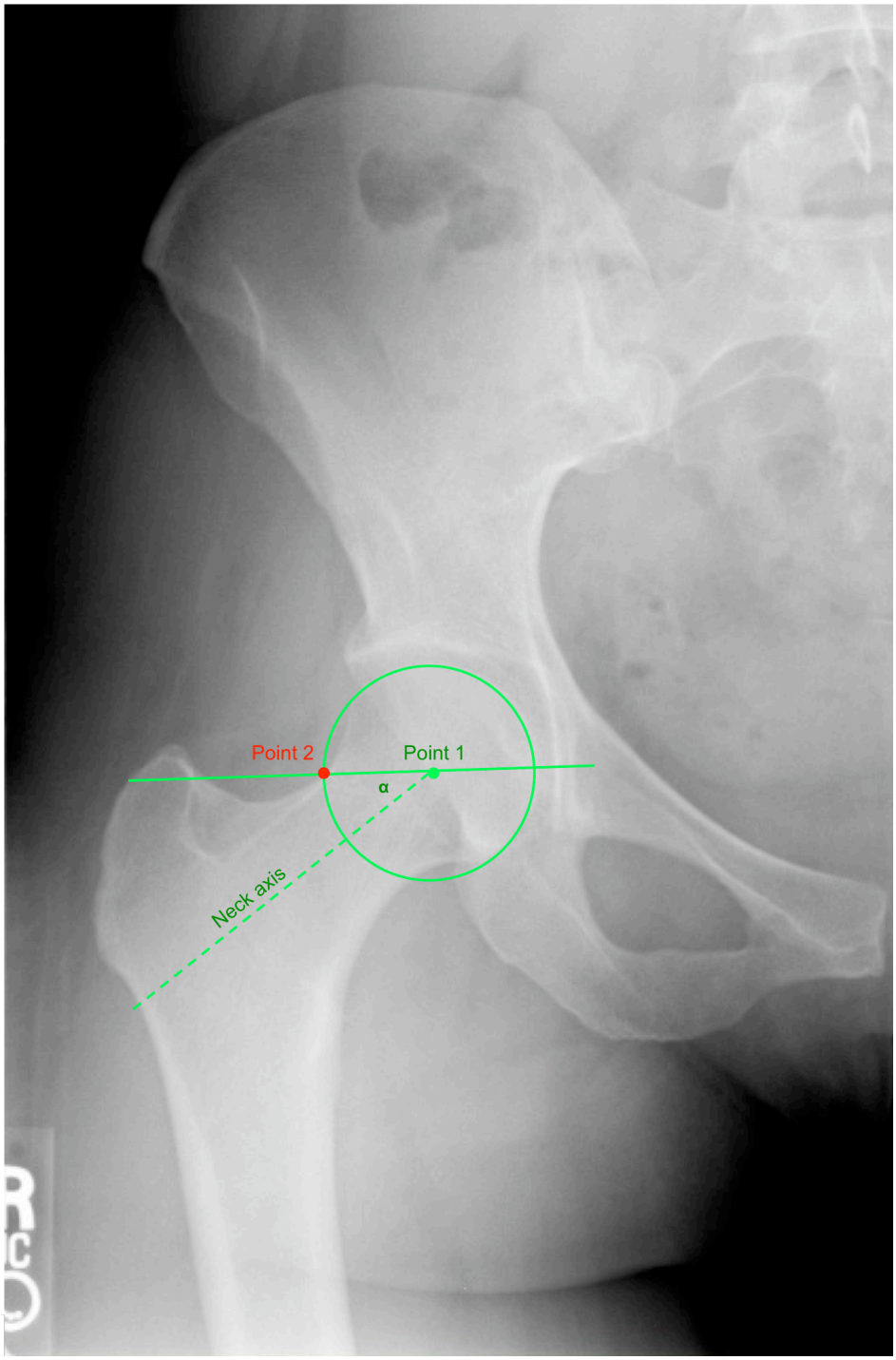
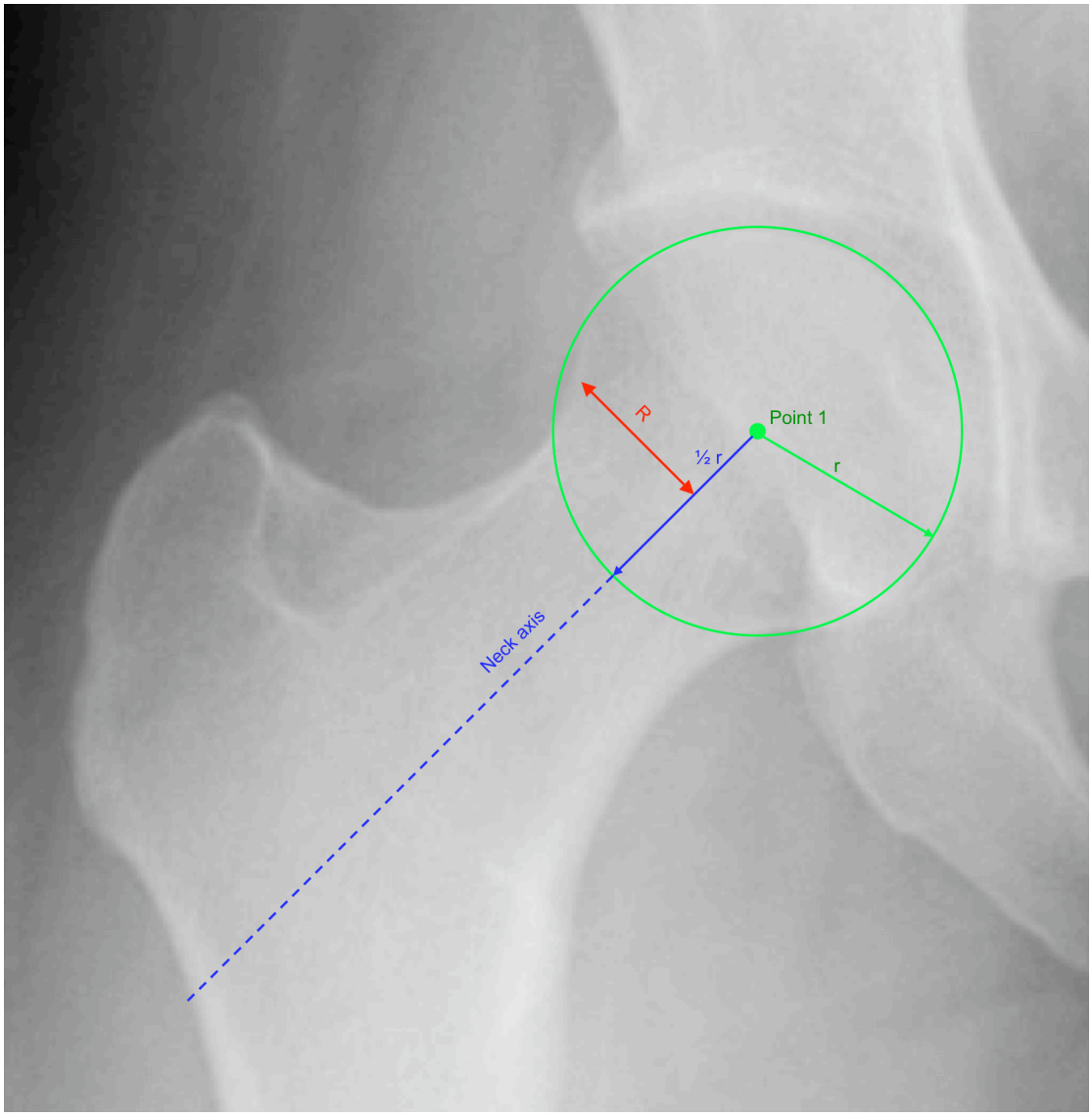


Figure 1. 7 Triangular (Gosvig) Index And Modified Triangular Index Height (MTIH)

Point 1 is the centre of the congruent circle placed over the femoral head. *r* (green) represents the radius of that circle. *r* is plotted along the femoral neck axis (blue) and the distance ½ *r* is marked. At this point, a line perpendicular to the femoral neck axis is plotted (red) and the distance *R* is measured to the femoral neck cortex. This distance *R* is the continuous variable MTIH. Triangular (Gosvig) Index is a dichotomous variable and is positive when *R* > *r* +2 *mm.* In this example Triangular Index is negative.



1.4 - Surgical Treatment Of Morphological Deformities

Surgical therapies are targeted at restoring the biomechanical properties of the femoroacetabular joint in order to prevent development of OA. Additionally, there are a variety of intra-articular soft tissue therapies that can be used to optimize outcome. Some surgical procedures related to DDH and FAI are discussed below.

1.4.1 - Developmental Dysplasia Of The Hip

Corrective surgical treatment for DDH includes hip arthroscopy and open osteotomy procedures.

Hip arthroscopy is a growing field most commonly used in diagnosis of intra-articular pathologies that are difficult to see with radiographic imaging techniques. Therapeutically it is used in the treatment of both non-structural intra-articular disorders and mild structural disorders. Non-structural procedures directed at treating the sequelae of biomechanical deformity include partial and total labral resection, labral repair and, in rare cases, focal chondroplasty[42].

Open procedures for DDH include both femoral and acetabular osteotomies. The principles of these procedures are to correct the joint dysplasia whilst avoiding over-correction that may lead to impingement. Correction of the morphological abnormality is performed on the side of the joint which has the largest deformity. Rotational pelvic osteotomy (aka periacetabular osteotomy) can be used to correct acetabular deformity, whilst intertrochanteric osteotomy can be used to correct cases with a femoral deformity. In cases of major DDH, a combination of these two concepts may be needed to restore joint biomechanics and preserve the longevity of the hip.

1.4.2 - Femoroacetabular Impingement

In the surgical treatment of FAI a range of arthroscopic and open procedures can be used that are primarily focused on relieving impingement forces.

Arthroscopic therapies are aimed at correcting underlying mild structural biomechanical deformity to prevent future sequelae. Such techniques include cam lesion debridement, however, this is somewhat controversial since there is little evidence about the degree of deformity correction that is needed[42,43]. In addition to these, soft tissue procedures similar to those described in the arthroscopic treatment of DDH are also employed.

Of the open surgical therapies for FAI, the trochanteric slide osteotomy with surgical dislocation of the hip is a well described procedure[42]. It also allows for augmentation of the joint using a variety of other surgical procedures under direct visualization. These include focal chondroplasty of the femoral head-neck junction, focal chondroplasty of the acetabular rim, labral repair and resection, relative femoral neck lengthening and trochanteric advancement. Since these procedures are relatively new there are few long-term follow-up studies looking at their efficacy, however, several short-term studies have shown some improvement in symptoms[44-46].

1.5 - Current Surgical Treatment Options For Severe Osteoarthritis

Despite advancements in pharmacological agents and in the surgical therapies previously mentioned, many patient progress to end stage OA of the hip. In these cases joint replacement surgeries are considered. The goals of such procedures are i) analgesia, ii) improved mobility & independence and iii) improved quality of life. Both hip resurfacing and total hip arthroplasty (THA) have advantages and disadvantages for individual patients. Additionally, both are costly operations that are not without risk with regard to morbidity and mortality.

Hip resurfacing offers some benefits over THA in appropriately selected candidates. It preserves proximal femoral bone stock, has a lower dislocation rate and makes for less technically demanding revision procedures[42]. Disadvantages include metal ion-associated problems, limitations in the setting of poor neck bone quality, early femoral neck fracture and lack of literature regarding implant failure.

THA remains the preferred surgical treatment for end-stage OA. There are several advantages to THA over hip resurfacing. These include a broader patient selection criteria, well documented long term efficacy, protection from femoral neck fracture, technical ease and variety of bearing surfaces[26,42]. Disadvantages include a higher rate of dislocation (than resurfacing), perceived activity limitation, larger excision of native bone (than resurfacing) and potential for excessive limb lengthening leading to antalgic gait and further sequelae[26,42].

1.6 - Morphological Theory Of Hip Disease

W.H. Harris first presented the theory that all cases of "primary" or "idiopathic" osteoarthritis of the hip are the result of morphological variance in the acetabulum or the proximal femur, or both[41]. 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, slipped capital femoral epiphysis (SCFE), Legg-Calfe-Pethes disease and most commonly developmental dysplasia of the hip (DDH). Additionally, the recent introduction of the concept of FAI and its association with OA is in keeping with Harris' theory.

Since Harris' theory was delivered, several studies have attempted to demonstrate relationships between morphological measurements designed to quantify hip deformities and future OA outcomes (**Table 1.3**). These studies have led to stronger evidence that more subtle subclinical variations in hip morphology are also associated with an increased risk of hip OA in later life[36]. 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, few studies give attention to validation of the morphological variables that they use to predict OA.

Further longitudinal investigation of how these morphological parameters 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 modifiable risk

factors, future therapeutic trials and ongoing research into the complex disease process and natural history of progression of OA.

The present study aimed to consolidate evidence produced in previous studies and address the limitations they each have. A large range of morphological parameters were included in order to scrutinize each one for reproducibility, but also to define the normal range of values in our randomly selected cohort. Following this validation process, the present study selected a nested case-control cohort from within a population-based cohort of demographic and race-matched women. By comparing morphological qualities of the hip joints in these women the present study aimed to demonstrate the relationships they have to severe OA over a long follow-up period. Specific project aims are outlined in the next section.

Table 1. 3 Previous Hip Morphology Studies

Author, Year	*AP Pelvis Morphological Measurements*	*OA Outcome Measures*	*Patient Selection*	*Number of Hips*	*Follow-Up Period*
Cooperman et al, 1983	*LCE, Ace Depth, Ext Index, Sharp, HTE*	*ROA*	*Presented to specialist Orthopaedic unit; >21 years of age; DDH; LCE <20° in one hip; No evidence of ROA; Intact Shenton's line; No Hx childhood hip disease*	*32*	*22 years*
Murphy et al, 1995	*LCE, HTE, Lat Sublux, Sup Sublux*	*ROA (K&L grade)*	*THA in contralateral hip secondary to DDH-related OA*	*286*	*25 years*
Lane et al, 2000	*Acetabular depth, LCE*	*ROA (K&L grade)*	*Random population*	*176*	*8 years*
Li et al, 2003	*LCE, HTE, Ext Index, Acetabular version, Acetabular ratio*	*Nil*	*Booked for surgery DDH*	*232*	*Nil*
Beck et al, 2005	*Coxa profunda, PGD*	*Intra-operative pattern of cartilage & labral damage*	*Booked for surgery for FAI*	*244*	*Nil*
Reijman et al, 2005	*ROA (K&L grade), JSW*	*ROA (K&L grade)*	*Baseline ROA (K&L score ≥ 1)*	*1904*	*6.6 years*
Ecker et al, 2007	*LCE, HTE, Alpha angle, Ext Index, FNSA, Coxa Profunda*	*ROA (Tonnis Grade)*	*Known OA in contralateral hip*	*119*	*Retrospective*
Gosvig et al, 2007	*Tri Index, Alpha angle, LCE, Acetabular ratio, Ext index, Head diameter*	*THA*	*Cases: Booked for THA due to OA Controls: Random population*	*2967*	*Nil*
Bardakos & Villar, 2008	*LCE, HTE, FNSA, MPFA, Alpha angle, PWS, Cross-over*	*ROA (Tonnis Grade)*	*Presented to specialist orthopaedic unit with symptomatic OA & radiographic FAI (PGD)*	*43*	*10 years*
Doherty et al, 2008	*Femoral head:neck ratio, FNSA, PGD*	*Symptomatic, clinically severe OA or THA*	*Cases: Surgical or Rheumatology Clinics Controls: Urology clinics. No symptoms & no radiographic OA*	*2076*	*Retrospective*
PRESENT STUDY	*LCE, HTE, Alpha angle, Tri Index, Ext Index, MTIH, Sharp, Acetabular version, Acetabular ratio, FNSA, MPFA, Femoral head:neck ratio, Coxa profunda, Protrusio, Cross-over, DHCEN, DACE, Neck width, Neck length, Femoral neck:length ratio, JSW, ROA (Altman grade)*	*THA*	*Random population*	*314*	*19 years*

[AP: anteriorposterior, OA: Osteoarthritis, LCE: lateral centre edge angle, Ace Depth: Acetabular Depth, Ext Ind: Extrusion index, HTE: horizontal toit externe, ROA: radiographic osteoarthritis, Hx: history, Lat Sublux: lateral subluxation, Sup Sublux: superior subluxation, DDH: developmental subluxation of the hip, FAI: femoroacetabular impingement, PGD: pistol grip deformity, JSW: joint space width, FNSA: femoral neck shaft angle, MPFA: modified proximal femoral angle, PWS: posterior wall sign, DHCEN: distance between centre of femoral heads, DACE: distance between acetabulums]

1.7 – Summary of Project Aims

Few previous studies have looked at the relationship of many morphological parameters and risk of severe OA over a long follow-up period. The aim of the present study was to demonstrate the relationship between subclinical variations in hip morphology and risk of developing future OA. The context of the present study against previous literature is shown in **Table 1.3**. The present study aims to overcome limitations of previous studies whilst drawing on their findings for context.

1.7.1 – Epidemiological Characteristics Of The Selected Population

In order to study the relationship between hip morphology and risk of THA, we gained access to a unique population-based cohort with 20 years of longitudinal data. The Chingford 1000 Women Study contains a well-described[47], population-based cohort of 1003 women that were prospectively studied since 1989. The aim of the present study was to select a representative sub-group from within this cohort and identify any baseline epidemiological differences between individuals who went on to undergo THA and those who did not.

1.7.2 – Development Of A New Hip Morphology Analysis Software

The measurement of morphological parameters is conducted by analysing anterior-posterior (AP) pelvis radiographs. Measurement of hard-copy radiographs is laborious and time-consuming. The present study aimed to develop a new software package capable of speeding up this process and allowing accurate analysis of a select group of previously investigated morphological parameters (**Table 1.4**). Testing the

reproducibility of these specific parameters using a validation study was also an important aim of the software design process.

Table 1. 4 Morphological Measurements In The Pelvis, Acetabulum & Proximal Femur.

The table refers to previously described morphological measurements that were used in the present study. Previous investigations that show association to OA are listed where they exist. Column 5 refers to the diagrams with definitions for each measurement. Some of the more simple morphological parameters are not demonstrated diagrammatically.

AP Pelvis Morphological Measurement	*Previous Associations To OA*	*Associated Deformity*	*Normal Control Value*	*Diagram*
PELVIS				
Distance between centre of femoral heads (mm)	*Nil*	*Nil*	*-*	*Figure 1.8*
Inter-acetabular width (mm)	*Nil*	*Nil*	*-*	*Figure 1.8*
ACETABULUM				
Acetabular Index of Depth to Width (ratio)	*Murphy et al, 1995*[48]	*DDH*	*48%*	*Figure 1.9*
Lateral Centre Edge Angle (degrees)	*Wiberg, 1939*[28]*;*	*DDH*	*>25 degrees*	*Figure 1.1*
Extrusion Index (ratio)	*Heyman & Herdon, 1950*[49]*; Li & Ganz, 2003*[50]	*DDH*	*<25%*	*Figure 1.10*
Horizontal Toit Externe (degrees) (aka Tonnis Angle, aka Acetabular Index)	*Tonnis, 1976*[30]*; Li & Ganz, 2003*[50]	*DDH*	*<10 degrees*	*Figure 1.3*
Sharp's Angle (degrees)	*Sharp, 1961*[29]*; Cooperman et al, 1983*[51]	*DDH*		*Figure 1.2*
Acetabular Tilt (degrees)		*DDH*	*Not previously described*	*Figure 1.11*
PROXIMAL FEMUR				
Triangular (Gosvig) Index (dichotomous)	*Gosvig et al, 2007*[1]	*Cam FAI*	*Absent*	*Figure 1.7*
Modified triangular (Gosvig) index height (mm)	*Gosvig et al, 2007*[1]	*Cam FAI*	*Not previously described*	*Figure 1.7*
Alpha Angle (degrees)	*Notzil et al, 2002*[39]*; Gosvig et al 2007*[1]	*Cam FAI*	*59 degrees*	*Figure 1.6*
Femoral neck width to length ratio	*Dincel et al, 2008*[52]	*NOF fracture*	*0.40*	*-*
Femoral head to neck ratio	*Doherty et al, 2008*[40]	*PGD*	*1.4*	*-*
Femoral neck shaft angle (degrees)	*Moore et al, 1994*[53]	*Varus / valgus*	*125 degrees*	*Figure 1.12*
Modified proximal femoral angle (degrees)	*Bardakos & Villar, 2008*[35]	*GT overgrowth*	*84*	*Figure 1.13*
OTHER				
Minimum JSW (mm)	*Kellgren & Lawrence, 1957*[10]*; Conrozier et al, 1998*[54]	*ROA*	*>2.5 mm*	*-*

Figure 1. 8 Inter-Acetabular Width (DACE) & Inter-Femoral Head Width (DHCEN).

DACE is marked as the distance between the most medial margin of each acetabulum. DHCEN is marked as the distance between two red points, each representing the centre point of the respective femoral head.

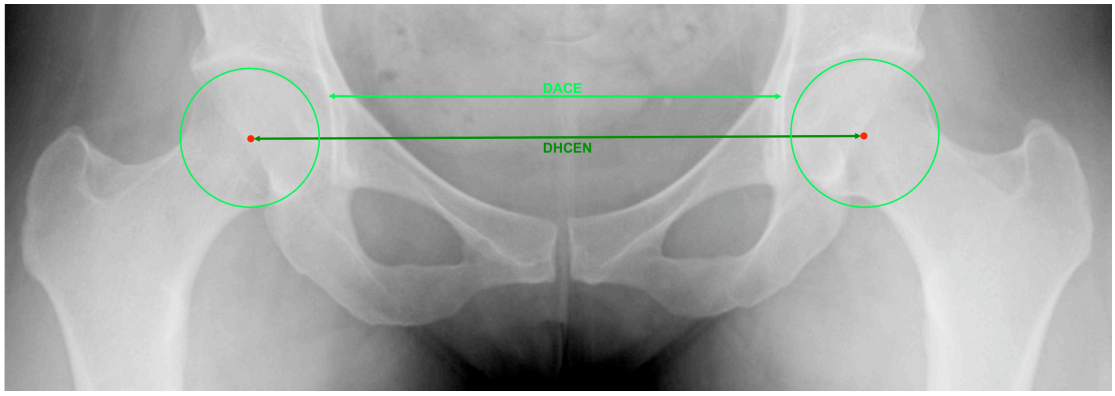


Figure 1. 9 Acetabular Depth & Width (ACE Depth & ACE Width).

Point 1 is the inferior medial edge of the acetabulum. It is located by following the posterior wall of the acetabulum down to the point where it meets the inferior cortex of the femoral head. Point 2 is the superior lateral edge of the acetabulum. Point 3 is the deepest point of the acetabulum (on an axis perpendicular to the line joining Point 1 & 2). Ace Width is the distance between point 1 and 2. Ace Depth is the perpendicular distance between the Ace Width and Point 3.

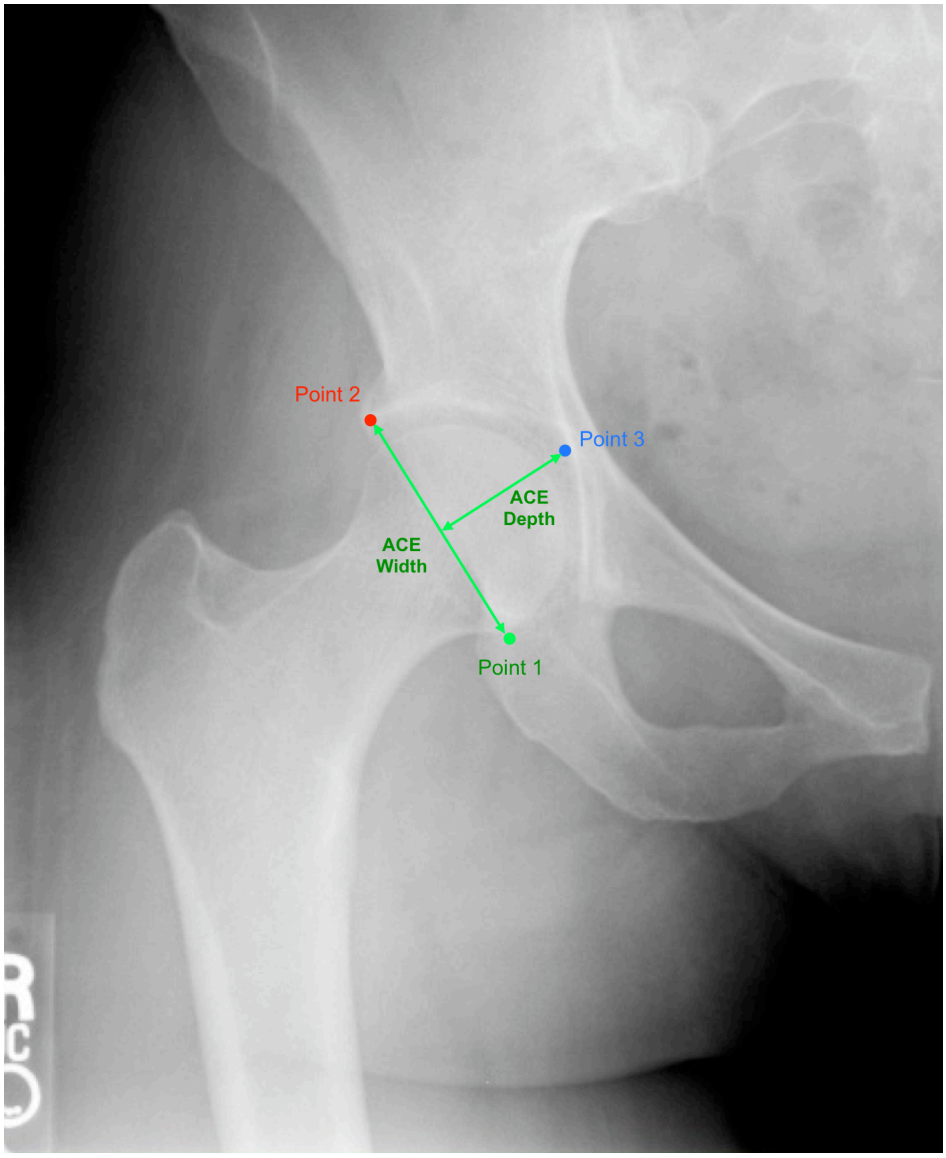


Figure 1. 10 Extrusion Index (Ext Ind).

Point 1 is the superior lateral edge of the acetabulum. The large green circle is congruent and superimposed over the femoral head. Extr Ind is calculated by measuring the distance X as a proportion of Y (Extr Ind = X/Y). All horizontal measurements are taken in the same axis as the inter-teardrop line (not marked).

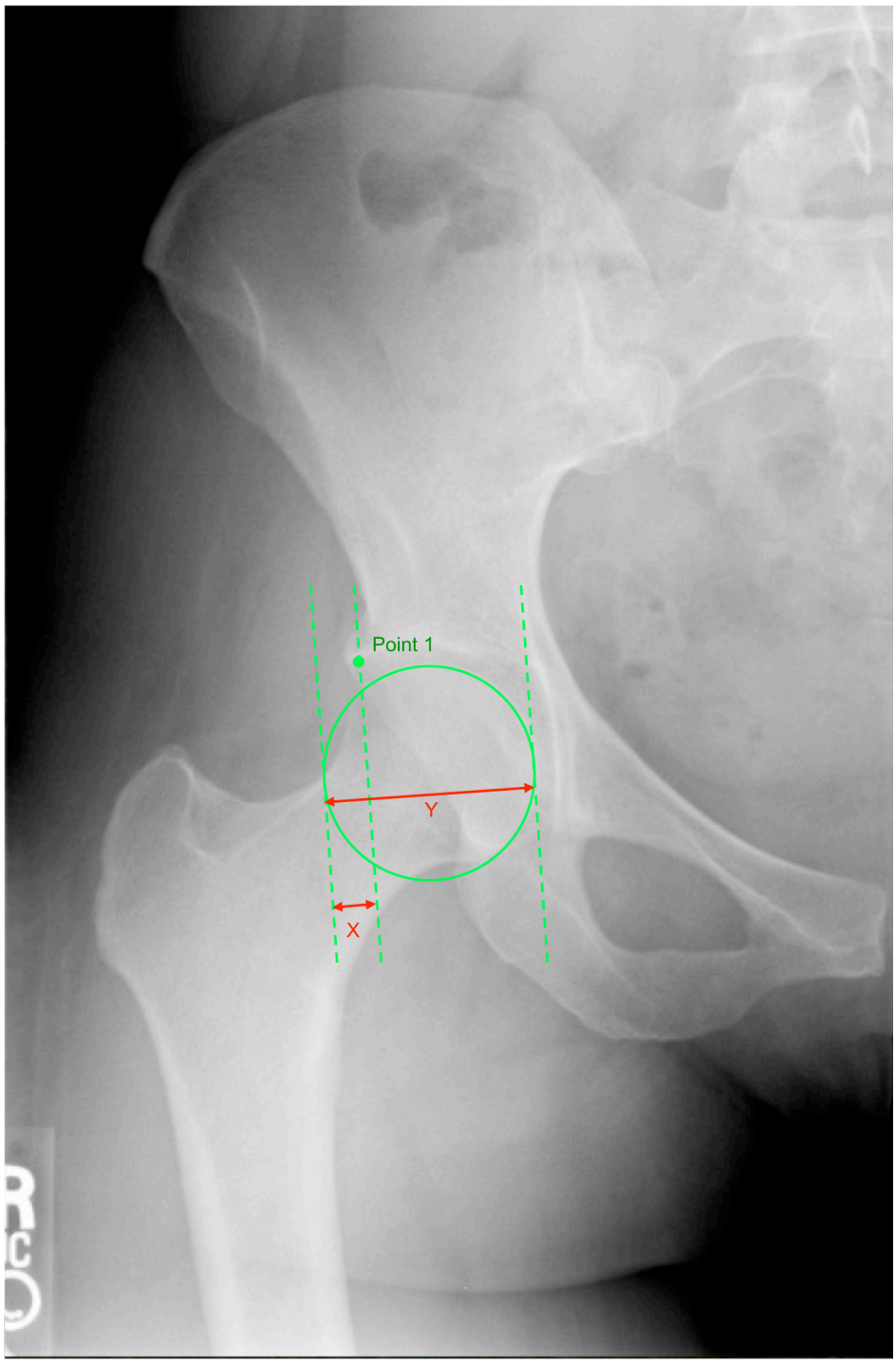


Figure 1. 11 Acetabular Tilt (Ace Tilt).

Point 1 is the inferior medial edge of the acetabulum. It is located by following the posterior wall of the acetabulum down to the point where it meets the inferior cortex of the femoral head. Point 2 is the superior lateral edge of the acetabulum. ACE Tilt is marked as the angle between the inter-teardrop line (horizontal) and the line joining Point 1 and Point 2.

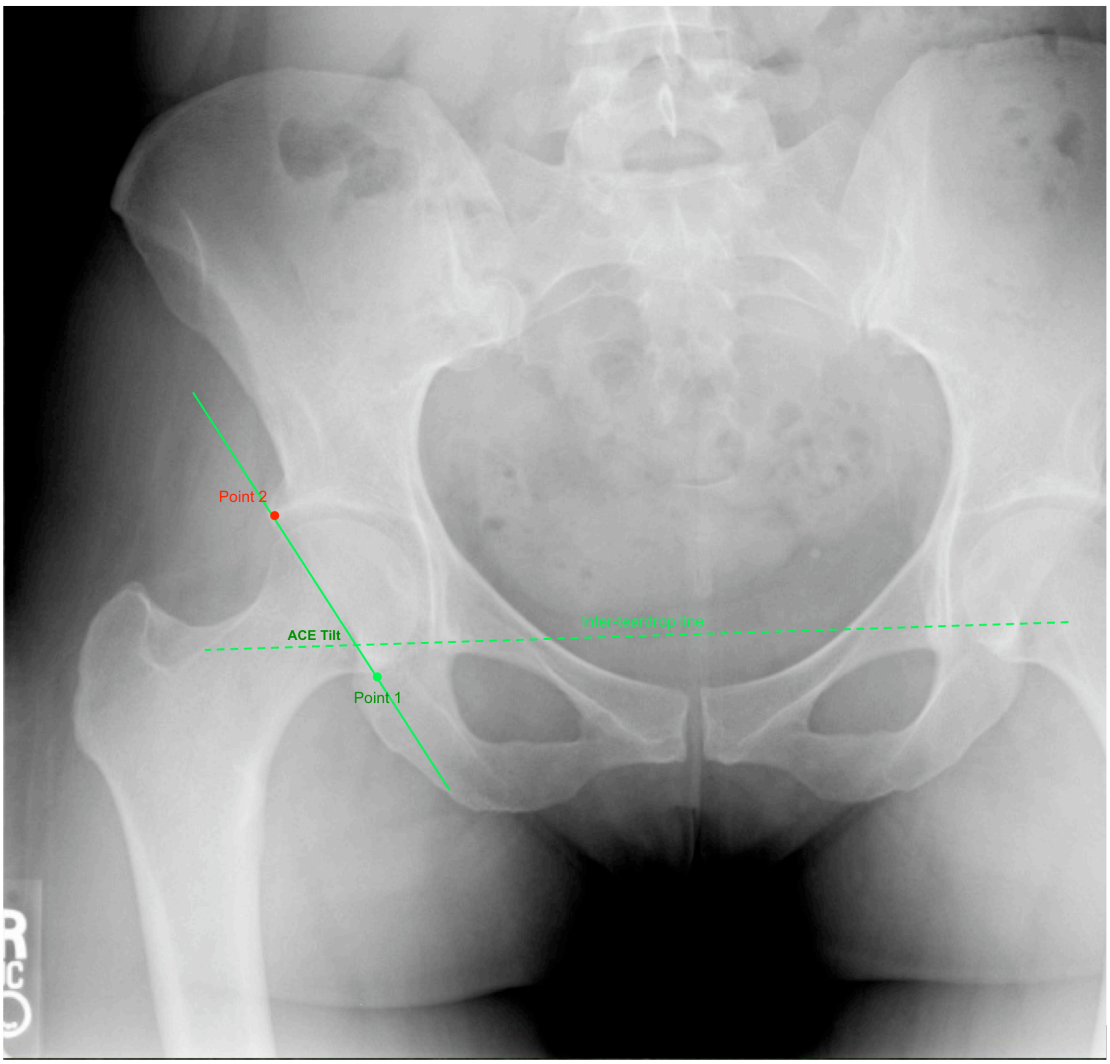


Figure 1. 12 Femoral Neck Shaft Angle (FNSA).

Point 1 is the centre of the congruent circle placed over the femoral head. Point 2 is the midpoint at the narrowest part of the femoral neck. FNSA is marked as the angle between the femoral shaft axis and the line joining Point 1 and Point 2 (the neck axis). Femoral shaft axis is calculated by finding the midpoint of the femoral shaft at the most distal point visible and at a level 2 cm below the lesser trochanter. The line joining these two points is the femoral shaft axis.

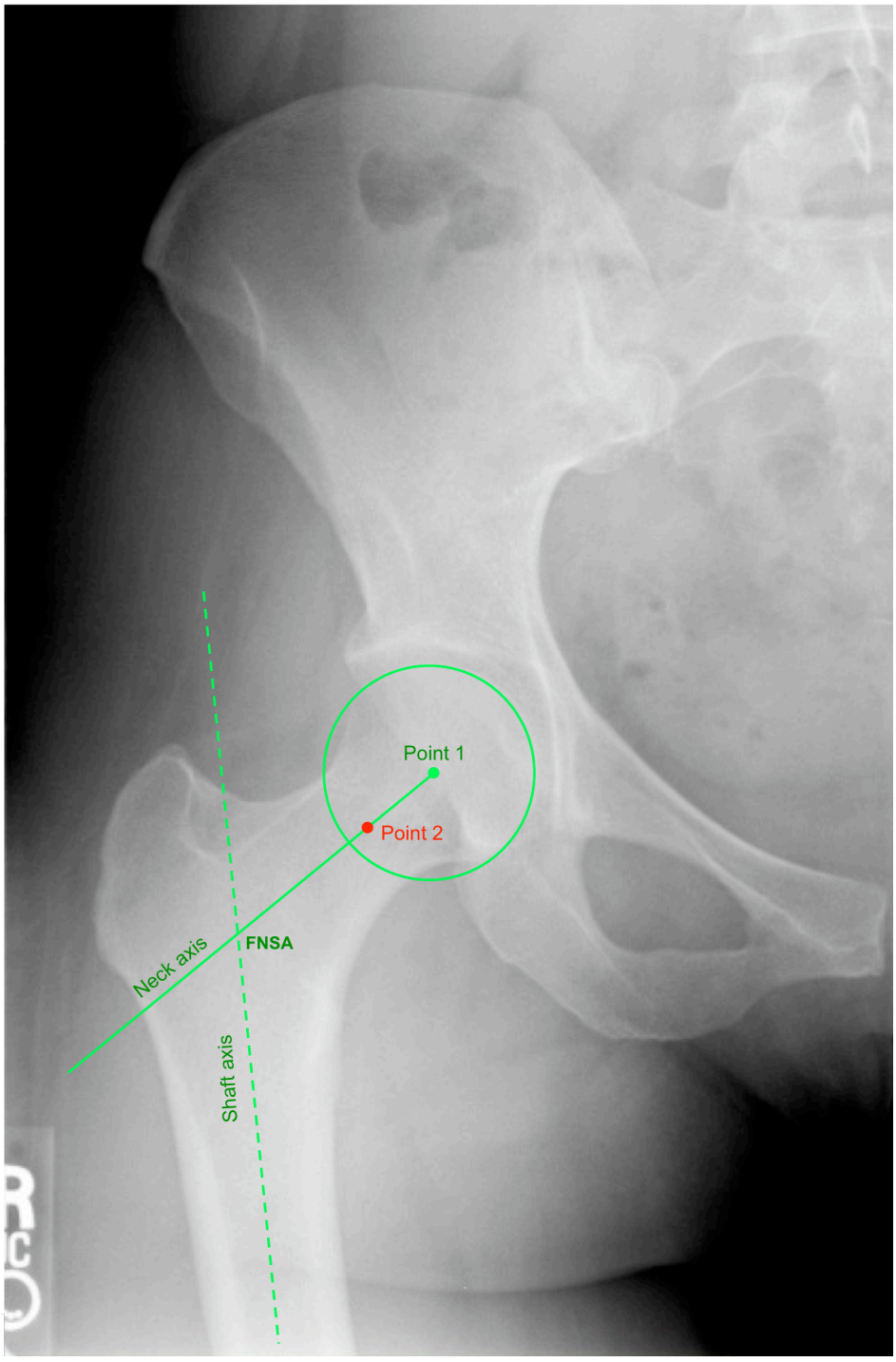
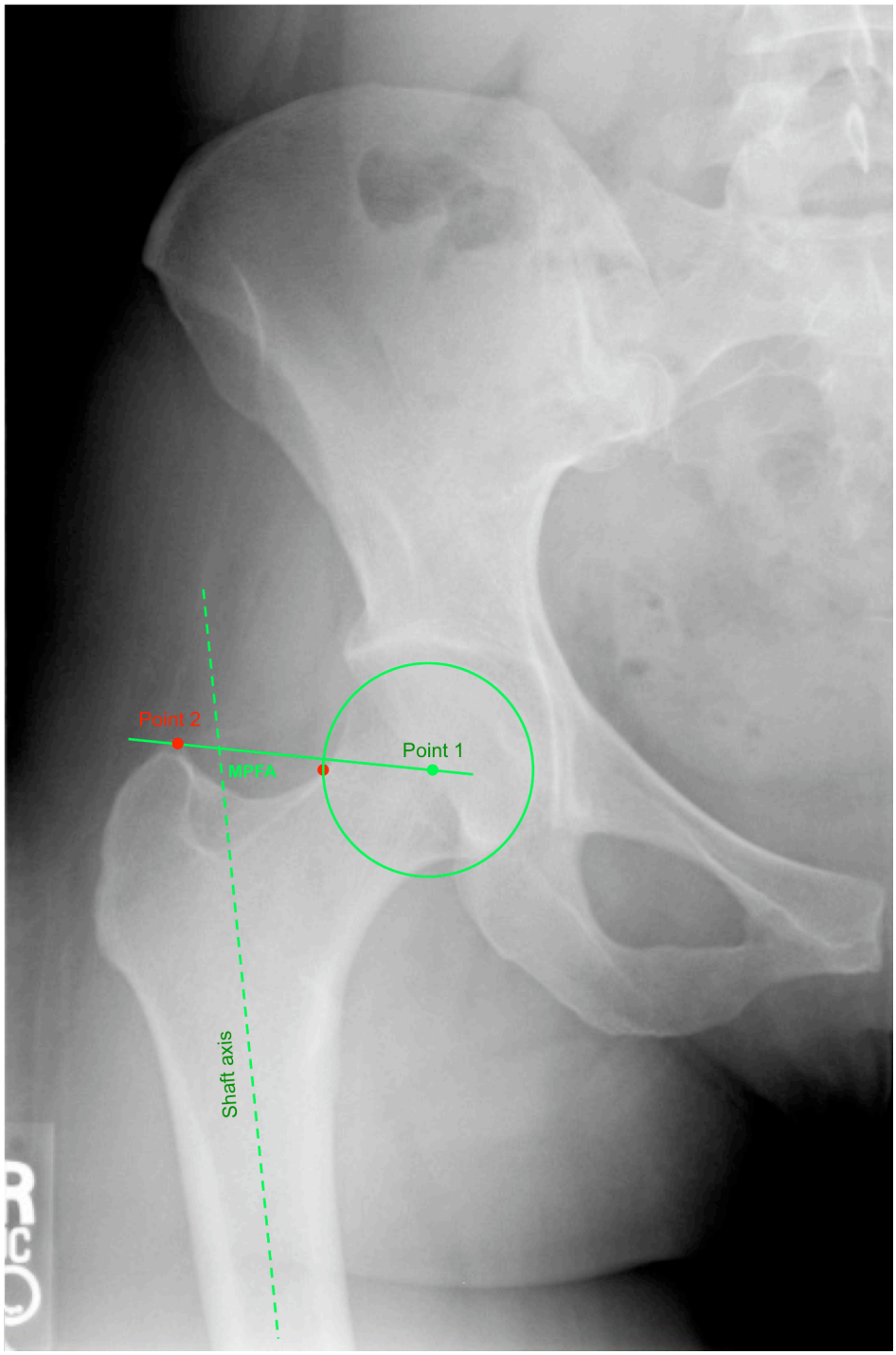


Figure 1. 13 Modified Proximal Femoral Angle (MPFA).

Point 1 is the centre of the congruent circle placed over the femoral head. Point 2 is the most superior tip of the greater trochanter. MPFA is marked as the angle between the femoral shaft axis and the line joining Point 1 and Point 2. Femoral shaft axis is calculated by finding the midpoint of the femoral shaft at the most distal point visible and at a level 2 cm below the lesser trochanter. The line joining these two points is the femoral shaft axis.



1.7.3 – Morphological Characteristics Of The Selected Population

Many of the morphological parameters described in the previous literature were not measured in large enough cohorts for normal population reference ranges to be given. We aimed to measure a select group of morphological parameters in a large sub-group of the Chingford 1000 Women Study and report the normal values. Correlations between individual morphological parameters were subsequently investigated in order to search for any previously undetected morphological patterns.

1.7.4 – Investigation Of The Relationship Between Hip Morphology Characteristics And Incidence Of Total Hip Arthroplasty

We searched the literature for previously described acetabular and proximal femoral morphological measurements (**Table 1.3).** In some cases these had already been demonstrated to have an association with OA outcomes. These measurements were then included in our analysis and measurements were correlated with THA records over the past 19 years. The aim was to identify individual morphological parameters which differed significantly between the THA group and the control group. Following the identification of any such relationships, the aim was to adjust the significance for epidemiological covariates (baseline age, height, weight & ROA) and then for other morphological covariates. Finally, we aimed to test each morphological parameter for the independence of its effect on THA risk.

1.7.5 – Overall Aim

The specific aim was to demonstrate isolated morphological parameters that are risk factors for future severe OA, as defined by THA, in a healthy population of women. In

achieving this aim it was necessary to develop a new methodology for measuring hip morphology and validate it for accuracy and reproducibility.

1.8 – Clinical Questions & Hypotheses

The aims of the present study lead into the following clinically relevant questions:

Is there a relationship between subclinical variations in hip morphology and future risk of end-stage osteoarthritis of the hip (defined by total hip arthroplasty)?

Is there an additive risk effect between individual morphological parameters and future risk of end-stage osteoarthritis of the hip (defined by total hip arthroplasty)?

These clinical questions are converted into broad and then specific hypotheses:

BROAD

i) Subclinical variations in hip morphology quantified using digitized AP pelvis radiographs can be used to predict 19-year risk of developing end-stage hip OA in a healthy group of women.

Null hypothesis: There is no relationship between subclinical variations in hip morphology measurements on AP pelvis radiographs and 19-year risk of developing end-stage hip OA in a healthy group of women.

SPECIFIC

In devising specific hypotheses for the present study, several individual morphological parameters were selected. These were chosen either because they have shown significant results in previous morphology analysis literature (alpha-angle, Sharp's angle, Ext Ind, LCE), or because they were biologically plausible measures of specific deformities (modified triangular index height).

The specific hypotheses are as follow:

i) An elevation in the alpha (α) angle (a measure of cam type FAI) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Elevated alpha (α) angle is not associated with risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

ii) An elevation in the Sharpe's angle (a measure of acetabular inclination) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Elevated Sharpe's angle is not associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph

iii) A reduction in the LCE angle (a measure of femoral head lateralisation) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Reduced LCE is not associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

iv) An elevation in the Modified triangular index height (a measure of cam type FAI) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Elevated modified triangular index height is not associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

v) An elevation in the extrusion index (a measure of femoral head lateralisation) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Elevated extrusion index is not associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph

1.9 - Structure of the Thesis

The thesis is presented in the following structure:

Chapter 2 presents the study methodology that was used in undertaking this project. It gives account of how the Chingford 1000 Women study was initiated and how individuals in that cohort were selected for inclusion. The design process of the hip morphology analysis software is also outlined.

Chapter 3 presents the baseline epidemiological characteristics of the Chingford 1000 Women study. These characteristics are juxtaposed against the sub-group that was randomly selected for the present study. Finally, case and control groups are compared for baseline similarity.

Chapter 4 reports an inter-user and intra-user variability study conducted to investigate reliability of the hip morphology analysis software. This study aims to validate future use of the software in hip morphology analysis of pelvis radiographs.

Chapter 5 reports the hip morphology characteristics of the women selected in the case-control sub-group that was selected for the present study. The correlation between shape measurements in the pelvis, acetabulum and proximal femur is also demonstrated.

Chapter 6 reports differences in measured hip morphology parameters between individuals who went on to undergo total hip arthroplasty at some point in the following 19 years and those who did not.

Chapter 7 is a discussion of the findings that are reported in Chapter 3 through to Chapter 6. Significant results are discussed and the potential avenues for future research are explored. Finally, limitations of the present study are acknowledged.

CHAPTER 2

STUDY METHODS

CHAPTER 2 – STUDY METHODS

2.1 – The Chingford Cohort Study

The prospect of analysing hip morphology in the Chingford 1000 Women Study cohort represented an excellent opportunity. Over a twenty year period the Chingford 1000 Women study has become an eminent database of epidemiological records and alongside the Framingham[55] and Rotterdam[56] studies it represents one of the world's largest prospective longitudinal cohort investigations for OA. Through collaboration with colleagues at King's College London, access to previous epidemiological data and clinical investigations was obtained. For these reasons, the present study represents a unique and valuable investigation.

The Chingford 1000 Women study is a well-described[57] cohort of randomly-selected healthy Caucasian volunteers that was initiated in 1989 by researchers at St Thomas' Hospital, London. All women aged between 45 and 65 years of age who were registered at the Handsworth General Practitioners' Clinic (Chingford, Essex) were invited to participate in the study and 1003 volunteered. At baseline, the women ranged between 45 and 65 years of age. They participated in yearly clinic visits over the first 10 years at which time morphometric, clinical, biological and radiological measurements were taken. In subsequent years, clinic visits were less frequent, however, telephone questionnaires were continued annually through to present day. These included details of any operations undergone in the previous year. Appendix A gives a full list of clinic visits and of specific data collected at various time-points.

2.2 - Inclusion Criteria For Hip Morphology Study

Annual patient surveys showed that a total of 32 women underwent THA due to hip OA during the 19 year follow-up period. This record was then validated via consensual written communication with each individual's general practitioner. The GP's of individuals that had indicated they underwent THA were asked to complete a validation form confirming date, site, indication and hospital of all previous lower limb arthroplasty surgery (see Appendix C). The same form was also sent to the GP's of another 50 randomly selected patients to screen for missed cases. This validation process confirmed 31 out of 32 THA cases (1 patient had passed away and GP records were not accessible) and failed to yield any unreported cases from the screening of the 50 randomly selected individuals.

The present study compares the 31 individuals who underwent THA (cases) with a control group of individuals. The control group (n=126) was randomly selected from the remaining 971 study participants and is approximately 4 times larger than the number of cases (n=31) in order to maximize statistical power of the study[58]. The overall design of the present investigation was that of a nested case-control type study that was selected from the original prospective longitudinal cohort design of the Chingford 1000 Women Study. The benefits of a nested case-control design include reductions in the amount of analyses, time and cost required to investigate biological precursors to diseases. In addition, it has the advantage that both cases and controls are selected form the same population cohort. The drawback of such a design is the slight loss in statistical power due to the type II error, however, this is considered to be acceptable due to the real efficiencies in cost and effort which are gained by analyzing only a subset of the entire cohort[58].

2.3 – Pelvis Radiographs

As part of an earlier focus on predictors of osteoporosis and neck of femur fracture, all women in the Chingford 1000 women study underwent AP pelvis x-rays at study year 2. The radiographer's protocol used in taking these x-rays is listed in **Table 2.1**. A standard magnification of 120% was assumed for all radiographs. Variations in patient positioning, patient body habitus and x-ray beam angulation bring a recognised component of pre-analytical threats to the reproducibility of the present study design.

Table 2. 1 Radiographer Protocol: AP Pelvis X-Rays

Patient supine
Knees flexed (small sand bag under knees)
Feet straight (sagittal 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 present study gained access to these plain film radiographs from the investigation archives. The films were digitized using a back-light scanner with a 24 mm opaque reference object placed in the top right corner of each image to calibrate size. For full protocol used in scanning the radiograph films see Appendix B.

Some pelvis films were too large for the standard scanner that was used. In such cases, the individual film was first scanned in left margin alignment and then scanned again in right margin alignment yielding 2 separate digitized images. These two images were merged together using the "Automerge" function in Adobe Photoshop CS3 Extended Version 10.0. Each final image was then inspected closely for artifact along the seam line and any film that showed irregularity was excluded from the study.

All digitized radiographs were initially stored as ".tif" files for maximum resolution quality. For the analysis phase using *Hip_morf 2.0* software, these files were too large for the computer's processor to make expeditious measurements. Radiographs were consequently compressed to ".jpeg" files using Apple iPhoto '08 Version 7.1.5. Protocol used for compression of files is listed in **Table 2.2**. Compressed radiographs were then used for hip morphology analysis.

Table 2. 2 Radiograph Compression Protocol.

Radiographs imported as .tif files into Apple iPhoto '08 Version 7.1.5 (approximate file size = 125 MB)
Radiographs rotated into correct orientation
Click "File" ⇒ "Export"
Kind = JPEG
JPEG Quality = Maximum
Size = Custom (set to 3000 pixels in maximum dimension)
"Export" (approximate file size = 2.5 MB)

2.4 – Hip Morphology Measurement Protocols

There was no suitable software available for efficiently analysing the selected morphological parameters in order to achieve the aims of the present investigation. However, a piece of software named *Hip_morf* had been developed within the department for a previous study into the genetic inheritance of FAI. *Hip_morf* had been designed specifically for quantifying several morphological parameters, mainly in the acetabulum. It measured seven separate parameters that were associated with FAI deformity (LCE, Ext Ind, Femoral head congruence, JSW, ACE ratio, Femoral head diameter & HTE). This was insufficient for the needs of the present study since our aims were to analyse all morphological parameters associated with OA, including those in the proximal femur and several newer shape measurements. Although it was insufficient, *Hip_morf* represented a good foundation from which to develop a new program. Thus, the capabilities of the old software were developed over a 6-month period in order to create an enlarged and specified package, tailor-made for the present study. This new software package was called *Hip_morf 2.0*.

Hip_morf 2.0 was developed in collaboration with our intradepartmental orthopaedic engineering team. During the development process, each of the original morphological parameters was revised for accuracy and ergonomic ease of measurement in an attempt to optimise inter-user reproducibility. For instance, several linear measurements were altered from distance between two points to distance between calipers, allowing for a quicker and more reliable measurement. A further 16 angular, linear and ratio morphological measurements were added (see **Table 2.3**). Constituent anatomic landmarks were defined for each of these measurements and programmed into the software so that morphology could be calculated.

The software was written using Matlab R2008b which provides a platform for making simple geometric calculations on a 2-dimensional radiograph. Each radiograph is visualised digitally as a JPEG file. and a total of 23 separate variables were measured in each hip joint. In addition to these geometric measurements there are a series of dichotomous variables and Altman ROA grading system by which each joint was graded. Every year-2 pelvis radiograph from the nested case-control group (n=157) was analysed in this fashion. Analysis of the included radiographs took 2 months.

2.4.1 - Design of *Hip_morf 2.0* software

Radiograph analysis using *Hip_morf 2.0* was designed to be straightforward and reproducible, and each investigator was issued with a User Guide (see **Appendix D**). The image of the selected radiograph appeared and at the top of the screen there was a prompt telling the user to click on a particular anatomical landmark. Once this is done the user then confirmed the point they had selected and the next prompt appeared. This process was followed throughout the analysis phase with the program continuing to prompt the user to click on various land marks until all constituent data coordinates had been recorded. The program then performed the necessary arithmetic and calculated all the included morphological parameters for the pelvis, acetabulum and proximal femur. This data was exported straight into a common separated variable (CSV) file which was later compiled with others and saved into a database.

In keeping with the aims of the present study, *Hip_morf 2.0* was specifically designed to quantify pelvis, acetabulum and proximal femur shapes in order to identify relationships between subclinical morphological variation and risk of THA. As discussed earlier, there are several previously well-described measurements that have shown some relationship to FAI and DDH. A comprehensive list of these

measurements, along with other newer shape models that were included, can be viewed in **Table 2.3**. In addition to linear measurements, angles and ratio measurements made using *Hip_morf 2.0,* presence of previous surgical implants and several dichotomous shape variables were also recorded. Finally, each hip was scored for Altman ROA grade and all data was stored along with the morphological variables in the CSV file.

Table 2. 3 List Of Data Recorded By *Hip_Morf 2.0.*

In the process of developing this software, new morphological parameters were added to the foundation provided by *Hip_morf.* Each of these new parameters is marked with the symbol *. In addition, those parameters which were part of the old program were revised to improve accuracy and reduce inter-user variability.

PELVIS

**Distance between centre of femoral heads (mm)*

**Inter-acetabular width (mm)*

ACETABULUM

Acetabular Width (mm)

Acetabular Depth (mm)

Acetabular Index of Depth to Width (ratio)

Lateral Centre Edge Angle (degrees)

Extrusion Index (ratio)

HTE (degrees)

**Sharpe's Angle (degrees)*

**Acetabular tilt (degrees)*

PROXIMAL FEMUR

Femoral head diameter (mm)

**Modified Triangular (Gosvig) Index – Height (mm)*

**Alpha Angle (degrees)*

**Femoral neck width (mm)*

**Femoral neck length (mm)*

**Femoral Neck Length : Neck Width ratio (%)*

**Femoral Head : Neck ratio (%)*

**Femoral neck shaft angle (FNSA)*

**Modified proximal femoral angle (MPFA)*

OTHER DICHOTOMOUS VARIABLES *(Yes/No)*

Minimum joint space width (JSW)

**Triangular Index (Gosvig Index)*

**Protrusio acetabuli*

**Coxa profunda*

**Cross-over sign*

**Hemiarthroplasty in situ*

**Total hip arthroplasty in situ*

**Dynamic hip screw in situ*

**Intra-medullary device in situ*

**Other internal fixation in situ*

2.4.2 – Inclusion Criteria For Individual Morphological Parameters

During the introduction, some background was given to individual morphological parameters that were selected for inclusion in the present study. Several morphological parameters have been previously associated with well-described biomechanical deformities of the hip. These are laid out concisely in **Table 1.3**, which also refers to individual diagrams demonstrating how these measurements are made (**Figures 1.3 – 1.13**). Measurements included in **Table 1.3** were all selected primarily because of their previously identified relationships to measures of OA outcome. This section describes specific reasons for including additional morphological measurements in the *Hip_morf 2.0* software design.

Acetabular tilt (Ace Tilt) is a newly devised morphological measurement and is described here for the first time. It is demonstrated diagrammatically in **Figure 1.11**. Specifically it was designed as a measure of acetabular version in the along the coronal plane and is very similar to Sharp's angle (**Figure 1.4**). As Ace Tilt increases, so too does the tendency for lateralisaton of the femoral head. When one then considers the weight-bearing forces running through the hip joint, it becomes obvious that this means less coverage of the femoral head and greater sheer forces on the remaining articular contact areas. Such contact may be related to the initiation of OA joint pathology. The reason for including Ace Tilt along with Sharp's angle was to scrutinize the reproducibility of the constituent anatomic landmarks of each measurement and compare the two. Since both measurements are aimed at quantifying the same deformity, identifying any weakness in their respective reproducibility was a goal.

Gosvig *et al*[1] first described the Triangular index as a dichotomous score calculated using the method demonstrated in **Figure 1.7.** It is used for measuring the presence or absence of a cam-type FAI on the proximal femur. Modified triangular index height (MTIH) is a new linear measurement that we selected from the constituent measurements used in scoring the traditional Triangular index (**Figure 1.7)**. This morphological parameter was added to the present study because it gives a linear quantification of the severity of any cam-type FAI, rather than a simple dichotomous score.

Protrusio acetabuli and coxa profunda are both dichotomous scoring variables originally used as surrogate measures acetabular depth. Protrusio acetabuli is positive when the medial edge of the femoral head is seen touching or protruding medially past the ilioischial line on the AP pelvis radiograph[37]. Coxa profunda is positive when the medial edge of the acetabulum is seen touching or protruding medially to the ilioischial line on the AP pelvis radiograph[37]. Each of these morphological measurements is defined diagrammatically in **Appendix D**. Both were included for comparison against the linear and ratio measurements used included in *Hip_morf 2.0* such as acetabular depth, acetabular width and acetabular depth-to-width ratio. In keeping with the aims of the present study, linear and ratio measurements are better able to quantify the more subtle deformities.

Cross-over sign was first described as a dichotomous method for scoring acetabular retroversion on a two-dimensional AP pelvis radiograph[59,60]. When the anterior wall of the acetabulum is seen protruding laterally to the posterior wall in the superior part of

the hip joint, the cross-over sign is positive. Cross-over sign is represented diagrammatically in **Appendix D**. Cross-over sign was included in the present study to search for prevalence in a healthy cohort and to search for any interaction with other morphological parameters. For instance, it is biologically plausible that the combination of positive cross-over sign and cam-type FAI may have an additive effect on OA risk due to focal stress loading at articular contact points.

Finally, presence of previous surgical implants (arthroplasty and internal fixation devices) was noted as part of the analysis. This observation was included as an exclusion criteria so that any hip with radiographic evidence of previous surgical treatment of severe OA or hip trauma was not included in further analysis.

2.5 – Validation of Radiograph Analysis Method

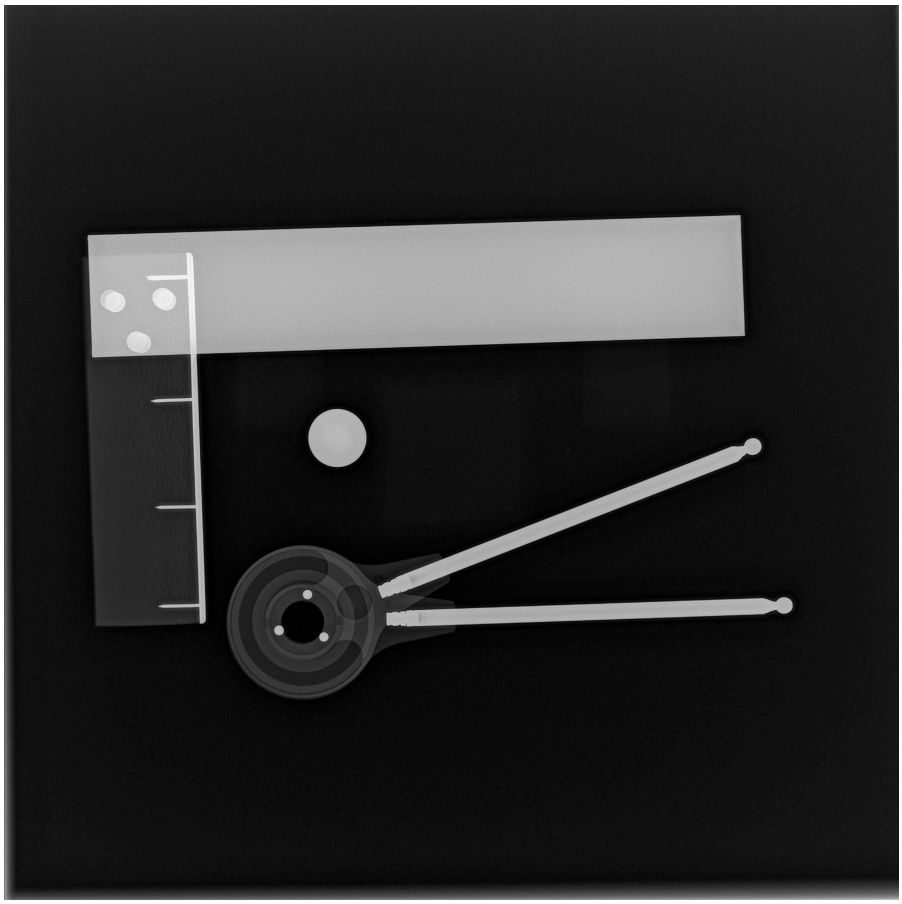
Validation of the *Hip_morf 2.0* software was split into three separate phases. Accuracy, calibration and reproducibility were each tested using the methodology described below. Accuracy and calibration of the software design were important constituents in defining any pre-analytical variability in the present methodology. Reproducibility of the actual radiograph analysis by individual software users represents analytical variability.

2.5.1 - Accuracy

Prior to analysis of pelvis radiographs, the *Hip_morf 2.0* measurement software was measured for accuracy. 4 sample radiographs were taken, each containing metallic objects of known size. This included items of fixed shape (a set square with a fixed angle and a coin) and a goiniometer that was set to a different angle in each image (see **Figure 2.1**). In each digitized radiograph, two separate linear measurements and two separate angle measurements (one fixed and one variable) were taken using the *Hip_morf 2.0* software. Output variables were then assessed for accuracy against the gold standard measurements. Gold standard for linear measurement was a ruler with one millimeter markings. For angles, two gold standards were used. A metal setsquare was used as the fixed right angle and a goiniometer was used for variable angles. Linear accuracy of the *Hip_morf 2.0* was demonstrated to be within 0.18 millimeters (standard error). Angular accuracy was demonstrated to be within 0.42 degrees (standard error). Dimensions for these accuracy measurements are given in **Figure 2.1**.

Figure 2. 1 Sample Radiograph Used For Testing *Hip_morf 2.0* Accuracy.

This radiograph shows radio-opaque object which were used as gold standard measures. The 10 pence coin has a diameter of 24 mm and was used as the reference object. Set square is a fixed right angle (90 degrees) on its inner surface. The radio-opaque long arm has the dimensions 51 mm x 273 mm when measured with a ruler. The goiniometer is set at 20 degrees in this images and was changed to 45, 80 and 125 degrees in subsequent images**.**



2.5.2 - Calibration

As discussed earlier in Chapter 2.3, each radiograph had a 24 millimeter opaque reference object placed in the top right corner when it was digitized. Consequently, each digital radiograph had this object as a calibration tool. The first step in the radiograph analysis process was for the user to measure the width of this reference object. The software then calculated the number of pixels in the measured diameter

and calibrated this number as 24 millimeters. All other linear measurements were referenced from this point.

2.5.3 – Reproducibility Analysis

The User Guide (**Appendix D**) that was distributed to each investigator aimed to reduce inter-user variability in exact-point definitions of the constituent anatomical landmarks used to calculate the various morphological measurements. In order to gauge the efficacy of this guide an inter-user variability study was performed. Following and introductory training session with the primary investigator, 6 investigators (4 clinicians, 1 medical student & 1 science student) each ran *Hip_morf 2.0* analyses on the same 10 randomly selected, randomised pelvis radiographs. Inter-user variability was assessed for each morphological parameter by calculating the coefficient of variation (CV). CV is calculated by dividing the standard deviation (σ) by the mean (μ). A low CV indicates a reproducible, and therefore reliable, measurement.

Following the inter-user variability study, the principle investigator conducted an intra-user variability study. 10 pelvis radiographs were analysed using *Hip_morf 2.0* on three separate occasions, thereby producing 30 sets of output data. These recordings were performed blinded to patient details and in an unknown order. Variability between each of these three sets of morphological data was assessed by again calculating CV. In both the inter-user and intra-user variability studies, the dichotomous output variables were analysed using the Kappa test.

CV was chosen above other variability measurements because it produces a single number between zero and 100 that can easily be compared between variables

regardless of the units in which they were measured or their absolute values. This meant that reproducibility across many variables could be efficiently demonstrated with the use of a universal figure. An example of how CV was calculated is presented below in **Example 1**.

Example 1. Calculation of Coefficient of Variation For Lateral Centre Edge Angle

Consider the following dataset of lateral centre edge (LCE) angles taken during the intra-observer reproducibility study as part of the present investigation. All units shown are degrees.

Specimen	Measure 1	Measure 2	Measure 3	MEAN	SD	VARIANCE
Pelvis 1 – left	21.54	20.61	19.85	20.67	0.85	0.72
Pelvis 1 – right	26.00	23.55	23.83	24.46	1.34	1.80
Pelvis 2 – left	34.30	34.10	31.96	33.45	1.30	1.68
Pelvis 2 – right	40.40	36.20	36.75	37.78	2.28	5.21
Pelvis 3 – left	25.83	26.97	26.70	26.50	0.60	0.35
Pelvis 3 – right	31.24	29.42	28.06	29.57	1.60	2.55
Pelvis 4 – left	39.57	37.46	37.60	38.21	1.18	1.39
Pelvis 4 – right	37.65	38.29	39.16	38.37	0.76	0.57
Pelvis 5 – left	35.96	32.10	33.87	33.98	1.93	3.73
Pelvis 5 – right	30.93	29.71	29.70	30.11	0.71	0.50
Pelvis 6 – left	21.63	20.54	20.70	20.96	0.59	0.35
Pelvis 6 – right	21.26	23.14	22.56	22.32	0.96	0.93
Pelvis 7 – left	26.47	25.79	25.90	26.05	0.37	0.13
Pelvis 7 – right	32.77	31.30	31.26	31.78	0.86	0.74
Pelvis 8 – left	31.23	32.53	33.18	32.31	0.99	0.99
Pelvis 8 – right	29.28	26.02	26.81	27.37	1.70	2.89
Pelvis 9 – left	35.11	35.08	33.04	34.41	1.19	1.41
Pelvis 9 – right	40.03	40.02	32.78	37.61	4.18	17.50
Pelvis 10 – left	36.12	34.72	33.04	34.63	1.54	2.38
Pelvis 10 – right	32.53	35.93	32.78	33.75	1.89	3.59

10 pelvis radiographs were analysed and in each specimen both a left and a right hip were measured. The measurements were repeated on 2 separate occasions, giving a total of 3 sets of data including a total of 60 measurements. Each "MEAN" figure shown was calculated by averaging measures 1, 2 and 3 from each respective hip joint. Each "Standard Deviation (SD)" was calculated from those same three measurements. "VARIANCE" is equal to the SD squared (SD^2). Further variability data was then calculated using the following formulae which were taken from Bland & Altman[61] (1996):

Sample Mean = Mean Of All Measurements

Common Variance = Mean Of All Variance

Common Standard Deviation = √Common Variance

95% Confidence intervals = Sample Mean +/- 1.96(Common Standard Deviation)

Coefficient of Variation = (Common Standard Deviation x 100) / Sample Mean

These are now calculated for the LCE intra-user intra-observer reproducibility dataset shown above:

LCE sample mean = **30.71 degrees**

Common Variance of LCE = **2.47**

Common Standard Deviation = √2.47 = **1.57 degrees**

95% Confidence Intervals = 30.71 +/– 1.96(1.57)

= 30.71 + 3.07 = **33.79 degrees**

= 30.71 – 3.07 = **27.63 degrees**

Coefficient of Variation = (1.57 x 100) / 30.71 = **5.12 %**

All data presented in the results section of this thesis was calculated in the fashion presented in this example which is consistent with the description by Bland & Altman[61] (1996).

The major limitation of CV is that as the mean value of a particular measurement approaches zero, the result approaches infinity and thus becomes meaningless. In parameters where this was the case CV was substituted by Intraclass correlation (ICC). ICC is a descriptive statistic that is specifically used for assessment of reproducibility of quantitative measurements in data that is structured in groups. In this case the groups are the individual hip joints from which those measurements are taken.

2.6 – Further Statistical Analyses

Epidemiological features of the nested case-control group were analysed for normality histogram symmetry. The baseline features of those in the case group were compared to those in the control group to ensure the two groups were similar. This was carried out using independent t-test for normally distributed variables and the Mann-Whitney U test for non-parametric variables.

Output variables from the *Hip_morf 2.0* analysis were initially validated via the inter-user and intra-user studies outlined in section 2.5. Following this, output variables for the entire nested case-control study were compiled in a cross correlation matrix and Pearson's correlation coefficient was used to describe the relationships between individual morphological parameters. Spearman's correlation coefficient was used in datasets that were non-parametric.

Hip morphology means were then compared between the control group and the group who underwent THA. Means were compared using independent t-test for parametrically distributed variables and the Mann-Whitney U test for non-parametric variables. Dichotomous variables were analysed using the chi^2 test.

For parameters where positive associations were identified with THA, multivariate logistic regression was performed using baseline height, weight, age and radiographic osteoarthritis (ROA) as covariates. Parameters that were statistically significant in this model were then combined in further multivariate analyses to assess their independent effect size. These tests of independence were all carried out using the original baseline covariates. For of the logistic regression analyses, hips were clustered into pairs according to the individual to whom they belonged in order to avoid interpreting them as entirely independent variables. Clustering is a commonly used statistical technique that acknowledges that hips from the same individual share epidemiological characteristics and are more likely to reach similar outcomes. Grouping these hips together weakens the power of the study by increasing type II error, thus making the results more conservative.

Following the application of exclusion criteria (for radiograph quality control), there were 26 THA case hips and 255 controls which were finally used in the comparison models described above. Using these numbers of included individuals, a power calculation was performed to determine least detectable differences. With 80% power at the 5% significance level, the present study was able to detect a percentage change of 8.4% in ratio measurements, such as Ext Ind, and 4.13 degrees in angular measurements, such as LCE.

CHAPTER 3

EPIDEMIOLOGICAL CHARACTERISTICS OF THE CHINGFORD 1000 WOMEN COHORT

CHAPTER 3 – EPIDEMIOLOGICAL CHARACTERISTICS OF THE CHINGFORD 1000 WOMEN COHORT

3.1 – Introduction

Prior to analysis of hip morphology focus is given to the epidemiological characteristics of the entire Chingford cohort and more specifically at the sub-group (n=157) that was randomly selected for the present study. 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 is subsequently reviewed. 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.

The Chingford 1000 Women study was initiated in 1989 and since that time there have been 270 women who have been lost to follow-up. The epidemiological characteristics of this group relative to those who remain actively enrolled in the study is also a consideration. **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. Occasionally, individuals who missed these clinics or decided to drop out subsequently changed their minds and attended future clinics. This explains why year 19 has fewer absentees than year 15. It should be noted that between baseline and year 2 there were 46 absentees.

Table 3. 1 Chronology Of Participation In Study

Follow-Up Clinic	*Remaining Participants*	*Absentees*	*Reasons for Absentees*
Year 1 (Baseline Clinic)	*n = 1003*	*n/a*	*n/a*
Year 2	*n = 957*	*n =46*	*Died 1; Moved 14; DNA 10; Dropped Out 2; N/R 18; Abroad 1*
Year 5	*n =861*	*n =142*	*Died 15; Moved 40; DNA 43; Dropped Out 44*
Year 10	*n =812*	*n =191*	*Died 41; Moved 60; DNA 10; Dropped Out 80*
Year 15	*n =680*	*n =323*	*Died 98; Moved 76; Dropped Out 89; N/R 60*
Year 19 (Telephone Survey)	*n =733*	*n =270*	*Died 104; Moved 62; Dropped Out 78; N/R 23; Very Ill 3*

[DNA: did not attend, N/R: no response]

The baseline epidemiological characteristics of individuals who remained enrolled in the study by year 15 are compared against those who were not present in that year (**Table 3.2**). This data is demonstrated to isolate relative differences between those two groups. There is a small albeit significant difference shown between these two groups using the independent t-test for comparison of means. On average, the drop-out group were older, smoked more, were less active and were heavier than the group than remained in enrolled. Age is a risk factor for OA, therefore it is possible that there was a higher incidence of THA in the drop-out group. BMI is less reliably associated with hip OA, but may also have an impact.

Table 3. 2 Baseline Epidemiological Data Of Patients Remaining Enrolled In Study At Year 15 Compared To Drop-Outs.

All data was tested for distribution (histogram appearance) and found to be parametric. Comparison of the means was performed using the independent sample t-test and the p-value significance is shown. Smoking status includes current and ex-smokers.

	Year 2 Data for Patients Remaining Enrolled at Year 15 (n = 680)	*Year 2 Data for Patients Not Enrolled at Year 15 (n = 323)*	*Significance (p-value)*
Age	*53.22 (5.77)*	*56.33 (6.03)*	*<0.01*
THA by year 19 (%)	*3.8*	*1.2*	*-*
Smoking Status (%)	*42.2*	*54.5*	*-*
Activity Level (maximum score 11)	*6.12 (1.67)*	*5.88 (1.80)*	*0.04*
Alcohol Consumption – Weekly (%)	*40.0*	*33.1*	*-*
Alcohol Consumption - Social Occasions Only (%)	*43.8*	*44.3*	*-*
BMI	*25.5 (4.27)*	*26.4 (5.37)*	*<0.01*
Height	*161.83 (5.77)*	*160.98 (5.93)*	*0.05*
Weight	*66.87 (10.80)*	*68.65 (14.07)*	*0.07*
Hip Circumference	*101.29 (8.52)*	*102.86 (11.76)*	*<0.01*
Waist Circumference	*78.44 (9.17)*	*81.29 (12.35)*	*<0.01*

[THA: total hip arthroplasty, BMI: body mass index]

3.2 – Characteristics of Individuals Included In Nested Case-Control Study

The first sub-group selected was the women who underwent THA at any time between the year-2 pelvis radiograph (1990) and the present day. There were 32 individuals in this group. Of these, 10 had undergone bilateral THA which meant there was a total of 42 individual replacements. One patient had missed the year-2 pelvis radiograph (patient number 235). This reduced the final number of case-individuals to 31 and the number of individual hip replacements to 40. To maximize statistical power, approximately 4 times the number of case individuals were selected at random to form

the control group (n=126). These individuals had not undergone any THA at study year 20.

The epidemiological characteristics of the case-control cohort (n=157) was compared to the entire Chingford 1000 Women Study cohort (n=1003) and it was found to be accurately representative (**Table 3.3**). The epidemiological characteristics of the THA case group (n=31) were then compared to those of the No THA, control group (n=126) (**Table 3.4**). The THA case group was significantly ($p < 0.05$) taller and heavier than the control No THA group, although their BMI was not significantly different.

It is pertinent to consider that if all controls were selected for all non-THA cases in the Chingford 1000 Women Study, then some of these may have gone on to develop OA, or may do in the future. This brings a conservative bias to the present study, since any such cases would actually weaken the results we are about to interpret in future chapters of this thesis. Conservative bias such as this ensures that we are never over-estimating the effects of the parameters that we are measuring.

Table 3. 3 Baseline Epidemiological Characteristics Of The Present Study vs Entire Chingford Cohort.

Randomly selected cohort represents the individuals used in the present study. (Histograms were used to determine normality of data distribution; For parametric data, paired t-test was used to determine significance of any difference between Entire Cohort and Randomly Selected Cohort. For non-parametric data, Mann-Whitney test was used to determine significance; # indicates non-parametric data group; * indicates significant difference)

	Entire Cohort (n=1003)	***Randomly Selected Cohort (n=157)***	*Significance (p-value)*
Mean Baseline Age, years (SD)	*54.23 (6.03)*	*54.68 (6.20)*	*0.30*
Mean Baseline BMI, (SD)	*25.61 (4.30)*	*25.56 (3.86)*	*0.89*
Mean Baseline Height, cm (Q1, Q3)	*161 (158, 165)*	*161 (158, 165)*[#]	*0.31*
Mean Baseline Weight, kg (SD)	*66.93 (11.85)*	*66.39 (10.31)*	*0.54*
Mean Baseline Waist Circumference, cm (SD)	*77.96 (10.02)*	*78.47 (9.37)*	*0.49*
Mean Baseline Hip Circumference, cm (SD)	*101.20 (9.29)*	*100.86 (8.37)*	*0.62*
Smoking Status, %	*46.2*	*42.69*	*-*
Activity Score, mean (SD)	*6.04 (1.72)*	*6.14 (1.57)*	*0.44*

[SD: standard deviation, Q1: 1st quartile, Q3: 3rd quartile]

Table 3. 4 Baseline Epidemiological Characteristics Of The Controls vs Cases.

The control group was randomly selected from the Chingford 1003 Women Cohort. The case group was all individuals in The Chingford 1000 Women cohort who underwent THA by year 20 follow-up. (Frequency histograms were used to determine normality of data distribution; For parametric data, paired t-test was used to determine significance of any difference between THA and No-THA group. For non-parametric data, Mann-Whitney test was used to determine significance; # non-parametric data group)

	No-THA Group (n=126)	***THA Group (n=31)***	***Significance (p-value)***
Mean Baseline Age, years (SD)	*54.35 (6.31)*	*56.03 (5.66)*	*0.15*
Mean Baseline BMI, (SD)	*25.43 (3.78)*	*26.11 (4.19)*	*0.40*
Mean Baseline Height, cm (Q1, Q3)	*160 (157, 164)*[#]	*164 (160.5, 168)*[#]	*<0.001*[*]
Mean Baseline Weight, kg (SD)	*65.48 (10.02)*	*70.09 (10.80)*	*0.03*[*]
Mean Baseline Waist Circumference, cm (SD)	*78.10 (8.98)*	*80.07 (10.92)*	*0.44*
Mean Baseline Hip Circumference, cm (SD)	*100.29 (8.22)*	*103.31 (8.71)*	*0.14*
Smoking Status, %	*41.94*	*50.00*	-
Activity Score, mean (SD)	*6.14 (1.55)*	*6.13 (1.65)*	*0.98*

[SD: standard deviation, Q1: 1st quartile, Q3: 3rd quartile]

3.3 - Summary

Individuals who dropped out of the Chingford 1000 Women study over the first 15 years were on average older, heavier, less active and smoked more than those who remained as ongoing participants. Due to the age difference, there is a possibility that the drop-out group had a higher incidence of OA - and therefore THA - than those who remained. The patients selected as part of the present nested case-control study were representative of the wider Chingford 1000 Women study cohort. However, the baseline characteristics of the subgroup that under went THA (case group) were taller and heavier than the control group.

CHAPTER 4

VALIDATION STUDY OF HIP MORPHOLOGY MEASUREMENT SOFTWARE

CHAPTER 4 - VALIDATION STUDY OF HIP MORPHOLOGY MEASUREMENT SOFTWARE

4.1 – Background

The *Hip-morf 2.0* software was designed in collaboration with intradepartmental orthopaedic engineering colleagues. The software allows sequential geometric measurements to be made on a digitized radiograph. The user follows a series of prompts and selects anatomical landmarks on each radiograph with the mouse cursor. Where there is ambiguity or uncertainty, the user referred to the User Guide (Appendix D). Intra-user and inter-user variability studies were performed to validate this new software. The goal of this was to quantify the accuracy and reproducibility with which radiograph measurements can be made using *Hip_morf 2.0.*

4.2 – Inter-user Variation Study

Continuous variables were assessed for reproducibility by calculating the coefficient of variation described in Chapter 2. Data from 6 investigators, each of whom analysed the same 10 radiographs, was compared and is displayed in **Table 4.1**. As CV approaches zero it indicates a reliably reproducible measurement. The corollary of this is that as it approaches 100 it indicates poor reproducibility.

As seen in the results, HTE and Extrusion index show a markedly elevated CV. In the case of HTE, consideration should be given to the near-zero nature of this angle measurement. Indeed, at times we even expect this variable to be negative. This elevation in CV is due to the proximity of the HTE mean to zero. Similarly, the Extrusion index is a ratio that always falls between zero and 1, which creates a near-zero mean. For these reasons, both of these variables were also tested for inter-class

correlation (ICC), which was calculated as 0.84 and 0.61 for Extrusion index and HTE respectively. Inter-user agreement remained poor despite the use of this alternative statistical method. This suggests ambiguity in the selection of two key radiographic anatomical landmarks – the medial edge, and to a lesser extent the lateral edge, of the weight-bearing sourcil of the acetabulum (Appendix D). Attention should be given to further clarifying these landmarks in the instruction given to radiograph readers prior to future studies.

Table 4. 1 Intra-Observer & Inter-Observer Reproducibility In The Assessment Of Hip Morphology Using Hip_morf 2.0 Software.

Data from the software validation study is demonstrated below. Coefficient of variation (CV) was used as a universal figure for comparison between different parameters since it is independent of measurement units and absolute values. In the case of dichotomous variables, Kappa value (K) was calculated.

Hip Morphological Parameter	***Intra-observer Reliability***				***Inter-observer Reliability***			
	Single Observer; 10 radiographs; 3 Analyses				***6 Observers; 10 radiographs; Single analysis***			
	Sample Mean	***95% CI***	***Variance***	***CV***	***Sample Mean***	***95% CI***	***Variance***	***CV***
PELVIS								
Distance between centre of femoral heads	*232.11*	*219.52 – 244.70*	*41.24*	***2.77***	*233.97*	*229.21 – 238.72*	*5.87*	***1.04***
Inter-acetabular width	*156.25*	*147.12 – 165.37*	*21.68*	***2.98***	*156.60*	*149.48 – 163.72*	*13.20*	***2.32***
ACETABULUM								
Acetabular Width	*64.04*	*59.4 – 68.67*	*3.69*	***3.69***	*64.77*	*60.07 – 69.47*	*5.75*	***3.70***
Acetabular Depth	*25.66*	*21.26 – 30.08*	*8.74*	***8.74***	*26.08*	*18.46 – 33.70*	*15.10*	***14.90***
Acetabular Index of Depth to Width	*0.40*	*0.34 – 0.46*	*7.93*	***7.93***	*0.40*	*0.29 – 0.52*	*0.003*	***14.34***
Lateral Centre Edge Angle	*30.71*	*27.6 – 33.79*	*5.11*	***5.11***	*29.69*	*23.52 – 35.85*	*9.89*	***10.60***
Extrusion Index	*0.26*	*0.20 – 0.31*	*11.12*	***11.12***	*0.28*	*0.16 – 0.39*	*0.003*	***20.68***
HTE	*5.59*	*3.70 – 7.49*	*17.22*	***17.22***	*5.97*	*0.91 – 11.04*	*6.68*	***43.26***
Sharpe's Angle	*37.83*	*36.5 – 39.15*	*1.78*	***1.78***	*38.93*	*35.80 – 42.06*	*2.55*	***4.10***
Acetabular Tilt	*55.08*	*53.42 – 56.73*	*1.53*	***1.53***	*56.09*	*51.64 – 61.03*	*6.37*	***4.50***
PROXIMAL FEMUR								
Femoral head diameter	*55.87*	*52.22 – 59.51*	*3.45*	***3.32***	*55.95*	*51.96 – 59.23*	*3.44*	***3.34***
Modified Triangular (Gosvig) Index - Height	*28.89*	*27.13 – 30.64*	*0.80*	***3.10***	*28.37*	*26.51 – 30.22*	*0.90*	***3.34***
Alpha Angle	*61.92*	*48.94 – 74.89*	*43.85*	***10.69***	*57.56*	*32.85 – 82.26*	*158.87*	***21.90***
Femoral neck width (min)	*41.02*	*38.77 – 43.26*	*1.31*	***2.79***	*40.79*	*39.08 – 42.52*	*0.77*	***2.15***
Femoral neck length	*56.63*	*52.74 – 60.53*	*3.95*	***3.51***	*57.45*	*51.73 – 63.18*	*8.53*	***5.08***
Femoral neck shaft angle (FNSA)	*131.76*	*128.50 – 135.0*	*2.80*	***1.27***	*132.76*	*128.2 – 137.3*	*5.37*	***1.74***
Modified proximal femoral angle (MPFA)	*82.44*	*78.23 – 86.65*	*4.61*	***2.60***	*82.93*	*78.50 – 87.37*	*5.11*	***2.72***
Triangular (Gosvig) Index #	-	-	-	***K = 0.26***	-	-	-	***K = 0.54***
OTHER								
Minimum JSW	*3.25*	*2.42 – 4.08*	*0.18*	***13.08***	*3.57*	*2.12 – 5.01*	*0.54*	***20.68***

[CV= Coefficient of Variation; # Dichotomous variable; K = Kappa test score]

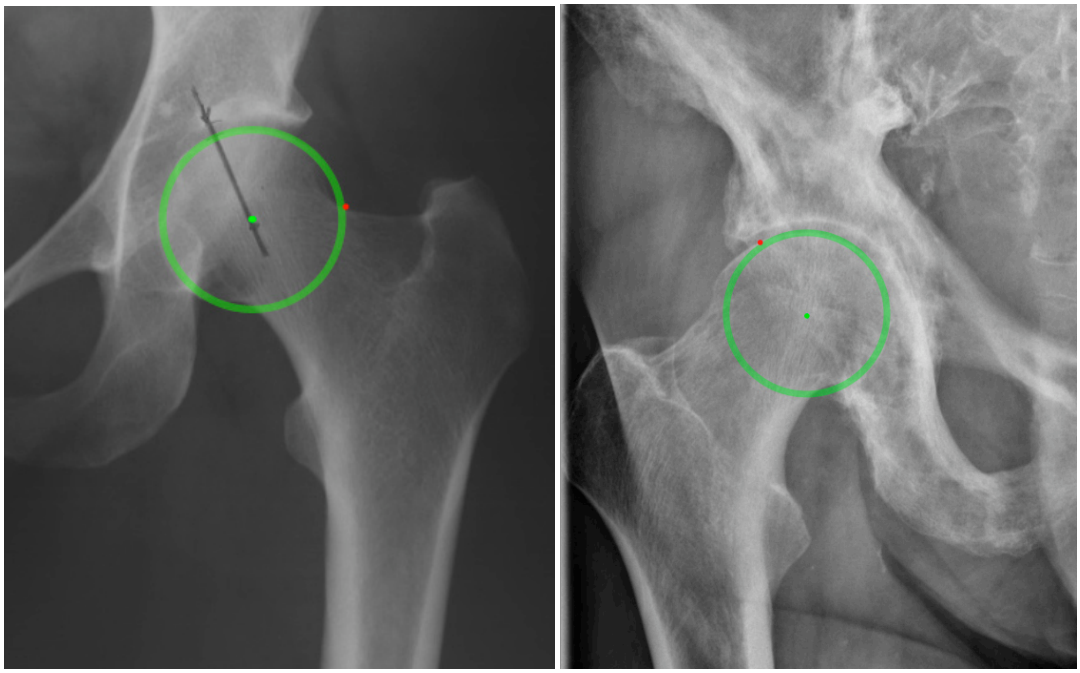
CV for acetabular depth, alpha angle and minimum joint space width were also significantly elevated. Acetabular depth is used in calculating acetabular ratio, in which the CV is also elevated. Both acetabular depth and width are calculated using separate radiologic anatomical landmarks (see Chapter 1) each of which is exposed to a degree of ambiguity. Our finding that acetabular depth has an elevated CV is in keeping with a previous study by Nelitz *et al*[62] which described poor inter-user and intra-user reproducibility in measuring this parameter. Acetabular depth relies on placement of three radiographic anatomical landmarks. Two of these are the points used in calculating acetabular width, which has a low inter-observer CV (**Table 4.1**). Consequently, these two points are unlikely to be the cause of acetabular depth variability. The third point is defined as the deepest point on the acetabulum, measured on a perpendicular axis to that of the acetabular width (**Appendix D**). Selection of this point appears to be ambiguous which led to an elevated CV.

Measurement of the alpha angle relies on the placement of a single point at the junction between the superior cortex of the femoral neck and a congruent circle placed over the femoral head. **Figure 4.1** demonstrates two examples, one of which illustrates how defining this precise point in certain cases may lead to unacceptable levels of variability. Another factor that affects the measurement of the alpha angle is the size and placement of the congruent circle that is placed over the femoral head. **Appendix D** stipulates that the *Hip_morf 2.0* user will place the circle so as it is "a best fit along the weight-bearing curvature of the superior and medial corticies". This gives a reference frame but is still open to subjectivity and subsequently contributes to the elevated CV.

Figure 4. 1 Selection Of Alpha Angle in *Hip_morf 2.0*

The selection of the alpha-angle can be ambiguous. In cases such as Example A, selection of the point where the femoral neck first breaks from the concentric circle (green) placed over the femoral head is straightforward (red point). However, in cases such as Example B, the superior cortex of the femoral neck and the overlying green circle form an asymptotic relationship that makes it difficult to select the exact point at which they meet. This brings ambiguity and subsequently an element of variability in measuring this parameter. N.B. these radiographs are examples only and were not used in the present study.

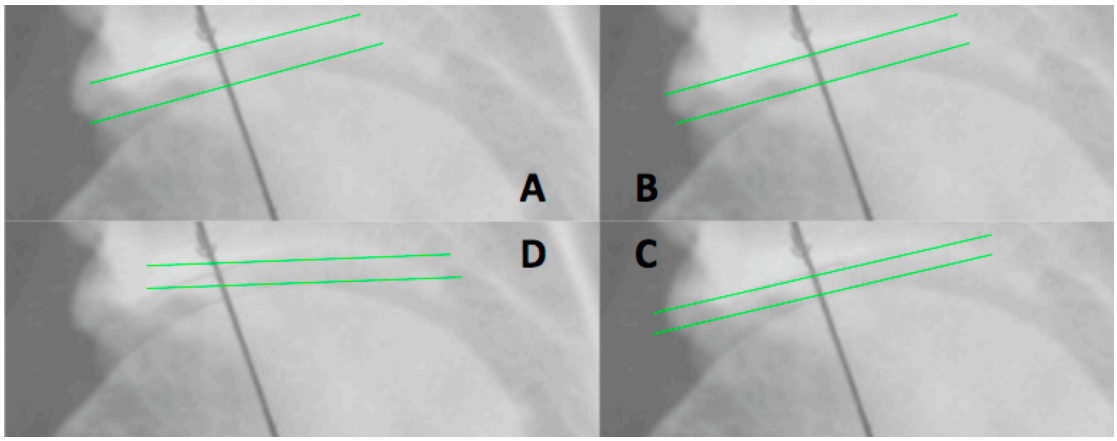
EXAMPLE A EXAMPLE B



JSW relies on the placement of a cursor across the femoroacetabular joint space. The corticies of the weight bearing sourcil of the acetabulum and the articular surface of the femoral head can be difficult to isolate. **Figure 4.2** demonstrates this phenomenon by showing 4 separate cursor widths over the same joint space. Each of these examples may appear correct to an individual user. More detailed definition regarding precise alignment of calipers may improve variability if added to the User Guide (**Appendix D**).

Figure 4. 2 Placement Of Minimum Joint Space Width Cursor In *Hip_morf 2.0.*

This diagram demonstrates ambiguity in measuring JSW in a right hip radiograph that has previously been marked. A) JSW is aligned with middle edge of each caliper; B) JSW is aligned directly beneath calipers; C) JSW is aligned with outside edge of each caliper; D) JSW is measured at a point away from previous markings – demonstrating ambiguity of acetabular cortex. More strict specification in user guide detailing how calipers should be aligned with JSW may reduce error between A, B & C. However, ambiguity demonstrated in D remains.



The remaining *Hip_morf 2.0* variables were reproduced with acceptable CV levels. This demonstrated three key issues. Firstly, that the computer interface was user-friendly and intuitive enough to allow first-time users to reach consensus in their results. Secondly, that the user guide (**Appendix D**) given to participants was effective at clarifying ambiguity surrounding precise location of some anatomic landmarks.

Finally, that there is validity in measuring these specific morphological parameters since they can be reproduced with an acceptable CV.

4.3 – Intra-user Variation Study

Prior to this study, the principle investigator had built up some experience using *Hip_morf 2.0* during the development phase of the software. Three separate analyses were then conducted by the principle investigator on the same 10 blinded, randomised radiographs with results displayed in **Table 4.1.** Continuous variables were again assessed for reproducibility by calculating the coefficient of variation described in Chapter 2. There was an overall improvement in reproducibility relative to the inter-user variation study.

Extrusion index and HTE again demonstrated high CV's, partially due to the mathematical reasons discussed earlier, and thus ICC's were calculated as 0.98 and 0.96 respectively for these two variables. ICC showed that reproducibility was adequate for both of these variables and thus weakens the theory that there is ambiguity surrounding the constituent landmarks. Previous studies that measure the HTE and the extrusion index do not acknowledge any ambiguity, nor do they quote figures for reproducibility[30,37,49,50,63].

JSW also showed markedly elevated CV. This is in part due to the technical difficulties in consistently defining the precise edges of the acetabular and femoral head corticies (**Figure 4.2**). However, there is also some lack of clarity in the User Guide (**Appendix D**) surrounding how the measurement calipers should be aligned relative to these corticies. Addressing this second issue may improve JSW reproducibility in future studies.

Measurement of the remaining variables showed an improved reproducibility relative to the inter-user variation study. The improvement seen in the intra-user variation study relative to the inter-user study suggests that interpretation of radiographs using *Hip_morf 2.0* is an acquirable skill. Repetition and practice can allow that skill to be learned and subsequent measurements can be reproducible.

4.4 - Summary

This study validated the reproducibility of most hip morphology measurements included in the *Hip_morf 2.0* software. In addition, it showed that as a single user becomes more familiar with the software and the User Guide the output data becomes more consistent. This indicates that analyses conducted by experienced *Hip_morf 2.0* users will produce more reliable data.

In those measurements where reproducibility was poor, the single biggest cause was ambiguity of one or more of the constituent radiological anatomic landmarks. This ambiguity was partly due to inadequate description of the landmarks in the User Guide, but also partly due to poor literature definitions of previously described morphological measurements. Extrusion index, HTE and JSW each showed a consistently elevated CV. However when ICC was calculated, Ext Ind and HTE showed adequate intra-user reproducibility and this should be considered when they are reviewed in later chapters.

CHAPTER 5

HIP MORPHOLOGY CHARACTERISTICS OF THE COHORT

CHAPTER 5 - HIP MORPHOLOGY CHARACTERISTICS OF THE COHORT

5.1 – Background

Pelvis radiographs from the randomly selected sub-group of patients (n=157) described in Chapter 3.3 were analysed using the *Hip_morf 2.0* software. Data from 314 individual hips was collated into an electronic database and exclusion criteria were then applied to rule out unsuitable and bad quality radiographs. Following this exclusion process, the data from the remaining radiographs was collated and is presented in this chapter. Finally, a correlation matrix was composed to investigate relationships between individual morphological parameters.

5.2 - Application of Exclusion Criteria

Each pelvis radiograph was performed in 1990 using the standardized radiographer protocol shown in **Table 2.1.** Exclusion criteria were introduced to ensure that radiographs being included in the present study were of a minimum quality standard. Some exclusion criteria apply only to an individual hip rather than an entire radiograph. **Table 5.1** shows how each of the exclusion criteria were applied and how many hips were excluded on account of each one. Pelvic tilt was estimated by measuring the distance between pubic symphysis and sacrococcygeal joint. As this distance increase, it indicates a more forward-tilted pelvis. Pelvic rotation was estimated by measuring the width of each obturator foramen and comparing the ratio between the two. A ratio near to one indicates a symmetrical and therefore centered pelvis.

Two radiographs (4 hip joints) were excluded due to poor x-ray quality. Poor x-ray quality was a subjective exclusion criteria applied by the principle investigator when a

radiograph was either grossly over-exposed or grossly under-exposed to the extent that constituent anatomic landmarks were not visible for the purposes of analysis.

Three hip joints (across two individuals) were excluded because they had a THA in situ. One hip joint was excluded because it had a DHS in situ, indicating previous trauma. 12 radiographs (24 hip joints) were excluded because they had excessive tilt, measured by distance between sacrococcygeal joint and pubic symphysis.

In total 32 individual hips were excluded. The number of hips that were excluded from the case group was 14 and from the control group the number was 18. This left 26 case hips and 255 control hips.

Table 5. 1 Exclusion Criteria Measurements Applied To The Selected Cohort Of Hips. (n = 314).

Note that the far right column reads number of hips excluded, rather than pelvises. For exclusion criteria 1, 2 & 3 both hips were ruled out. However, for exclusion criteria 4 & 5 only the individual hip was ruled out of the study.

Exclusion Parameter	***Mean Value Across All Radiographs (± SD)***	***Measurement Range***	***Acceptable Range (Reference)***	***Number of Hips Excluded***
Ratio of obturator foramen widths (ratio)	1.00 (0.1)	0.7 – 1.6	0.56 – 1.8 (Tonnis, 1976[30]; Boniforti, 1997[64])	0
Sacrococcygeal joint to pubic symphysis distance (mm)	46.1 (16.9)	2.6 – 92.0	15 – 72 (Siebenrock et al., 2003[60])	24
Poor Quality Radiograph (%)	1.25	-	0	4
Arthroplasty In Situ at year 2 Radiograph (%)	<0.01	-	0	3
Internal Fixation in situ at year 2 radiograph (%)	<0.01	-	0	1
				Total = 32 hips *Cases = 14* *Controls = 18*

5.3 – Morphology Measurements

Following implementation of the exclusion criteria, continuous and dichotomous morphology measurements from the remaining hips were collected and are displayed in **Table 5.2** and **Table 5.3** respectively. The range of measurements, mean and standard deviation of each variable is given. Normal values for two new morphological parameters are reported here for the first time. Acetabular tilt and modified triangular index are described in Chapter 1.3. Each was found to have acceptable reproducibility in the *Hip_morf 2.0* intra-user variation study (**Table 4.1**).

Data from each continuous variable was assessed for distribution using histogram appearance. For the purposes of further statistical analysis, histogram appearance was used as the final determinant of distribution normality.

Table 5. 2 Hip Morphology Measurements Of The Included Radiographs. (n = 282 hip joints)

Hip Morphological Parameter (n=280)	***Range***	***Mean***	***SD***	***Distribution***
PELVIS				
Distance between centre of femoral heads (mm)	*190.1 – 257.1*	*224.9*	*12.3*	*Parametric*
Inter-acetabular width (mm)	*127.6 – 183.8*	*154.0*	*9.4*	*Parametric*
ACETABULUM				
Acetabular Width (mm)	*52.0 – 74.0*	*61.6*	*3.7*	*Parametric*
Acetabular Depth (mm)	*16.6 – 36.9*	*25.6*	*3.6*	*Parametric*
Acetabular Index of Depth to Width (ratio)	*0.3 – 0.6*	*0.42*	*0.05*	*Parametric*
Lateral Centre Edge Angle (degrees)	*12.5 – 50.5*	*40.0*	*6.9*	*Parametric*
Extrusion Index (ratio)	*0.01 - 0.73*	*0.22*	*0.11*	*Parametric*
HTE (degrees)	*0.04 – 32.5*	*5.1*	*3.9*	*Non-parametric*
Sharpe's Angle (degrees)	*27.2 – 47.3*	*37.2*	*3.5*	*Parametric*
Acetabular Tilt (degrees)	*42.6 – 67.8*	*55.0*	*4.7*	*Parametric*
PROXIMAL FEMUR				
Femoral head diameter (mm)	*45.6 – 63.4*	*54.8*	*3.1*	*Parametric*
Modified Triangular (Gosvig) Index Height (mm)	*20.5 – 37.4*	*27.0*	*2.4*	*Parametric*
Alpha Angle (degrees)	*35.5 – 123.7*	*49.3*	*12.5*	*Non-parametric*
Femoral neck width (mm)	*29.4 - 46.2*	*38.3*	*3.1*	*Parametric*
Femoral neck length (mm)	*32.5 – 77.1*	*54.5*	*7.0*	*Parametric*
Femoral Neck length to neck width ratio	*0.7 – 2.0*	*1.4*	*0.2*	*Parametric*
Femoral head to neck ratio	*1.0 – 1.74*	*1.43*	*0.1*	*Parametric*
Femoral neck shaft angle (degrees)	*105.8 – 145.4*	*129.6*	*5.8*	*Parametric*
Modified proximal femoral angle (degrees)	*59.0 – 98.1*	*82.0*	*5.8*	*Parametric*
OTHER				
Minimum JSW (mm)	*0.93 – 5.89*	*3.71*	*0.75*	*Parametric*

Table 5. 3 Hip Morphology Dichotomous Variables In Included Variables. (n = 282)

Hip Morphology Parameter	*Percentage Positive*
Protrusio acetabuli	*1.1*
Coxa Profunda	*53.4*
Crossover sign (acetabular retroversion)	*4.6*
Triangular (Gosvig) Index	*5.7*

5.4 – Altman Atlas Radiographic Osteoarthritis Grading

Following *Hip_morf 2.0* analysis, each pelvis radiograph was graded for baseline level of ROA using the Altman Atlas[11]. Results are shown in **Table 5.4**. With the exception of medial joint space narrowing (JSN), where 16.7% of hips showed some degeneration, all other measures of ROA were found to be in keeping with that which would be expected in the normal population[2,65]. In previous prevalence estimates of ROA in Caucasian populations over the age of 55, the range is from 5 – 25%[65,66]. This range is wide because the ROA scoring systems that are used to define incident ROA differ between studies. Previous large population studies report the prevalence of THA in women with a mean age 60-65 to be within the range 1.57 – 3.2% [67,68].

The finding that 16.7% of women in the present study had significant medial JSN at baseline is not surprising since 20% of the individuals selected were included because they went on to undergo THA during the follow-up period. When we consider that only 32 out of 1003 women (3.2%) in the entire Chingford 1000 Women study underwent THA during the follow-up, it becomes apparent that the prevalence of OA in this group is most likely in keeping with the expected population average.

Previous studies have demonstrated the subjectivity and shortcomings of radiographic OA scoring techniques[69-71]. In addition, the THA literature is replete with studies that demonstrate the relationship between radiographic OA and future risk of THA[72-74]. For these reasons, the present study does not focus on discussing the relationship between baseline Altman ROA grade and THA. Rather, baseline ROA is used as a covariate in logistic regression models to avoid any confounding effects it may have on predicting associations between morphological parameters and future THA.

Table 5. 4 Radiographic Osteoarthritis Grading

Each radiograph was graded for OA using the Altman OA Atlas[11]. This consists of scoring osteophytes and joint space loss on a scale from 0 to 3 and marking as present/absent a series of "other" radiographic features of OA, seen below. Numbers shown under the grading columns represent percentage of hips that achieved each score.

Altman Atlas Osteoarthritis Features	***Grading***			
	0	***1***	***2***	***3***
Marginal Osteophytes				
- Superior acetabular (%)	*92.6*	*6.7*	*0.4*	*0.4*
- Superior femoral (%)	*91.1*	*7.1*	*1.8*	*0*
- Inferior femoral (%)	*94.7*	*4.3*	*1.1*	*0*
- Inferior acetabular (%)	*94.7*	*5.3*	*-NA-*	*-NA-*
Joint space width (subjective)				
- Superior (%)	*92.6*	*5.7*	*1.4*	*0.4*
- Medial (%)	*83.3*	*15.6*	*0.4*	*0.4*
Other				
Acetabular subchondral sclerosis (%)	*99.6*	*0.4*	*-NA-*	*-NA-*
Acetabular subchondral cysts (%)	*90.4*	*9.6*	*-NA-*	*-NA-*
Femoral head flattening (%)	*96.8*	*3.2*	*-NA-*	*-NA-*
Femoral subchondral sclerosis (%)	*98.9*	*1.1*	*-NA-*	*-NA-*
Thickening of medical femoral calcar (%)	*98.6*	*1.4*	*-NA-*	*-NA-*

NA = not applicable, used in dichotomous variables where grading is only 0 or 1.

5.5 – Correlations Between Measurement Parameters

All continuous output variables from the *Hip_morf 2.0* analysis were compiled in a correlation matrix to assess how closely they are each linked with one another (**Table 5.5**). The aim of this exercise was to confirm the presence known relationships and also to search for previously undetected patterns in morphology. This was in keeping with our goal of producing descriptive morphology data relating not only to absolute measurements but also the overall shape models within which these exist.

There were many positive results in this analysis (p value < 0.05). Linear measurement parameters were represented most frequently both in number and in strength of correlation. Body height (see the bottom row of **Table 5.5)** correlated significantly

with every simple length, height, width and diameter measurement. This was an expected relationship since taller people have larger bones and joints. In keeping with this finding, all simple linear measurements showed strong and significant correlations with each another.

Table 5. 5 Measurement Correlation Matrix.

This table demonstrates relationships between continuous output variables generated by the *Hip_morf 2.0* software. For parametric data, Pearson's Correlation Coefficients is shown with p-value in brackets. For non-parametric data, Spearman's Correlation Coefficient is shown with p-value in brackets. Significant relationships of which are of interest are highlighted in yellow. Correlation coefficients above 0.7 were considered positive for discussion purposes. However several weaker correlations were discussed due to biological interest. (** denotes non-parametric data). (n=282)

	Distance between centre of femoral heads (mm)	*Inter-acetabular width (mm)*	*Acetabular Width (mm)*	*Acetabular Depth (mm)*	*Acetabular Index of Depth to Width (ratio)*	*Lateral Centre Edge Angle (degrees)*	*Extrusion Index (ratio)*	*HTE (degrees)***	*Sharpe's Angle (degrees)*	*Acetabular Tilt (degrees)*	*Femoral head diameter*	*Modified Triangular (Gosvig) Index - Height*	*Alpha Angle***	*Femoral neck width (min)*	*Femoral neck length*	*Femoral neck length to width ratio*	*Femoral head to neck ratio*	*Femoral neck shaft angle (FNSA)*	*Modified proximal femoral angle (MPFA)*	*Minimum JSW*
Distance between centre of femoral heads (mm)																				
Inter-acetabular width (mm)	0.91 (0.00)																			
Acetabular Width (mm)	0.64 (0.00)	0.43 (0.00)																		
Acetabular Depth (mm)	0.25 (0.00)	0.24 (0.00)	0.91 (0.00)																	
Acetabular Index of Depth to Width (ratio)	-0.23 (0.70)	0.06 (0.29)	0.00 (0.99)	0.90 (0.00)																
Lateral Centre Edge Angle (degrees)	-0.28 (0.00)	-0.16 (0.01)	-0.06 (0.35)	-0.15 (0.01)	-0.13 (0.03)															
Extrusion Index (ratio)	0.26 (0.00)	0.15 (0.01)	0.00 (0.99)	0.00 (0.99)	0.13 (0.03)	-0.80 (0.00)														
*HTE (degrees)***	0.05 (0.40)	-0.14 (0.81)	0.02 (0.73)	-0.04 (0.51)	-0.34 (0.57)	-0.48 (0.00)	0.28 (0.00)	*												
Sharpe's Angle (degrees)	0.09 (0.14)	0.07 (0.28)	-0.10 (0.87)	-0.01 (0.87)	0.20 (0.00)	-0.64 (0.00)	0.40 (0.00)	0.28 (0.00)												
Acetabular Tilt (degrees)	0.04 (0.53)	0.02 (0.71)	-0.53 (0.37)	0.41 (0.00)	0.47 (0.00)	-0.68 (0.00)	0.48 (0.00)	0.38 (0.00)	0.68 (0.00)											
Femoral head diameter	0.68 (0.00)	0.49 (0.00)	0.81 (0.00)	0.34 (0.00)	0.01 (0.94)	-0.09 (0.15)	0.10 (0.09)	-0.03 (0.65)	0.03 (0.63)	0.04 (0.55)										
Modified Triangular (Gosvig) Index - Height	0.59 (0.00)	0.42 (0.00)	0.68 (0.00)	0.35 (0.00)	0.07 (0.24)	-0.17 (0.01)	0.14 (0.02)	-0.02 (0.69)	0.02 (0.77)	0.01 (0.88)	0.65 (0.00)									
*Alpha Angle***	0.27 (0.00)	0.20 (0.00)	0.16 (0.01)	0.14 (0.02)	0.10 (0.11)	-0.24 (0.00)	0.24 (0.00)	0.11 (0.07)	0.02 (0.78)	0.08 (0.17	0.13 (0.03)	0.53 (0.00)	*							
Femoral neck width (min)	0.64 (0.00)	0.46 (0.00)	0.70 (0.00)	0.70 (0.00)	0.02 (0.78)	-0.26 (0.00)	0.26 (0.00)	0.07 (0.24)	0.09 (0.13)	0.09 (0.13)	0.72 (0.00)	0.76 (0.00)	0.55 (0.00)							
Femoral neck length	0.26 (0.00)	0.19 (0.00)	0.18 (0.00)	0.06 (0.29)	-0.01 (0.86)	-0.02 (0.81)	0.05 (0.45)	-0.04 (0.56)	-0.01 (0.88)	-0.05 (0.45)	0.25 (0.00)	0.07 (0.25)	0.02 (0.76)	0.11 (0.08)						
Femoral neck length to width ratio	-0.16 (0.01)	-0.88 (0.14)	-0.23 (0.00)	-0.12 (0.05)	-0.02 (0.75)	0.13 (0.03)	-0.10 (0.09)	-0.08 (0.17)	-0.05 (0.36)	-0.09 (0.15)	-0.18 (0.02)	-0.36 (0.00)	-0.30 (0.00)	-0.47 (0.00)	0.82 (0.00)					
Femoral head to neck ratio	-0.24 (0.00)	-0.16 (0.01)	-0.19 (0.00)	-0.10 (0.10)	-0.02 (0.80)	0.28 (0.00)	-0.26 (0.00)	-0.10 (0.08)	-0.10 (0.09)	-0.09 (0.45)	-0.05 (0.43)	-0.42 (0.00)	-0.72 (0.00)	0.072 (0.00)	0.09 (0.12)	0.50 (0.00)				
Femoral neck shaft angle (FNSA)	0.04 (0.49)	0.04 (0.49)	-0.74 (0.22)	-0.17 (0.01)	-0.15 (0.02)	-0.05 (0.41)	0.04 (0.51)	0.18 (0.00)	0.00 (0.96)	0.03 (0.57)	0.09 (0.14)	-0.08 (0.20)	0.02 (0.74)	0.00 (0.98)	-0.27 (0.00)	-0.25 (0.00)	0.06 (0.29)			
Modified proximal femoral angle (MPFA)	0.07 (0.26)	0.08 (0.20)	-0.12 (0.04)	-0.08 (0.20)	-0.03 (0.67)	-0.10 (0.09)	0.12 (0.05)	0.13 (0.03)	0.07 (0.20)	0.01 (0.84)	0.06 (0.33)	0.04 (0.53)	0.24 (0.00)	0.00 (0.95)	0.15 (0.01)	0.13 (0.03)	0.05 (0.39)	0.57 (0.00)		
Minimum JSW	0.14 (0.02)	0.03 (0.60)	0.19 (0.00)	0.03 (0.63)	-0.06 (0.34)	-0.20 (0.00)	0.10 (0.10)	0.11 (0.06)	0.06 (0.32)	0.09 (0.13)	0.15 (0.01)	0.03 (0.59)	-0.03 (0.65)	0.09 (0.13)	0.05 (0.44)	-0.02 (0.75)	0.02 (0.78)	0.15 (0.01)	0.06 (0.33)	
Height	0.57 (0.00)	0.44 (0.00)	0.50 (0.00)	0.27 (0.00)	0.06 (0.29)	-0.06 (0.33)	0.06 (0.29)	-0.08 (0.21)	0.08 (0.21)	0.00 (0.95)	0.54 (0.00)	0.48 (0.00)	0.21 (0.00)	0.49 (0.00)	0.26 (0.00)	-0.05 (0.42)	-0.16 (0.01)	-0.03 (0.59)	0.03 (0.62)	0.10 (0.11)

There were several angle measurements that showed correlations. The LCE angle showed an inverse relationship to both Sharp's angle (Pearson's coefficient = -0.64; p <0.001) and Acetabular tilt (Pearson's coefficient = -0.68; p<0.001). This is purely an observational relationship and whilst it is significant, it only a mild association and does not imply any links in causality of disease. It indicates that in hips where acetabular coverage is extensive they are more likely to have reduced lateral version of the acetabulum (i.e. the acetabulum faces further towards the floor). This concept is accompanied by the presence of other significant but equally mild correlations between the Extrusion index and the LCE (Pearson's coefficient = -0.80; $p < 0.001$), Sharpe's angle (Pearson's coefficient = 0.40; $p < 0.001$) and Acetabular tilt (Pearson's coefficient = 0.48; $p < 0.001$).

There was a correlation between Acetabular tilt and Acetabular depth:width ratio (Pearson's coefficient = 0.47; $p < 0.001$). This indicates that a deeper acetabulum is more likely to have increased lateral version of the acetabulum whilst a shallow acetabulum is more likely to have reduced lateral version of the acetabulum.

There was a correlation between alpha angle and modified triangular index (Pearson's coefficient = 0.53; $p < 0.001$). Both of these parameters were designed as quantitative measures of cam lesion deformity in the proximal femur. This correlation suggests that both measurements are linked to a common morphological phenomenon. Given that modified triangular index is a more consistently reproducible variable (see **Table 4.1**) this association indicates that it may be the more useful measurement.

5.6 - Summary

The hip morphology characteristics of the nested case-control cohort were analysed using the new *Hip_morf 2.0* software that we developed and previously validated (Chapter 4). Application of the radiograph exclusion criteria led to a disproportionate loss of case hips (n = 14) versus control hips (n = 18). The range of values for two new morphological variables are reported here for the first time. These are acetabular tilt and modified triangular index height.

A correlation matrix was used to demonstrate relationships between all measured morphological variables (**Table 5.5**). Body height correlated with all linear measurements in the pelvis and proximal femur. The LCE angle was mildly correlated inversely with two measures of lateral acetabular inclination (Acetabular tilt & Sharp's angle). Acetabular tilt correlated with the Acetabular depth:width ratio. Finally, alpha angle correlated with the modified triangular index height.

CHAPTER 6

RELATIONSHIP BETWEEN HIP MORPHOLOGY AND INCIDENCE OF TOTAL HIP ARTHROPLASTY

CHAPTER 6 – RELATIONSHIP BETWEEN HIP MORPHOLOGY AND INCIDENCE OF TOTAL HIP ARTHROPLASTY

6.1 – Background

Morphological data from the THA case group (n = 31) was compared to that from the control group (n = 126). Initially, data from each woman was separated into two separate groups, one from each hip joint. In total there were 40 case hips analysed and 274 control hips. Following application of the exclusion criteria, the numbers included in the present analyses dropped to 26 THA case hips and 255 control hips. Univariate associations between individual morphological parameters and 19-year risk of THA were identified. Following identification of these parameters, multivariate logistic regression analysis was performed to account for possible confounding variables. Further modeling was then used to measure the independence of each parameter as a risk factor for THA. For all logistic regression analyses and tests of independence, hips were clustered into pairs according in order to account for the assumption of independent variable sources.

6.2 – Associations Between Morphological Parameters And Risk Of Total Hip Arthroplasty

Morphological data from the *Hip_morf 2.0* analysis was divided into control and case groups and compared for significant differences (**Table 6.1**). Initially each variable was analysed for distribution by assessing histogram symmetry. In parametric data sets, comparison of the means was conducted using the independent t-test analyses. In nonparametric data sets, comparison of the means was conducted using the Mann Whitney U test. In dichotomous data sets, comparison between the two groups was

conducted using the chi^2 test. In all three comparison models a P value of < 0.05 was taken as a significant difference between the case and control groups.

There were 5 linear measurements that showed significant association with THA. Inter-femoral head width, inter-acetabular width, modified triangular index height and femoral neck width were all larger in the group of women who went on to have THA during the 19-year follow-up period. However, each of these measurements showed a positive Pearson's correlation with body height during the previous analysis in Chapter 5. Multivariate analysis is therefore required to account for the height difference between the case and control groups. Joint space width was significantly reduced in the group of women who went on to have THA during the 19-year follow-up period.

There were three angle measurements that showed significant association with THA. HTE and alpha angle were both larger in the case group of women who went on to have THA during the 19-year follow-up period, whereas LCE was smaller in the same group. HTE and LCE are both measurements that demonstrate a shallow acetabulum. Alpha angle is a measure of cam lesion FAI. The validation study in Chapter 4 demonstrated that HTE was a poorly reproducible parameter.

There were two ratio measurements that showed significant association with THA. Extrusion index was elevated in the group of women who went on to have THA during the 19-year follow-up period, whereas femoral head-to-neck ratio was smaller. Extrusion index is a measurement that demonstrates acetabular coverage of the femoral head[50]. This result indicates that a hip joint where a larger percentage of the femoral head protrudes from the acetabulum there is a larger chance of THA in the

future. The femoral head-to-neck ratio is used to quantify pistol grip deformity[40]. This result indicates that a smaller femoral head, relative to the femoral neck width is a risk factor for THA.

Finally there was one dichotomous variable that showed significant association with THA. The triangular index, described by Gosvig *et al*[1], was positive in a larger percentage of individuals that went on to have THA during the 19-year follow-up period. The triangular index is a measure of cam lesion FAI and is validated for use throughout a range of femoral rotation[1].

Table 6. 1 Morphological Predictors Of Hip Osteoarthritis (Surgical Endpoint).

For each morphological parameter, the mean value of the group who underwent THA was compared to the control group. Where data was normally distributed (parametric), independent t-test analysis was used to assess and significant difference between the two groups. Where data was non-parametric, Mann-Whitney U tests was used. Where data was dichotomous, chi^2 tests were used. [*THA = Total Hip Arthroplasty; * indicates significant result (based on an alpha level of significance of p < 0.05); ** indicates significant result following Bonferroni correction (adjusted alpha level of significance of p < 0.0022)]*

Predictor	*Entire Group, Mean (SD) (n=282)*	*CONTROL Group: No THA by Year 19, Mean (SD) (n=255)*	*THA by Year 19, Mean (SD) (n=26)*	*Significance (p-value)*
PELVIS				
Distance between centre of femoral heads (mm)	224.9 (12.3)	224.0 (11.9)	233.7 (12.5)	<0.001**
Inter-acetabular width (mm)	154.0 (9.4)	153.4 (9.1)	159.8 (10.4)	0.001**
ACETABULUM				
Acetabular Width (mm)	61.7 (3.7)	61.6 (3.6)	62.6 (4.2)	0.16
Acetabular Depth (mm)	25.6 (3.6)	25.5 (3.6)	26.2 (4.2)	0.35
Acetabular Index of Depth to Width (ratio)	0.42 (0.05)	0.41 (0.05)	0.42 (0.05)	0.79
Lateral Centre Edge Angle (degrees)	32.9 (6.9)	33.4 (6.8)	30.0 (7.2)	0.002**
Extrusion Index (ratio)	0.22 (0.1)	0.2 (0.1)	0.3 (0.15)	0.01*
HTE (degrees)	5.1 (3.9)	4.9 (3.8)	6.8 (4.5)	0.04*
Sharpe's Angle (degrees)	37.2 (3.5)	37.2 (3.5)	37.3 (3.5)	0.89
Acetabular Tilt (degrees)	55.0 (4.6)	54.9 (4.7)	55.6 (3.8)	0.46
PROXIMAL FEMUR				
Femoral head diameter	54.8 (3.1)	54.7 (3.1)	55.7 (2.6)	0.12
Modified Triangular (Gosvig) Index - Height	27.0 (2.4)	26.8 (2.3)	28.5 (2.9)	<0.001**
Alpha Angle	49.3 (12.5)	48.1 (10.9)	60.7 (20.2)	<0.001**
Femoral neck width (min)	38.3 (3.1)	38.1 (3.0	40.2 (2.9)	0.001**
Femoral neck length	54.5 (7.0)	54.4 (6.7)	55.4 (9.7)	0.39
Femoral neck length to width ratio	1.4 (0.2)	1.4 (0.2)	1.4 (0.3)	0.12
Femoral head to neck ratio	1.4 (0.1)	1.44 (0.08)	1.40 (0.09)	0.001**
Femoral neck shaft angle (FNSA)	129.6 (5.8)	129.5 (5.8)	130.3 (6.0)	0.534
Modified proximal femoral angle (MPFA)	82.0 (5.8)	81.9 (5.8)	82.4 (5.0)	0.712
OTHER				
Minimum JSW	3.7 (0.7)	3.7 (0.7)	3.2 (0.9)	0.001**
DICHOTOMOUS VARIABLES				
Protrusio acetabuli	1.1	1.3	0	1.00
Coxa Profunda	53.5	53.0	56.2	0.75
Crossover sign (acetabular retroversion)	4.6	5.6	0.0	0.13
Triangular (Gosvig) Index	5.7	2.7	34.6	<0.001**

6.3 - Associations Between Radiographic Osteoarthritis And Risk Of Total Hip Arthroplasty

The Altman Atlas[11] grading system for scoring radiographic OA. There are a number of constituent scoring areas of which joint space loss and osteophyte severity are the main two. The overall prevalence of OA at baseline is presented in **Table 6.2**. In addition to the regular Altman OA grading system, each hip was also given a dichotomous score for prevalent osteophytes or joint space narrowing (JSN). A positive osteophyte (OP) score was defined as an Altman grade of 2 or higher in any of the original osteophyte grading. A positive JSN score was defined as an Altman grade of 2 or higher in any of the original JSN grading. These dichotomous results are also displayed at the end of **Table 6.2**. Both baseline JSN (OR 29.97, p = 0.005) and baseline OP (OR 8.95, p = 0.006) were strongly associated with 19-year risk of THA during univariate analysis. These results were then adjusted for baseline age, height and weight using logistic regression. Following logistic regression, baseline JSN (OR 25.23, p = 0.006) and baseline OP (OR 7.76, p = 0.35) still showed strong associations with 19-year risk of THA.

As a result of these relationships, both dichotomous scores baseline OA were included as a covariates in the multivariate logistic regression analysis ahead. This is to adjust for the effects they may have on the primary analysis of morphological parameters.

Table 6. 2 Altman Osteoarthritis Grades As Predictors Of Total Hip Arthroplasty.

Independent t-test were used to compare the mean values for those Altman grades where the mean values are shown. Below the broken line, dichotomous Altman scores for osteophyte and JSN are shown. A grade of 2 or higher in the original osteophyte or JSN was given a positive score respectively. All dichotomous scores are marked with * and in these grades results between THA cases and controls were compared using the chi^2 test.

	Entire Group, Mean (SD) (n=282)	***CONTROL Group: No THA by Year 19, Mean (SD) (n=255)***	***THA by Year 19, Mean (SD) (n=26)***	***Significance (p-value)***
ALTMAN GRADES				
Marginal Osteophytes				
- Superior acetabular	0.09 (0.33)	0.06 (0.24)	0.21 (0.58)	0.004
- Superior femoral	0.11 (0.36)	0.06 (0.29)	0.31 (0.55)	<0.001
- Inferior femoral	0.06 (2.86)	0.04 (0.21)	0.19 (0.49)	0.001
Joint space width (subjective)				
- Superior	0.10 (0.37)	0.06 (0.23)	0.29 (0.71)	<0.001
- Medial	0.17 (0.42)	0.12 (0.34)	0.49 (0.61)	<0.001
Other				
*- Inferior acetabular osteophyte (% positive)**	5.00	4.3	8.3	0.270
*Acetabular subchondral sclerosis (% positive)**	9.6	7.3	20.8	0.012
*Acetabular subchondral cysts (% positive)**	0.40	0.40	0.00	1.000
*Femoral head flattening (% positive)**	1.1	0.40	4.30	0.074
*Femoral subchondral sclerosis (% positive)**	3.2	0.00	18.8	<0.001
*Thickening of medical femoral calcar (% positive)**	1.4	0.90	4.30	0.132
*Dichotomous Osteophyte Grade (% positive)**	2.83	1.28	10.42	0.004
*Dichotomous JSN Grade (% positive)**	2.14	0.43	10.42	0.001

6.4 – Correlation Between Morphological Variables And Epidemiological Covariates

Hip morphology parameters were compared to epidemiological covariates to identify significant correlations and identify potential confounding variables. Pearson's correlation coefficient was used to identify relationships in parametric datasets whereas Spearman's correlation coefficient was used in non-parametric datasets. Results from this analysis are displayed as p-values only in **Table 6.3**. There were several positive correlations that are worth discussing.

Absolute measures of individuals' body size such as height and weight each showed correlation to the majority of linear measurements taken in the pelvis radiographs. This demonstrates two issues: i) if individual linear measurements are to be assessed as risk factors for THA, over and above the effects of height and weight, they must first adjusted for these parameters before independent effect size can be shown, and ii) individual linear measurements within the pelvis could be combined with epidemiological parameters to create new risk profile algorithms that use their ratios to offset this relationship.

Baseline JSW was demonstrated to have a positive correlation to both baseline activity score and age. This is in keeping with previous literature that links JSW (a constituent of ROA grading) to age and high impact or supraphysiologic activity levels[24,72,73].

There were few relationships between angular measurements and epidemiological covariates. Of interest, however, was the positive correlation between Alpha angle and weight. There is no biologically plausible explanation for this since cam-type FAI has

not been shown to be linked to body weight. Alpha angle effect will be adjusted for this epidemiologic covariate in the logistic models ahead.

Table 6. 3 Association Between Hip Morphology Parameters And Epidemiological Covariates (p-values only)

Pearson's correlation coefficients were performed, however only p-values are shown for significance.

Hip Morph Parameter	*Age*	*BMI Baseline*	*Weight Baseline*	*Height Baseline*	*Activity Score*
PELVIS					
Distance between centre of femoral heads (mm)	0.21	0.08	<0.001	<0.001	0.28
Inter-acetabular width (mm)	0.15	0.04	<0.001	<0.001	0.16
ACETABULUM					
Acetabular Width (mm)	0.02	0.24	<0.001	<0.001	0.72
Acetabular Depth (mm)	0.44	0.14	0.001	<0.001	0.66
Acetabular Index of Depth to Width (ratio)	0.89	0.28	0.19	0.42	0.58
Lateral Centre Edge Angle (degrees)	0.47	0.84	0.21	0.43	0.19
Extrusion Index (ratio)	0.37	0.55	0.19	0.12	0.42
HTE (degrees)	0.84	0.39	0.19	0.17	0.60
Sharp's Angle (degrees)	0.27	0.33	0.07	0.06	0.67
Acetabular tilt (degrees)	0.95	0.09	0.10	0.92	0.35
PROXIMAL FEMUR					
Femoral head diameter	0.08	0.05	<0.001	<0.001	0.75
Modified Triangular (Gosvig) Index - Height	0.047	0.01	<0.001	<0.001	0.53
Alpha Angle	0.63	0.34	0.03	0.004	0.40
Femoral neck width (min)	0.10	<0.001	<0.001	<0.001	0.84
Femoral neck length	0.01	0.54	0.08	<0.001	0.64
Femoral neck length to width ratio	0.14	0.002	0.001	0.49	0.62
Femoral head to neck ratio	0.58	<0.001	<0.001	0.01	0.72
Femoral neck shaft angle (FNSA)	0.68	0.86	0.89	0.93	0.82
Modified proximal femoral angle (MPFA)	0.32	0.07	0.09	0.92	0.03
OTHER					
Minimum JSW	0.03	0.10	0.14	0.40	0.01

6.5 – Multivariate Logistic Regression Analysis Of Hip Morphology Data

The relationships between individual hip morphology parameters and THA shown in **Table 6.1** do not account for the potentially confounding effects of epidemiological covariate relationships described in **Table 6.3** and **Table 3.4** or for the effects of baseline ROA grade shown in **Table 6.2**. In order to adjust for epidemiological covariates and for baseline ROA grades, univariate and multivariate logistic regression models were conducted to calculate the independent effect size of morphological parameters on risk of THA. These results are shown as odds ratios in **Table 6.4**.

Initially, epidemiological characteristics (baseline age, height and weight) were added as covariates in a multivariate logistic regression analysis. Alpha angle (OR 1.044, degrees; $p = 0.002$), Ext Ind (OR 1.073, percent; $p < 0.001$), HTE (OR 1.159, degrees; $p = 0.011$) and LCE (OR 0.872, degrees; $p < 0.001$) all remained highly significant as predictors of THA. The Bonferroni correction was the used to adjust the level of significance to account for multiple comparisons. A p-value of 0.0022 was used as the adjusted alpha level of significance, based on the present study's analysis of 23 separate variables. Following this correction, alpha angle, Ext Ind and LCE remained significant as predictors of THA. HTE was no longer significant.

Altman ROA grading was consolidated into two dichotomous variables as discussed previously in **Section 6.3**. These two variables (OP and JSN) were then added to the logistic regression as covariates alongside age, height and weight. Following this regression model, alpha angle (OR 1.040, degrees; $p = 0.010$), HTE (OR 1.159, degrees; $p = 0.024$), LCE (OR 0.871, degrees; $p < 0.001$) and Ext Ind (OR 1.079, degrees; $p < 0.001$) each still had a significant effect on THA risk. Bonferroni correction was again applied to adjust the alpha level of significance. Following this

correction, Ext Ind and LCE remained significant as predictors of THA. Alpha angle and HTE were no longer significant.

Table 6. 4 Univariate And Multivariate Logistic Regression Analysis For Morphological Parameters With Significant Association To Total Hip Arthroplasty.

Hip Morph Parameter	***Univariate Analysis OR (p value)***	***Multivariate Analysis***				
		Height OR (p value)	***Height & Weight OR (p value)***	***Height Weight & Age OR (p value)***	***Height, Weight, Age & JSN OR (p value)***	***Height, Weight, Age, JSN & OP OR (p value)***
Extrusion Index (%)	1.066 (<0.001)**	1.067 (<0.001)**	1.066 (<0.001)**	1.073 (<0.001)**	1.078 (<0.001)**	1.079 (<0.001)**
HTE (degrees)	1.118 (0.036)*	1.114 (0.047)*	1.149 (0.039)*	1.159 (0.011)*	1.146 (0.044)*	1.159 (0.024)*
MTIH (mm)	1.270 (0.011)*	1.179 (0.152)	1.149 (0.215)	1.100 (0.436)	1.050 (0.68)	1.096 (0.45)
Alpha Angle (degrees)	1.051 (0.001)**	1.045 (0.006)*	1.043 (0.007)*	1.044 (0.002)**	1.039 (0.018)*	1.040 (0.010)*
LCE (degrees)	0.890 (0.001)**	0.890 (0.001)**	0.890 (0.001)**	0.872 (<0.001)**	0.871 (<0.001)**	0.871 (<0.001)**

* indicates significant result (based on an alpha level of significance of $p < 0.05$)

** indicates significant result following Bonferroni correction (adjusted alpha level of significance of $p < 0.0022$)

[HTE: Horizontal Toit Externe, MTIH: Modified triangular index height, LCE: Lateral Centre Edge Angle, OR: Odds Ratio, JSN: Baseline Joint Space Narrowing, OP: Baseline Osteophytes]

6.6 – Independent Effect Size Of Individual Morphological Parameters On Risk Of Total Hip Arthroplasty

Following multivariate logistic regression, 4 morphological parameters (Alpha angle, HTE, LCE and Ext Ind) were shown to have a positive association to risk of THA following adjustment for epidemiological covariates and baseline ROA. These 4 parameters were then assessed for independence from one another by systematically adding other morphological parameters to the multivariate logistic regression model as extra covariates. Results for these tests of independence are demonstrated in **Table 6.5**. Odds ratios are used to quantify the effect of the principle morphological parameter (column 1) on THA risk when adjusted for height, weight, age, OP, JSN and the list of covariate morphological parameters in column 2. The total effect of size of the principle morphological parameter (column 1) and all the covariates (columns 2) is demonstrated by the pseudo R^2 value (column 5).

LCE was the only morphological parameter that maintained significant independent effect on risk of THA when results were adjusted for each of the three other variables (**Table 6.5**). Following the application of the Bonferroni correction for multiple comparisons, there were two remaining significant results. For each one-degree reduction in LCE, there was a 12.4% elevation in 19-year risk of THA, even after results were adjusted for baseline epidemiological characteristics, baseline ROA and alpha angle. For each one-percent elevation in Ext Ind, there was a 7.3% elevation in 19-year risk of THA, even after results were adjusted for baseline epidemiological characteristics, baseline ROA and alpha angle

Finally, alpha angle, HTE, LCE and Ext Ind were grouped into dichotomous variables to assess for interaction. Each variable was split into upper and lower 50% groups. Interaction effects between these and other morphological variables were analysed. There were no significant interactions detected between alpha angle and the acetabular morphological parameters (HTE, LCE & Ext Ind). However, there was limited statistical power to detect such interactions.

Table 6. 5 Independent Effects Of Morphological Parameters With Positive Association To Total Hip Arthroplasty.

All analyses have already been adjusted for baseline height, weight, age, osteophytes & joint space narrowing. Following Bonferroni correction for multiple comparison of 23 continuous variables, level of significance was set at $p \leq 0.0022$. Pseudo R^2 indicates the total effect size of all covariates tested on chances of THA.

Hip Morph Parameter	*Covariates*	*Odds Ratio*	*CI 95%*	*P value*	*Pseudo R^2*
Alpha Angle		1.040	1.016 – 1.075	0.010*	0.182
(degrees)	*+LCE*	1.036	1.001 – 1.073	0.046*	0.300
	+ Ext Ind	1.034	1.003 – 1.068	0.032*	0.283
	+ HTE	1.032	0.997 – 1.069	0.073	0.2457
LCE		0.871	0.811 – 0.947	<0.001**	0.227
(degrees)	+ alpha	0.876	0.811 – 0.947	<0.001**	0.300
	+ Ext Ind	0.901	0.838 - 969	0.005*	0.279
	+ HTE	0.869	0.783 – 0.965	0.009*	0.227
HTE		1.159	1.035 – 1.298	0.024*	0.179
(degrees)	+ alpha	1.137	0.989 – 1.307	0.070	0.246
	+ LCE	0.996	0.852 – 1.164	0.963	0.276
	+ Ext Ind	1.070	0.955 – 1.199	0.243	0.267
Ext Ind		1.079	1.034 – 1.114	<0.001**	0.210
(percentage)	+ alpha	1.073	1.030 – 1.118	0.001**	0.283
	+ LCE	1.026	0.988 – 1.064	0.176	0.279
	+ HTE	1.064	1.021 – 1.108	0.003*	0.267

* indicates significant result (based on an alpha level of significance of $p < 0.05$)

** indicates significant result following Bonferroni correction (adjusted alpha level of significance of $p < 0.0022$)

6.7 – Summary

Mean values of morphological parameters were compared between the THA case and the control sub-groups. Positive associations to THA were identified in 11 variables. Additionally, it was discovered that the THA case sub-group had a higher prevalence of baseline ROA than the control group. A correlation matrix comparing morphological parameters to epidemiological covariates demonstrated several additional relationships.

Multivariate logistic regression was used to adjust the effect size of each morphological parameter for epidemiological covariates. The effect size of alpha angle, LCE and Ext Ind on risk of THA remained highly significant, even after the Bonferroni correction was used to adjust for multiple comparisons. Each one-degree increase in alpha angle was associated with a 4.4% increase in THA risk. Each one-degree reduction in LCE was associated with an 11% increase in THA risk. Each one-percent increase in Ext Ind was associated with a 7.3% increase in THA risk.

Baseline ROA was then added to the logistic regression analysis and the Bonferroni correction was again applied to the acceptable level of significance. The effect sizes of LCE (OR 1.079, degrees; $p < 0.001$) and Ext Ind (OR 0.871; $p < 0.001$) remained significant.

Further analyses were then conducted to search for the independent effect size of each variable by adjusting for other morphological parameters. However, following Bonferroni correction, few individual morphological variables retained a significant effect size once epidemiological characteristics, baseline ROA and all other morphological variables were adjusted for. LCE and Ext Ind both remained significant

predictors of THA when results were adjusted for alpha angle, baseline epidemiological characteristics and baseline ROA.

Finally, interaction analyses were performed to identify dependence of individual effect sizes. There were no significant interactions identified.

CHAPTER 7

DISCUSSION

CHAPTER 7 - DISCUSSION

7.1 - Summary of Results

OA of the hip has a complex pathogenesis and represents a leading cause of disability and burden of disease in our society. Biomechanical factors associated with the development of this disease process have previously been reported, but few studies have linked simple geometric measurements made on AP pelvis radiographs to long-term risk of severe OA in a healthy population.

The present study had 4 separate aims:

1. To demonstrate that sub-group selected for the present study was representative of the entire Chingford 1000 Women study cohort. To demonstrate that the baseline epidemiological characteristics of the THA case group were similar to those of the control group.

2. To develop, validate and implement a new software program for expeditious and accurate analysis of AP pelvis radiographs, in order to quantify morphological parameters in the hip.

3. To describe the normal range of values for a large variety of morphological parameters in the hip and to search for patterns in morphology by looking at correlations between them.

4. To identify any significant differences in baseline hip morphology between Caucasian women who progressed to develop severe OA (defined by THA) over the 19-year follow-up period versus those who did not (controls).

The overall goal of this investigation was to strengthen our understanding of the relationship between hip morphology and the pathogenesis of severe OA. Improved understanding of this relationship may assist clinicians in identifying high-risk individuals to be targeted for future therapeutic interventions, optimization of modifiable risk factors and ongoing research into the complex disease process and natural history of progression of OA.

7.1.1 - Summary of Positive Findings

The present study analysed the variation in hip shapes in all women who under went THA and a randomly selected control group from the Chingford 1000 Women cohort. Of the 157 included individuals, there were 31 cases and 126 controls. Epidemiological characteristics of each group were compared at baseline. The two groups were not significantly different in baseline age, BMI or activity level. However, the THA case sub-group was shown to be taller and heavier at baseline than the control sub-group. These epidemiological characteristics were later used as covariates in the logistic regression analysis in order to calculate the independent effects of the morphological variables.

We designed a new software package called *Hip_morf 2.0* specifically for the present study. This was developed from the foundation of existing software that was unsuitable for our analysis, but which did provide a helpful foundation for our development. *Hip_morf 2.0* was capable of efficiently measuring a series of selected hip morphology parameters and was validated for accuracy and reproducibility. Although most hips were reproducible, several morphological parameters were shown

to have limited reproducibility. HTE, Ext Ind and JSW were shown to be poorly reproducible parameters when analysed using the CV of their respective output data variables. There are two possible reasons for this variability. Firstly, it could be due to the limitations of CV as a measure of reproducibility when the mean value of a measurement approaches zero. This possible reason was accounted for by also calculating ICC in morphological parameters where that was the case. The second cause of variability could be ambiguity of the definitions of the constituent radiographic anatomical landmarks that are used to define each variable. Ambiguity of this nature leads to increased variance amongst users, and subsequently affects the CV. In the case of JSW, sclerotic cortical margins in the acetabulum and femoral head can be difficult to precisely define. In this instance of high CV, it is arguable that a linear measurement is inferior to a semi-quantitative assessment, given the discrepancy of time and effort needed to complete each. Further work is needed to improve the reproducibility of these parameters.

All of the readings for this study were done by the primary investigator because the intra-observer reproducibility was better than that produced by multiple observers in the validity study. 314 hips were measured using the purpose-designed *Hip_morf 2.0* software. Following implementation of quality control exclusion criteria, data from 282 individual hips remained. Each hip was scored for ROA grading using the Altman Atlas[11].

Body height was shown to have a statistically significant association to most linear measurements. In addition, Ext Ind and LCE showed a strong correlation with one another (Pearson's correlation = -0.80; p-value <0.001). There were also several other weak correlations seen in **Table 5.5** but none that were considered strong enough to be

of significant biological relevance. The mild positive correlations between LCE and both Sharp's angle and Acetabular tilt were discussed earlier in the results section. It should be noted that these were purely observational findings and at that stage of the analysis were not related to OA.

Eleven morphological shape variables were initially identified as being associated to 19-year THA risk. There was also a higher prevalence and severity of ROA features in the case sub-group. The alpha-angle was significantly greater in the THA cases than in the controls (60.7 degrees vs 48.1 degrees; $p < 0.001$). The lateral centre edge angle (LCE) was significantly smaller in the cases than the controls (30.0 degrees vs 33.4 degrees; $p = 0.002$). The Extrusion Index (Ext Ind) was significantly greater in the THA cases than in the controls (30% vs 20%; $p < 0.001$). Significant morphological measures were then adjusted for epidemiological covariates (baseline age, height, weight & radiographic osteoarthritis) using a multivariate logistic regression analysis. Alpha angle (Odds ratio 1.040, degrees; $p = 0.01$), LCE (Odds ratio 0.871, degrees: $p < 0.001$) and Ext Ind (Odds ratio 1.079, percent; $p < 0.001$) each remained significantly associated with THA. Following Bonferroni correction, LCE and Ext Ind remained highly significant as independent predictors of THA. We can therefore say that these variables predict THA and that their effect are independent of baseline age, height, weight and ROA.

The mild positive correlations between LCE and both Sharp's angle and Acetabular tilt that were identified earlier in the shape correlation matrix were not reflected in the analysis between morphology and THA. As mentioned, LCE was shown to have a strong association with THA, whereas neither Sharp's angle nor Acetabular tilt had

any significant relationship. This may have been due to type II statistical error because of the small number of THA cases that were available for analysis in the present study. Alternatively, it may be accurate and these two measures of acetabular tilt simply have no relationship to THA, even though they share this weak correlation with LCE which does. Either way, this does reinforce the need to analyse a larger number of THA case hips to improve the power of the study.

7.1.2 – Relevance of Positive Findings

Baseline epidemiological characteristics of the selected case-control sub-group (n = 157) were representative of the entire Chingford 1000 Women Study (n = 1003). However, within this subgroup those women who went on to under go THA were heavier and taller than the randomly selected controls. There has been debate about the impact of BMI on risk of THA. In one recent population study into epidemiological risk factors for hip OA and THA, height was shown to have small but significant effect size on THA risk[67]. Whilst the effect of both height and weight were adjusted for during subsequent multivariate logistic regression analysis, it is still an interesting observation that out of the entire Chingford 1000 Women Cohort the group of 32 women who underwent THA were taller and heavier than the average, but did not have significantly different BMI. In another study of a healthy cohort by Lanyon et al[75], it was demonstrated that taller individuals may not have proportionately wider hip joint spaces. Radiographic joint space width is a surrogate measure of articular cartilage stock and thus less articular cartilage may be a possible mechanism by which taller individuals have a higher prevalence of hip OA. The present study demonstrated quantitative measurement of joint space width to be poorly reproducible and there was no significant relationship between minimum JSW and body height.

The development and validation of the *Hip_morf 2.0* software demonstrated a novel and rapid mechanism for measuring a range of morphological variables in the pelvis. In the case of most specific morphological parameters, the User Guide (Appendix D) and software interface provided adequate means for accurate and reproducible measurements. However, there were several individual measurements that were exposed as being poorly reproducible. The *Hip_morf 2.0* software represents a unique and useful tool that can be used in future hip morphology studies not only in the remainder of the Chingford pelvis radiographs (i.e. study years 8 & 20), but also in other epidemiologically described cohorts where pelvis radiographs have been collected and in new morphology investigations that have not yet been initiated.

There is an abundance of literature that links ROA grade to risk of future OA[24]. The purpose of measuring ROA in the present study was so that effect size of morphological parameters could be adjusted for baseline prevalence of OA in order to assess the independence of morphology on risk of THA. As demonstrated earlier, there was a higher baseline prevalence of ROA in the case group than in the control group, which undoubtedly contributed to those individuals in the case group undergoing THA during the 19-year follow-up period. However, the effect size of the morphological variables remained significant even after the baseline ROA was taken into account (**Table 6.3**).

The present study demonstrates the positive independent association between alpha angle (measured on an AP pelvis radiograph) and THA for the first time. Alpha angle was first described using MR scans by Notzli[39] as a quantitative measure of asphericity at the femoral head-neck junction. This measurement was then assessed on plain radiographs in various axis planes for validity[76]. It was found to be most

sensitive in detecting femoral head asphericity on lateral XR view, Dunn 45 degree view and cross table view in internal rotation[76]. Subclinical deformity at this junction is related to cam type FAI (and subsequently OA)[77,78] and the alpha angle is the best single angle measure for detecting this deformity[79]. The results from the present study demonstrate that alpha angle measured on an AP pelvis radiograph has a significant independent association to future risk of THA and thus is a useful clinical tool that can be used in assessing risk of hip OA.

Lateral Centre Edge (LCE) Angle was first described by Wiberg[28] in 1939 as a quantitative measure of acetabular dysplasia. This measure continues to be used for the purpose of diagnosing DDH[30] (when the value is < 25 degrees) but also more recently it has been shown to be useful for measuring pincer-type FAI[37] (when the value is > 39 degrees). The present study demonstrates that LCE has a significant independent association to future risk of THA even when it is within the previously defined normal limits (26-38 degrees). This association was demonstrated as an inverse relationship, meaning that in this population it was subclinical dysplasia rather than pincer-type FAI that predicted THA. It is also useful to consider here that a very large LCE would be in keeping with pincer-type FAI, and may be associated with elevation in OA risk. It may be possible that if this angle was analysed in a much larger cohort that individuals with a very small, but also a very large LCE would show increased tendency to develop hip OA. This effect was not in the present study, where a inverse linear relationship was found. However, it is plausible that in larger cohorts such a relationship may become apparent.

7.1.3 – Outcomes of Hypotheses

BROAD

i) Subclinical variations in hip morphology quantified using AP pelvis radiographs can be used to predict risk of developing end-stage hip OA over a 19-year follow-up period.

Null hypothesis: There is no relationship between subclinical variations in hip morphology measurements on AP pelvis radiographs and risk of developing end-stage hip OA over a 19-year follow-up period.

OUTCOME: Null hypothesis rejected.

SPECIFIC

i) An elevation in the alpha (α) angle (a measure of cam type FAI) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Elevated alpha (α) angle is not associated with risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

OUTCOME: Null hypothesis rejected.

ii) An elevation in the Sharpe's angle (a measure of acetabular inclination) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Elevated Sharpe's angle is not associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph

OUTCOME: Hypothesis rejected.

iii) A reduction in the LCE angle (a measure of femoral head lateralisation) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Reduced LCE is not associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

OUTCOME: Null hypothesis rejected.

iv) An elevation in the Modified triangular index height (a measure of cam type FAI) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Elevated modified triangular index height is not associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

OUTCOME: Hypothesis rejected.

v) An elevation in the extrusion index (a measure of femoral head lateralisation) is associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph.

Null hypothesis: Elevated extrusion index is not associated with an increased risk of THA over a 19 year follow-up period, when measured on a baseline AP pelvis radiograph

OUTCOME: Null hypothesis rejected.

7.2 - Limitations Of The Present Study

Several limitations exist with the design of the present study. Whilst they are presented in categories according to methodological, clinical and statistical, it is also important and useful to consider those that represent pre-analytical versus those that represent analytical threats to repeatability. Each of these threats was minimized where possible, however, limitations still remain and are discussed below.

7.2.1 – Methodology Limitations

The nested case-control design of the present study was somewhat altered from convention, which introduced limitations that warrant discussion. Some of the benefits of a classic prospective longitudinal cohort study include the collection of exposure data before the time of disease onset and the added benefit of a recorded time sequence in analyzing cause-effect relationships. In addition, a cohort study has very low levels of type II statistical error (and high levels of power) since all individuals who do not develop disease outcome are followed to the conclusion of the investigation. This also allows for calculation of disease incidence within the cohort and subsequent external comparisons with other populations. As discussed earlier, the original design of the Chingford 1000 Women study was as a prospective longitudinal cohort study. The benefits that were gained in selecting a nested case-control study from within this original design include reductions in cost, time and resources pertaining to the actual morphological analyses that were made. Whilst the drawbacks of the nested case-control study design include a reduction in statistical power due to introduction of type II error, the benefits were pragmatic and the use of this study design was considered justified.

The present study makes assumptions about the accuracy of the radiographer's protocol that was used in conducting the AP pelvis radiographs. This is a pre-analytical threat to the reproducibility of the present study. In practice there is undoubtedly a small margin of error encountered when measuring x-ray focal point, focal distance and patient positioning. The use of the radiograph exclusion criteria (**Chapter 5.2**) was designed to minimize the inclusion of radiographs with excessive tilt & rotation. Despite these criteria, there is an element of variability that may affect the appearance of all hip morphology parameters on the AP radiograph. A recent study described a new software package that uses radiographic anatomical landmarks to calculate standardized pelvis orientation on 2-dimensional pelvis radiographs[80]. This allowed subsequent measurements to be made from a normalized tilt and rotation. Developments such as this could benefit future retrospective morphology studies by standardizing accuracy of measurements made on older radiographs.

Variability results showed that the majority of morphological measurements used in the present study were reproducible to acceptable levels. However, some anatomic landmarks can be difficult to define with absolute clarity. This leads to variability in some morphology measures that weakens their use in this nested case-control study. HTE, Ext Ind and JSW were all shown to have positive association to THA, however these results are weakened by the poor reproducibility they showed.

Calibration of the radiographs used in this study was only made to between the software *Hip_morf 2.0* and the actual radiographs using the standardized opaque object in the upper right corner. However, this method did not calibrate the individual

person against the radiograph. As a result there is no way of correcting or adjusting for magnification of bones caused by variation in the distance between the pelvis and the radiograph film/slide. Such magnification is an accepted flaw in radiography of obese individuals. One method of adjusting for this magnification is for each individual to have a standard sized radio-opaque object taped over the greater trochanter during each x-ray. This allows for correction of depth in the radiograph during the subsequent analyses. Since these were old radiographs we did not have this opportunity and thus this was not available. Most of the morphological parameters of interest were not linear measurements and thus exact linear calibration was not essential to the present study's findings.

7.2.2 – Clinical Limitations

Due to the implementation of the radiograph exclusion criteria, there was a disproportionate loss of case hips (n = 14) relative to control hips (n = 18) which were initially selected at a ratio of 1:4. This reduced the power of the present study since only 26 case hips were included in the final analysis. This effect could not have been overcome by analysing more pelvises, since all THA's from the Chingford 1000 Women Study were included in the case group of the present study. Due to small number of case radiographs, outliers may have affected means, despite use of non-parametric tests.

The present study recognizes the shortcomings of THA as a clinical endpoint for painful hip OA. It should be emphasized that in the United Kingdom public access to THA is very high through the state-funded National Health System. Nonetheless, there may have been women who developed severe OA but never under went THA for medical reasons or because they made informed decisions to avoid surgery. A recent

Canadian study demonstrated that despite a higher prevalence of severe hip OA, under use of THA for personal reasons is 3 times higher among women than men[81].

Although the present study has a prolonged period of follow-up and supports hip morphology as a predictor of THR, we cannot fully rule out that the variations in hip morphology that were identified are themselves very early features of OA. One possible solution to overcome this issue would be to repeat the morphological analysis on future radiographs taken from the same cohort of women. These radiographs do exist and were taken at study years 8 and 20. Comparison between the original radiographs and the subsequent one would provide unique data on how these morphological variables change with time in the same individuals, if at all.

The morphological findings that were demonstrated in this study were all conducted in middle-aged Caucasian females. Whilst the Chingford 1000 Women Cohort are a well-described population of healthy women, it may be not be possible to draw inferences from the findings in this study and apply them to other populations that include men and individuals from a broader variety of racial backgrounds.

7.2.3 - Statistical Limitations

During the intra-observer and inter-observer validation studies, coefficient of variation (CV) was used to quantify the reproducibility of each morphological measurements made during the analysis. The advantage of this test is that it that it includes the mean for each parameter that it quantifies and thus allows for easy comparison between different variables. This test has two recognized weaknesses. Firstly, it is mathematically poor when the mean is near to zero since this gives a very small

denominator and thus an elevated CV value. An example of this weakness is the HTE parameter that produced a disproportionately high CV in relation to other parameters. When HTE was assessed using intra-class correlation coefficients the results where much better suggesting that the CV was not a suitable test for this coefficient. The second recognized weakness is the lack of objective cut-off point for acceptable reproducibility. The present study use a CV of <10 as an acceptable level of variance, however, it is acknowledged that this is a somewhat arbitrary figure.

Independent t-tests were used in the present study to compare mean values of morphological variables between the THA cases group and the THA control group. This test is commonly used in medical statistics and carries the following assumptions i) normal distribution within each sub-group ii) equal variance within each sub-group, and iii) data was sampled independently from individual cases. Each dataset was tested for normality prior to application of t-test. In non-parametric datasets, t-test was substituted by the Mann Whitney U test which gives lower statistical power in its results and also assumes that the data was sampled independently from individual cases. Analyses at the hip specific level do not violate this assumption, however when incorporating person specific data such as height, this assumption is violated and subsequent logistic regression analyses were performed with hip data joined into clusters according to the individuals they belonged to (i.e. two hips to each individual). Clustering allows for individual hips that share epidemiological characteristics to be grouped together for improved biological plausibility.

Multivariate logistic regression (MVLR) analysis was used to estimate the conditional expectation (i.e.. the mean) of each dependant variable given fixed values of independent variables (i.e. the covariates). Thus is estimates how the dependant variable alone affects the risk of THA. This analysis allowed clustering of hips into pairs, improving biological plausibility. MVLR makes assumptions i) that each sample is representative of the wider population, ii) that independent variables (covariates) are error free or that there is homoscedasticity, and iii) that the predictors are linearly independent of one another. These first two assumptions are addressed in earlier chapters, however the third assumption raises an important issue – the multiple comparisons problem.

The multiple comparison problem arises when one considers a set of many statistical inferences simultaneously. The more outcome measures that are introduced to such an analysis, the higher the likelihood that a relationship will be found between the morphological parameter and OA, due to chance. A p-value of 0.05 means that there is a 5% chance of picking up a spurious association by chance (i.e. false positive). If we therefore performed 20 analyses, by definition there should be one false positive. The present study compares a number of morphological parameters for their relationship with a single OA outcome measure (THA). The associations that we observed had a number of conservative biases and such high levels of statistical significance that they are unlikely to be false positives. Nonetheless, we performed a Bonferroni correction for multiple comparisons that moved the alpha level for significance to a p-value of 0.0022. Following this correction, several associations remained positive and this demonstrates the true strength of the results of this study in the most conservative fashion. A less conservative analysis would accept all relationships with a p value of

less than 0.05 as significant. If we analyse the results presented in **Table 6.4** and **Table 6.5** in this less conservative fashion, we see an abundance of strong relationships between measures of hip morphology and risk of future THA.

Finally, and following on from the previous point, we must consider the presence of type II statistical error that may have an affect on the power of the present study. Type II error concerns cases where we have decided in favour of the null hypothesis when it is in fact false. Study power is directly affected by Type II error through the formulae:

$$Study\ power = 1 - \beta$$

Where β is the level of type II error for a detectable effect size. In medical statistics it is conventional to select a β value of 0.2 which will then allow for a corresponding study power of 0.8 = 80%. When we calculate our detectable affect size, the input variables needed include population size (fixed at n = 157), statistical power (fixed at 80%) and significance (conventionally 5% or p value < 0.05). Some detectable effect sizes from the present study were presented in this fashion earlier in **Chapter 2.6**, however, a limitation we must now address is that our significance was subsequently altered via the Bonferroni correction. By reducing the risk of type I statistical error in our model, where the detectable effect size is fixed and so too is the population size, we increase the risk of type II statistical error and therefore reduce the power of the study. In summary, it may have been possible that in the present study some morphological parameters were found to show no association to THA when in fact they were associated (false negatives).

7.3 - Clinical Relevance

The present study validated a new method of analysing hip morphology using AP pelvis radiographs. This analysis methodology was then applied to a sub-group of the Chingford 1000 Women cohort study. Significant associations between hip morphology and long-term risk of THA were identified, although there were also some weaknesses that have been addressed. Whilst it is recognized that further investigation into these relationships is essential to consolidate the present findings, particularly in populations that include males and mixed racial backgrounds, it is possible that clinical implementation of the present results could be made.

AP pelvis radiographs are cheap, easily accessible and deliver far less radiation dosage than more complex radiographic imaging. They are also available in hundreds of thousands of patients worldwide, often taken for other reasons. In addition, pelvis radiographs are available in many other large cohort study populations. In the orthopaedic clinic and general practice setting they may be able to play a role along with other risk factors, in predicting an individual's future risk of OA. The present study delivers the validated methodology (*Hip-morf 2.0*) and preliminary results needed to initiate larger scale investigations that could strengthen the statistical power of the relationships that were demonstrated. It is likely that as our understanding of the pathogenesis of OA improves more globally, the biomechanical factors measured through morphological parameters may be combined with genetic, metabolic and systemic inflammatory parameters to form an overall risk assessment tool. This is important because it allows for the targeting of high-risk patients for lifestyle interventions (weight loss, exercise), pharmacological agents (glucosamine, diacerein)

and surgical procedures. It also helps identify high-risk patients for inclusion into further clinical trials of disease modifying therapies and interventions.

7.4 - Implications for Future Research

The present study recognizes the assumptions made by using THA as the outcome measure for OA. Future research projects in the present cohort could use OA outcomes such as ROA measured on year 8 and year 20 radiographs. This would allow investigation of the relationships between morphological parameters and 19-year risk of ROA in addition to THA.

In addition, *Hip_morf 2.0* analyses of all radiographs from years 2, 8 and 20 of the Chingford 1000 Women study could be initiated for an epidemiological demonstration of how the constituent morphological parameters change with time over a 19 year period. This may also give us an objective picture of which "normal" changes the pelvis undergoes in its morphological appearance throughout middle age. Future analysis of morphological parameters in these radiographs would also aim to improve the reproducibility of HTE, by addressing the concerns outlined earlier. A useful extension to the present investigation would be to analyse JSW again in the year 20 follow-up radiographs. This could be used to determine whether there is a linear relationship between chronological activity scores and joint space loss over the follow-up period.

If appropriate regional ethics approval could be gained, cadaveric radiograph studies would be of value in determining the effects of sagital tilt and axial rotation on the appearance of other individual morphological parameters. A pelvis of known size and proportion could be x-rayed in a series of different tilts and rotations (e.g. 5 degree

intervals) and the effects of such movements could be plotted. This type of future study would help us to normalize results from individual pelvises by taking into account the level of tilt and rotation and adjusting for them accordingly.

The power of these analyses becomes particularly impressive when combined with the overwhelming database of stored DNA samples, serological data and epidemiological profiles collected from each participant over the 20-year follow-up period. If genetic predictors could be isolated for particular variation in hip morphology, this would become a breakthrough investigation into the origins and pathogenesis of hip OA.

7.5 - Conclusion

A new software package called *Hip_morf 2.0* was developed and validated. It measures 23 morphological parameters in the pelvis, acetabulum and proximal femur. *Hip_morf 2.0* was used to investigate the relationship between variations in hip morphology and 19 year risk of severe OA in the hip in a group of 157 Caucasian women. THA was used as the only outcome measure in assessing whether an individual had developed severe OA. The present study found that alpha angle, LCE and Ext Ind were each significantly associated with future risk of THA, even after they were adjusted for baseline age, height and weight. An increase in alpha angle of one degree equated to a 4.4% increase in 19-year risk of THA. Each a one-degree elevation in LCE equated to a 12.8% elevation in 19-year risk of THA. Each one-percent increase in Ext Ind equated to a 7.3% increase in 19-year risk of THA. When these results were further adjusted for baseline ROA, LCE (OR = 0.871; degrees) and Ext Ind (OR = 1.079; percent) remained highly significant ($p < 0.001$). Each of these morphological parameters may be important predictors of OA that can be simply used in an outpatient setting to assist in stratifying risk of future THA.

CHAPTER 8

CONFERENCES, COURSES & PUBLICATIONS

CHAPTER 8 – CONFERENCES, COURSES & PUBLICATIONS

8.1 MSc Related Conferences

British Orthopaedic Research Society Annual Meeting, Newcastle-Upon-Tyne, 22-23 June 2009. Poster presentation. "*Fluctuation in Body Mass Index During Middle Age Affects Risk Of Total Knee And Hip Replacement Due To Osteoarthritis: A 19 Year Prospective Study Of 1003 Women*".

Poster received Highly Commended Prize

American College of Rheumatologists Annual Scientific Meeting, Philadelphia, USA, 17-21 October 2009. Poster presentation. "*Morphological Variations in Hip Shape: Validation of New Hip Measurement Software and Provisional Association with Total Hip Replacement. The Chingford Study."*

8.2 MSc Related Courses

- Medical Innovation: Enabling Change in the NHS and Beyond. Lecture series, Said Business School, University of Oxford, 21st Jan – 4th March 2009
- Skills Course in Musculoskeletal Ultrasound, Nuffield Orthopaedic Centre, Oxford, 15-19th January 2009
- SPSS Statistical Training Course, Medical Sciences Division, University of Oxford, 15-19th December 2008
- Presentation Skills Course, Medical Science Division, University of Oxford, 22nd April 2009.
- AO North America: Basic Principles in Operative Fracture Management, La Jolla, California, USA. 22-25th August, 2009

8.3 MSc Related Publications

Abstract in press - Journal of Bone And Joint Surgery (Br)

AS Nicholls, MK Javaid, N Bottomley, M Daniels, D Hart, T Spector, AJ Carr, NK Arden "*Fluctuation in Body Mass Index During Middle Age Affects Risk Of Total Knee And Hip Replacement Due To Osteoarthritis: A 19 Year Prospective Study Of 1003 Women*".

Published under proceedings of the British Orthopaedic Research Society Annual Meeting, Newcastle-Upon-Tyne, 22-23 June 2009.

Abstract in press – Arthritis & Rheumatism

AS Nicholls, H Gill, T Pollard, A Kiran, D Hart, T Spector, D Murray, AJ Carr, NK Arden

Morphological Variations in Hip Shape: Validation of New Hip Measurement Software and Provisional Association with Total Hip Replacement. The Chingford Study.

Published under proceedings of the American College of Rheumatologists Annual Scientific Meeting, Philadelphia, USA, 17-21 October 2009. Abstract submitted for presentation.

APPENDICES

APPENDIX A

CHINGFORD STUDY												
		Year										
Parameter		1	2	3	4	5	6	8	9	10	11	13	15
Non-medical Information													
Date of birth		✓											
Address & phone		✓											
GP		✓											
Hospital number		✓											
Social area number		✓											
Body Measurement													
Weight	current, max, min, age 20	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Height	current, max, loss	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Blood pressure	current measurement	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Waist	"	✓	✓	✓	✓								
Hips	"	✓	✓	✓	✓								
Thighs	"	✓	✓	✓	✓								
Quads	"	✓	✓	✓	✓	✓							
Grip	"	✓	✓	✓	✓								✓
Dolorimeter	"			✓									
Pulse	"				✓								
Sway	"					✓		✓					
Teeth	count, denture count, age					✓							
Spirometry													✓
Cataract & sight test													✓
Get up & Go test													✓
Bone & Joint Data													
DIP, PIP, CMC	duration, stiffness, pain, swelling	✓	✓	✓		✓				✓			✓
Hands	duration, stiffness, pain, current status	✓	✓	✓	✓	✓	✓	✓		✓			✓
Knees	OA, duration, stiffness, pain, swelling, injuries, bending	✓	✓	✓	✓	✓	✓	✓		✓			✓
Hips	BMD, duration, stiffness, pain, current status			✓	✓	✓	✓	✓		✓			✓
Spine	BMD, duration, stiffness, pain, current status, frac grad	✓		✓	✓	✓	✓	✓	✓	✓			✓
Whole body	BMD, body composition							✓		✓			✓
Other joints	OA, general	✓				✓				✓			
Carpal tunnel	symptoms			✓									
Fibromyalgia	"			✓									
Tennis elbow	date					✓							
Frozen shoulder	"					✓							
Other diseases	type			✓									
Hypermobility										✓	✓		
knee radiograph		✓	✓			✓				✓			✓
Hand radiograph		✓	✓	✓							✓		

Spine radiograph		✓			✓				✓				
hip radiograph			✓					✓					
foot radiograph							✓					✓	
Lower limb biomechanics													
MRI Knee												✓	
Chemical Pathology													
Lipids	glucose, cholesterol, triglyceride		✓	✓	✓			✓		✓			
Sex hormones	DHEA, SHBG, oestradiol												
SMAC					✓	✓	✓						
IGG, RF				✓									
Latex													
Serum & Urine		✓	✓	✓	✓		✓	✓	✓	✓	✓		✓
DNA					✓			✓	✓		✓		✓
Medical History													
Current medication	type, dose	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Steroids	type, dose, date	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Blood pressure	date	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Diuretics	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Diabetes	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Thyroid	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Cancer	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Cardiovascular dis.	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Gasterectomy	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Colecystitis	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Ortho operations	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Fractures	type, date	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Falls	number, type, x-ray						✓	✓	✓	✓	✓	✓	✓
Operations/illnesses	type, date	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Accidents	type, age								✓	✓	✓	✓	✓
Reproductive History													
Menarche	age	✓											
Periods	status, regularity						✓	✓	✓	✓			
Menopause	age	✓	✓	✓	✓								
Hysterectomy	age, indication, ovaries removed	✓	✓	✓	✓		✓	✓	✓	✓			
Births	number, date	✓							✓				
Gynae operations	type	✓	✓										
OCP	age, duration	✓											
HRT	status, age, duration, type	✓	✓	✓	✓		✓	✓	✓	✓			
Family History													
Arthritis	status, joints affected, family occurrence	✓	✓						✓	✓			
Obesity	parental occurrence	✓							✓	✓			
Fractures	family occurrence	✓							✓	✓			
Height loss	"	✓							✓	✓			
General	family details, willingness to join, medical history								✓	✓			
General Health	SF36,GHQ,HAQ,MRC Back pain												
General well-being	better, same, worse			✓	✓	✓			✓				✓
Sleep	"			✓	✓				✓				✓

Headaches	"			✓	✓				✓			✓
Pain	amount, effect				✓	✓			✓			✓
Dizziness	amount					✓						✓
Emotions	better, same, worse			✓	✓	✓			✓			✓
Decision making	"			✓	✓				✓			✓
Memory	general state									✓		✓
function						✓						✓
Lifestyle												
Hand dominance		✓										
Diet	calcium intake	✓			✓		✓					
Occupation	own, husband	✓	✓				✓					
Activity	ability, type, amount	✓			✓	✓	✓		✓			
Driving	status, age								✓			
Smoking	current status, max, duration	✓						✓	✓	✓		
Alcohol intake	amount	✓										
Footwear	type, duration, injury, bunions									✓		

APPENDIX B

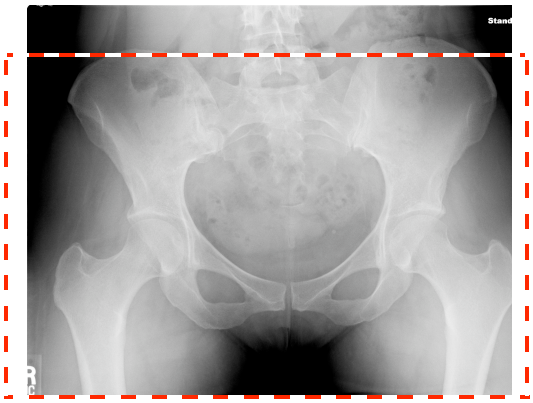
For Further Queries:

Dr. Alex Nicholls
07599130676
alexander.nicholls@ndos.ox.ac.uk

PROTOCOL FOR SCANNING AP PELVIS RADIOGRAPHS

Align the *bottom edge* of the X-ray film with the bottom edge of the scanner.

The film should then be *centered horizontally* in the scanner as seen below (red dashed line ----- indicates boundary of scanner).



Acceptable
✓

A standardised metal disc should be placed in the top LEFT (patient's RIGHT) corner of the scanned section of the film (see below in yellow). The *entire circumference* must be visible.

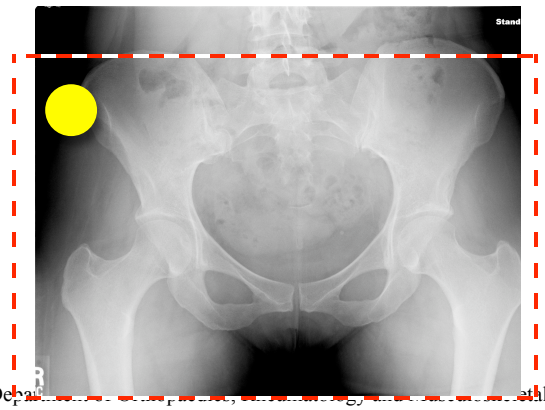


Image 1. This image (below) is an example of a perfectly scanned radiograph

Acceptable

✓

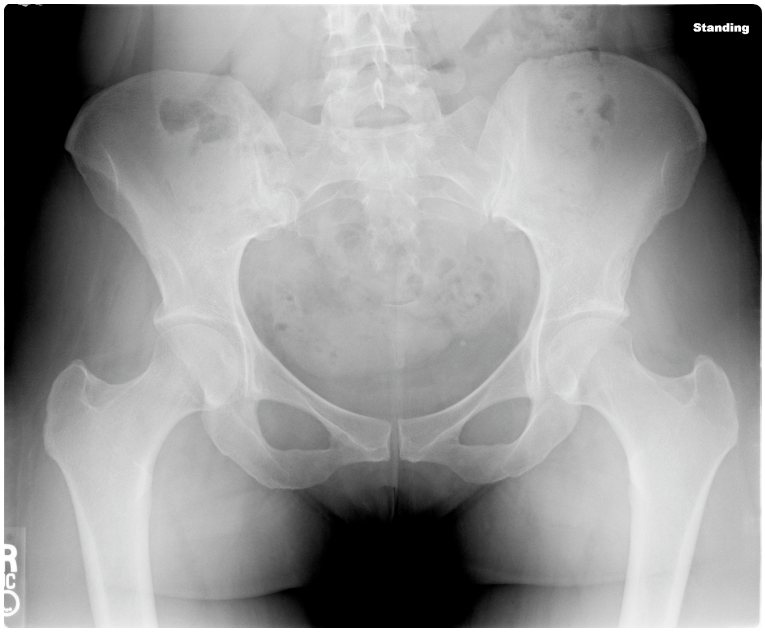


Image 2. More specifically, this image (below) contains *all the data* we need.

Acceptable

✓



Image 3. In this example (below) the top of the pelvis has been cropped out but the key features we are interested (image 2) in are still included.

Acceptable ✓

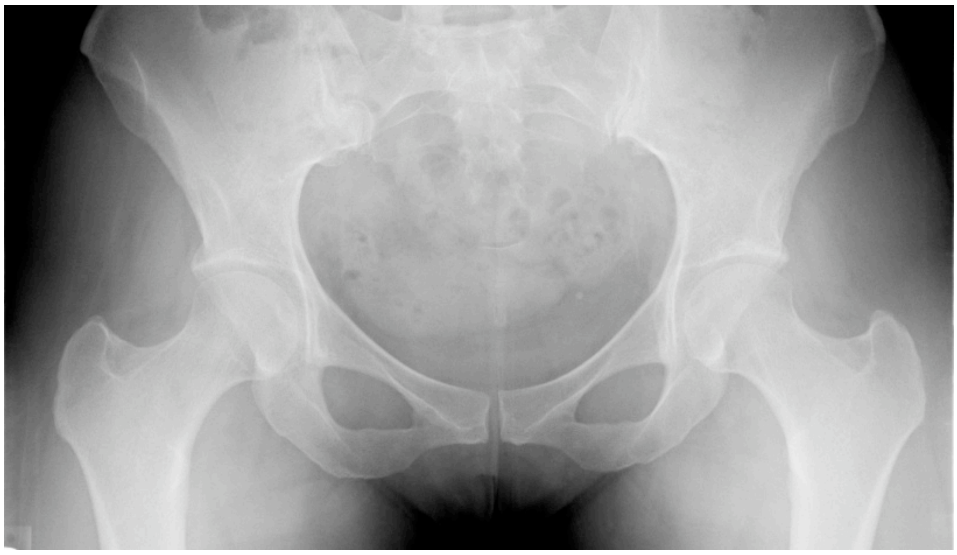


Image 4. In this example (below) the proximal femurs have been cropped out.

Unacceptable ✗



Image 5. In this example (below) the proximal femurs have been cropped out.

Unacceptable

✗

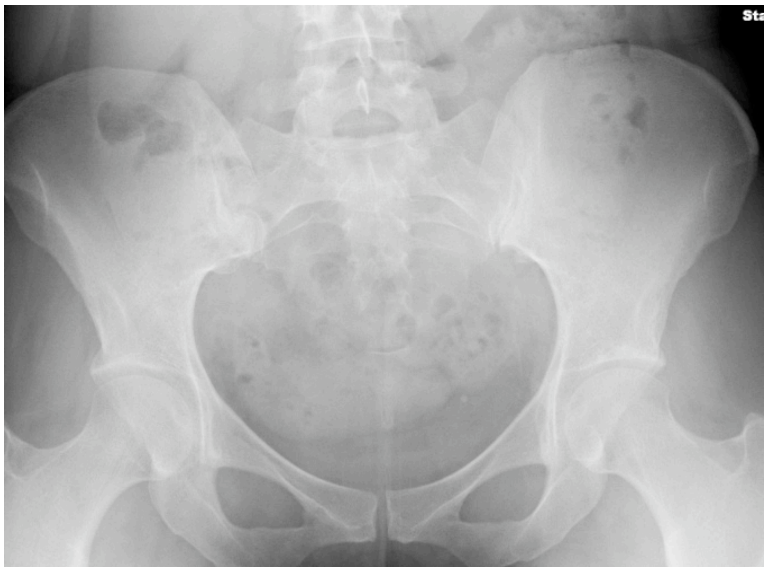
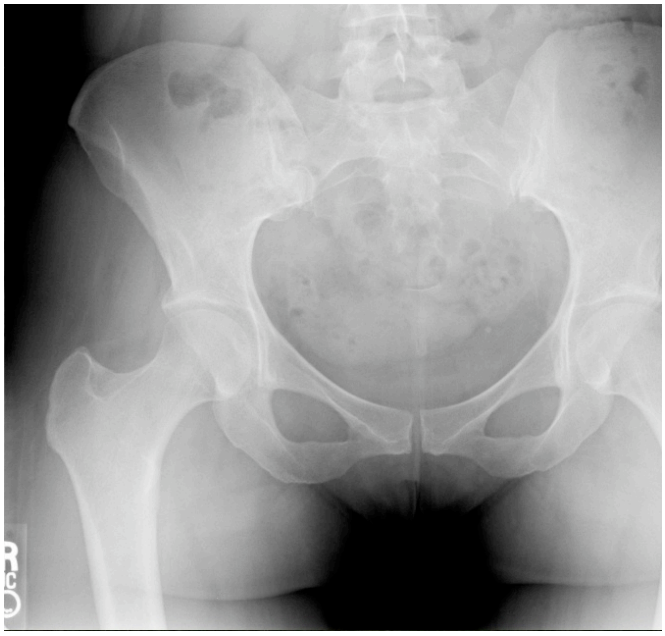


Image 6. If the width of the scanner is too narrow to include both hips properly (as in image 5) then every effort should be made to scan the RIGHT hip properly, Then repeat this process for the LEFT side saving 2 files for that pelvis.

Acceptable (Only if scanner too narrow to include both hips)

✓



APPENDIX C

Chingford 1000 Women Study

Investigation Into Predictors Of Osteoarthritis In The Hip & Knee

Correspondence:
Alexander Nicholls
Botnar Research Centre
Nuffiled Department of Orthopaedic Surgery
University of Oxford, Oxford, OX3 7LD
alexander.nicholls@ndos.ox.ac.uk

TOTAL JOINT REPLACEMENT RECORD

PATIENT INITIALS_____ Study No._____

Date of Birth_____/_____/_____(dd/mm/yy)

1. Is there a record of previous **Total Hip Replacement (THR)**? ☐ Yes ☐ No

If yes,

2. Which hip was replaced? ☐ Left ☐ Right ☐ Both

3. What was the indication for the THR?

☐ Osteoarthritis ☐ Rheumatoid Arthritis ☐ Trauma / Fracture ☐ Other (specify)_____

4. What was the date of the procedure? _____/_____/_____(dd/mm/yy)

5. At which hospital did the operation take place?_____

1. Is there a record of previous **Total Knee Replacement (TKR)**?)? ☐ Yes ☐ No

If yes,

2. Which hip was replaced? ☐ Left ☐ Right ☐ Both

3. What was the indication for the TKR?

☐ Osteoarthritis ☐ Rheumatoid Arthritis ☐ Trauma / Fracture ☐ Other (specify)_____

4. What was the date of the procedure? _____/_____/_____(dd/mm/yy)

5. At which hospital did the operation take place?_____

APPENDIX D

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
University of Oxford
Nuffield Orthopaedic Centre
Windmill Road
OXFORD, OX3 7LD
Telephone: +44(0) 1865 227664
Fax: +44(0) 1865 737640
e-mail: alexander.nicholls@ndorms.ox.ac.uk

CHINGFORD HIP MORPHOLOGY & OSTEOARTHRITIS STUDY
Protocols For Measurements Of Hip Morphology Using *Hip_Morf 2.0* Software Package

Dear Colleague,

Thank you for your participation the Chingford Hip Morphology & Osteoarthritis Study. The *Hip_morf 2.0* software package was written in our department and has been specifically designed to quantify a variety of morphological variations in the pelvis, femoroacetabular joint and proximal femur. Quantification of these parameters allows us to correlate linear relationships between hip morphology and future disease. The measurements that you take will be used in our inter-observer variability study, an important component in the validation of this software.

Whilst the software is designed to be self explanatory, there will be instances when you have specific questions about exact definitions of anatomical landmarks. In the interests of preserving present and future repeatability, I will ask that you follow the protocols laid out in the attached guide as they relate to each step.

You personal "Observer Number" is _____

Once again, thank you very much for your valued contribution.

Kind regards,

Alex Nicholls

REFERENCE BALL

Centre and resize reference circle over dark radio-opaque object in top LEFT of radiograph.
Click “Set Ref”

MAIN MENU

Enter appropriate identification details

Investigation Year	☐ Year 2		☐ Year 8		☐ Year 20	
Observer Number	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
Viewing Number	☐ 1st	☐ 2nd	☐ 3rd	☐ 4th	☐ 5th	

Altman Osteoarthritis Grade

Complete the following scoring template as per Altman Atlas for Radiographic Osteoarthritis[11].

Marginal Osteophytes

Superior acetabular	☐ 0	☐ 1	☐ 2	☐ 3
Superior femoral	☐ 0	☐ 1	☐ 2	☐ 3
Inferior femoral	☐ 0	☐ 1	☐ 2	☐ 3
Inferior acetabular	☐ Present		☐ Absent	

Joint Space Narrowing

Superior	☐ 0	☐ 1	☐ 2	☐ 3
Medial	☐ 0	☐ 1	☐ 2	☐ 3

Other

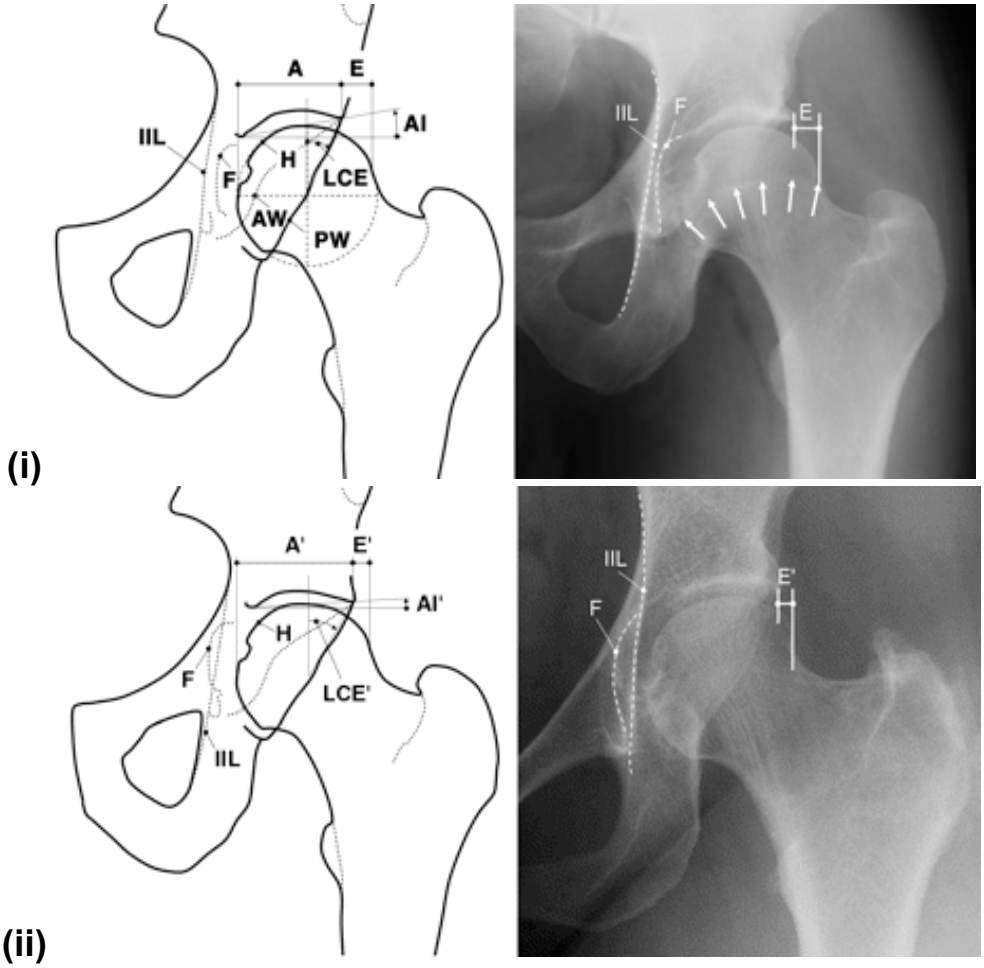
Acetabular subchondral cyst	☐ Present	☐ Absent
Acetabular subchondral sclerosis	☐ Present	☐ Absent
Femoral subchondral sclerosis	☐ Present	☐ Absent
Flattening of femoral head	☐ Present	☐ Absent
Thickening of medial femoral calcar (buttressing)	☐ Present	☐ Absent

Complete the following morphological observations using the definitions below. Only mark box of feature is present.

Coxa Profunda

Floor of the acetabular fossa touches or is medial to the ilioischial line[82,83] (see Figure 1)

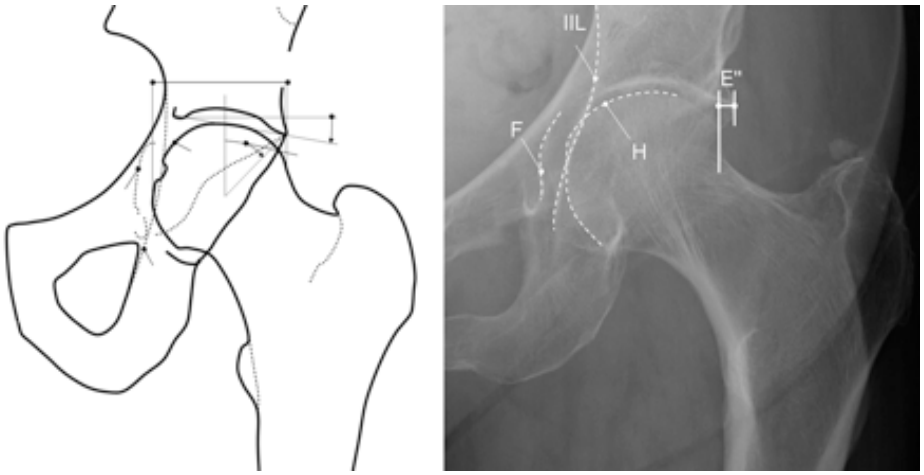
Figure 1. (i) Normal – Floor of acetabulum (F) lies lateral to the ilioischial line (IIL) (ii) Coxa Profunda – F lies medial to IIL. (images lifted verbatim from Tannast *et al,* 2007[37])



Protrusio Acetabuli
Medial margin of the femoral head overlaps the ilioischial line medially[82,83]. (see Figure 2)

Figure 2. (i) Protrusio Acetabuli – Medial margin of femoral head (H) lies medial to the ilioischial line (IIL) (image lifted verbatim from Tannast *et al,* 2007[37])

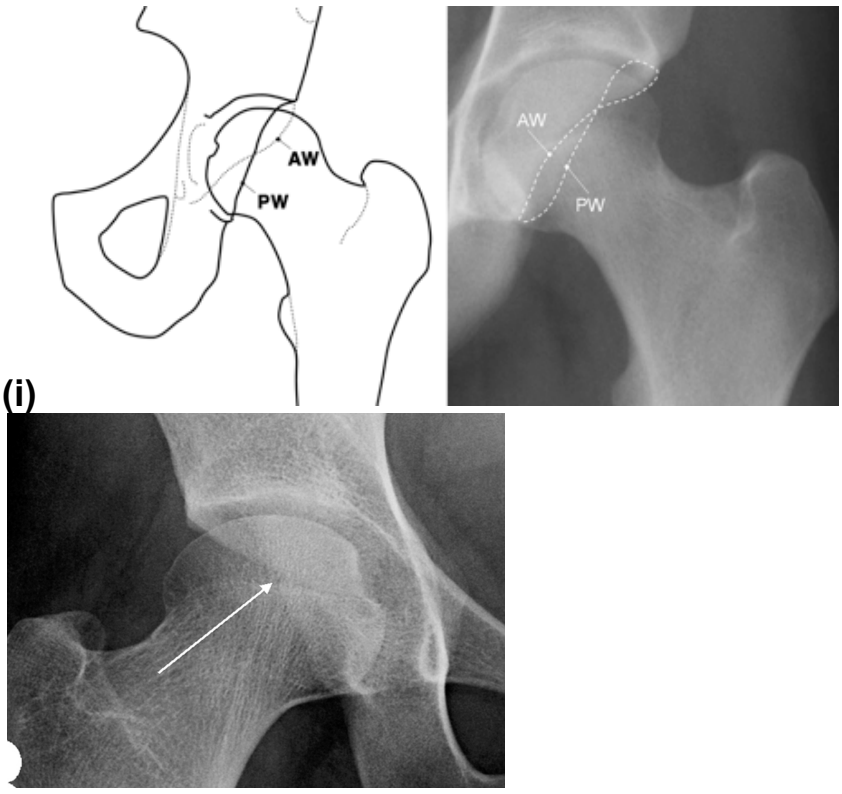
(i)



Crossover Sign

Anterior border of the acetabulum crosses the posterior border, medial to the lateral edge of the acetabulum[82,84] (see Figure 3)

Figure 3. (i) Crossover Sign – Superior portion of the anterior wall (AW) of the acetabulum lies lateral to the posterior wall (PW). (image lifted verbatim from Tannast *et al,* 2007[37])



(i)

Complete the following surgical observations using the definitions below. Only mark box of feature is present.

Total Hip Arthroplasty (THA) in situ
Hemiarthroplasty in situ



THA



Hemiarthroplasty

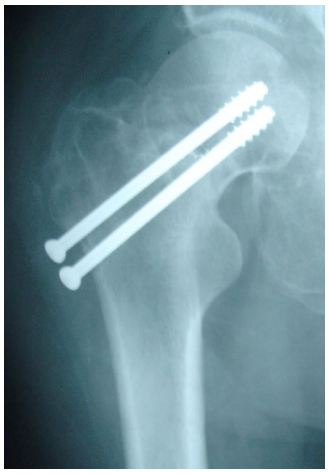
Other Fixation Devices in situ
Intramedullary device (IMD); Dynamic Hip Screw (DHS); Cannulated Screws



IMD



DHS



Cannulated Screws

ANATOMICAL LANDMARKS (Definitions)

Horizontal Reference

Adjacent to each acetabulum, mark the most inferior tip of the teardrops (RIGHT followed by LEFT)

Radiographic teardrop[85]:

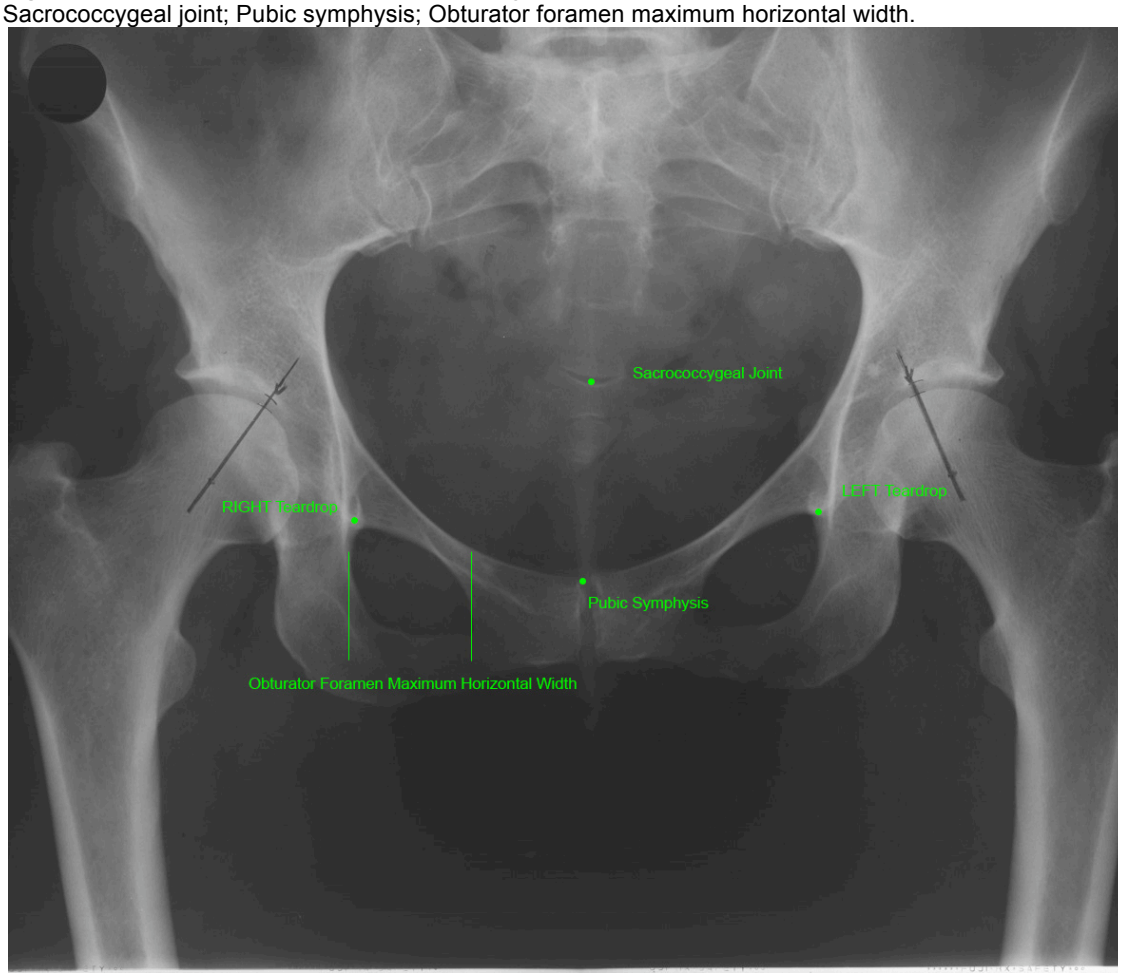
-true floor of acetabulum corresponds to the radiographic teardrop;

-teardrop lies in the inferomedial portion of the acetabulum, just above the obturator foramen;

-the lateral and medial lips corresponds to the external and internal acetabular walls, respectively

-see Figure 4

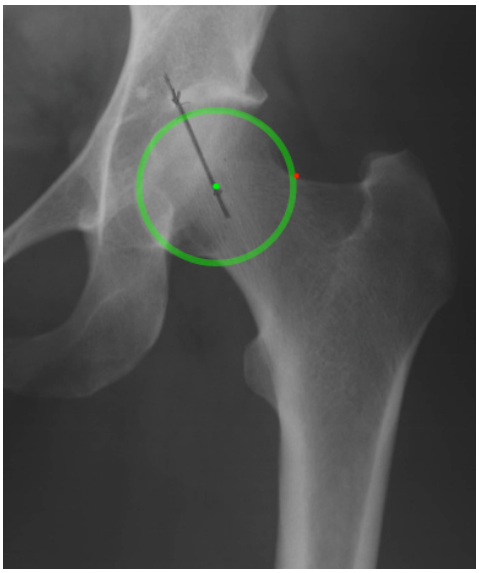
Figure 4. Points marked on this AP Pelvis radiograph include: RIGHT & LEFT Teardrops; Sacrococcygeal joint; Pubic symphysis; Obturator foramen maximum horizontal width.

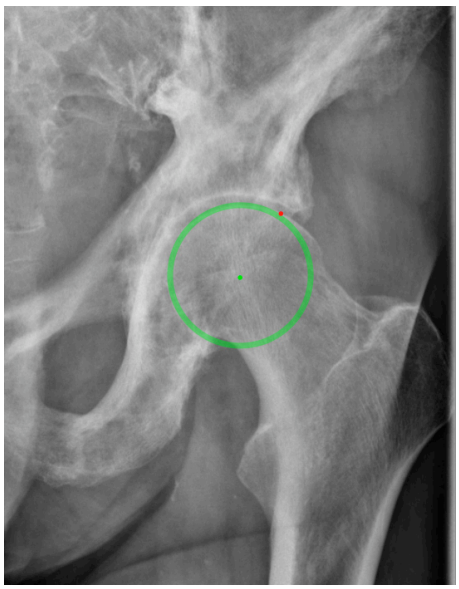


Centre of Femoral Head

Centre the green circle over the femoral head and resize it to make a best fit along the weight-bearing curvature of the superior and medial corticies. (see Figure 5)

Figure 5. Congruent circle placed over the femoral head (green ring). The centre of the circle marks the centre of the femoral head (green point). The start of the femoral neck is the marked (red point) where the superior lateral cortex of the femoral neck first breaks away from the circle of the femoral head. Multiple examples are provided





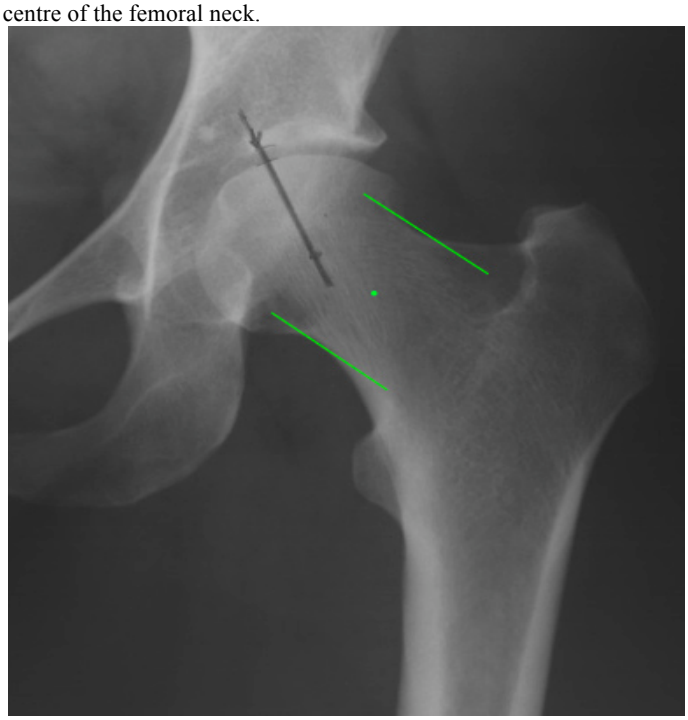
Start of femoral neck

Mark the point at which the lateral cortex of the femoral neck is first seen breaking from the femoral head circle - as marked in *Centre of Femoral Head*. (see Figure 5)

Centre of Femoral Neck

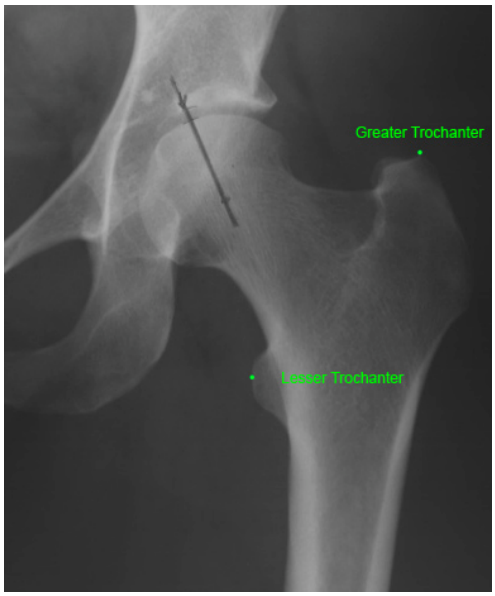
Rotate measurement calipers so they are approximately parallel with the femoral neck axis. Centre the calipers over the cross-sectional midpoint of the femoral neck. Resize calipers to fit the narrowest point on the femoral neck. Calipers should touch the most superficial edge of both corticies. Calipers can be rotated by holding “SHIFT” key, clicking on the lateral caliper and swing mouse from side to side. (see Figure 6)

Figure 6. Callipers are shown here marking the narrowest part of the femoral neck. The midpoint between the two callipers (green point) represents the centre of the femoral neck.



Lesser Trochanter
Mark at most medial prominence of the lesser trochanter. (see Figure 7)

Figure 7. Greater Trochanter & Lesser Trochanter are marked as per protocol on this LEFT Hip radiograph

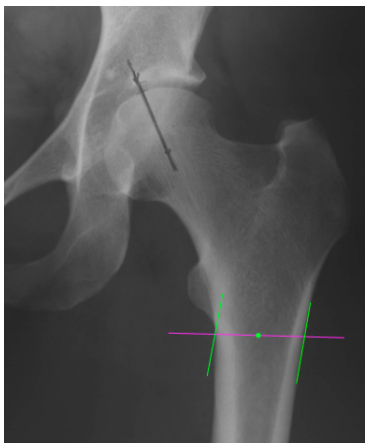


Femoral Axis – Reference Point 1
Purple line will appear at 2cm below the lesser trochanter. Select the midpoint (axial plane) of the femoral shaft on this line. Resize calipers to meet lateral and medial corticies to ensure it is the midpoint.

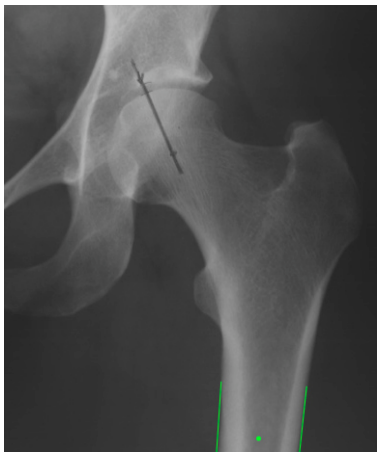
Femoral Axis – Reference Point 2
Select the midpoint (axial plane) of the most distal part femoral shaft visible on the film . Resize calipers to meet lateral and medial corticies to ensure it is the midpoint.

Figure 8. (i) Femoral axis reference point 1. Calipers should be positioned so that the green point lies on the pink line representing 2 cm below the lesser trochanter. (ii) Femoral axis reference point 2. Calipers should be positioned so that the green point is as distal as possible on the film.

(i)

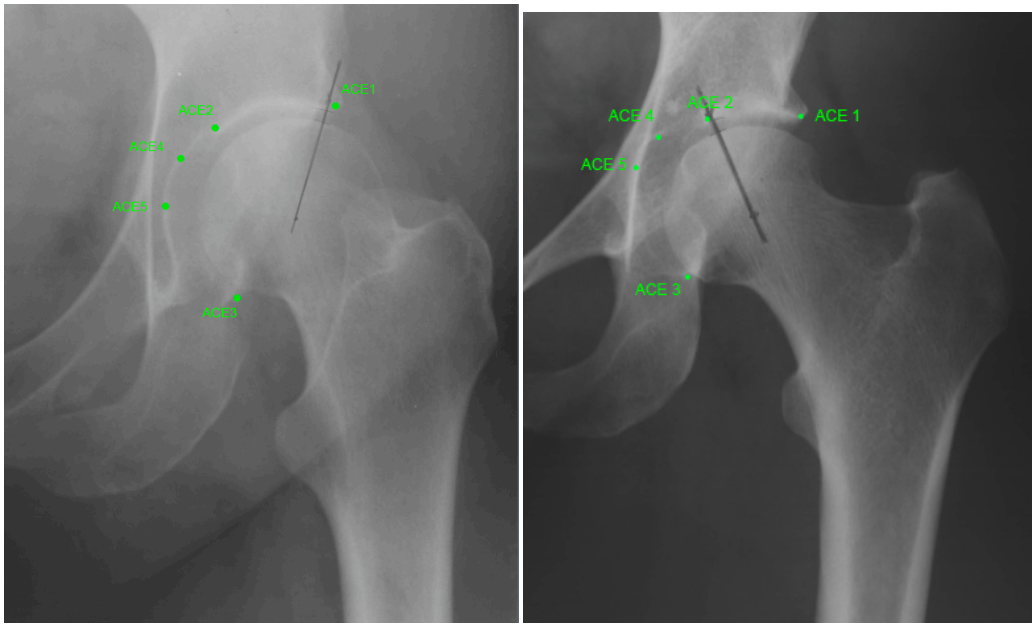


(ii)



Acetabulum – Reference Point 1
Mark the superior lateral rim of the acetabulum. This should be the lateral edge of the sclerotic margin of the weight-bearing sourcil. If an osteophyte is present, DO NOT mark it with this point. (see Figure 9)

Figure 9. The following points are marked on various LEFT Hip radiographs. ACE 1 – Acetabular reference point 1; **ACE 2 –** Acetabular reference point 2; **ACE 3 –** Acetabular reference point 3; **ACE 4 –** Acetabular reference point 4; **ACE 5 –** Acetabular reference point 5.



Acetabulum – Reference Point 2
Mark the medial edge of the sclerotic weight bearing sourcil. (see Figure 9)

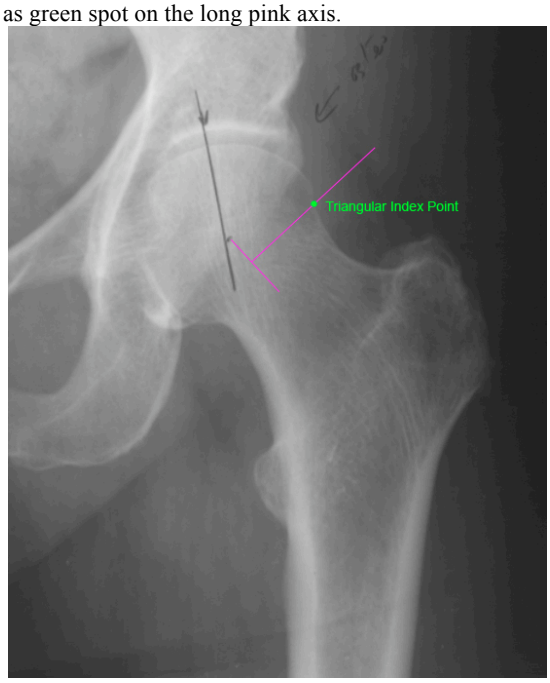
Acetabulum – Reference Point 3
Mark the inferior rim of the acetabulum. This point is best reproduced by finding the junction between the inferior medial rim of the femoral head and the posterior wall of the acetabulum. (see Figure 9)

Acetabulum – Reference Point 4
A cross will appear that is orientated so that one axis is parallel to the line joining acetabular reference points 1 and 3. Using this as a guide to the laterl version of the acetabulum, find the deepest point. (see Figure 9)

Acetabulum – Reference Point 5
A cross will appear that is orientated so that one axis is parallel to the true horizontal reference line (drawn earlier). Using the perpendicular (vertical) axis, find the most medial point within the acetabulum. (see Figure 9)

Triangular Reference Point[1]
A pink T-shaped structure will appear over the ipsilateral femoral head and neck. On the long axis, mark the point at which the pink line crosses the superior lateral cortex of the femoral head/neck.

Figure 10. Triangular Reference Point[1]**.** Point is marked as green spot on the long pink axis.



Greater Trochanter
Mark at the most superior prominence of the greater trochanter. (see Figure 7)

Sacrococcygeal Joint
Mark at the horizontal midpoint of this joint, directly in the centre of the S5 & Coccyx. (see Figure 4)

Pubic Symphysis
Mark the point on the pubic symphysis that is in line with the upper cortex of the superior pubic ramii. (see Figure 4)

Obturator Foramen
The calipers will appear perpendicular to the true horizontal line. Resize calipers over the Obturator foramen to find the maximum horizontal width. DO NOT alter the tilt of the calipers as this will mean we are not measuring true horizontal width. (see Figure 4)

USER GUIDE REFERENCES (Appendix D)

1. Gosvig KK, Jacobsen S, Palm H, Sonne-Holm S, Magnusson E. *A new radiological index for assessing asphericity of the femoral head in cam impingement. J Bone Joint Surg Br 2007;89-10:1309-16.*
2. Altman RD, Gold GE. *Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15 Suppl A:A1-56.*
3. Clohisy JC, Carlisle JC, Beaule PE, Kim YJ, Trousdale RT, Sierra RJ, Leunig M, Schoenecker PL, Millis MB. *A systematic approach to the plain radiographic evaluation of the young adult hip. J Bone Joint Surg Am 2008;90 Suppl 4:47-66.*
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1. Gosvig KK, Jacobsen S, Palm H, Sonne-Holm S, Magnusson E. A new radiological index for assessing asphericity of the femoral head in cam impingement. *J Bone Joint Surg Br 2007;89-10:1309-16.*

2. Yelin E, Murphy L, Cisternas MG, Foreman AJ, Pasta DJ, Helmick CG. Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons with 1997. *Arthritis Rheum 2007;56-5:1397-407.*

3. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Rheum Dis Clin North Am 2008;34-3:515-29.*

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