

Aspects of Early Hip Osteoarthritis

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Abstract

Osteoarthritis develops secondary to the action of hostile biomechanics upon susceptible cartilage. Cam morphology describes a loss of concavity at the femoral head-neck junction resulting in femoral impaction against the acetabular rim within a functional range of movement. This impaction is termed femoroacetabular impingement and can result in pain and cause damage to adjacent articular cartilage that progresses to osteoarthritis. Cam morphology is a target for joint preservation strategies.

The first study in this thesis compares hip development in academy football players with controls from local schools. The results provide strong evidence that cam morphology can develop in response to intense sporting activity during adolescence. At present, it is not possible to recommend activity modification as the cardiovascular benefits of exercise are likely to outweigh potentially detrimental effects on hip morphology. Nevertheless, individuals participating in high-level sports during youth may represent a high risk cohort for osteoarthritis warranting surveillance.

Diagnostic tools currently available only allow identification of late joint degeneration when disease is irreversible. Advances in the field of disease biomarkers may overcome this challenge. The second study of this thesis explored the prognostic value of compositional MRI. Baseline delayed gadolinium-enhanced MRI of cartilage was able to predict the development of radiographic hip osteoarthritis in asymptomatic individuals within five years. As well as identifying individuals who are likely to benefit from intervention, compositional MRI may allow the evaluation of treatment efficacy within short timeframes.

A number of interventions aimed at joint preservation are under investigation for treating cam morphology femoroacetabular impingement. Arthroscopic surgery is increasingly performed to restore the concavity at the femoral head-neck junction and prevent impaction against the acetabular rim. A feasibility study was performed for a proposed randomised controlled study comparing operative and non-operative treatment. The study protocol was developed for the 'Femoroacetabular Impingement Trial' (FAIT).

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Abbreviations

AOR	Anterior Offset Ratio
AP	Anteroposterior
AUC	Area Under the Curve
COMP	Cartilage Oligomeric Matrix Protein
CT	Computerised Tomography
CTX-II	C-Telopeptide of Type II Collagen
dGEMRIC	Delayed Gadolinium Enhanced MRI of Cartilage
FABER	Flexion Abduction External Rotation
FADIR	Flexion Adduction Internal Rotation
FAI	Femoroacetabular Impingement
FAIM	Femoroacetabular Impingement MRI Study
FAIT	Femoroacetabular Impingement Trial
HADS	Hospital Anxiety and Depression Score
HAGOS	Hip and Groin Outcome Score
HES	Hospital Episode Statistics
HHS	Harris Hip Score
HOOS	Hip Disability and Osteoarthritis Outcome Score
HOS	Hip Outcome Score
ICC	Intra/Inter Class Correlation
iHOT	International Hip Outcome Tool
JSW	Joint Space Width

LatJSW	Joint Space Width at Lateral Sourcil
MedJSW	Joint Space Width at Medial Sourcil
MinJSW	Minimum Joint Space Width
MRI	Magnetic Resonance Imaging
NAHS	Non-Arthritic Hip Score
NICE	National Institute for Health and Care Excellence
OARSI	Osteoarthritis Research Society International
OHS	Oxford Hip Score
OPCS	Operating Procedure Codes
PAQ-A	Physical Activity Questionnaire for Adolescents
PAQ-C	Physical Activity Questionnaire for Children
PDFS	Proton Density Fat Saturation
PROMS	Patient Reported Outcome Measures
RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristic
ROI	Region of Interest
SD	Standard Deviation
SDD	Smallest Detectable Difference
SER	Surgical Equipoise Ratio
SUFE	Slipped Upper Femoral Epiphysis
TE	Echo Time
TR	Repetition Time
WATSf	Water Selective (fluid)

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Thesis Summary

Osteoarthritis develops secondary to the action of hostile biomechanics upon susceptible cartilage. The identification of specific aetiological factors and disease phenotypes has provided an opportunity to develop strategies for preventing osteoarthritis development and progression. At present, the only effective treatment for osteoarthritis is joint arthroplasty for advanced disease, and there are no effective treatments for early degeneration. Cam morphology of the hip is increasingly recognised as an important risk factor for osteoarthritis and this disease phenotype is a target for joint preservation strategies. A loss of concavity at the femoral head-neck junction results in femoral impaction against the acetabular rim within a functional range of movement and this is termed femoroacetabular impingement. Femoroacetabular impingement can result in pain and cause damage to adjacent articular cartilage that progresses to osteoarthritis.

Recent studies suggest that cam morphology may develop in response to sporting activity during adolescence. This raises the possibility that activity modification may prevent cam formation hence future hip osteoarthritis. Once cam morphology has developed, proposed strategies to prevent osteoarthritis include physiotherapy or surgery to modify adverse joint biomechanics, perhaps combined with pharmaceuticals to reduce cartilage susceptibility. This thesis explores different strategies for preventing hip osteoarthritis secondary to cam morphology and addresses some of the barriers to their implementation.

The first study in this thesis compared hip development in academy football players with controls from local schools. The results provide strong evidence that intense sporting activity during adolescence promotes epiphyseal hypertrophy and extension that gives rise to cam morphology. However, this mechanism does not account for all

cam morphology, and some individuals develop a normal hip shape despite intense sporting activity. At present, it is not possible to recommend activity modification as a means of preventing the development of cam morphology and future osteoarthritis. The cardiovascular benefits of exercise are likely to outweigh potentially detrimental effects on hip morphology. Nevertheless, individuals participating in high-level sports during youth may represent a high risk cohort that warrants surveillance.

Only a small proportion of individuals with cam morphology develop subsequent osteoarthritis. A significant hurdle to the development of preventative strategies is that it is not possible to accurately identify which individuals are at greatest risk and hence may benefit from intervention. Diagnostic tools currently available only allow the identification of late joint degeneration when disease is likely irreversible, however, advances in the field of disease biomarkers may help overcome this challenge. Imaging and biochemical markers of early joint degeneration appear sensitive to changes in cartilage composition that precede structural damage. This may facilitate optimal patient selection for preventative strategies.

The second study of this thesis investigated the prognostic value of compositional MRI. This demonstrated that baseline delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) was able to predict the development of radiographic hip osteoarthritis in asymptomatic individuals within five years. As well as identifying individuals who are likely to benefit from intervention, compositional MRI may also allow the evaluation of treatment efficacy within short timeframes.

A number of interventions aimed at joint preservation are under investigation for individuals with cam morphology femoroacetabular impingement. Although currently only offered to patients with symptoms, if proven to be safe and effective, they may also have a role in asymptomatic populations, perhaps in conjunction with a screening tool.

A procedure that is increasingly performed is arthroscopic osteochondroplasty to restore the concavity at the femoral head-neck junction and prevent impaction against the acetabular rim. Surgery has been shown to improve symptoms in the short term, but it remains unclear whether it can prevent the development or progression of osteoarthritis, or whether it is superior to non-operative interventions. Physiotherapy and activity modification also demonstrate the ability to improve symptoms.

The final aspect of this thesis was to perform a feasibility study for a proposed randomised controlled study comparing operative and non-operative treatment of cam morphology femoroacetabular impingement. This demonstrated a clinical need for a study and that patient and surgeon opinion was permissive. Critically, patients indicated that equal importance should be placed on improving symptoms and preventing osteoarthritis. Accordingly, a study protocol was developed for the 'Femoroacetabular Impingement Trial' (FAIT) (NCT01893034).

Chapter 1 Introduction and Literature Review

1.1 Current Clinical Challenges

Osteoarthritis is the most common joint disease worldwide affecting an estimated 10% of males and 18% of females over 60 years of age¹. The resultant pain and loss of function can be debilitating and in developed countries represents a large socioeconomic burden, costing between 1% and 2.5% of gross domestic product². Osteoarthritis treatment primarily consists of pain management with joint arthroplasty for advanced disease³⁻⁵. Arthroplasty surgery is an extremely effective intervention in late symptomatic disease and relieves pain, restores function, and improves quality of life⁶. However, limitations include the possibility of surgical complications or persistent pain and stiffness, as well as the finite lifespan of prostheses^{3,4,7}. There remains no effective treatment to address the morbidity experienced during early disease⁸. Given the ageing global population and increasing prevalence of osteoarthritis^{9,10}, disease prevention and the treatment of early osteoarthritis represents a research priority.

Our current inability to develop effective treatments for early osteoarthritis stems from a number of sources. First, it is not possible to accurately predict which individuals will develop osteoarthritis and hence may benefit from intervention. The aetiology of osteoarthritis is complex and multifactorial, but there has been progress on this front with better characterisation of risk factors. Varus or valgus alignment of the knee^{11,12} and cam morphology of the hip¹³ are two examples, however, even taking these factors into account, the positive predictive value for future disease remains limited¹⁴. Additional factors must be important, such as cartilage susceptibility to hostile biomechanics. Preventative strategies are most likely to be effective when addressing the underlying disease aetiology through risk factor modification or mitigation of their effect. One

explanation offered for the failure of therapies aimed at preventing the development and progression of osteoarthritis to date has been the failure to recognise and address specific disease phenotypes responsible for joint failure¹⁵.

Second, conventional imaging modalities are only able to diagnose advanced osteoarthritis at a stage when pathology is likely irreversible. Pain also reflects a relatively late stage of disease and approximately 80% of individuals have structural cartilage damage at the onset of knee symptoms¹⁶. Pain is very non-specific and there is only a weak relationship between structural damage and symptoms¹⁷⁻¹⁹. The development of new biomarkers to diagnose early and potentially reversible osteoarthritis is likely to be a prerequisite to the success of preventative therapies. Sensitive biomarkers of disease may also offer the ability to evaluate the efficacy of therapies within a shorter timeframe than is currently possible^{20,21}.

Third, no intervention has demonstrated the ability to prevent the development or progression of structural osteoarthritis, defined as cartilage degeneration irrespective of whether a patient has symptoms. Treatment strategies under investigation include physiotherapy and surgery to modify hostile biomechanics, and pharmaceuticals to reduce cartilage susceptibility. Modifying a single risk factor in isolation may be inadequate to prevent disease progression²², highlighting the importance of carefully characterising the disease phenotype. Should a clinician identify a patient at high risk of developing osteoarthritis or disease progression, it currently remains unclear what management plan they should implement.

1.2 Scope of Thesis

This thesis focuses on a specific phenotype of hip osteoarthritis that develops secondary to cam morphology of the hip. The aim is to explore whether it might be possible to modify risk factors, identify individuals at greatest risk of osteoarthritis progression, and prevent progression with surgical intervention. It starts with a literature review of recent advances in our understanding of early osteoarthritis aetiology, diagnosis, and treatment.

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- Glyn-Jones S, Palmer AJR, Agricola R, Price AJ, Vincent TL, Weinans H, Carr AJ. *A Seminar in Osteoarthritis. Lancet* 2015 Jul 25;386 (9991):376-87. PMID: 25748615.

1.3 Aetiology of Hip Osteoarthritis

The identification of risk factors is central to understanding disease aetiology and selecting targets for osteoarthritis prevention and treatment. Longitudinal studies of large population cohorts have provided important insights and there is an increasing appreciation that osteoarthritis develops through the action of hostile biomechanics upon a susceptible joint. Biological pathways within a joint are now known to be mechanosensitive²³. Biomechanical factors may be modifiable and offer potential targets for intervention.

Joint biomechanics are dictated by anatomical and functional factors. Anatomical factors include joint morphology, which has attracted increasing attention as an aetiological factor for hip osteoarthritis. Hip dysplasia, where there is reduced acetabular coverage of the femoral head, is a long established risk factor for osteoarthritis²⁴. The prevalence of hip dysplasia varies significantly depending on the population studied and the adopted diagnostic criteria. A general population cohort from Denmark consisting of 1332 males and 2288 females estimated the prevalence of dysplasia as 4.3% in males and 3.6% in females²⁵. In the same cohort, the prevalence was found to range between 5.4% to 12.8% depending on the diagnostic criteria²⁶. The absence of agreed diagnostic criteria is a significant limitation in all studies of hip morphology.

Hip dysplasia is a potent risk factor for osteoarthritis²⁷. It has been estimated to play a role in 20% to 40% of all hip osteoarthritis²⁸⁻³⁰ and 48% of those receiving hip arthroplasty surgery before the age of 50³¹. The childhood conditions Legg-Calvé-Perthes disease and slipped upper femoral epiphysis (SUFE) also predispose to osteoarthritis³²⁻³⁵, and represented the underlying aetiology in 9.5% and 6.2% of patients receiving hip arthroplasty before the age of 50, respectively³¹. The remaining proportion of hip osteoarthritis was traditionally considered idiopathic²⁹. This view is countered by the

high prevalence of subclinical deformities associated with femoroacetabular impingement that have been identified amongst cases previously deemed idiopathic³¹.

Femoroacetabular impingement results from abnormal contact between the proximal femur and acetabulum secondary to a loss of concavity at the femoral head-neck junction (cam morphology) or acetabular overcoverage of the femoral head (pincer morphology) (Figure 1-1). Whereas all hips impinge at the extremes of movement³⁶, this abnormal contact takes place within a functional range of movement. Although cam and pincer morphology may co-exist, the two conditions are distinct³⁷ and give rise to different patterns of joint pathology³⁸.

Pincer morphology may be localised as with acetabular retroversion, or global as with coxa profunda or protrusio acetabuli³⁹. It is associated with pain but does not appear to increase the risk of developing osteoarthritis^{27,40}. Cam morphology may result from conditions such as SUFE, Legg-Calvé-Perthes disease, or femoral neck fracture malunion, although the majority arise without apparent pre-existing hip disease⁴¹ (Figure 1-2). Contrary to pincer morphology, cam morphology can give rise to pain⁴² and osteoarthritis¹⁴ (Figure 1-3).

Figure 1-1 - Schematic Lateral View of the Hip a) Normal b) Cam c) Pincer

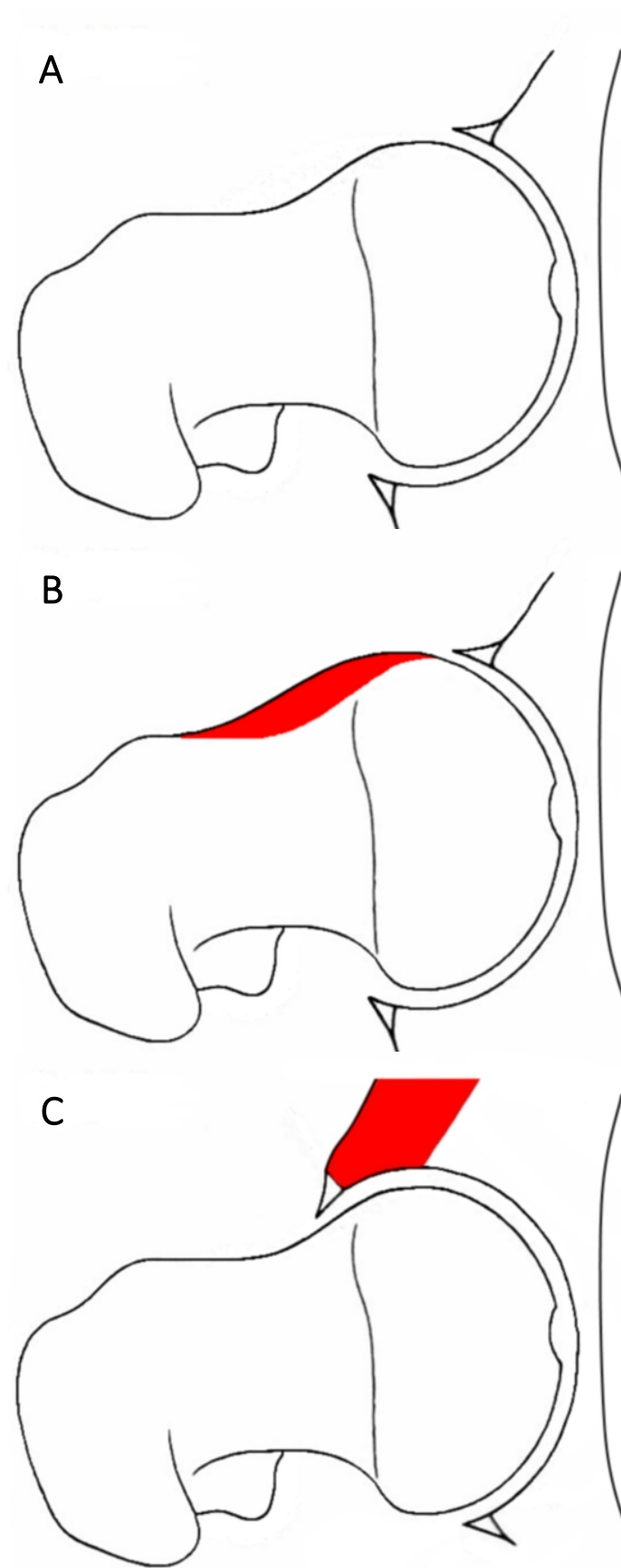
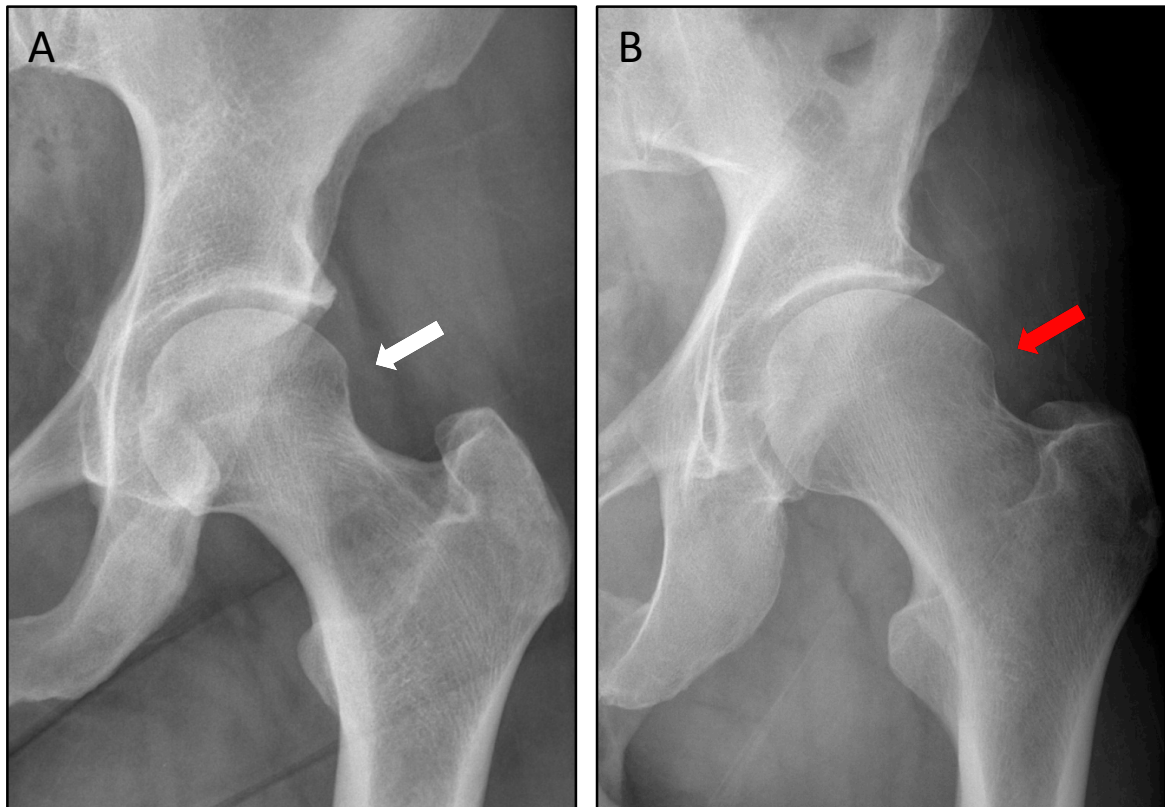


Figure 1-2 - Radiographs Demonstrating Cam Morphology

Anteroposterior radiographs of a normal hip (A) and a hip with cam morphology (B). In a normal hip, the concavity of the femoral head-neck junction (white arrow) allows an extensive range of hip movement without impingement of the femur against the acetabular rim. In cam morphology femoroacetabular impingement, the loss of this concavity at the anterior and superior head-neck junction (red arrow) results in impaction of the femur against the acetabular rim when the hip moves into flexion and internal rotation. This results in damage to the labrum and may progress to involve the acetabular cartilage with development of osteoarthritis.

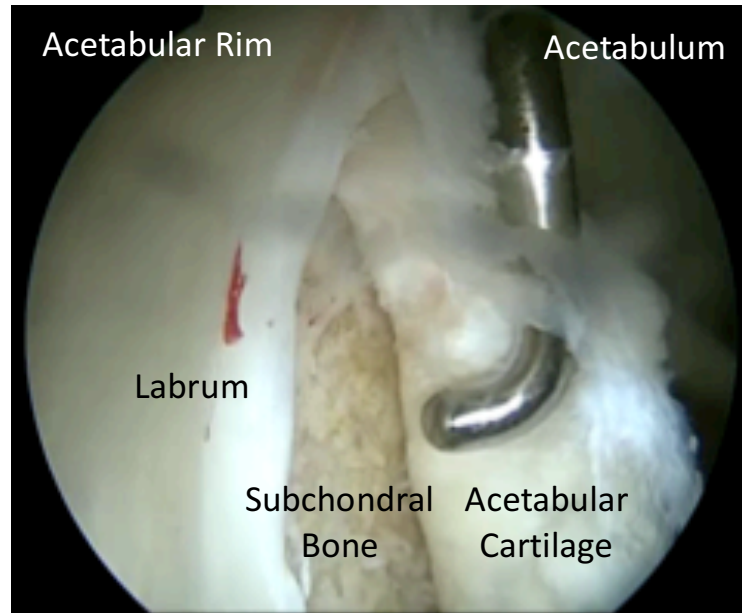


A recent systematic review concluded that it is not possible to determine the true prevalence of cam morphology in the general population or selected subgroups, primarily due to heterogeneous populations and diagnostic criteria⁴³. Prevalence ranged from 5% to 75%, however, did appear consistently higher in males. A cross-sectional study of 2081 skeletally mature young healthy adults found that 35% males and 10% females displayed cam morphology⁴⁴. In a systematic review of asymptomatic populations of males and females the overall prevalence of cam morphology was 37%, but was 54.8% in athletes and 23.1% in the general population. Sporting activity is a recognised but poorly-defined risk factor for hip osteoarthritis⁴⁵, and high activity levels during adolescence may promote the development of cam morphology⁴⁶⁻⁴⁸.

A prospective study of the CHECK cohort consisting of 1002 volunteers with early symptomatic osteoarthritis reveals that cam morphology can confer up to a 10-fold increased risk of developing end-stage disease within five years⁴⁹. These findings are supported by a prospective study of the Chingford cohort consisting of 1003 females recruited from the general population and followed for 20 years. Cam morphology was associated with both osteoarthritis and future hip arthroplasty⁵⁰. It also conferred an increased risk of hip osteoarthritis progression in the Johnson County Osteoarthritis Project⁵¹. In these cohorts, the greater the size of the cam morphology, the greater the risk of developing osteoarthritis. A number of cross-sectional and case-control studies report a higher prevalence of cam morphology in individuals with radiographic osteoarthritis^{25,52}. Causality is supported by the cartilage damage seen intra-operatively at the specific sites where impingement takes place^{39,53} (Figure 1-3) and early osteoarthritis can be detected using compositional MRI techniques (delayed Gadolinium-Enhanced MRI of Cartilage) in asymptomatic patients with cam morphology⁵⁴.

Figure 1-3 - Arthroscopic Appearance of a Hip with Cam Lesion Femoroacetabular Impingement

The aspherical femoral head enters the acetabulum on hip flexion and internal rotation leading to delamination of the acetabular cartilage from the underlying subchondral bone and the development of osteoarthritis. Modified from Glyn-Jones et al⁸.



Despite the strong association between cam morphology and the development of osteoarthritis, the majority of individuals with this morphology will not develop osteoarthritis. Depending on cohort characteristics and the diagnostic criteria for cam morphology, the positive predictive value for future osteoarthritis ranges from 6-25%, whereas the negative predictive value ranges from 98-99%¹³. Whilst individuals with normal hip morphology are extremely unlikely to develop osteoarthritis, cam morphology must be accompanied by other risk factors for osteoarthritis to develop. These risk factors may include acetabular morphology, the nature and intensity of activity, or intrinsic susceptibility to hostile biomechanics. The interaction between risk factors is an area of particular interest for future studies (Figure 1-4).

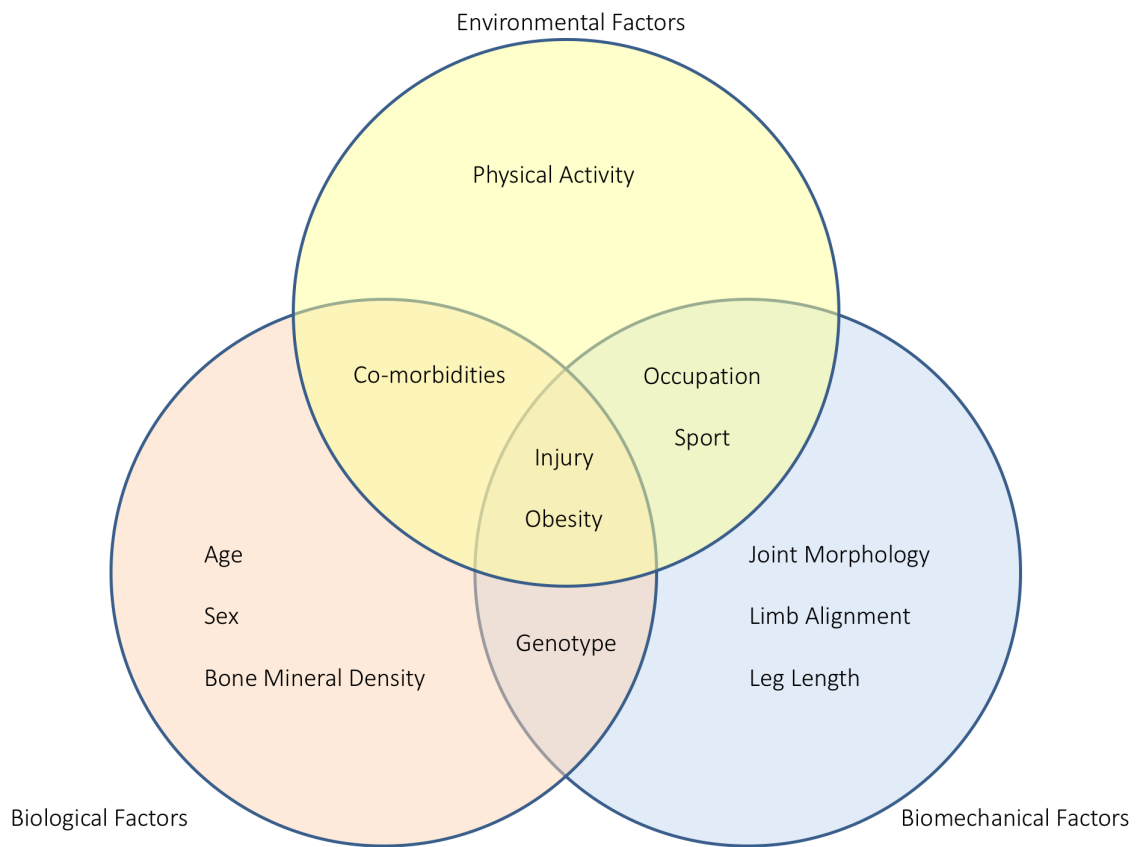
Susceptibility to abnormal morphology is in part determined by systemic factors. Age remains the strongest risk factor for osteoarthritis⁵⁵ and this may reflect a reduction in regenerative capacity and accumulation of risk factors. Osteoarthritis is also more

common in females and although the role of oestrogens has been extensively investigated, the mechanism remains unclear. Studies are complicated by the gender differences in predisposing biomechanics in hip osteoarthritis, where based on prevalence, dysplasia is more likely to represent the aetiological factor in females compared with cam morphology in males.

Injury may cause bone or cartilage damage that makes the joint more susceptible to further insult, for example, labral pathology may adversely affect joint biomechanics^{56,57}. Interestingly, obesity confers a far smaller risk of developing hip osteoarthritis⁵⁸ compared with knee osteoarthritis⁵⁹.

A strong genetic predisposition to osteoarthritis has been recognised through family-based studies. Genome-wide association studies, such as that performed by the Arthritis Research UK Osteoarthritis Genetics (arcOGEN) Consortium⁶⁰, have now identified 11 loci associated with osteoarthritis. The effect sizes are small (odds ratio 1.11 – 1.21)⁶⁰, but consistent with those for other similar complex traits. It is unlikely that genomics alone will reliably identify individuals who will develop disease, but may inform a predictive model. Single-nucleotide polymorphisms (SNPs) have been associated with a number of known risk factors⁶¹. SNPs in the genes DIO2 and FRZB appear to influence proximal femur morphology⁶² and vulnerability to adverse morphology⁶³. It is therefore possible that genetic susceptibility to hip osteoarthritis may be mediated by hip morphology and cartilage metabolism. Epidemiological studies have demonstrated that siblings of patients with cam morphology have a 2.8 relative risk of having the same deformity compared with spouse controls⁶⁴, however, it is not possible to separate out environmental factors such as activity levels. There is also significant racial variation and the prevalence of cam morphology is much lower in Chinese populations compared with White European populations⁶⁵.

Figure 1-4 - Interaction of Risk Factors for Osteoarthritis



1.4 Diagnosis

The clinical diagnosis of osteoarthritis requires that patients have symptoms, and the prevention or alleviation of these is the goal of any intervention. It is these symptoms that prompt patients to seek medical attention outside of screening or research programmes. Symptoms of hip osteoarthritis are principally pain and stiffness⁶⁶ that limit function and are measured quantitatively using validated patient reported outcome measures (PROMs).

There are several limitations to using symptoms to diagnose osteoarthritis when investigating strategies for preventing the development and progression of disease. Symptoms may develop only once there is advanced and likely irreversible disease. This

may follow a period of earlier subclinical structural change, when intervention is more likely to be successful. Symptoms may arise from adjacent structures rather than the hip, fluctuate significantly over time, and are influenced by concurrent distant pathology and pain pathway modulation⁶⁷.

In this thesis, structural osteoarthritis is defined as cartilage degeneration in the absence of inflammatory or crystal arthropathy, irrespective of whether a patient has symptoms. This definition aims to describe osteoarthritis at an early stage. Clinical osteoarthritis is defined as structural osteoarthritis in the presence of symptoms. Although cartilage pathology may be preceded by changes within synovium and bone, cartilage degeneration appears to be the common endpoint of all osteoarthritis phenotypes (Appendix A.1). As our understanding of disease pathogenesis improves, measures relating to other joint structures are likely to gain validity⁶⁸.

The limitation to using structural osteoarthritis to diagnose osteoarthritis is the poor correlation between symptoms and structure¹⁷⁻¹⁹ and our inability to reliably predict whether early cartilage degeneration will progress to clinical osteoarthritis. Consequently, there is no guarantee that treating structural osteoarthritis will provide clinical benefit. Studies investigating structural disease must therefore also take symptoms into account⁶⁹.

Structural osteoarthritis is assayed using a rapidly expanding array of biomarkers (Figure 1-5). This expansion has been driven by advancing technology, an appreciation that osteoarthritis is a condition of the whole joint, and a need to diagnose the earliest disease to facilitate patient selection into clinical trials and measure treatment efficacy within an acceptable timeframe. In order to identify potential biomarkers for early cartilage degeneration, an understanding of cartilage biology is required.

Figure 1-5 - Biomarkers for the Diagnosis of Osteoarthritis. Modified from Palmer et al²⁰.

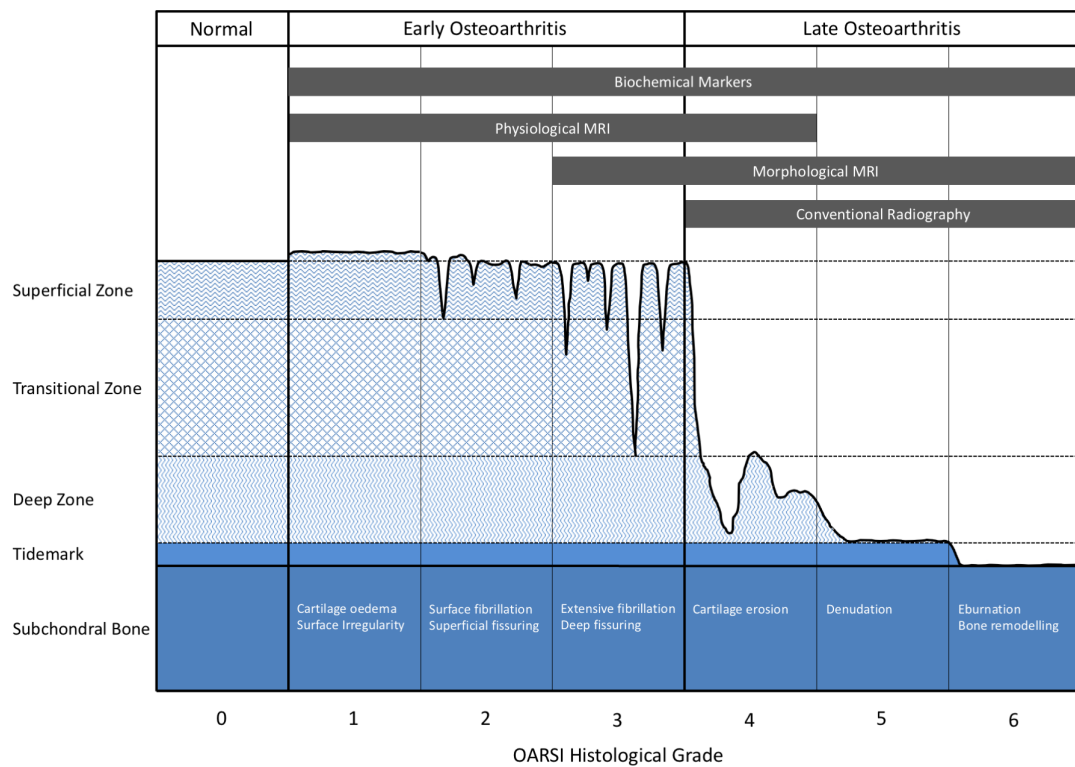
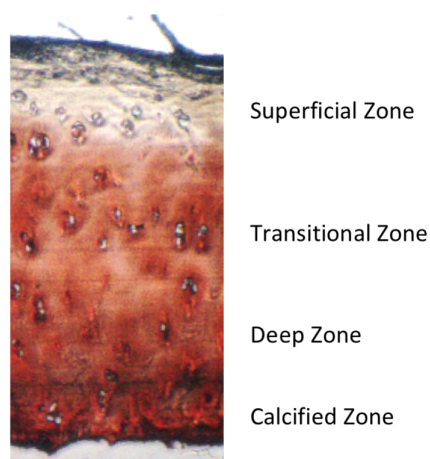


Figure 1-6 - 10 micron osteochondral section with safranin-o stain: OARSI Grade II (x10 magnification)



1.4.1 Cartilage Biology in Osteoarthritis

Healthy hyaline cartilage requires strict regulation of architecture and biochemical composition⁷⁰. Although chondrocytes represent only 1% of cartilage volume, they are critical for maintaining this extracellular matrix⁷¹. The structural framework of cartilage comprises collagens, proteoglycans and glycoproteins. Collagen type II is the principal structural protein in a meshwork that receives stabilisation from other collagen types and non-collagenous proteins such as cartilage oligomeric matrix protein (COMP). This meshwork provides cartilage with tensile strength⁷². Aggrecan and other proteoglycans are embedded in this meshwork. Tissue fluid also lies within this architecture and consists mostly of water, representing up to 80% of the wet weight of cartilage⁷¹, but also contains metabolites and a high concentration of cations to balance the negatively charged glycosaminoglycans. These cations create an osmotic pressure that draws water into the cartilage providing compressive resistance⁷².

Cartilage is divided into superficial, middle (transitional), deep and calcified zones which differ in their matrix composition and architecture (Figure 1-6). The superficial layer has a relatively low glycosaminoglycan content but a high collagen content with fibres orientated parallel to the cartilage surface. This layer is first affected in osteoarthritis⁷³. The middle zone has a higher glycosaminoglycan content, and collagen fibres are orientated obliquely to the cartilage surface. Glycosaminoglycan content is highest in the deep zone where collagen fibres are orientated perpendicularly to the cartilage surface. The transition from cartilage into subchondral bone is denoted as the tidemark.

The earliest change in osteoarthritis is cartilage glycosaminoglycan depletion that is directly proportional to disease severity⁷⁴. Glycosaminoglycan degradation leads to a more permeable matrix and an increase in water content with matrix hypertrophy. This

reduces in the ability of cartilage to resist deformation⁷⁵. Collagen content is maintained during the early stages of disease, although fibre orientation is disrupted⁷⁶. Despite these histological changes, the macroscopic appearance of cartilage remains unaffected⁷⁷. Furthermore, disease is potentially reversible during its early stages, as chondrocytes have the potential to synthesise new matrix molecules to replace those that have degraded. This stage of osteoarthritis is the target of novel compositional imaging strategies. As osteoarthritis progresses, chondrocytes are no longer able to synthesise matrix molecules at the same rate as degradation, and progressive structural damage takes place. Surface fibrillations deepen and become fissures that eventually reach subchondral bone. Superficial fibrillated cartilage fragments break away and cartilage thickness decreases with simultaneous enzymatic degradation of the remaining matrix leaving only subchondral bone⁷⁸. At this stage, osteoarthritis is not reversible. Osteoarthritis does not take place uniformly across articular surfaces of a synovial joint, but commences in a localised area and lesions then gradually extend to incorporate adjacent cartilage⁷⁹.

The Osteoarthritis Research Society International (OARSI) grading provides a histological scoring system for the severity of osteoarthritis⁷³. Grade I and II changes describe cartilage oedema and the condensation of collagen fibres with early glycosaminoglycan depletion. The superficial zone remains intact, although there may be some microscopic fibrillation and fissuring, and the middle and deep zones are unaffected. Grade III changes are seen when vertical fissures extend into the middle zone, but there is still no significant cartilage loss. Grade IV osteoarthritis describes increased fissuring and results in cartilage erosion. Grade V and VI osteoarthritis describe almost complete erosion of the articular cartilage with changes affecting the underlying bone such as sclerosis and eburnation (Figure 1-5). Structural osteoarthritis is

principally assessed using imaging modalities, although biochemical markers are increasingly investigated in a research setting.

1.5 Imaging

1.5.1 Radiography

Osteoarthritis is traditionally diagnosed using plain film radiography which allows visualisation of ossified structures and features of degenerative change. Osteophyte formation is often the earliest sign of osteoarthritis, with subsequent narrowing of the joint space width, sclerosis of subchondral bone, and development of subchondral cysts. Scoring systems include those proposed by Kellgren and Lawrence⁸⁰ and OARSI⁸¹, however, measurement of joint space width (JSW) is more sensitive and reliable^{82,83}. JSW remains the only structural end-point accepted by the European Medicines Agency and Food and Drug Administration to prove efficacy of disease-modifying osteoarthritis drugs⁸⁴, yet this measure has many limitations⁸⁵. Loss of JSW is only evident when there is cartilage loss, representing a late stage of osteoarthritis when disease is likely irreversible. It also lacks sensitivity and is unable to detect localised cartilage damage, limiting the ability to diagnose early disease⁸⁶⁻⁹⁰. Standardisation of image acquisition is also essential and weightbearing radiographs of the hip have improved sensitivity over non-weightbearing films for the diagnosis of osteoarthritis⁹¹. The usually slow progression of osteoarthritis and the limited responsiveness to change¹⁹ also means that when JSW is used as an outcome measure in clinical trials, large cohorts are required with long follow-up^{19,92}. A reduction in minimum JSW greater than or equal to 0.5mm at any position is thought to be clinically relevant^{83,93}. Despite these limitations, radiography is relatively inexpensive and readily available and continues to play a role in both clinical and research settings.

1.5.2 Magnetic Resonance Imaging (MRI)

MRI can be utilised in three different modes:

- i) Morphological MRI: Visualisation of cartilage morphology at high resolution, allowing identification of pre-radiographic structural change.
- ii) Whole Joint Assessment: Semi-quantitative assessment of all joint structures to evaluate global intra-articular pathology seen in early osteoarthritis.
- iii) Compositional MRI: Assessment of the biochemical composition of cartilage.

1.5.2.1 Morphological MRI

MRI confers many advantages over radiography and allows the assessment of joint structures in three dimensions and at high resolution²⁰. As a result, it is more sensitive at detecting early structural osteoarthritis⁸⁶⁻⁹⁰. OARSI now recommend MRI for the assessment of cartilage morphology⁶⁹. Cartilage measurements include thickness, volume, and surface area⁹⁴. Short-term changes in cartilage morphology can reliably predict clinical and structural osteoarthritis progression in the knee⁹⁵⁻⁹⁷. MRI has traditionally only been able to diagnose cartilage loss associated with late disease, however, higher field strengths and advancing technology mean it is increasingly possible to diagnose early degenerative change such as fibrillation and fissuring of the cartilage surface. There are limitations to morphological measurements and they fail to take account of functional adaptation⁹⁸ or cartilage oedema observed during the very earliest stages of disease⁹⁹.

1.5.2.2 Whole Joint Assessment

The appreciation that osteoarthritis is a disease of the whole joint (Appendix A.1) has provided an impetus to image all joint structures⁶⁸. There are several scoring systems for the knee, and specific to the hip is the Hip Osteoarthritis MRI Scoring System (HOAMS)⁹⁰ and Scoring Hip Osteoarthritis with MRI (SHOMRI)¹⁰⁰. These scores

evaluate a large number of features including chondral lesions, subchondral cysts, osteophytes, bone marrow oedema, labral pathology, paralabral cysts, loose bodies, synovitis, joint effusion, ligamentum teres integrity, and greater trochanter tendinosis or bursitis. The predictive value of cartilage measurement for osteoarthritis progression in the knee is increased when non-cartilaginous articular pathology such as bone marrow lesions, meniscal status and synovitis are also taken into account¹⁰¹. Longitudinal studies using semi-quantitative scores have not been published for the hip to date.

1.5.2.3 Compositional MRI

Compositional MRI offers the potential to diagnose pre-structural osteoarthritis by evaluating the biochemical properties of tissues²⁰. The best validated compositional sequence is delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC). An indirect measure of cartilage glycosaminoglycan content is achieved with intravenous delivery of negatively charged ionic contrast. The diffusion of contrast into cartilage is dictated by charge repulsion against the negatively charged cartilage glycosaminoglycans. Studies have shown excellent correlation between in vivo dGEMRIC values and the histological severity of hip cartilage osteoarthritis¹⁰². In addition, dGEMRIC can detect glycosaminoglycan depletion in acetabular cartilage in vivo at the site of impingement in asymptomatic individuals with cam morphology⁵⁴. It can also predict future osteoarthritis in patients with hip dysplasia¹⁰³. However, clinical applicability is limited by a long scanning protocol and the requirement of potentially nephrotoxic contrast agent that is not necessary for other compositional MRI techniques¹⁰⁴.

Sodium scanning is an alternative method of indirect glycosaminoglycan measurement. Cartilage tissue fluid contains a high concentration of cations through charge attraction to the negatively charged cartilage glycosaminoglycans. Cation concentration declines with glycosaminoglycan depletion in early osteoarthritis, and can be quantified using

MRI through the excitation of sodium ions as opposed to the conventional hydrogen ions. Although the technique shows promise¹⁰⁵, it requires high field strengths and special hardware and is not widely adopted for osteoarthritis diagnosis.

Chemical Exchange Saturation Transfer (CEST) allows selective measurement of signal arising from protons bound to different molecules and can be used as an assay of cartilage glycosaminoglycan content¹⁰⁶. Studies suggest comparable performance to other compositional sequences^{107,108}, however, ultra-high field strengths are optimal and further research is required to determine the value of this technique.

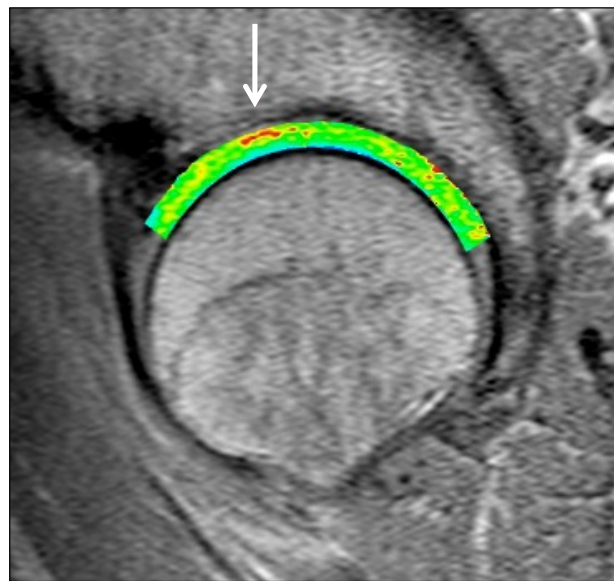
MRI protocols that may have greater clinical relevance and can be used on conventional clinical MRI platforms are under development. These sequences include T2 mapping, T2* mapping, T1Rho mapping and diffusion techniques. They are responsive to proton mobility within cartilage, which is dependent on tissue architecture and biochemistry.

T2 mapping is widely available on clinical MRI platforms and increasingly used in clinical studies, albeit mostly in the knee¹⁰⁹ (Figure 1-7). It appears particularly responsive to collagen fibre orientation¹¹⁰ and can detect early osteoarthritis in patients with femoroacetabular impingement^{111,112}. Studies in the knee suggest that T2 mapping improves sensitivity in the detection of early osteoarthritis cartilage lesions compared with morphological MRI¹¹³ and baseline values predict longitudinal morphological cartilage degeneration^{114,115}. However, T2 mapping has several limitations and requires further validation. T2 values are higher in superficial cartilage compared with deep cartilage where collagen fibres are more densely packed¹¹⁶. Given the superficial cartilage layer is lost as osteoarthritis progresses, T2 mapping is likely to be less valuable in advanced disease^{111,117-119}. Magic angle artefact is also present with curved articular surfaces where T2 values are focally raised secondary to collagen fibre orientation relative to the static magnetic field¹²⁰. T2 values are also sensitive to joint loading¹²¹⁻¹²³,

thought to result from increased anisotropy of collagen fibres during compression¹²⁴, and it is recommended that T2 mapping is performed after a period of off-loading the joint. T2 mapping may be less sensitive than dGEMRIC at detecting early degenerative change¹²⁵.

Figure 1-7 - Sagittal T2 Mapping of the Hip of Healthy Volunteer with Cam Morphology

Although there was no evidence of structural degeneration, the white arrow indicates a region of high T2 mapping relaxation times at the site of impingement consistent with early degenerative change of the acetabular cartilage.



T2* mapping has advantages over T2 mapping in the ability to perform 3D image acquisition at high image resolution with short scan times¹²⁶, whilst it is also widely available on clinical MRI platforms. T2* mapping differs from T2 mapping in that it is a gradient echo rather than spin echo sequence, and values also reflect local field inhomogeneity that may infer additional information pertaining to cartilage biochemistry¹²⁶. T2* mapping is sensitive to collagen fibre orientation¹²⁷, but unlike T2 mapping, most studies demonstrate a decrease in T2 values with increasing cartilage degeneration. Values correlate with histological severity of cartilage degeneration in the hip¹²⁸ and are lower in the cartilage of patients with symptomatic femoroacetabular impingement compared with controls^{129,130}. There is also a correlation between T2* values and the severity of cartilage damage seen at the time of arthroscopy in patients with femoroacetabular impingement¹³¹. However, some studies have found an increase in T2* values with advancing severity of cartilage degeneration^{132,133}, hence further validation of this sequence is required to determine the value of T2* mapping in discriminating between healthy and diseased cartilage. The sequence is also influenced by joint loading and this must be taken into account¹³⁰.

T1 Rho mapping is an increasingly adopted compositional sequence that also probes the interaction between water and the local macromolecular environment, but at a lower frequency than T2¹³⁴. As with T2 sequences, T1 Rho values are highest at the articular surface¹³⁵ and increase with cartilage degeneration¹³⁶. T1 Rho mapping may be more sensitive than T2 mapping for the diagnosis of early osteoarthritis^{137,138}, although these sequences probably provide complimentary information¹³⁹. Uncertainty remains as to the cartilage properties that determine T1 Rho values. Some studies suggest T1 Rho is responsive to cartilage glycosaminoglycan content¹⁴⁰, whilst others have not shown a correlation with any single cartilage constituent¹⁴¹. Nevertheless, T1 Rho values are higher in the acetabular cartilage of patients with femoroacetabular impingement

compared with healthy controls^{112,135}. These studies also concluded that regional cartilage analysis is more sensitive than global measures in femoroacetabular impingement¹¹². Limitations of T1 Rho mapping include the high specific absorption rate (SAR) that can result in heating of tissues, and this is particularly problematic in the hip due to the deep location of the joint and thin cartilage.

Diffusion-weighted MRI is sensitive to the translational motion of protons through cartilage. The apparent diffusion coefficient is low in healthy cartilage because the diffusion of water molecules is restricted, but increases in degenerate cartilage¹⁴². The sequence may be more sensitive to structural degradation than changes in biochemical composition¹⁴², but further studies are required. Diffusion MRI may provide valuable information for the evaluation of early osteoarthritis¹⁴³⁻¹⁴⁶, however, it remains at an early stage of development for musculoskeletal applications and there are few published clinical studies. The majority of studies to date evaluate cartilage after matrix-associated autologous chondrocyte transplantation (MACT) in the knee¹⁴⁷⁻¹⁵⁰ where a correlation with clinical outcome has been demonstrated¹⁵¹. There are no clinical studies evaluating hip osteoarthritis.

1.5.3 Computerised Tomography (CT)

Computerised tomography (CT) offers excellent three-dimensional assessment of osseous morphology but limited evaluation of soft tissue, and hence is not widely adopted for the diagnosis of early osteoarthritis. When combined with intra-articular contrast, CT can be employed to identify cartilage defects and estimate cartilage glycosaminoglycan content¹⁵². However, MRI has several advantages and permits imaging of all joint structures alongside non-invasive compositional assessment without the need for ionising radiation.

1.6 Biochemical Markers

Biochemical markers can be effector molecules, such as cytokines and enzymes, or extracellular matrix constituents, such as precursors or degradation products of collagen and proteoglycan. Their concentrations reflect tissue metabolism and can be measured in blood, urine, or synovial fluid. The BIPED classification stratifies biomarkers into 'burden of disease', 'investigative', 'prognostic', 'efficacy of intervention', or 'diagnostic'¹⁵³. A plethora of biochemical markers have been proposed, but at present none are sufficiently well validated for use in clinical practice. CTX-II (C-terminal telopeptide of collagen type II) and COMP are markers of tissue degradation and remain the most widely investigated and best performing biochemical markers across all BIPED categories¹⁵³.

'Diagnostic' biomarkers aim to identify patients with pathology. Urinary CTX-II and serum COMP are both raised in patients with osteoarthritis compared with healthy controls^{154,155}. Sensitivity and specificity are poor for all biochemical markers, and inferior to imaging measures. In knee osteoarthritis diagnosed using the Kellgren-Lawrence Score, the area under the curve (AUC) has been reported as 0.70 (95% CI 0.57 to 0.81) for urinary CTX-II, 0.73 (95% CI 0.58 to 0.86) for radiographic JSW, and 0.82 (95% CI 0.72 to 0.91) for MRI measurements. Combining CTX-II with MRI measurements gives an AUC of 0.84 (95% CI 0.77 to 0.92)¹⁵⁶. When measured systemically, biochemical markers may originate from any site, hence their value is limited unless disease is confined to the specific joint under investigation, which in practice is rarely the case. Synovial fluid assays overcome this problem, but are limited by acceptability to patients and the potential absence of an effusion. Recent developments suggest that post-translational protein modification may be joint-specific and this warrants further investigation¹⁵⁷.

The potential value of 'prognostic' biochemical markers is large and may allow the identification of patients most likely to benefit from intervention. Urinary CTX-II and serum COMP perform reasonably well in predicting the incidence and progression of radiographic hip and knee osteoarthritis in longitudinal cohort studies¹⁵⁸⁻¹⁶⁰. The predictive value of urinary CTX-II (odds ratio 3.2) is greater than JSW (odds ratio 1.4), but lower than MRI measurements (odds ratio 4.8). Combining CTX-II with MRI measurements has the greatest prognostic value for structural knee osteoarthritis progression (odds ratio 5.8)¹⁵⁶. Biochemical markers have only shown a limited ability to predict symptoms¹⁶⁰. The interpretation of assay results is limited by an incomplete understanding of the biological activity they signify and whether it is relevant to clinical osteoarthritis¹⁶¹. Further validation is essential given biochemical markers are already used extensively as outcome measures in clinical studies to assess 'efficacy of intervention'¹⁶².

The number of 'investigative' biomarkers has increased rapidly with expansion of the field referred to as 'omics' where biological molecules are characterised and quantified. Interesting findings include a proteomic study of cartilage that identified biomarkers that appear to be joint-specific¹⁶³.

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

1.7 Treatment

Potential strategies for the treatment of early osteoarthritis range from pharmaceuticals to joint preserving surgery (Table 1-1), but no treatment has yet been approved for osteoarthritis prevention by the National Institute for Health and Care Excellence (NICE), Medicines and Healthcare Products Regulatory Agency (MHRA), or the Food and Drug Administration (FDA). These regulatory bodies require evidence of concurrent structural modification and symptom improvement⁶⁹.

An improved understanding of disease pathogenesis and advances in the field of biomarkers offer the potential to identify patients at greatest risk of disease, diagnose the earliest osteoarthritis, and measure treatment efficacy within a short timeframe. This may facilitate a paradigm shift from the treatment of advanced osteoarthritis with arthroplasty surgery to preventative strategies and therapies targeting early disease. The term 'arthrostasis' has been introduced to describe the concept of preventing disease progression¹⁶⁴.

The goal of any treatment should be to improve pain and function, and this should include future symptoms that may develop in association with structural osteoarthritis. At present, no therapy has demonstrated sufficient effectiveness such that it could be applied to individuals who remain asymptomatic. Accordingly, all interventional studies to date are in symptomatic patients. Strategies adopted for the treatment of early hip osteoarthritis are discussed below, with a focus on the sequelae of cam morphology and femoroacetabular impingement. Interventions are more likely to be effective when addressing the causality, however, this approach is limited by our incomplete understanding of disease aetiology.

1.7.1 Lifestyle Modification

Aetiological factors may be amenable to lifestyle changes. Hip osteoarthritis is thought to arise from the action of hostile biomechanics upon a susceptible joint, with joint biomechanics determined by anatomical and functional factors. It is pertinent that high activity levels during adolescence may promote the development of cam morphology⁴⁶⁻⁴⁸ and activity modification may offer a preventative strategy for hip osteoarthritis. This relationship requires careful elucidation before advising the avoidance of sporting activity given the cardiovascular benefits and the current obesity epidemic.

Activity modification may also offer a role in improving symptoms and preventing the development or progression of osteoarthritis after the development of pathological hip morphology. Given cam morphology can result in osteoarthritis secondary to impaction of the femoral head-neck junction against the acetabular rim^{39,53}, avoidance of activities that exacerbate impingement is likely to be beneficial.

Weight loss in obese patients reduces the risk of developing symptomatic knee osteoarthritis¹⁶⁵ and improves symptoms once there is evidence of disease¹⁶⁶. This may not apply to the hip where obesity confers a far smaller risk of developing osteoarthritis⁵⁸.

1.7.2 Physiotherapy

Physiotherapy is effective at improving symptoms of advanced hip osteoarthritis¹⁶⁷, and abductor volume and function decreases with osteoarthritis severity¹⁶⁸. It also offers therapeutic potential in early hip osteoarthritis, especially in disease arising secondary to cam morphology¹⁶⁹. However, the evidence to date is very limited and it remains unclear which patients are most likely to benefit from physiotherapy intervention and what physiotherapy protocol should be followed. Amongst all published studies, regimes

tend to focus on strengthening core hip musculature and the consensus is that passive range of movement exercises are likely to be counterproductive¹⁶⁹. The goal of physiotherapy should be to reduce the force and frequency of impingement, and as well as improving symptoms, this may also reduce the risk of developing osteoarthritis.

In order to encourage therapy adoption and compliance, a plausible mechanism of action is important. The value of physiotherapy is frequently challenged when the underlying disease aetiology is thought to be structural. A prevalent perception is that pathological anatomy must be corrected. However, hostile biomechanics are both anatomical and functional. Core muscle strengthening may improve posture and reduce pelvic inclination, decreasing the likelihood of impingement during a functional range of motion. Improved movement control may allow the femur to be brought to a stationary position prior to impaction against the acetabulum. Activity modification is likely to be a valuable adjunct with avoidance of movements that bring the hip into an impingement position¹⁷⁰. Clinical tests for hip pain secondary to impingement have limited sensitivity and specificity¹⁷¹, whilst cam morphology on imaging studies may be incidental. It is possible that physiotherapy is beneficial through the treatment of other sources of hip pain.

Robust studies are required to investigate the effectiveness of physiotherapy and activity modification compared with alternative treatment strategies, and to inform efforts to optimise a non-operative protocol. Small cohort studies suggest non-operative measures that include physiotherapy, activity modification, non-steroidal anti-inflammatory drugs, and intra-articular steroid injections may prevent the need for surgery in 39-89% patients over 12-28 months^{172,173}.

1.7.3 Surgery

The aim of joint preservation surgery for early hip osteoarthritis is to correct any pathological anatomy that gives rise to hostile biomechanics and to repair any associated damage to the joint.

Osteoarthritis progression secondary to hip dysplasia is successfully delayed by reorientating the acetabulum. In addition to sustained symptomatic improvement, hip survival rates exceed 80% at 10 years¹⁷⁴. More recently, surgery to recontour the proximal femur or acetabulum has been proposed for patients with symptomatic femoroacetabular impingement with the goal of improving symptoms and preventing the development or progression of osteoarthritis.

In the case of cam morphology femoroacetabular impingement, surgery is performed to re-contour the femoral head-neck junction and restore the concavity, hence preventing impaction against the acetabular rim within a functional range of movement. This may be supplemented by acetabular rim resection if there is overcoverage of the femoral head. The procedure to reshape the hip is termed osteochondroplasty (Figure 1-8).

Symptomatic cam morphology is almost always associated with labral pathology, and in more advanced disease, there may also be acetabular chondropathy adjacent to the site of impingement³⁹. Labral tears are either debrided or repaired, chondral flaps can be excised or secured with fibrin glue, and in the case of full thickness cartilage lesions, cartilage regeneration techniques may be employed, such as microfracture (Appendix A.3).

Surgery for cam morphology femoroacetabular impingement has demonstrated symptomatic benefit beyond five years¹⁷⁵, however, evidence to date is confined to small cohort studies¹⁷⁶. It also remains unclear whether surgery can promote arthroplasty, and

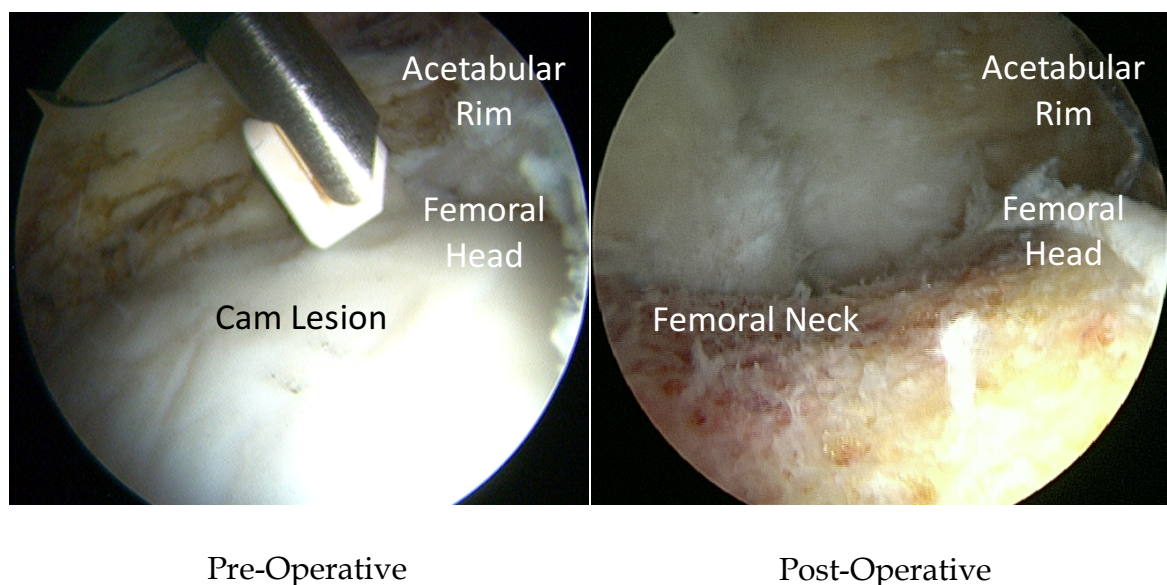
studies have demonstrated progressive radiographic osteoarthritis despite improved post-operative pain and function^{177,178}.

As with physiotherapy, the optimum surgical strategy for the treatment of cam morphology femoroacetabular impingement remains uncertain. Procedures may be performed open or arthroscopically, although most studies report a lower complication rate with arthroscopic procedures and outcomes that are equal or superior to open procedures¹⁷⁹⁻¹⁸². It is also unclear whether labral repair is superior to labral debridement, although studies suggest outcomes may be superior with labral preservation¹⁸³⁻¹⁸⁵. What is clear is that surgical outcomes are worse in the presence of osteoarthritis¹⁸⁶⁻¹⁸⁹.

Randomised controlled trials with long-term follow-up are required to determine whether these joint-preserving operations prevent clinical and structural osteoarthritis progression¹⁹⁰.

Figure 1-8 - Arthroscopic Osteochondroplasty for Cam Morphology Femoroacetabular Impingement

Arthroscopic appearance of the femoral head-neck junction in a patient with cam lesion femoroacetabular impingement before and after surgical correction. The pre-operative image (left) shows the cam lesion adjacent to the acetabular rim, above which a radiofrequency ablation device is held. The post-operative image (right) shows the head-neck junction after resection of the cam lesion using a burr to recreate the normal concavity of a head-neck junction. Modified from Glyn-Jones et al⁸.



1.7.4 Pharmaceuticals

Pharmaceutical agents, especially paracetamol and non-steroidal anti-inflammatory drugs, play a key role in symptom management^{191,192}. Intra-articular steroid injections may also provide a clinically significant short-term improvement in pain, although most studies address patients with advanced osteoarthritis¹⁹³. An increasing number of pharmaceutical agents are also under investigation as potential disease modifying agents (Appendix A.2). Whereas physiotherapy and surgery aim to address the hostile biomechanics, pharmaceutical agents may reduce cartilage susceptibility and promote arthrostasis. Interestingly, the disease modifying effect of doxycycline is negated in knees that are varus aligned²². The optimum treatment strategy for early osteoarthritis may be to combine physiotherapy or surgery that correct hostile biomechanics with pharmaceutical agents that reduce cartilage susceptibility. Nevertheless, no treatment to date has demonstrated the ability to prevent the development or progression of hip osteoarthritis.

Table 1-1- Summary Table of Treatment Strategies with Potential Disease-Modifying Properties**Modified from Glyn-Jones et al⁸.**

CLASS OF INTERVENTION	INTERVENTION	OUTCOME	ADDITIONAL COMMENTS
Lifestyle Modification	Weight Loss ^{165,166,194,195}	Symptom improvement and reduced risk of developing symptomatic osteoarthritis. MRI and biochemical marker evidence of structural modification.	Potential role as primary prevention strategy.
	Exercise ¹⁹⁶ (Strength and Aerobic Capacity)		
Surgery (i) Modification of joint biomechanics	Peri-Articular Osteotomy ^{174,197} (Correct mechanical axis of knee or orientation of acetabulum)	Established technique for improvement of symptoms and probably joint survival.	Recent studies suggest potential for cartilage regeneration after these procedures.
	Debridement of FAI lesions ¹⁹⁸	Symptom improvement sustained beyond five years.	Small cohort studies only. Structural modification not yet demonstrated. RCTs underway.
	Joint distraction ¹⁹⁹ (6 -12 weeks)	Sustained symptomatic improvement with evidence of cartilage regeneration.	Best evidence to date that cartilage can regenerate in an osteoarthritic joint.
(ii) Regenerative Techniques	Microfracture of Subchondral Bone ²⁰⁰	Modest improvement in pain and defect filling.	Produces mechanically inferior fibrocartilage rather than hyaline cartilage.
	Cell Based Therapies ^{200,201} (Autologous Chondrocyte Implantation)	Modest improvement in pain and defect filling.	May provide more durable repair tissue than microfracture but further studies required. Technique expensive.
Pharmaceutical: (i) Targeting Cartilage Degradation	Glucosamine and Chondroitin ²⁰² Hyaluronic Acid ²⁰³	Meta-analyses fail to demonstrate improvement in symptoms or structure over placebo.	Conflicting results from different studies.
	Doxycycline ²⁰⁴	Structural modification but no symptomatic benefit.	Limited by side effects
	FGF-18 (intra articular) ²⁰⁵	Structural modification but no symptomatic benefit.	Primary outcome measure of structural change in medial compartment not demonstrated.
(ii) Targeting Bone Remodelling	Strontium Ranelate ²⁰⁶	Improvement in symptoms and structure.	Limited by side effects.

1.8 Conclusions

An improved understanding of osteoarthritis aetiology and pathogenesis yields an increasing array of potential targets for preventing disease development and progression. Advances in the field of imaging and biochemical markers may facilitate the application of proposed interventions by allowing the diagnosis of early and potentially reversible disease and measuring treatment efficacy within short timeframes.

Joint preservation strategies are most likely to be successful when addressing specific disease phenotypes and their underlying aetiology¹⁵. The majority of hip osteoarthritis appears to arise secondary to developmental dysplasia or cam morphology³¹. These result in a reproducible pattern of joint degeneration that commences in the superolateral acetabulum³⁸. Osteoarthritis arising secondary to cam morphology is the focus of this thesis.

The proposal that cam morphology forms during adolescence in response to intense sporting activity raises the exciting possibility of preventing the development of adverse joint biomechanics. Once cam morphology has developed, improvements in the accuracy of predictive models and performance of diagnostic tools may permit selection of minimally symptomatic individuals for early intervention. Treatment strategies aimed at joint preservation in individuals with cam morphology include lifestyle modification, physiotherapy, pharmaceuticals, and surgery.

The treatment of early osteoarthritis when patients remain minimally symptomatic requires that interventions have proven efficacy and an acceptable adverse event profile. Surgery is therefore currently reserved for symptomatic patients, however, this may change as further research allows more accurate patient selection and optimisation of treatment regimes. Combined treatment modalities may prove more effective by addressing both hostile biomechanics and cartilage susceptibility.

1.9 Thesis Aims and Objectives

This thesis aims to explore different strategies for the prevention of hip osteoarthritis secondary to cam morphology and address some of the barriers to their implementation.

Critical challenges for the development of preventative strategies are:

- i) The aetiological factors that are responsible for the development of cam morphology are not well understood
- ii) It is not possible to identify which individuals with cam morphology will develop future osteoarthritis
- iii) The optimal management option for patients with symptomatic cam morphology femoroacetabular impingement is not known

The following studies have been designed to address certain aspects of these challenges:

Chapter 2:

Aim: Evaluate different methods of quantifying cam morphology and osteoarthritis.

A multitude of measurements have been described and applied to diverse imaging modalities. Measurements that demonstrate the greatest validity and reproducibility in published literature to date will be selected and adopted as outcome measures for subsequent studies within this thesis. Intra-observer and inter-observer reproducibility will be evaluated for measurements performed within each study.

Chapter 3:

Aim: Characterise aetiological factors responsible for cam morphology development.

The aetiology of cam morphology remains uncertain, but recent studies suggest it may be associated with vigorous sporting activity during adolescence. Should this prove to be the case, it may be possible to reduce the risk of future hip osteoarthritis by modifying sporting activities. To explore the effect of physical activity on hip development, hip morphology will be compared between academy football players and controls from local schools in a prospective cross-sectional cohort study of individuals aged 9-18.

Chapter 4:

Aim: Determine whether compositional MRI can predict future hip osteoarthritis.

It may not be feasible to prevent the development of cam morphology, which is prevalent within the adult population. Only a small proportion of individuals with cam morphology develop degenerative disease and it is not currently possible to identify which individuals are at greatest risk of osteoarthritis. This limits the ability to target those most likely to benefit from intervention. Studies suggest that compositional MRI may have prognostic value, and this chapter investigates whether baseline dGEMRIC can predict osteoarthritis development in an asymptomatic population within five years.

Chapter 5:

Aim: Establish national trends in the uptake of arthroscopic hip procedures.

A number of treatment modalities demonstrate the ability to improve symptoms in cam morphology femoroacetabular impingement. Despite the sparsity of evidence for long-term symptomatic benefit or a reduction in the risk of osteoarthritis, hip arthroscopy is

increasingly adopted as routine care to treat femoroacetabular impingement. A search of the Hospital Episode Statistics Database is performed to establish trends in current clinical practice and establish whether there may be an indication for surgical trials.

Chapter 6:

Aim: Determine the feasibility of a clinical trial to establish the optimal treatment of patients with symptomatic femoroacetabular impingement.

The final step of this thesis is a feasibility study for a randomised controlled trial to compare physiotherapy and activity modification with hip arthroscopy for symptom improvement and osteoarthritis prevention in patients with symptomatic femoroacetabular impingement. This randomised controlled trial was subsequently commenced and recruitment finished in July 2016. The protocol is contained within the appendix (Appendix E).

Chapter 2 Quantitative Imaging of the Hip

2.1 Abstract

Introduction:

Studies investigating the development of cam morphology and osteoarthritis require robust outcome measures with good validity and reproducibility. A large number of measures have been adopted in the literature and those reported to perform best have been adopted as outcome measures in this thesis. These are alpha angle to quantify cam morphology, epiphyseal extension ratios to characterise epiphyseal morphology, and joint space width and compositional MRI to evaluate osteoarthritis severity. The aim of this chapter is to refine the outcome measures and determine the reproducibility of each measurement.

Methods:

Readings were performed by two independent observers (clinical orthopaedic research fellows with a specialist interest in hip imaging) and repeated 12 months later. Reproducibility was assessed using intra-class and inter-class correlations and Bland-Altman plots. The smallest detectable difference in measurements was calculated as the standard deviation of the mean difference between intra-observer readings from the same radiograph multiplied by 1.96 (95% confidence interval).

Results:

Intra-class and inter-class correlations were greater than 0.90 for all measurements besides radiographic alpha angle where the inter-class correlation was 0.83. There was no evidence of systematic bias or reader drift during the period of the study. The

smallest detectable difference in joint space width measurements ranged from 0.21mm to 0.41mm.

Conclusions:

The measurements selected as outcome measures all demonstrate excellent reproducibility. Radiographic alpha angles are susceptible to variability given it remains undetermined whether mild asphericity at the superolateral femoral head should be considered as cam morphology. This is not encountered with alpha angles measured on MRI. The smallest detectable differences in joint space width are all smaller than the 0.5mm that is deemed clinically significant. Insight into the strengths and weaknesses of each measurement facilitates the appropriate interpretation of results of future studies.

2.2 Introduction

Robust methods for the quantification of cam morphology and early osteoarthritis are required to study disease pathogenesis and treatment strategies. Measurements must demonstrate validity and reproducibility. Validity refers to the degree with which a measurement reflects the concept under investigation (accuracy). Reproducibility describes variation in repeat measurements and hence the stability and consistency of readings (precision) (Appendix B.1). A range of alternative measurements have been adopted to quantify cam morphology and hip osteoarthritis. These are considered in detail in order to select optimal outcome measures for subsequent studies.

2.3 Assessment of Cam Morphology

2.3.1 Magnitude of Cam Morphology

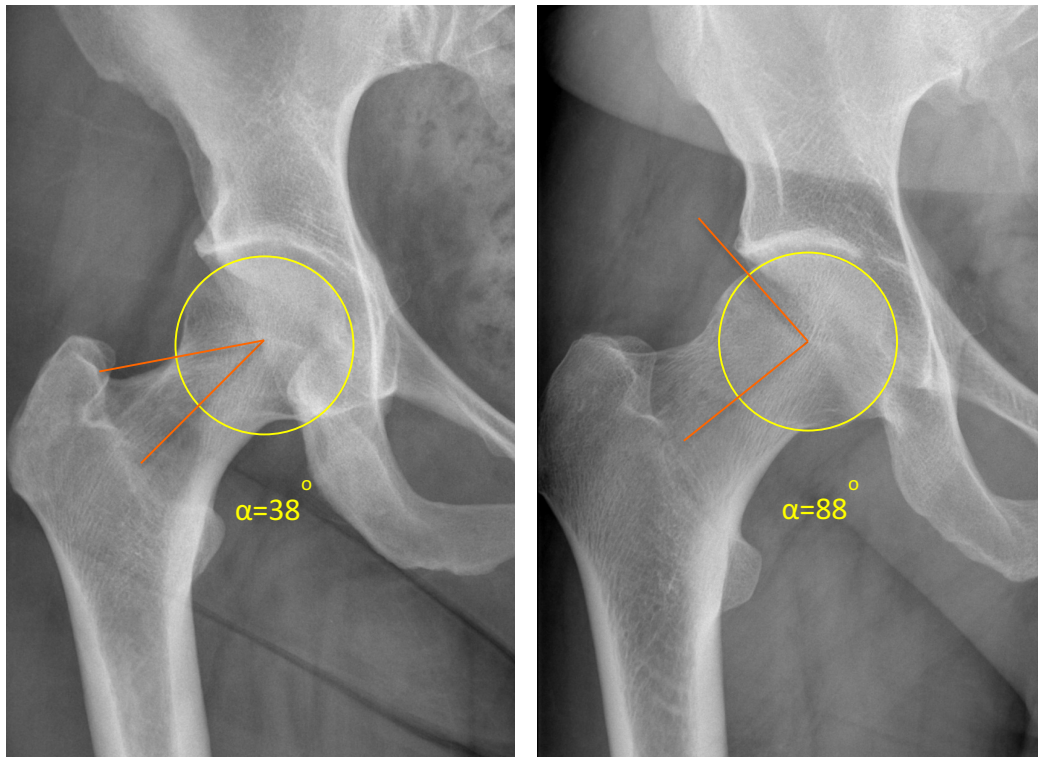
A large number of measurements have been proposed for the quantification of cam morphology and applied to a range of imaging modalities. Cam morphology is most frequently measured on anteroposterior pelvic radiographs due to the availability of this projection in large cohort studies. This projection will therefore be used to illustrate each measurement, however, three-dimensional imaging strategies are more sensitive for the diagnosis of cam morphology²⁰⁷, as will be discussed.

2.3.1.1 Alpha Angle

The alpha angle was first described by Notzli et al²⁰⁸ when the measurement was applied to axial oblique MR images. A line is drawn from the centre of a best-fit circle surrounding the femoral head to the midpoint of a line transecting the narrowest portion of the femoral neck. Another line is then drawn from the centre of the best-fit circle to where the contour of the femoral head first exits the best-fit circle. The angle between

these two lines is denoted the alpha angle and increases with loss of concavity at the head-neck junction²⁰⁸ (Figure 2-1).

Figure 2-1: Normal Morphology and Cam Morphology Alpha Angle Measurements

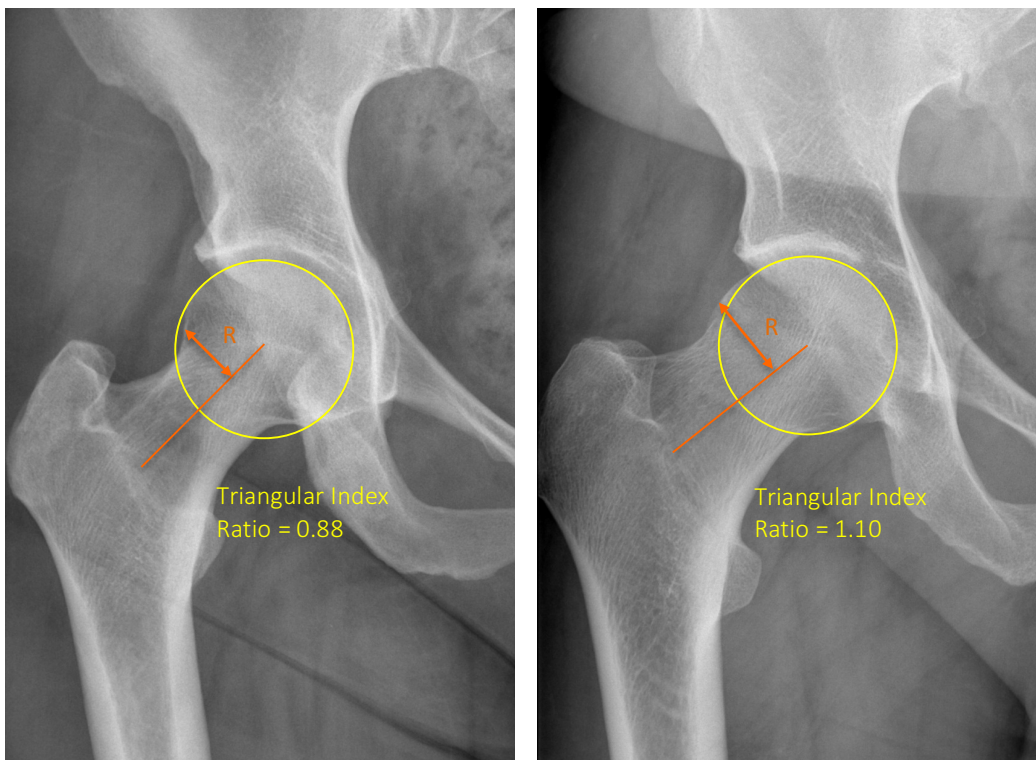


Notzli reported a mean alpha angle of 42 degrees for an asymptomatic control group compared with 74 degrees in patients with clinical femoroacetabular impingement, and suggested that angles greater than 50 degrees were abnormal²⁰⁸. The threshold for defining cam morphology has since been extensively investigated and there is no agreed value. Defining a threshold is further complicated by the application of this measurement to different imaging protocols and different cohorts. The alpha angle has shown variable, albeit satisfactory reproducibility¹⁴. The focus of this thesis is to study hip morphology that predisposes to osteoarthritis. Alpha angle validity is demonstrated by its ability to predict chondropathy²⁰⁹ and future osteoarthritis¹³. It is the most widely used measure of cam morphology in the current literature²¹⁰.

2.3.1.2 Triangular Index

Gosvig proposed an alternative measure of cam morphology denoted as the triangular index²¹¹. To determine this value, a best-fit circle around the femoral head and a line along the femoral neck axis are plotted, as with the calculation of the alpha angle. A point is then marked along the femoral neck axis at one-half radius lateral to the centre of the best-fit circle. From here, a line is drawn perpendicularly to the outer border of the femoral head-neck junction. The length from this point to the centre of the best-fit circle is recorded (R) (Figure 2-2).

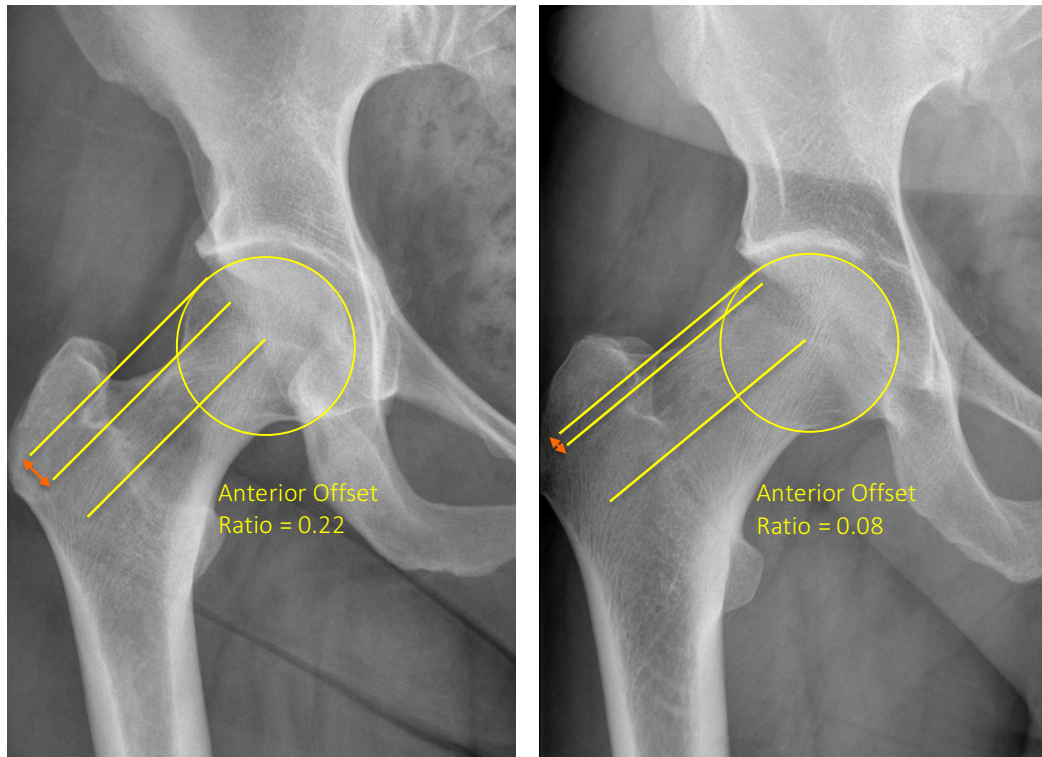
Figure 2-2: Normal Morphology and Cam Morphology Triangular Index Measurements



Gosvig stated that cam morphology is diagnosed when the length of line R exceeds the radius of the best-fit circle by >2mm on a radiograph with 1.2 magnification. It is also suggested that the triangular index is more reproducible than the alpha angle and less susceptible to inaccuracies resulting from variations in hip rotation on both anteroposterior and lateral radiographs²¹¹. The binary outcome that does not account for the size of the femoral head is a significant limitation of this measurement. However, triangular index has also been adopted as a continuous variable by expressing R as a ratio of the best-fit circle radius⁵⁰ (Figure 2-2). Triangular index has not been widely adopted in large longitudinal cohort studies and lacks the validity of alpha angle.

2.3.1.3 Offset

A number of alternative measurements focus on the offset between the femoral head and neck. A reduced head-neck offset is associated with symptomatic femoroacetabular impingement²¹². There are many different measurements of femoral head-neck offset²¹³⁻²¹⁵. The 'anterior offset ratio' (AOR) is frequently adopted^{215,216}. A line is drawn along the central axis of the femoral neck (that does not necessarily pass through the centre of the femoral head) and parallel lines are then drawn along the anterior cortex of the femoral neck and along the most distant portion of the femoral head. The anterior offset is the perpendicular distance between these two parallel lines, and the AOR is calculated by dividing this value by the diameter of the femoral head (Figure 2-3).

Figure 2-3: Normal Morphology and Cam Morphology Anterior Offset Ratio Measurements

Cam morphology is diagnosed if the AOR is less than 0.17^{215,216}. As with most offset measurements, a limitation of this value is the subjective placement of the line along the central neck axis, offering less reproducible readings than the Gosvig ratio and alpha angle²¹⁷. As with the triangular index, offset measurements have not been widely adopted in large longitudinal cohort studies and lack the validity of alpha angle.

2.3.2 Alpha Angle as a Measure of Cam Morphology

Alpha angle is adopted as the primary measure of cam morphology in this thesis given the measurement has demonstrated good validity and reproducibility, and its widespread adoption in the current literature allows comparisons between studies.

However, there is significant variation in how alpha angle is measured, which must be considered during study design and data analysis.

2.3.2.1 Imaging Strategy

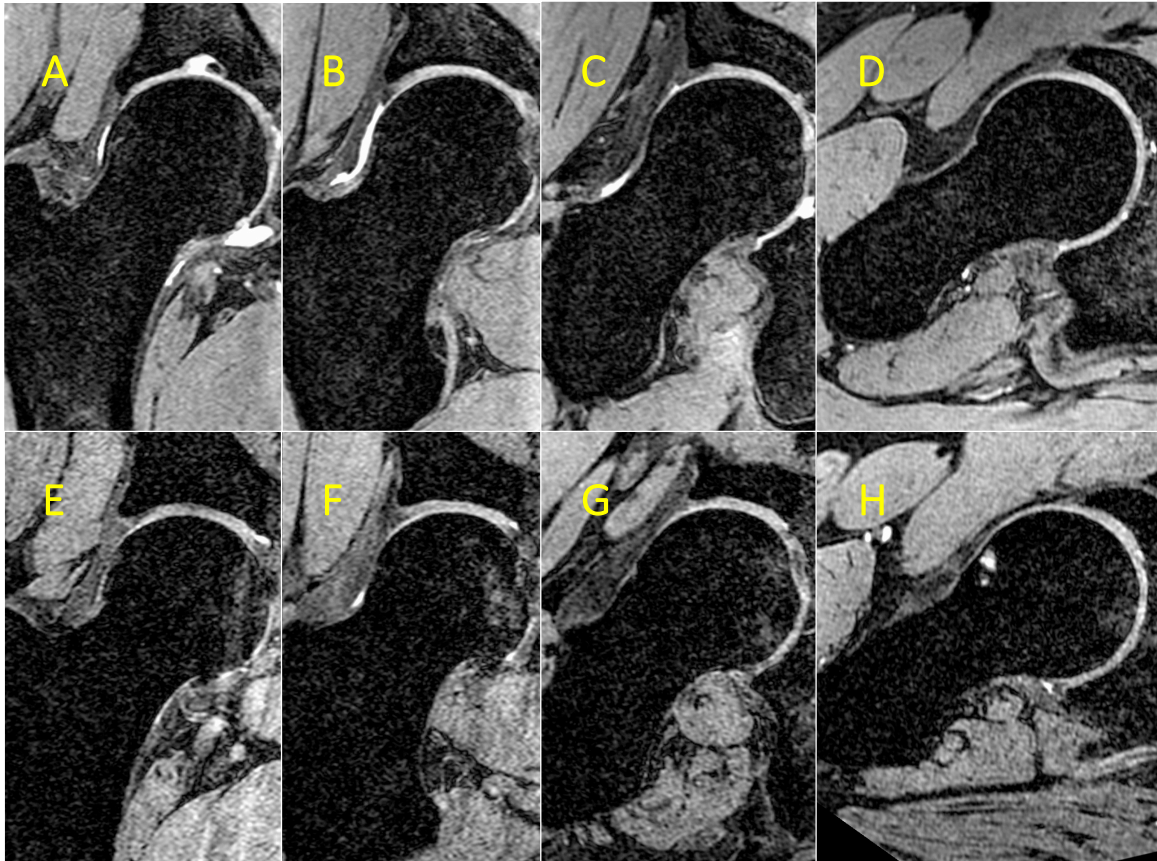
Measurements to quantify cam morphology are sensitive to the imaging strategy employed^{217,218}. Radiography is the most widely adopted modality given it is rapid to acquire images, relatively inexpensive, and readily available. Anteroposterior pelvis radiographs are available for a number of large longitudinal cohort studies^{13,18,50,51} and as a result cam morphology has been most extensively researched with alpha angle measurements on this projection. In a clinical setting, femoral head-neck asphericity is frequently assessed on an anteroposterior radiograph given this is the first-line investigation in most instances of hip pain. However, asphericity may be missed on this view and lateral projections are recommended²¹⁸. Frequently adopted lateral views for imaging the proximal femur include cross-table lateral, Dunn view, and frog-leg lateral. Although the Dunn view in 45 degrees of hip flexion may be slightly more sensitive for the detection of cam morphology²¹⁹, the cross-table lateral view with internal rotation is comparable and positioning is more straight-forward²¹⁸. Intra- and inter-observer reliability is higher for cross-table lateral views, although a higher radiation dose may be required²²⁰. Studies report very conflicting conclusions as to the value of frog leg lateral views for the quantitative measurement of cam morphology^{221,222}. A combination of anteroposterior pelvis and cross-table lateral hip with internal rotation views are the recommended radiographic protocol for clinical investigation of cam morphology²¹⁸. This protocol also allows evaluation of acetabular morphology that is critical for the complete evaluation of femoroacetabular impingement²¹⁶.

Alpha angles may be maximal at the anterior or superior head-neck junction, however, they are most frequently maximal at an anterosuperior location^{53,212,223-225}. As a result,

cam morphology may not be fully visualised when imaging planes are limited to anteroposterior and lateral views²⁰⁷. CT and MRI have been utilised to allow three-dimensional assessment of morphology²²⁶. MRI may be preferred given it does not require ionising radiation and allows simultaneous assessment of the soft tissues such as cartilage and labrum. A disadvantage is that unlike CT, fully automated segmentation of bone morphology is not currently possible. Radial slices around the femoral neck axis allow direct assessment of head-neck morphology at any location. These are described in terms of a clockface with 12 o'clock superior, 3 o'clock anterior, 6 o'clock inferior, and 9 o'clock posterior for both the left and right hip. Radial slices are now considered the optimal method of quantifying cam morphology (Figure 2-4). Relying on only anteroposterior and lateral radiographs may fail to detect asphericity in over a third of cases²⁰⁷. Notzli measured the alpha angle on only an axial oblique MRI and this fails to identify 54% of cases where the alpha angle is raised when considering all radial planes²²⁵. In conclusion, to optimally evaluate cam morphology, a radiographic protocol should include an anteroposterior and cross-table lateral view, and three-dimensional CT or MRI protocols should include imaging in radial planes. An issue that has not been well addressed to date is whether the MRI sequence employed influences cam morphology measurements. Measurements of cam morphology conventionally refer to bone rather than cartilage, although it may be important to also consider overlying cartilage morphology. A 3D gradient-echo water selective (Philips WATSf) pulse sequence was selected to measure cam morphology for the studies described in this thesis, as this provides excellent contrast between bone and cartilage, and good visualisation of cartilage morphology (Figure 2-4).

Figure 2-4 - Three Dimensional MRI of the Hip in Radial Planes

Superoanterior radial MRI planes in a participant with normal hip morphology (A-D) and cam morphology (E-H): 12 o'clock (A&E), 1 o'clock (B&F), 2 o'clock (C&G), and 3 o'clock (D&H). Note loss of head-neck concavity on anterosuperior radial slices (G&H) in the participant with cam morphology and associated impingement cysts on the anterior femoral neck (H).



2.3.2.2 Thresholds to Define Cam Morphology

There are no agreed diagnostic criteria to define cam morphology and this has resulted in a wide range of reported prevalence. Proposed alpha angle diagnostic thresholds range from 50 degrees to 83 degrees^{208,211,217}. These thresholds are frequently based on statistical analysis, for example, 95% confidence intervals or standard deviations away from the mean within a cohort. Other authors have noted a bimodal distribution of alpha angle measurements. In a combined dataset of two general population cohorts consisting of 2005 participants, a normal distribution was noted up to an alpha angle of 60 degrees

on anteroposterior radiographs. It was proposed that this bimodal distribution represented two discrete populations, and that alpha angles above 60 degrees define the presence of cam morphology in both males and females¹⁴. Interestingly, a bimodal distribution is not seen with other measures of cam morphology such as the Gosvig ratio, and this distribution may reflect the measurement tool rather than the pathology.

Alpha angle thresholds derived from statistical analysis may not offer values of clinical relevance, whereas general population longitudinal cohort studies provide insight into values that may represent pathological morphology. The CHECK cohort consists of individuals aged 45 to 65 years at baseline with early symptomatic osteoarthritis of the hip or knee. At baseline, no participant demonstrated radiographic hip osteoarthritis (Kellgren-Lawrence <2). Within 5 years of follow-up, 2.76% had developed hip osteoarthritis (Kellgren-Lawrence ≥ 2) (n=723)¹³. The Chingford cohort consists of a general population cohort of females aged 44 to 67 years at baseline recruited from a General Practice in London. Within 19 years of follow-up, 11% had developed incident radiographic hip osteoarthritis (Kellgren-Lawrence ≥ 2) (n=487)⁵⁰. When these two cohorts were combined, an alpha angle threshold of 78 degrees (95% CI 62 – 87 degrees) on an anteroposterior pelvis radiograph gave rise to the greatest area under the ROC curve at 0.69 (95% CI 0.62 – 0.75) and this was proposed as the threshold for pathological cam morphology in males and females¹⁴. It is likely that this threshold is different for each imaging strategy employed, and radiographs are less sensitive than radial plane MRI for the diagnosis of cam morphology²⁰⁷. Furthermore, the development of hip osteoarthritis secondary to cam morphology is likely to be influenced by a number of factors including activity levels, acetabular morphology, and inherent joint susceptibility⁸. The positive predictive value of cam morphology measured using the alpha angle for the development of osteoarthritis is thought to be as low as 6-25%¹³.

There appears to be dose-response to the magnitude of cam morphology and it may be more valuable to study this relationship than to apply artificial diagnostic thresholds. Prospective study of the Chingford cohort gave an odds ratio 1.05 (95% CI 1.02-1.09) for every degree increase in alpha angle above 65 degrees on baseline anteroposterior radiographs for predicting the development of radiographic osteoarthritis at 19 years.

2.3.2.3 Measuring Cam Morphology in the Adolescent Hip

There are specific challenges to measuring alpha angles in skeletally immature hips. It may not be clear whether changes in hip morphology with age are pathological or represent normal development, and this may only be established by following hips to skeletal maturity. Also, whereas alpha angle is conventionally measured on bone morphology, in developmentally immature hips the secondary ossification centre does not provide an accurate representation of overall hip morphology, which is primarily determined by the epiphyseal cartilage and articular cartilage²²⁷ (Figure 2-5). Alpha angle measurements on articular cartilage rather than bone may be more clinically relevant at all stages of hip development given it is overlying cartilage that abuts the chondrolabral junction in femoroacetabular impingement. In early hip development, bone alpha angles are elevated because the femoral head ossification centre is small relative to the metaphysis. Alpha angle measurements in the FAIM cohort (Chapter 3) demonstrate that this remains the case at the 2 o'clock and 3 o'clock positions at 12 years of age (Figure 2-6 & Figure 2-7). Cartilage alpha angles increase during adolescence at all anterosuperior clockface positions, compatible with the development of cam morphology in a subset of individuals (Figure 2-7). Conversely, bone alpha angles continue to decline between ages 9 and 12 at the 3 o'clock position. Cartilage alpha angles therefore appear to have greater validity over bone alpha angles as a measure of hip shape during development and are selected as the primary outcome measure for subsequent studies in this thesis.

Figure 2-5 - Coronal MRI of Skeletally Immature Hip of a Nine Year Old Male

Morphological measurements of the ossified femoral head may not provide an accurate representation of hip shape in skeletally immature hips



Figure 2-6 - Bone (A) and Cartilage (B) Alpha Angle Measurements at 3 o'clock in Nine Year Old Male

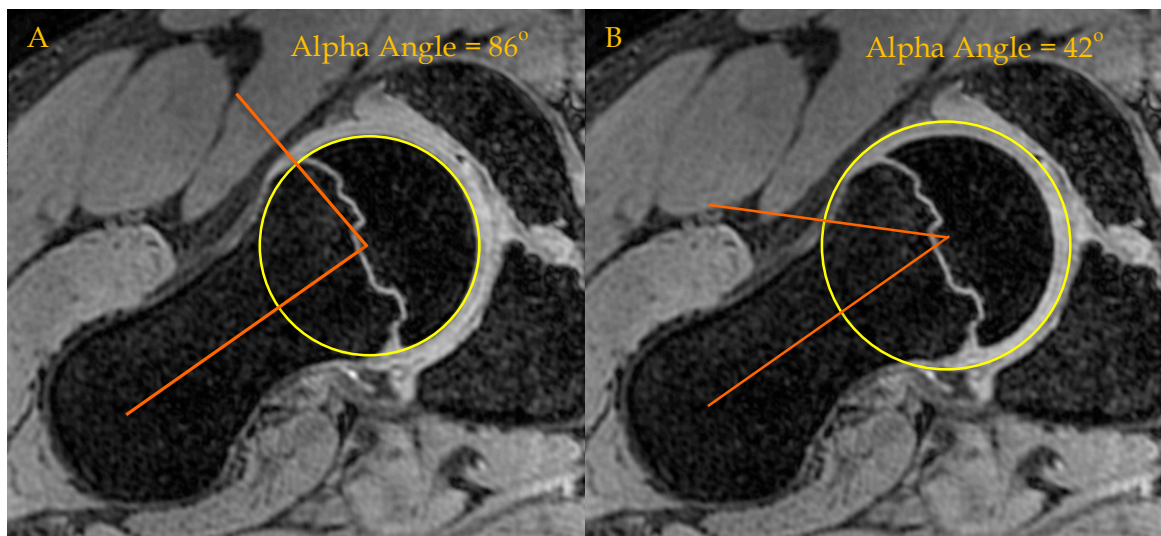
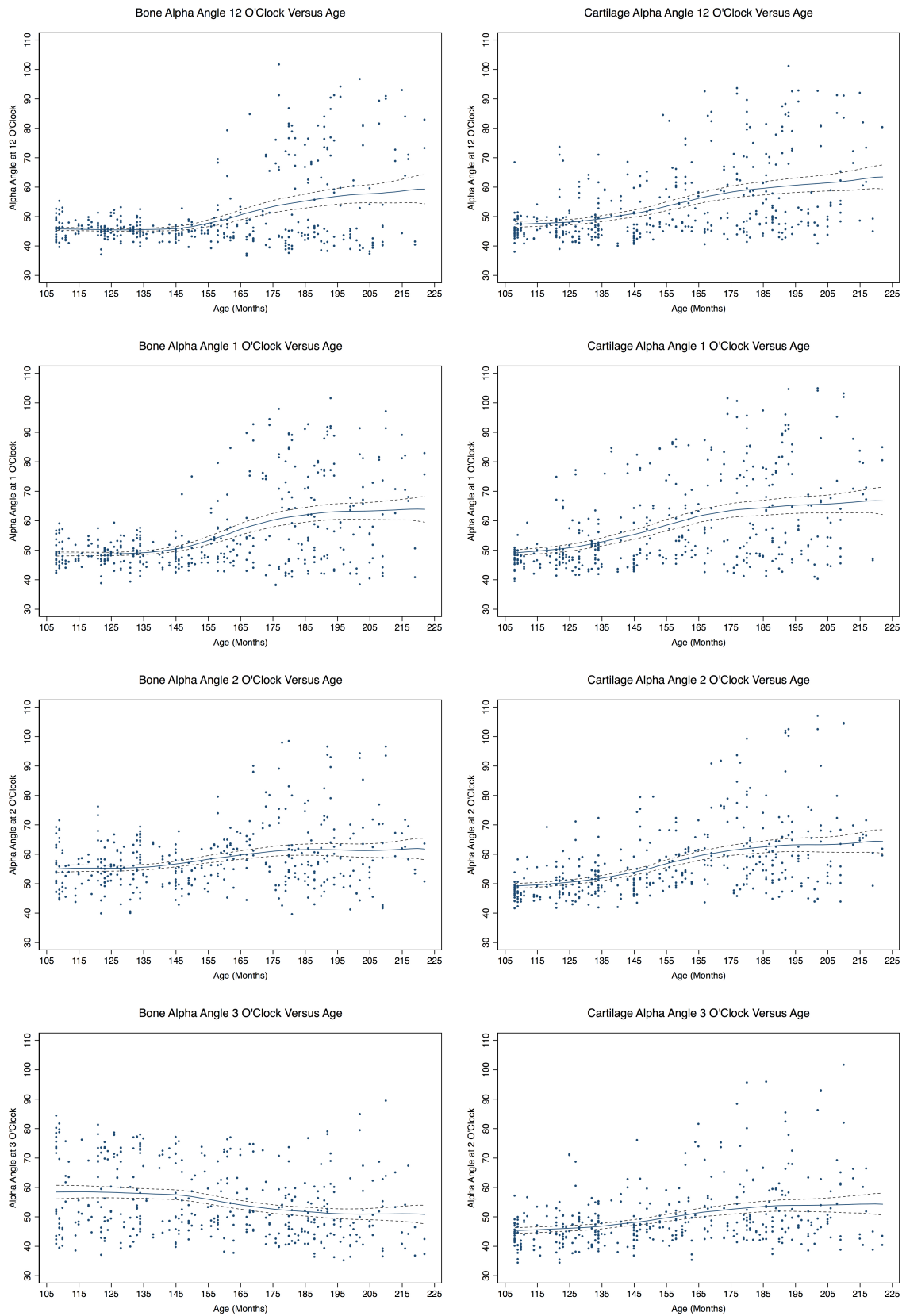


Figure 2-7 - Cartilage and Bone Alpha Angle versus Age in the FAIM Cohort



2.4 Quantification of Physeal Morphology

Epiphyseal extension is proposed as a mechanism of cam morphology development²²⁸, and robust measures of physeal morphology are therefore required. Studies to date quantify epiphyseal extension as the distance from the medial femoral head to the most distal extent of the epiphysis along a line parallel to the axis of the femoral neck (created by a line extending from the centre of a best-fit circle surrounding the femoral head to the midpoint of a line transecting the narrowest portion of the femoral neck) and divided by the diameter of the femoral head²²⁹. This quantitative measurement is termed 'epiphyseal extension' in this thesis. Epiphyseal extension can be measured at each clockface on radial MRI planes (Figure 2-8).

SUFE is also postulated as a potential mechanism of cam morphology development^{32,230-233}. The ratio between epiphyseal extension at opposing sides of the femoral head is termed 'physeal ratio' and is used to quantify physeal tilt (Figure 2-8). Physeal tilt measurements give rise to opposing trends in epiphyseal extension and SUFE (Figure 2-9).

Figure 2-8 - Epiphyseal Extension Measurements at 1 O'Clock Position

12 year old male participants with normal (A) and early cam (B) morphology. Superior epiphyseal extension = $x/\text{diameter}$. Inferior epiphyseal extension = $y/\text{diameter}$. Physeal ratio = superior epiphyseal extension/inferior epiphyseal extension.

A: Superior epiphyseal extension = 0.85 Inferior epiphyseal extension = 0.56 Physeal ratio = 1.52.
B: Superior epiphyseal extension = 1.06 Inferior epiphyseal extension = 0.60 Physeal ratio = 1.77.

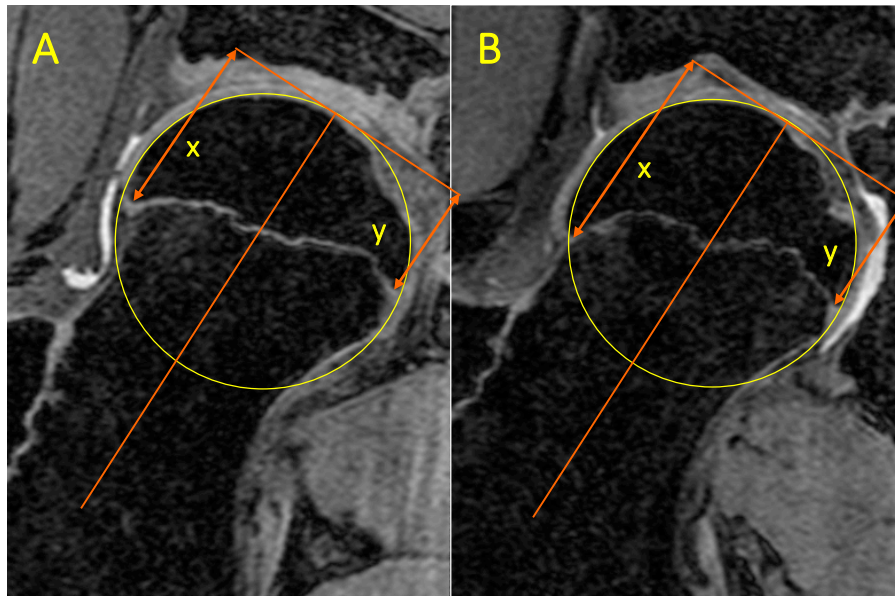
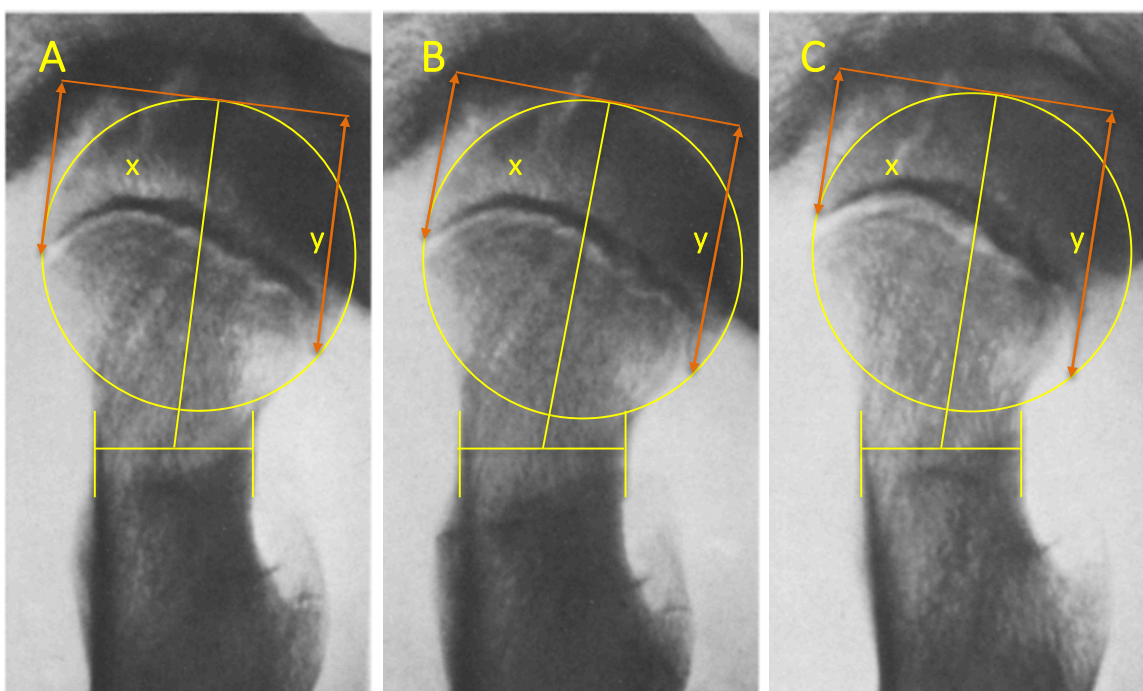


Figure 2-9 - Physeal Measurements on Lateral Radiographs with Increasing Severity of SUFE. Modified from Billing et al 1994²³⁴.

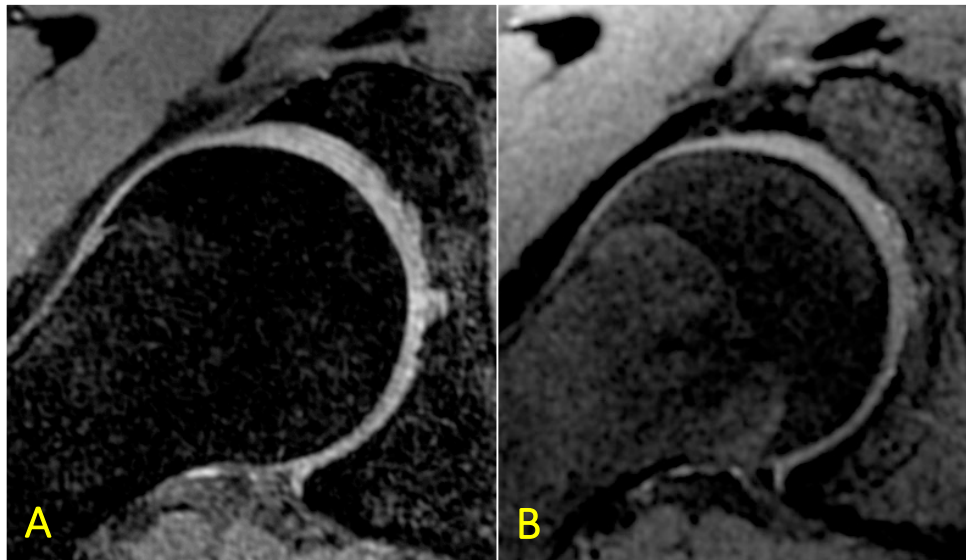
A: Superior epiphyseal extension = 0.56 Inferior epiphyseal extension = 0.80 Physeal ratio = 0.70.
B: Superior epiphyseal extension = 0.49 Inferior epiphyseal extension = 0.76 Physeal ratio = 0.64.
C: Superior epiphyseal extension = 0.43 Inferior epiphyseal extension = 0.73 Physeal ratio = 0.60.



Once a physis is closed it is difficult to define the physeal scar on the gradient-echo water selective (WATSf) MRI sequence, therefore, a 3D proton density with fat saturation (PDFS) MRI sequence was included for the FAIM cohort that explored physeal development (Figure 2-10).

Figure 2-10 - MRI of Skeletally Mature Hip to Visualise Physeal Morphology

3 O'Clock Co-registered WATSf (A) and PDFS (B) MRI



2.5 Assessment of Degenerative Change

2.5.1 Morphological Measures

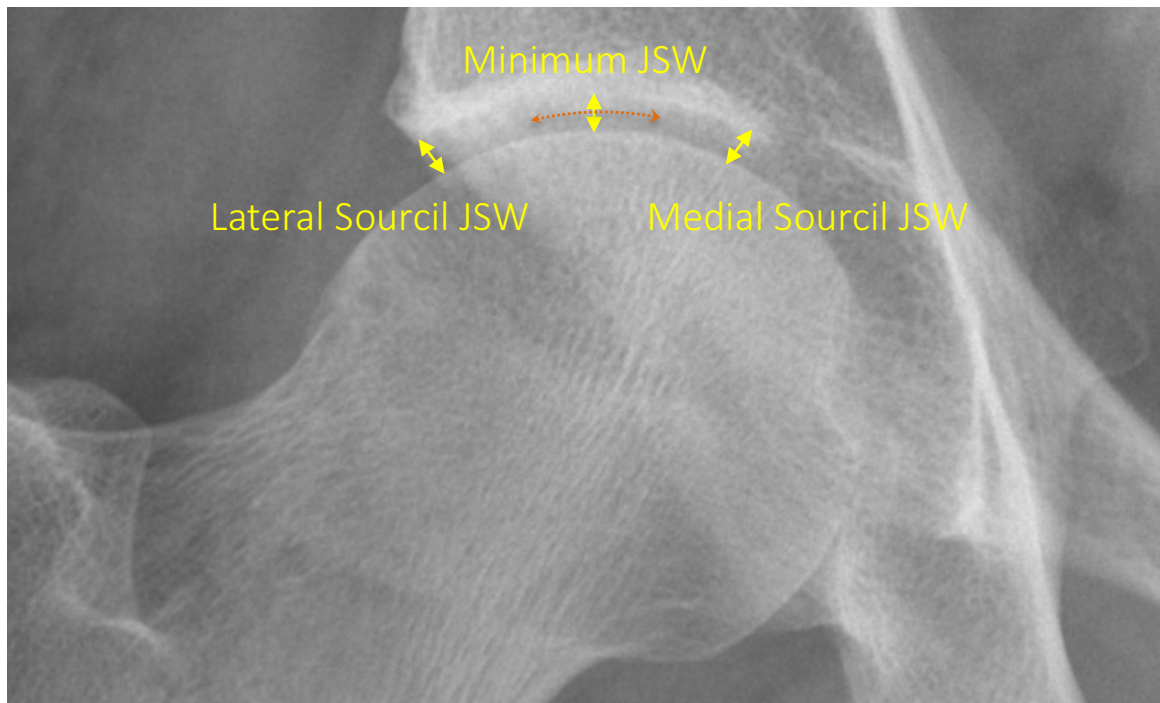
Scoring systems for radiographic hip osteoarthritis include those proposed by Kellgren and Lawrence⁸⁰ and OARSI⁸¹, however, measurement of joint space width (JSW) is more sensitive and reliable^{82,83}. A reduction in minimum JSW greater than or equal to 0.5mm at any position is thought to be clinically relevant^{83,93}. Therefore, osteoarthritis is said to have progressed when the magnitude of change in minJSW is greater than the smallest detectable difference (SDD) of the measurement technique, and becomes clinically relevant at 0.5mm. Measurement error may be minimised by evaluating radiographs side by side²³⁵ but this does not allow blinding when investigating the outcome of surgical intervention. All paired readings within this thesis are therefore read independently.

There are different radiographic patterns to hip osteoarthritis progression, which may result in concentric, superolateral, or superomedial migration of the femoral head relative to the acetabulum^{93,236}. Osteoarthritis secondary to cam morphology initiates within the superolateral acetabulum^{38,39}. A limitation to the minJSW is that it may lack sensitivity to change if measured at a different location on serial images, which is overcome by serial JSW measurements at a fixed location⁹³. In this thesis, in addition to minJSW, JSW is measured at the medial and lateral source for longitudinal imaging studies (Figure 2-11).

MRI is more sensitive than radiography at detecting early structural osteoarthritis⁸⁶⁻⁹⁰ and OARSI recommend MRI for the assessment of cartilage morphology⁶⁹. Quantitative measurements of cartilage morphology require an MRI sequence that allows accurate segmentation of cartilage. Cartilage volume is the most frequently adopted outcome

measure and is able to account for disease heterogeneity. However, morphological MRI does not take account of functional adaptation⁹⁸ or cartilage oedema observed during the very earliest stages of disease⁹⁹. Conversely, compositional MRI offers this potential and is an area of focus within this thesis.

Figure 2-11 - Radiographic Joint Space Width Measurements



2.5.2 Compositional MRI

Compositional MRI is susceptible to a large number of factors that must be controlled during studies. These may include physiological variables such as cartilage loading¹²² or the delivery of contrast to the joint after intravenous administration²³⁷. Analytical factors include the mathematical algorithm used for image analysis. In addition, it may not be possible to compare results between studies due to the heterogeneity of pulse sequences. A further challenge is that, unlike for knees⁹⁴, there is no agreed method of selecting regions of interest in hip cartilage.

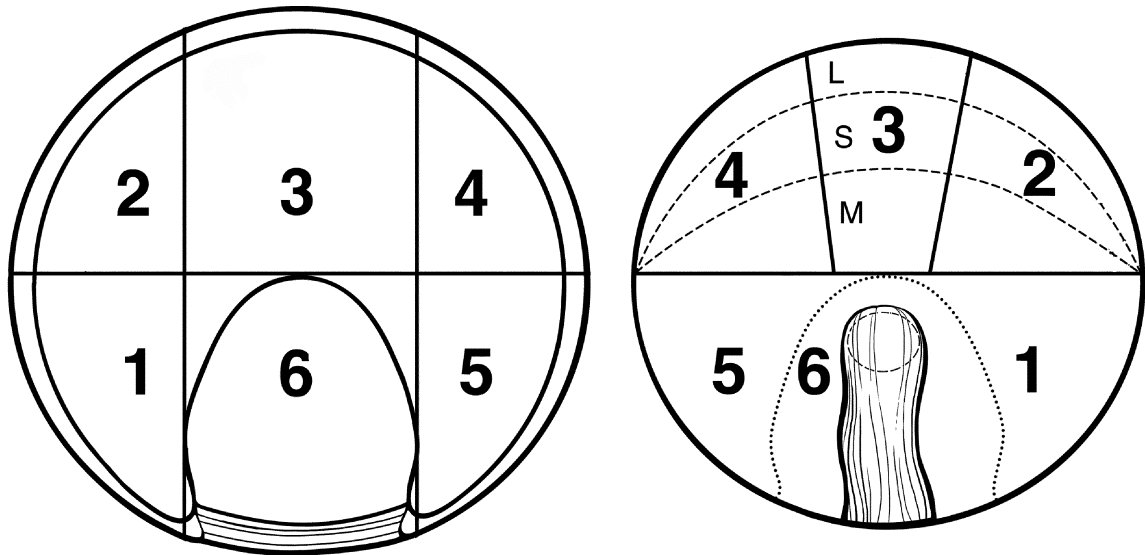
Osteoarthritis does not develop uniformly across the articular surfaces of a synovial joint⁷⁹. Therefore, averaging relaxation times across the entire joint is insufficiently sensitive to detect early disease and regional evaluation is superior¹¹². A systematic and reproducible method of defining regions of the acetabular and femoral cartilage is therefore required. Absolute values from individual regions can be assessed in isolation, or as a ratio to global cartilage values for an individual⁵⁴. This latter approach is preferred since each hip then acts as an internal control for physiological variables.

Several methods have been described for dividing the acetabular and femoral cartilage into regions. To ensure imaging studies are aligned with clinical findings, segmentation schemes are frequently based on maps developed to describe intra-articular pathology during hip arthroscopy. Two main approaches have been adopted in the orthopaedic literature: The 'geographic zone'²³⁸ and 'clock-face'²³⁹ approaches.

The geographic zones are superimposed as two vertical lines either side of the cotyloid fossa and a perpendicular horizontal line positioned at the superior margin of the cotyloid fossa, producing six zones. Corresponding zones are superimposed upon the femoral head where the superior zones are divided into medial (M), superior (S) and lateral (L) regions²³⁸ (Figure 2-12).

Figure 2-12 – Geographic Zones of Right Hip

Modified from Ilizaliturri et al 2008²³⁸.



The clockface zones are orientated such that 12 o'clock is the most superior aspect of the acetabulum and the 6 o'clock position represents the middle of the transverse ligament (Figure 2-13). The 3 o'clock position is always taken as the anterior position, hence the map is inverted for left and right hips²³⁹. The clockface system has also been adapted for the femoral head²⁴⁰ (Figure 2-14).

Figure 2-13 - Clockface Zones of Right Hip

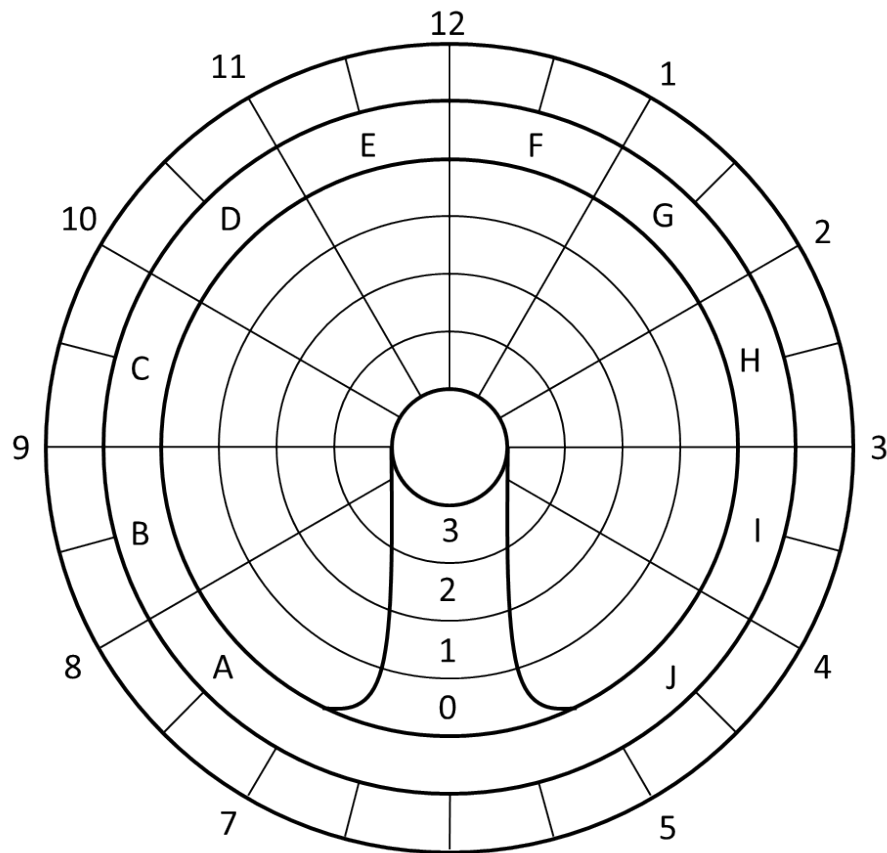
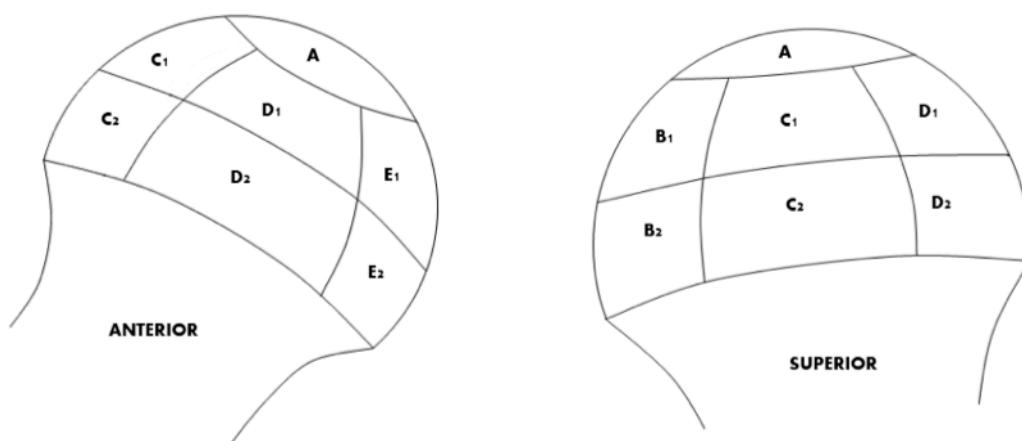


Figure 2-14 - Clockface Scheme for Femoral Head



The geographic zone is proposed to be more reproducible than the clockface approach²³⁸ by selecting intra-articular landmarks that are more easily visible during arthroscopy. However, the clockface system is more widely used in clinical practice and correlates well with the radial planes adopted for the evaluation of cam morphology (2.3.2). The studies in this thesis orientate the 12 o'clock position parallel to the axis of the proximal femoral diaphysis when the patient is supine, whether on the traction table for hip arthroscopy or for the acquisition of MR images.

2.5.3 Compositional MRI Acquisition

There is no standardised approach to compositional MRI acquisition. In order to facilitate correlation between compositional MRI, morphological MRI, and arthroscopic appearances, studies in this thesis acquire two-dimensional images in the true sagittal plane (Figure 2-15). Hips are positioned in 15 degrees of internal rotation and study participants lie supine. This protocol offers a compromise between the anteversion axis of the acetabulum and femoral neck. Femoral and acetabular cartilage is segmented using the clockface approach (Figure 2-16) adopting the following region nomenclature:

Aa Anterior Acetabular Cartilage

ASa AnteroSuperior Acetabular Cartilage

SAa SuperoAnterior Acetabular Cartilage

SPa SuperoPosterior Acetabular Cartilage

PSa PosteroSuperior Acetabular Cartilage

Pa Posterior Acetabular Cartilage

Af Anterior Femoral Cartilage

ASf AnteroSuperior Femoral Cartilage

SAf SuperoAnterior Femoral Cartilage

SPf SuperoPosterior Femoral Cartilage

PSf PosteroSuperior Femoral Cartilage

Pf Posterior Femoral Cartilage

Figure 2-15 - Localiser Images for Compositional MRI Acquisition

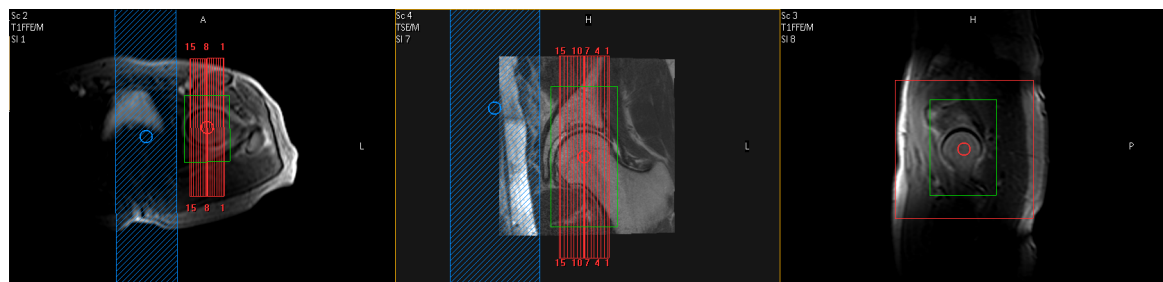
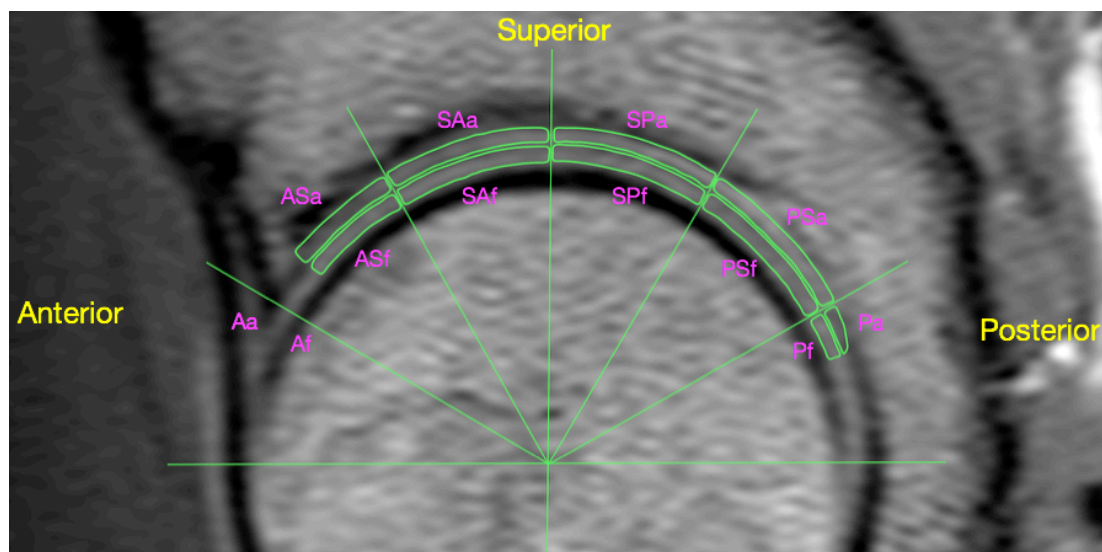


Figure 2-16 - Segmented Regions of Interest on Sagittal Image using Clockface Methodology



2.6 Methods: Reproducibility Studies

Reproducibility was studied for each of the imaging outcome measures adopted in this thesis. Measurements were repeated by the principal investigator (AJRP) 12 months after the initial measurements (intra-observer reproducibility), and also by an orthopaedic clinical research fellow with experience of musculoskeletal imaging research (inter-observer reproducibility). Radiographic reproducibility readings were performed for the entire SibKid Cohort (58 hips) (Chapter 4). Images were selected at random from the FAIM cohort for morphological MRI readings ensuring these included ten hips with an open physis and ten with a closed physis (Chapter 3). Measurements were performed on each hip in five planes, hence there were 100 readings. Compositional MRI reproducibility readings were performed on five MRI slices from five randomly selected hips within the SibKid Cohort, giving rise to 214 regions of interest.

Reproducibility was assessed using intra-class and inter-class correlations (single measures and absolute agreement) and Bland Altman plots. The smallest detectable difference in measurements was calculated as the standard deviation of the mean difference between intra-observer readings from the same radiograph multiplied by 1.96. Statistical analysis was performed using STATA 14.1 (College Station, TX, USA).

2.6.1 Imaging Protocols

2.6.1.1 Radiography

Supine anteroposterior and cross-table lateral radiographs were acquired for the measurement of alpha angle and joint space width (Chapter 4 & Appendix E). Anteroposterior radiographs were performed with study participants weight-bearing. A 20mm calibration was suspended below the pubic symphysis for calibration of JSW measurements. The x-ray beam was centred in the midline and a point midway between the superior border of the public symphysis and a line connecting the anterior superior

iliac spines²¹⁶. With respect to rotation, the radiograph was repeated if the obturator foramen index was outside 0.7-1.4²⁴¹. Cross-table lateral radiographs were performed with study participants supine. The x-ray beam was positioned parallel to the table and orientated 45 degrees to the index hip centred on the femoral head. Each hip was positioned in 15 degrees of internal rotation with the aid of a wedge²¹⁶. Radiographs were analysed using custom-developed OxMorf 2.1.0 software. Alpha angle was measured on anteroposterior and lateral radiographs. Osteophytes were not taken into account when measuring alpha angle. Minimum JSW, and JSW at the lateral and medial sourcil was measured on anteroposterior radiographs.

2.6.1.2 Magnetic Resonance Imaging

MRI was performed on a 3 Tesla Philips Achieva X-series platform (Philips Healthcare, Eindhoven, Netherlands) using either a torso coil (Chapter 3) or two flexible surface coils (medium and large) centred on the femoral head (Chapter 4 & Appendix E). Patients were supine with feet internally rotated 15 degrees using a wedge. Protocols are specific to each study and full details are provided in individual chapters.

Morphological MRI measurements were performed on radial planes. Three-dimensional multi-planar reconstructions created radial slices around the axis of the femoral neck at 30 degree intervals using OsiriX Software (Version 6.0.2 64 Bit, Pixmeo, Geneva, Switzerland). The coronal axis (12 o'clock position) was referenced along the axis of the proximal femur diaphysis. Radial slices were imported into OxMorf 2.1.0 software for the measurement of alpha angle and epiphyseal extension.

Compositional MRI measurements were performed on true sagittal images. Regions of interest were developed based on clockface methodology (Figure 2-16). The most lateral slice selected for analysis was that where femoral and acetabular cartilage was first present in two adjacent regions of interest. The most medial slice selected for analysis

was adjacent to the medial sourcil, hence all segmented cartilage was located within the weight-bearing region of the hip joint. Femoral and acetabular cartilage was segmented separately and cartilage was not segmented beyond where there was adjacent femoral and acetabular cartilage, hence did not include the chondrolabral junction. Average relaxation times were calculated for each region of interest. Quantitative maps were generated using custom code (MATLAB R2015a, MathWorks, Natick, MA, USA) on co-registered images.

2.7 Results: Reproducibility Studies

2.7.1 Alpha Angle (Radiographs)

The intra-observer ICC for alpha angle measured on anteroposterior and lateral radiographs (58 hips) was 0.983 (95% CI 0.971 – 0.990) and the inter-observer ICC 0.830 (95% CI 0.729 – 0.895). Bland-Altman Plots in Appendix B-1 & Appendix B-2.

2.7.2 Alpha Angle (MRI)

The intra-observer ICC for alpha angle measured on MRI radial planes (five planes in 20 hips: ten with open physis and ten with closed physis) was 0.962 (95% CI 0.931 – 0.977) and the inter-observer ICC 0.956 (95% CI 0.935 – 0.970). Bland-Altman Plots in Appendix B-3 & Appendix B-4.

2.7.3 Epiphyseal Extension (MRI)

The intra-observer ICC for epiphyseal extension measured on MRI radial planes (five planes in 20 hips: ten with open physis and ten with closed physis) was 0.976 (95% CI 0.964 – 0.984) and the inter-observer ICC 0.970 (95% CI 0.947 – 0.982). Bland-Altman Plots in Appendix B-5 & Appendix B-6.

2.7.4 Joint Space Width (Minimum)

The intra-observer ICC for minJSW measured on anteroposterior radiographs (58 hips) was 0.990 (95% CI 0.983 – 0.994) and the inter-observer ICC 0.932 (95% CI 0.887 – 0.959). Mean minJSW was 3.79mm (SD 0.98) and the smallest detectable difference was 0.21mm. Bland-Altman Plots in Appendix B-7 & Appendix B-8.

2.7.5 Joint Space Width (Medial and Lateral Sourcil)

The intra-observer ICC for JSW at the medial and lateral sourcil measured on anteroposterior radiographs (58 hips) was 0.993 (95% CI 0.988 – 0.996) and the inter-observer ICC 0.990 (95% CI 0.984 – 0.994). Mean lateral sourcil JSW was 4.75mm (SD 1.27) and the smallest detectable difference was 0.41mm. Bland-Altman Plots in Appendix B-9 & Appendix B-10.

2.7.6 Compositional MRI (dGEMRIC)

The intra-observer ICC for dGEMRIC T1 relaxation time (five hips and 214 regions of interest) is 0.990 (95% CI 0.986 – 0.992) and the inter-observer ICC 0.980 (95% CI 0.974 – 0.984). Mean T1 relaxation time was 457.4ms (SD 83.5) and the smallest detectable difference was 23.8ms. Bland-Altman Plots in Appendix B-11 & Appendix B-12.

2.8 Discussion

Studies investigating the development of cam morphology and subsequent osteoarthritis require outcome measures with strong validity and reproducibility. Outcome measures were selected based on performance in the existing literature as:

- Cam Morphology
 - Alpha Angle
- Pysis Morphology
 - Epiphyseal Extension
 - Physeal Ratio
- Osteoarthritis Severity
 - Joint Space Width (minimum, medial sourcil, lateral sourcil)
 - dGEMRIC Ratio

Reproducibility studies were performed for each of the variables using two readers with favourable results. The reported reproducibility for alpha angle is variable, however, our results are very similar to those reported in large cohort studies^{211,217}. Retrospective clinical studies that do not report the use of specialist methods for measuring the alpha angle describe poor reproducibility²¹³. The custom-designed software used in these studies is likely to have facilitated our strong reproducibility results. A key factor ensuring good intra-observer reproducibility is likely to be reader experience. Strong inter-observer reproducibility is enhanced with training and at least one hundred readings were made under supervision prior to performing independent measurements. This approach may not be feasible when applying measures to the routine clinical setting.

Interestingly, the difference in ICC between intra-observer and inter-observer reproducibility for radiographic alpha angle is primarily explained by the discrepancy in

readings from a single participant (Appendix B-2 & Figure 2-17). Exclusion of this participant in the analysis improves inter-observer ICC from 0.830 to 0.982. Subtle asphericity at the superolateral femoral head is a common feature of anteroposterior radiographs and it remains undetermined whether this should be classed as cam morphology. Whilst the asphericity may sometimes represent osteophyte formation, this is not universally the case. It is noteworthy that this superolateral asphericity is not seen with MRI radial planes and it is therefore likely to be a consequence of projecting a three-dimensional shape onto a two-dimensional image.

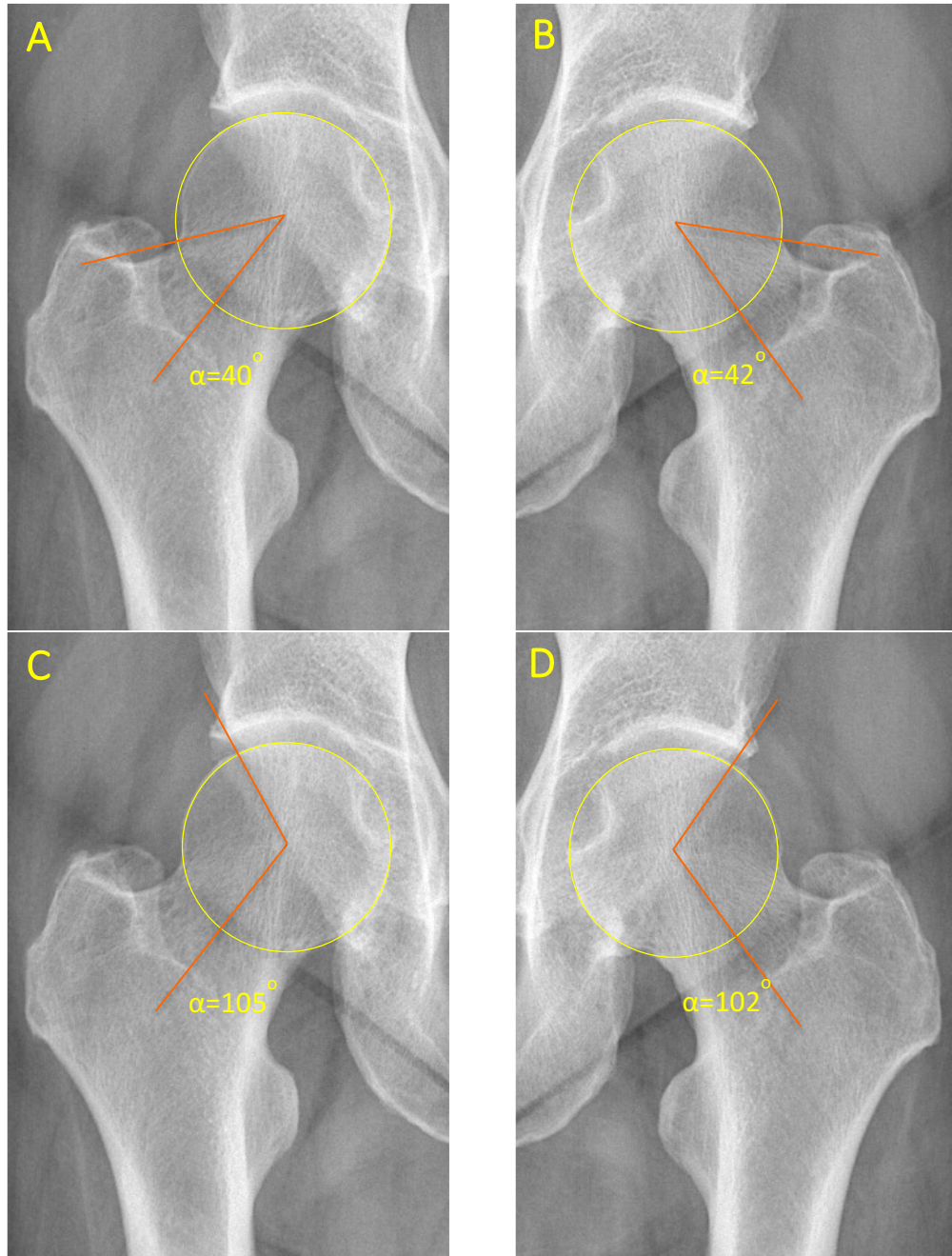
Reproducibility for cartilage alpha angle measured on MRI is also excellent. ICCs are slightly lower than for radiographic alpha angle but with less variability between readings (Appendix B-1, Appendix B-2, Appendix B-3, & Appendix B-4). This results in fewer outliers, but less precision due to a slightly less clearly demarcated interface between the femoral head and surrounding tissues.

The alpha angle threshold for defining cam morphology remains undetermined, particularly for the cartilage alpha angle that has been less widely reported in literature to date. It is also likely that the normal range for alpha angles will be different on each radial plane given the femoral neck is not perfectly cylindrical. It may be more appropriate to treat alpha angle as a continuous variable rather than defining thresholds.

Epiphyseal extension reproducibility compares favourably with similar reported physeal measurements²⁴². Measurements of the physeal scar in hips with a closed physis are technically more challenging, however, using co-registered WATSf and PDFS sequences there is no statistically significant difference in the reproducibility of closed physis measurements compared with open physis measurements.

Figure 2-17 – Inter-Observer Variation in Radiographic Alpha Angle Measurement

Reader 1 (A & B) and Reader 2 (C & D) Measurement of Right (A & C) and Left (B & D) Hips on the Same Anteroposterior Radiograph



The reproducibility of all joint space width measurements was excellent. Inter-observer reproducibility was higher for sourcil measurements compared with minimum joint space width, which is thought to be due to greater consistency in the location of measurement. The smallest detectable difference of minimum joint space width of 0.21mm for minimum JSW and 0.41mm for sourcil JSW is less than the 0.5mm that is thought to represent a clinically relevant change^{83,93}. The greater smallest detectable difference for sourcil measurements is thought to be largely due to the greater joint space width frequently present at the medial and lateral sourcil.

Reproducibility of dGEMRIC values was also excellent and comparable to similar studies^{54,243}. The reproducibility of the area of each region of interest was much less strong, however, this had little impact on the average T1 relaxation time given cartilage values were similar between adjacent regions. Conversely, if any adjacent bone was included within the region of interest, this has a dramatic effect on the average T1 relaxation time given the extremely short relaxation time for bone. Observers therefore made a particular effort to ensure only cartilage was segmented. There was some variation in the reproducibility of different regions of the hip. The lowest reproducibility was within the posterior acetabular cartilage where the region boundary is less clearly defined, however, all ICCs remains above 0.9 (Figure 2-16 & Appendix B-13). The complex protocol and requirement for nephrotoxic contrast may limit the utility of dGEMRIC in clinical studies. Alternative non-invasive protocols such as T2 mapping offer greater feasibility and using the same methodology demonstrate comparable reproducibility with intra-observer ICC 0.975 (95% CI 0.969-0.979) and inter-observer ICC 0.956 (95% CI 0.948 – 0.964) (Appendix B-14).

In summary, all the outcome measures discussed have demonstrated validity in published studies and we have demonstrated excellent intra-observer and inter-observer reproducibility with little evidence of systematic bias or observer drift. Insight into the

strengths and weaknesses of each measurement facilitates the appropriate interpretation of results of future studies.

Chapter 3 Aetiology of Cam Morphology (FAIM)

3.1 Abstract

Introduction:

Cam morphology is increasingly thought to develop during adolescence in association with intense sporting activity. However, evidence to date is inconsistent and not all studies demonstrate differences between elite athletes and control populations. Epiphyseal extension is proposed as a mechanism of developing cam morphology, but studies have only identified a weak association. It remains unclear if exercise volume or intensity is more important and whether there is a safe level of activity. In addition, it is not known whether specific sports result in a greater risk of developing cam morphology. There is a very high prevalence of cam morphology amongst professional football (soccer) players, and this study compares hip development in male academy football players aged 9–18 years from an English Premiership Football Club with an age-matched general population control group of males and females in a cross-sectional study to better understand cam morphology pathogenesis.

Methods:

Academy footballers were randomly selected from each age group and invited to participate in the study (n=103). An age-matched general population cohort of males (n=52) and females (n=55) was recruited through public engagement events. Assessments were performed mid-season and included morphological MRI of both hips at 3T (WATSf). Morphological measurements were performed on 30 degree radial slices using custom-designed software. Cartilage alpha angle and epiphyseal extension were measured to assess cam morphology.

Results:

Alpha angle and epiphyseal extension increased most rapidly between ages 12-14 with no statistically significant increase thereafter. Highest absolute values and the greatest increase in alpha angle and epiphyseal extension were co-localised at the 1 o'clock position. Mean maximum alpha angle in individuals with a closed physis was 80.2 degrees (SD 15.4) for footballers, 77.6 degrees (SD 11.3) for male controls, and 60.6 degrees (SD 11.0) for female controls. Linear regression modelling was used to predict maximum alpha angle with age, sex, and activity level as covariates. Maximum alpha angle increased with age and was 6.7 degrees greater in males than females ($p=0.005$). Compared with individuals who play no regular sport, alpha angles were 4.03 degrees higher in individuals who play sport for a school or club ($p=0.041$) and 7.73 degrees higher in individuals who compete at a national or international level ($p=0.035$). General activity levels measured with the Physical Activity Questionnaire, BMI, leg dominance, and type of sport did not predict alpha angle. There was a strong association between alpha angle and adjacent epiphyseal extension in males ($r^2=0.50$) but not in females.

Conclusions:

Sporting activity during adolescence increases the risk of developing cam morphology. Activity intensity, measured as competitive level, appears to be more important than activity volume, measured using the Physical Activity Questionnaire. The action of kicking a ball was not shown to increase the risk of cam morphology. Although there are many causes of cam morphology, epiphyseal extension is a salient mechanism, especially in young active males. There remains insufficient evidence to recommend activity modification during adolescence at this time and the cardiovascular benefits of exercise are likely to outweigh effects on hip morphology. Athletes may warrant surveillance due to an increased risk of developing cam morphology and osteoarthritis.

3.2 Introduction

The aetiology of cam morphology is not well understood²⁴⁴ and the aim of the Femoro-Acetabular Impingement MRI study (FAIM) is to investigate the pathogenesis of this condition. An improved understanding may aid the development of preventative strategies for hip osteoarthritis. Recent studies suggest that cam morphology may develop in response to vigorous loading of the hip during adolescence, and that activity levels may be a greater determinant of hip shape than genetic predisposition²⁴⁵.

3.2.1 Normal Hip Development

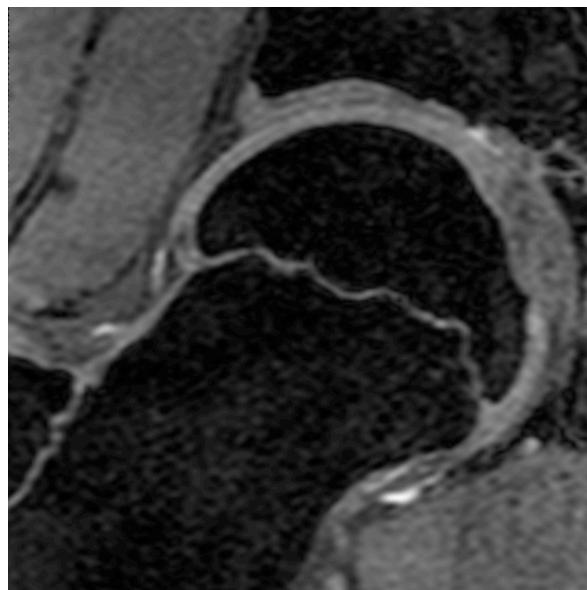
Long bones develop through endochondral ossification, where a pre-existing hyaline structure is replaced with bone, and intramembranous ossification, where bone is deposited directly upon the diaphysis. The first evidence of ossification is seen at eight weeks gestation within the centre of the diaphysis, denoted the primary ossification centre. Secondary ossification centres develop within the epiphysis approximately six months after birth. These ossification centres give rise to two zones of growth: i) The horizontal layer of cartilage that lies between the primary and secondary ossification centres called the physis. This is responsible for longitudinal bone growth. ii) The spherical layer of cartilage that surrounds the secondary ossification centre and gives rise to transverse and spherical growth. This epiphyseal cartilage lies beneath the articular cartilage and is responsible for shaping the articular surfaces (Figure 3-1).

The junction between the metaphysis and epiphysis is of particular interest in the development of cam morphology, as this dictates the shape of the eventual head-neck junction. In the immature hip there is a discrete circumferential fibrochondroosseous structure at this site that consists of the ossification groove of Ranvier and the perichondrial fibrous ring of La Croix. This structure is thought to be responsible for lateral expansion and structural support of the physis. The groove of Ranvier is a wedge

of proliferative cells, whereas the ring of La Croix is an overlying fibrous band that is continuous with the metaphyseal periosteum²⁴⁶. Whether this lateral expansion of the physis takes place by interstitial growth from the physis or appositional growth from the perichondrium have been subject to extensive debate²⁴⁷. Since the physis is wider than the diaphysis, a process of funnelisation is required to maintain the diameter of the diaphysis as it increases in length. During this process, osteoclasts resorb the peripheral metaphyseal bone shortly after it is produced²⁴⁸.

Bone growth is responsive to both physiological and mechanical factors. Interplay between growth hormones and sex hormones regulate chondrocyte proliferation and differentiation, thereby orchestrating bone growth followed by physeal closure during adolescence. Mechanical loading is also recognised as a key factor for normal bone development and chondrocyte mechanotransduction appears to be mediated through their primary cilium²⁴⁹.

Figure 3-1 – Epiphyseal Cartilage and Articular Cartilage



3.2.2 Disorders of the Physis

Many genetic and endocrine conditions disrupt normal bone growth. The physis is also particularly susceptible to traumatic injury given that it lies between the rigid metaphysis and epiphysis. Injuries involving the physis account for between 15% and 30% of all skeletal injuries in children²⁵⁰. A resultant disruption to the epiphyseal circulation may inhibit physeal growth, or if the epiphysis is brought into direct contact with the metaphysis, a bone bridge may result.

SUFE describes a condition where the femoral neck translates anteriorly and rotates externally relative to the femoral head through a cleavage line passing across the proliferative and hypertrophic zones of the physis. SUFE is the most common hip disorder affecting adolescents and the average age is 12 years for males and 11 years for females²⁵¹. Although the majority of cases are deemed idiopathic, risk factors include those that reduce the resistance to shear, such as endocrine disorders, and those that increase stress across the femoral physis, such as femoral or acetabular retroversion²⁵². More than 80% children diagnosed with SUFE are obese, and this probably reflects a combination of endocrine and mechanical predisposition²⁵³.

Sub-clinical SUFE giving rise to a prominent femoral metaphysis has been a widely adopted theory for the development of cam morphology^{32,230-233}. SUFE certainly can be a cause of cam morphology and some authors propose that it may account for up to 44% of cases²³¹ (Figure 3-2). Interestingly the sex ratio of cam morphology is similar to that of SUFE²⁵¹. However, the hypothesis that subclinical SUFE is the dominant aetiological factor for cam morphology has been brought into question by recent studies, such as the absence of posterior tilt on lateral hip radiographs of symptomatic patients with femoroacetabular impingement²²⁸.

Epiphyseal extension along the anterosuperior femoral neck is an increasingly recognised phenomenon in individuals with cam morphology²²⁸ and may represent a distinct pathology that gives rise to cam morphology (Figure 3-3). Epiphyseal extension could be considered an adaptive rather than pathological process and finite element models of the hip show high mechanical stress on impact loading precisely where a cam deformity most frequently develops. Subtle morphological changes in physeal development have been reported in association with many sports²⁵⁴, including the proximal humeral physis in baseball²⁵⁵, suggesting activity levels may represent a key aetiological factor.

Figure 3-2 – AP Radiograph Demonstrating Cam Morphology Secondary to SUFE



Figure 3-3 – AP Radiograph Demonstrating Cam Morphology Secondary to Epiphyseal Extension



3.2.3 Studies Investigating the Development of Cam Morphology

Consistent with a disorder of physeal growth, the prevalence of cam morphology is constant throughout all age groups after physeal closure^{13,256,257}. Studies have therefore focused on morphological changes that take place around the time of physeal closure.

Monazzam et al performed a retrospective study of 225 abdominal CTs of patients aged 2 to 19 with no known orthopaedic hip pathology. Alpha angles were measured at the 3 o'clock position and no cam morphology (alpha angle greater than 55 degrees) was evident between ages 4 and 10²⁵⁸. After 10 years of age, an increasing number of individuals exhibited raised alpha angles with an asymmetrical head neck offset associated with cam morphology. Bixby et al performed a retrospective study of 132 patients who underwent CTs for abdominal pain aged 12 to 18²¹⁴ performing morphological measurements on radial slices. In all planes there was extension of the epiphysis away from the articular surface in patients with a closed compared with an open physis, consistent with normal growth. Average alpha angles were higher and femoral head-neck offsets were lower at the 1:30 o'clock position in patients with a closed compared with an open physis, whilst the opposing trend was observed at all other clockface positions. This emphasises the additional information gained by assessing radial slices. The prevalence and magnitude of cam morphology was greater in males than females.

Kienle et al assessed changes in femoral morphology over 1 year in a prospective MRI study of 64 asymptomatic school pupils aged between 9 and 17²⁵⁹. During the study period, there was no significant increase in alpha angle or head-neck offset on radial slices. In fact, with physeal closure there was a decrease in alpha angle at the 1 o'clock position. Overall, average alpha angle was higher in participants with an open physis compared with a closed physis. However, no individuals with an open physis had an

alpha angle above 55 degrees compared with 8% individuals with a closed physis, adding further weight to the proposal that cam lesion morphology develops around the time of physeal closure. As found in the study by Bixby et al²¹⁴, the epiphysis extended away from the articular cartilage with increasing age until the physis closed. Extension was similar for both sides of the physis, hence the tilt angle did not change, consistent with normal growth. In contrast, Siebenrock et al described localised epiphyseal extension in the anterosuperior position as a cause of cam morphology in patients with femoroacetabular impingement²²⁸.

Sporting activity during adolescence is increasingly implicated in the development of cam morphology, although this was first noted in 1971²³². There is an extremely high prevalence of cam morphology amongst elite athletes. Kapron et al performed radiographs of 67 male collegiate American Football players and 78% displayed at least one sign of cam morphology²⁶⁰. Studies have since looked at changes in hip morphology during adolescence in relation to activity levels. The hypothesis is that increased loading may result in a subclinical SUFE or physeal adaptation that leads to cam morphology.

Carsen et al.²⁶¹ recruited 44 volunteers pre and post physeal closure. This asymptomatic cohort consisted of males aged 10-12 and 15-18, and females aged 8-10 and 14-18. No participant exhibited cam lesion morphology on MRI (alpha angle greater than 50.5 degrees at 3 o'clock) prior to physeal closure whereas 14% displayed cam morphology after physeal closure. The fact that alpha angles were higher after physeal closure is contrary to the CT study of Bixby et al.²¹⁴ and highlights potential differences between cohorts, imaging modalities, and methods of measuring morphology. Daily activity levels were assessed using a validated questionnaire and found to be higher in participants with cam morphology, further supporting physeal loading as an aetiological factor.

Siebenrock et al investigated the development of cam morphology in male ice hockey²²⁹ and basketball players^{47,262}. MRI of 77 elite ice hockey players aged 9 to 36 years of age revealed cam morphology in 6% hips with an open physis and 56% of hips with a closed physis. This is consistent with the age of onset seen in other studies but with a much higher prevalence compared with general population cohorts²⁵⁹. The difference in alpha angle between an open and closed physis was again specific to the radial slice, with increases at the 1 and 2 o'clock positions and decreases at the 9 and 10 o'clock positions. The highest absolute values and greatest change was seen at 1 o'clock. Few studies have assessed symptoms and signs in relation to cam morphology, and a greater increase in anterosuperior alpha angle was seen in symptomatic compared with asymptomatic joints. There was also a statistically significant negative correlation between anterosuperior alpha angles and internal rotation. This raises the possibility of clinically identifying individuals that are developing cam morphology.

To further understand the effect of elite sports on hip development during skeletal immaturity, Siebenrock et al recruited 37 male basketball players aged 9 to 25 and 38 age-matched non-athletic controls⁴⁷. MRI demonstrated that alpha angle was greatest at the 1 o'clock position for athletes but 12 o'clock for controls. Athletes had higher alpha angles throughout the anterosuperior quadrant both pre and post physeal closure, albeit this was more pronounced after closure. Considering pre and post physeal closure alpha angles within each group, there was no statistically significant change in any radial slice for the control group, but a significant increase at 12, 1, and 2 o'clock for the athletes. It is interesting that there was no significant difference at 3 o'clock given other studies have shown an increase in alpha angle at this position in general population cohorts²⁶¹. Considering an alpha angle greater than 55 degrees in any plane, 9% of control hips displayed cam lesions compared with 89% of athlete hips. Later, Siebenrock studied physeal changes in this cohort, excluding those above 22 years of age²⁶². Athletes had

greater epiphyseal extension than control subjects in all positions both before and after physeal closure. However, this difference between groups was smaller after physeal closure, contrary to expectation given cam deformity is thought to develop at the time of physeal closure. Interestingly, there was no difference in epiphyseal extension at the 1 o'clock position between athletes with an open and closed physis, even though alpha angle was highest at the 1 o'clock position. In the control group, there was greater epiphyseal extension in all positions after physeal closure, consistent with the studies of Monazzam²⁵⁸ and Bixby²¹⁴. A possible explanation is that epiphyseal extension takes place earlier in athletes. Overall the correlations between epiphyseal extension and alpha angle were not strong.

A sport attracting particular attention with respect to cam morphology pathogenesis is football (soccer), given it is the most widely played sport in the world. It is hypothesised that kicking places significant stress through the physis, which may affect hip development. The prevalence of cam morphology in football players remains unclear. Gerhardt et al performed anteroposterior and frog-lateral radiographs on 96 elite male and female adult football players and found cam morphology in 68% males and 50% females²⁶³. Using the same radiographic protocol, Johnson et al compared hip morphology of 50 former elite football players with 50 control participants of both sexes and did not find a difference in the prevalence of cam morphology²⁶⁴. Cam morphology was seen in 60% of male subjects and 56% male controls, and 36% female subjects and 32% of female controls. Such a high prevalence in the control group does bring the nature of this group into question.

Also using anteroposterior and frog-leg radiographs, Agricola et al imaged 89 elite youth football players aged 12 to 19 and compared the morphology with control radiographs from a database⁴⁸. Statistical Shape Modelling was used to automatically measure alpha angle and head-neck junction was graded qualitatively. They found that alpha angles

exceeding 60 degrees were already evident at 12 years of age in both athletes and controls, suggesting that morphological changes may start prior to this age. Alpha angles above 60 degrees were present in 26% of football players and 17% of controls, which did not reach statistical significance. Cam morphology did not appear to be related to leg dominance and only limited data were available on activity levels of the control group. The authors followed up 63 of the football players with repeat imaging two years later²⁶⁵. The average alpha angle increased from 59.4 degrees at baseline to 61.3 degrees at follow-up. There was no change in the prevalence of cam morphology based on the alpha angle, but they did report qualitative changes consistent with the development of cam morphology. Whereas the work by Siebenrock et al²²⁹ suggested that epiphyseal extension may precede cam formation, in this study the baseline measures of epiphyseal extension did not predict subsequent cam formation. The significance of epiphyseal extension therefore remains unclear. Nevertheless, in hips without cam morphology at baseline, reduced internal rotation did predict the development of cam morphology at follow-up, hence cartilaginous structures may be present at an early age that later ossify to become a cam deformity.

3.3 Remaining Areas of Uncertainty

The studies discussed above provide valuable insight into the pathogenesis of cam morphology, however, many questions remain. It appears that cam deformities develop near the time of physeal closure, but it is not known at what age changes are first seen. Several studies report that no participants display cam morphology when the physis is open^{259,261}, however, others report cam morphology as early as 10 years of age^{47,258}. Distinguishing normal growth from pathological changes in morphology is a challenge.

The alpha angle is a validated measure of femoral head asphericity that is used extensively in both research and clinical practice²⁰⁸. While most studies demonstrate increasing prevalence of cam morphology as skeletal maturity is reached, some studies demonstrate a fall in alpha angle with advancing age^{214,259}. Alpha angles in the skeletally immature individuals must therefore be interpreted with caution²⁶⁵. All the studies discussed measure the bone alpha angle, however, the ossification centre of the immature hip does not accurately reflect the shape of the cartilaginous femoral head. Cartilage alpha angles should therefore be considered (Chapter 2). Epiphyseal extension may offer a more valid assessment of hip development²²⁸, but the relationship between epiphyseal extension and subsequent cam morphology is not strong in studies to date^{262,265}. The ability to compare cohorts is severely limited by the different imaging modalities, methods of quantifying morphology, and thresholds for pathology.

There is increasing evidence that high activity levels during skeletal immaturity increase the risk of developing cam morphology. However, the nature of the activity that induces cam morphology remains unknown. Football is thought to invoke significant stress across the proximal femoral physis, particularly in the kicking leg, however morphology has not been shown to correlate with leg dominance²⁶⁵. Indeed, studies have not universally demonstrated an increased prevalence in footballers over control groups²⁶⁴, although studies are frequently limited by small sample sizes and the confounding factor that a high proportion of the general population play football during youth. Furthermore, studies in football have all been performed using radiographs, which lack sensitivity for diagnosing cam morphology²⁰⁷. Retired football players have significantly increased rates of hip osteoarthritis than control groups²⁶⁶⁻²⁶⁸, and this may reflect an increased prevalence of cam morphology.

Football players are an excellent population to investigate the pathogenesis of cam morphology for several reasons. First, football is the most widely played sport in the

world, hence findings are likely to be applicable to the general population. Second, members of elite football academies follow an intense training programme from eight years of age. This standardised exercise programme, during which players have limited opportunity to participate in other sports, provides a well-controlled population for study. Third, football clubs continue to increase the duration and intensity of training, and this trend is now being replicated in other sports. This stems from work by Ericsson et al who concluded that many characteristics traditionally believed to reflect innate talent are actually the result of intense practice for a minimum of 10 years²⁶⁹. An extension of this work to football suggests that the discriminating feature between national/international and provincial football players is accumulating 10,000 hours of practice^{270,271}. In theory, the sooner this target is reached, the sooner a player becomes an expert. It is not known whether this intense physical activity during growth is to the detriment of player health.

3.4 Pilot Study

A pilot study was performed to estimate the prevalence of cam morphology in adult football players in order to confirm whether these individuals represent a high-risk population to study cam pathogenesis. MRI scans of senior players from a Premiership Football Club referred for imaging of the hip or groin during the 2011/12 season were analysed. This population consisted of 17 players (33 hips) with a mean age 22 years (range 17–28).

The alpha angle was measured using OxMorf 2.1.0 software on coronal and axial MRI images (Chapter 2). Cam morphology was defined as an alpha angle greater than 60 degrees on either view.

81% players exhibited cam morphology, which was bilateral in 92% of players with imaging of both hips. This represented a symptomatic cohort, and may not be representative of all football players, however, the indication for imaging in the majority of cases was the assessment of an acute muscular injury rather chronic hip pain. The imaging protocol was not optimal for the assessment of cam morphology and radial slices were not available. Cam morphology prevalence is likely to have been underestimated as a consequence²⁰⁷. Conclusions were that the prevalence of cam morphology is extremely high among Premiership Football Players and that this population represents an excellent cohort for the study of cam morphology pathogenesis.

3.5 Aims

- 1) Characterise morphological changes at the physis during cam development
- 2) Explore the age of cam morphology development
- 3) Compare hip development in an athletic and control population
- 4) Compare hip development in male and female participants
- 5) Investigate the influence of activity levels on hip development

3.6 Ethical Approval

Oxford University Medical Sciences Inter-Divisional Research Ethics Committee (MSD-IDREC-C2-2013-11)

3.7 Study Design

The ideal study design is a longitudinal study that allows the assessment of hip development within an individual. However, this requires that a cohort is followed

throughout adolescence and the research questions may not be answered for many years. Therefore, a cross-sectional study was proposed in the first instance, and the cohort will then be followed longitudinally. Longitudinal studies require significant resources and results from cross-sectional data ensure optimal design of the longitudinal study. Hip development in footballers (athletes) was compared with an age-matched general population control group. This thesis reports the study design and results from the cross-sectional element of this research project.

3.7.1 Sample Age and Sex

The chronological age of proximal femoral physis closure is variable and estimated to be an average of 13 years for females and 15 years for males^{272,273}. However, given the decreasing age of SUFE presentation²⁵¹, proximal femoral physeal closure may take place earlier than suggested by historical studies²⁷². This observation is consistent with the decreasing age of sexual maturity²⁷⁴. In a cohort that included both sexes, Kienle et al. reported an average age of proximal femoral physeal closure to be 13.4 ± 1.5 years (range 11-16)²⁵⁹. The criteria used to define physeal closure is also a source of variability.

The development of cam morphology is thought to commence around the time of physeal closure. Several studies report the absence of cam morphology whilst the physis remains open^{259,261}, however, others report cam morphology as early as ten years of age^{47,258}. Therefore, the youngest age group in this study was selected as nine years. Football players sign with a club and commence standardised training aged eight years and clinical experience has shown that patients below this age are less tolerant of MRI. The upper age was selected as 18 years as at this age all participants would be expected to have reached lower limb skeletal maturity²⁷².

In order to compare hip development in females and males, the general population cohort includes both sexes. The well-documented differences in the prevalence of cam

morphology between males and females may reveal valuable insights into the pathogenesis. Although participation in female football is growing rapidly worldwide, there is not yet equality with respect to player development. The footballer (athlete) cohort therefore includes only males, however, the Premiership Football Club where this study was carried out will have their first intake of female academy players in 2016, allowing subsequent extension of this study to include female footballers. The high injury rates reported in adolescent female footballers is a particular concern and an area of current research²⁷⁵.

3.7.2 Sample Size

All calculations were performed for a statistical significance of 5% and power of 80% using a two-sided t-test. The primary outcome measure was maximum alpha angle at the anterosuperior femoral head-neck junction measured on MRI radial slices. For the purposes of sample size calculations, only one hip was considered for each participant. The desired detectable difference and standard deviation are based on comparable cohorts.

In order to investigate the age of cam morphology development, the study sought to detect differences in alpha angle pre and post physeal closure in an athlete cohort and a general population control cohort. The smallest change in alpha angle is reported in control populations and Carsen et al. found a mean change of 4.85 degrees and a maximum standard deviation of 7.05 degrees²⁶¹. Calculations reveals 35 participants are required either side of physeal closure for each study population. Furthermore, 35 participants should be followed-up until after physeal closure for the longitudinal portion of this study.

This study also aimed to investigate differences in the alpha angle between the athlete cohort and general population controls. When the physis is open, Siebenrock et al. found

a mean difference of 6.2 degrees between athletes and controls and a maximum standard deviation of 7.4 degrees. Once the physis had closed there was a mean difference of 16.9 degrees and a maximum standard deviation of 7.6 degrees⁴⁷. This is comparable to the reported 15 degree expected difference in alpha angle between patients with cam morphology and normal morphology²²⁴. Calculations reveal 24 participants are required pre-physeal closure in each cohort, and 5 patients post-physeal closure in each cohort. Siebenrock et al. excluded symptomatic individuals from their control cohort, which is not the case in this study, hence a greater number of participants may be required.

3.7.3 Study Population

The study design offers three cohorts to investigate cam lesion pathogenesis with the intention of extending the study to female footballers in the future. These groups are male footballers (athletes), male controls, and female controls. Participants were recruited from the age of 9 to 18. Taking into account the sample size calculations, expected age of physeal closure, and available resource, adequate power was anticipated with a male athlete cohort of 100 and a general population cohort of 50 males and 50 females (Table 3-1). Cohorts were loaded for younger age groups to: i) Ensure an adequate number of individuals have an open physis to satisfy the power calculations. ii) Enhance the longitudinal component of the study as drop-out rates can be as high as 30% in athletic cohorts due to national and international relocation to continue their careers²⁶⁵. This is more common in players over the age of 16 on completion of their education.

Table 3-1 - FAIM Recruitment Target

Age	Number of Participants		
	Athletes	Controls	
	Male	Male	Female
9	20	10	10
10	20	10	10
11	10	5	5
12	10	5	5
13	10	5	5
14	10	5	5
15	10	5	5
16-18	10	5	5
Total	100	50	50

3.7.4 Inclusion and Exclusion Criteria

Inclusion criteria were solely whether or not a participant was a member of a target population. Since a control group was sought that represented an accurate cross-section of the general population, it was accepted that this group might also contain some academy football players and high-level athletes.

To ensure a representative cohort of athletes and general population controls, the only exclusion criteria were previous hip surgery, because prior procedures are likely to influence hip development, contraindications to MRI, and an inability to provide informed consent.

3.7.5 Recruitment

3.7.5.1 Athletes

The study was performed in collaboration with Southampton Football Club. Academy players train in an age group defined by whether their birthday falls before or after 31st August. An Under 10 player was born before 31st August 2004. Participants were recruited in relation to their team rather than chronological age to facilitate the scheduling of assessments and to minimise disruption to their football training and education. The football club allocated every academy player a study ID and provided the research team these IDs and the team to which each player belonged. This ensured no personal details were shared prior to a player consenting to participate in the study. Study IDs by team were entered into STATA 14.1 (College Station, TX, USA) in ascending order. Each ID was assigned a random number based on a uniform distribution with range 0-1 and a seed on 17051982. These random numbers were then placed in ascending order within each team and the first 10 or 20 IDs were invited to participate (Table 3-1). These IDs were passed onto the football club, who provided invitation packs to the selected players to take home to their parents. When a player declined participation, the next ID from that age group was selected.

Individuals under 16 years of age required written consent from parents in order to participate. Since academy football players often reside large distances from the club, living with host families for training days, it was not always possible to arrange face-to-face meetings with parents. The invitation pack included an invitation letter, participant information sheet, MRI safety form, consent form (with example of completed form), and a stamped addressed envelope for return. Queries were addressed through e-mail or telephone communication. Participants were also able to hand completed packs to staff at the football club.

3.7.5.2 Controls

Permission was sought from local schools to recruit a control population. A variety of forums were used to advertise the study, from delivering assemblies at schools, setting up stalls at parent-teacher meetings, and placing study information in newsletters. Emphasis was placed on explaining that individuals of all activity levels were sought, and that the primary aim was to understand how hips develop. A concern was that the collaboration with a football club might bias control groups towards more active individuals. At engagement events, interested parents were handed an invitation pack. The newsletter text contained a phone number and e-mail address that interested parties could use to request an invitation pack.

3.7.6 Patient and Public Involvement

An essential issue to address with this research design was the potential impact of the results on player careers. If a football club is informed of previously undiagnosed pathology, the earning potential of a player may be adversely affected. Conversely, awareness of pathology might allow the football club to modify training or provide tailored strength and conditioning exercises to the benefit of a player. Therefore, the opinion of players and their parents was sought on how the data should be managed at parent engagement events organised by the football club. In total, the project outline was presented to 50 parents, and their ideas and concerns were sought. There was unanimous agreement from parents that the future health of their children outweighed future earning potential. As a result, very few had an objection to sharing all player data with the football club. The research team held reservations given the significance of many potential MRI findings, such as mild dysplasia, is not known in the context of footballer performance during their playing years. The approach was therefore to only pass on information relating to the presence and magnitude of cam lesion morphology

to the club medical team. The consent form included a statement asking whether or not participants were agreeable for details of their hip shape to be passed onto the football club. This required a 'yes' or 'no' response, and participants who declined the release of this information remained welcome to participate in the study. The justification for passing on information relating to cam morphology was that the prevalence amongst footballers is expected to be very high, and should a player develop symptomatic femoroacetabular impingement, physiotherapy is an effective management strategy¹⁶⁹. Team coaches and club management who oversee player transfers did not have access to study data.

3.8 Questionnaire

Participants completed a questionnaire on the day of assessment. Younger participants received assistance from parents and guardians, and if they were not present for the assessment, arrangements were made to complete the questionnaire during the preceding week.

3.8.1 Patient Demographics and Past Medical History

The following information was collected:

Demographics:

- i) Date of Birth
- ii) Sex
- iii) Dominant Hand
- iv) Dominant Leg
- v) Weight
- vi) Height
- vii) Ethnicity

Past Medical History:

- i) Medical Conditions
- ii) Menstrual history (if female)
- iii) Medications
- iv) Supplements
- v) Musculoskeletal History
 - a. Legg-Calve-Perthes, SUFE, Avascular Necrosis, or Dysplasia
 - b. Surgery
 - c. Fractures
 - d. Acute injuries in past year (unable to play sport for more than 2 weeks)
 - e. Chronic injuries in past year (modified activity for more than 4 weeks)

3.8.2 Activity Levels

Academy football players commence intensive training at eight or nine years of age and follow a standardised age-specific training programme. Their principal playing position was documented. The control population was expected to include a wide range of activity levels. Accurate quantification of sports and exercise is challenging and this study used the validated Physical Activity Questionnaire for Older Children (PAQ-C) and for Adolescents (PAQ-A)²⁷⁶. This collects data on sport and exercise undertaken during the last seven days to provide an estimate of physical activity levels. It offers the potential to differentiate between active and inactive children, but does not provide a measurement of duration, frequency, or intensity²⁷⁷. Participants were asked to complete this to reflect an average week during the current or most recent school term.

An estimation of the intensity of exercise undertaken was obtained by recording participation in competitive sports using a three tier classification. This is referred to as 'Activity Level':

1 = 'No Sport' No regular sport besides physical education classes at school

2 = 'Sport' Regularly play for school or club team

3 = 'Athlete' Compete at national or international level

3.9 Imaging

3.9.1 MRI Protocol

MRI scans were performed on a 3 Tesla Philips Achieva X-series platform (Philips Healthcare, Eindhoven, Netherlands) using a torso coil centred on the femoral heads. The right hip was imaged first in all participants. Two morphological sequences were used (Chapter 2):

- 1) 3D Water Selective Fluid (WATSf) to image joint cartilage and bone:

Repetition time (TR) 13.65ms, echo time (TE) 6.9ms, flip angle 30 degrees, bandwidth 145Hz/pixel, field of view 150mm x 150mm x 70mm, acquisition matrix 248 x 188 x 88 (interpolated to 512 x 512 x 175), averages 2, acquired in true sagittal orientation.

- 2) 3D Proton Density Fat Saturation (PDFS) to image the physeal scar and labrum:

Repetition time (TR) 1300ms, echo time (TE) 40ms, flip angle 90 degrees, bandwidth 243Hz/pixel, field of view 140mm x 140mm x 65mm, acquisition matrix 216 x 216 x 100 (interpolated to 224 x 224 x 100), averages 2, acquired in true sagittal orientation.

3.9.2 MRI Multi-Planar Reformat

Three-dimensional multi-planar reconstructions were performed using OsiriX Software (Version 6.0.2 64 Bit, Pixmeo, Geneva, Switzerland). Radial slices were acquired around the axis of the femoral neck at 30 degree intervals. The coronal axis (12 o'clock position) was positioned parallel to the axis of the proximal femur diaphysis.

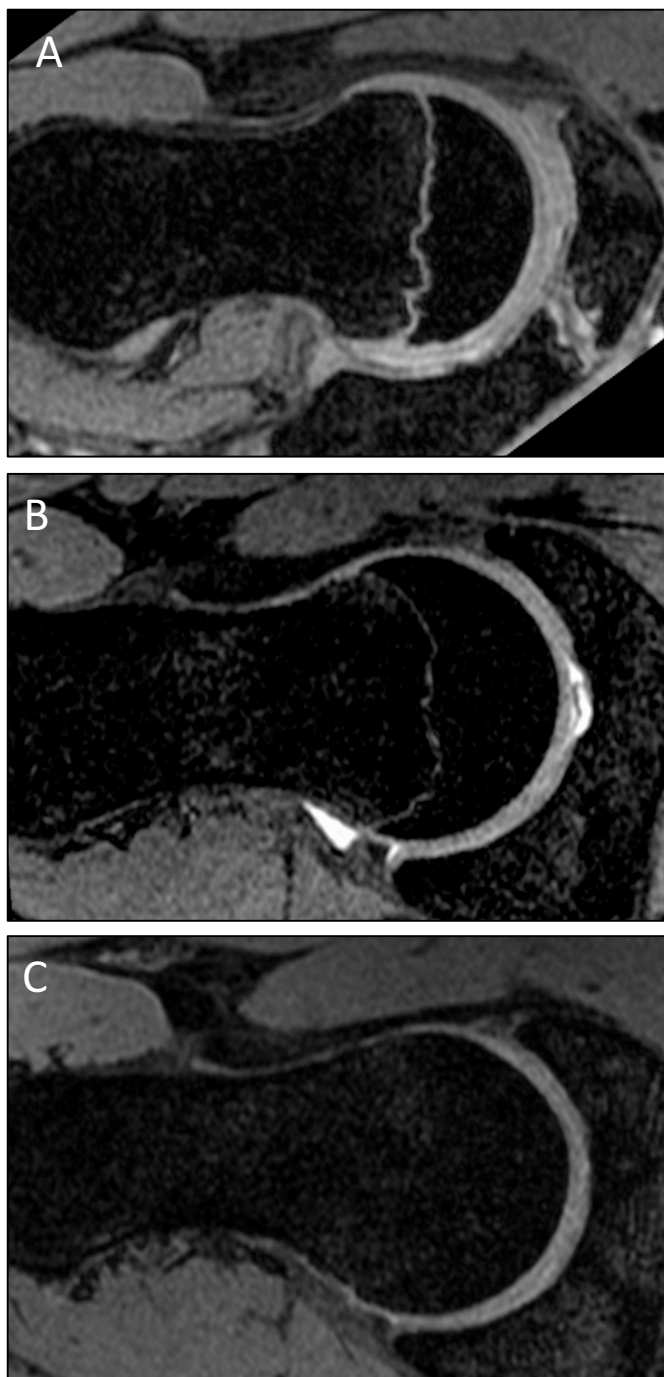
3.9.3 Morphological Measurements

Alpha angle (cartilage) and epiphyseal extension at the anterosuperior and posteroinferior head-neck junction were measured using OxMorf 2.1.0 software (Chapter 2). Measurements were performed by the Principal Investigator (AP) who was blinded to participant information. Reproducibility readings were performed by an Academic Orthopaedic Clinician (SF). Radial slices from 11 o'clock, 12 o'clock, 1 o'clock, 2 o'clock, and 3 o'clock were analysed. These were selected given they include the most frequent locations of cam morphology²²⁵. Pilot data and comparable studies suggested mean alpha angles were greatest at 1 o'clock^{47,259}, hence readings are centred around this position. Alpha angle was treated as a continuous variable rather than applying a threshold to define cam morphology.

The physis of each hip was scored as either open, partially closed, or closed (Figure 3-4). A physis was deemed partially closed when there was contact between the epiphysis and metaphysis but the physis remained visible on the WATSf MRI sequence. When considering physeal closure as a binary variable, a partially closed physis was considered closed.

Figure 3-4 – Appearances of an Open, Partially Closed, and Closed Pysis on WATSf MRI Sequence

A: Open Pysis B: Partially Closed Pysis C: Closed Pysis



3.9.4 Statistical Analysis and Data Diagnostics

Statistical calculations were performed using STATA 14.1 (College Station, TX, USA). The distribution of values was examined using histograms and kernel density plots. Comparison of means was undertaken using an independent two-tailed Student's t test for normally distributed data and a Wilcoxon rank sum test for data that was not normally distributed. Linear regression modelling was adopted to explore variables that predict change in alpha angle and epiphyseal extension with age. Stepwise estimation identified variables for inclusion in multivariate analysis as age, gender, and activity level. Residual plots of the regression models demonstrated normal distributions but with evidence of heteroscedasticity (Appendix C-2). Therefore, the Huber White Sandwich estimator was adopted with clustering for laterality to account for the inclusion of left and right hips that are not independent measurements (*'cluster'* command). Interactions were evaluated with linear regression predictions of each combination of variables that predict maximum alpha angle and epiphyseal extension (*'predxcon'* command). None reached statistical significance, hence no interaction terms were included in the multivariate models. The overall effect of factor variables on outcome was tested with ANOVA methodology (*"contrast"* function). There were missing data for MRI outcomes in five hips due to incomplete scans and the remaining dataset was complete. No imputation was performed. Statistical significance was set at $p < 0.05$.

3.10 Cohort Characteristics

210 individuals participated in the study and the final cohort consisted of 103 male football players from Southampton Football Academy, 52 male controls, and 55 female controls (Table 3-2). Two football players declined the invitation to participate.

The recruitment target was exceeded: Recruitment of controls continued until assessments were complete for 50 males and 50 females. Football players invited to participate who were initially uncertain but subsequently wished to take part were permitted to do so. MRI scans were incomplete due to claustrophobia, or uninterpretable due to movement artefact, in five hips (two male footballers and one female control).

Table 3-2 - Study Participants

Age	Number of Participants		
	Football Academy	Controls	
	Male	Male	Female
9	16	11	9
10	17	8	4
11	13	7	3
12	12	7	3
13	11	6	5
14	9	2	6
15	11	10	9
16-18	14	5	16
Total	103	52	55

3.10.1 Activity Levels

Within the study cohort, Physical Activity Questionnaire (PAQ) score decreased with increasing participant age, and this was the case for both controls and academy football players (Table 3-3 & Figure 3-5). Conversely, the Activity Level remained similar across all age groups (Table 3-4). There was a positive correlation between PAQ and Activity level (Figure 3-6). Mean PAQ was 3.08 for 'Athletes', compared with 2.79 for 'Sport' ($p=0.008$) and 2.25 for 'No Sport' ($p<0.001$).

Table 3-3 - Mean and Standard Deviation of Physical Activity Questionnaire (PAQ)

Age Category (years)	Football Academy		Male Controls		Female Controls	
	Mean PAQ	Standard Deviation	Mean PAQ	Standard Deviation	Mean PAQ	Standard Deviation
9-10	3.44	0.429	3.10	0.472	2.96	0.525
11-12	3.36	0.682	3.28	0.560	3.72	0.793
13-14	2.98	0.736	2.87	0.607	2.30	0.570
15-16	2.51	0.662	2.22	0.649	2.14	0.663
17-18	2.17	0.416	2.14	0.544	2.21	0.604
All Ages	3.08	0.727	2.86	0.698	2.42	0.688

Table 3-4 - Mean and Standard Deviation of Category of Activity Level

Age Category (years)	Football Academy		Male Controls		Female Controls	
	Mean Activity Level	Standard Deviation	Mean Activity Level	Standard Deviation	Mean Activity Level	Standard Deviation
9-10	3.00	0	1.67	0.488	1.55	0.522
11-12	3.00	0	1.79	0.425	1.57	0.535
13-14	3.00	0	1.75	0.463	1.58	0.515
15-16	3.00	0	1.77	0.439	1.74	0.562
17-18	3.00	0	2.00	0.000	1.67	0.816
All Ages	3.00	0	1.75	0.437	1.64	0.557

Figure 3-5 - Box and Whisker Plot of Physical Activity Questionnaire Score Versus Age*

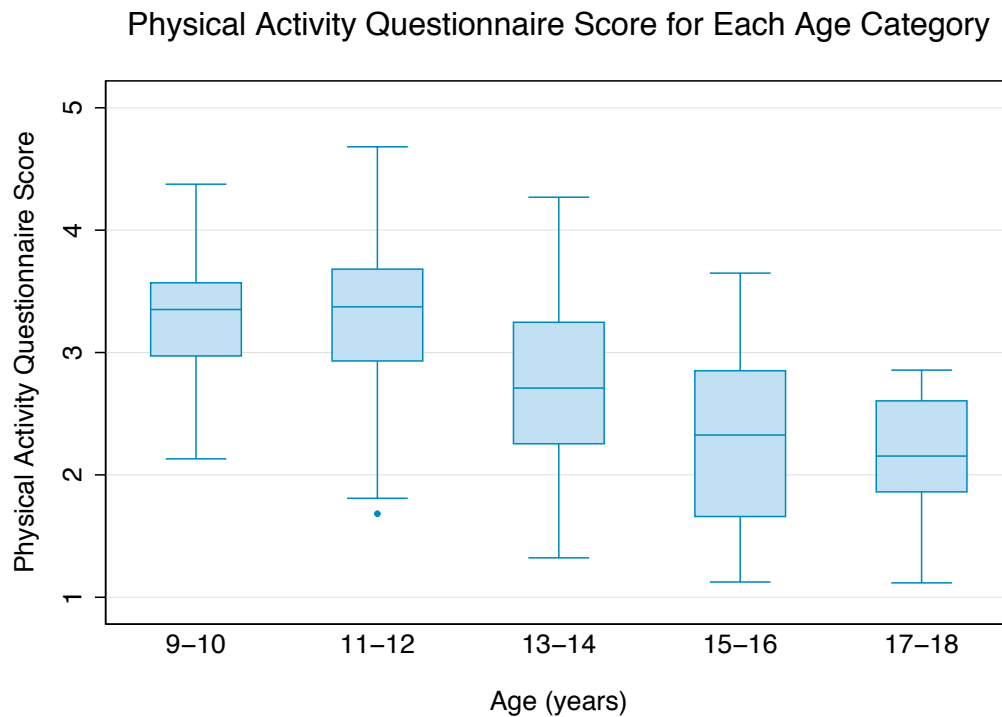
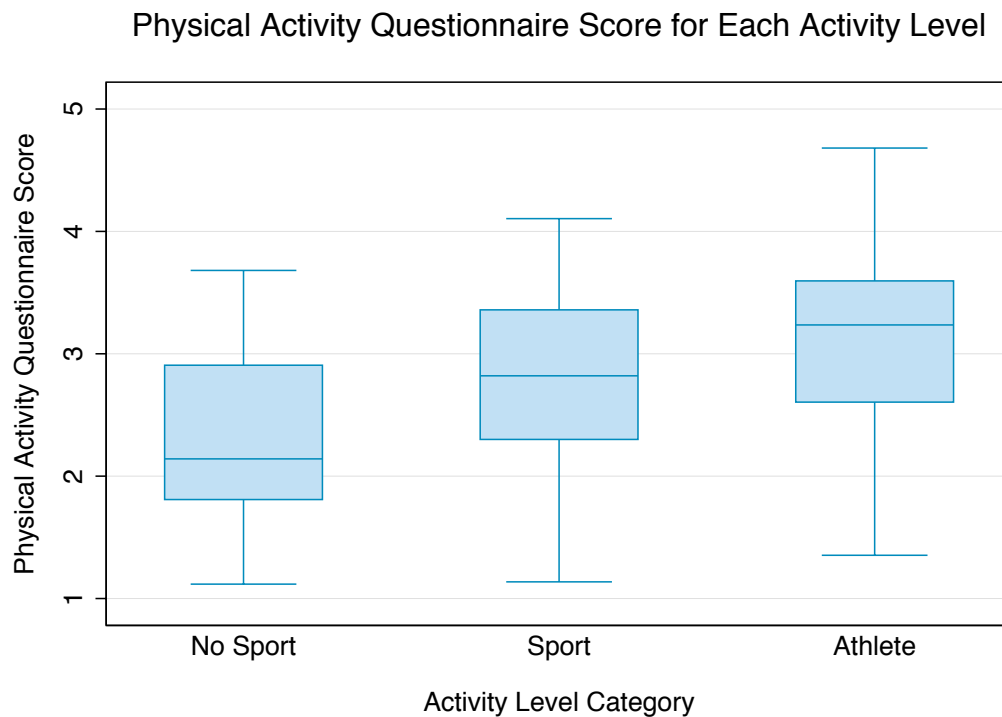


Figure 3-6 - Box and Whisker Plot of Physical Activity Questionnaire Score Versus Activity Level*



*Boxes represent the median with 25th and 75th percentiles. Whiskers represent the limits of the data. Values greater than 1.5 times the interquartile range are considered outliers.

3.10.2 Body Mass Index

Mean BMI increased with age in all cohorts (Table 3-5), and comparisons were therefore made using regression analysis with months of age as a covariate. There was no statistically significant difference in BMI between male controls and female controls ($p=0.92$), whereas male footballers had a statistically significantly lower BMI than control males (coefficient 0.93 $p=0.033$) and control females (coefficient 0.98 $p=0.026$).

Regression analysis with months of age as a covariate did not identify a statistically significant relationship between BMI and the Physical Activity Questionnaire. Conversely, there was a statistically significant difference in BMI between 'Athletes' and participants who play 'Sport' (coefficient 0.84 $p=0.035$) and 'No Sport' (coefficient 1.10 $p=0.028$). Therefore, 'Athletes' had a higher BMI than participants who play 'Sport', but a lower BMI than participants who play 'No Sport'.

Table 3-5 - Mean and Standard Deviation of Body Mass Index

Age Category (years)	Football Academy		Male Controls		Female Controls	
	Mean BMI	Standard Deviation	Mean BMI	Standard Deviation	Mean BMI	Standard Deviation
9-10	16.53	1.60	17.97	2.53	17.05	2.03
11-12	17.23	1.32	18.37	1.89	20.22	3.20
13-14	19.16	1.74	20.51	5.11	22.31	4.41
15-16	21.56	1.23	21.37	2.73	20.91	3.61
17-18	22.42	2.01	22.76	0.69	20.87	1.99
All Ages	18.49	2.59	19.50	3.25	20.35	3.71

3.10.3 Physeal Closure

In the football academy cohort there were 135 hips with an open physis and 68 hips with a closed physis. In the male control group there were 80 hips with an open physis and 24 with a closed physis, and in the female control group there were 32 hips with an open physis and 76 hips with a closed physis.

Physeal closure was later in males than females. In males, the physis remained open in all participants aged 12 years and closed between the ages of 13 and 16 (Figure 3-7, Figure 3-8). In females, the physis remained open in all participants aged 10 years and closed between the ages of 11 and 12 (Figure 3-9). There was no difference in the age of physeal closure between academy football players and male controls.

Figure 3-7 – Stage of Physeal Development in Each Age Group for Academy Football Players (n=206 hips)

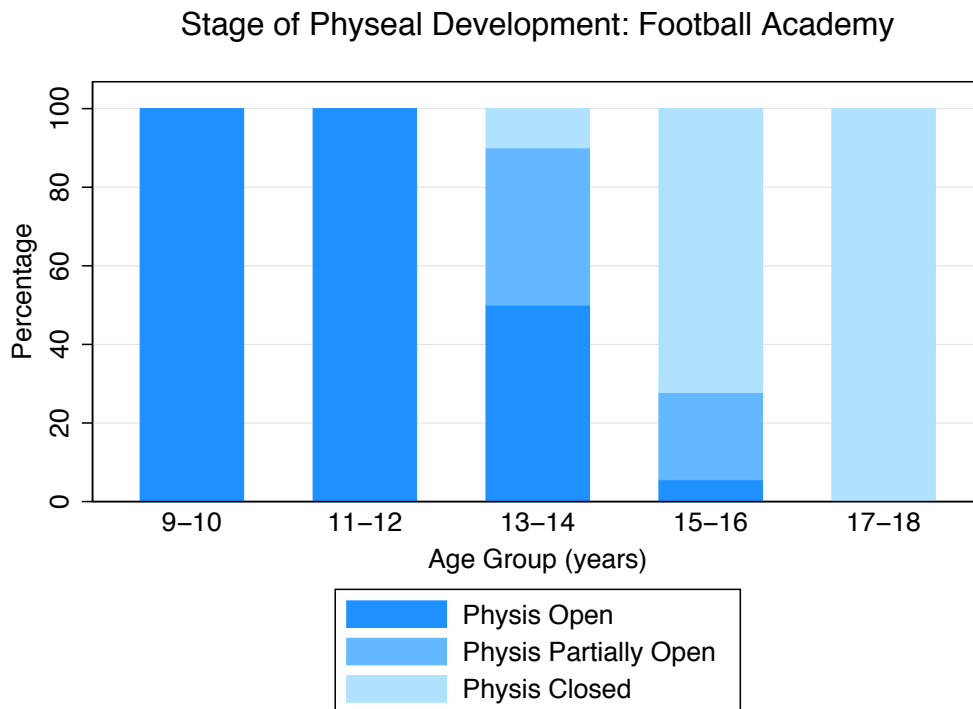


Figure 3-8 – Stage of Physeal Development in Each Age Group for Male Participants (n=104 hips)

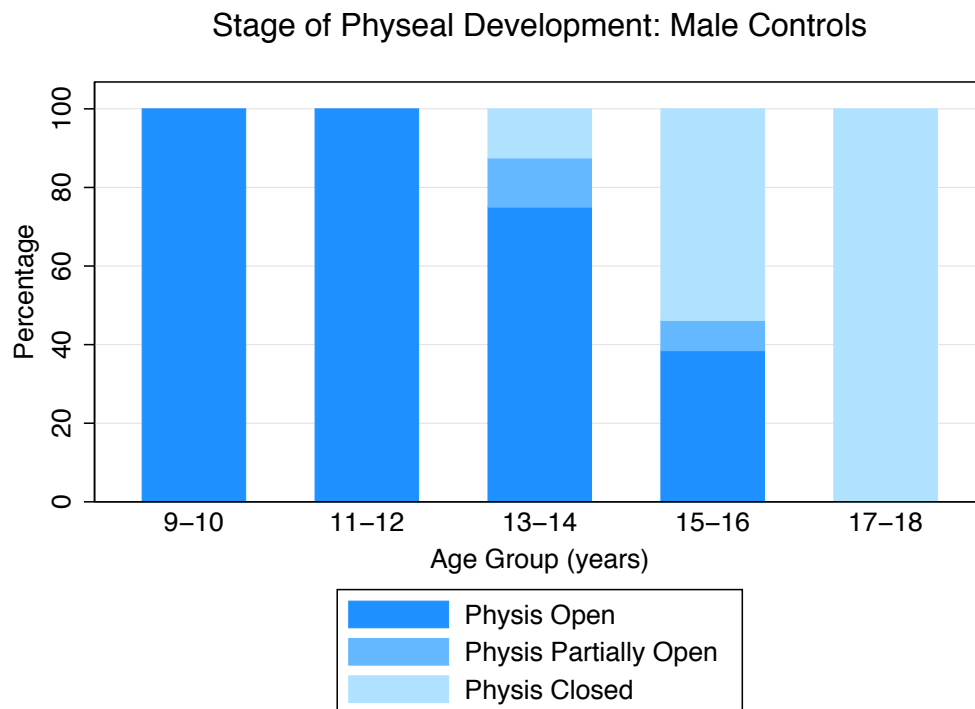
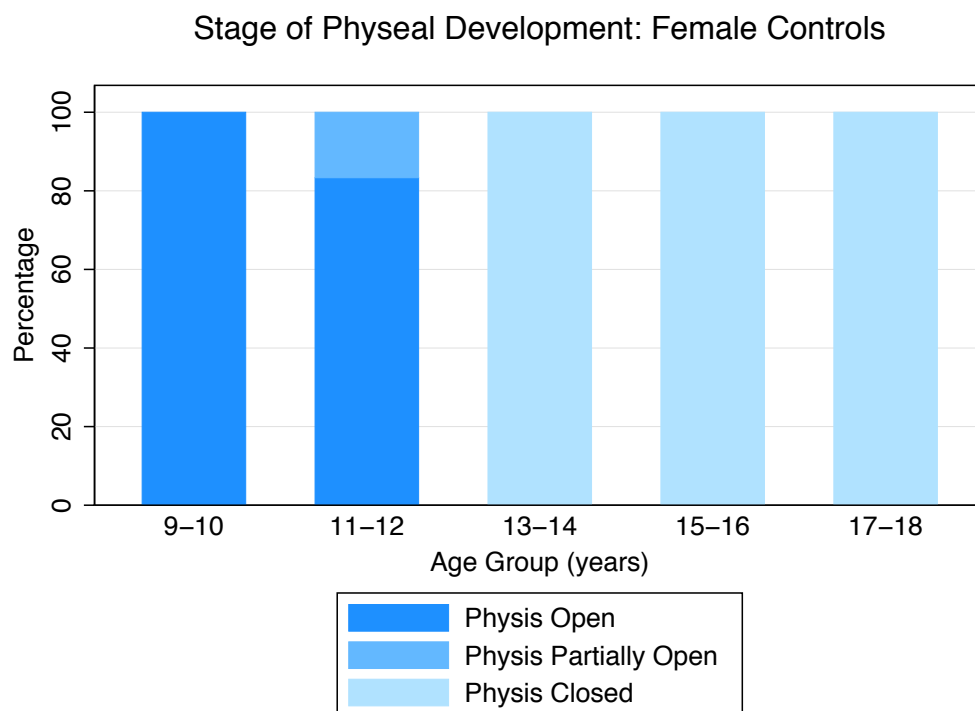


Figure 3-9 – Stage of Physeal Development in Each Age Group for Female Participants (n=110 hips)



3.11 Qualitative MRI Morphology

The salient observation was that hypertrophy and extension of the epiphysis is the most common mechanism of cam morphology development amongst study participants. The resultant asphericity is extremely prevalent within the footballer cohort beyond 14 years of age as the physis approaches closure (Figure 3-10). Hypertrophy was classically maximal at the 1 o'clock position, but in extreme cases also involve the 12 o'clock through to 3 o'clock positions (Figure 3-11). The length of epiphyseal extension along the femoral neck did not necessarily reflect the degree of asphericity (Figure 3-10).

Figure 3-10 - Increasing Asphericity of the Femoral Head secondary to Epiphyseal Hypertrophy (A-C)

MRI of Academy Football Players Aged 14-16 Years of Age at the 1 O'Clock position

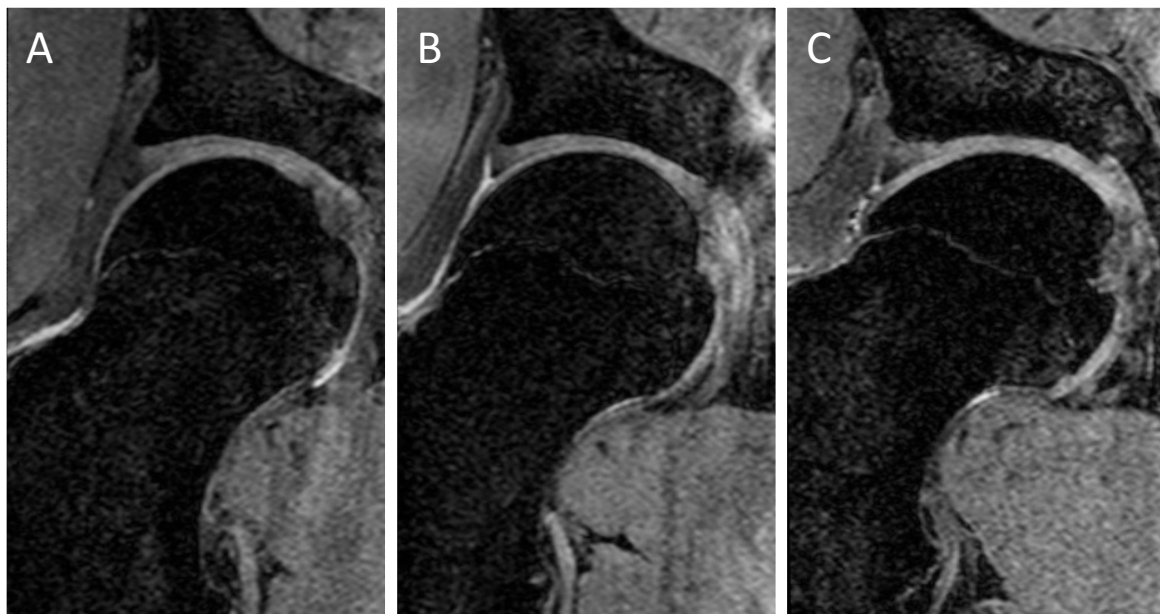
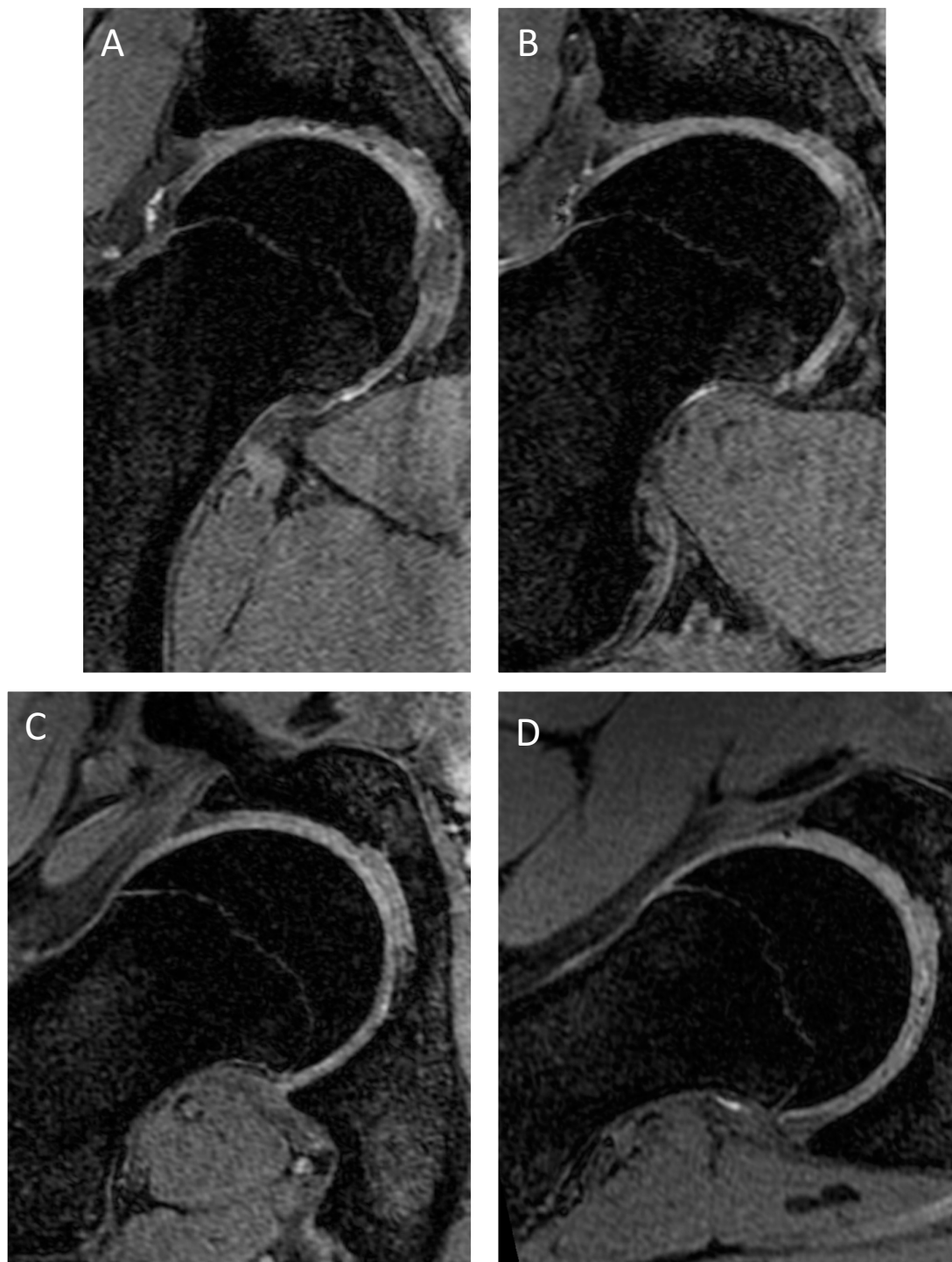


Figure 3-11 – Radial Images of Cam Morphology

MRI of an Academy Football Player Aged 16 Years at the 12 O’Clock (A), 1 O’Clock (B), 2 O’Clock (C) and 3 O’Clock (D) Position



There was no evidence of epiphyseal extension in any participant at nine years of age, however, by 11 years of age there was frequently early extension of the epiphysis that may continue to hypertrophy and give rise to cam morphology (Figure 3-12).

Figure 3-12 – Characteristic Appearances of Skeletally Immature Hips

Academy Football Players Aged 9 (A) and 11 (B) Years of Age at the 1 O’Clock position

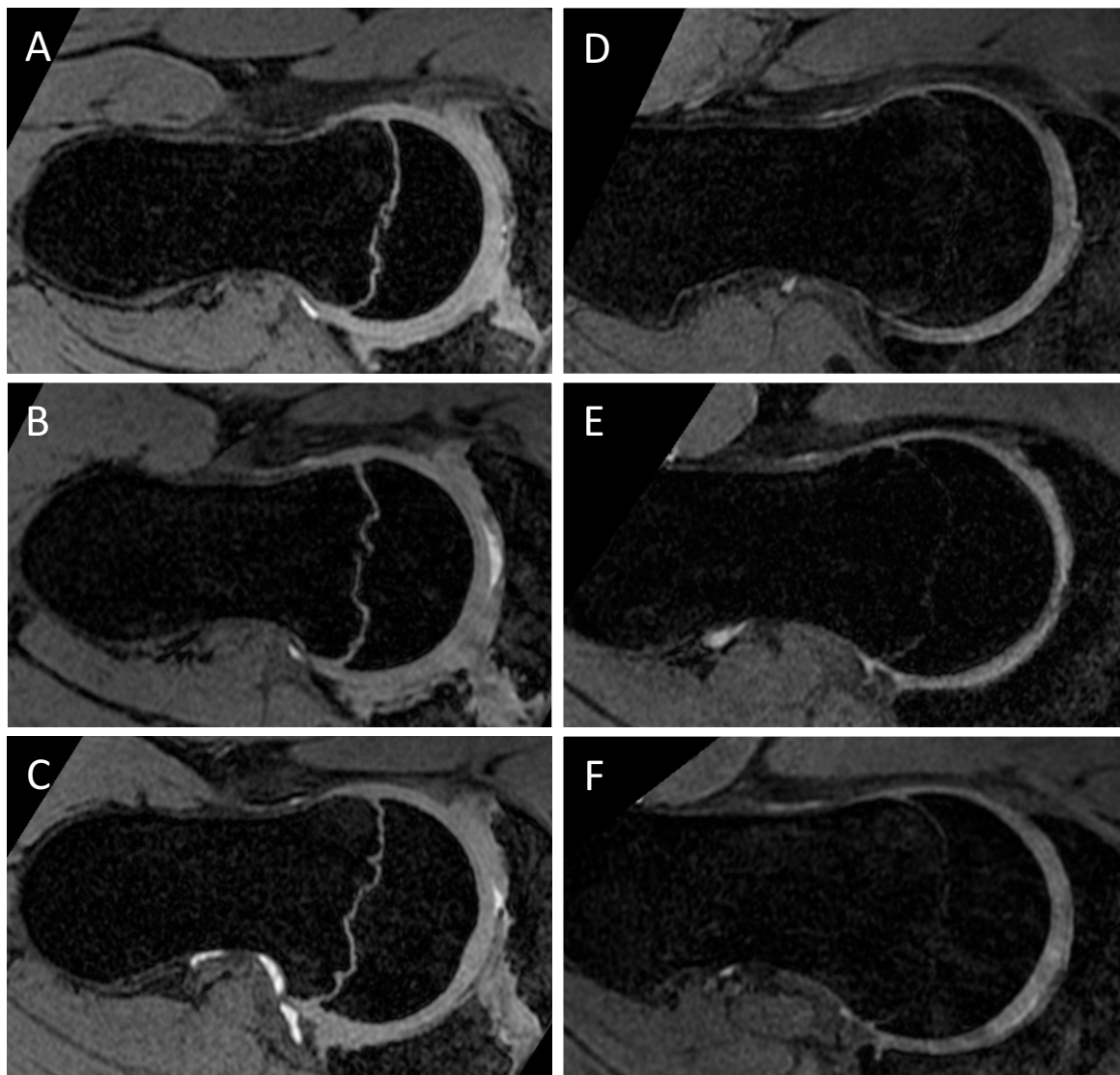


Epiphyseal hypertrophy and extension at the 3 o’clock position was extremely rare and was only evident in the presence of adjacent anterosuperior epiphyseal extension. It was not identified as the cause of asphericity at this position in any participant (Figure 3-11). Instead, asphericity at the 3 o’clock position was dictated by metaphyseal morphology. Three principal morphological phenotypes were identified, although these were not distinct (Figure 3-13): i) normal morphology with a significant femoral head-neck offset and concavity (A & D) ii) reduced femoral head-neck offset and concavity resulting in

mild asphericity (B & E) iii) retroversion of the femoral head that may be associated with loss of femoral head-neck offset and concavity. These phenotypes were present both pre and post physeal closure and there was no apparent association with epiphyseal extension or hypertrophy (Figure 3-13).

Figure 3-13 – Morphology Phenotypes at the 3 O’Clock Position

MRI of Academy Football Players Aged 10 (A-C) and 14-16 (D-F) Years. Three phenotypes were identified: i) Normal (A & D) ii) Reduced Concavity/Offset (B & E) iii) Retroversion (C & F)



Appearances at the 11 o'clock and 12 o'clock position are difficult to interpret. There is often isointense tissue at the head-neck junction of the 11 o'clock and 12 o'clock position in association with epiphyseal extension at the 1 o'clock position (Figure 3-15). In younger age groups the appearance is likely to represent the Perichondrial Fibrous Ring of La Croix (Figure 3-14).

Figure 3-14 – Morphological Appearance at 12 O'Clock Position of 9 Year Old Participant

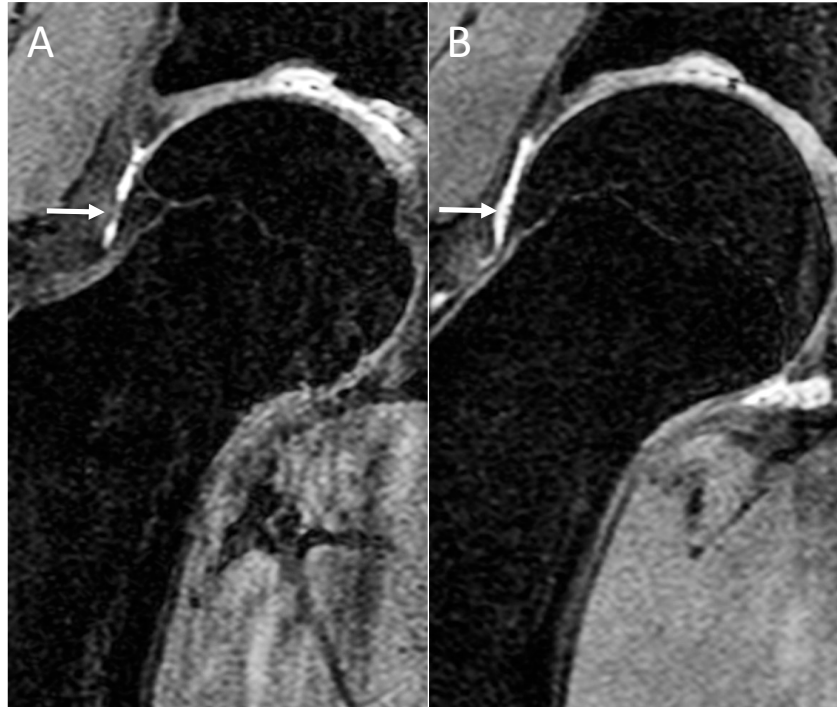
MRI of Academy Football Player Demonstrating Perichondrial Fibrous Ring of La Croix (white arrow)



Imaging of individuals at the time of physeal closure suggests that this structure contributes to the definitive cam morphology. It is not clear whether this structure ossifies (Figure 3-15).

Figure 3-15 - Morphological Appearance at 12 O'Clock Position at Time of Physeal Closure

MRI Demonstrating Loss of Concavity at Femoral Head-Neck Junction at the Site of the Perichondrial Fibrous Ring of La Croix (white arrow) in a 12 Year Old (A) and 14 Year Old (B) Academy Football Player



WATSf (C) and PDFS (D) Imaging of Femoral Head-Neck Junction Demonstrating Loss of Concavity at the Site of the Perichondrial Fibrous Ring of La Croix (white arrow) in a 13 Year Old Academy Football Player. There is a Different Signal Intensity in Apparently Discrete Structures



3.12 Quantitative MRI Morphology: Alpha Angle

3.12.1 Alpha Angle at Different Positions on the Femoral Neck

There was limited correlation between alpha angle in adjacent positions on the clockface (Appendix C-3, Appendix C-4). The study primary outcome measure was maximum alpha angle on all clockface positions to account for variation in the location of cam morphology. Alpha angle was highest at the 1 o'clock position in male participants and the 2 o'clock position in female participants (Table 3-6, Table 3-7, Table 3-8).

3.12.2 Alpha Angle Pre and Post Physeal Closure

The distribution of alpha angles across the clockface positions remained constant in participants with an open physis compared with those with a closed physis (Figure 3-16, Figure 3-17, Table 3-6, Table 3-7, Table 3-8). There was a statistically significant increase in alpha angle at all positions on the clockface in male participants and the greatest increase was at the 1 o'clock position (Table 3-6, Table 3-7). In females, there was a statistically significant increase in alpha angle at the 1 o'clock and 2 o'clock positions only, with the greatest increase at the 2 o'clock position (Table 3-8).

Figure 3-16 - Mean Alpha Angle at Each Position of the Femoral Neck for All Participants with an Open Physis with 95% Confidence Intervals

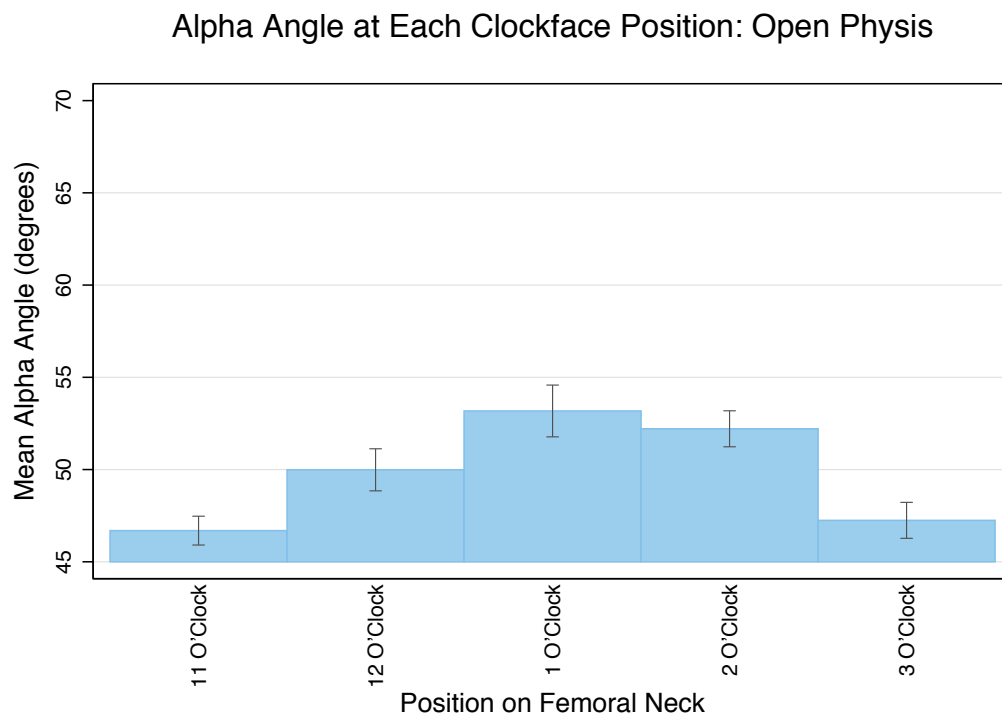


Figure 3-17 - Mean Alpha Angle at Each Position of the Femoral Neck for All Participants with a Closed Physis with 95% Confidence Intervals

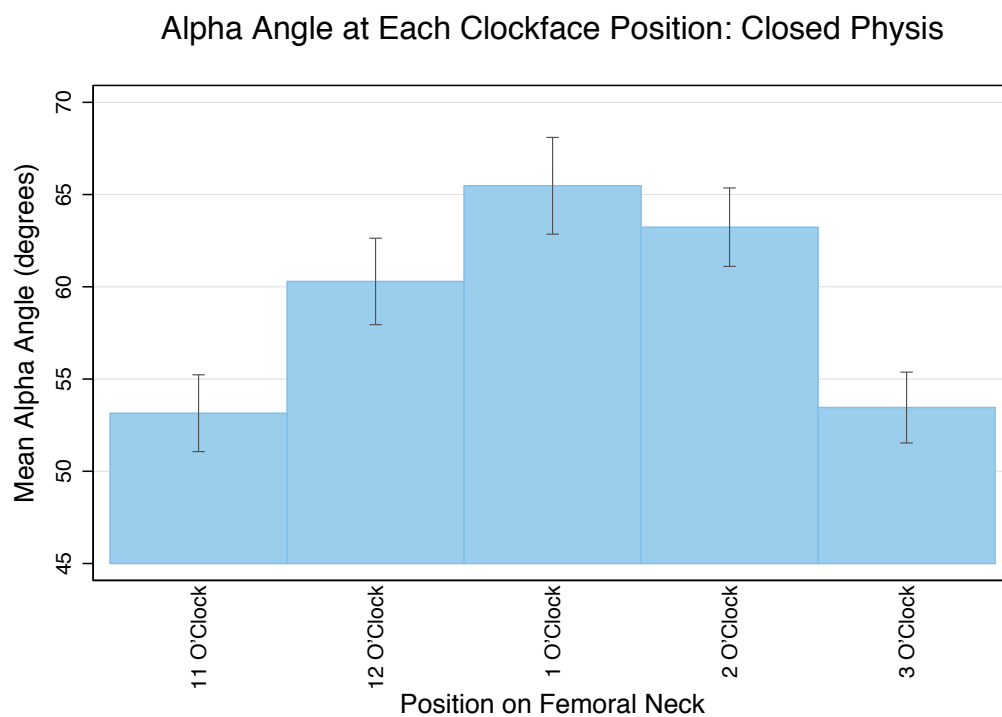


Table 3-6 - Mean Alpha Angle at each Position Pre and Post Physeal Closure: Athletes

Clockface Position	Open Physis		Closed Physis		T Test	
	Mean	Standard Deviation	Mean	Standard Deviation	Difference	P Value
11 O'Clock	46.68	6.50	59.91	15.91	+13.23	<0.001
12 O'Clock	50.04	9.86	68.23	15.52	+18.19	<0.001
1 O'Clock	53.92	12.22	75.69	16.73	+21.77	<0.001
2 O'Clock	52.43	8.61	69.84	16.03	+17.41	<0.001
3 O'Clock	46.30	8.03	58.30	15.26	+11.99	<0.001
Maximum All Positions	58.65	13.07	80.20	15.38	+21.56	<0.001

Table 3-7 - Mean Alpha Angle at each Position Pre and Post Physeal Closure: Male Controls

Clockface Position	Open Physis		Closed Physis		T Test	
	Mean	Standard Deviation	Mean	Standard Deviation	Difference	P Value
11 O'Clock	46.60	5.26	49.09	9.68	+2.49	0.010
12 O'Clock	50.10	8.28	65.60	14.16	+15.51	<0.001
1 O'Clock	53.34	11.01	71.95	11.07	+16.87	<0.001
2 O'Clock	52.71	6.64	68.71	12.68	+15.34	<0.001
3 O'Clock	48.94	7.93	57.33	11.75	+8.39	<0.001
Maximum All Positions	57.41	10.00	77.56	11.32	+19.08	<0.001

Table 3-8 - Mean Alpha Angle at each Position Pre and Post Physeal Closure: Female Controls

Clockface Position	Open Physis		Closed Physis		T Test	
	Mean	Standard Deviation	Mean	Standard Deviation	Difference	P Value
11 O'Clock	46.93	7.40	48.37	9.58	+1.44	0.448
12 O'Clock	49.49	7.88	51.51	10.30	+2.02	0.324
1 O'Clock	49.61	5.06	54.29	11.75	+4.68	0.032
2 O'Clock	50.03	6.52	55.59	6.86	+5.56	<0.001
3 O'Clock	46.99	5.41	47.90	6.79	+0.91	0.504
Maximum All Positions	53.36	7.98	60.59	11.02	+7.23	0.001

3.12.3 Alpha Angle with Age

Alpha angle increased with age at all positions on the femoral neck and regression analysis gave the greatest correlation coefficient at the 1 o'clock position for academy football players, male controls, and female controls (Appendix C-5, Appendix C-6). Increase in alpha angle was most rapid between 12 to 14 years of age, with only a small increase in alpha angle after 14 years of age. There was a comparable trend across all clockface positions (Figure 3-18, Figure 3-19, Figure 3-20, Figure 3-21, Figure 3-22, Figure 3-23) and for each group of participants (Appendix C-7, Appendix C-8, Appendix C-9, Appendix C-10, Appendix C-11, Appendix C-12).

Figure 3-18 - Alpha Angle at 11 o'clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

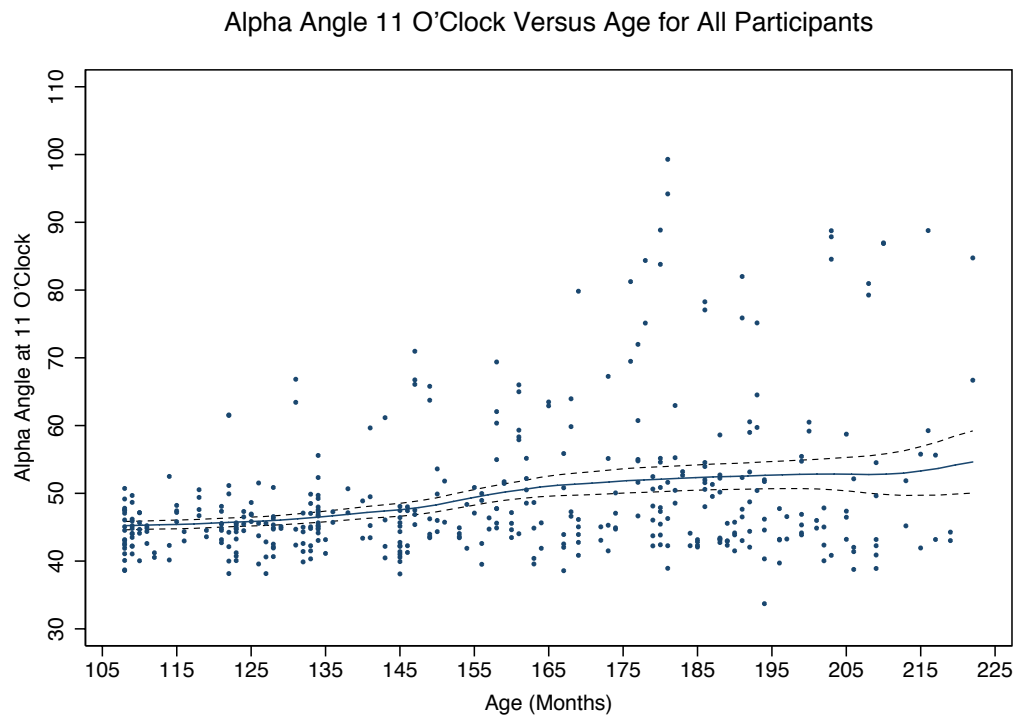


Figure 3-19 - Alpha Angle at 12 O'Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

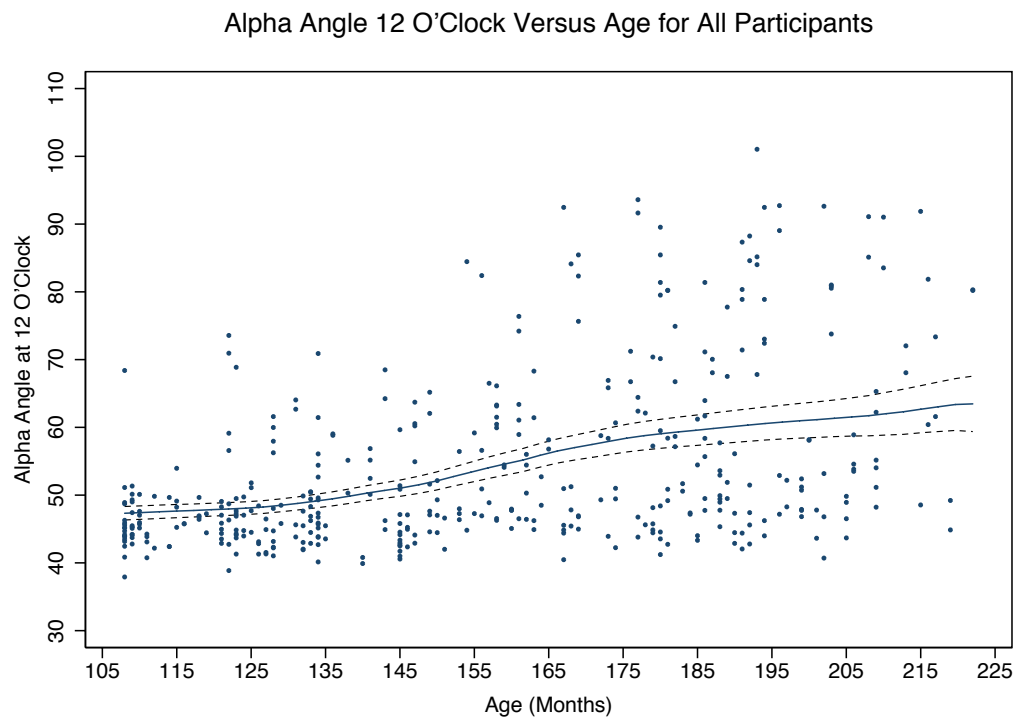


Figure 3-20 - Alpha Angle at 1 O'Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

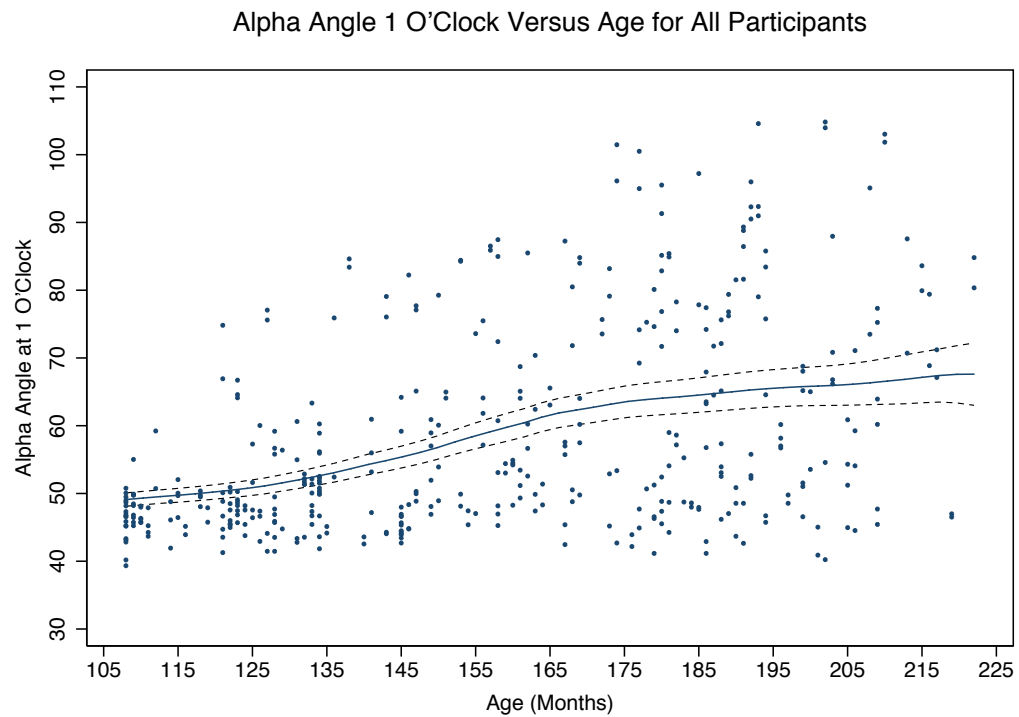


Figure 3-21 - Alpha Angle at 2 O'Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

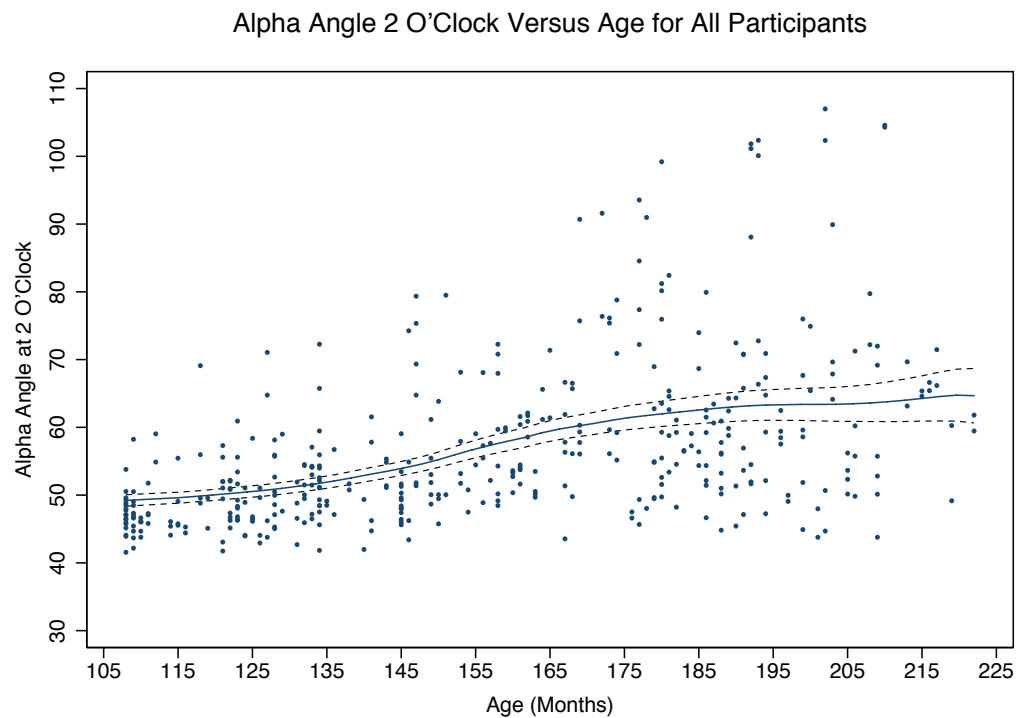


Figure 3-22 - Alpha Angle at 3 O'Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

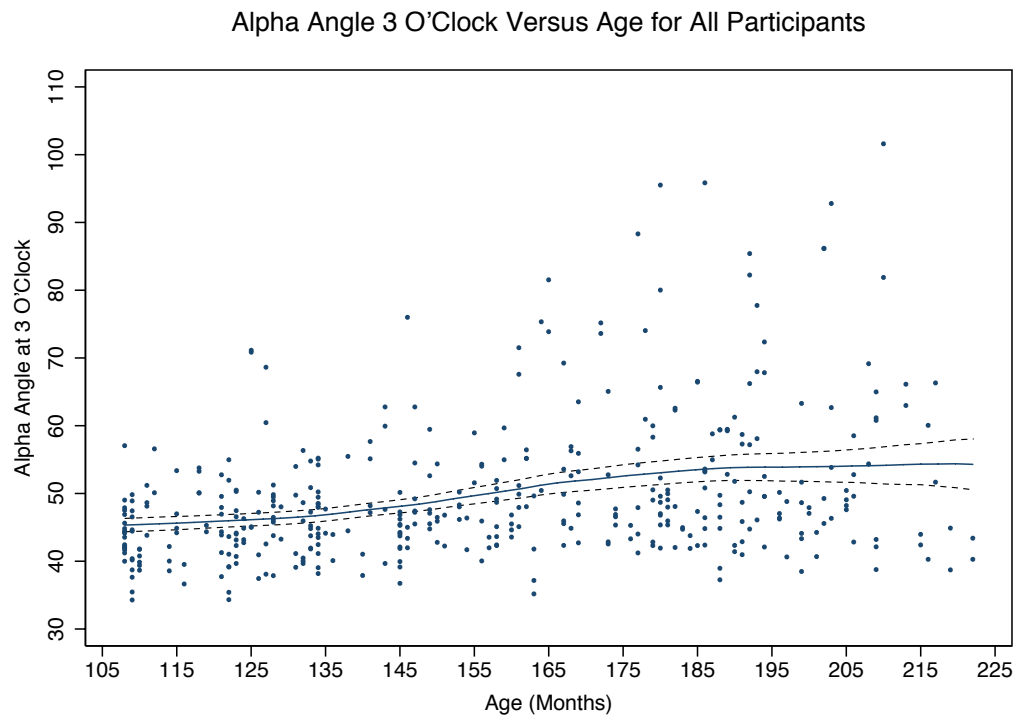
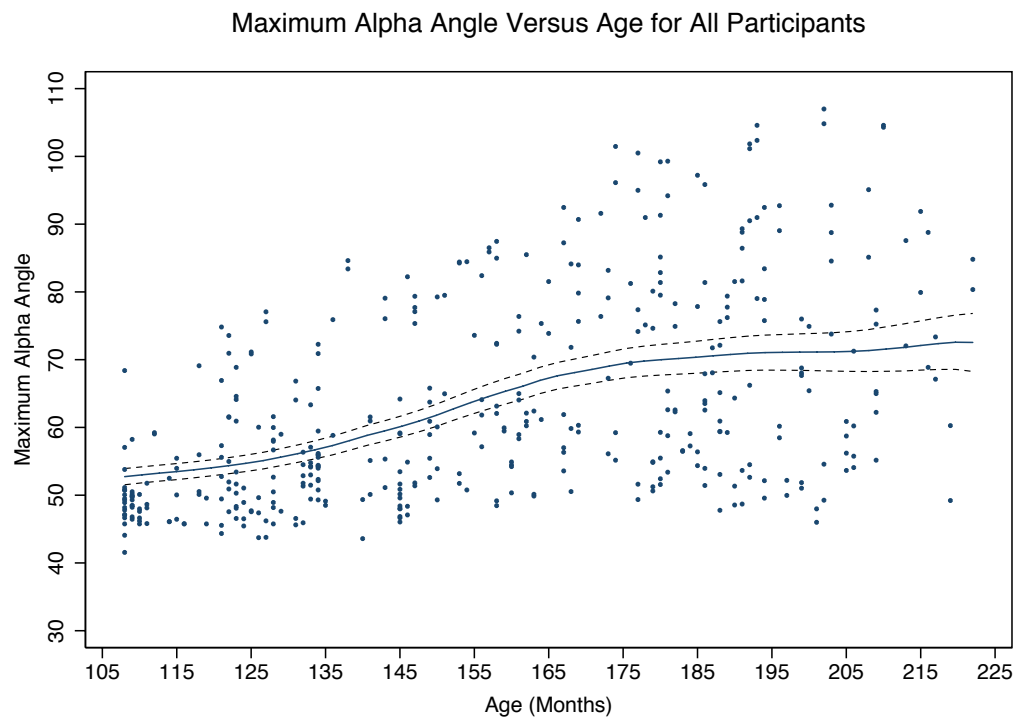


Figure 3-23 - Maximum Alpha Angle Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals



3.12.4 Predictors of Maximum Alpha Angle

See Table 3-9, Table 3-10 & Table 3-11

Maximum alpha angle increased with age and the greatest increase was seen within age categories 11-12 and 13-14 years. Alpha angles were 6.05 degrees lower in females than in males ($p=0.031$), and when including age and activity level as co-variables, were 6.66 degrees lower ($p=0.005$). Alpha angle increased with BMI, however, this was no longer statistically significant when including age, gender, and activity level as covariates (Appendix C-32). There was no difference in alpha angle between dominant and non-dominant legs.

There was a positive association between activity levels and alpha angle that remained present when including age and gender as covariates. Individuals who play sport for a school or club team have a maximum alpha angle 4.03 degrees greater than individuals who play no regular sport ($p=0.041$). Alpha angles are 7.63 degrees higher in individuals competing at a national or international level ($p=0.035$). There was also a statistically significant difference between male footballers, male controls, and female controls (Appendix C-30). Female controls have a maximum alpha angle 7.42 degrees lower than male controls ($p=0.004$), and male controls have a maximum alpha angle 4.33 degrees lower than male football academy players ($p=0.042$) (Appendix C-30).

Alpha angle fell with an increasing Physical Activity Questionnaire (PAQ) score, however, this was secondary to decreasing PAQ scores with age as there was no statistically significant relationship between PAQ and alpha angle when including age and gender as covariates (Appendix C-30).

Within the footballer cohort, highest alpha angles were found in those who played as a striker (Table 3-10). Within the control population, no difference in average alpha angle was found between individuals whose primary sport was football or rugby, compared with individuals who played non-kicking sports or did not participate in regular sport (Table 3-11).

Table 3-9 - Predictors of Maximum Cartilage Alpha Angle

		Number of Hips	Univariate Regression			Multivariate Regression*		
			Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value
Months of Age		420	0.242	0.14 – 0.34	0.020	0.268	0.17 – 0.37	0.019
Age Category (years)	9-10	118	-	-	-			
	11-12	92	6.08	5.94 – 6.21	0.001			
	13-14	80	16.23	7.42 – 25.03	0.027			
	15-16	100	17.97	9.37 – 26.56	0.024			
	17-18	30	18.48	13.67 – 23.29	0.013			
Physis	Open	247	-	-	-			
	Closed	168	13.24	6.73 – 19.74	0.025			
Gender	Male	310	-	-	-	-	-	-
	Female	110	-6.05	-9.74 – 2.35	0.031	-6.66	-7.26 – -6.06	0.005
BMI		420	1.40	1.02 – 1.78	0.013			
Dominant Leg	Dominant	231	-	-	-			
	Non Dominant	189	0.856	-38.21 – 39.93	0.827			
Cohort	Male Control	104	-	-	-			
	Female Control	110	-3.37	-4.22 – -2.52	0.013			
	Football Academy	206	4.05	-0.36 – 8.46	0.054			
Activity Level	No Sport	70	-	-	-	-	-	-
	Sport	140	6.21	3.37 – 9.05	0.023	4.03	0.74 – 7.33	0.041
	Athlete	210	10.50	4.38 – 16.61	0.029	7.63	2.23 – 13.04	0.035
Physical Activity Questionnaire		420	-3.15	-5.58 – -0.71	0.039			

*Age, Gender and Activity Level as Covariates

Table 3-10 - Relationship Between Playing Position and Maximum Cartilage Alpha Angle in Footballers

		Number of Hips	Univariate Regression			Multivariate Regression*		
			Coefficient	95% Confidence Intervals	p value	Coefficient	95% Confidence Intervals	p value
Playing Position	Midfielder	70	-	-	-	-	-	-
	Goalkeeper	22	1.99	-6.98 – 10.97	0.217	1.87	-7.03 – 10.77	0.228
	Winger	28	5.17	-16.41 – 26.74	0.202	0.06	-33.24 – 33.35	0.986
	Defender	66	6.50	-2.68 – 15.69	0.070	3.18	-8.59 – 14.95	0.180
	Striker	20	7.99	7.70 – 8.27	0.002	5.51	3.32 – 7.71	0.020

*Age and Gender as Covariates

Table 3-11 - Relationship Between Type of Sport and Maximum Cartilage Alpha Angle in Controls

		Number of Hips	Univariate Regression			Multivariate Regression**		
			Coefficient	95% Confidence Intervals	p value	Coefficient	95% Confidence Intervals	p value
Sport Activity	No Regular Sport	72	-	-	-	-	-	-
	Football or Rugby	62	6.56	-4.27 – 17.39	0.082	4.61	-31.24 – 40.47	0.349
	All Other Sports	80	6.77	-5.42 – 18.95	0.090	4.75	-1.60 – 11.09	0.067

**Age, Gender, and Activity Level as Covariates

3.13 Quantitative MRI Morphology: Epiphyseal Extension

3.13.1 Epiphyseal Extension at Different Positions on the Femoral Neck

The distribution of physeal extension measurements across the clockface positions was different to the alpha angle (Table 3-12, Table 3-13, Table 3-14) and extension at the 11 o'clock was proportionately much greater compared with the other clockface positions (Figure 3-24, Figure 3-25).

3.13.2 Epiphyseal Extension Pre and Post Physeal Closure

The distribution of epiphyseal extension across the clockface was different between individuals with an open or closed physis (Figure 3-24, Figure 3-25). There was a statistically significant increase in epiphyseal extension at all clockface positions (Table 3-12, Table 3-13, Table 3-14). Epiphyseal extension at 11 o'clock was greatest in all individuals with an open physis. The greatest increase in epiphyseal extension was at 1 o'clock in academy football players (Table 3-12), but 2 o'clock in male and female controls (Table 3-13 & Table 3-14). Once the physis closed, epiphyseal extension was greatest at the 1 o'clock position in male participants (Table 3-12, Table 3-13), and 2 o'clock position in female participants, precisely as seen for alpha angle (Table 3-14). Maximum epiphyseal extension measurements therefore best reflect values at the 11 o'clock position in individuals with an open physis and 1 o'clock in individuals with a closed physis, limiting the value of this outcome measure. The relationship between alpha angle and epiphyseal extension was therefore investigated at the 1 o'clock position.

Figure 3-24 - Mean Epiphyseal Extension in Participants with an Open Physis

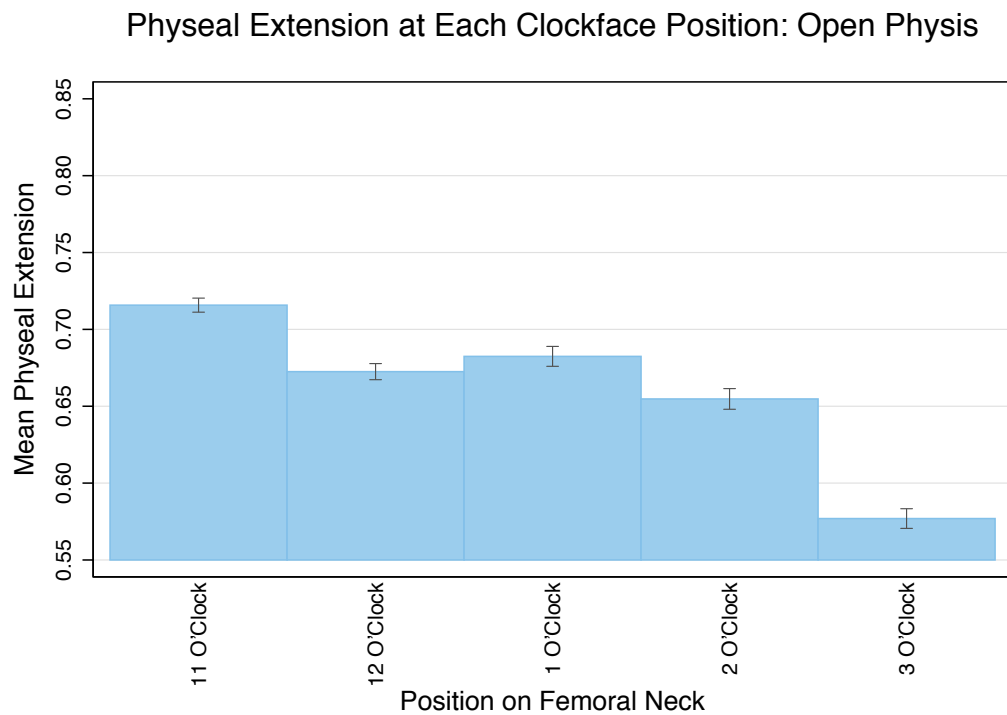


Figure 3-25 - Mean Epiphyseal Extension Ratio in Participants with a Closed Physis

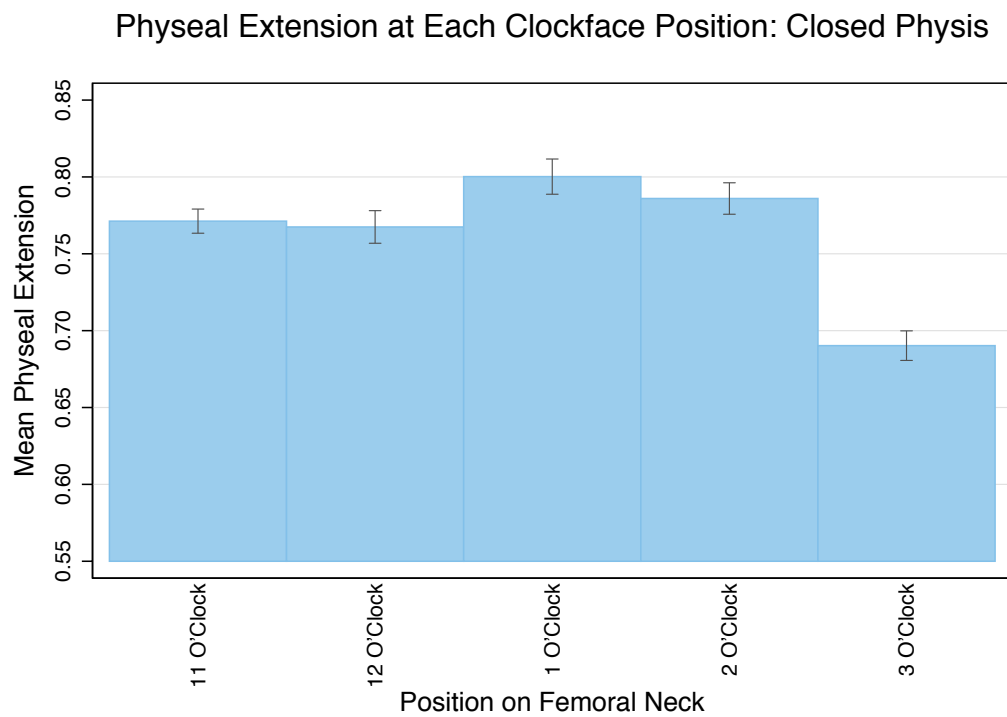


Table 3-12 - Mean Epiphyseal Extension at each Position Pre and Post Physal Closure: Athletes

Clockface Position	Open Physis		Closed Physis		T Test	
	Mean	Standard Deviation	Mean	Standard Deviation	Difference	P Value
11 O'Clock	0.711	0.038	0.795	0.054	+0.084	<0.001
12 O'Clock	0.667	0.038	0.800	0.068	+0.133	<0.001
1 O'Clock	0.681	0.053	0.840	0.074	+0.159	<0.001
2 O'Clock	0.657	0.055	0.792	0.074	+0.135	<0.001
3 O'Clock	0.576	0.047	0.693	0.076	+0.118	<0.001
Maximum All Positions	0.723	0.042	0.865	0.063	+0.142	<0.001

Table 3-13 - Mean Epiphyseal Extension at each Position Pre and Post Physal Closure: Male Controls

Clockface Position	Open Physis		Closed Physis		T Test	
	Mean	Standard Deviation	Mean	Standard Deviation	Difference	P Value
11 O'Clock	0.720	0.035	0.755	0.044	+0.035	<0.001
12 O'Clock	0.679	0.044	0.770	0.061	+0.091	<0.001
1 O'Clock	0.685	0.049	0.809	0.044	+0.124	<0.001
2 O'Clock	0.650	0.052	0.801	0.061	+0.151	<0.001
3 O'Clock	0.570	0.056	0.695	0.052	+0.125	<0.001
Maximum All Positions	0.730	0.036	0.846	0.046	+0.116	<0.001

Table 3-14 - Mean Epiphyseal Extension at each Position Pre and Post Physeal Closure: Female Controls

Clockface Position	Open Physis		Closed Physis		T Test	
	Mean	Standard Deviation	Mean	Standard Deviation	Difference	P Value
11 O'Clock	0.726	0.033	0.753	0.044	+0.028	0.002
12 O'Clock	0.681	0.047	0.738	0.061	+0.056	<0.001
1 O'Clock	0.680	0.055	0.760	0.062	+0.080	<0.001
2 O'Clock	0.659	0.053	0.772	0.055	+0.113	<0.001
3 O'Clock	0.600	0.051	0.686	0.053	+0.086	<0.001
Maximum All Positions	0.735	0.038	0.803	0.048	+0.069	<0.001

3.13.3 Epiphyseal Extension with Age

Epiphyseal extension increased with age at all positions on the femoral neck and regression analysis demonstrated the greatest correlation coefficients at the 1 o'clock position in footballers and 2 o'clock position in male and female controls (Appendix C-13 & Appendix C-14). As with alpha angle, the increase in the epiphyseal extension is most rapid between 12 and 14 years of age, with only a small increase in epiphyseal extension beyond 14 years of age. There was a comparable trend across all clockface positions (Figure 3-26, Figure 3-27, Figure 3-28, Figure 3-29, Figure 3-30, Figure 3-31) and for each group of participants (Appendix C-15, Appendix C-16, Appendix C-17, Appendix C-18, Appendix C-19, Appendix C-20).

Figure 3-26 – Epiphyseal Extension at 11 O’Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

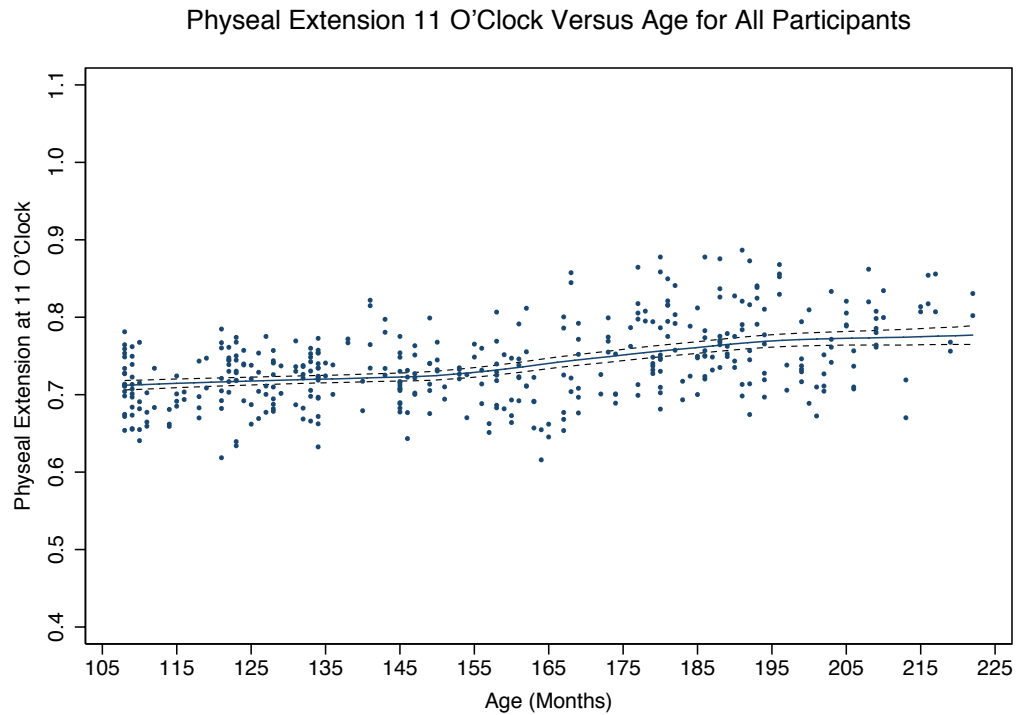


Figure 3-27 - Epiphyseal Extension at 12 O’Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

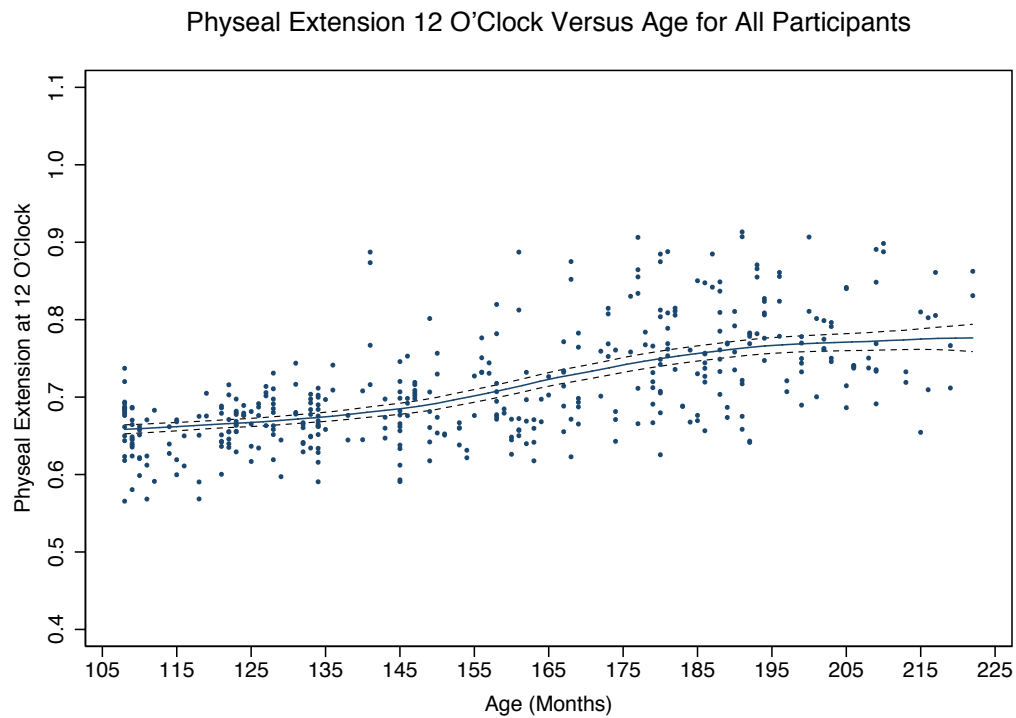


Figure 3-28 - Epiphyseal Extension at 1 O'Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

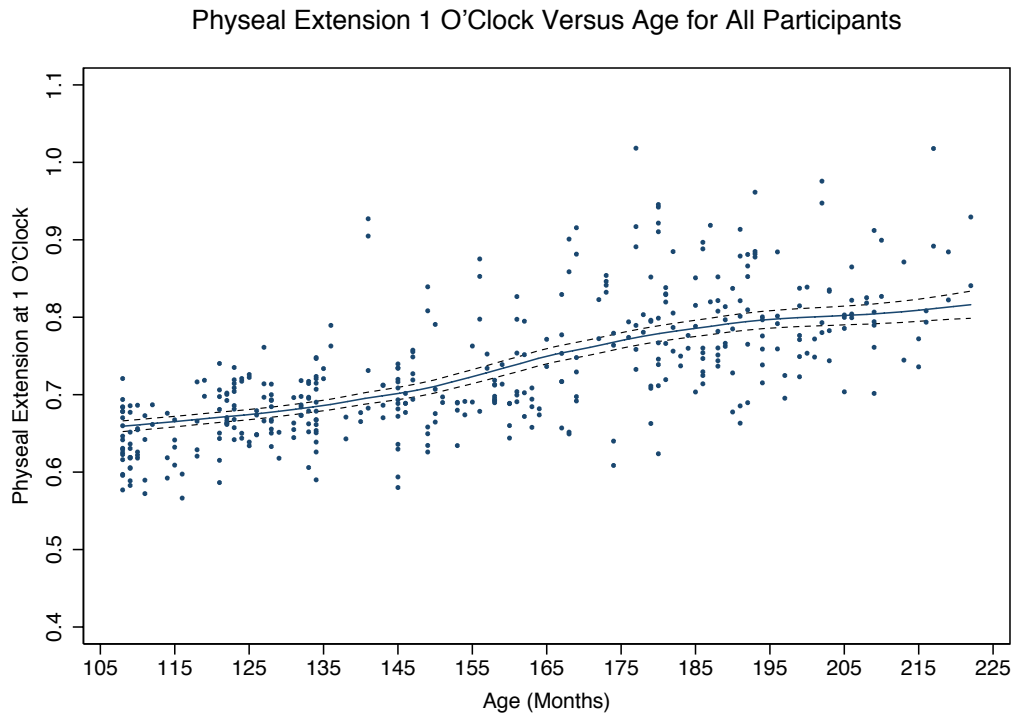


Figure 3-29 - Epiphyseal Extension at 2 O'Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

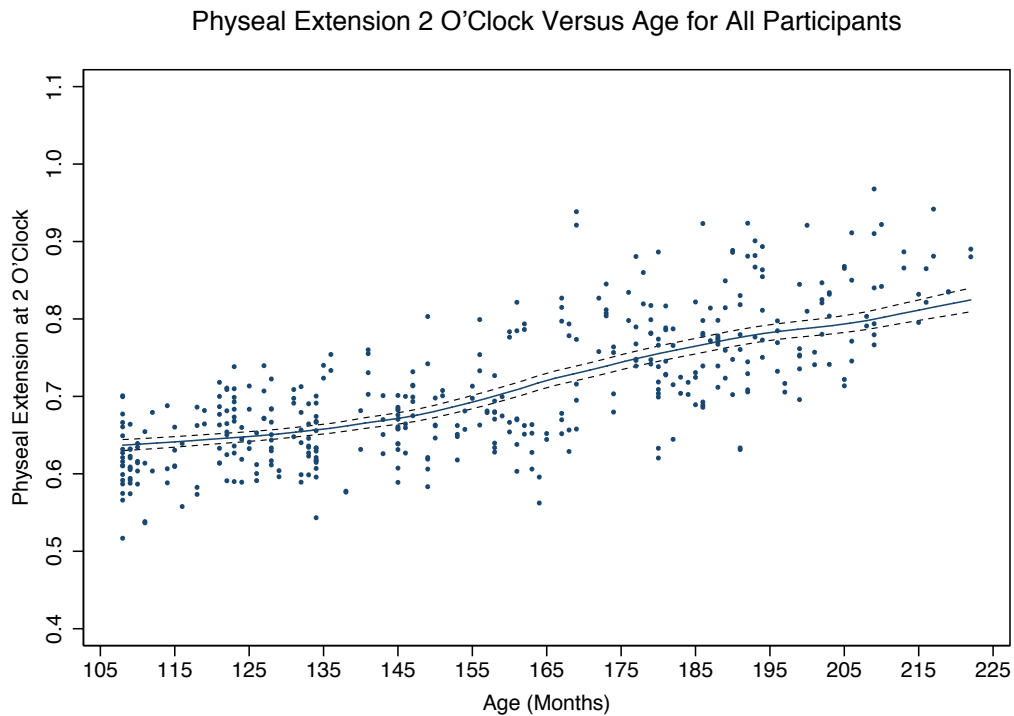


Figure 3-30 - Epiphyseal Extension at 3 O'Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals

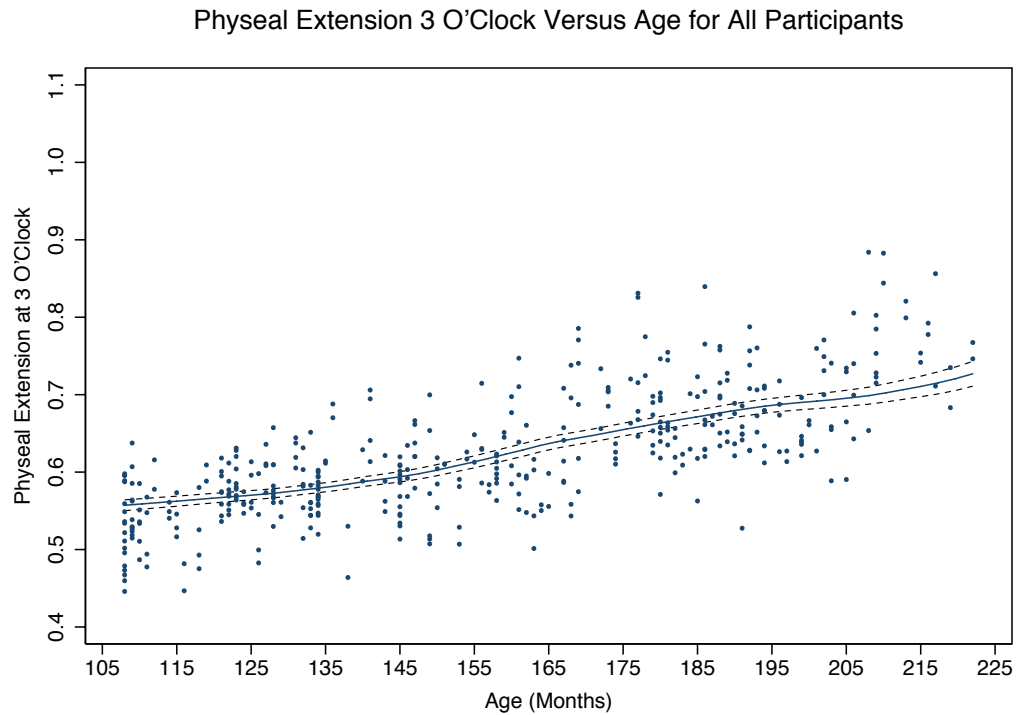
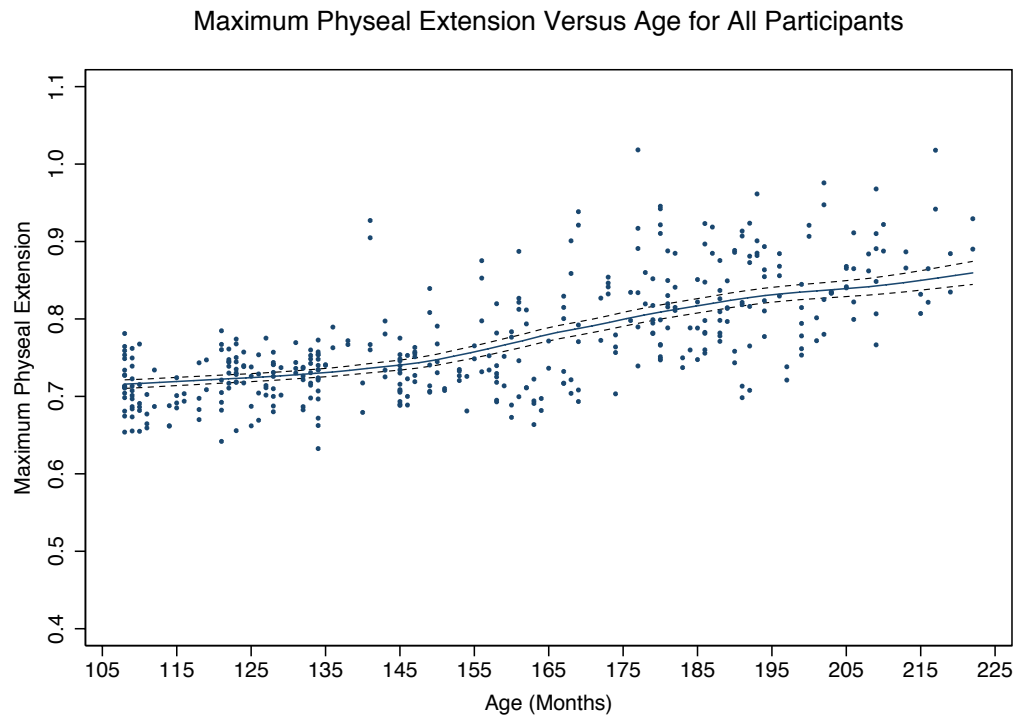


Figure 3-31 - Maximum Epiphyseal Extension Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals



3.13.4 Predictors of Epiphyseal Extension at 1 O'Clock

See Table 3-15, Table 3-16 & Table 3-17

Epiphyseal extension at the 1 o'clock position increased with age and the greatest increase was seen within age categories 11-12 and 13-14 years, as with the alpha angle. Contrary to the alpha angle, there was no statistically significant difference in epiphyseal extension between male and female participants, including when age and activity level were included as covariates. Epiphyseal extension increased with BMI, however, this effect was greatly diminished when including age, gender, and activity level as covariates (Appendix C-33). There was no difference in epiphyseal extension between dominant and non-dominant legs.

There was a positive association between activity levels and epiphyseal extension that remained present when including age and gender as covariates. Individuals who play sport for a school or club team have an epiphyseal extension measurement at 1 o'clock that is 0.017 greater than individuals who play no regular sport ($p=0.043$). The epiphyseal extension ratio is 0.032 greater in individuals competing at a national or international level ($p=0.022$). There was also a statistically significant difference between male footballers, male controls, and female controls (Appendix C-31). Female controls have an epiphyseal extension ratio 0.006 lower than male controls ($p=0.034$), and male controls have an epiphyseal extension ratio 0.026 lower than male football academy players ($p=0.049$) (Appendix C-31).

Epiphyseal extension fell with an increasing Physical Activity Questionnaire (PAQ) score, however, as with alpha angle, this was secondary to decreasing PAQ scores with age and there was no statistically significant relationship between PAQ and epiphyseal extension when including age and gender as covariates (Appendix C-31).

Within the footballer cohort, there was no statistically significant difference in epiphyseal extension between playing position when including age and gender as covariates (Table 3-16). Within the control population, no difference in epiphyseal extension was found between individuals whose primary sport was football or rugby, compared with individuals who played non-kicking sports or did not participate in regular sport (Table 3-17).

Table 3-15 – Predictors of Epiphyseal Extension at 1 O’Clock

		Number of Hips	Univariate Regression			Multivariate Regression*		
			Coefficient	95% Confidence Intervals	p value	Coefficient	95% Confidence Intervals	p value
Months of Age		420	0.0018	0.0018 – 0.0019	<0.0001	0.0019	0.0024 – 0.0317	0.002
Age Category (years)	9-10	118	-	-	-			
	11-12	92	0.0384	0.0276 – 0.0492	0.014			
	13-14	80	0.0929	0.0848 – 0.1011	0.004			
	15-16	100	0.1375	0.0804 – 0.1945	0.021			
	17-18	30	0.1571	0.0840 – 0.2301	0.023			
Physis	Open	247	-	-	-			
	Closed	168	0.1169	0.1006 – 0.1331	0.007			
Gender	Male	310	-	-	-	-	-	-
	Female	110	0.0085	-0.0064 – 0.0234	0.087	-0.0058	-0.0203 – -0.0087	0.124
BMI		420	0.0127	0.0103 – 0.0150	0.009			
Dominant Leg	Dominant	231	-	-	-			
	Non Dominant	189	0.0047	-0.1828 – 0.1923	0.802			
Cohort	Male Control	104	-	-	-			
	Female Control	110	0.0221	0.0191 – 0.0252	0.013			
	Football Academy	206	0.0205	0.0030 – 0.0381	0.043			
Activity Level	No Sport	70	-	-	-	-	-	-
	Sport	140	0.2442	0.0068 – 0.0421	0.036	0.0171	0.0024 – 0.0317	0.043
	Athlete	210	0.0274	0.0096 – 0.0452	0.033	0.0322	0.0183 – 0.0020	0.022
Physical Activity Questionnaire		420	-0.0397	-0.0552 - -0.0243	0.019			

*Age, Gender and Activity Level as Covariates

Table 3-16 – Relationship Between Playing Position and Epiphyseal Extension at 1 O’Clock in Footballers

		Number of Hips	Univariate Regression			Multivariate Regression*		
			Coefficient	95% Confidence Intervals	p value	Coefficient	95% Confidence Intervals	p value
Playing Position	Midfielder	70	-	-	-	-	-	-
	Goalkeeper	22	-0.0249	-0.1147 – 0.0649	0.176	-0.0257	-0.1160 – 0.0645	0.171
	Winger	28	0.0211	-0.0734 – 0.1157	0.216	-0.0142	-0.0648 – 0.0364	0.174
	Defender	66	0.0341	-0.0816 – 0.1499	0.166	0.0112	-0.1109 – 0.1332	0.453
	Striker	20	0.0192	0.0100 – 0.0294	0.024	0.0021	-0.0116 – 0.0158	0.306

*Age and Gender as Covariates

Table 3-17 – Relationship Between Type of Sport and Epiphyseal Extension at 1 O’Clock in Controls

		Number of Hips	Univariate Regression			Multivariate Regression**		
			Coefficient	95% Confidence Intervals	p value	Coefficient	95% Confidence Intervals	p value
Sport Activity	No Regular Sport	72	-	-	-	-	-	-
	Football or Rugby	62	0.0193	-0.0124 – 0.0510	0.082	0.0077	-0.1499 – 0.1652	0.647
	All Other Sports	80	0.0269	-0.0046 – 0.0585	0.059	-0.0034	-0.0705 – 0.0637	0.639

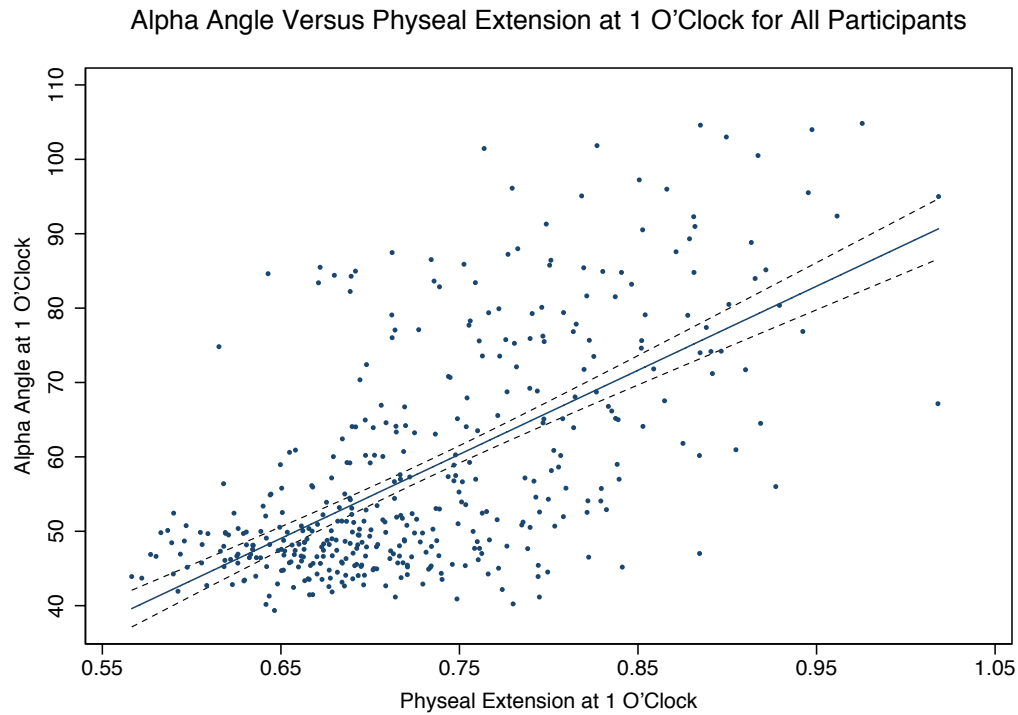
**Age, Gender, and Activity Level as Covariates

3.14 Relationship Between Epiphyseal Extension and Alpha Angle

The strongest correlation between epiphyseal extension and alpha angle was at the 1 o'clock position, with progressively weaker correlations either side of this location (Table 3-18, Figure 3-32). This relationship was seen in male but not female participants (Table 3-19). In male footballers, 50% of the variability in alpha angle is explained by the adjacent epiphyseal extension (Table 3-19). Outliers with a high alpha angle and low epiphyseal extension are compatible with cam morphology secondary to SUFE.

Table 3-18 - Regression of Epiphyseal Extension and Alpha Angle in All Participants

Clockface Position	Correlation Coefficient	95% Confidence Intervals	Statistical Significance	R ² Value
11 O'Clock	80.12	-89.99 – 250.24	0.105	0.154
12 O'Clock	99.21	41.33 – 157.08	0.029	0.299
1 O'Clock	112.99	25.04 – 200.94	0.039	0.398
2 O'Clock	79.89	-54.36 – 214.13	0.084	0.332
3 O'Clock	59.40	-52.83 – 171.62	0.094	0.202
Maximum All Positions	128.71	56.40 – 201.02	0.028	0.382

Figure 3-32 - Alpha Angle Versus Epiphyseal Extension at 1 O'Clock with Linear Regression Fit and 95% Confidence Intervals**Table 3-19 - Regression of Epiphyseal Extension and Alpha Angle in Each Population**

Clockface Position	Football Academy		Male Controls		Female Controls	
	Regression Coefficient	R ² value	Regression Coefficient	R ² value	Regression Coefficient	R ² value
11 O'Clock	99.81	0.229	47.15	0.082	36.08	0.030
12 O'Clock	116.43	0.401	101.23	0.279	55.86	0.130
1 O'Clock	126.24	0.498	130.78	0.491	53.62	0.129
2 O'Clock	108.66	0.463	82.67	0.423	38.88	0.163
3 O'Clock	87.94	0.330	68.48	0.296	22.61	0.054
Maximum All Positions	140.45	0.464	130.10	0.379	104.14	0.285

3.15 Quantitative MRI Morphology: Physeal Ratio

The ratio between epiphyseal extension on opposing sides of the femoral head was used as a measure of physeal tilt and termed 'physeal ratio' (Chapter 2). The change in physeal ratio with age was different at each clockface (Table 3-20, Appendix C-21, Appendix C-22). There was a decrease at the 11 o'clock and 12 o'clock positions (extension of the inferior physis relative to the superior physis) and an increase at the 2 o'clock and 3 o'clock positions (extension of the anterior physis relative to the posterior physis) (Table 3-20, Appendix C-24, Appendix C-25, Appendix C-26, Appendix C-27, Appendix C-28, Appendix C-29). The same trend was seen across each cohort (Appendix C-23). There was only limited correlation with alpha angle (Figure 3-33, Figure 3-34, Table 3-21). The greatest correlation was at the 3 o'clock position and the overall direction of change of the physeal ratio opposed that expected in SUFE (Figure 3-35 & Figure 2-9). Once the physis has closed, the physeal ratio is greatest at the 1 o'clock position (Figure 3-33 and Figure 3-34) and is highest in the footballer cohort (Appendix C-21 & Appendix C-22).

Table 3-20 - Regression of Physeal Ratio and Months of Age in All Participants

Clockface Position	Correlation Coefficient	95% Confidence Intervals	Statistical Significance	R ² Value
11 O'Clock	-0.0035	-0.004 - -0.003	0.008	0.331
12 O'Clock	-0.0017	-0.002 - -0.001	0.008	0.089
1 O'Clock	0.0000	-0.004 - 0.004	0.975	0.000
2 O'Clock	0.0012	-0.002 - 0.004	0.123	0.033
3 O'Clock	0.0018	-0.000 - 0.004	0.051	0.219
Maximum All Positions	-0.0008	-0.005 - 0.003	0.215	0.019

Figure 3-33 - Mean Physeal Ratio in Participants with an Open Physis

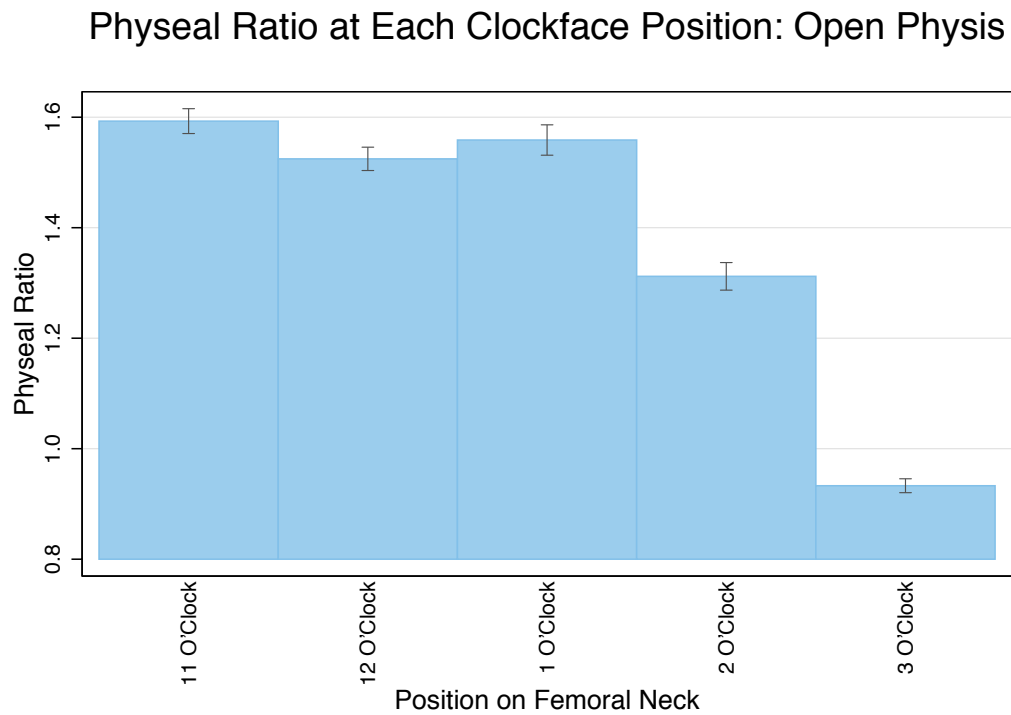


Figure 3-34 - Mean Physeal Ratio in Participants with a Closed Physis

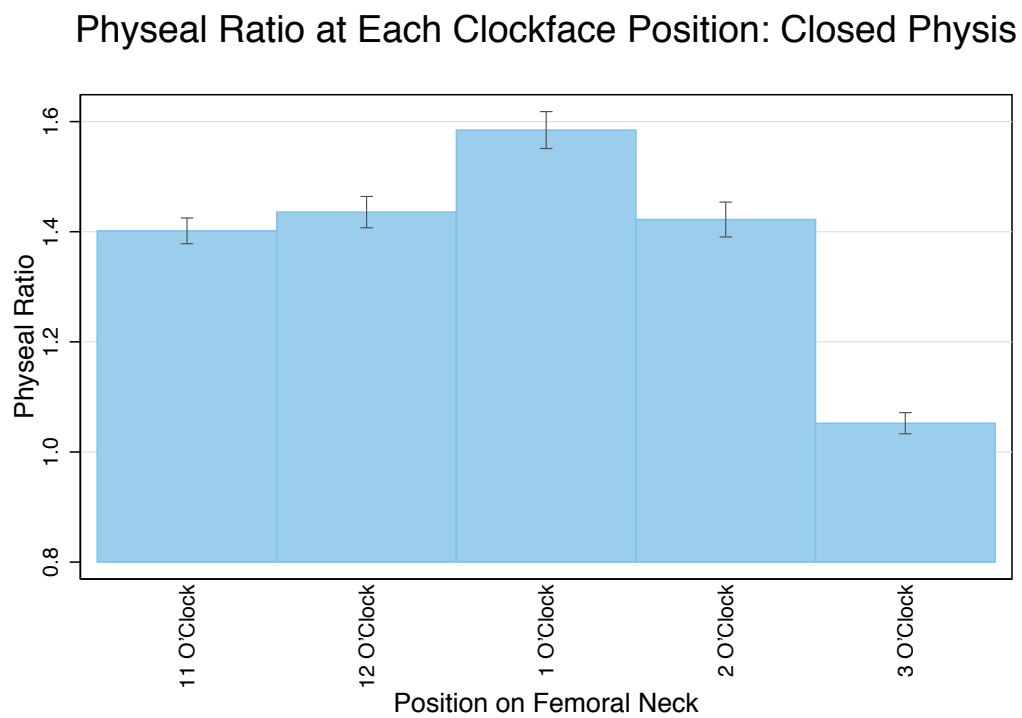
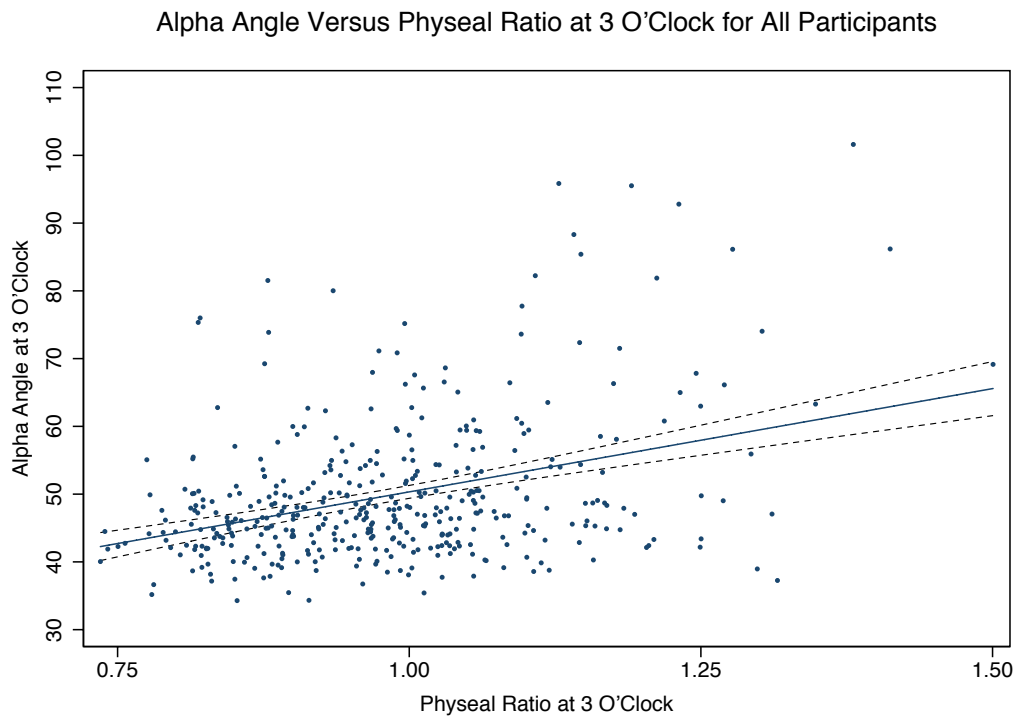


Table 3-21 - Regression of Physeal Ratio and Alpha Angle in All Participants

Clockface Position	Correlation Coefficient	95% Confidence Intervals	Statistical Significance	R ² Value
11 O'Clock	-5.641	-72.50 – 61.22	0.478	0.011
12 O'Clock	0.065	-24.09 – 24.22	0.978	0.000
1 O'Clock	8.286	-13.87 – 30.44	0.132	0.015
2 O'Clock	9.540	-10.53 – 29.61	0.104	0.028
3 O'Clock	30.486	23.86 – 37.11	0.011	0.134
Maximum All Positions	0.737	-47.77 – 49.25	0.879	0.000

Figure 3-35 - Alpha Angle Versus Physeal Ratio at 3 O'Clock with Linear Regression Fit and 95% Confidence Intervals



3.16 Discussion

The study aim was to improve our understanding of cam morphology pathogenesis. In particular, we sought to describe morphological changes at the physis that take place during adolescence, explore at what age cam morphology develops, and investigate whether there is an association between the development of cam morphology and participant demographics or activity levels.

Within this cohort of athletes and controls, epiphyseal hypertrophy and extension along the femoral neck was the salient mechanism of cam morphology development. These changes were maximal at the 1 o'clock position. Epiphyseal morphology was relatively uniform at this position amongst individuals aged 9-10 years, but with advancing physiological age there was increasing variation. Asphericity at the 3 o'clock position was infrequent and dictated by metaphyseal rather than epiphyseal morphology. The relative proportion of different metaphyseal morphologies were similar within in each age group. Factors that influence epiphyseal extension and hypertrophy are therefore likely to be different to those that dictate metaphyseal morphology and asphericity at the 3 o'clock position. Appearances at the 11 o'clock and 12 o'clock positions demonstrate that the epiphysis is not the sole contributor to cam morphology at this location. Discrete tissue obliterates the femoral head-neck concavity and it not known whether this tissue subsequently ossifies. Selective follow-up radiographic or computerised tomography studies may warrant consideration. A hypothesis is that this tissue represents hypertrophy of the Perichondrial Fibrous Ring of La Croix. The presence of fibrous tissue diminishing the femoral head-neck concavity represents a significant limitation of radiographic studies performed to date and may explain discordances between radiographic and clinical findings^{244,265}.

Cam morphology was quantified using the alpha angle, which increased most rapidly between the ages of 12 and 14. This finding is consistent with reports from comparable studies that describe cam development within the same age range^{259,261}. The prevalence of cam morphology within females from this cohort was insufficient to make a robust comparison between the age of cam development between sexes. Nevertheless, cam morphology may develop at a slightly younger age in females given their earlier physeal closure.

The increase in alpha angle correlates with the qualitative observation of differential epiphyseal extension between participants that commences at 10 years of age. Epiphyseal hypertrophy and extension represented the salient mechanism of cam development in this cohort. Quantitative measures of epiphyseal extension also increased most rapidly between ages 12 to 14 years. Past studies concluded that epiphyseal extension precedes the development of cam morphology^{262,265}, whereas data from this study demonstrates a concomitant association. The likely explanation is that in this study alpha angle was measured on cartilage rather than bone, hence it was possible to detect morphological changes that precede ossification.

The age at which cam morphology develops may indicate a critical period of hip development when the physis is sensitive to potentially modifiable physiological or environmental factors. It is of note that the timing of cam morphology development corresponds with the average age of SUFE presentation²⁵¹. Studies to date have shown that alpha angle remains constant after physeal closure²⁶⁵ and results from this study do not reveal a statistically significant change in maximum alpha angle after 14 years of age. Persisting plasticity beyond 14 years of age cannot be ruled out, however, interventions to influence the development of cam morphology are most likely to be effective when implemented prior to the age that cam morphology first develops. The cross-sectional study design and the absence of an established threshold to define cam morphology

makes it difficult to differentiate normal growth from the development of pathological morphology. Bone alpha angles were extremely similar amongst all participants until 12 years of age, beyond which there was a sudden increase in the range of alpha angle values (Figure 2-7). This increasing range of values is compatible with the development of cam morphology in a proportion of individuals. A possible interpretation is that cam morphology is only present beyond 12 years of age, as concluded in a number of studies^{259,261}. However, the range of cartilage alpha angles has already started to increase at age 10 years and likely reflects early physeal changes that precede ossified epiphyseal extension. The planned longitudinal element of this study will further elucidate the timing of cam morphology development.

The distribution of alpha angles and epiphyseal extension in this study is similar to that reported in comparable cohorts²²⁹. The highest absolute value and greatest increase in alpha angle was at the 1 o'clock position for males and 2 o'clock for females. There was no statistically significant difference in alpha angles at the 1 o'clock and 2 o'clock positions, however, gender differences remain possible. The quantitative measures of epiphyseal extension accurately reflect qualitative observations.

Whereas this study demonstrates an increase in alpha angle with age at all clockface positions, other studies have reported higher alpha angles in healthy volunteers with an open physis compared with a closed physis²⁵⁹. This finding can be reproduced using data from this study when measuring the bone alpha angle rather than cartilage alpha angle. In the skeletally immature hip the ossified femoral head is small relative to the metaphysis, which gives rise to a raised alpha angle but does not necessarily reflect cam morphology. Alpha angle measurements in relation to bone must be interpreted with caution in the immature skeleton (Chapter 2).

Epiphyseal extension also increased with age at all clockface positions, as reported in other studies and consistent with normal development²¹⁴. The highest absolute value and greatest increase in epiphyseal extension was again at the 1 o'clock and 2 o'clock positions, adding support to an association with alpha angle²²⁸. Results from this study demonstrate stronger correlations between measurements of epiphyseal extension and alpha angle than have previously been reported²⁶². In males, 50% of the variability in alpha angle was explained by adjacent epiphyseal extension. It is likely that epiphyseal extension is a salient mechanism of cam morphology development, but not the only mechanism. Furthermore, the measure adopted to quantify epiphyseal extension in this study provides only limited assessment of epiphyseal morphology that can give rise to asphericity. It is not sensitive to epiphyseal hypertrophy without extension (Figure 3-10). The relationship between epiphyseal extension and alpha angle is particularly weak in females. It is possible that an alternative aetiology of cam morphology dominates in females, such as femoral asphericity secondary to dysplasia.

Epiphyseal hypertrophy and extension are not responsible for raised alpha angles at the 3 o'clock position where asphericity is dictated by metaphyseal morphology. Although femoral head retroversion was identified as a potential cause of asphericity during qualitative assessment, this morphology had a similar prevalence amongst all age groups. No cases of SUFE were identified and quantitative study data countered the hypothesis that SUFE is a significant aetiological factor for the development of cam morphology. At the 3 o'clock position, there was a positive correlation between the physeal ratio and alpha angle, indicating greater epiphyseal extension anteriorly relative to posteriorly, contrary to that expected in SUFE.

Factors were sought that predict alpha angle and epiphyseal extension. Both alpha angle and epiphyseal extension were greater in males than females, as has been widely reported in general population cohorts⁴⁴. The explanation for this gender difference

remains unknown, however, physiological and environmental factors may be important. Interestingly, the sex ratio for cam morphology is similar to that in SUFE²⁵¹, perhaps indicating that the physis is more susceptible to external factors in males. BMI was not associated with alpha angle or epiphyseal extension.

Activity levels were strongly associated with both alpha angle and epiphyseal extension. There was a stepwise increase from participants who play no regular sport, to participants who play sport for a school or club, and then participants who compete at a national or international level. A comparable study also found increased alpha angles⁴⁷ and epiphyseal extension²⁶² in athletes compared with a control group. Conversely, two other studies comparing alpha angles in elite footballers and a control population failed to demonstrate a statistically significant difference, probably due to insufficient statistical power^{48,264}. The FAIM cohort is significantly larger and provides strong evidence that high activity levels during adolescence promote the development of cam morphology secondary to epiphyseal extension and that there appears to be a dose-response relationship.

Activity levels are extremely challenging to quantify. In this study, the competitive level of sport participation was used as a surrogate measure of exercise intensity. General activity levels measured using the PAQ did not predict cam morphology. PAQ is particularly responsive to exercise frequency, and scores are significantly higher in younger age groups as it records playground activities. The results from this study suggest sport rather than general activity is more important in the aetiology of cam morphology. The use of electronic activity trackers may aid future studies, but even these are not able to accurately record exercise intensity and joint loading.

This study reproduced the findings of a previous study that there is no difference in alpha angle or epiphyseal extension between dominant and non-dominant legs⁴⁸. This

counters the hypothesis that the action of kicking imparts force across the physis that stimulates epiphyseal extension. Footballers are encouraged to develop kicking skills with both feet and this may partially explain the findings, however, no difference was detected in the magnitude of cam morphology within the control group between those who played kicking and non-kicking sports. At present, the aetiology of cam morphology is not sufficiently understood to recommend activity modification as a preventative strategy. However, individuals participating in high level sports during adolescence should be acknowledged to be at greater risk of cam morphology and may warrant surveillance.

3.16.1 Limitations

There are limitations to this study. First, the cross-sectional study design can only provide limited information on longitudinal changes in hip morphology and repeat assessment of this cohort is planned. Furthermore, whilst demonstrating association, the study does not demonstrate causality with respect to the development of cam morphology. Second, the control group may not be entirely representative of the general population as individuals who regularly participate in sport may be more likely to volunteer for a project investigating the effects of exercise. Nevertheless, there were statistically significant differences in cam morphology between the control group and athlete cohort. Third, activity levels were ascertained using questionnaires completed by participants, whereas electronic activity trackers may have provided more objective data. Fourth, alpha angle and epiphyseal extension are two-dimensional measurements applied to a complex three-dimensional structure and only provide a limited assessment. Three-dimensional active shape modelling may provide further insight, however, further validation is required to allow clinical translation of this technique. Finally, the magnitude of alpha angle that is pathological remains unknown, whilst cam

morphology alone is known to have a poor predictive value for pain and osteoarthritis¹³. Therefore, the clinical relevance of these findings is unclear, but will be further addressed with the longitudinal element of the study.

3.17 Conclusions

Cam morphology develops during adolescence and is associated with adjacent epiphyseal extension. The highest absolute values and greatest increase in alpha angle and epiphyseal extension are at the 1 o'clock position. There are many causes of cam morphology, however, in an active male cohort epiphyseal extension appears to be a salient mechanism. Conversely, there was little evidence of this pathogenesis in females. Activity level during adolescence is strongly associated with the development of cam morphology, and exercise intensity may be more important than volume. Nevertheless, the cardiovascular benefits of exercise outweigh the potential effects on hip morphology.

Chapter 4 Validation of Compositional MRI (SibKid Study)

4.1 Abstract

Introduction:

Delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) is able to detect glycosaminoglycan loss in acetabular cartilage of asymptomatic individuals with cam morphology. The aim of this study is to explore the relationship between hip morphology and dGEMRIC values, and to determine whether baseline dGEMRIC can predict radiographic osteoarthritis.

Methods:

Prospective study of individuals with a family history of osteoarthritis who underwent clinical evaluation including radiographic and dGEMRIC assessment at baseline and five year follow-up. Cam morphology was defined as an alpha angle greater than 60 degrees and osteoarthritis development as joint space width narrowing greater than 0.5mm on anteroposterior radiographs. dGEMRIC values of different cartilage regions were correlated with alpha angle. Baseline variables underwent ROC analysis for diagnosing future radiographic osteoarthritis.

Results:

The study comprised 34 individuals (26 cam morphology and 8 normal morphology) at baseline and 29 (23 cam morphology and 6 normal morphology) at follow-up. 9 participants demonstrated clinically relevant joint space narrowing between assessments. Superoanterior acetabular cartilage dGEMRIC value was significantly lower in participants with cam morphology ($p < 0.001$). There was a negative correlation

between the size of the alpha angle and dGEMRIC value of the adjacent acetabular cartilage, which was greatest superoanteriorly ($r=-0.697$). There was a positive correlation between baseline dGEMRIC and change in joint space width ($r=0.392$). ROC analysis of combined baseline variables gave an AUC of 0.75 for prediction of radiographic osteoarthritis.

Conclusions:

Cam size and position determines the severity and location of progressive cartilage damage. Baseline dGEMRIC is able to predict radiographic osteoarthritis. Compositional MRI offers the potential to identify patients who may benefit from early intervention to prevent the development of osteoarthritis.

4.2 Introduction

It may not be possible or feasible to prevent the development of cam morphology. Therefore, alternative strategies are required to prevent the development or progression of hip osteoarthritis. The success of preventative strategies is likely to depend on the ability to accurately identify individuals at risk of future osteoarthritis, or to diagnose early disease when it remains potentially reversible. In addition, sensitive diagnostic tools may permit the evaluation of treatment efficacy within a short timeframe. Compositional MRI offers this potential, however, it requires further validation as an assay of osteoarthritis²⁰.

Delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) is able to detect glycosaminoglycan loss²⁷⁸ seen in early osteoarthritis⁷⁰. Cartilage dGEMRIC values correlate with the magnitude of cam deformity in patients with symptomatic femoroacetabular impingement²⁷⁹, and asymptomatic volunteers⁵⁴. Individuals with cam morphology also have lower dGEMRIC values than healthy controls in the absence of radiographic osteoarthritis²⁸⁰. In hip dysplasia, dGEMRIC correlates with pain and severity of hip dysplasia, supporting its role as a sensitive marker of early osteoarthritis²⁸¹.

It may eventually be possible to select asymptomatic individuals for intervention to prevent future osteoarthritis. At present there remains only limited evidence that baseline dGEMRIC values predict disease progression. In patients with hip dysplasia, dGEMRIC predicted the success of a peri-acetabular osteotomy in patients within 24 months¹⁰³.

In order to explore the clinical value of dGEMRIC for predicting the development and progression of osteoarthritis secondary to cam morphology femoroacetabular

impingement, a cohort of healthy volunteers was followed up five years after initial assessment⁵⁴.

4.3 Aims

- 1) Explore whether dGEMRIC values correlate with the size and position of cam morphology
- 2) Determine whether baseline dGEMRIC predicts radiographic osteoarthritis progression at five-year follow-up.

4.4 Methods

4.4.1 Ethics

Ethics approval was granted by Oxfordshire Research Ethics Committee B (07Q1605/26).

4.4.2 Population

At baseline, participants were selected from a prospective longitudinal cohort of individuals considered at high risk of developing osteoarthritis (SibKids)^{282,283}. SibKids are the offspring of families where at least two siblings received total hip arthroplasty for end-stage osteoarthritis, with their spouses recruited as controls²⁸⁴. The original cohort comprised 123 SibKids (62 males and 61 females) and 80 spouse controls (39 males and 41 females)²⁸². SibKids and their spouse controls were selected for baseline dGEMRIC if both hips fulfilled the following criteria:

- 1) No investigation or treatment for hip pain within the previous two years.
- 2) Minimum joint space width greater than 2.5mm and Kellgren-Lawrence Grade less than 2 on anteroposterior radiographs.

- 3) No radiographic evidence of dysplasia or pincer morphology.

Each participant received dGEMRIC evaluation of a single hip selected at baseline based upon the greatest suspicion of femoroacetabular impingement on clinical assessment and radiographic appearance. All participants who received baseline dGEMRIC assessment were invited to return for five-year follow-up⁵⁴.

4.4.3 Questionnaire

Participants completed a Non-Arthritic Hip Score²⁸⁵ and Oxford Hip Score²⁸⁶ on the day of assessment. Past medical history was sought prior to assessment to ensure there were no contraindications to MRI or intravenous contrast. Royal College of Radiologists guidelines were followed for the use of ionic contrast, and where indicated, renal function was checked prior to assessment.

4.4.4 Clinical Assessment

The Principal Investigator performed the clinical examination for each participant. Passive range of movement was measured with a goniometer. Special tests relevant to femoroacetabular impingement included FADIR (groin discomfort on flexion, adduction, and internal rotation) and FABER (groin discomfort on flexion, abduction, and external rotation).

4.4.5 Radiographic Assessment

A standing anteroposterior and cross-table lateral radiograph was acquired at baseline and follow-up. Anteroposterior radiographs were performed with the beam centred in the midline between the superior border of the pubic symphysis and a line connecting the anterior superior iliac spines²¹⁶. Radiographs were repeated if the obturator foramen index was outside 0.7-1.4²⁴¹. Lateral radiographs were performed with the beam parallel

to the table and orientated 45 degrees to the index hip centred on the femoral head. The hip was positioned in 15 degrees of internal rotation with the aid of a wedge²¹⁶.

Radiographs were analysed non-sequentially using OxMorf 2.1.0-dev6 software in a non-sequential manner by two observers. Osteoarthritis progression was assessed on the anteroposterior radiograph using minimum joint space width (minJSW) and joint space width at the lateral sourcil (latJSW) and medial sourcil (medJSW). JSW values were corrected using a 20mm calibration ball. The smallest detectable difference in JSW was calculated as $1.96 \times$ standard deviation of the mean difference in JSW between two readings from the same radiograph. A clinically relevant reduction in minJSW was considered to be greater than 0.5mm⁹³. Cam morphology was evaluated on the anteroposterior and cross-table lateral radiograph using the alpha angle²⁰⁸(Chapter 2). For the purposes of this study, cam morphology was defined as an alpha angle greater than 60 degrees on anteroposterior radiographs, as proposed in a longitudinal study of two general population cohorts¹⁴.

4.4.6 MRI Protocol

The imaging protocol performed at baseline was repeated at follow-up. MRI scans were performed using the same 3 Tesla Philips Achieva X-series platform (Philips Healthcare, Eindhoven, Netherlands) with two flexible surface coils (medium and large) as was used at baseline.

4.4.6.1 Morphology

Prior to administering contrast for the dGEMRIC scan, the index hip was imaged with a 3D Gradient Echo sequence (WATSf) with repetition time (TR) 13.65ms, echo time (TE) 6.9ms, flip angle 30 degrees, bandwidth 145Hz/pixel, field of view 150mm x 150mm x 70mm, acquisition matrix 248 x 188 x 88 (interpolated to 512 x 512 x 175), acquired in a true sagittal orientation. Scan time was 8 minutes. Three-dimensional multiplanar

reconstructions were produced as radial slices around the axis of the femoral neck at 30 degree intervals. The coronal axis (12 o'clock position) was positioned parallel to the axis of the proximal femur diaphysis. Cam morphology was quantified by measuring the alpha angle on each of the radial slices.

4.4.6.2 dGEMRIC

0.2mM/Kg of Magnevist (dimeglumine gadopentetate [Gd-DTPA²⁻], Bayer Schering Pharma, Berlin, Germany) was administered intravenously. A standardised exercise protocol was completed comprising a 10 minute walk on a treadmill at 4km per hour, followed by 150 hip movements (50 flexion, 50 internal rotation, 50 external rotation) in order to ensure full perfusion of the gadolinium into the articular cartilage²⁸⁷. 75 minutes after contrast administration the dGEMRIC sequence was commenced. Sequence parameters comprised sagittal inversion-prepared 3D-turbo-field-echo (TFE) with repetition time (TR) 6.0ms, echo time (TE) 2.9ms, flip angle 12 degrees, bandwidth 289Hz/pixel, inversion times (Ti) 2100, 1200, 600, 250, and 105ms, field of view 180mm x 180mm, slice thickness 3mm, acquisition matrix 208 x 209 (interpolated to 512 x 512). The first slice was aligned with the most medial aspect of the femoral head and the remaining slices extending laterally with no gap between slices providing three-dimensional coverage of the joint (Figure 2-15). To attain sufficient signal-to-noise at the short Tis, TR_{short} was held constant at 2200ms for each Ti. Scan time was 45 minutes. Quantitative T1 maps were generated using custom code (MATLAB R2015a, MathWorks, Natick, MA, USA) fitting a basic inversion recovery model equation on co-registered images.

4.4.7 Segmentation

Baseline and follow-up sagittal dGEMRIC images were manually segmented using OsiriX Software (Version 6.0.2 64 Bit, Pixmeo, Geneva, Switzerland) by a single observer

(academic orthopaedic clinician) who was blind to the time point of the scan and the presence of cam morphology. Regions of interest were developed based on a clock face around the centre of the femoral head at 30 degree intervals (Figure 2-16). Regions were referenced from the 12 o'clock position that passes through the centre of the femoral head parallel to the axis of the proximal femur diaphysis. The 3 o'clock boundary was positioned perpendicular to this line and represented an anterior position for both left and right hips. Femoral and acetabular cartilage was segmented separately and regions of interest were not extended beyond where there was adjacent femoral and acetabular cartilage, hence did not include the chondrolabral junction. Regions of interest were denoted as:

Aa Anterior Acetabular Cartilage

ASa AnteroSuperior Acetabular Cartilage

SAa SuperoAnterior Acetabular Cartilage

SPa SuperoPosterior Acetabular Cartilage

PSa PosteroSuperior Acetabular Cartilage

Pa Posterior Acetabular Cartilage

Af Anterior Femoral Cartilage

ASf AnteroSuperior Femoral Cartilage

SAf SuperoAnterior Femoral Cartilage

SPf SuperoPosterior Femoral Cartilage

PSf PosteroSuperior Femoral Cartilage

Pf Posterior Femoral Cartilage

Mean T1 relaxation time was calculated for each region of interest (ROI) within the medial and lateral joint, since degenerative change secondary to cam morphology was anticipated to develop laterally^{38,54}. T1 values within each ROI were expressed as a ratio of the mean T1 relaxation time for all segmented cartilage. This technique overcomes physiological variables that influence the delivery of contrast agent to the joint²³⁷, which limit the ability to investigate longitudinal change or compare absolute values between participants. Each hip therefore acts as an internal control⁵⁴.

4.4.8 Statistical Analysis

Statistical analysis was performed using STATA 12.0 (College Station, TX, USA). Longitudinal change in outcome measures was assessed using paired t-tests after confirming normality with kernel density plots. Correlation was evaluated using linear regression and expressed as a correlation coefficient. Reproducibility was assessed using the intra-class coefficient of correlation (ICC) for absolute agreement. Level of significance was set at $p < 0.05$.

Receiver operating characteristic (ROC) analysis was performed on individual variables with a binary outcome of radiographic progression at the lateral sourcil greater than 0.5mm. In addition to individual variables, a combined variable for alpha angle on AP radiograph, dGEMRIC ratio in SAa, and a positive impingement test was generated. Individual variables were rescaled to have a SD of 1 (denoted by underlining), hence the aggregate biomarker weight gives an estimate of importance¹⁵⁶.

Combined = $(0.70 \times \text{Radiographic AP alpha angle}) + (0.50 \times \text{Baseline SAa dGEMRIC ratio}) + (0.28 \times \text{Positive Impingement})$

4.4.9 Reproducibility

The primary observer repeated all morphological measurements and the segmentation of five randomly selected hips (214 regions of interest) 12 months after their original readings. A second observer performed the same measurements. Intra-observer ICCs were 0.983 for radiographic alpha angle, 0.962 for MRI alpha angle, 0.990 for minimum joint space width, 0.993 for joint space width at the medial and lateral sourcil, and 0.990 for the mean T1 value in each region of interest. Inter-observer ICCs were 0.830 for radiographic alpha angle, 0.956 for MRI alpha angle, 0.932 for minimum joint space width, 0.990 for joint space width at the medial and lateral sourcil, and 0.980 for the mean T1 value in each region of interest. The smallest detectable difference was 0.21mm for minimum JSW and 0.41mm for lateral JSW (Chapter 2).

4.5 Results

4.5.1 Cohort Characteristics

At baseline 34 individuals participated in the study (15 female, 19 male, mean age 52 years, range 36 – 67) and 29 individuals (14 female, 15 male, mean age 57 years, range 41 – 72) returned for follow-up. This equates to a 14.7% loss to follow-up. Of the five participants who did not return for repeat assessment, two could not attend because they had geographically relocated, and we were unable to contact three participants. Follow-up assessments took place an average 58 months (range 52 – 62) after baseline assessment.

Two participants who attended follow-up did not receive a repeat dGEMRIC scan. One participant had developed a medical contra-indication to MRI, and the other had developed impaired renal function precluding the administration of contrast. An additional two follow-up dGEMRIC scans were not interpretable due to a technical failure of the MRI scanner hardware.

Defining cam morphology as an alpha angle greater than 60 degrees on baseline anteroposterior radiographs of the index hip¹⁴, the cohort included 26 individuals with cam morphology and 8 individuals with normal morphology. After loss to follow-up, the cohort comprised 23 individuals with cam morphology and 6 individuals with normal morphology. The cohort with follow-up dGEMRIC scans comprised 20 individuals with cam morphology and 5 individuals with normal morphology.

Within the cohort (n=29), minJSW fell from mean 3.70mm (SD 0.80) to 3.41mm (SD 0.90) (paired t-test p=0.013). Defining progression as reduction in minJSW greater than 0.5mm, eight participants displayed radiographic disease progression (28%). Given cam lesion femoroacetabular impingement results in chondropathy at the lateral

acetabulum^{38,54}, JSW was also measured at the lateral sourcil where JSW fell from mean 4.80mm (SD 0.90) to 4.43mm (SD1.19) (paired t-test $p<0.001$). Defining progression as reduction in JSW >0.5 mm at the lateral sourcil, nine participants displayed progressive radiographic disease (31%).

Mean alpha angle on baseline AP radiographs in participants with greater than 0.5mm minimum JSW reduction was 84.97 degrees (SD 19.58) compared with 78.74 degrees (SD 21.40) in those without progression ($p=0.55$). Mean alpha angle on baseline AP radiographs in participants with greater than 0.5mm lateral sourcil JSW reduction was 88.05 degrees (SD 21.24) compared with 77.04 degrees (SD 18.50) in those without progression ($p=0.33$). There was no longitudinal change in alpha angle with mean 78.46 degree (SD 25.64) at baseline and 78.89 (SD 25.76) at follow-up ($p=0.67$).

Oxford Hip Score fell from mean 46.93 (SD 2.49) at baseline to 45.69 (SD 4.42) (paired t-test 0.091) at follow-up. Non-Arthritic Hip Score fell from mean 97.80 (SD 3.62) at baseline to mean 94.40 (SD 11.53) (paired t-test 0.064) at follow-up. There was no correlation with radiographic or MRI measures of osteoarthritis.

4.5.2 Global dGEMRIC Values

At baseline, the mean T1 relaxation time of all cartilage was 468.70ms (SD 39.99) for participants with normal morphology and 450.82ms (SD 30.15) for participants with cam morphology ($p=0.11$). At follow-up, the mean relaxation time was 402.15ms (SD 27.79) for participants with normal morphology and 421.43ms (SD 21.78) for participants with cam morphology ($p=0.07$). The decrease in average T1 relaxation between baseline and follow-up for all participants was highly significant ($p<0.001$).

4.5.3 Regional Variation in dGEMRIC Values

At baseline, one-way analysis of variance showed spatial heterogeneity in T1 relaxation times across all segmented regions of interest for both acetabular cartilage ($p<0.001$) and femoral cartilage ($p<0.001$) in patients with cam morphology. Conversely, there was no significant heterogeneity in patients with normal morphology in either acetabular cartilage ($p=0.10$) or femoral cartilage ($p=0.09$). At follow-up, there was spatial heterogeneity in acetabular cartilage ($p<0.001$) and femoral cartilage ($p=0.001$) in participants with cam morphology. Participants with normal morphology demonstrated spatial heterogeneity in acetabular cartilage ($p=0.026$) but not femoral cartilage ($p=0.56$).

T1 relaxation times for each region are expressed as absolute values and as a ratio of the mean value of all segmented cartilage within the joint (Table 4-1 & Table 4-2).

Average dGEMRIC ratio was lower in all regions of the lateral hip in participants with cam morphology compared with participants with normal morphology, however, this only reached statistical significance within superoanterior acetabular cartilage (region SAa) ($p=0.002$) (Table 4-3).

4.5.4 Longitudinal Change

In participants with cam morphology, there was a statistically significant decrease in the dGEMRIC ratio within the lateral superoanterior acetabular cartilage (SAa) between baseline and follow-up ($p=0.018$) (Figure 4-1 & Table 4-4). The decrease observed in the posterosuperior acetabular cartilage (PSa) almost reached statistical significance ($p=0.056$). There was no statistically significant change in any other region in participants with cam morphology or any region in participants with normal morphology (Table 4-5).

Chapter 4: Validation of Compositional MRI (SibKid Study)

Table 4-1 - Absolute Relaxation Times of Cartilage

Baseline								
	Lateral Half of Joint				Medial Half of Joint			
Region	Normal Morphology		Cam Morphology		Normal Morphology		Cam Morphology	
	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation
Aa	391.46	43.15	396.58	49.36	395.98	46.86	403.91	51.91
ASa	466.69	102.50	428.11	82.49	446.04	145.69	531.89	82.83
SAa	514.15	119.45	448.39	80.44	460.03	160.09	440.87	69.53
SPa	519.51	102.95	465.27	84.42	467.21	119.56	451.96	74.76
PSa	489.96	71.76	463.90	82.73	470.59	103.76	457.52	75.38
Pa	455.53	47.74	441.30	62.68	433.72	70.45	431.98	60.08
Af	480.91	76.30	480.47	81.51	438.73	84.62	495.51	89.51
ASf	525.52	123.15	495.96	91.25	549.58	137.96	492.12	108.05
SAf	507.71	145.27	467.37	78.99	524.33	163.81	458.22	98.72
SPf	479.80	129.34	443.92	69.66	486.78	149.77	441.97	80.81
PSf	443.84	74.14	433.74	69.30	467.49	111.98	450.34	85.82
Pf	411.47	61.18	403.37	52.81	421.72	130.42	395.10	121.46
Five Year Follow-Up								
	Lateral Half of Joint				Medial Half of Joint			
	Normal Morphology		Cam Morphology		Normal Morphology		Cam Morphology	
	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation
Aa	350.72	29.73	380.50	18.61	350.72	29.73	386.07	21.77
ASa	403.97	52.48	493.45	47.40	374.28	45.89	396.73	45.33
SAa	447.93	67.80	404.59	51.36	404.02	74.25	411.29	50.05
SPa	442.38	71.42	421.58	50.73	406.85	59.07	425.84	51.93
PSa	416.18	49.75	420.04	49.34	389.20	45.95	431.66	50.95
Pa	401.37	48.85	407.05	43.48	383.97	44.17	408.76	47.39
Af	428.56	42.15	450.77	37.76	458.32	42.15	451.40	32.38
ASf	433.28	72.29	456.35	54.62	438.49	83.50	453.47	59.07
SAf	405.48	78.66	431.53	52.29	411.47	89.07	435.07	60.19
SPf	397.39	69.25	411.10	48.95	397.24	77.67	417.38	57.72
PSf	381.36	46.95	405.25	51.00	401.55	61.87	417.21	56.21
Pf	359.14	31.06	390.55	47.63	367.77	34.45	406.79	51.21

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Table 4-2 - Ratio Relaxation Times of Cartilage

Baseline								
	Lateral Half of Joint				Medial Half of Joint			
Region	Normal Morphology		Cam Morphology		Normal Morphology		Cam Morphology	
	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation
Aa	0.8128	0.0934	0.9029	0.0831	0.8234	0.1019	0.9197	0.0886
ASa	0.9476	0.0694	0.9397	0.0815	0.8870	0.1221	0.9713	0.2327
SAa	1.0571	0.0863	0.9912	0.0901	0.9220	0.1933	0.9980	0.2194
SPa	1.0735	0.0588	1.0331	0.0856	0.9597	0.2354	1.0259	0.2281
PSa	1.0172	0.1309	1.0308	0.0893	0.9739	0.2381	1.0426	0.2440
Pa	0.9446	0.0462	0.9801	0.0940	0.8894	0.1608	0.9852	0.2457
Af	1.0274	0.1784	1.1316	0.1009	0.8952	0.0969	1.1931	0.4118
ASf	1.0942	0.2143	1.1496	0.3237	1.1559	0.2648	1.1411	0.3715
SAf	1.0468	0.2459	1.0704	0.2825	1.0779	0.2263	1.0514	0.3415
SPf	0.9841	0.2268	1.0062	0.2406	0.9879	0.1772	1.0006	0.2598
PSf	0.9115	0.1594	0.9807	0.2296	0.9529	0.1490	1.0263	0.2925
Pf	0.8352	0.1130	0.9002	0.1708	0.8352	0.1089	0.9083	0.3632
Five Year Follow-Up								
	Lateral Half of Joint				Medial Half of Joint			
	Normal Morphology		Cam Morphology		Normal Morphology		Cam Morphology	
	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation	Mean T1 Relaxation Time (ms)	Standard Deviation
Aa	0.9313	0.0320	0.9239	0.0791	0.9313	0.0320	0.9400	0.0936
ASa	0.9511	0.0755	0.9379	0.0734	0.8780	0.1122	0.9476	0.0789
SAa	1.0666	0.0646	0.9659	0.0574	0.9528	0.1362	0.9891	0.1173
SPa	1.0493	0.0488	1.0127	0.0502	0.9612	0.1079	1.0277	0.1045
PSa	0.9839	0.0561	1.0090	0.0529	0.9151	0.0891	1.0442	0.1034
Pa	0.9431	0.0346	0.9755	0.0677	0.9023	0.0946	0.9834	0.1175
Af	1.1289	0.0519	1.1236	0.1446	1.0922	0.0519	1.1327	0.1001
ASf	1.0362	0.1663	1.1164	0.1495	1.0506	0.1875	1.1037	0.1126
SAf	0.9572	0.1543	1.0438	0.1115	0.9703	0.1579	1.0500	0.0914
SPf	0.9361	0.1374	0.9858	0.0785	0.9343	0.1460	1.0010	0.0764
PSf	0.8953	0.1040	0.9692	0.0726	0.9452	0.1049	1.0008	0.0741
Pf	0.8401	0.1006	0.9319	0.0909	0.8607	0.0903	0.9734	0.0730

Table 4-3 - Difference in dGEMRIC Ratio between Participants with Cam and Normal Morphology

Mean dGEMRIC ratio in participants with normal hip morphology subtracted by mean dGEMRIC ratio in participants with cam morphology at five year assessment						
	Lateral Joint			Medial Joint		
	Change in dGEMRIC ratio	Standard deviation	Statistical Significance (p value)	Change in dGEMRIC ratio	Standard deviation	Statistical Significance (p value)
Aa	-0.0059	0.0529	0.877	+0.0138	0.2163	0.877
ASa	-0.0132	0.0429	0.723	+0.0696	0.1348	0.118
SAa	-0.1007	0.0619	0.002	+0.0363	0.2789	0.554
SPa	-0.0367	0.0847	0.155	+0.0665	0.2142	0.218
PSa	-0.0251	0.1068	0.357	+0.1290	0.1873	0.018
Pa	-0.0324	0.0822	0.316	+0.0811	0.2032	0.168
Af	-0.0394	0.2567	0.960	+0.0405	0.2134	0.998
ASf	-0.0803	0.3327	0.304	+0.0530	0.2697	0.419
SAf	-0.0866	0.1856	0.163	+0.0797	0.1764	0.146
SPf	-0.0497	0.1204	0.289	+0.0666	0.1410	0.163
PSf	-0.0074	0.0919	0.074	+0.0557	0.0899	0.179
Pf	-0.0918	0.0920	0.060	+0.1127	0.0737	0.071

Figure 4-1 - Longitudinal Change in dGEMRIC Ratio in Participants with Cam Hip Morphology

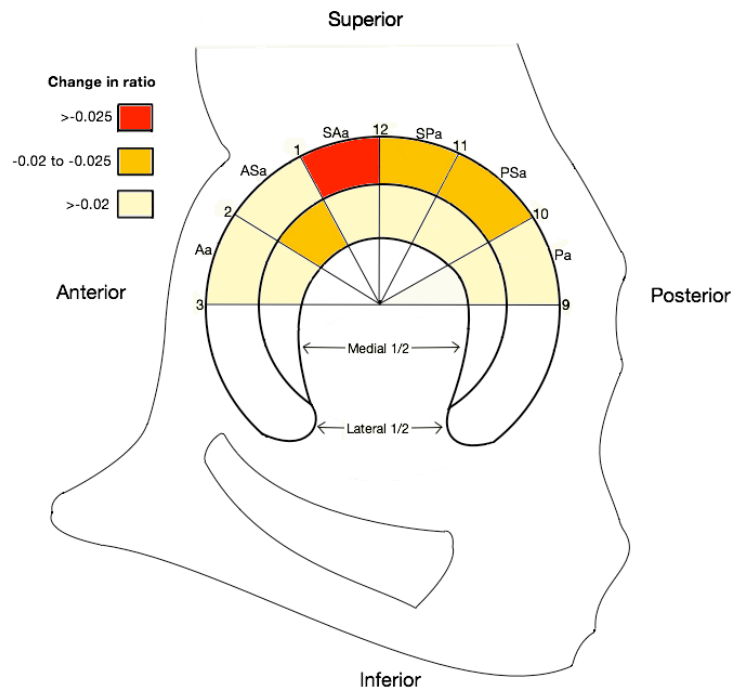


Table 4-4 - Longitudinal Change in dGEMRIC Ratio in Participants with Cam Hip Morphology

Change in mean dGEMRIC ratio in participants with cam hip morphology between baseline and five-year assessment						
	Lateral Joint			Medial Joint		
	Change in dGEMRIC ratio	Standard Deviation	Statistical Significance (p value)	Difference in dGEMRIC ratio	Standard deviation	Statistical Significance (p value)
Aa	+0.0541	0.0600	0.2801	+0.1400	0.1162	0.431
ASa	-0.0018	0.0727	0.5039	-0.0237	0.2436	0.594
SAa	-0.0253	0.0633	0.0181	-0.0089	0.2226	0.917
SPa	-0.0204	0.0704	0.0563	+0.0019	0.2632	0.935
PSa	-0.0218	0.0720	0.2346	+0.0015	0.2864	0.959
Pa	-0.0046	0.1151	0.6452	-0.0018	0.2631	0.791
Af	-0.0606	0.4989	0.6435	-0.0604	0.5368	0.555
ASf	-0.0332	0.3744	0.6475	-0.0375	0.4754	0.638
SAf	-0.0267	0.3301	0.7068	-0.0014	0.3889	0.962
SPf	-0.0204	0.2673	0.7124	+0.0004	0.2761	0.961
PSf	-0.0115	0.2598	0.8777	-0.0254	0.3231	0.668
Pf	+0.0317	0.1985	0.3726	+0.6500	0.4176	0.375

Table 4-5 - Longitudinal Change in dGEMRIC Ratio in Participants with Normal Hip Morphology

Change in mean dGEMRIC ratio in participants with cam hip morphology between baseline and five-year assessment						
	Lateral Joint			Medial Joint		
	Change in dGEMRIC ratio	Standard deviation	Statistical Significance (p value)	Change in dGEMRIC ratio	Standard deviation	Statistical Significance (p value)
Aa	+0.0784	0.0854	0.094	+0.0400	0.1439	0.144
ASa	+0.0035	0.0793	0.798	-0.0090	0.1629	0.420
SAa	+0.0095	0.0512	0.391	+0.0308	0.1965	0.539
SPa	-0.0242	0.0443	0.554	+0.0016	0.2854	0.610
PSa	-0.0334	0.0692	0.873	-0.0588	0.3101	0.440
Pa	-0.0015	0.1350	0.531	+0.0129	0.2859	0.931
Af	+0.1845	0.1946	0.496	+0.1969	0.2564	0.624
ASf	-0.0582	0.2019	0.277	-0.1053	0.3198	0.228
SAf	-0.0896	0.2407	0.221	-0.1076	0.2174	0.128
SPf	-0.0480	0.2251	0.310	-0.0535	0.1598	0.200
PSf	-0.0162	0.1765	0.597	-0.0077	0.1697	0.556
Pf	+0.0048	0.1302	0.950	+0.0255	0.1345	0.542

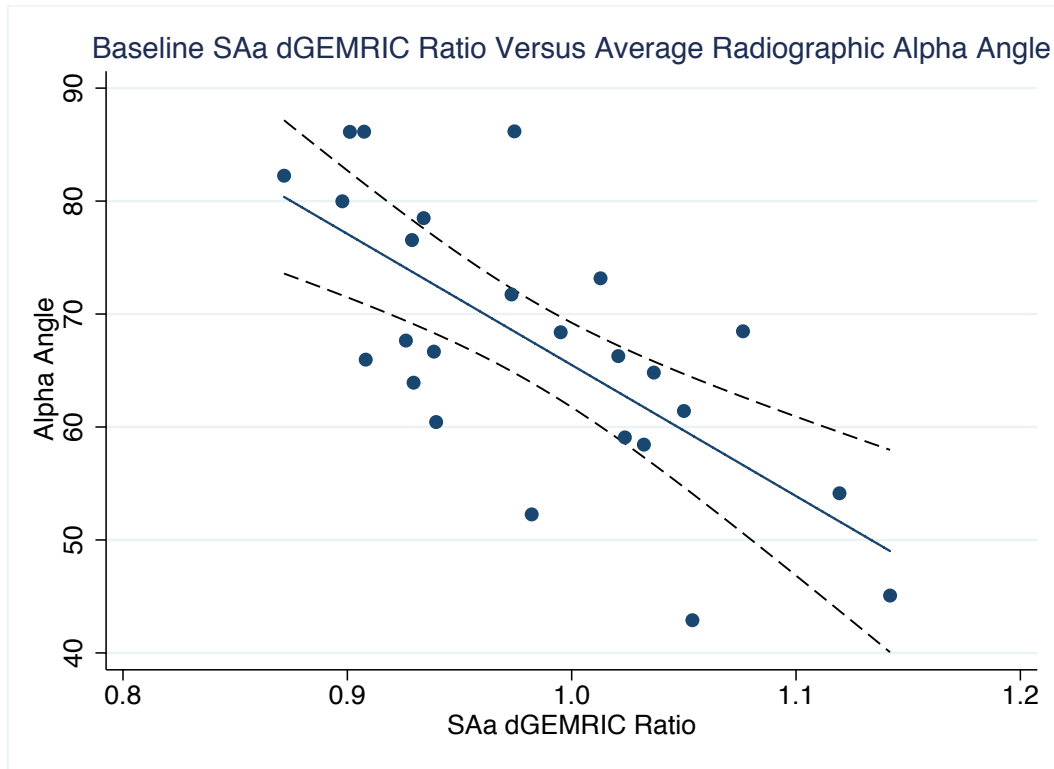
4.5.5 Spatial Localisation of Alpha Angle and dGEMRIC Ratio

In order to explore the relationship between cam lesion location and follow-up dGEMRIC measurements, three additional regions of interest were devised. These were created in order to increase the sampling area and improve the validity of results since anteversion of the acetabulum means there are fewer anterior acetabular cartilage regions as one moves laterally when using true sagittal imaging. These three regions were anterior (Aa+ASa), superior (ASa+SAa), and posterior (SAa+SPa) within the lateral acetabulum.

Alpha angle measured in all positions demonstrated a statistically significant correlation with dGEMRIC ratio in the superior acetabulum (SAa+SPa) except when measured at the 2 o'clock position. Alpha angles measured anteriorly (3 o'clock MRI and lateral radiograph) but at no other position correlated with dGEMRIC ratio within the anterior acetabulum (Aa + ASa). Alpha angle measurements performed at the 2 o'clock position on MRI did not correlate with the dGEMRIC ratio in any region (Table 4-6). The strongest correlation was between average radiographic alpha angle and the dGEMRIC ratio in SAa of the lateral acetabulum (Figure 4-2).

Table 4-6 - Relationship between Follow-Up dGEMRIC Ratio and Alpha Angle Measurements

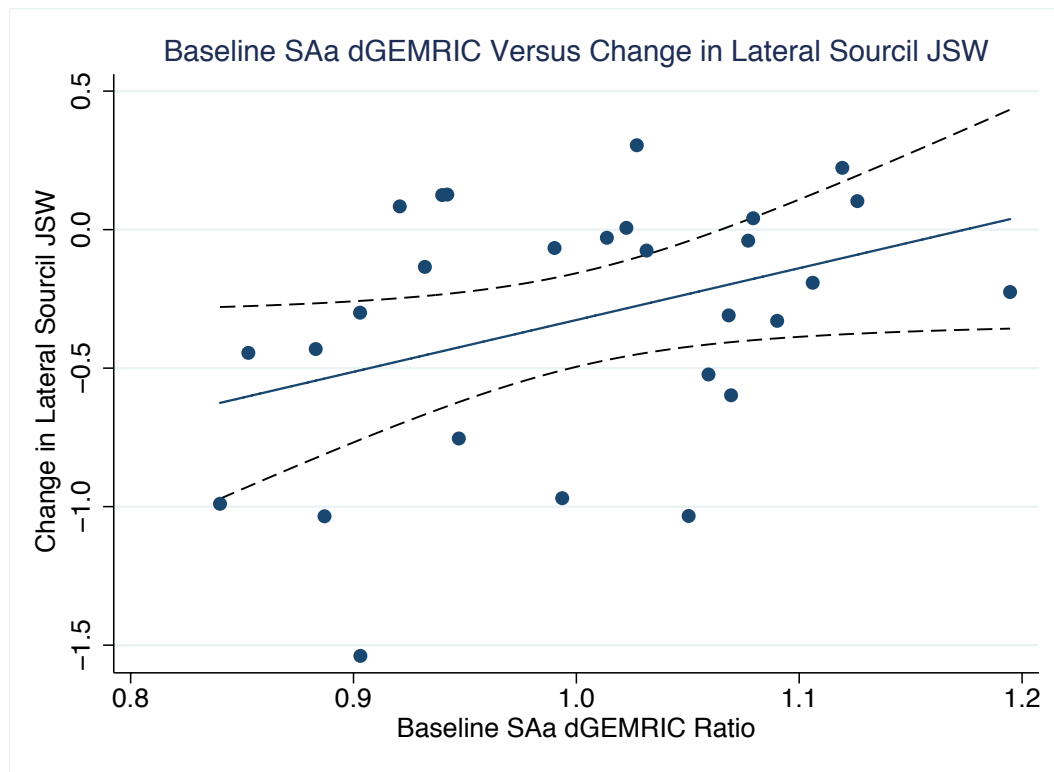
Position of Measurement	Mean Alpha Angle Measurement [SD]		Aa + ASa Lateral Joint	ASa + SAa Lateral Joint	SAa + SPa Lateral Joint		SAa Lateral Joint	SPa Lateral Joint
MRI 12 O'Clock	70.37 [22.79]	R Value	-0.002	-0.251	-0.425		-0.412	-0.322
		P Value	0.497	0.113	0.017		0.020	0.058
MRI 1 O'Clock	73.44 [15.04]	R Value	-0.16	-0.458	-0.513		-0.522	-0.355
		P Value	0.222	0.011	0.004		0.004	0.041
MRI 2 O'Clock	69.18 [9.84]	R Value	-0.096	-0.056	-0.096		0.029	0.029
		P Value	0.324	0.394	0.324		0.446	0.446
MRI 3 O'Clock	60.77 [13.94]	R Value	-0.362	-0.465	-0.505		-0.415	-0.481
		P Value	0.038	0.01	0.005		0.020	0.008
Anteroposterior Radiograph	79.47 [21.72]	R Value	-0.056	-0.408	-0.57		-0.617	-0.347
		P Value	0.396	0.021	0.001		0.001	0.045
Lateral Radiograph	56.39 [14.26]	R Value	-0.398	-0.407	-0.337		-0.302	-0.288
		P Value	0.024	0.022	0.050		0.071	0.082
Average MRI: Clockface Positions	68.44 [10.15]	R Value	-0.273	-0.579	-0.677		-0.597	-0.562
		P Value	0.094	0.001	<0.001		0.001	0.002
Average Radiograph AP and Lateral	68.26 [14.44]	R Value	-0.221	-0.516	-0.663		-0.697	-0.459
		P Value	0.144	0.004	<0.001		<0.001	0.011

Figure 4-2: SAa dGEMRIC versus Average Radiographic Alpha Angle with 95% Confidence Intervals

4.5.6 Relationship between dGEMRIC and Change in Joint Space Width

No region demonstrated a statistically significant correlation with change in minimum JSW. Baseline superior anterior acetabulum (SAa) and superior acetabulum (SAa+SPa) within the lateral joint correlated with change in lateral sourcil JSW (SAa: $r=0.392$ $p=0.032$ and SAa+SPa: $r=0.398$ $p=0.030$) (Table 4-3 & Figure 4-3). These two regions also correlated with the ratio between the change in medial sourcil JSW and lateral sourcil JSW (SAa: $r=0.764$ $p=0.001$ and SAa+SPa: $r=0.387$ $p=0.046$). This demonstrates that patients with a low dGEMRIC ratio in SAa or SAa+SPa experience a reduction in lateral sourcil JSW rather than medial sourcil JSW.

Figure 4-3 - Change in JSW at Lateral Sourcil versus SAa dGEMRIC Ratio



4.5.7 Predictive Models for Osteoarthritis Development

A reduction in lateral sourcil JSW of 0.5mm was used for differentiating individuals with or without evidence of osteoarthritis development and 9 out of 29 participants exceeded this threshold. Measurements selected as potential predictors of future osteoarthritis were dGEMRIC ratio in region SAa of the lateral acetabulum, positive impingement test on hip examination, and alpha angle. The alpha angle measured on an AP radiograph performed best at identifying progression with a ROC Area 0.694 (95% CI: 0.472-0.917) (Figure 4-4 & Table 4-7). This exceeded the ROC Area of 0.617 (95% CI: 0.398-0.836) for SAa dGEMRIC ratio and 0.542 (95% CI: 0.352-0.732) for positive impingement sign on hip examination (Figure 4-5 & Table 4-8).

There is no statistically significant difference in the performance of any variable in predicting JSW reduction at the lateral sourcil. As a single variable, alpha angle on an AP

radiograph performs best, and values exceeding 88.65 degrees can predict the development of clinically relevant osteoarthritis with a sensitivity of 77.8% and specificity of 75.0% where 75.9% of individuals are classified correctly. When combining all variables, the confidence intervals no longer cross a ROC area of 0.5 demonstrating a statistically significant predictive value. The combined variable consisting of AP alpha angle, SAa dGEMRIC ratio, and a positive impingement test performs better than any individual variable with an area under the curve (AUC) of 0.750 (95% CI: 0.541 – 0.959) and can provide a sensitivity of 55.6% and specificity of 90.0% where 79.2% of individuals are classified correctly (Figure 4-6 & Table 4-9).

Figure 4-4 - ROC Curves for Osteoarthritis Development: Alpha Angle Measurements

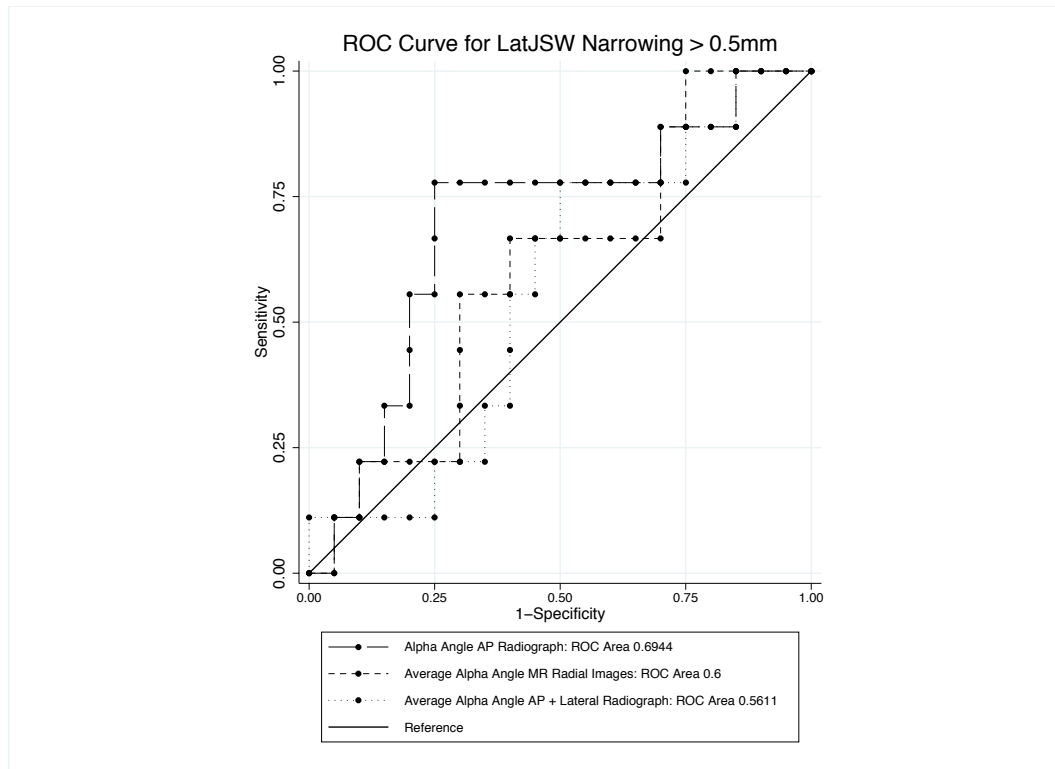


Table 4-7 - ROC Area for Osteoarthritis Development: Alpha Angle Measurements

	ROC Area	95% Confidence Intervals
AP Radiograph Alpha Angle	0.694	0.472 – 0.917
Average MRI Alpha Angle	0.600	0.376 – 0.824
Average Radiograph Alpha Angle	0.561	0.336 – 0.786

Figure 4-5 - ROC Curves for Osteoarthritis Development: AP Alpha Angle, SAa dGEMRIC Ratio, and Clinical Impingement

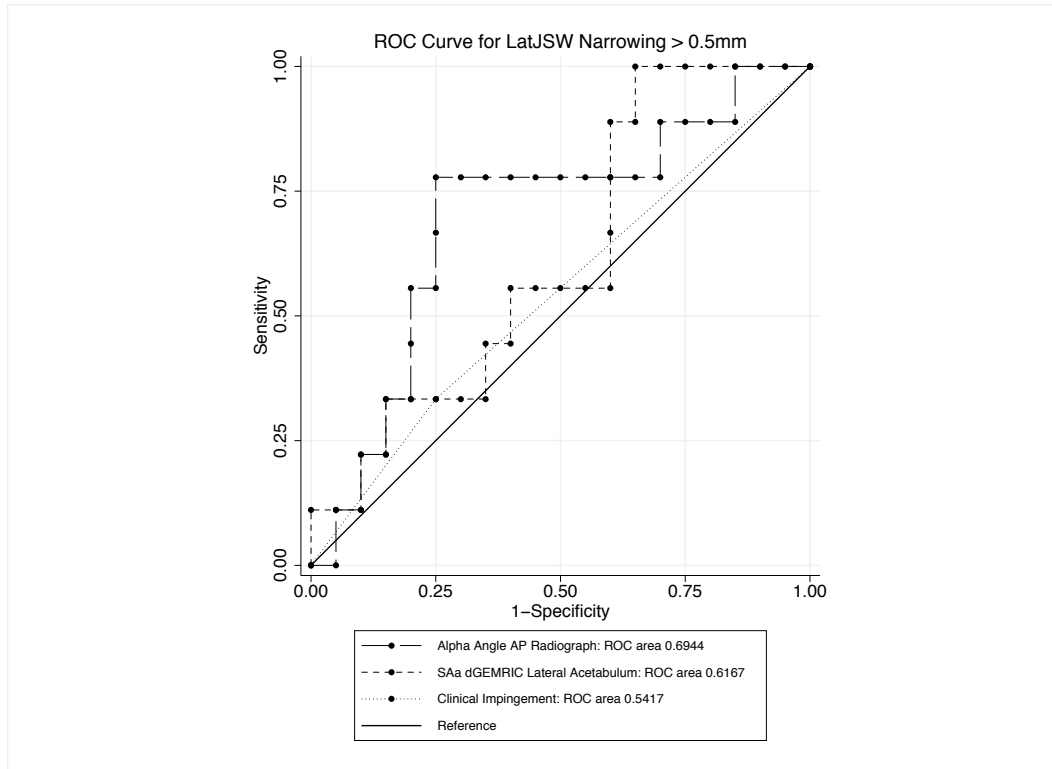


Table 4-8 - ROC Area for Osteoarthritis Development: AP Alpha Angle, SAa dGEMRIC Ratio, and Clinical Impingement

	ROC Area	95% Confidence Intervals
Alpha Angle AP Radiograph	0.694	0.472 – 0.917
SAa dGEMRIC Ratio Lateral Acetabulum	0.617	0.398 – 0.836
Positive Impingement Test	0.542	0.352 – 0.732

Figure 4-6 - ROC Curves for Osteoarthritis Development: Combined Predictive Factors

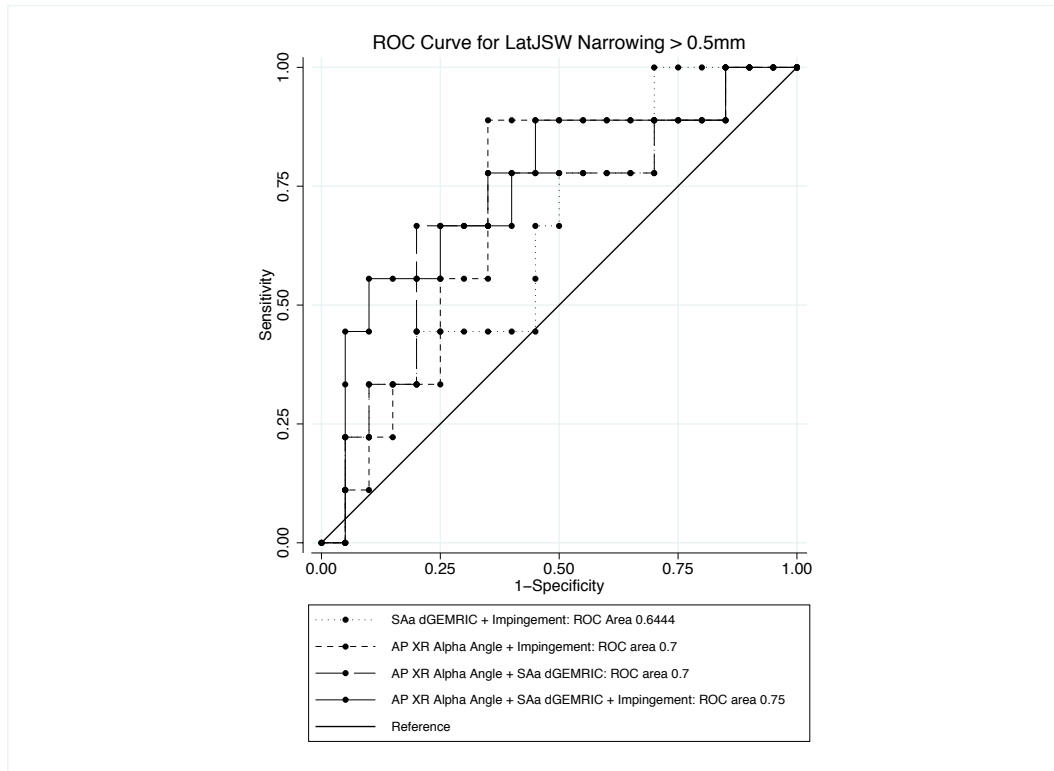


Table 4-9 - ROC Area for Osteoarthritis Development: Combined Predictive Factors

	ROC Area	95% Confidence Intervals
SAa dGEMRIC + Impingement	0.644	0.426 – 0.863
AP Radiograph Alpha Angle + Impingement	0.700	0.491 – 0.909
AP Radiograph Alpha Angle + SAa dGEMRIC	0.700	0.478 – 0.922
AP Radiograph Alpha Angle + SAa dGEMRIC + Impingement	0.750	0.541 – 0.959

4.6 Discussion

The development of therapies for the treatment of early osteoarthritis requires the ability to accurately identify individuals at greatest risk of developing osteoarthritis, or to diagnose pre-structural disease when it remains potentially reversible. The aims of this chapter were to explore the relationship between dGEMRIC values and hip morphology, and to determine whether baseline dGEMRIC can predict radiographic osteoarthritis within five years in individuals with cam morphology.

Consistent with SibKids having been selected as an ‘at risk’ population, study participants demonstrated overall disease progression with a reduction in average joint space width between baseline assessment and five-year follow-up. Nevertheless, the cohort remained largely asymptomatic. The prevalence of cam morphology in this cohort is significantly greater than within the general population⁴⁴, which may confer their increased risk of osteoarthritis. There may also be a genetic predisposition to osteoarthritis within this cohort²⁸⁴, which could be conferred as a susceptibility to developing cam morphology, or a susceptibility of cartilage to cam morphology. It is difficult to fully separate out genetic and environmental factors. The proposal that joint failure commences at the lateral acetabular margin secondary to cam morphology was supported by our dGEMRIC data³⁸.

Our results demonstrate higher glycosaminoglycan levels in weightbearing regions of femoral and acetabular cartilage. This has also been demonstrated in histological studies²⁸⁸ and reproduced in other compositional MRI studies of the hip^{280,289,290}, supporting the validity of our dGEMRIC technique.

There was no statistically significant difference in absolute global dGEMRIC values between participants with normal or cam morphology at baseline or follow-up. This finding was anticipated given we detected only early focal disease. Averaging relaxation

times across the entire joint is recognised to be insufficiently sensitive to detect early disease and studies demonstrate the superiority of regional evaluation¹¹². Our average relaxation times are comparable to those reported in other studies^{243,280}, acknowledging differences in the disease severity between cohorts, specific pulse sequence employed, and post-processing methodology. Previous analysis of the baseline dGEMRIC values gave higher average values as a result of different post-processing methodology⁵⁴.

Spatial variation in dGEMRIC values was more heterogeneous in hips with cam morphology suggesting the presence of localised cartilage damage in this population. The same finding was demonstrated in a dGEMRIC study of asymptomatic volunteers compared with patients with symptomatic femoroacetabular impingement²⁴³. Cam morphology is widely acknowledged to give rise to degenerative change at the superoanterior lateral aspect of the acetabulum³⁸. This was also the region most frequently affected and demonstrating the greatest longitudinal change in our study (SAa). Similar MRI studies also identified this region as the primary location of chondropathy in patients with cam morphology^{243,280}. We therefore adopted this region as a potential biomarker of degenerative change secondary to cam morphology.

Osteoarthritis is thought to develop when an aspherical femoral head enters the acetabulum on flexion and internal rotation²⁹¹ leading to damage of the chondrolabral junction and adjacent cartilage²⁹². The location of cam lesions on the femoral neck varies between individuals and therefore the resultant labral and chondral damage is expected to develop in different regions of the acetabulum⁵³. Our data supports this pathogenesis, where only alpha angles measured anteriorly correlated with dGEMRIC values in the anterior acetabulum. Furthermore, the magnitude of alpha angles measured superiorly correlated with dGEMRIC values in the superior but not anterior acetabulum (Table 4-6). This co-localisation provides further support to the proposed mechanism of osteoarthritis development secondary to cam morphology.

The precise relationship between cam lesion position and the resultant acetabular damage is challenging to study because cam morphology is rarely confined to a single discrete location at the femoral head-neck junction. In addition, the threshold for a pathological alpha angle is likely to depend on a number of factors including activity levels. Interestingly, the dGEMRIC ratio in the superior acetabulum correlated with alpha angles measured at all positions and suggests this region rarely escapes damage. Possible explanations are that average alpha angles were greatest at the 12 o'clock and 1 o'clock positions (Table 4-6) or that even very anterior cam lesions will abut the superior acetabulum when the hip lies in a flexed and internally rotated impingement position. The strongest correlation was seen between average alpha angle on radiographs and region SAa in the lateral acetabulum, further supporting the use of this region as a potential biomarker for degenerative change secondary to cam morphology. It is not clear why alpha angle measurements at the 2 o'clock position did not correlate with dGEMRIC index, whereas there were statistically significant correlations at all other positions.

There was no correlation between dGEMRIC ratio and reduction in minJSW in any region. The vast majority of dGEMRIC studies report the same observation^{279,281} and this is expected given the hip joint has different modes of failure²³⁶ and minimum JSW is not co-localised to the segmented dGEMRIC regions of interest. Joint failure secondary to cam morphology commences within the superior lateral acetabulum³⁸, and accordingly dGEMRIC values in this region (SAa and SAa+SPa) correlate with a reduction in JSW at the lateral source (Figure 4-3). This suggests baseline dGEMRIC may be able to predict future osteoarthritis.

Whilst 30% of the general population have cam morphology, morphological measurements have a low positive predictive value for future osteoarthritis¹³. At present it is not possible to identify which individuals with cam morphology will develop

osteoarthritis and hence may benefit from early intervention, such as pharmaceuticals or arthroscopic surgery⁸.

The results of this study demonstrate that dGEMRIC enhances our ability to predict the development of clinically relevant osteoarthritis within five years. Alpha angle measured on an anteroposterior radiograph displayed the greatest predictive value for clinically relevant joint space loss. This finding is consistent with large cohort studies demonstrating that alpha angle measured on anteroposterior radiographs predicts future osteoarthritis^{49,50}. A possible explanation as to why this alpha angle measurement performs so well may be that it measures cam morphology in a superior position immediately adjacent to the weight-bearing cartilage. We found that alpha angles exceeding 88.65 degrees predict the development of clinically relevant osteoarthritis with a sensitivity 77.8% and specificity 75.0% (Figure 4-4 & Table 4-7). This threshold is higher than the 60 degrees often used to define the presence of a cam deformity and more similar to the pathological threshold of 78 degrees proposed in larger longitudinal cohort studies¹⁴.

A combination of baseline variables consisting of the dGEMRIC ratio in region ASa of the lateral joint, alpha angle on anteroposterior radiograph, and clinical impingement test, performed better than any individual variable at predicting osteoarthritis progression. The combined variable provides an AUC of 0.75 with a sensitivity of 55.6% and specificity of 90.0% where 79.2% of individuals are classified correctly. In developmental dysplasia of the hip, dGEMRIC has been shown to predict failure after peri-acetabular osteotomy with an AUC of 0.977¹⁰³. This performance is superior to that demonstrated in our study and may reflect a later stage of disease in a symptomatic cohort. Combining measures of hip morphology, examination findings and dGEMRIC offers better risk stratification than is currently available for the development of osteoarthritis in individuals with cam morphology. This may be valuable for the

selection of high-risk individuals for enrolment in clinical trials of proposed treatment strategies. Hip arthroscopy is increasingly performed to restore the concavity of the head-neck junction with the aim of improving symptoms and preventing osteoarthritis²⁹³. In addition to aiding patient selection, dGEMRIC may facilitate the assessment of treatment efficacy within short timeframes.

A salient finding is that dGEMRIC does not appear to offer a large improvement over alpha angle for predicting the development of osteoarthritis. Given dGEMRIC requires potentially nephrotoxic intravenous contrast agent^{294,295}, long scan times, and complex post-processing image analysis at significant expense, its role may be limited to a research setting. However, alternative non-invasive compositional MRI sequences may offer superior performance and greater clinical utility²⁰. In vitro studies have also raised uncertainty as to the value of using sulphated glycosaminoglycan content as a biomarker of early osteoarthritis²³⁷.

There are limitations to this study. First, the sample size is limited and we report five year follow-up data from an initial cohort of 34 participants. However, our data demonstrates a potential role for compositional MRI in predicting future osteoarthritis in asymptomatic populations. Second, our outcome measure for identifying participants who developed clinically relevant degenerative change secondary to cam morphology was a reduction in radiographic JSW at the lateral sourcil. MRI measurements of cartilage morphology may represent a superior outcome measure⁶⁹, however, our MRI protocol already exceeded 60 minutes and we did not wish to add additional sequences to ensure acceptability to participants. Third, it is unlikely that dGEMRIC will be feasible in routine clinical practice given the long scanning times and requirement for potentially nephrotoxic intravenous contrast agent. Therefore, future research should focus on alternative compositional MRI sequences with validation against dGEMRIC.

4.7 Conclusions

The results of this study confirm that cam morphology is associated with progressive localised cartilage damage within the superior lateral acetabulum. The severity and location of acetabular chondropathy is correlated with the size and position of the cam lesion upon the femoral neck. This adds further support to a biomechanical aetiology of osteoarthritis secondary to cam morphology. Baseline dGEMRIC is able to predict radiographic joint space narrowing secondary to cam morphology, and this predictive value further increases when combined with alpha angle and clinical findings. This confirms that compositional MRI has the potential to identify high-risk patients for inclusion into clinical trials, and may also facilitate the evaluation of new preventative strategies. Although limitations of dGEMRIC may prevent its adoption in routine clinical care, an increasing number of alternative compositional MRI sequences are available that may offer superior performance and warrant further investigation. The demand for diagnostic and predictive tools in early osteoarthritis is likely to intensify given the increasing number of proposed treatment strategies.

Chapter 5 Hip Arthroscopy: Temporal Trends 2001-2014

5.1 Abstract

Introduction:

Hip arthroscopy is increasingly adopted for the treatment of a number of hip pathologies including femoroacetabular impingement. Studies from the USA demonstrate a 365% increase in the number of procedures performed between 2004-2009 and 250% increase between 2007-2011. However, there remains limited evidence of long term efficacy or superiority over alternative management options for many of the treated conditions and hip arthroscopy is not universally funded across England. The aim of this study is to describe temporal trends in the adoption of hip arthroscopy in England between 2002-2013 and to forecast trends for the next ten years.

Methods:

A search of the Hospital Episodes Database was performed for all codes describing arthroscopic hip procedures with patient age, sex, and area of residence.

Results:

11,329 hip arthroscopies were performed in NHS hospitals in England between 2002-2013. The number of hip arthroscopies performed increased by 727% ($p < 0.0001$) during this period and is forecast to increase by 1388% in 2023. Females represent 60% of all patients undergoing hip arthroscopy ($p < 0.001$). Median age category is 40-44 for females and 35-39 for males and the average age decreased during the study period ($p < 0.0001$). There is significant regional variation in procedure incidence. In the final year of this

study the highest incidence was in the Southwest (8.63/100,000 population) and lowest in East Midlands (1.29/100,000 population).

Conclusions:

The increase in number of hip arthroscopies performed in England reflects trends in USA and continued increases are forecast. Evidence from robust clinical trials is required to justify the increasing number of procedures performed and regional variation suggests potential inequality in the provision of this intervention.

Text modified from:

- Palmer AJR, Malak TT, Broomfield J, Holton J, Majkowski L, Thomas GER, Taylor A, Andrade AJ, Collins G, Watson K, Carr AJ, Glyn-Jones S. *Past and Projected Temporal Trends in Arthroscopic Hip Surgery in England between 2002 and 2013. BMJ Open Sport and Exerc Med* 2016 Mar 21;2(1). PMID: 27900161.

5.2 Introduction

Cam morphology is now a recognised risk factor for hip pain and osteoarthritis, however, the development of preventive strategies is limited by the low predictive value of morphological measures for future disease^{13,296}. Modalities such as compositional MRI offer the potential of enhanced risk stratification to select patients most likely to benefit from early intervention (Chapter 4). Imaging biomarkers may also facilitate the evaluation of treatment efficacy within a short time frame^{20,297}. An increasing number of joint preserving strategies are proposed. Although these often improve symptoms in the short-term, none to date have demonstrated long-term benefit or an ability to prevent the development or progression of osteoarthritis (Chapter 1). Surgical treatment of symptomatic cam morphology femoroacetabular impingement has been proposed as a superior therapeutic option to conservative measures since it allows the underlying aetiology to be addressed. Surgical restoration of the femoral head-neck concavity is thought to prevent impaction against the acetabular rim and subsequent damage to adjacent articular cartilage. Secondary pathology such as labral tears and chondral lesions are addressed simultaneously²⁹⁸.

Surgery for cam morphology femoroacetabular impingement can be performed open or arthroscopically. Ganz described a surgical approach to the hip that allows access to the femoral head and acetabulum without the risk of avascular necrosis in 2001²⁹⁹, and this represents an established technique and historical gold standard for treating femoroacetabular impingement³⁰⁰. A mini-open approach has also been described, but remains less widely adopted³⁰¹. The arthroscopic approach confers potential benefits over open surgery and most studies report lower complication rates and outcomes that are equal to or better than open approaches¹⁸². Indeed, the number of hip arthroscopies performed each year is rising at a much faster rate than open procedures³⁰² and specialist

advisors to NICE have concluded that arthroscopic surgery is likely to replace open surgery for femoroacetabular impingement³⁰³.

Hip arthroscopy was first described in 1931³⁰⁴, although implementation has only been possible more recently after technical advances were made that allow adequate distraction of the femoral head from the acetabulum and joint instrumentation with arthroscopic devices.³⁰⁵ It is adopted for an increasing number of hip pathologies. In an acute setting, joint irrigation can be performed arthroscopically for the management of septic arthritis.³⁰⁶ Fixation of femoral head fractures is also possible arthroscopically.³⁰⁷ In an elective setting, hip arthroscopy is used in the treatment of a range of intra-capsular conditions including femoroacetabular impingement,³⁰⁸ but also labral pathology,³⁰⁹ chondral lesions,³¹⁰ instability,³¹¹ synovial chondromatosis,³¹² and ligamentum teres injuries.³¹³ Applications continue to expand and hip arthroscopy is also used to facilitate hip reduction in infants with developmental dysplasia of the hip (DDH)³¹⁴ and for the treatment of extra-capsular pathology including iliopsoas tendon and iliotibial band pathology.³¹⁵

An increasing number of arthroscopic hip procedures are performed each year worldwide. In Korea, there was a two-fold increase between 2007 and 2010³¹⁶. In the USA there was an increase of 365% between 2004 and 2009³¹⁷ and 250% between 2007 and 2011³¹⁸, where an estimated 70,000 procedures are performed annually³¹⁹. The number of hip arthroscopy procedures performed by Orthopaedic Trainees in the USA increased 18-fold between 1999 and 2009³⁰⁴. Despite the rapid uptake, there are very few studies reporting long-term outcomes for arthroscopic hip surgery and these are limited to cohort studies. This is particularly salient given the increasing questions raised over the efficacy of arthroscopic knee surgery³²⁰. Robust trials are required to compare the efficacy of arthroscopic hip surgery with non-operative interventions to help establish

the optimum treatment strategy for cam morphology femoroacetabular impingement¹⁹⁰. However, study design requires an understanding of current clinical practice.

The adoption of hip arthroscopy in the UK has not been described. It is not universally funded by Clinical Commissioning Groups, which may give rise to geographical variation in practice. The aim of this study is to describe temporal trends in the adoption of hip arthroscopy since 2002 and to project trends for the next ten years. As well as informing research programmes, the publication of temporal trends may aid decision-making by surgeons and commissioning bodies. Regional variation is of particular interest given the perceived inequalities in the commissioning landscape.

5.3 Methods

Data was collected from the Hospital Episode Statistics (HES) database.³²¹ The HES database contains data on patients attending NHS hospitals in England for treatment. Each entry represents a single episode of care and codes are assigned to diagnoses and procedures during that episode. Anonymised data was requested using Operating Procedure Codes (OPCS-4) specific to hip arthroscopy and included patient age, gender, and area of residence between the years 2002 and 2013. The search included all arthroscopic procedures that were combined with joint-specific codes for the hip (Table 5-1). The generic nature of these codes and their modification through different iterations of OPCS-4 codes within the period of this search meant it was not possible to formally analyse trends in individual procedures or diagnoses. Several procedures may be performed within the same joint during arthroscopic hip surgery, for example, chondroplasty and labral repair. When several codes were encountered within the same patient episode, only the primary code was counted to prevent duplication. To aid data analysis, the Health and Social Care Information Centre geographical regions in England

were grouped as the North (North East (q30), North West (q31), Yorkshire and the Humber (q32)), Midlands (East Midlands (q33), West Midlands (q34), East of England (q35)), South East (South East Coast (q37), South Central (q38)), South West (q39), and London (q36). The number of procedures performed in each region was calculated per 100,000 population. Projections were made using the Drift method and are provided with 95% prediction intervals. Forecasts are equal to the last value plus the average change seen in historical data, so that the forecast for time $T + h$ is given by:

$$\hat{y}_{n+h|n} = y_n + \frac{h}{n-1}(y_n - y_1).$$

All statistical tests were performed using STATA Version 13.1 (College Station, TX, USA). Relationships between variables were explored using a Chi-Square Test. Statistical analysis of trends was performed using simple linear regression for continuous variables and Wilcoxon Rank-Sum methodology for categorical variables. A p value less than 0.05 was taken as the threshold for significance.

5.3.1 Hip Arthroscopy Codes

Procedure codes were identified for arthroscopy of the hip (Z90.2 or Z84.3).

Table 5-1 - OPCS Codes for Arthroscopic Joint Preserving Hip Surgery

OPCS-4 Code	Description
W831	Endoscopic Drilling of lesion of Articular Cartilage
W832	Endoscopic Fixation of Lesion of Articular Cartilage
W833	Endoscopic Shaving of Articular Cartilage
W834	Endoscopic Articular Abrasion Chondroplasty
W835	Endoscopic Articular Thermal Chondroplasty
W836	Endoscopic Excision of Articular Cartilage
W837	Endoscopic Osteochondral Autograft
W838	Other Endoscopic Therapeutic Procedure
W839	Unspecified Endoscopic Therapeutic Procedure
W841	Endoscopic Repair of Intra-Articular Ligament
W842	Endoscopic Reattachment of Intra-Articular Ligament
W843	Endoscopic Division of Synovial Plica
W844	Endoscopic Decompression of Joint
W845	Endoscopic Drilling of Epiphysis for Repair of Articular Cartilage
W846	Endoscopic Excision of Synovial Plica
W847	Endoscopic Repair of Superior Labrum Anterior to Posterior Tear
W848	Other Endoscopic Therapeutic Procedure
W849	Unspecified Endoscopic Therapeutic Procedure
W861	Endoscopic Removal of Loose Body from Joint
W868	Other Endoscopic Therapeutic Procedure
W869	Unspecified Endoscopic Therapeutic Procedure
W881	Diagnostic Endoscopic Examination of Joint and Biopsy of Lesion
W888	Other Specified Diagnostic Examination of Joint
W889	Unspecified Endoscopic Diagnostic Examination of Joint
W891	Endoscopic Chondroplasty
W898	Other Endoscopic Therapeutic Procedure
W899	Unspecified Endoscopic Therapeutic Procedure
W831	Endoscopic Drilling of lesion of Articular Cartilage

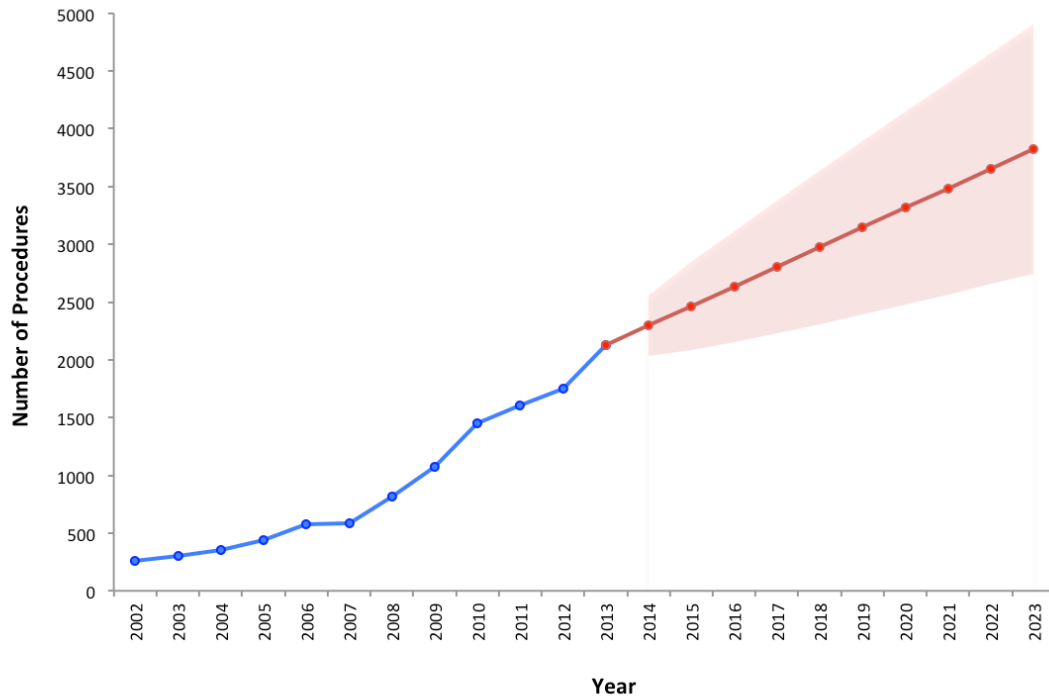
5.4 Results

5.4.1 Total Number of Procedures

11,329 hip arthroscopies were performed in NHS hospitals in England between 2002 and 2013. There was a statistically significant increase of 727% ($p < 0.0001$) during this period and a projected increase of 1388% by 2023 (Table 5-2 & Figure 5-1).

Table 5-2 - Observed and Forecast Total Number of Hip Arthroscopies with 95% Prediction Intervals (PI)

Year	Total Number	
	Observed	Forecast (95% PI)
2002	257	-
2003	300	-
2004	357	-
2005	441	-
2006	575	-
2007	585	-
2008	815	-
2009	1070	-
2010	1449	-
2011	1601	-
2012	1754	-
2013	2125	-
2014	-	2295 (2037, 2553)
2015	-	2465 (2085, 2844)
2016	-	2634 (2152, 3117)
2017	-	2804 (2228, 3381)
2018	-	2974 (2308, 3640)
2019	-	3144 (2392, 3896)
2020	-	3318 (2478, 4149)
2021	-	3484 (2566, 4401)
2022	-	3653 (2655, 4652)
2023	-	3823 (2744, 4092)

Figure 5-1 - Observed and Forecast Total Number of Hip Arthroscopies with 95% Prediction Intervals (PI)

5.4.2 Patient Demographics

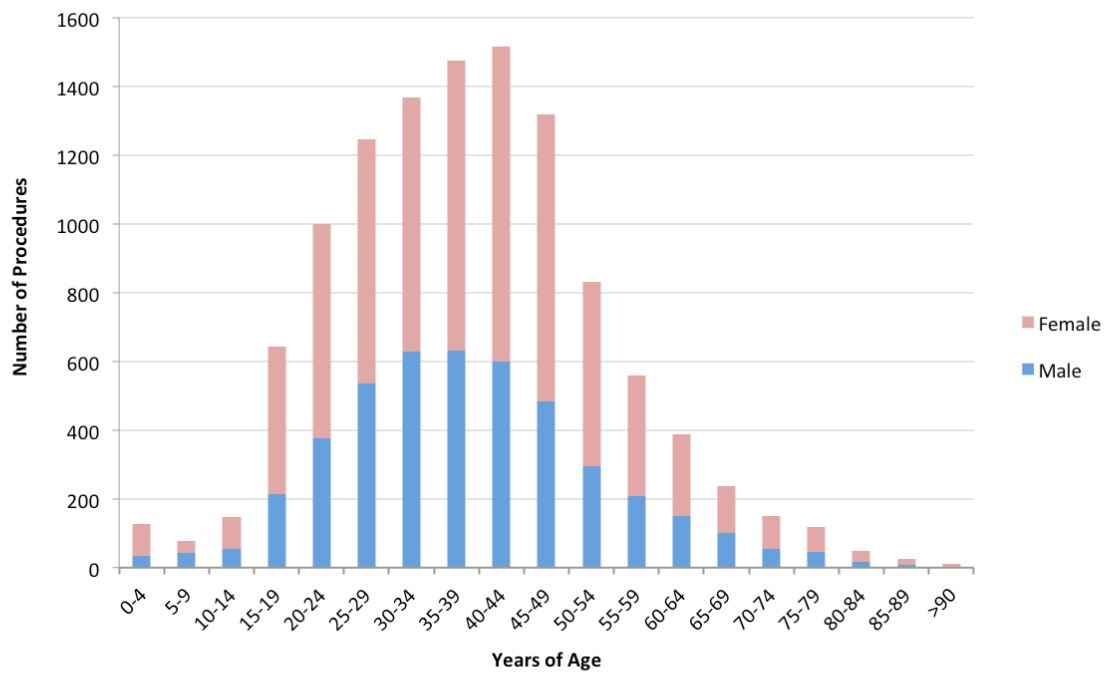
Arthroscopic hip procedures are performed more frequently in females (60.3%) than males (39.7%) ($p < 0.001$) (Table 5-2 & Figure 5-2). Females accounted for between 56.3% and 64.1% of cases throughout all years of the study and there was no statistically significant change in these proportions with time ($p = 0.289$) (Table 2).

Females were older at the time of surgery with a median age range 40-44 years compared with 35-39 for males (Table 5-3) although this was not statistically significant ($p = 0.075$). The age of patients undergoing surgery is decreasing ($p < 0.0001$ $z = -0.544$) and this trend is present for males ($p < 0.0001$ $z = -3.96$) and females ($p < 0.0001$ $z = -3.83$). The age group with the greatest increase in procedure rate is 20-24 years.

Table 5-3 - Observed Number of Hip Arthroscopies for Males and Females

Year	Female	Median Age	Male	Median Age	Ratio Female : Male
2002	154	40-44	103	40-44	1.50
2003	169		131		1.29
2004	210		147		1.43
2005	253		188		1.35
2006	342	40-44	233	35-39	1.47
2007	375		210		1.79
2008	511		304		1.68
2009	629		441		1.42
2010	861	40-44	588	35-39	1.46
2011	968		633		1.53
2012	1079		675		1.60
2013	1272		853		1.49

Figure 5-2 - Histogram Illustrating Number of Arthroscopic Hip Procedures 2002-2013 by Age and Sex



5.4.3 Regional Variation

There has been a statistically significant increase in the number of arthroscopic hip procedures performed in all regions of England since 2002 ($p < 0.0001$) with a concurrent change in the relative number of procedures performed between regions ($p < 0.0001$) trending towards the Southwest and Southeast (Table 5-4). Nationwide, the incidence of hip arthroscopy procedures has risen from 0.51 to 4.09 per 100,000 population (Table 5-4). The greatest growth has taken place in the Southwest (1640%) and the smallest in the Midlands (355%). Considering all regions, the most rapid rate of increase took place between 2006 and 2009, beyond which there has been continued divergence in the number of procedures performed per capita in each region (Figure 5-3). An increase in the number of procedures continues in the Southwest, Southeast, and North of England, whereas there is evidence of plateau in the Midlands and London (Figure 5-3). In the final year of this study, the highest number of procedures per capita was performed in the Southwest (8.63 per 100,000 population) and lowest in the East Midlands (1.29 per 100,000 population) Strategic Health Authority Region (Figure 5-4). This represents a 6.69 fold difference between regions.

Table 5-4 - Regional Variation in Arthroscopic Hip Procedures in England per 100,000 Population

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
North	0.51	0.53	0.43	0.54	0.53	0.83	1.29	2.10	2.68	3.19	3.00	4.40
Midlands	0.55	0.64	0.93	1.03	1.42	1.27	1.47	1.73	2.21	2.22	1.83	2.50
London	0.34	0.34	0.52	0.51	0.83	0.67	1.36	1.66	2.03	2.18	2.50	2.30
South East	0.58	0.81	0.97	1.37	1.79	1.70	2.38	2.97	4.07	4.03	5.55	5.34
South West	0.50	0.58	0.67	1.09	1.05	1.05	1.65	2.28	4.25	5.24	6.75	8.63
England	0.51	0.59	0.71	0.87	1.10	1.10	1.57	2.08	2.82	3.09	3.36	4.09

Figure 5-3 - Regional Variation in Arthroscopic Hip Procedures in England per 100,000 Population

Data represented as a non-weighted moving average over two years

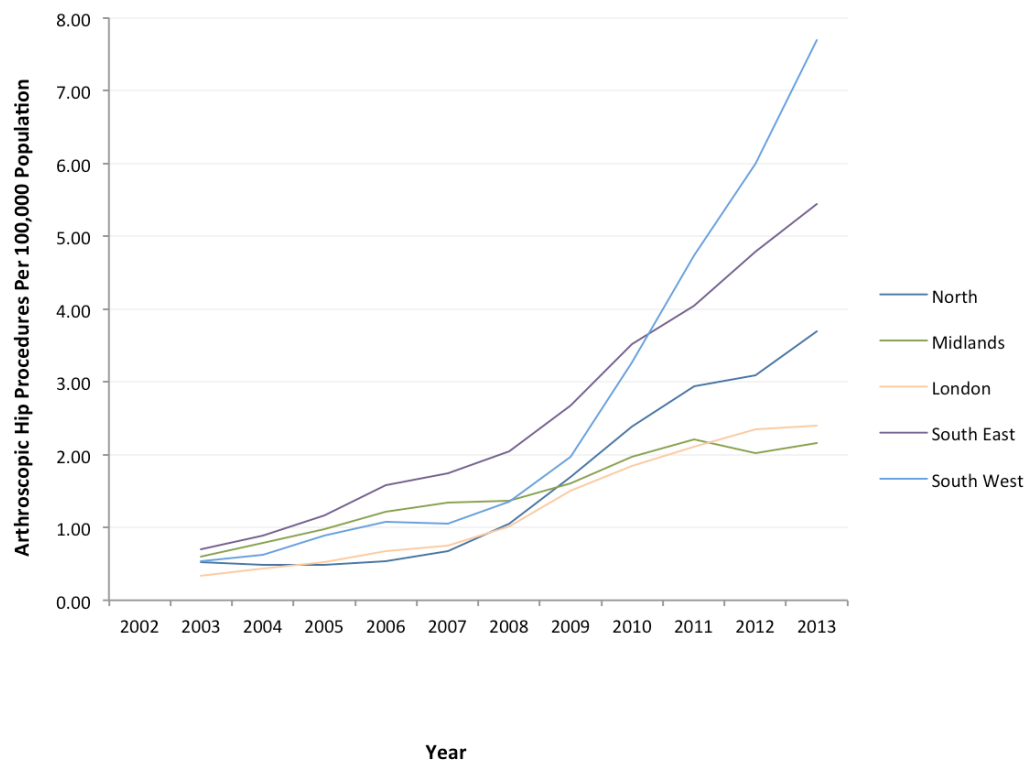
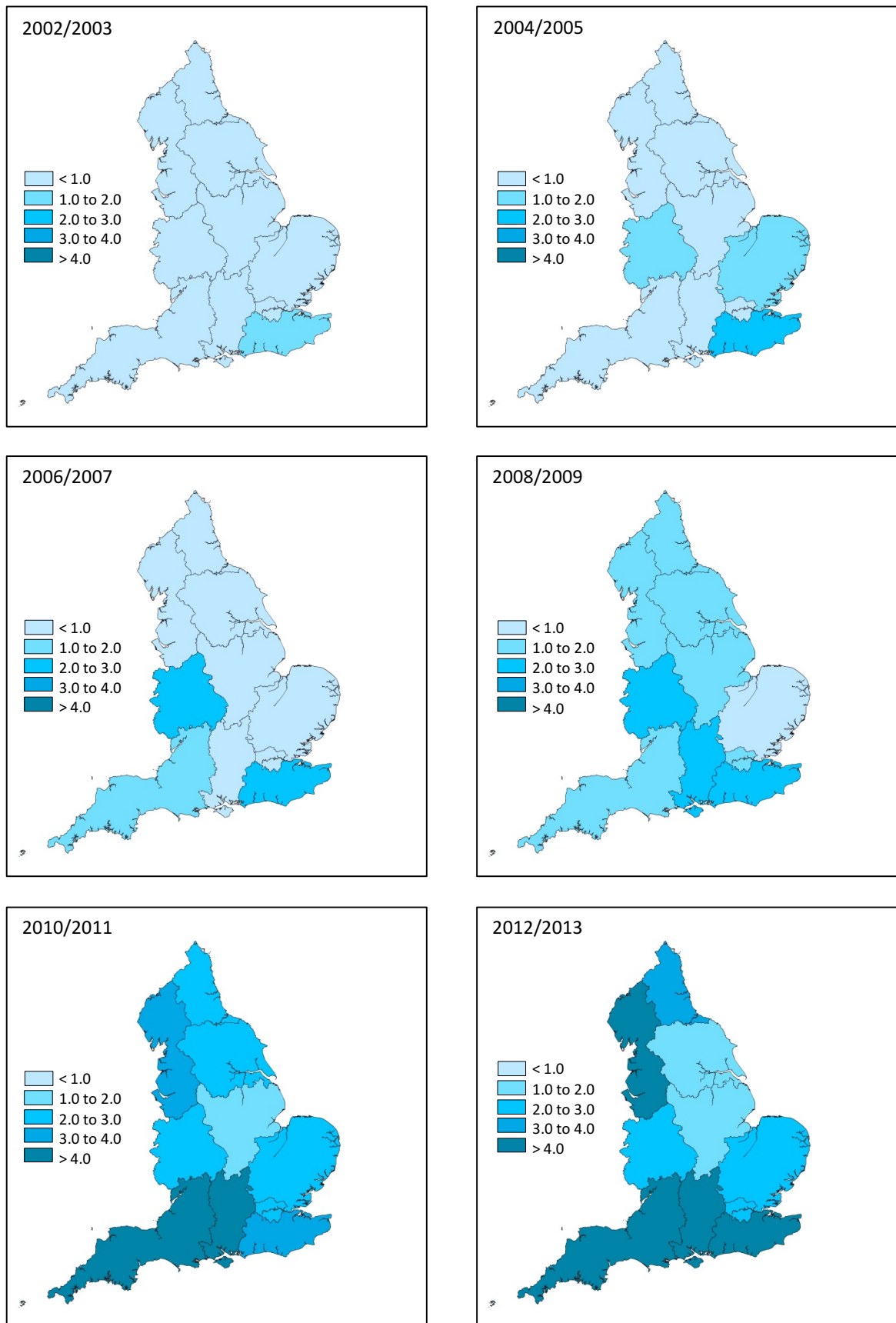


Figure 5-4 - Number of Arthroscopic Hip Procedures in Each Strategic Healthy Authority Region



5.5 Discussion

The aim of this study was to describe temporal trends in the adoption of hip arthroscopy and to project future trends. The number of arthroscopic hip procedures performed in England has risen by 727% since 2002 and this trend is projected to continue over the next 10 years despite limited evidence of long term efficacy or superiority over alternative management options for many of the treated conditions. Although it is not possible to ascertain from this dataset what percentage of procedures were performed for femoroacetabular impingement, this represents one of the most frequent indications in comparable studies from the USA³¹⁸. These increasing trends mirror those of subacromial decompression and rotator cuff repair of the shoulder, again in the absence of robust evidence to demonstrate clinical effectiveness³²². Increasing questions are also being raised over the efficacy of arthroscopic knee surgery³²⁰.

The rate of increase in the number of arthroscopic hip procedures is broadly in line with that reported in the USA where a 365% increase was reported between 2004 and 2009³¹⁷ and a 250% increase between 2007 and 2011³¹⁸. The incidence of hip arthroscopy reported in Korea is comparable to that in England at 5.17 per 100,000 in 2010.³¹⁶ Studies from the USA have calculated procedure incidence using the PearlDiver Patient Records Database and hence are not representative of the general population. Our study underestimates the number of hip arthroscopy procedures performed in England since it does not include those undertaken in private healthcare.

Several factors are likely to be driving the increase in the number of hip arthroscopies. Conditions such as femoroacetabular impingement and labral tears are increasingly recognised as a source of pain and future osteoarthritis⁴⁹ by both clinicians and patients. Demand is buoyed by outcomes from cohort studies, which report good short term and medium term outcomes for a wide range of arthroscopic hip procedures.^{323,324} Guidance

from the National Institute for Health and Clinical Excellence (NICE) may have also played a role. In 2007, NICE highlighted the uncertain efficacy of hip arthroscopy for the treatment of femoroacetabular impingement, whereas in 2011, they concluded that there was adequate evidence of symptom improvement in the short and medium term. There is no strong inflection of the trend line at these time points and it is not possible to say with any certainty that they influenced practice. In the USA, there was an eighteen-fold increase in the number of hip arthroscopies performed by candidates of the American Board of Orthopaedic Surgery between 1999 and 2009³⁰⁴ and a 600% increase between 2006 and 2010³²⁵. Hip arthroscopy is now an established procedure within training programmes and this is particularly salient given the procedure has a very steep learning curve³²⁶.

Hip arthroscopy is more frequently performed in females (60.3%) than in males (39.7%) in England and this has not changed during the period of study. The same gender ratio was reported in the USA where 63% patients are female.³¹⁸ Additional studies from the USA and Korea have reported more equal gender distributions with females representing 52.9%³¹⁷ and 51.9%,³¹⁶ respectively. The higher number of procedures in females is an interesting finding given femoroacetabular impingement, one of the most frequent indications for hip arthroscopy,³¹⁸ has a higher prevalence in males.⁴⁴ The HES database does not utilise sufficiently specific codes to explore the indications for surgery or the nature of procedure performed, and this is an area for future research. There are likely to be gender-specific indications for arthroscopic hip surgery.

Median age at hip arthroscopy is 40-44 years for females and 35-39 years for males, although there is no statistically significant difference in age. These ages are comparable to studies in the USA^{317,318}, and slightly younger than a study from Korea.³¹⁶ In the USA, the greatest increase in the number of procedures was seen in patients <30 years of age,³¹⁸ as is the case in our study. This may relate to the publication of good outcomes in

active young adults who are able to return to high level sporting activities.³²⁷ Conversely, outcomes are worse in older patients.¹⁸⁸

There is significant regional variation in the incidence of hip arthroscopy in England with continuing divergence. The highest incidence is seen in the Southwest and the lowest is in East Midlands. Regional variation is also seen in the USA, albeit less pronounced with a 2.05 fold difference between regions³¹⁷ compared with the 6.69 fold difference in this study. Key factors are likely to be local expertise in hip arthroscopy and the local commissioning of services in England. Hip arthroscopy is not funded on the NHS in many regions given the limited evidence of efficacy available for many arthroscopic hip procedures. Indeed, equipoise is present within surgeon and patient communities for the arthroscopic treatment of femoroacetabular impingement¹⁹⁰. Results from robust clinical trials will inform decision makers and may give rise to more standardised care.

Our forecast rise in the number of arthroscopic hip procedures of 1388% between 2002 and 2023 will accentuate challenging funding decisions within the NHS. It is difficult to quantify the cost of hip arthroscopy procedures due to their heterogeneous nature. A study from America estimated an average direct cost of \$11,850 for arthroscopic treatment of femoroacetabular impingement and concluded that this was cost effective in patients without evidence of osteoarthritis at \$21,700 per Quality Adjusted Life Year (QALY)³²⁸. These results were replicated in a study from Scotland with an estimated a cost of £19,335 per QALY, meeting the NICE threshold for cost-effective inventions.³²⁹ Cost-analysis is required for the diverse spectrum of hip conditions treated arthroscopically.

There are several limitations to this study. As already discussed, limitations of the HES database are the exclusion of procedures performed within the private healthcare sector

and the limited codes available to determine the precise indication and nature of procedure performed. Inclusion of new OPCS-4 codes for specific diagnoses and arthroscopic hip procedures would greatly facilitate the study of clinical activities. At present it is not possible to accurately code the array of different procedures performed. In the USA, codes for femoral and acetabular osteochondroplasty were introduced in 2011 to overcome the same difficulties. In England, the three most frequently used codes in the final year of this study were 'endoscopic excision of articular cartilage', 'endoscopic decompression of joint', and 'other endoscopic therapeutic procedure'.

5.6 Conclusions

The number of arthroscopic procedures continues to increase in line with observations from other countries. Evidence from robust clinical trials is required to justify the increasing number of procedures performed. The demographics of patients receiving hip arthroscopy are not necessarily consistent with our current knowledge of the conditions targeted by arthroscopic surgery. This highlights possible uncertainty as to who is most likely to benefit from intervention. Patient selection is likely to be critical to favourable outcomes. Research in this field would be facilitated by the addition of new OPCS-4 codes for specific diagnoses in the young adult hip and for arthroscopic hip procedures.

Chapter 6 Feasibility Study

6.1 Abstract

Introduction:

The number of surgical procedures performed each year to treat femoroacetabular impingement continues to increase. Although there is evidence that surgery can improve symptoms in the short-term, there is little evidence of long-term benefit or an ability to prevent the development of osteoarthritis. In addition, the superiority of surgery over non-operative interventions has not been demonstrated. A feasibility study was therefore conducted to determine whether patient and surgeon opinion was permissive of a randomised controlled trial comparing operative and non-operative management of femoroacetabular impingement.

Methods:

Surgeon opinion was obtained using validated questionnaires at a Specialist Hip Meeting (n = 61) and patient opinion was obtained from clinic patients with a new diagnosis of femoroacetabular impingement (n=31).

Results:

Surgeon responses to clinical scenarios demonstrated clinical equipoise for operative versus non-operative management of femoroacetabular impingement. 77% of surgeons who routinely perform femoroacetabular impingement surgery were willing to recruit patients into a RCT and 90% of patients were willing to participate. 75% of surgeons believed it was appropriate to randomise patients to non-operative treatment for 12 months or longer. Conversely, only 26% of patients felt this was acceptable, but 94%

were willing to continue non-operative treatment for 6 months in the absence of symptom improvement. More patients were concerned about their risk of developing osteoarthritis than their current symptoms, although most patients felt the two were of equal importance.

Conclusions:

This study suggests that a randomised controlled trial comparing operative and non-operative management of femoroacetabular impingement is both necessary and feasible. As well as informing future trials investigating the treatment of femoroacetabular impingement, the findings are also relevant to clinical trials in other fields. Crucially, patients without life-threatening pathology appear willing to trial a treatment for six months without improvement in their symptoms.

Text modified from:

- Palmer AJR, Thomas G, Pollard T, Rombach I, Taylor A, Arden N, Beard D, Andrade T, Carr A, Glyn-Jones S. *The Feasibility of Performing a Randomised Controlled Trial for Femoroacetabular Impingement Surgery. Bone Joint Res February 2013;2:33-40.*
PMID: 23610700

6.2 Introduction

Randomised controlled trials are considered to be the optimal study design for comparing the efficacy and effectiveness of treatments. However, they are particularly difficult to perform in the field of surgery due to challenges with blinding, standardising procedures, and a lack of acceptance by patients and surgeons^{330,331}. Of original research articles in surgical journals, only 7% are RCTs³³² and treatments in surgery are half as likely to be based on evidence from RCTs than in medicine^{333,334}. Furthermore, as a result of the above difficulties, RCTs pertaining to surgical intervention may be poorly constructed and may not always represent the ideal study type³³¹.

A RCT is not always possible because once a procedure has been accepted as best practice, it may be considered unethical to allocate patients to an alternative treatment³³⁵. RCTs require a setting of equipoise, a situation where both patients and clinicians feel a genuine conscious uncertainty as to the optimal management strategy³³⁶. Equipoise can relate to either an individual or a community. Individual equipoise refers to a setting where an individual is undecided as to the optimal treatment. Community equipoise refers to a setting where individuals may not display equipoise, but broadly equal numbers of individuals within a community are proponents of each different treatment. Individual equipoise is considered necessary for trial recruitment, whereas community equipoise is considered necessary for a trial to be ethically acceptable³³⁶.

Patient preference for a particular treatment is a frequent cause of trial abandonment, primarily because patients often have a preferred treatment in mind^{337,338}. Equipoise is therefore essential within the patient population, but is highly dependent on the information made available to them. Measurement of surgeon and patient preference is a crucial aspect of feasibility assessment³³⁶, and is increasingly requested by funding

bodies. Feasibility studies seek to determine whether a study is possible, and to estimate important parameters for the design of the main study³³⁹.

Cam and pincer morphology femoroacetabular impingement can give rise to hip pain and stiffness²⁹⁶, whilst cam morphology is also recognised to be a salient risk factor for hip osteoarthritis^{13,27}. Therapies therefore offer the potential to improve symptoms and also prevent the development or progression of osteoarthritis. Treatment options include physiotherapy and activity modification, or surgery to reshape the pathological morphology and address any associated soft-tissue damage (Chapter 1). Cohort studies suggest that each of these treatment modalities is able to improve symptoms^{169,198,300,340}, however, there is no evidence that either can arrest or delay the onset of osteoarthritis. Given the rapidly increasing number of hip arthroscopies performed each year targeting femoroacetabular impingement, there are increasing calls for a study comparing operative and non-operative intervention²⁹³. Femoroacetabular impingement surgery carries a small, albeit significant risk of complications that must be justified with superior outcomes over non-operative interventions^{182,341,342}. A RCT is therefore proposed to determine whether surgery in patients with femoroacetabular impingement is superior to non-operative intervention for improving symptoms and delaying the onset of osteoarthritis.

The aims of this study are to ascertain whether specialist hip surgeons believe that a RCT for femoroacetabular impingement management is required, to establish whether there is evidence of surgeon and patient equipoise, and to determine whether patients are willing to participate in such a trial. Information gained may also help to decide the optimum trial design. Three areas of design were identified as being crucial to trial feasibility: Which patients should be included in a RCT? How long are patients and surgeons prepared to continue a treatment if symptoms do not improve? What should be used as the primary outcome measure?

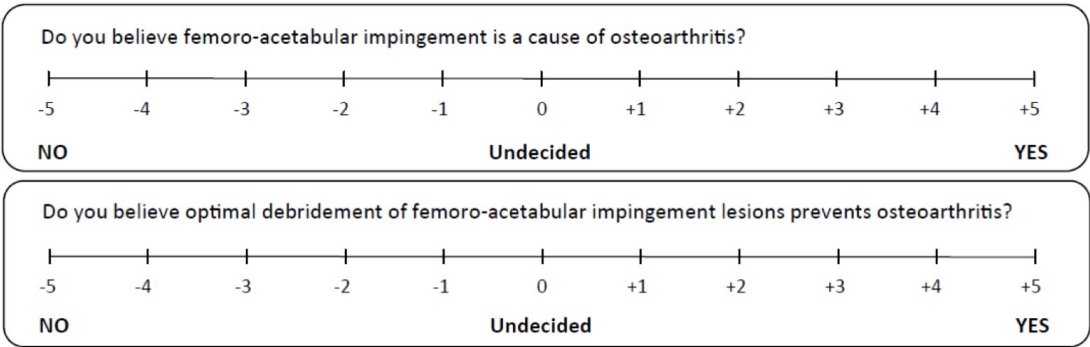
6.3 Materials and Methods

Two questionnaires were designed to ascertain surgeon and patient preferences (Appendix D-1 & Appendix D-2).

6.3.1 Surgeon preference

A written questionnaire was developed to establish surgeon preferences using a combination of questions requiring discrete ‘yes’ or ‘no’ responses, and validated bidirectional linear analogue scales requiring surgeons to mark their responses from -5 to +5 (Figure 6-1)³³⁶. Data were collected at the 2012 meeting of the British Hip Society during a session focusing on young adult hip pathology. This forum has a high attendance by consultant surgeons specialising in the management of femoroacetabular impingement. Responses were analysed in numerical format and using a surgical equipoise ratio (SER)³³⁶. This scale comprises three digits, representing the number of surgeons with negative value responses, those at zero, and those with positive value responses.

Figure 6-1 - Example Questions using a Bidirectional Linear Scale



6.3.2 Patient preference

A Patient Information Leaflet was developed with the aid of a patient advocate, attached to which was a written questionnaire. This included a description of femoroacetabular impingement and how it results in damage to the labrum and articular cartilage. It also contained an overview of conservative and surgical treatment options, along with a discussion of the potential risks and benefits of each. Conservative management was said to comprise weekly physiotherapy and activity modification, and surgical treatment was said to comprise hip arthroscopy, with labral debridement or repair, and osteochondroplasty. During a three week period, all patients aged between 18 and 65 years with newly diagnosed femoroacetabular impingement, seen in clinic at the Nuffield Orthopaedic Centre in Oxford and Royal Berkshire Hospital in Reading, were invited to read through the Patient Information Leaflet and answer the questionnaire to identify preferences for the management of their hip pathology. The 11-point bidirectional scale was used to ask patients whether their principal concern was the risk of developing arthritis or their current pain, and a linear scale from 0 to 24 months (with three-month divisions) was used to ask patients how long they would be happy to trial non-operative management if their symptoms did not improve. Patients were seen again immediately after they completed the questionnaire to address any further questions.

6.4 Results

6.4.1 Surgeon preference

Questionnaires were completed by 61 surgeons, 30 of whom indicated that they routinely performed surgery for femoroacetabular impingement. Of these 30 surgeons who routinely performed femoroacetabular impingement surgery, six (20%) performed less than ten procedures annually, four (13%) performed between ten and 20, six (20%) performed between 20 and 30, four (13%) performed between 30 and 50, three (10%) performed between 50 and 100, and seven (23%) performed greater than 100 procedures per year. The preferred surgical approach was arthroscopic (53%, $n = 16$), followed by arthroscopic and mini-open (30%, $n = 9$), followed by open only (17%, $n = 5$). The questionnaire also asked surgeons to state their preferred Patient Reported Outcome Measure (PROM) and some responded with multiple measures. The most frequently used PROM was the Non-Arthritic Hip Score (NAHS)²⁸⁵ (49%), followed by the Oxford hip score (OHS)²⁸⁶ (20%), Hip Disability and Osteoarthritis Outcome Score (HOOS)³⁴³ (18%), Harris hip score (HHS)³⁴⁴ (9%) and the Hip Outcome Score³⁴⁵ (9%).

Of all surgeons surveyed, 75% stated that they would modify their practice in response to level 1 evidence demonstrating femoroacetabular impingement surgery was superior to conservative management in delaying the onset of osteoarthritis. This question was answered by 28 surgeons who routinely perform femoroacetabular impingement surgery, of whom 21 (75%) said they would modify their practice, and 20 surgeons who do not routinely perform femoroacetabular impingement surgery, of whom 15 (75%) said they would modify their practice. Of the surgeons who routinely perform surgery for femoroacetabular impingement, 23 of 28 who responded (82%) indicated that they were willing to participate in a multi-centre RCT.

Approximately 75% of surgeons found it appropriate to randomise patients to non-surgical management for greater than 12 months, and of those surgeons who did not believe this was appropriate, the shortest specified length of time was six months. This question was answered by 28 surgeons who routinely perform femoroacetabular impingement surgery, of whom 20 (71%) believed greater than 12 months was appropriate, and 20 surgeons who do not routinely perform femoroacetabular impingement surgery, of whom 16 (80%) believed greater than 12 months was appropriate.

The responses to questions using the bidirectional linear scale are both tabulated (Table 6-1) and displayed as histograms (Figure 6-2, Figure 6-3, Figure 6-4, Figure 6-5, Figure 6-6, Figure 6-7, Figure 6-8). Not every surgeon responded to every question. The three digits of the surgical equipoise ratio (SER) represent the sum of the scores within the '-5 to -1', followed by scores of '0', followed by scores within the range '+1 to +5'. The majority of surgeons believed femoroacetabular impingement is a cause of osteoarthritis with a SER of 7:6:39 for 'no', 'undecided' and 'yes', respectively (Figure 6-2), although the belief that optimal debridement of femoroacetabular impingement lesions prevented the development of osteoarthritis was more controversial, with an SER of 13:19:20 for 'no', 'undecided' and 'yes', respectively (Figure 6-3). When asked whether they would manage a patient non-operatively or operatively on first presentation, the SER was 29:6:15 and 10:6:34 for mild and severe symptoms, respectively, representing 'non-operatively', 'undecided' and 'operatively' (Figure 6-4 & Figure 6-5). Considering the subgroup of 23 surgeons who routinely perform femoroacetabular impingement surgery and who were willing to recruit patients into a RCT, the SER was 12:2:9 for mild symptoms and 3:1:19 for severe symptoms, representing 'non-operatively', 'undecided' and 'operatively', respectively (Figure 6-6 & Figure 6-7). Evidence of early osteoarthritis was likely to make a surgeon less likely to perform femoroacetabular impingement

surgery, giving a SER of 35:4:8, representing 'yes' (less likely), 'undecided' and 'no', respectively (Figure 6-8).

Table 6-1 - Surgeon Responses to Each of the Questions asked using a Bidirectional Linear Scale

Question	Surgical Equipoise Scale		
	No	Undecided	Yes
Do you believe FAI is a cause of osteoarthritis?			
All surgeons (n = 52)	7	6	39
Surgeons who routinely perform FAI surgery (n = 28)	2	2	24
Surgeons who do not routinely perform FAI surgery (n=24)	5	4	15
Does optimal debridement of FAI lesions prevent OA?			
All surgeons (n = 52)	13	19	20
Surgeons who routinely perform FAI surgery (n = 28)	3	8	17
Surgeons who do not routinely perform FAI surgery (n=24)	10	11	3
	Non-operative	Undecided	Operative
How do you manage patients with mild symptoms on first presentation (limits sports)?			
All surgeons (n = 61)	29	6	15
Surgeons who routinely perform FAI surgery (n = 30)	13	3	12
How do you manage patients with severe symptoms on first presentation (limits daily activity)?			
All surgeons (n = 61)	10	6	34
Surgeons who routinely perform FAI surgery (n = 30)	5	1	22
	Yes	Undecided	No
Does evidence of early osteoarthritis on imaging make you less likely to perform FAI surgery?			
All surgeons (n = 61)	35	4	8
Surgeons who routinely perform FAI surgery (n = 30)	20	0	8

Figure 6-2 – Surgeon Feasibility Question 1

Response to the question ‘Do you believe FAI is a cause of osteoarthritis?’

The responses of surgeons who routinely perform FAI surgery are represented in blue and those who do not are in pink.

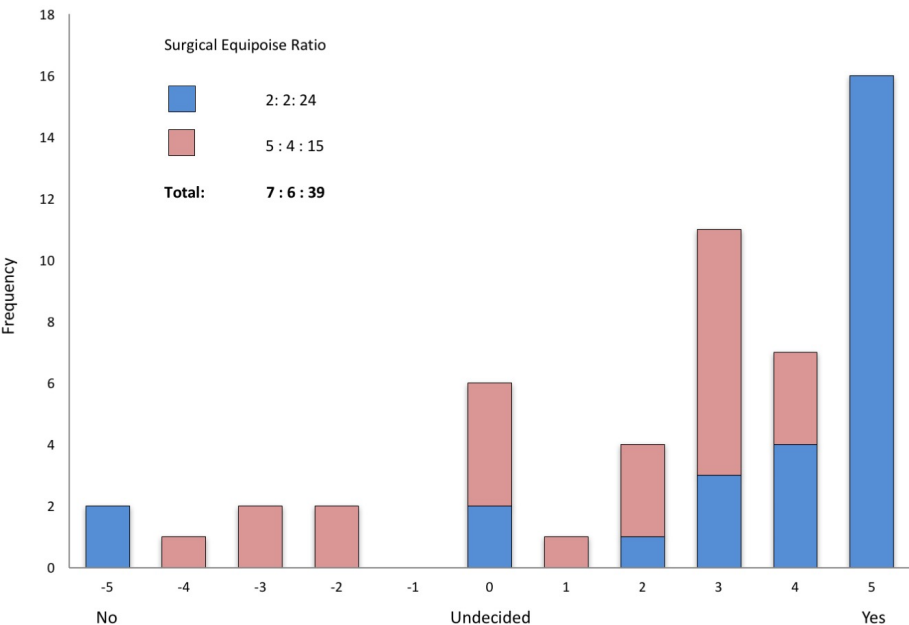


Figure 6-3 – Surgeon Feasibility Question 2

Response to the question ‘Does optimal debridement of FAI prevent osteoarthritis?’

The responses of surgeons who routinely perform FAI surgery are represented in blue and those who do not are in pink.

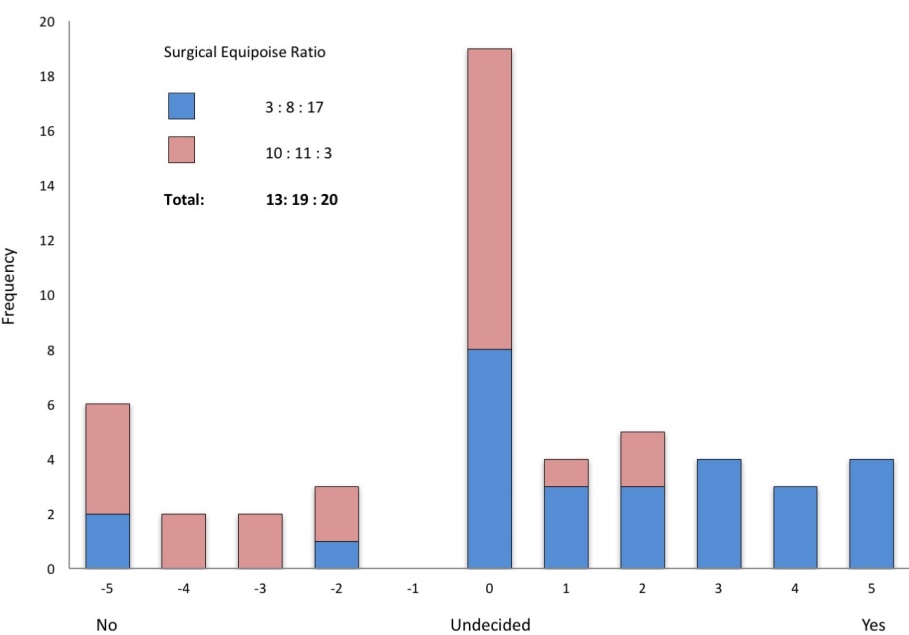
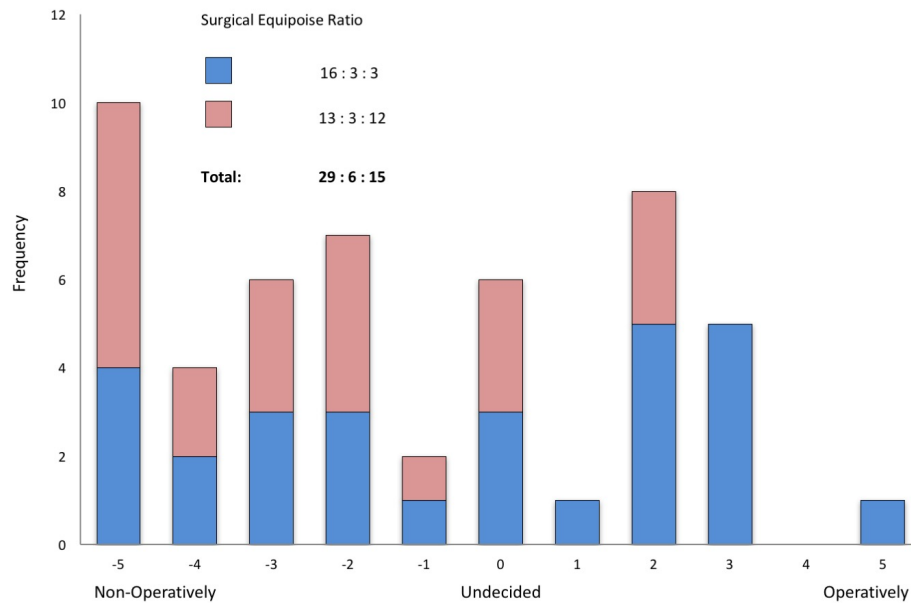


Figure 6-4 – Surgeon Feasibility Question 3

Response to the question 'How do you manage patients with mild symptoms on first presentation (limits sports)?'

The responses of surgeons who routinely perform FAI surgery are represented in blue and those who do not are in pink.

**Figure 6-5 – Surgeon Feasibility Question 4**

Response to the question 'How do you manage patients with severe symptoms on first presentation (limits daily activity)?'

The responses of surgeons who routinely perform FAI surgery are represented in blue and those who do not are in pink.

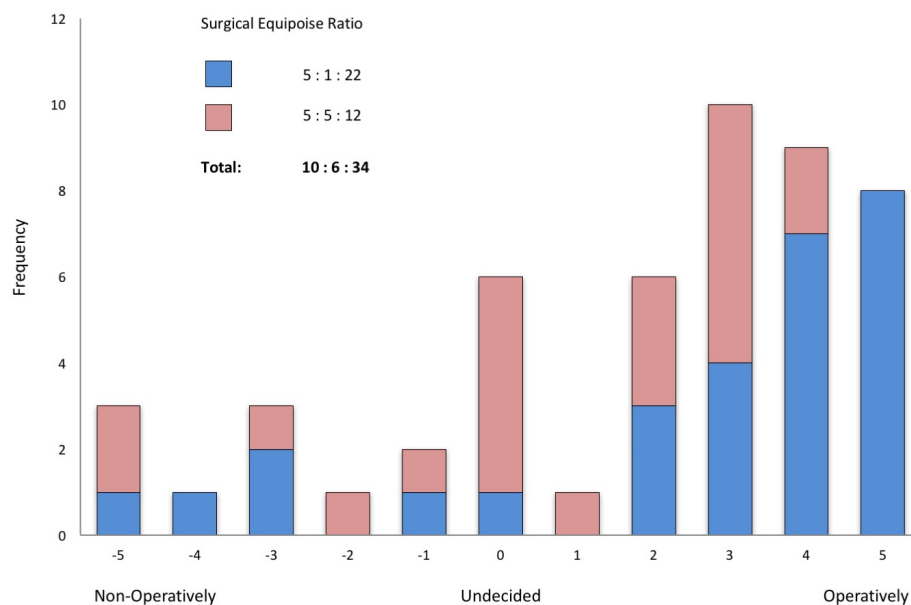


Figure 6-6 – Surgeon Feasibility Question 5

Response to the question 'How do you manage patients with mild symptoms on first presentation (limits sports)?'

Subgroup of 23 surgeons who routinely perform FAI surgery and who would be willing to recruit patients into a randomised controlled trial.

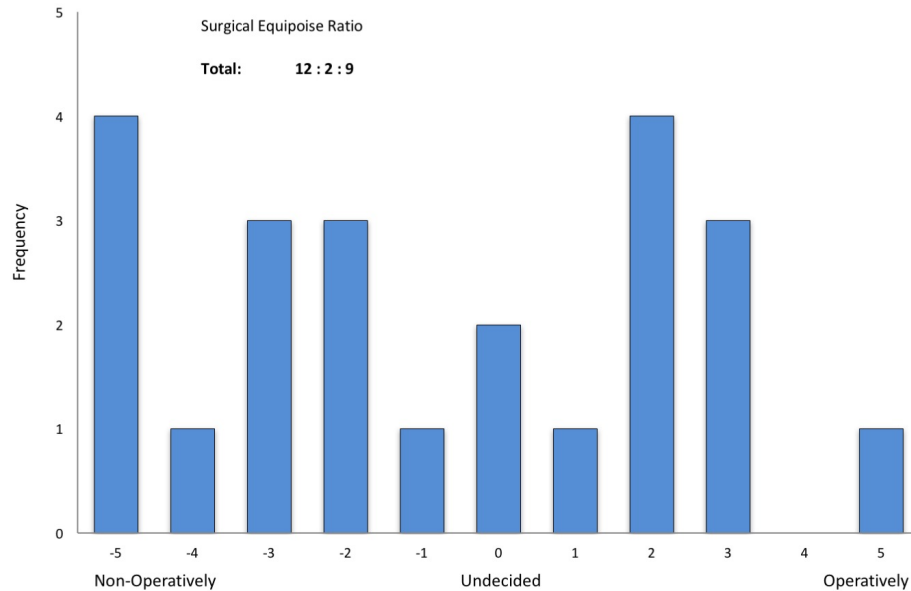


Figure 6-7 – Surgeon Feasibility Question 6

Response to the question 'How do you manage patients with severe symptoms on first presentation (limits daily activity)?'

Subgroup of 23 surgeons who routinely perform FAI surgery and who would be willing to recruit patients into a randomised controlled trial.

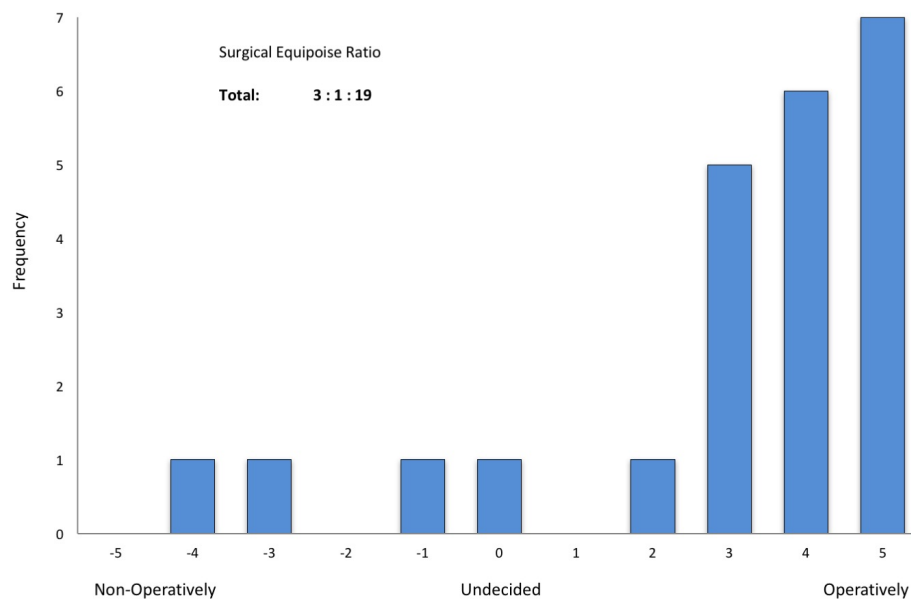
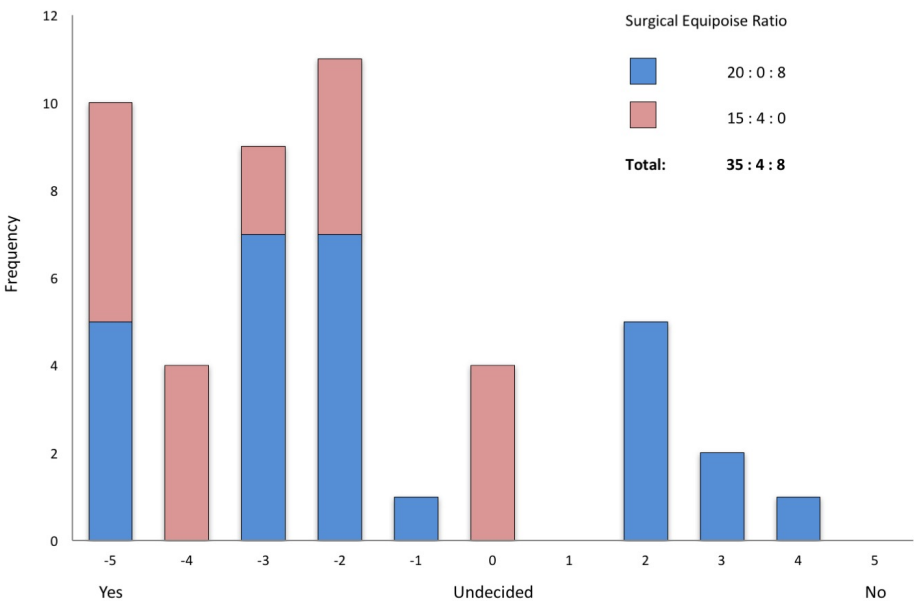


Figure 6-8 – Surgeon Feasibility Question 7

Response to the question ‘Does evidence of early osteoarthritis on imaging make you less likely to perform FAI surgery?’

The responses of surgeons who routinely perform FAI surgery are represented in blue and those who do not are in pink.



6.4.2 Patient preference

Questionnaires were completed by 31 patients (19 female and 12 male) with a mean age of 37 years (21 to 63). Prior to onset of symptoms, 26 patients (84%) reported regular participation in sporting activities. A total of 28 patients (90%) stated that they would be willing to participate in a trial randomising to either operative or non-operative management. Of the three remaining patients, two indicated that they would find randomisation to the non-operative arm unacceptable, and one found randomisation to the operative arm unacceptable.

When asked whether they were more concerned about future arthritis or their current pain, 12 patients (39%) indicated arthritis, five (16%) current pain, and the remaining 14 patients (45%) felt them to be of equal importance. When asked how long they were prepared to trial physiotherapy if their symptoms did not improve, the mean response was 7.5 months (3 to 18), with the majority (94%, n = 29) indicating that they found greater than or equal to six months to be acceptable (Table 6-2, Figure 6-9, Figure 6-10).

Table 6-2 - Patient Responses to Each of the Questions asked using a Bidirectional Linear Scale

Question	Patient response		
	Future Arthritis	Equal Importance	Current Pain
What is more important: Treating your current pain or reducing your future risk of arthritis?	12	14	5
How long would you be prepared to trial physiotherapy before wishing to have surgery if your symptoms did not improve?	Mean 7.5 months (3 to 18)		

Figure 6-9 – Patient Feasibility Question 1

Response to the question ‘What is more important: treating your current pain or reducing your future risk of arthritis?’

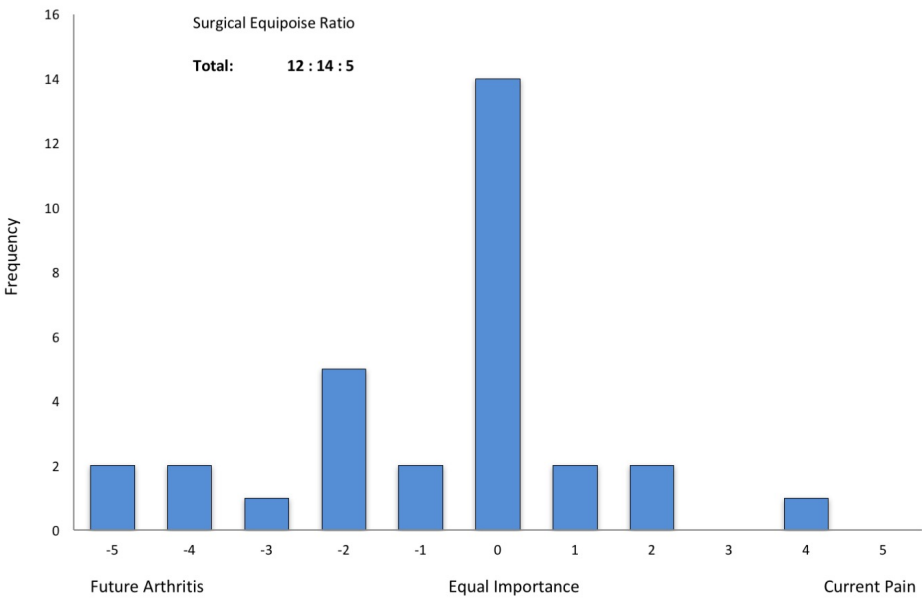
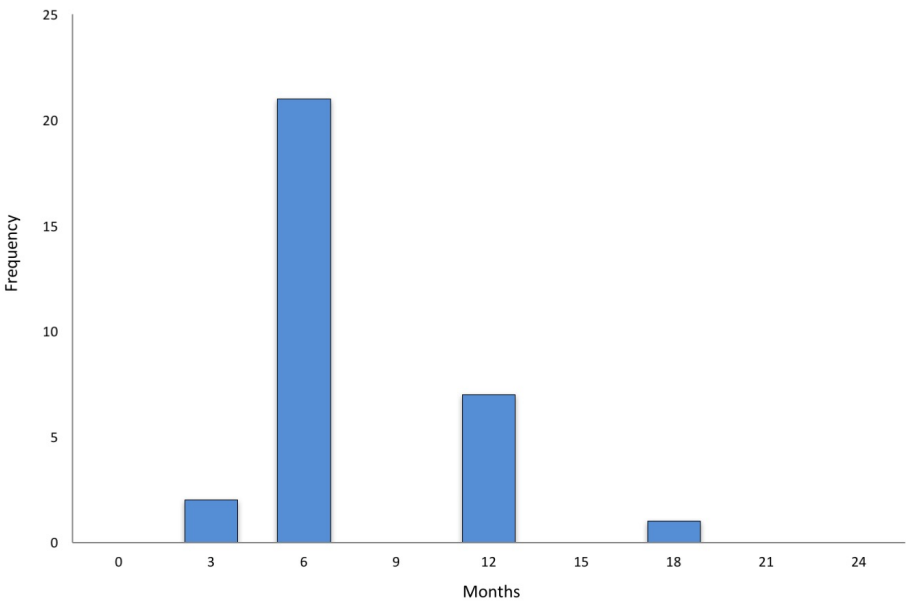


Figure 6-10 – Patient Feasibility Question 2

Response to the question ‘How long would you be prepared to trial physiotherapy before wishing to have surgery if your symptoms did not improve?’



6.5 Discussion

The value of this feasibility study is threefold: i) determines whether there is a study requirement ii) establishes whether surgeon and patient opinion is permissive of the proposed trial, and iii) provides guidance for trial design.

This study suggested there is a requirement for a RCT comparing operative and non-operative management of femoroacetabular impingement, as have subsequent feasibility studies from the UK³⁴⁶, USA³⁴⁷, and Canada³⁴⁸. The number of surgical procedures performed each year to treat femoroacetabular impingement continues to rise exponentially²⁹³. This finding may reflect increasing evidence that surgery can improve symptoms in the short-term, although evidence to date primarily consists of level IV studies^{198,300,340}. The primary concern of patients was more frequently the prevention of osteoarthritis rather than their current pain, although most felt they were of equal importance. This highlights the fact that studies should investigate the potential disease-modifying benefits of intervention, in addition to symptom management. Importantly, 75% of surgeons said they would modify their clinical practice in response to level 1 evidence showing femoroacetabular impingement surgery slowed the development of osteoarthritis compared with conservative management strategies.

The results of this study also suggest that surgeon and patient opinion was permissive for a RCT, and that there was evidence of equipoise. The ideal position of equipoise for a trial is when both patient and clinician have no preference for alternative treatment strategies. In reality, this theoretical model is rarely seen. Community equipoise describes disagreement within an expert clinical body as to the preferred treatment strategy. If the majority of clinicians strongly believe one treatment is superior to another, it may not be ethical to randomise patients to the treatment that is perceived to be inferior. When members of the public were asked to specify the degree of community

equipoise they would require to cast an approving vote on an ethical committee, half believed a RCT was unethical when community equipoise is disturbed beyond 70% of clinicians favouring one of the treatment options³⁴⁹. Adopting this threshold, this study demonstrates adequate community equipoise, as when surgeons were asked their preferred treatment for a patient with mild and severe symptoms, no more than 70% of surgeons favoured either treatment option. When presented with patients experiencing mild symptoms, 58% of surgeons favoured non-operative management, whereas with patients experiencing severe symptoms, 68% of surgeons favoured operative management (Figure 6-4 & Figure 6-5). These findings suggest it is ethical to perform a RCT for all symptom severities.

An individual is in equipoise when they themselves do not display a preference for one treatment option over another. This is considered essential if clinicians are to willingly recruit patients into a trial, and also minimises researcher bias for either treatment arm³⁵⁰. In this study, individual equipoise is illustrated when a surgeon marks 'undecided' as their preferred treatment option for a given clinical scenario. As the number of surgeons without a treatment preference increases, the number of surgeons willing to recruit patients would be expected to rise. Although a study may require relatively few surgeons for adequate recruitment, if no surgeon displays individual equipoise, trial recruitment is unlikely to be possible. We found that 12% of surgeons were undecided as to whether to adopt operative or non-operative management in patients with both mild and severe symptoms. Whereas for mild symptoms this represented an equal number of surgeons who did and did not perform femoroacetabular impingement surgery, for severe symptoms, the vast majority were surgeons who did not routinely perform femoroacetabular impingement surgery (Figure 6-4 & Figure 6-5). This suggests that few surgeons would be willing to recruit patients into a RCT; however, this was not the case. 77% of surgeons who routinely perform femoroacetabular impingement surgery were

willing to recruit patients into a RCT. This supports the theory that individual equipoise in clinicians is not essential for patient recruitment³⁵¹. Surgeons who had a strong preference for one treatment arm were still willing to recruit patients into a trial (Figure 6-6 & Figure 6-7). Depending on the trial design, a feasibility study in the USA also found 77.4% surgeons who routinely perform femoroacetabular impingement surgery were willing to recruit patients into a study comparing operative and non-operative treatment³⁵².

A RCT for femoroacetabular impingement management with operative and non-operative treatment arms should achieve a high rate of patient recruitment, as 90% of patients indicated that they were willing to participate. This is higher than a study from the USA, where 28% were willing, 40% were probably willing or unsure, and 32% were unwilling to participate³⁴⁷. Recruitment and drop-out rates are conditional on trial design. A crucial factor is the length of time patients are randomised to non-surgical treatment. While 75% of surgeons indicated that it is appropriate to adopt a non-operative treatment strategy for one year or more, only 26% of patients found this acceptable. This is likely to result in low recruitment rates and high drop-out rates. Given that the majority of patients surveyed (94%) found six months to be acceptable, cross-over to a surgical treatment arm must be allowed at this time point in order to ensure success of the trial. In the USA, 77.4% surgeons were willing to enrol patients to a study with cross-over allowed at six months, however, only 41.6% were willing to enrol patients if this was 12 months³⁵². This finding dictates the timing of primary outcome measure collection and sample size of such a trial, and feasibility therefore depends on the ability to detect a clinically relevant difference within six months. Measuring osteoarthritis progression within this timeframe is only possible using compositional imaging or biochemical markers of disease (Chapter 1). The finding that patients are willing to pursue a treatment strategy for six months without improvement in their

symptoms may have important implications for clinical trials addressing other orthopaedic pathology.

When considering the inclusion criteria for a RCT, there was strong community opinion that surgeons are less likely to perform femoroacetabular impingement surgery in the presence of early osteoarthritis (Figure 6-8). This is consistent with an increasing body of evidence demonstrating worse outcomes once there is evidence of osteoarthritis¹⁸⁶⁻¹⁸⁹. A specific definition for early osteoarthritis was avoided as there are many classifications, and few are commonly used in a clinical setting. Nevertheless, surgeon responses combined with current evidence suggest it would be unacceptable to perform femoroacetabular impingement surgery on patients with established osteoarthritis. It is proposed that trial inclusion should be limited to patients with a Tönnis grade³⁵³ or Kellgren-Lawrence score⁸⁰ less than two. Outcome measures should include the Non-Arthritic Hip Score as this is most frequently used in current clinical practice and ensures applicability of study findings.

This study supports the proposal that a RCT addresses arthroscopic surgery, given this is the most frequently adopted approach with lower complication rates¹⁸² (Chapter 5). Surgery aims to both address the underlying aetiology by correcting the pathological morphology (osteochoondroplasty), and treat any associated soft tissue damage such as chondropathy or labral pathology (Chapter 1). An additional possible treatment arm is arthroscopic lavage without osteochoondroplasty as a pseudo-placebo. Although not considered in this feasibility study, others have shown that only 25% of surgeons are willing to operate without addressing the abnormal morphology. Nevertheless, a RCT study is currently underway to address this research question³⁵⁴.

There are limitations to this feasibility study. The patients and surgeons completing our questionnaires do not necessarily represent national or international opinion, although

this is one of the largest published surgical feasibility studies to date. In addition, not every surgeon answered every question and a higher number of surgeons who do not routinely perform femoroacetabular impingement surgery did not complete all of the questionnaire. This may be because they did not feel sufficiently well informed to provide a response, but it could also reflect survey design.

It is important to acknowledge that a patient may be more likely to consent to a trial in theory than in practice when approached by the trial team, although similar studies to ours have reliably predicted recruitment rates in the subsequent trial³⁵⁵⁻³⁵⁷. It is also challenging to ensure there is no demonstration of bias towards the operative treatment arm. If symptoms do not improve with non-operative therapy, it is possible to consider surgery. However, the reverse is not possible since surgery reflects an irreversible and potentially definitive procedure. As a result, patients may interpret this to mean surgery is the optimum treatment. This is a significant hurdle when comparing non-operative and operative treatment arms in a RCT.

6.6 Conclusions

Feasibility studies are an essential element to trial design. This study demonstrates that there is clinical need for a RCT comparing operative and non-operative management of femoroacetabular impingement and this appears feasible in terms of both surgeon and patient opinion. Consensus opinion is a dynamic concept, and while surgeon and patient opinions currently appear permissive, this may not be the case in the future. Important findings from this study that are relevant to the design of other clinical trials are that individual surgeon equipoise does not appear to be essential to patient recruitment, and that surgeons expressing a strong preference for a treatment strategy may still be willing to recruit patients into a RCT. Also, patients are willing to pursue a treatment strategy

for six months, even if their symptoms do not improve. Specific to a RCT comparing operative and non-operative treatment of femoroacetabular impingement, surgery is most frequently performed arthroscopically and equal importance should be placed on improving symptoms and preventing the development or progression of osteoarthritis. Outcome measures should include the Non-Arthritic Hip Score, as this is most frequently used in clinical practice and facilitates clinical translation. The findings from this study informed trial design for the Femoroacetabular Impingement Trial (FAIT)³⁵⁸ (Appendix E).

Chapter 7 Conclusions

7.1 Summary of Findings

The aim of this thesis was to explore different strategies for the prevention of hip osteoarthritis that develops secondary to cam morphology and to address some of the barriers to their implementation. There were three main objectives:

- i) Investigate the aetiology of cam morphology with a view to identifying potentially modifiable predisposing factors.
- ii) Determine whether compositional MRI can identify individuals at high risk of developing hip osteoarthritis and hence may benefit from intervention.
- iii) Evaluate the feasibility of a study comparing the efficacy of non-operative versus operative intervention for symptomatic femoroacetabular impingement.

In addressing the first objective, results from this thesis demonstrate that high activity levels during adolescence increase the risk of developing cam morphology. The prospective cross-sectional cohort study that was performed is significantly larger than comparable studies to date. In addition, quantitative assessment of non-osseous morphology was carried out in order to overcome the limitations of osseous measurements in a skeletally immature hip. Compared with individuals who play no regular sport, maximum alpha angles were 4.03 degrees higher in individuals who play sport for a school or club ($p=0.041$), and 7.73 degrees higher in individuals who compete at a national or international level ($p=0.035$). The salient mechanism of cam formation was epiphyseal hypertrophy and extension that was maximal at the 1 o'clock position. There was a strong relationship between alpha angle and adjacent epiphyseal extension ($r^2=0.51$). The prevalence of cam morphology was lower in females and on average alpha

angles were 6.7 degrees lower than in males ($p=0.005$). When cam morphology was present in females, there was only a weak association with epiphyseal extension. There appear to be important gender differences in the development of cam morphology.

Alpha angles increase most rapidly between 12 and 14 years of age, however, early morphological changes consistent with the development of cam morphology are evident as early as ten years of age. Interventions that aim to modify the pathogenesis of cam morphology are therefore most likely to be effective when implemented during early pre-adolescent years. Males participating in high-level sports are at particularly high risk of developing cam morphology and subsequent osteoarthritis. Avoidance or modification of certain activities during this critical period of hip development offers a potential means of reducing the risk of cam formation. It is not yet clear what aspect of sporting activity promotes epiphyseal hypertrophy and extension. There was no difference in the magnitude of cam morphology between dominant and non-dominant legs, or between participants who participate in kicking and non-kicking sports. At present, there remains insufficient evidence to recommend activity modification during skeletal immaturity and the cardiovascular benefits of exercise are likely to outweigh any potentially detrimental effects on hip morphology. However, further studies comparing hip development in individuals from different sports may identify specific loading patterns that predispose to cam formation. An important finding from this thesis is that athletes may warrant surveillance due to their significantly elevated risk of developing cam morphology and secondary osteoarthritis.

The second objective of this thesis was to determine whether compositional MRI can aid the identification of individuals most likely to develop hip osteoarthritis. The prevalence of cam morphology within the general population is not known due to the absence of agreed diagnostic criteria, but is estimated at approximately a quarter of males and a smaller proportion of females. Whilst cam morphology is an important risk factor for hip

osteoarthritis, morphological measurements have a low positive predictive value. Depending on cohort characteristics and the diagnostic criteria used for cam morphology, the positive predictive value for future osteoarthritis ranges from 6-25% within 5-19 years, even in a symptomatic population¹³. Given most individuals with cam morphology will not develop osteoarthritis¹³, and the poor correlation between symptoms and structure¹⁸, identifying individuals who are most likely to benefit from intervention remains a significant clinical challenge.

This thesis reports the first study to show that baseline compositional MRI can predict future hip osteoarthritis in individuals with cam morphology. The dGEMRIC values of acetabular cartilage were significantly lower in asymptomatic individuals with cam morphology compared with those who have normal hip morphology ($p < 0.001$). Furthermore, the distribution of dGEMRIC values correlated with the location of cam morphology, and there was a strong correlation between dGEMRIC values and the magnitude of the adjacent alpha angle ($r = 0.697$, $p < 0.001$). This supports the biomechanical aetiology of osteoarthritis that develops secondary to cam morphology. The most significant finding was that baseline dGEMRIC in an asymptomatic population can predict the development of radiographic osteoarthritis within five years. There was a statistically significant correlation between baseline dGEMRIC and subsequent joint space width narrowing. In addition, ROC analysis combining dGEMRIC values with radiographic alpha angle and clinical examination gave an AUC of 0.75 for the development of clinically relevant radiographic osteoarthritis.

Compositional MRI may become a valuable screening tool for individuals with diagnosed cam morphology, or individuals at high risk of cam morphology, such as athletes. Outcomes may facilitate the selection of individuals most likely to benefit from intervention, and may also permit the evaluation of treatment efficacy within shorter timeframes than is possible using conventional imaging techniques. The clinical

application of dGEMRIC is likely to be limited by the complex imaging protocol and the requirement of potentially nephrotoxic contrast agent. However, an increasing number of alternative compositional MRI sequences are available that may offer superior performance and warrant further investigation²⁰.

The final objective of this thesis was to evaluate the feasibility and optimal study design of a clinical trial to compare treatment strategies for patients with symptomatic femoroacetabular impingement. There is currently very limited evidence to guide clinical decisions for this patient population. Proposed therapies range from physiotherapy and activity modification, through to arthroscopic surgery to restore the concavity at the femoral head-neck junction. A search of the Hospital Episodes Database revealed a 727% increase in the number of arthroscopic hip procedures performed in England between 2002 and 2013. This increase is comparable to similar observations in the USA. A requirement for evidence of efficacy was identified. In addition to improving symptoms, surgery is purported to reduce the risk of osteoarthritis progression by correcting adverse joint morphology. There remains no evidence to date that surgery is superior to non-operative measures, or that it offers disease-modifying properties.

The feasibility study reported in this thesis demonstrated that surgeon and patient opinion was permissive of a randomised controlled trial comparing operative and non-operative management of femoroacetabular impingement. A finding of particular interest was that more patients were concerned about their risk of developing osteoarthritis than their current symptoms. A further salient finding was that 94% of patients were willing to continue non-operative treatment for six months in the absence of symptom improvement, but only 26% patients were willing to continue for 12 months. These findings are likely to have relevance to clinical trials in other fields. Based on the results of the feasibility study, a protocol was developed for the Femoro-Acetabular Impingement Trial (FAIT). This is a randomised controlled trial comparing

physiotherapy and activity modification with arthroscopic surgery for improving symptoms and preventing osteoarthritis in patients with symptomatic femoroacetabular impingement (NCT01893034). The results of this study should provide valuable data to support treatment and funding decisions.

7.2 Future Directions

Two valuable cohorts were developed during the course of this thesis and longitudinal assessment of these may provide some answers to present and future research questions. FAIM is a cohort of 210 individuals recruited between the ages of 9 and 18 years and consists of professional athletes and controls. FAIT is a cohort of 214 individuals aged 18 to 60 years who presented to healthcare professionals with symptomatic femoroacetabular impingement, but no evidence of osteoarthritis.

Since performing the studies described in this thesis, further assessments have been carried out. At baseline, the assessment of FAIM participants consisted of clinical examination, morphological MRI, compositional MRI, and urine collection. These assessments will be repeated at three-year follow-up. FAIT participants have received serial assessments with clinical examination, pelvic radiographs, morphological MRI, compositional MRI, as well as serum and urine collection. Methodology has been standardised to allow comparisons between cohorts, and will be applied to future cohorts both locally and as part of research collaborations.

One of the greatest challenges in this field remains the inability to identify individuals at greatest risk of future osteoarthritis. This prevents the implementation of joint preserving strategies at a time when they are most likely to be effective. Longitudinal assessment of the FAIM and FAIT cohorts may inform the development of a risk stratification tool. A predictive model is likely to incorporate biochemical and imaging

markers of early joint degeneration. Although the prognostic performance of biomarkers has been limited to date, this is an active field of research. Whereas systemic biochemical markers have traditionally been limited by their inability to locate the site of disease, recent proteomic studies raise the possibility of joint specificity¹⁶³. There have also been significant advances in the development of compositional MRI, in part facilitated by the increasing availability of ultra-high field strength MRI²⁰. The results from longitudinal assessment of the FAIM and FAIT cohorts may facilitate the translation of these techniques from the research setting to routine clinical care.

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Appendix A - Introduction

A.1 Pathogenesis of Osteoarthritis

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

A.1.1 Cartilage

The main structural protein of cartilage is type II collagen. This provides a meshwork that receives stabilisation from other collagen types and non-collagenous proteins, such as cartilage oligomeric matrix protein (COMP), and provides cartilage with tensile strength. Aggrecan and other proteoglycans are embedded within this framework, and draw water into the cartilage, providing compressive resistance. Cartilage architecture and biochemical composition are strictly regulated by chondrocytes in response to changes in their chemical and mechanical environment⁷¹. On activation, they produce a number of inflammatory response proteins such as cytokines, including IL-1 β , IL-6 and TNF- α , and matrix degrading enzymes including the metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTSes). Some of these appear to have important pathogenic effects, such as the collagenases (MMP-1, 3 and 13) and aggrecan-degrading-degrading enzymes (ADAMTS-4 and 5). Others may have beneficial matrix remodelling roles in healthy cartilage²³. Proteases, including ADAMTS-5, are upregulated in a highly mechanosensitive fashion in mice following

surgical joint destabilisation, and are downregulated on joint immobilisation.³⁵⁹. This supports a potential role for addressing hostile joint biomechanics as a preventative strategy.

The innate immune system is activated in osteoarthritis. Chondrocytes express multiple Toll-Like Receptors (TLRs)³⁶⁰ activated by damage-associated molecular patterns (DAMPs). In osteoarthritis, DAMPS comprise extracellular matrix molecules that include the glycosaminoglycan hyaluronan³⁶¹. Calcium pyrophosphate and sodium urate crystals also bind chondrocyte TLR receptors and may therefore play a role in the aetiology of osteoarthritis³⁶². The finding that the expression and activation of complement is abnormally high in human osteoarthritic joints³⁶³ is intriguing. COMP is a potent activator of the alternative complement pathway³⁶⁴ while proteoglycans such as fibromodulin target the classical pathway³⁶⁵. Chondrocytes also express receptors that bind advanced glycation end-products (AGEs)³⁶⁶, which accumulate in aging tissues. This results in a phenotypic shift to catabolism³⁶⁷ and may help explain the increasing prevalence of osteoarthritis with age.

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

A.1.2 Subchondral Bone

Subchondral cortical bone forms an interface between the calcified cartilage below the 'tidemark' and the underlying trabecular bone. Marked changes are seen in the structure and composition of both the cortical plate and trabecular bone in osteoarthritis^{368,369}. In fact, aspects of endochondral ossification are reinitiated in osteoarthritis and the

tidemark advances with associated vascular penetration. This is accompanied by the formation of osteophytes and subchondral cysts. Advances in imaging now allow bone marrow lesions to be identified on MRI that correlate with a number of histological changes including microfractures at different stages of healing³⁷⁰. These lesions localise to areas with the most severe cartilage damage. Some studies suggest that changes in subchondral bone and osteophyte formation precede cartilage degeneration^{371,372}, but such studies are always biased by the sensitivity of the detection methodology⁸⁵. More recent work demonstrates that like chondrocytes, osteoblasts respond to mechanical stimulation with the expression of inflammatory cytokines and degradative enzymes³⁷³. These may act directly on cartilage, or changes in the mechanical properties of subchondral bone may have deleterious effects on overlying cartilage. Conversely, subchondral bone remodelling may result from increased loading through loss of cartilage integrity. Subchondral bone is highly innervated and probably contributes to the generation of pain in disease.

A.1.3 Synovium

Synovitis is a frequent feature of osteoarthritis, even in early disease. In established osteoarthritis there is proliferation of synoviocytes and tissue hypertrophy, with increased vascularity³⁷⁴. Synoviocytes synthesise lubricants such as hyaluronic acid³⁷⁵ and lubricin³⁷⁶. These contribute to optimal joint function but display reduced lubricating capacity in subsets of patients with osteoarthritis^{375,377}. Like chondrocytes and osteoblasts, synoviocytes also release inflammatory mediators and degradative enzymes. Activation is likely secondary to inflammatory mediators and cartilage matrix molecules released during an initial insult to the joint, after which synovial tissue drives progressive joint degeneration in a positive feedback cycle³⁷⁴. Synovitis predicts the development and progression of symptoms (odds ratio 9.2, 95% CI 3.2 to 26.3)³⁷⁸ and possibly cartilage loss (odds ratio 2.7, 95% CI 1.4 – 5.1)³⁷⁹, although the relationship with

structural change is less consistent. It is often difficult to compare study findings due to different patient populations and methods of diagnosing synovitis, however, synovitis may represent a rational target for intervention.

A.1.4 Systemic Inflammation

Osteoarthritis is primarily seen as a local disease confined to the joint and studies investigating the relationship with systemic markers of inflammation yield conflicting results. A recent systematic review suggests that serum CRP is associated with symptoms rather than radiographic osteoarthritis³⁸⁰ and pain may represent a marker of systemic inflammation³⁸¹. It is not understood why obesity remains a risk factor for osteoarthritis in non-weight-bearing joints³⁸². Adipokines released from adipose tissue have been proposed as mediators of this effect, however, their role is speculative and not borne out in clinical studies³⁸³.

A.2 Pharmaceutical Treatment

Many patients who develop osteoarthritis do not have identifiable risk factors amenable to intervention. Furthermore, it is not known whether the correction of risk factors is sufficient to reverse a catabolic tissue phenotype. Pharmaceutical agents already play a key role in symptom control, particularly paracetamol and non-steroidal anti-inflammatories^{191,192}, but an increasing number of drugs are also under investigation as DMOADs.

A.2.1 Supplementation

Chondroitin and glucosamine have demonstrated anti-inflammatory and anti-catabolic properties *in vitro*³⁸⁴ and their ability to improve symptoms or delay structural progression of osteoarthritis has been extensively investigated in clinical trials. Results have been conflicting, purportedly due to different study designs and patient

populations, investigator bias, or the use of different drug formulations. Studies tend to report more positive findings when using glucosamine sulphate rather than glucosamine hydrochloride, however, assuming glucosamine is the active ingredient, there is no available rationale to explain this effect³⁸⁵. Overall the literature does not indicate that chondroitin or glucosamine confer a clinically relevant benefit²⁰² and they are not recommended in guidelines published by international bodies^{192,202,386}. However, it is noteworthy that both have safety profiles comparable with placebo.

Hyaluronic acid is a glycosaminoglycan found in synovial fluid that acts as a lubricant, but concentrations decline in osteoarthritis³⁷⁵. Hyaluronic acids have been widely used as viscosupplementation administered via intra-articular injections, however, debate over efficacy and safety continues. A recent meta-analysis concludes that there is no clinically relevant benefit with respect to pain or function²⁰³, neither is there is convincing evidence of structural benefit. Lubricin is a glycoprotein that acts synergistically with hyaluronic acid³⁸⁷, but displays reduced lubricating capacity in subsets of patients with osteoarthritis³⁷⁷. Supplementation restores normal joint lubrication and may be chondroprotective^{377,388}, offering therapeutic potential.

A.2.2 Enzyme Inhibition

An alternative strategy is to target degradative enzymes. Doxycycline is a potent MMP inhibitor and randomised controlled trials have demonstrated reduced JSW narrowing compared with placebo, but little improvement in pain or function²⁰⁴. This small potential benefit appears to be outweighed by adverse events²⁰⁴. Other broad MMP inhibitors have demonstrated neither structural or symptomatic benefit and frequently result in musculoskeletal toxicity³⁸⁹. Upstream intracellular signalling molecules, such as inducible nitric oxide synthase (iNOS), have also been targeted with disappointing results³⁹⁰.

A.2.3 Bone Metabolism

Bisphosphonates have been used in an attempt to reverse subchondral bone changes seen in osteoarthritis through their inhibition of osteoclast activity. Randomised controlled trials have investigated the effect of risedronate in knee osteoarthritis where a reduction in urinary CTX-II was demonstrated compared with placebo, but without a reduction in JSW narrowing^{391,392}. Furthermore, the symptomatic improvement seen in one cohort³⁹¹ was not reproduced in a larger multi-national study³⁹². More recently, a single dose of zoledronic acid was shown to improve pain and the size of bone marrow lesions at six months³⁹³. Strontium ranelate, in addition to osteoclast inhibition and osteoblast stimulation, enhances chondrocyte matrix production in vitro³⁹⁴. A randomised controlled trial showed that strontium ranelate therapy for three years reduces radiographic joint space narrowing over placebo, accompanied by a modest improvement in symptoms and a reduction in urinary CTX-II²⁰⁶. Further studies of strontium ranelate may be indicated, however, side effect profiles are likely to limit its clinical utility in osteoarthritis³⁹⁵.

A.2.4 Anti-Inflammatory Therapy

A number of proposed therapeutic agents target inflammation. Intra-articular steroid injections are widely used to improve symptoms, but do not modify structure³⁹⁶. Methotrexate is also under investigation in patients with synovitis³⁹⁷. It is hoped biologic agents targeting components of the inflammatory cascade might transform the treatment of osteoarthritis in the same manner as rheumatoid osteoarthritis³⁹⁸, but results to date are disappointing.

Anakinra, a recombinant IL-1 receptor antagonist, improved symptoms in patients with knee osteoarthritis compared with placebo, but the effect was not sustained beyond four days post intra-articular injection³⁹⁹. When AMG 108, a monoclonal antibody against the

IL-1 receptor, was administered subcutaneously or intravenously in patients with knee osteoarthritis there was no clinical benefit and the death of a patient was attributed to neutropenia secondary to this agent⁴⁰⁰.

Anti-TNF therapy has also been trialled in osteoarthritis⁴⁰¹. Adalimumab, a monoclonal antibody to TNF- α , has not demonstrated a therapeutic effect in hand osteoarthritis⁴⁰², however, promising results have been reported in inflammatory knee osteoarthritis⁴⁰³.

Given the adverse effects of biologic therapies, systemic treatment is perhaps best justified when disease affects several joints, such as in hand osteoarthritis, whereas single joint osteoarthritis of the knee or hip may be best approached with intra-articular injections of slow release medication⁴⁰⁴.

A.2.5 Growth Factors

Recombinant human bone morphogenetic protein (BMP-7) and fibroblast growth factor (FGF-18) have been proposed as DMOADs given they promote cartilage repair in vitro⁴⁰⁵. A recent clinical trial found intra-articular FGF-18 did not reduce cartilage loss in the medial knee compartment or improve symptoms, but did demonstrate structural modification in the lateral compartment compared with placebo at one year²⁰⁵.

A.2.6 Stem Cell Therapy

Stem cell therapy may have an application in osteoarthritis and multipotent mesenchymal stem cells are found in healthy and diseased cartilage⁴⁰⁶. Kartogenin is a molecule that promotes chondrocyte differentiation and cartilage repair in animal models of established osteoarthritis⁴⁰⁷. Whether this or similar molecules will translate to the clinical arena remains to be seen.

A.3 Cartilage Repair and Regeneration Techniques

A variety of surgical strategies aim to repair localised cartilage lesions²⁰¹. These can be divided into techniques that transplant autologous cartilage and those that seek to stimulate regeneration.

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

Microfracture seeks to stimulate generation of new cartilage at sites of focal full-thickness defects. It involves traumatising subchondral bone using a pick to release chondroprogenitor cells. Although these differentiate into mechanically inferior fibrocartilage rather than hyaline cartilage²⁰¹, the technique is inexpensive and easy to perform, and is the most widely used regenerative approach.

Limitations in the above procedures have driven the field of tissue engineering and development of more advanced regenerative techniques. Autologous chondrocyte implantation (ACI) has been in development since the 1980s where chondrocytes are arthroscopically harvested and cultured, before implantation into the cartilage defect several weeks later. The technique has undergone several iterations, but to date it remains unclear whether ACI confers improved clinical outcomes over more simple techniques such as microfracture²⁰⁰. Latest developments comprise alternative sources of cell, including mesenchymal and embryonic stem cells, utilisation of growth factors, and implantation of cells into three-dimensional scaffolds or matrices that support growth, differentiation, and maintenance of a chondrogenic phenotype²⁰¹.

There is little evidence that the above techniques modify the development of osteoarthritis. Cartilage repair is unlikely to be successful if the joint environment

remains biologically or mechanically hostile, but may provide an important adjunct to the correction of aetiological factors.

Appendix B – Quantitative Imaging

B.1 Validity, Reliability and Reproducibility

B.1.1 Measurement Error

Measurements are prone to errors that may arise from many sources and may pertain to the observer, the measurement tool, or physiological variation. The performance of a measurement may be viewed in terms of accuracy and precision. Accuracy reflects the degree to which measured values deviate from true values, hence validity. In imaging studies, it is difficult to establish true values, and measurements are usually compared with an existing gold-standard technique.

Precision errors describe the repeatability and reproducibility of a measurement, which is critical when assessing longitudinal change. Repeatability describes the variation in repeat measurements made on the same subject under identical conditions, where all variability represents measurement error. Reproducibility describes the variation in repeat measurements under changing conditions. Examples of changing conditions are when the same measurement is performed by different observers, or by the same observer but after a period of time.

B.1.2 Reproducibility Statistics

Precision errors may be quantified using several statistical methods and those most frequently used are Intraclass Correlation Coefficient (ICC), Coefficients of Variation (CV), Standard Error Measurement (SEM), and Limits of Agreement (LA). ICCs and CVs assess reliability, which determines the ability to discriminate between subjects after taking measurement error into account. LAs assess agreement, which is the absolute

difference between values after repeated measurements and can be used to determine the smallest difference that is detectable within a cohort.

Correlation coefficients evaluate relative reliability and assess the magnitude of measurement error relative to the underlying variability of the true values. As the correlation coefficient of two measurements on the same subject increases, it suggests that less of the variability is derived from measurement error. A coefficient of 1 suggests perfect correlation between readings with no measurement error, whereas a coefficient of 0 suggests no correlation between readings. There are no predefined limits of acceptability for a measurement tool. Interclass Correlation Coefficients (Pearson's Correlation) does not account for systematic differences in values and looks for association rather than agreement⁴⁰⁸. Systematic bias can be detected using a paired t-test, although this is influenced by the amount of random variation between tests. Intraclass Correlation Coefficients (ICC) can be used in a way that is sensitive to systematic bias⁴⁰⁹, and also has the advantage of being a univariate rather than bivariate test, which allows the assessment of repeated measures. However, all correlation coefficients are influenced by the range and distribution of the data and is only relevant to other cohorts when data is of equal heterogeneity. Correlation coefficients should therefore not be reported alone.

CV and SEM measure absolute reliability by assessing the variation between measurements in relation to the mean value of all the measurements. CV is expressed as a percentage and is often used to supplement ICCs, since it is unaffected by the range and distribution of data and accounts for heteroscedasticity. It only has a useful interpretation if the measurement scale is positive with zero as the minimum value. Careful interpretation is essential, as CV of 10% means that 68% of the differences between tests lie within 10% of the mean⁴¹⁰. An alternative method of assessing absolute reliability is the SEM, but in addition to similar limitations as for CVs, it is affected by

heteroscedasticity and does not carry the advantage of providing a dimensionless statistic to compare performance between measurement tools. Furthermore, the many different methods used to calculate this statistic are often a source of confusion.

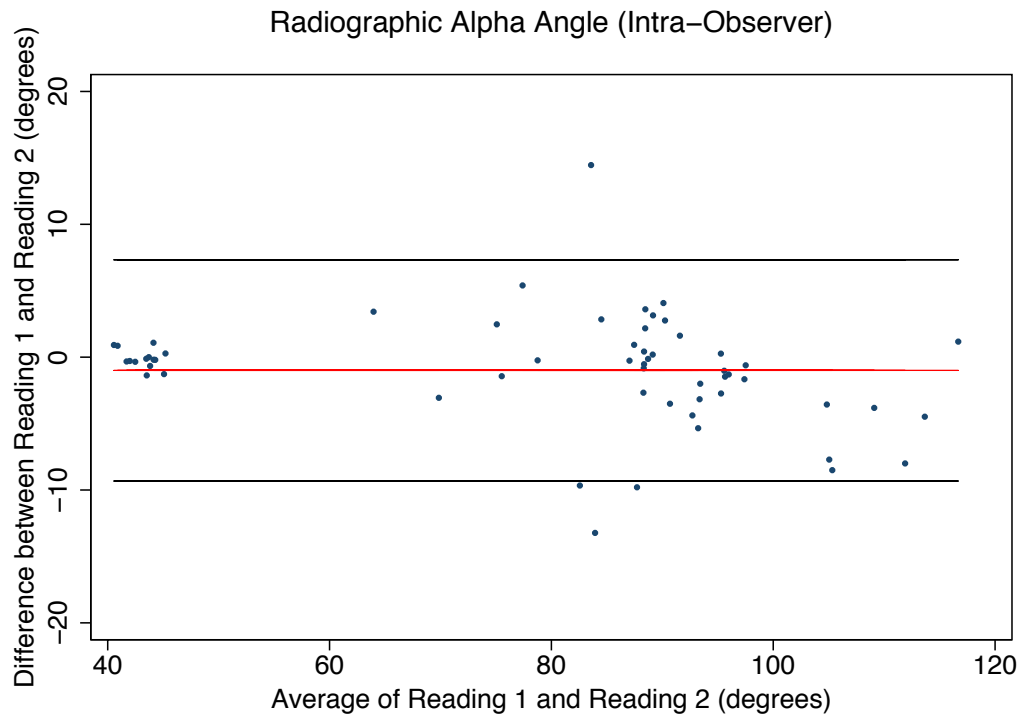
LAs quantify the absolute disparity between two measurements in relation to the mean value of all the measurements⁴¹¹. This accounts for systematic bias that is not considered with ICCs or CVs. Assuming the mean difference between readings is zero and values are normally distributed, the limits of agreement are defined as $-1.96 \times \text{SD}$ and $+1.96 \times \text{SD}$, where SD is the standard deviation of the differences between measurements. This defines the range in which 95% of values will agree and is often used to determine the Smallest Detectable Difference (SDD) in measurements.

When performing the above calculations, the root of mean squares (rather than the arithmetic mean) is used to calculate standard deviation and the degrees of freedom is correct for the dataset in order to avoid underestimation of imprecision by up to 25% and 41%, respectively⁴¹². With the exception of CV, when there is evidence of heteroscedasticity, data should be logarithmically transformed prior to reliability and agreement testing. All of the above measures of precision are estimates and it is therefore necessary to calculate Confidence Intervals (CIs).

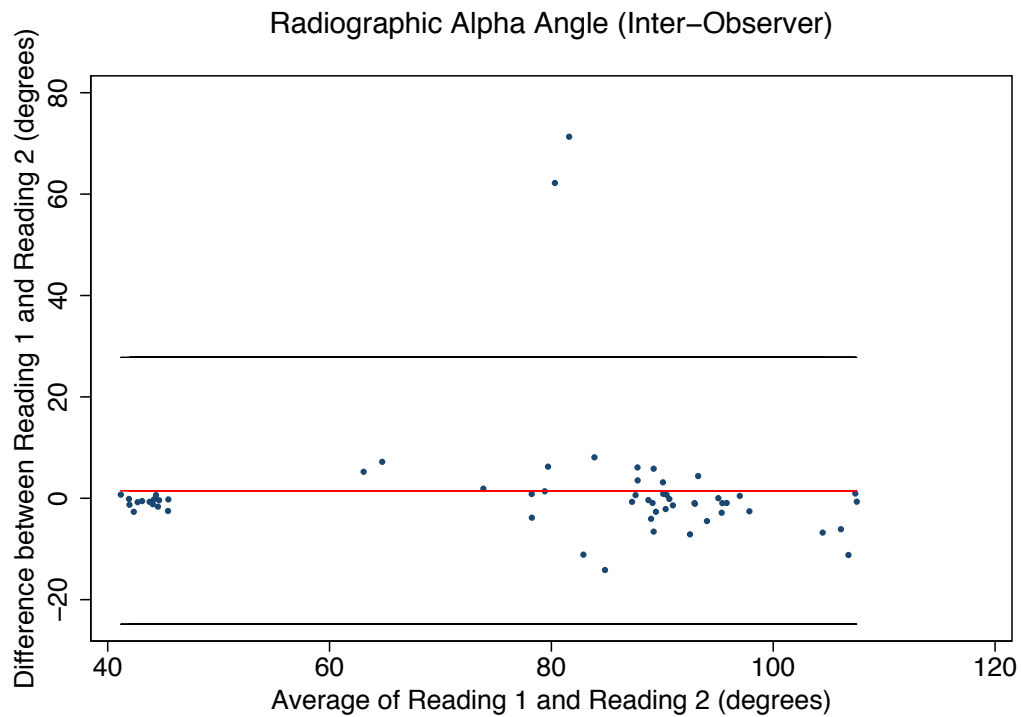
B.2 Bland-Altman Plots for Imaging Outcome Measures

Bland-Altman plots have been produced to illustrate intra-observer and inter-observer reproducibility for each of the imaging outcome measures. Plots include the mean difference between the two measurements (red line) and 95% limits of agreements calculated as $1.96 \times \text{standard deviation}$ (black lines).

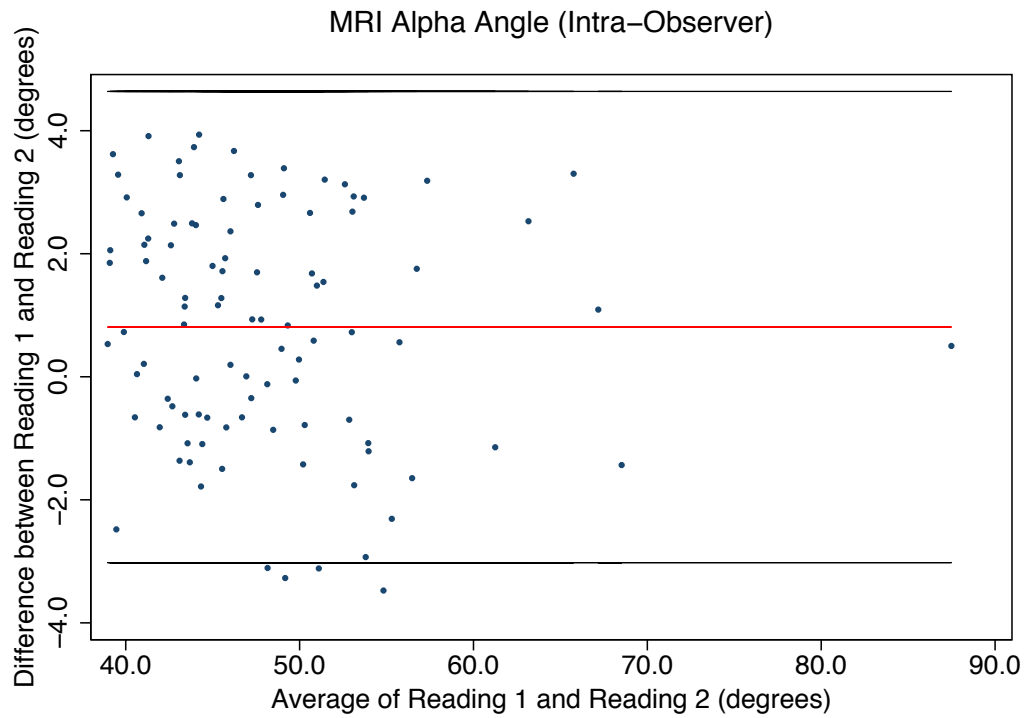
Appendix B-1 - Bland-Altman Plot for Radiographic Alpha Angle Intra-Observer Reproducibility



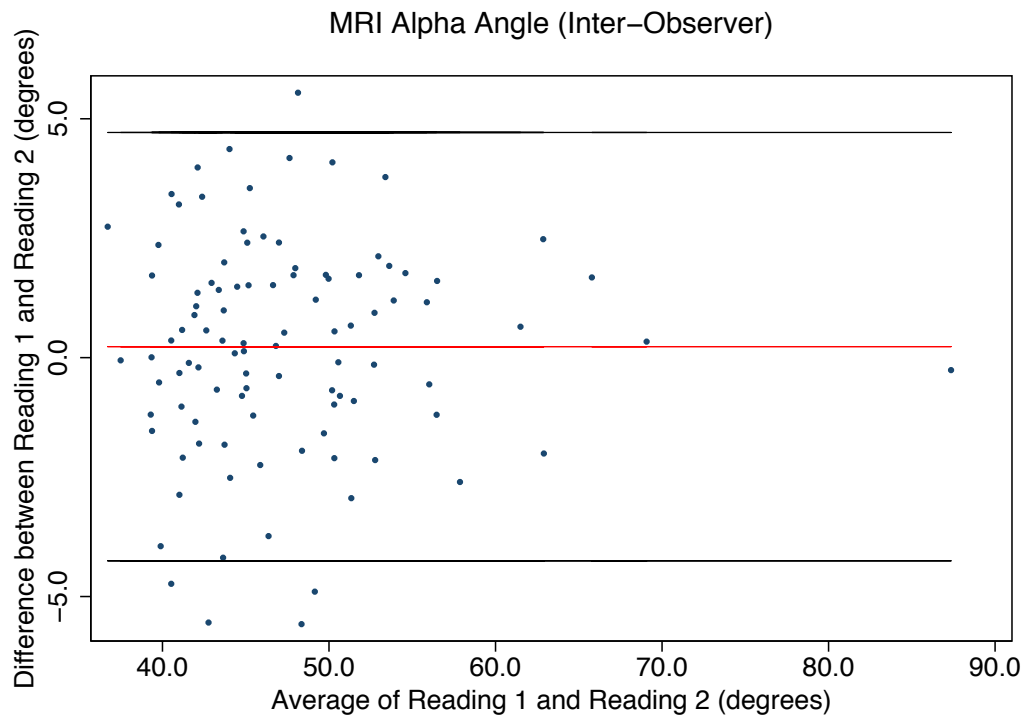
Appendix B-2 - Bland-Altman Plot for Radiographic Alpha Angle Inter-Observer Reproducibility



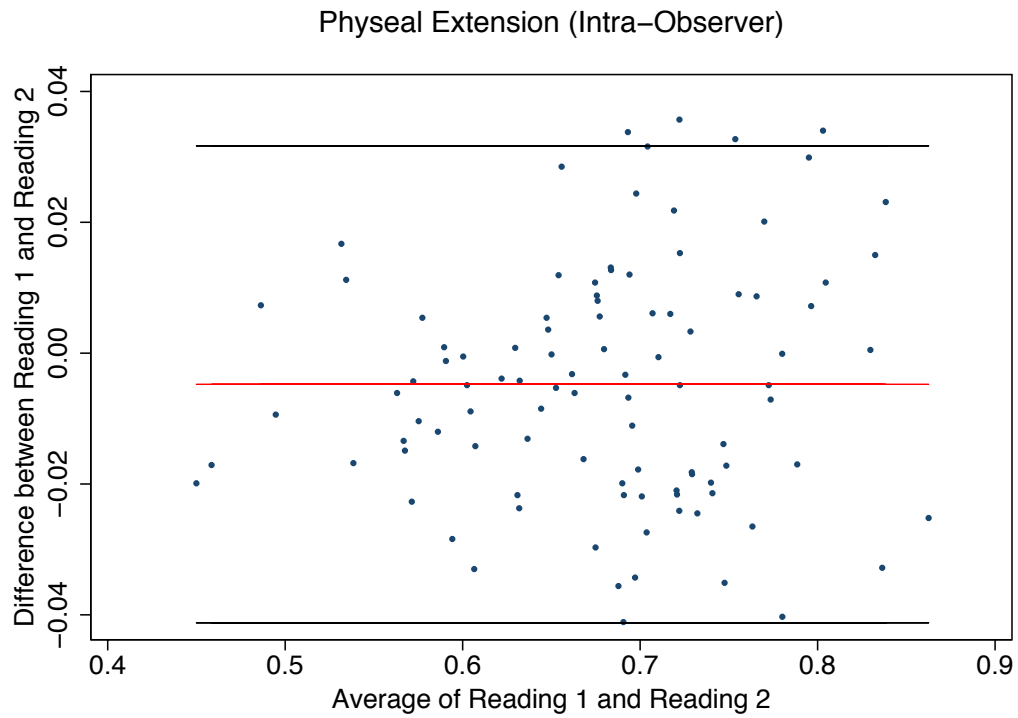
Appendix B-3 - Bland-Altman Plot for MRI Alpha Angle Intra-Observer Reproducibility



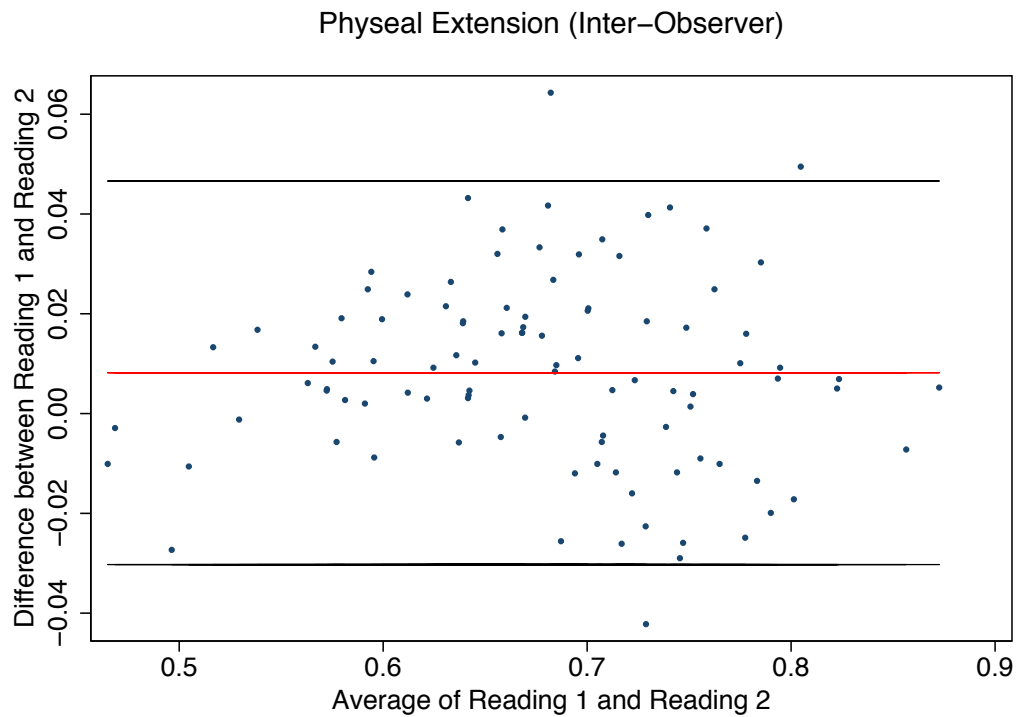
Appendix B-4 - Bland-Altman Plot for MRI Alpha Angle Inter-Observer Reproducibility



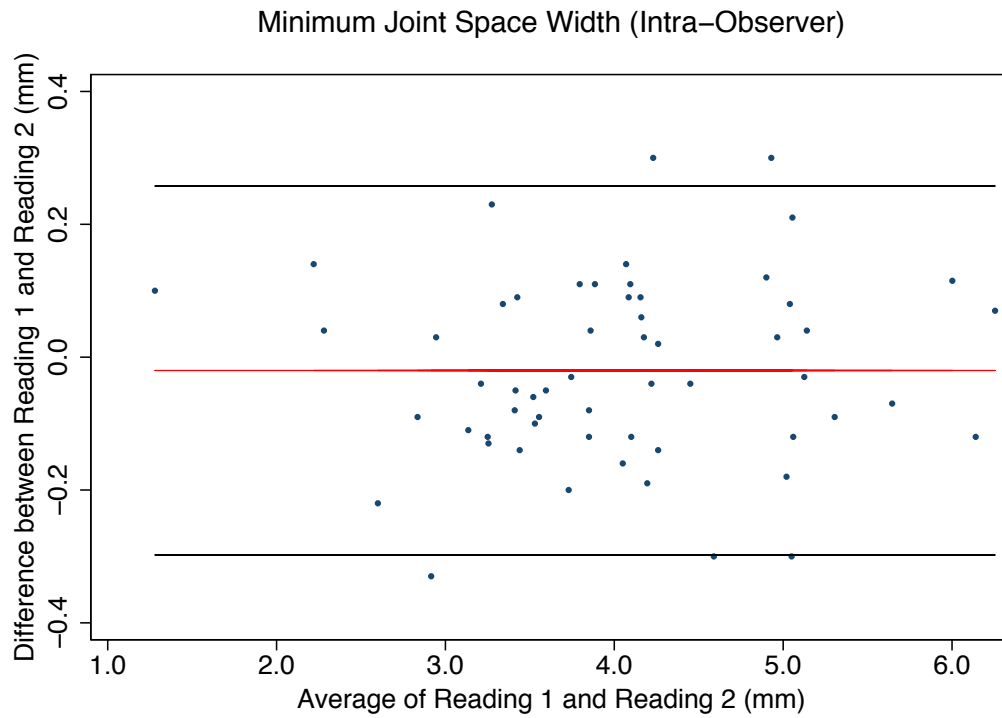
Appendix B-5- Bland-Altman Plot for MRI Epiphyseal Extension Intra-Observer Reproducibility



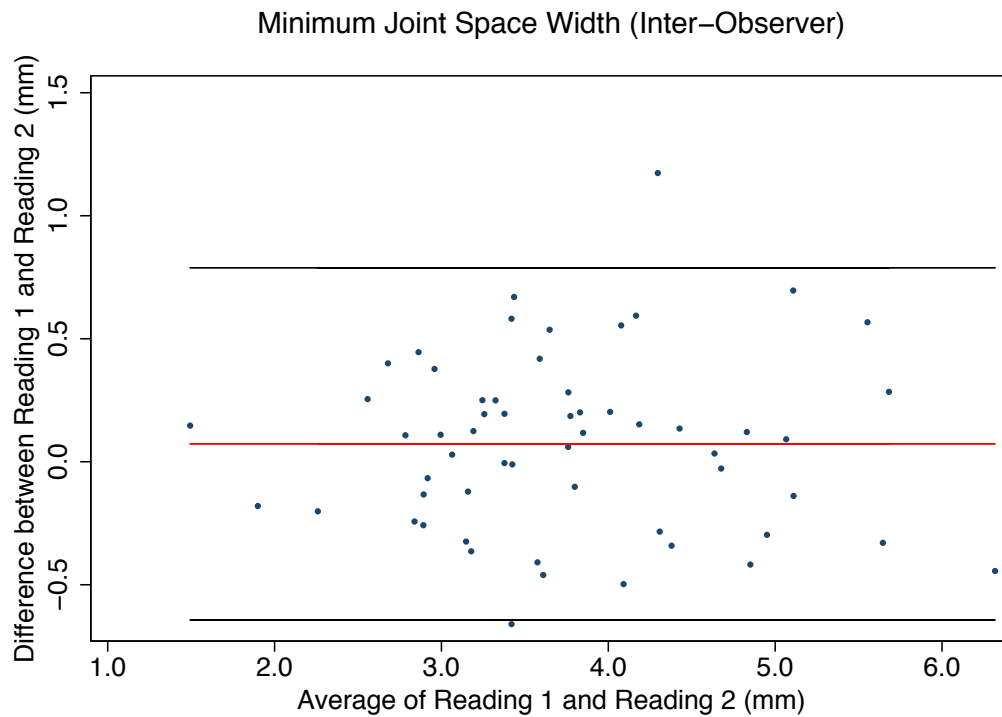
Appendix B-6 - Bland-Altman Plot for MRI Epiphyseal Extension Inter-Observer Reproducibility



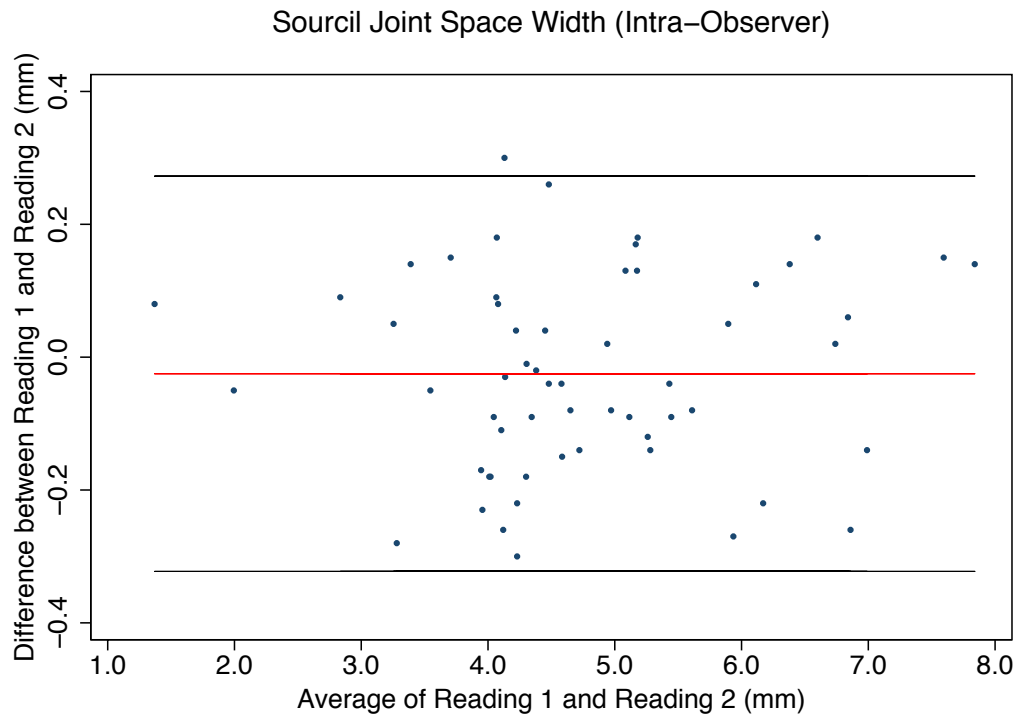
Appendix B-7 - Bland-Altman Plot for Minimum Joint Space Width Intra-Observer Reproducibility



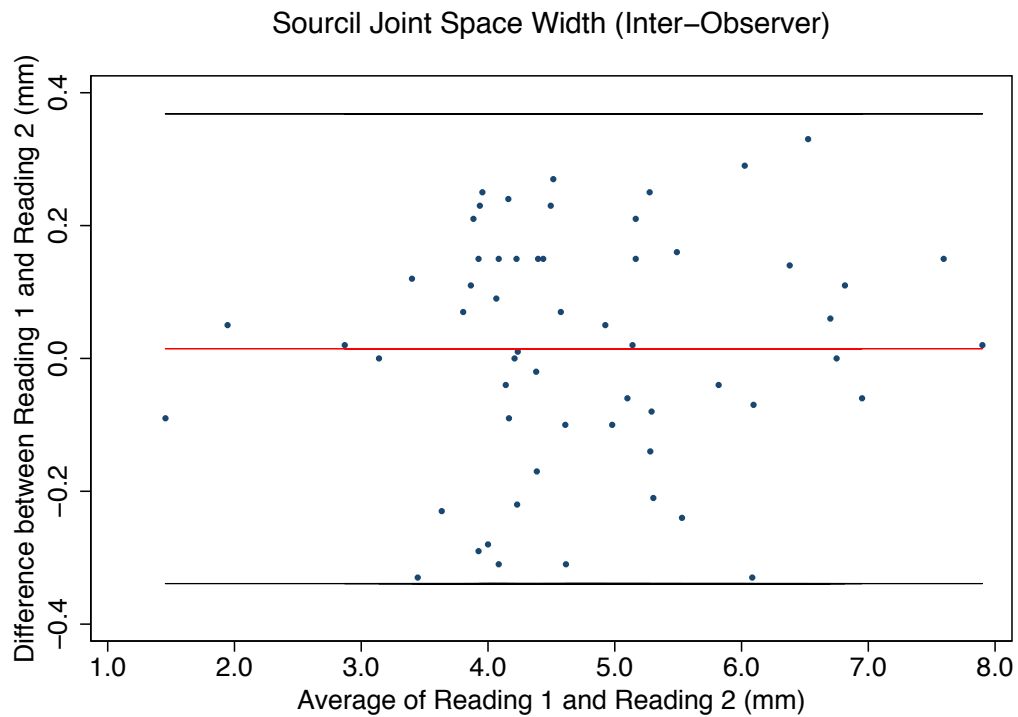
Appendix B-8 - Bland-Altman Plot for Minimum Joint Space Width Inter-Observer Reproducibility



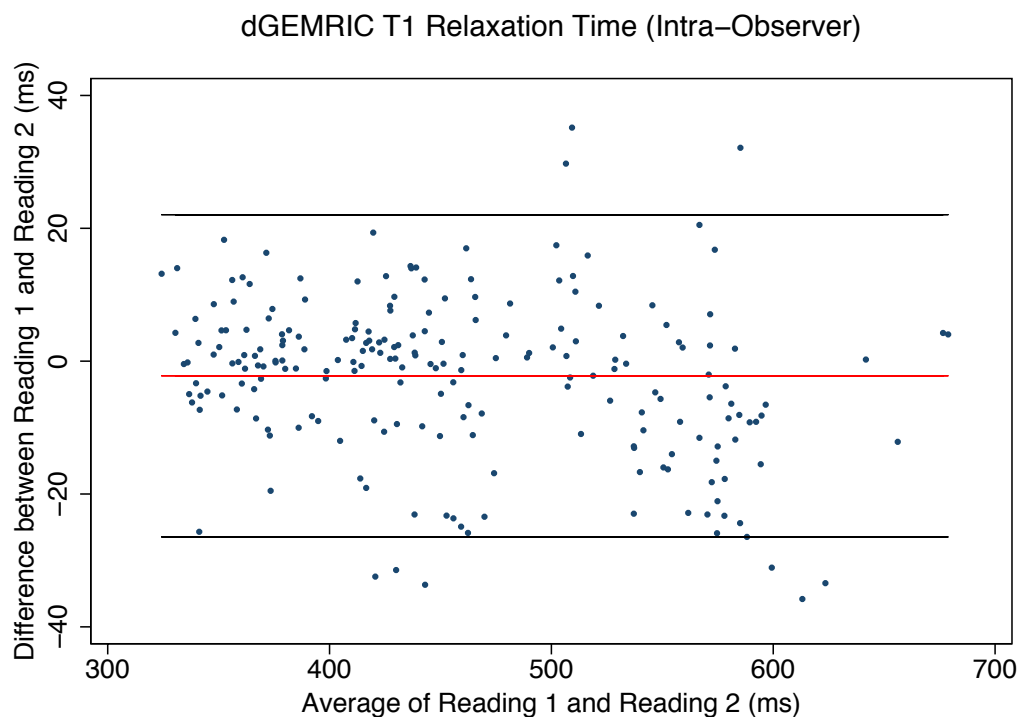
Appendix B-9 - Bland-Altman Plot for Sourcil Joint Space Width Intra-Observer Reproducibility



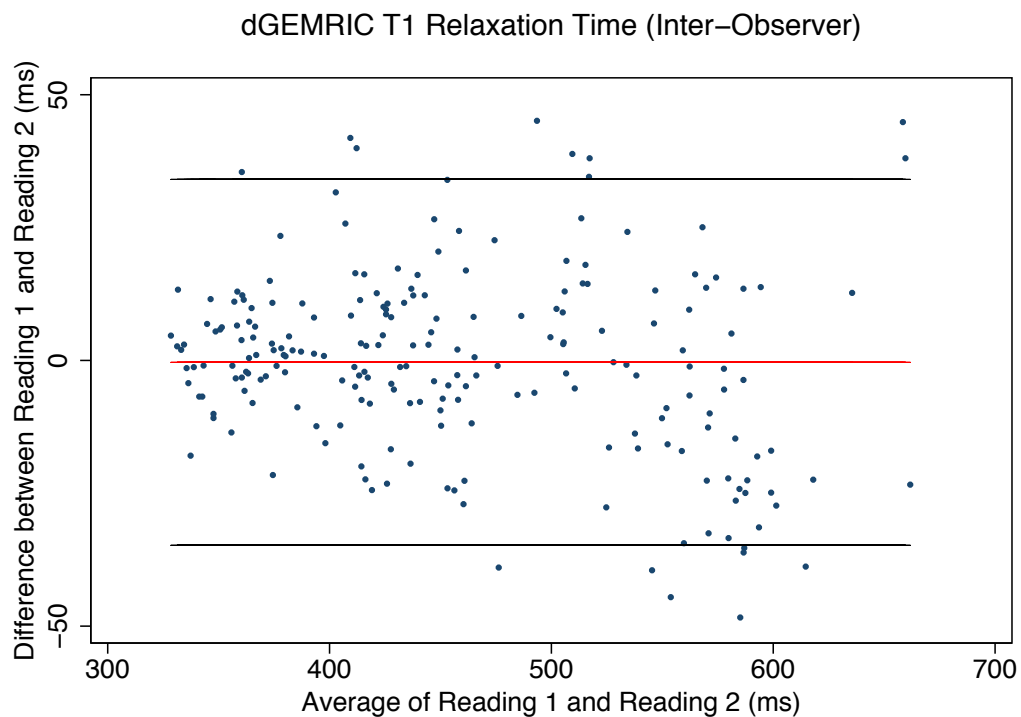
Appendix B-10 - Bland-Altman Plot for Sourcil Joint Space Width Inter-Observer Reproducibility



Appendix B-11 - Bland-Altman Plot for dGEMRIC T1 Relaxation Time Intra-Observer Reproducibility



Appendix B-12 - Bland-Altman Plot for dGEMRIC T1 Relaxation Time Inter-Observer Reproducibility



Appendix B-13 - Reproducibility of Each Region of Interest for dGEMRIC Compositional MRI

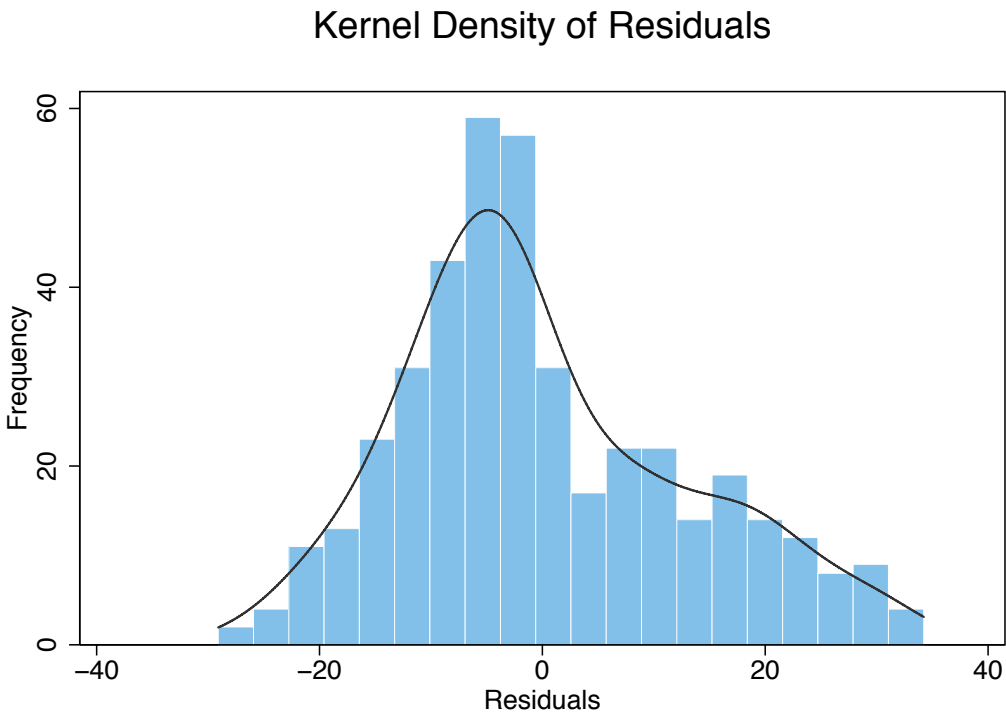
	Intra Observer Reproducibility					Inter Observer Reproducibility				
	Mean T1 Relaxation Time (ms)		ICC	RMSCoV	SDD	Mean T1 Relaxation Time (ms)		ICC	RMSCoV	SDD
	Observation 1	Observation 2				Observation 1	Observation 2			
ASa	424.196 (±79.218)	427.078 (±83.378)	0.994	1.981	15.856	424.196 (±79.218)	430.198 (±87.359)	0.974	4.358	35.117
SAa	447.031 (±85.638)	445.859 (±87.388)	0.994	1.984	18.239	447.031 (±85.368)	455.661 (±98.489)	0.964	5.479	45.135
SPa	464.888 (±76.499)	464.077 (±77.564)	0.989	2.395	21.856	464.888 (±76.499)	472.771 (±90.693)	0.961	5.004	43.122
PSa	462.590 (±69.173)	464.247 (±73.092)	0.987	2.459	22.117	462.590 (±69.173)	463.243 (±77.320)	0.979	3.139	29.143
Pa	445.776 (±64.313)	439.726 (±62.922)	0.956	4.144	35.205	445.776 (±64.313)	430.765 (±63.736)	0.917	5.753	41.937
ASf	490.323 (±93.339)	496.487 (±96.296)	0.980	3.838	35.032	490.323 (±93.339)	481.759 (±93.259)	0.972	4.447	39.439
SAf	476.626 (±95.097)	483.461 (±97.659)	0.982	3.627	32.879	476.626 (±95.097)	473.672 (±89.428)	0.984	3.420	32.320
SPf	464.464 (±88.880)	470.869 (±95.367)	0.986	3.333	27.663	464.460 (±88.88)	468.042 (±91.175)	0.991	2.534	22.112
PSf	460.845 (±84.354)	464.315 (±90.692)	0.992	2.334	19.991	460.845 (±84.354)	466.801 (±93.352)	0.985	3.282	27.471
Pf	435.233 (±89.791)	441.047 (±94.616)	0.991	2.801	21.609	435.233 (±89.791)	444.553 (±100.7)	0.984	3.799	27.546

Appendix B-14 - Reproducibility of Each Region of Interest for T2 Mapping Compositional MRI

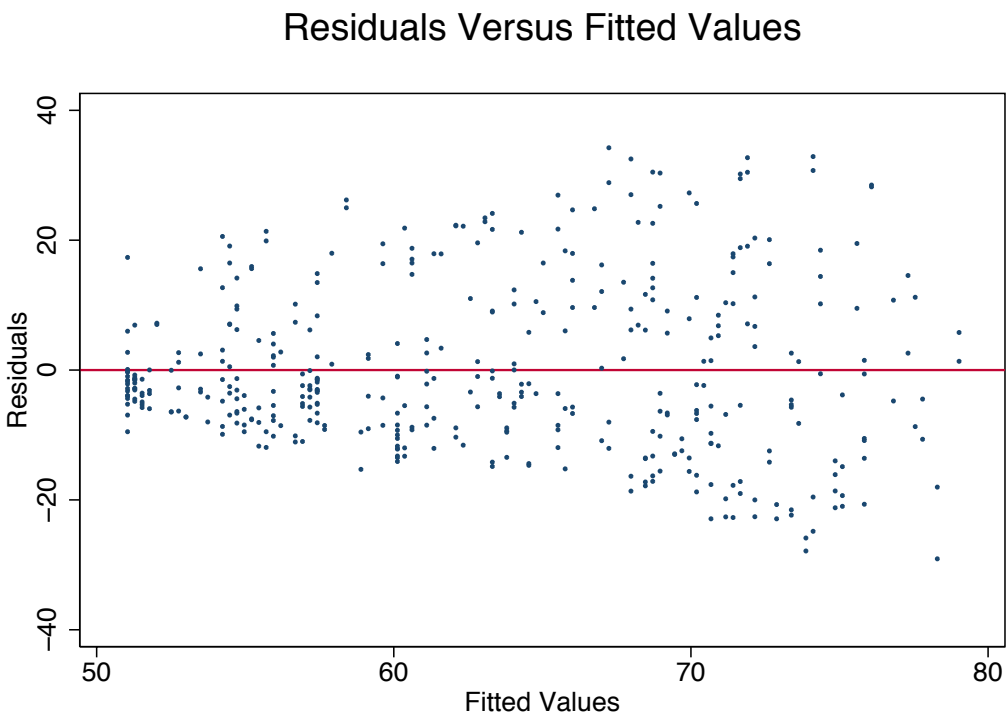
	Intra Observer Reproducibility					Inter Observer Reproducibility				
	Mean T1 Relaxation Time (ms)		ICC	RMSCoV	SDD	Mean T1 Relaxation Time (ms)		ICC	RMSCoV	SDD
	Observation 1	Observation 2				Observation 1	Observation 2			
ASa	44.052 (±7.006)	42.970 (±7.400)	0.983	3.038	15.856	43.659 (±7.536)	44.961 (±7.104)	0.959	4.692	3.218
SAa	43.824 (±6.250)	42.081 (±7.06)	0.945	5.322	18.239	44.154 (±7.521)	45.736 (±6.865)	0.956	4.733	2.823
SPa	47.872 (±5.561)	46.592 (±6.508)	0.948	4.220	21.856	48.747 (±7.351)	49.847 (±6.590)	0.966	3.664	2.845
PSa	50.852 (±6.378)	50.264 (±6.917)	0.990	1.921	22.117	51.283 (±7.055)	51.983 (±6.571)	0.977	2.789	2.497
Pa	43.147 (±9.681)	41.783 (±11.194)	0.968	6.111	35.205	44.093 (±9.439)	45.271 (±8.584)	0.956	5.965	4.748
ASf	46.317 (±4.664)	45.816 (±4.723)	0.991	1.350	35.032	46.237 (±4.745)	46.684 (±4.651)	0.991	1.319	0.831
SAf	41.051 (±4.861)	39.482 (±5.243)	0.933	4.771	32.879	39.446 (±5.360)	40.996 (±4.889)	0.938	4.525	1.892
SPf	40.941 (±3.192)	39.775 (±3.563)	0.925	3.371	27.663	39.823 (±4.405)	41.085 (±3.934)	0.925	4.349	2.238
PSf	43.832 (±3.366)	43.105 (±3.393)	0.970	1.913	19.991	42.730 (±3.885)	44.002 (±3.369)	0.921	4.794	3.218
Pf	39.582 (±6.338)	38.570 (±6.846)	0.983	3.072	21.609	37.861 (±6.081)	39.976 (±5.531)	0.851	8.380	4.842

Appendix C - FAIM

Appendix C-1 - Kernel Density Plot of Residuals for Regression of Maximum Alpha Angle with Age



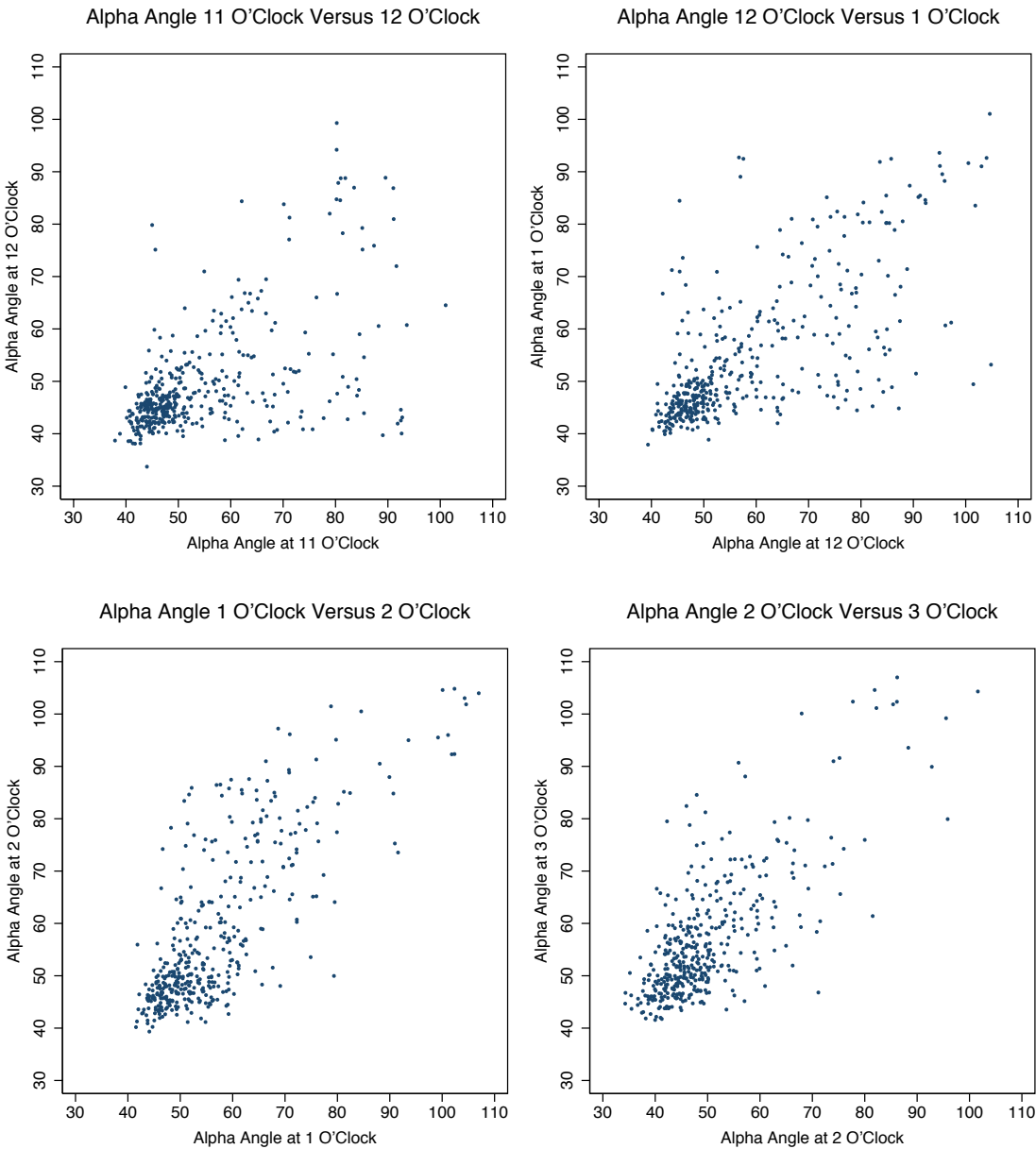
Appendix C-2 - Residuals Versus Fitted Values for Regression of Maximum Alpha Angle with Age



Appendix C-3 - Correlation Coefficient for Alpha Angle Measured at Each Clockface Position

Clockface Position	11 o'clock	12 o'clock	1 o'clock	2 o'clock	3 o'clock	Average All Positions	Maximum All Positions
11 o'clock		0.55	0.46	0.45	0.36	0.68	0.55
12 o'clock	0.55		0.69	0.61	0.46	0.83	0.79
1 o'clock	0.46	0.69		0.77	0.56	0.88	0.91
2 o'clock	0.45	0.61	0.77		0.74	0.85	0.82
3 o'clock	0.36	0.46	0.56	0.74		0.74	0.63
Average All Positions	0.68	0.83	0.88	0.85	0.74		0.91
Maximum All Positions	0.55	0.79	0.91	0.82	0.63	0.91	

Appendix C-4 - Alpha Angle Adjacent Clockface



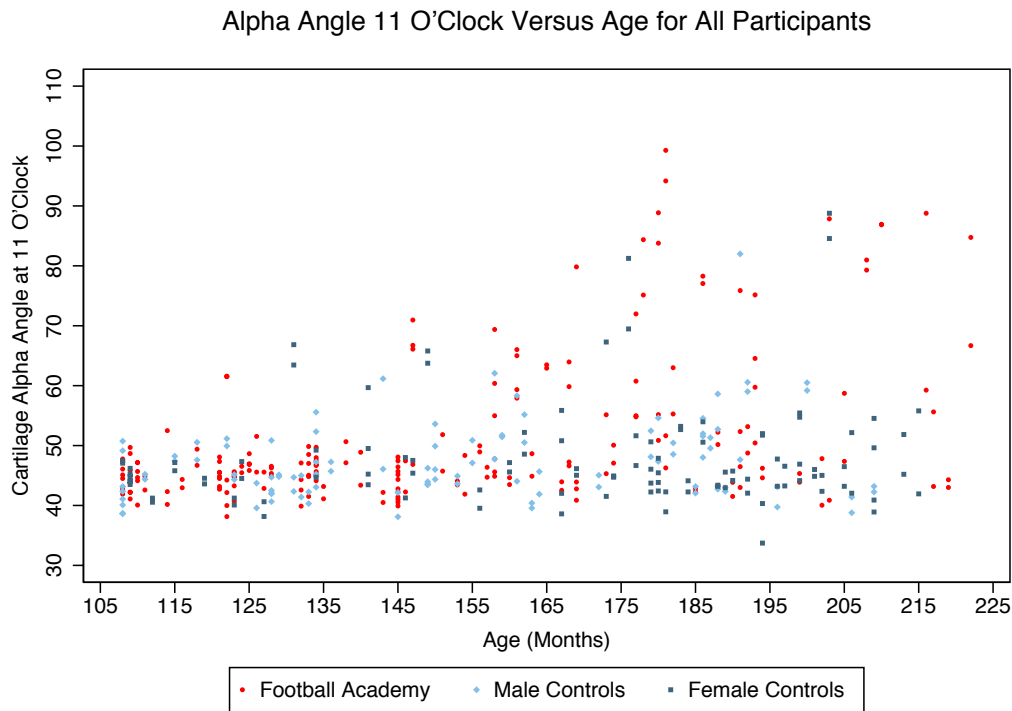
Appendix C-5 - Regression Coefficient of Alpha Angle and Months of Age in All Participants

Clockface Position	Correlation Coefficient	95% Confidence Intervals	Statistical Significance	R ² Value
11 O'Clock	0.106	0.052 – 0.161	0.026	0.106
12 O'Clock	0.189	0.164 – 0.214	0.007	0.213
1 O'Clock	0.218	0.052 – 0.384	0.033	0.211
2 O'Clock	0.187	0.174 – 0.200	0.003	0.248
3 O'Clock	0.112	-0.038 – 0.262	0.067	0.118
Maximum All Positions	0.242	0.143 – 0.341	0.020	0.264

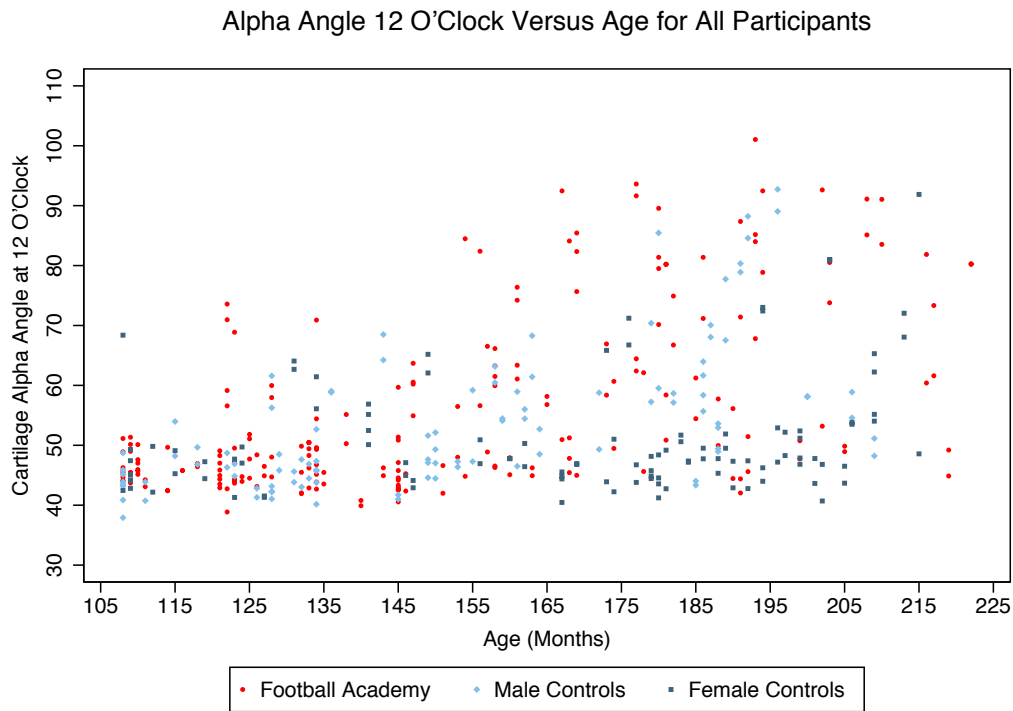
Appendix C-6 - Regression Coefficient of Alpha Angle and Months of Age

Clockface Position	Football Academy		Male Controls		Female Controls	
	Regression Coefficient	R ² value	Regression Coefficient	R ² value	Regression Coefficient	R ² value
11 O'Clock	0.191	0.241	0.063	0.079	0.030	0.002
12 O'Clock	0.274	0.343	0.247	0.376	0.071	0.057
1 O'Clock	0.333	0.372	0.264	0.344	0.091	0.079
2 O'Clock	0.269	0.359	0.230	0.407	0.077	0.119
3 O'Clock	0.181	0.215	0.143	0.192	0.015	0.006
Maximum All Positions	0.345	0.403	0.300	0.448	0.122	0.136

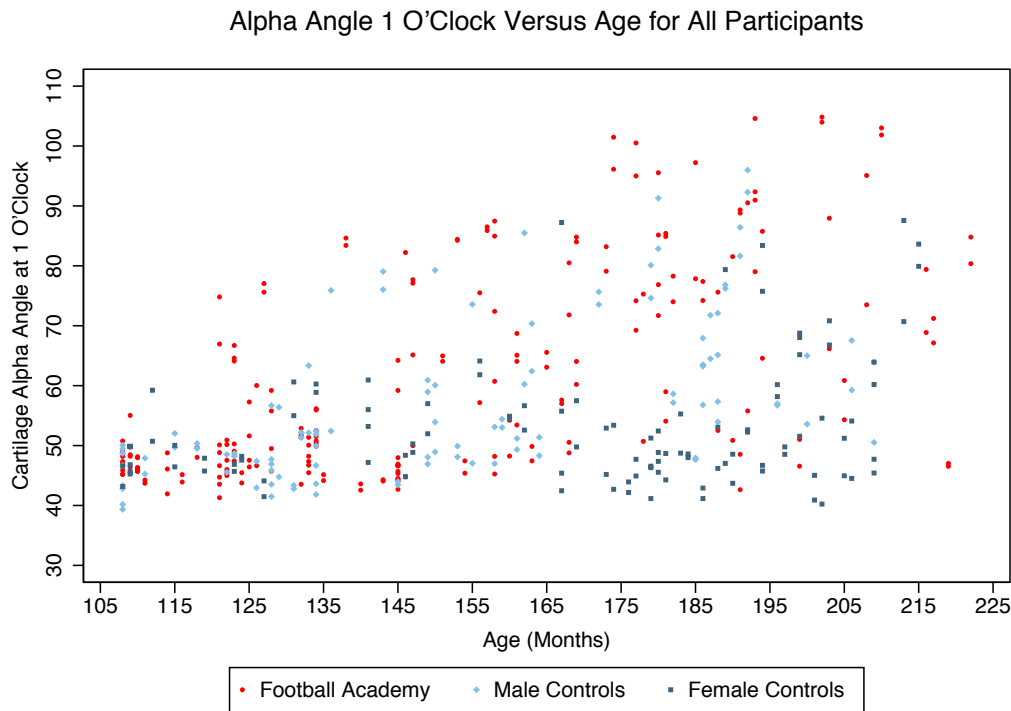
Appendix C-7 – Cartilage Alpha Angle at 11 O’Clock Plotted Versus Age for Each Cohort



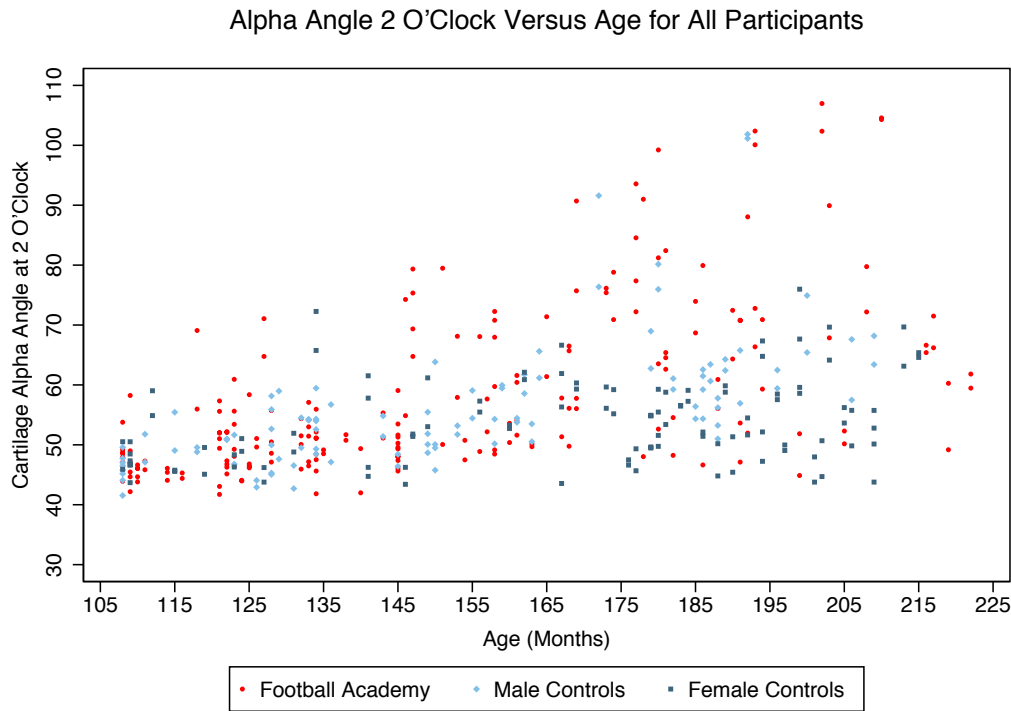
Appendix C-8 - Cartilage Alpha Angle at 12 O’Clock Plotted Versus Age for Each Cohort



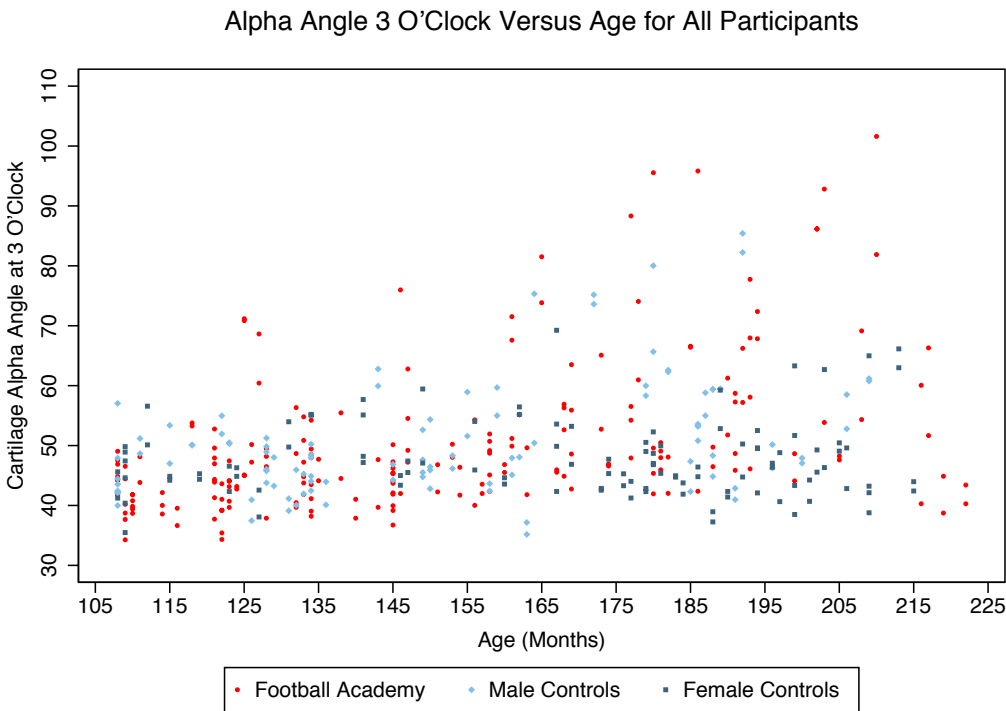
Appendix C-9 - Cartilage Alpha Angle at 1 O’Clock Plotted Versus Age for Each Cohort



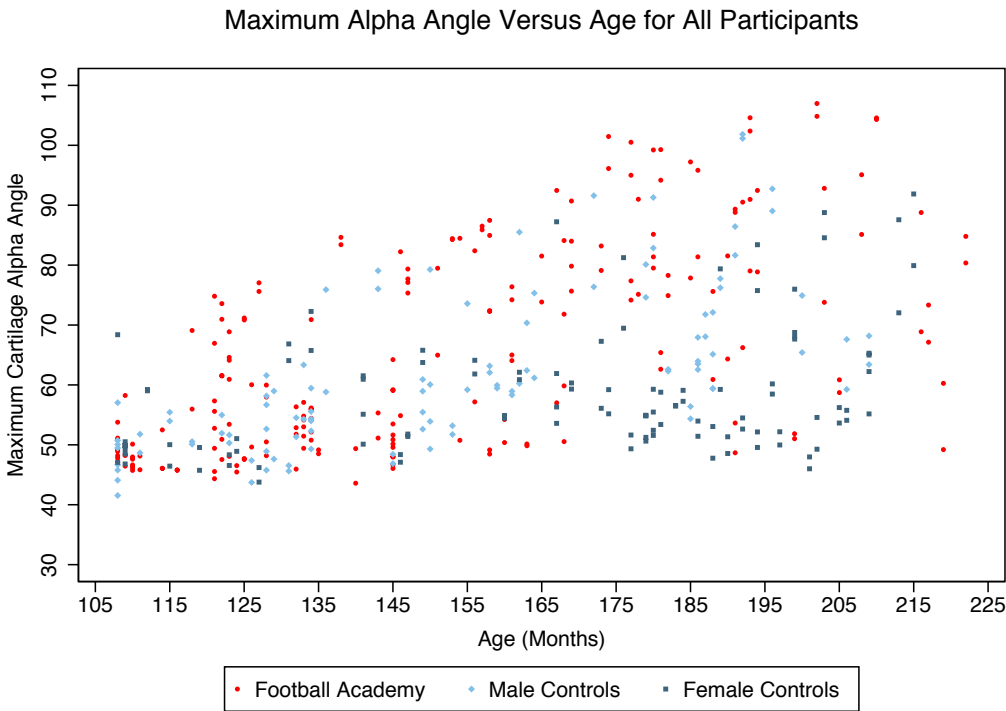
Appendix C-10 - Cartilage Alpha Angle at 2 O’Clock Plotted Versus Age for Each Cohort



Appendix C-11 - Cartilage Alpha Angle at 3 O’Clock Plotted Versus Age for Each Cohort



Appendix C-12 - Maximum Alpha Angle Plotted Versus Age for Each Cohort



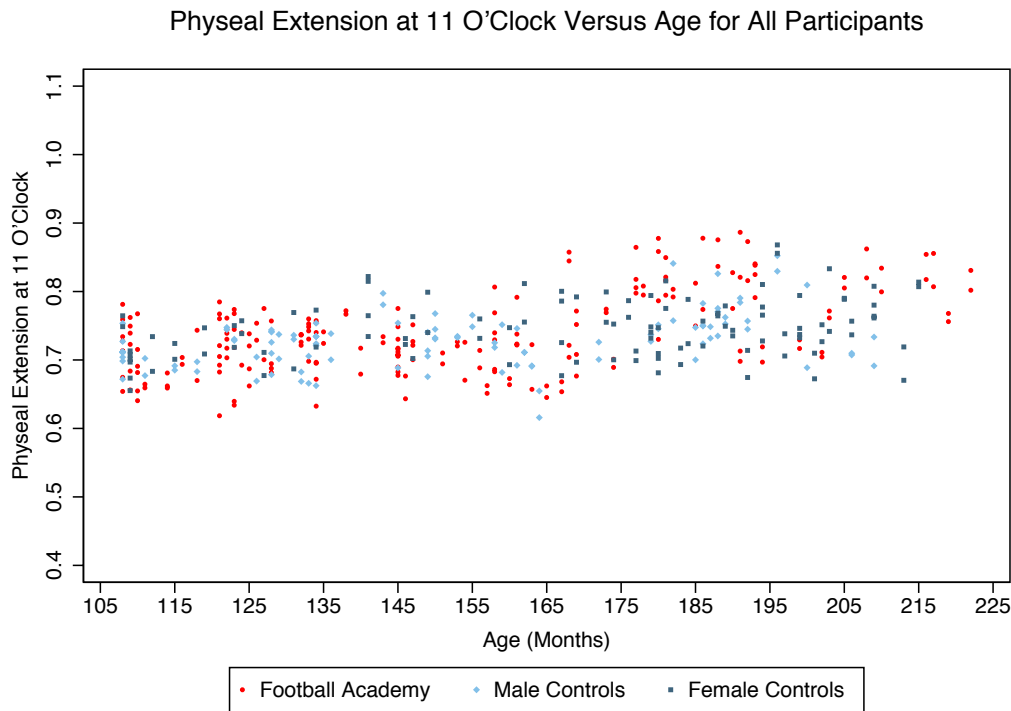
Appendix C-13 – Regression Coefficient of Epiphyseal Extension and Months of Age in All Participants

Clockface Position	Correlation Coefficient	95% Confidence Intervals	Statistical Significance	R ² Value
11 O’Clock	0.0007	0.0006 – 0.0009	0.010	0.220
12 O’Clock	0.0014	0.0014 – 0.0014	0.000	0.407
1 O’Clock	0.0018	0.0018 – 0.0019	0.000	0.487
2 O’Clock	0.0020	0.0016 – 0.0025	0.012	0.564
3 O’Clock	0.0018	0.0017 – 0.0020	0.004	0.546
Maximum All Positions	0.0016	0.0016 – 0.0016	0.001	0.485

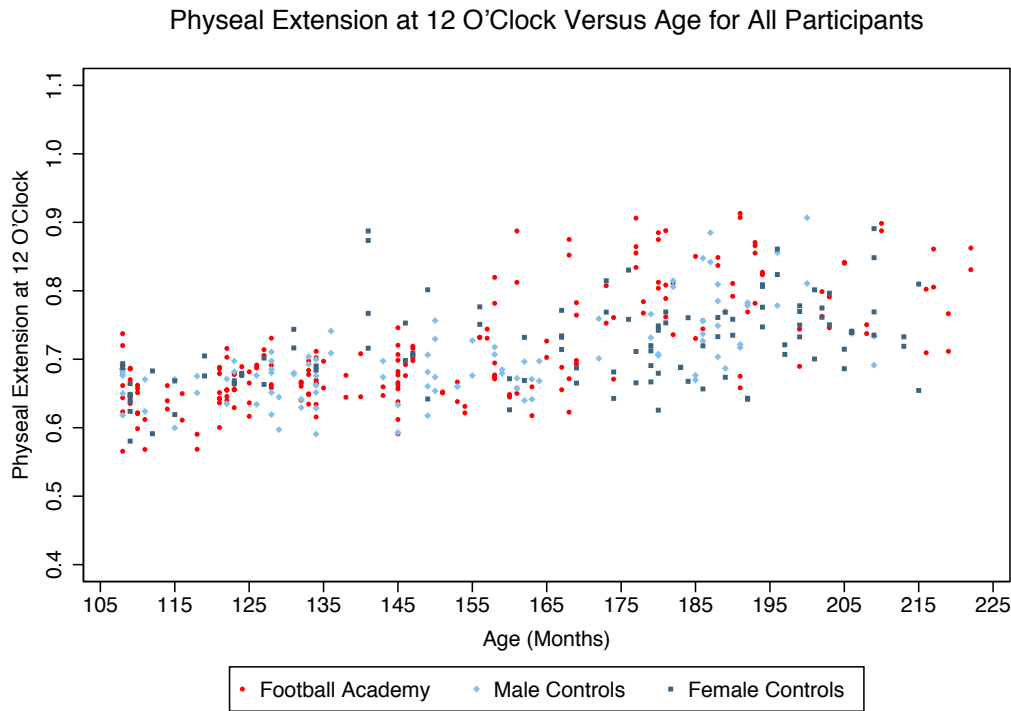
Appendix C-14 - Regression Coefficient of Epiphyseal Extension and Months of Age

Clockface Position	Football Academy		Male Controls		Female Controls	
	Regression Coefficient	R ² value	Regression Coefficient	R ² value	Regression Coefficient	R ² value
11 O’Clock	0.0010	0.315	0.0006	0.165	0.0004	0.092
12 O’Clock	0.0018	0.523	0.0014	0.421	0.0009	0.205
1 O’Clock	0.0024	0.606	0.0019	0.608	0.0011	0.259
2 O’Clock	0.0021	0.548	0.0022	0.591	0.0017	0.537
3 O’Clock	0.0019	0.531	0.0020	0.592	0.0014	0.492
Maximum All Positions	0.0020	0.548	0.0016	0.573	0.0010	0.323

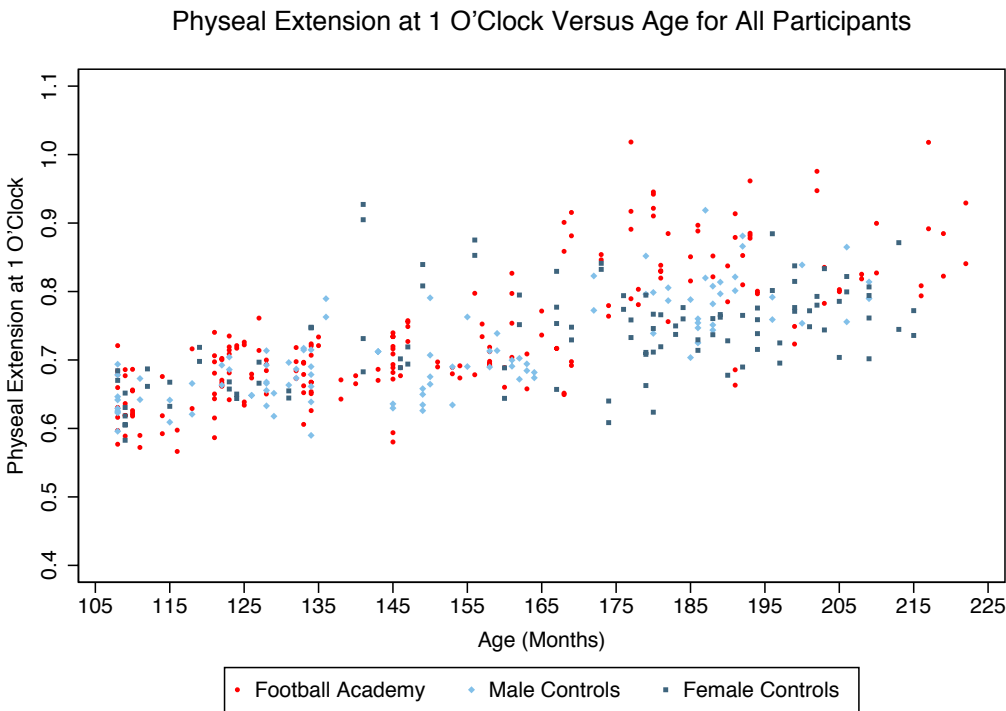
Appendix C-15 - Epiphyseal Extension at 11 O’Clock Plotted Versus Age for Each Cohort



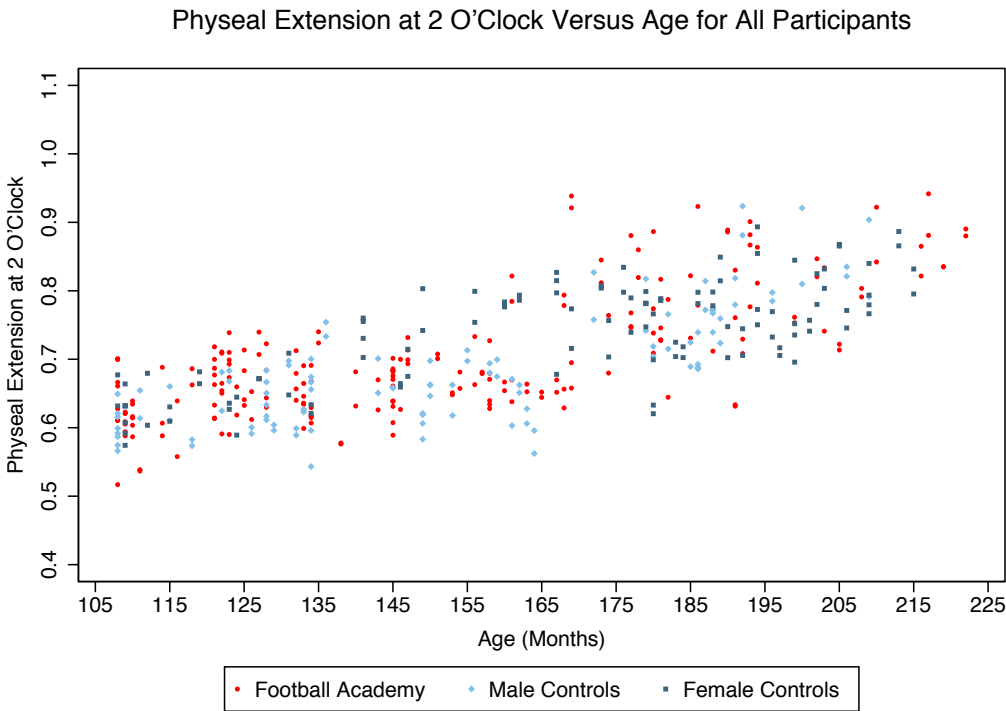
Appendix C-16 - Epiphyseal Extension at 12 O’Clock Plotted Versus Age for Each Cohort



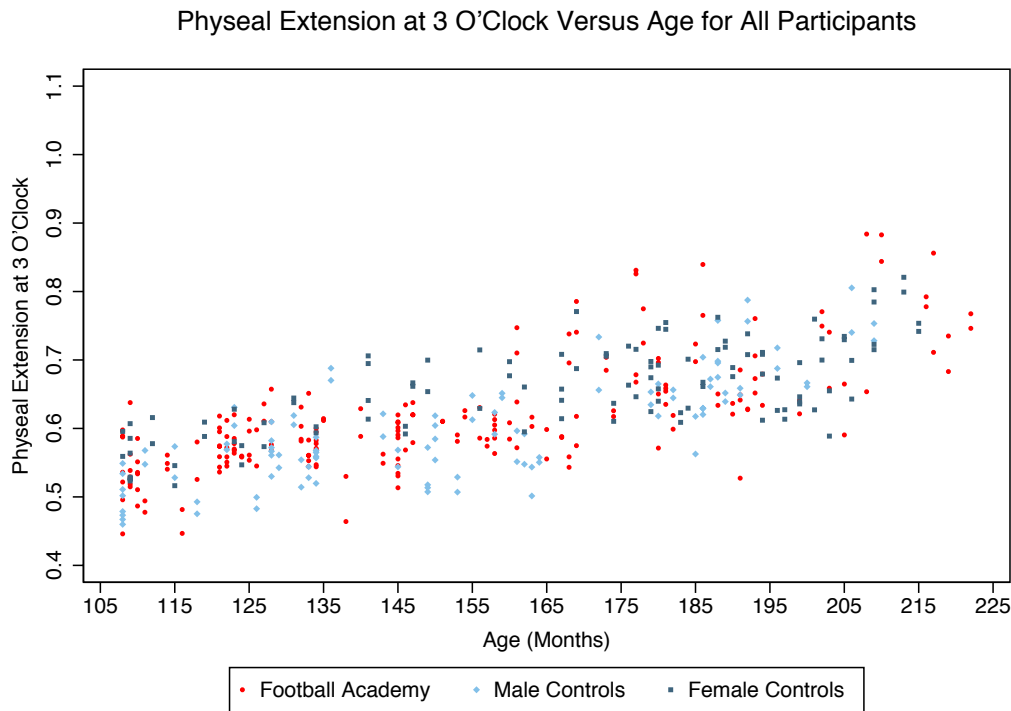
Appendix C-17 - Epiphyseal Extension at 1 O’Clock Plotted Versus Age for Each Cohort



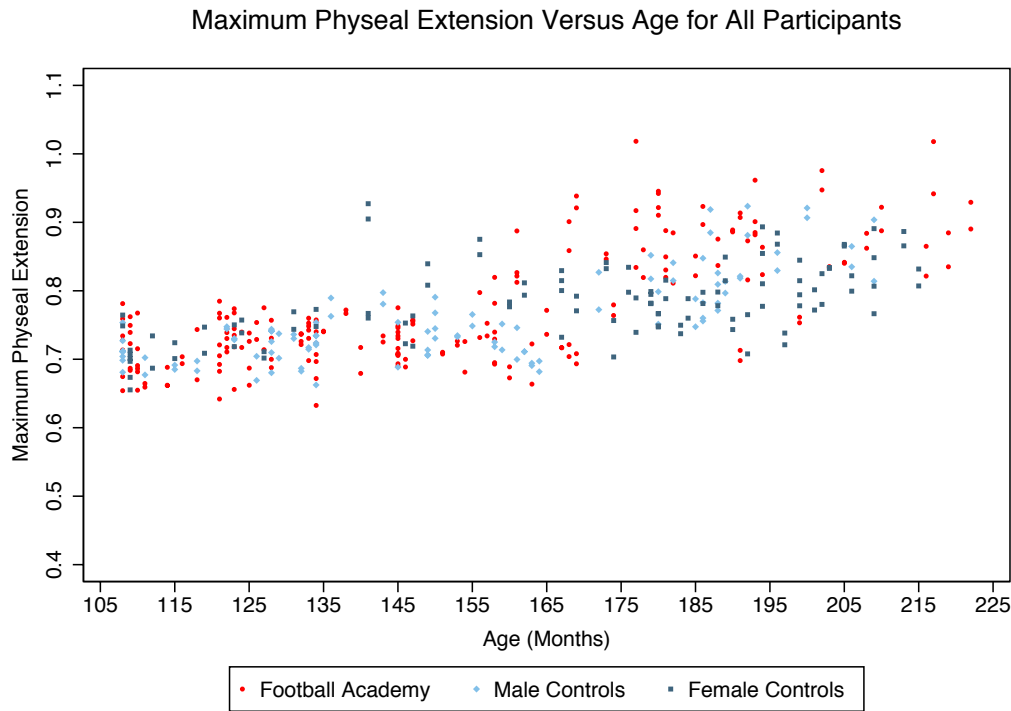
Appendix C-18 - Epiphyseal Extension at 2 O’Clock Plotted Versus Age for Each Cohort



Appendix C-19- Epiphyseal Extension at 3 O’Clock Plotted Versus Age for Each Cohort



Appendix C-20 – Maximum Epiphyseal Extension Plotted Versus Age for Each Cohort



Appendix C-21 - Mean Physeal Ratio at each Clockface Position in Participants with an Open Physis

Clockface Position	Football Academy		Male Controls		Female Controls	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
11 O'Clock	1.63	0.19	1.56	0.16	1.52	0.16
12 O'Clock	1.55	0.18	1.49	0.15	1.49	0.17
1 O'Clock	1.58	0.25	1.53	0.18	1.55	0.20
2 O'Clock	1.32	0.22	1.30	0.16	1.32	0.18
3 O'Clock	0.94	0.10	0.92	0.09	0.96	0.11
Maximum All Positions	1.71	0.21	1.64	0.14	1.61	0.18

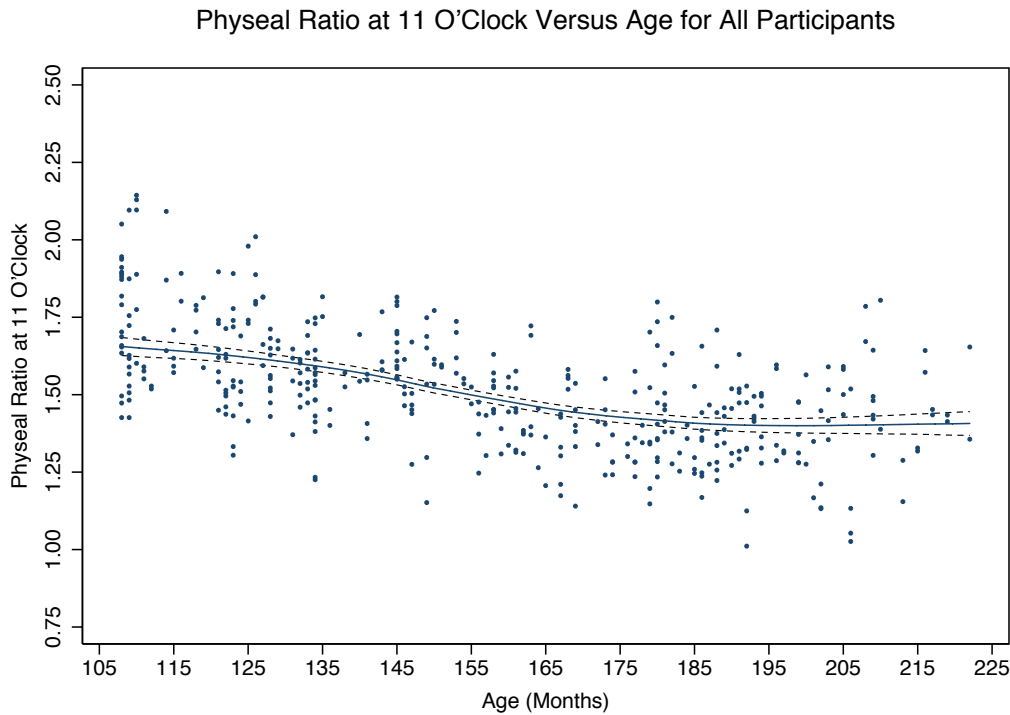
Appendix C-22 - Mean Physeal Ratio at each Clockface Position in Participants with a Closed Physis

Clockface Position	Football Academy		Male Controls		Female Controls	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
11 O'Clock	1.49	0.15	1.31	0.12	1.35	0.13
12 O'Clock	1.54	0.19	1.43	0.13	1.34	0.15
1 O'Clock	1.66	1.89	1.57	0.17	1.52	0.24
2 O'Clock	1.43	0.24	1.40	0.15	1.42	0.19
3 O'Clock	1.06	0.14	1.05	0.11	1.05	0.12
Maximum All Positions	1.75	0.17	1.61	0.15	1.59	0.21

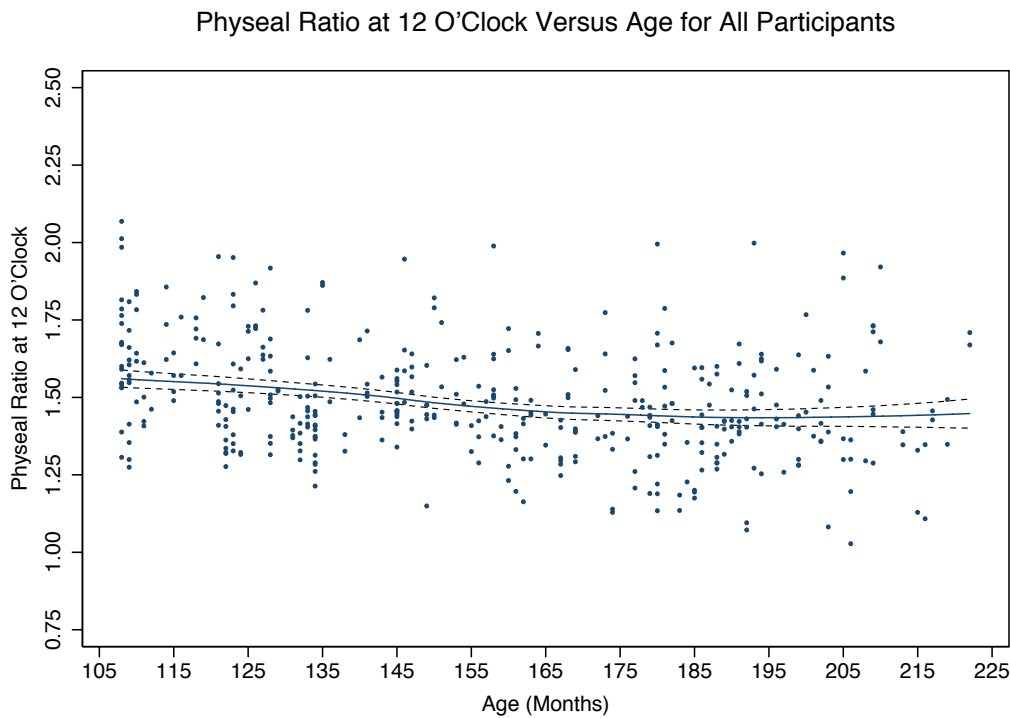
Appendix C-23 - Regression Coefficient of Physeal Ratio and Months of Age

Clockface Position	Football Academy		Male Controls		Female Controls	
	Regression Coefficient	R ² value	Regression Coefficient	R ² value	Regression Coefficient	R ² value
11 O'Clock	-0.0029	0.247	-0.0048	0.595	-0.0023	0.211
12 O'Clock	-0.0008	0.022	-0.0018	0.141	-0.0018	0.126
1 O'Clock	0.0008	0.011	-0.0008	0.021	-0.0000	0.000
2 O'Clock	0.0013	0.030	-0.0001	0.001	0.0018	0.092
3 O'Clock	0.0018	0.199	0.0018	0.237	0.0016	0.183
Maximum All Positions	-0.0004	0.004	-0.0020	0.169	0.0002	0.001

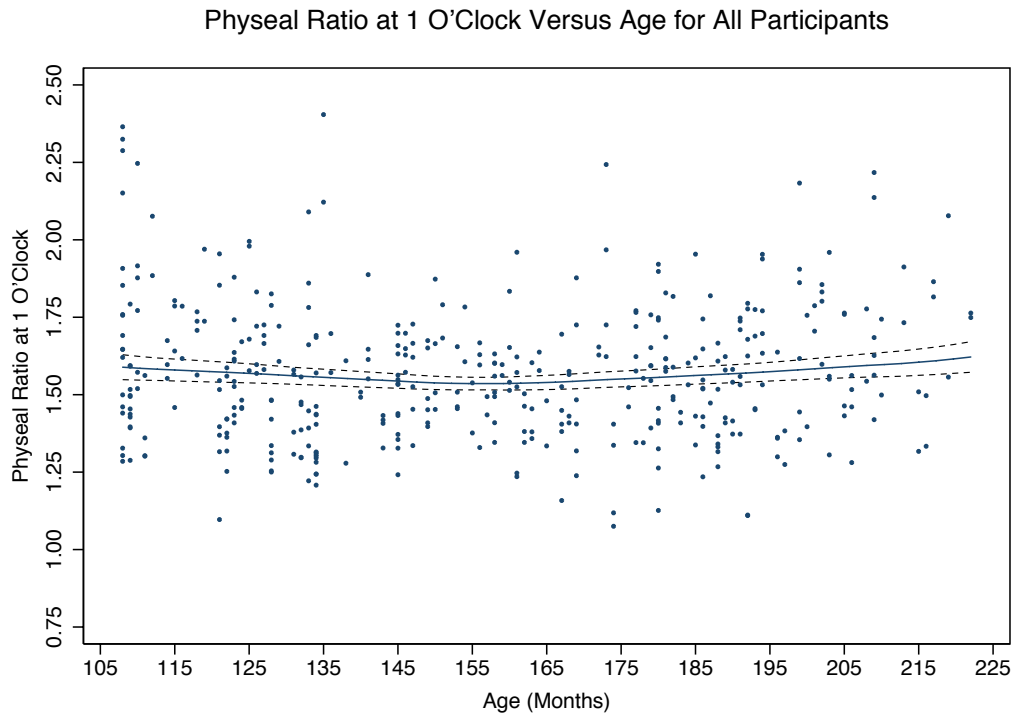
Appendix C-24 - Physeal Ratio at 11 O’Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals



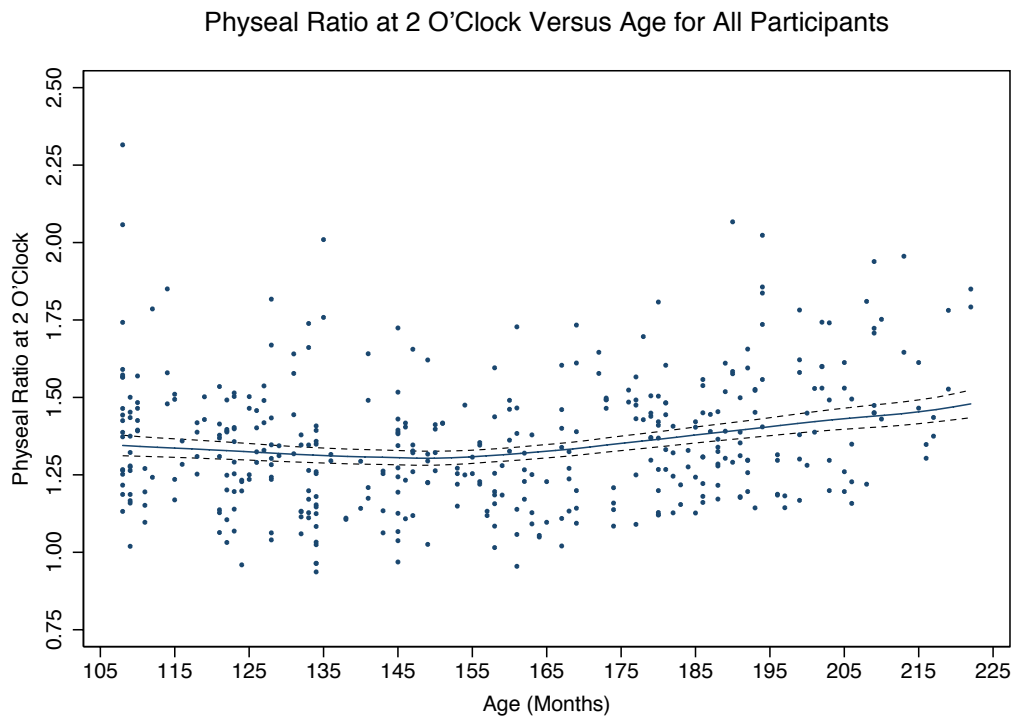
Appendix C-25 - Physeal Ratio at 12 O’Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals



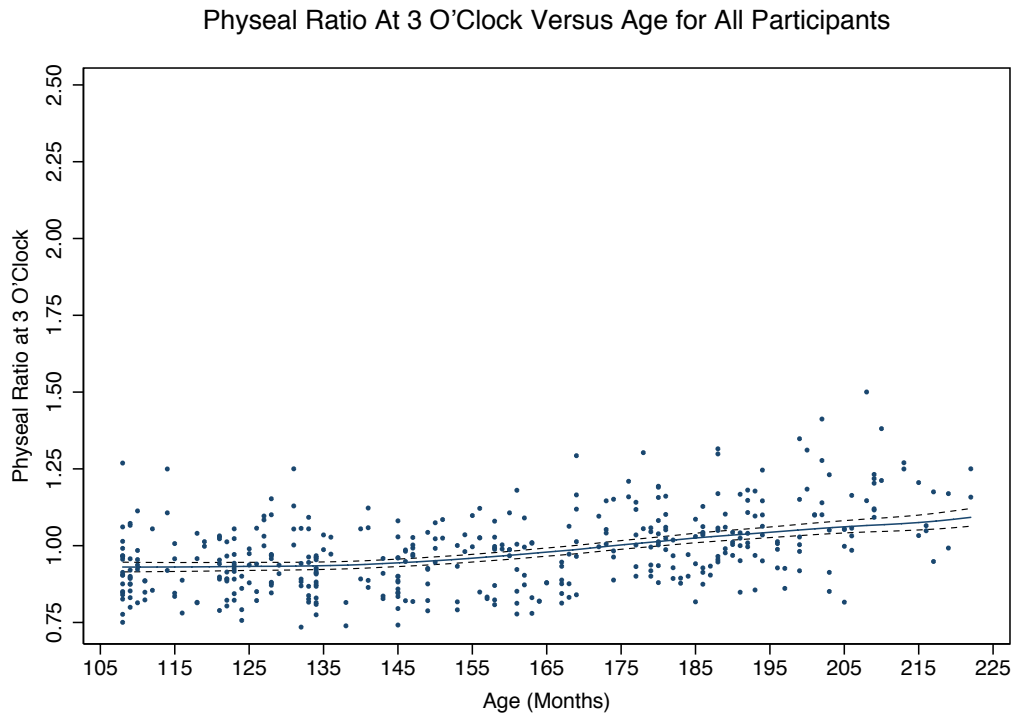
Appendix C-26 - Physeal Ratio at 1 O’Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals



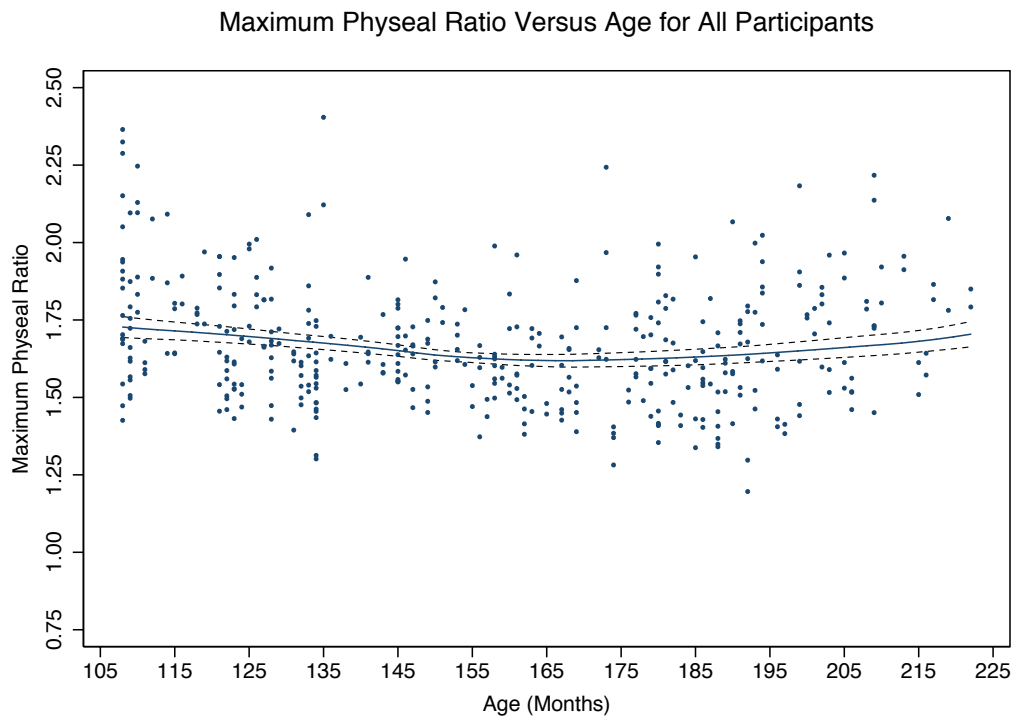
Appendix C-27 - Physeal Ratio at 2 O’Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals



Appendix C-28 - Physeal Ratio at 3 O’Clock Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals



Appendix C-29 - Maximum Physeal Ratio Plotted Against Age with Polynomial Regression Fit and 95% Confidence Intervals



Appendix C-30 - Predictors of Maximum Cartilage Alpha Angle

		Number of Hips	Univariate Regression			Multivariate Regression 1*			Multivariate Regression 2**			Multivariate Regression 3***		
			Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value
Months of Age		420	0.242	0.14 – 0.34	0.020	0.268	0.17 – 0.37	0.019	0.273	0.18 – 0.37	0.018	0.290	0.10 – 0.480	0.033
Age Category (years)	9-10	118	-	-	-									
	11-12	92	6.08	5.94 – 6.21	0.001									
	13-14	80	16.23	7.42 – 25.03	0.027									
	15-16	100	17.97	9.37 – 26.56	0.024									
	17-18	30	18.48	13.67 – 23.29	0.013									
Physis	Open	247	-	-	-									
	Closed	168	13.24	6.73 – 19.74	0.025									
Gender	Male	310	-	-	-	-	-	-				-	-	-
	Female	110	-6.05	-9.74 – 2.35	0.031	-6.66	-7.26 – -6.06	0.005				-9.64	-14.75 – -4.53	0.027
BMI		420		1.02 – 1.78	0.013									
Dominant Leg	Dominant	231	-		-									
	Non Dominant	189	0.856	-38.21 – 39.93	0.827									
Cohort	Male Control	104	-	-	-				-	-	-			
	Female Control	110	-3.37	-4.22 – -2.52	0.013				-7.42	-8.01 – -6.83	0.004			
	Football Academy	206	4.05	-0.36 – 8.46	0.054				4.33	0.67 – 7.99	0.042			
Activity Level	No Sport	70	-	-	-	-	-	-						
	Sport	140	6.21	3.37 – 9.05	0.023	4.03	0.74 – 7.33	0.041						
	Athlete	210	10.50	4.38 – 16.61	0.029	7.63	2.23 – 13.04	0.035						
Physical Activity Questionnaire		420	-3.15	-5.58 – -0.71	0.039							1.52	-6.48 – 9.53	0.250

*Age, Gender, and Activity Level as Covariates **Age, Gender, and Cohort as Covariates ***Age, Gender, and Physical Activity Questionnaire as Covariates

Appendix C-31 - Predictors of Epiphyseal Extension at 1 O'Clock

		Number of Hips	Univariate Regression			Multivariate Regression 1*			Multivariate Regression 2**			Multivariate Regression 3***		
			Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value
Months of Age		420	0.0018	0.0018 – 0.0019	<0.001	0.0019	0.0024 – 0.0317	0.002	0.0019	0.0018 – 0.0020	0.002	0.0019	0.0017 – 0.0021	0.006
Age Category (years)	9-10	118	-	-	-									
	11-12	92	0.0384	0.0276 – 0.0492	0.014									
	13-14	80	0.0929	0.0848 – 0.1011	0.004									
	15-16	100	0.1375	0.0804 – 0.1945	0.021									
	17-18	30	0.1571	0.0840 – 0.2301	0.023									
Physis	Open	247	-	-	-									
	Closed	168	0.1169	0.1006 – 0.1331	0.007									
Gender	Male	310	-	-	-	-	-	-				-	-	-
	Female	110	0.0085	-0.0064 – 0.0234	0.087	-0.0058	-0.0203 – -0.0087	0.124				-0.0214	-0.0506 – 0.0077	0.068
BMI		420	0.0127	0.0103 – 0.0150	0.009									
Dominant Leg	Dominant	231	-	-	-									
	Non Dominant	189	0.0047	-0.1828 – 0.1923	0.802									
Cohort	Male Control	104	-	-	-				-	-	-			
	Female Control	110	0.0221	0.0191 – 0.0252	0.013				-0.0062	-0.0105 – -0.0029	0.034			
	Football Academy	206	0.0205	0.0030 – 0.0381	0.043				0.0225	0.0003 – 0.0447	0.049			
Activity Level	No Sport	70	-	-	-	-	-	-						
	Sport	140	0.2442	0.0068 – 0.0421	0.036	0.0171	0.0024 – 0.0317	0.043						
	Athlete	210	0.0274	0.0096 – 0.0452	0.033	0.0322	0.0183 – 0.0020	0.022						
Physical Activity Questionnaire		420	-0.0397	-0.0552 – -0.0243	0.019							-0.0010	-0.0253 – 0.0234	0.701

*Age, Gender, and Activity Level as Covariates **Age, Gender, and Cohort as Covariates ***Age, Gender, and Physical Activity Questionnaire as Covariates

Appendix C-32 - Predictors of Maximum Cartilage Alpha Angle

		Number of Hips	Univariate Regression			Multivariate Regression 1*			Multivariate Regression 2**			Multivariate Regression 3***		
			Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value
Months of Age		420	0.242	0.14 – 0.34	0.020	0.252	0.12 – 0.38	0.026	0.258	0.13 – 0.38	0.025	0.281	0.07 – 0.50	0.038
Age Category (years)	9-10	118	-	-	-									
	11-12	92	6.08	5.94 – 6.21	0.001									
	13-14	80	16.23	7.42 – 25.03	0.027									
	15-16	100	17.97	9.37 – 26.56	0.024									
	17-18	30	18.48	13.67 – 23.29	0.013									
Physis	Open	247	-	-	-									
	Closed	168	13.24	6.73 – 19.74	0.025									
Gender	Male	310	-	-	-	-	-	-				-	-	-
	Female	110	-6.05	-9.74 – 2.35	0.031	-6.70	-7.23 – -6.17	0.004				-9.76	-15.22 – -4.30	0.028
BMI		420		1.02 – 1.78	0.013	0.297	-0.23 – 0.82	0.088	0.276	-0.25 – 0.81	0.096	0.165	-0.30 – 0.63	0.139
Dominant Leg	Dominant	231	-		-									
	Non Dominant	189	0.856	-38.21 – 39.93	0.827									
Cohort	Male Control	104	-	-	-				-	-	-			
	Female Control	110	-3.37	-4.22 – -2.52	0.013				-7.45	-7.98 – -6.92	0.004			
	Football Academy	206	4.05	-0.36 – 8.46	0.054				4.58	0.44 – 8.72	0.045			
Activity Level	No Sport	70	-	-	-	-	-	-						
	Sport	140	6.21	3.37 – 9.05	0.023	4.09	0.69 – 7.49	0.042						
	Athlete	210	10.50	4.38 – 16.61	0.029	7.93	1.99 – 13.87	0.037						
Physical Activity Questionnaire		420	-3.15	-5.58 – -0.71	0.039							1.51	-6.53 – 9.56	0.252

*Age, Gender, BMI, and Activity Level as Covariates **Age, Gender, BMI, and Cohort as Covariates ***Age, Gender, BMI, and Physical Activity Questionnaire as Covariates

Appendix C-33 - Predictors of Epiphyseal Extension at 1 O'Clock (Age, Gender, Activity, and BMI as Covariates)

		Number of Hips	Univariate Regression			Multivariate Regression 1*			Multivariate Regression 2**			Multivariate Regression 3***		
			Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value	Coefficient	95% Confidence Intervals	P value
Months of Age		420	0.0018	0.0018 – 0.0019	<0.001	0.0017	0.0014 – 0.0020	0.008	0.0017	0.0014 – 0.0020	0.008	0.0017	-0.0017 – 0.0017	<0.001
Age Category (years)	9-10	118	-	-	-									
	11-12	92	0.0384	0.0276 – 0.0492	0.014									
	13-14	80	0.0929	0.0848 – 0.1011	0.004									
	15-16	100	0.1375	0.0804 – 0.1945	0.021									
	17-18	30	0.1571	0.0840 – 0.2301	0.023									
Physis	Open	247	-	-	-									
	Closed	168	0.1169	0.1006 – 0.1331	0.007									
Gender	Male	310	-	-	-	-	-	-				-	-	-
	Female	110	0.0085	-0.0064 – 0.0234	0.087	-0.0063	-0.0203 – 0.0077	0.110				-0.0238	-0.0502 – 0.0026	0.055
BMI		420	0.0127	0.0103 – 0.0150	0.009	0.0038	-0.0001 – 0.0076	0.051	0.0038	0.0004 – 0.0072	0.045	0.0032	-0.0006 – 0.0070	0.059
Dominant Leg	Dominant	231	-	-	-									
	Non Dominant	189	0.0047	-0.1828 – 0.1923	0.802									
Cohort	Male Control	104	-	-	-				-	-	-			
	Female Control	110	0.0221	0.0191 – 0.0252	0.013				-0.0066	-0.0105 – -0.0028	0.029			
	Football Academy	206	0.0205	0.0030 – 0.0381	0.043				0.0259	0.0068 – 0.0451	0.037			
Activity Level	No Sport	70	-	-	-	-	-	-						
	Sport	140	0.2442	0.0068 – 0.0421	0.036	0.0178	0.0039 – 0.0317	0.039						
	Athlete	210	0.0274	0.0096 – 0.0452	0.033	0.0360	0.0260 – 0.0461	0.014						
Physical Activity Questionnaire		420	-0.0397	-0.0552 – -0.0243	0.019							-0.0012	-0.0253 – 0.0230	0.649

*Age, Gender, BMI, and Activity Level as Covariates **Age, Gender, BMI, and Cohort as Covariates ***Age, Gender, BMI, and Physical Activity Questionnaire as Covariates

Appendix D - Feasibility Study

Appendix D-1 - Surgeon Questionnaire

British Hip Society Questionnaire 2012

Current Opinion in Surgery for Non-Arthritic Hip Pathology

Dear Surgeon,

Thank you for your time spent completing this brief questionnaire. Hospital Episode Statistics reveal that the number of surgical procedures performed each year for non-arthritic hip pathology is rising exponentially, however, considerable controversy remains as to the indications for surgery, optimal approach, and whether surgery modifies the risk of developing osteoarthritis. There may be a role for randomised controlled trials to address some of these controversies, however, this is only appropriate in a setting of equipoise. With this questionnaire we hope to obtain a consensus of opinion to guide future research into this field.

Yours sincerely,

Mr Antony Palmer (Research Fellow), Mr Thomas Pollard (Consultant Orthopaedic Surgeon), Mr Adrian Taylor (Consultant Orthopaedic Surgeon), Mr Tony Andrade (Consultant Orthopaedic Surgeon), Professor Fares Haddad (Consultant Orthopaedic Surgeon) and Mr Sion Glyn-Jones (Consultant Orthopaedic Surgeon).

Do you routinely perform elective non-arthroplasty hip surgery? (please circle) **YES** **NO**

If yes, approximately how many such procedures do you perform each year?

<10 **10-20** **20-30** **30-50** **50-100** **>100**

In your opinion, what is the optimum imaging protocol for femoro-acetabular impingement?

X-Ray alone **MRI alone** **X-Ray + CT** **X-Ray + MRI** **X-Ray + MRI + CT**

What is your preferred surgical approach for isolated labral pathology?

Open **Open + Arthroscopic** **Arthroscopic**

What is your preferred surgical approach for the debridement of femoro-acetabular impingement lesions?

Open **Open + Arthroscopic** **Arthroscopic**

What is your preferred Patient Reported Outcome Measure for patients with non-arthritic hip symptoms?

NAHS **HOS** **HOOS** **OHS** **Other**

Do you believe femoro-acetabular impingement is a cause of osteoarthritis?

-5 -4 -3 -2 -1 0 +1 +2 +3 +4 +5
NO **Undecided** **YES**

Do you believe optimal debridement of femoro-acetabular impingement lesions prevents osteoarthritis?

-5 -4 -3 -2 -1 0 +1 +2 +3 +4 +5
NO **Undecided** **YES**

Overall, do you consider labral repair to be:										
-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
Harmful			No Effect				Effective			
Overall, do you consider surgical debridement of femoro-acetabular impingement lesions to be:										
-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
Harmful			No Effect				Effective			
Considering femoro-acetabular impingement, do you believe the majority of surgeons in the UK perform:										
-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
Open Surgery			Equal Proportion of Open and Arthroscopic				Arthroscopic Surgery			
On first presentation, how would you most likely manage an FAI patient with mild/moderate symptoms? (limits sporting activities only)										
-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
Non-Operatively			Undecided				Operatively			
On first presentation, how would you most likely manage an FAI patient with severe symptoms? (limits activities of daily living)										
-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
Non-Operatively			Undecided				Operatively			
Does evidence of early osteoarthritis on imaging make you less likely to perform FAI surgery:										
-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
Yes			No Effect				No			
Is intra-articular injection of local anaesthetic and steroid helpful in predicting the outcome of surgery?										
-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
Yes			Undecided				No			
Would level 1 evidence that FAI debridement arrested OA change your current practice?			YES	NO						
Would you be willing to participate in a randomised controlled trial (RCT) for FAI surgery?			YES	NO						
Would you be willing to allocate patients to a non-treatment arm of an RCT for 1 year or more?			YES	NO						
If no, how long do you feel is acceptable?										
If an RCT is not possible, would you be willing to participate in an uncontrolled prospective study?			YES	NO						

Appendix D-2 - Patient Questionnaire



Patient Questionnaire for Research Study into the Treatment of Femoroacetabular Impingement

1) Age:

2) Sex:

3) Sports you played regularly when first diagnosed with femoroacetabular impingement:

4) One possible research study is to offer patients the option of being randomly allocated to physiotherapy or surgery when first diagnosed with femoroacetabular impingement. We would then review patients every six months and perform repeat MRI scans to monitor how the condition of the hip cartilage changes over time with each treatment. Patients would be free to withdraw from the study at any point to start a different treatment. When first diagnosed, would you have considered participating in such a study?

Yes

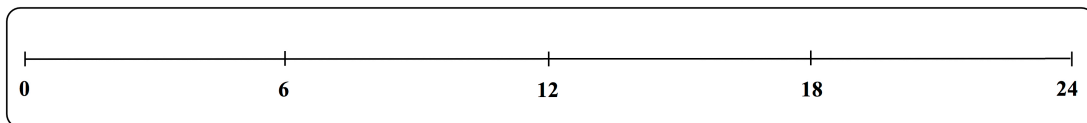
No

5) If not, please circle the treatment option that you would have found unacceptable?

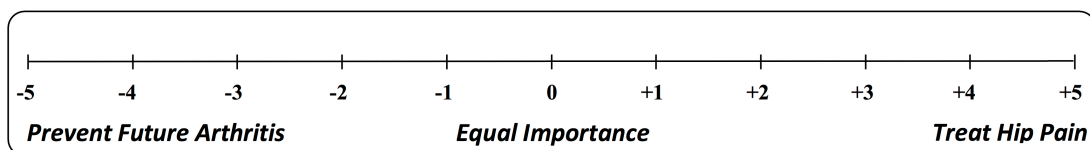
Specialist Physiotherapy

Keyhole Surgery

6) Please mark on the scale below how many months you would be prepared to trial physiotherapy before wishing to have surgery if your symptoms did not improve?



7) If it was found that femoroacetabular impingement increased your risk of arthritis, please mark on the scale below what you felt was more important to you when first diagnosed. Would it have been to treat your hip pain or to reduce your risk of developing future arthritis?



Appendix E - FAI Trial (FAIT) Protocol

A Randomised Controlled Trial of Surgical versus Non-Surgical Treatment of Femoroacetabular Impingement

E.1 Abstract

Background:

Femoroacetabular Impingement (FAI) describes abnormalities in the shape of the femoral head and neck, or abnormalities in the orientation of the acetabulum. As a consequence of this abnormal morphology, when the hip flexes and internally rotates, the femoral head-neck junction abuts the acetabular rim resulting in labral damage and delamination of the adjacent cartilage. In the short-term FAI can give rise to pain and disability, and in the long-term it significantly increases the risk of developing end-stage osteoarthritis. Symptoms improve with physiotherapy or surgery, but it remains unknown which treatment option is most effective. Furthermore, FAI is a potentially modifiable cause of osteoarthritis and it is not known whether either treatment delays or arrests the development of osteoarthritis.

Methods:

FAIT is a blinded superiority-type randomised controlled trial to compare physiotherapy and activity modification with arthroscopic surgery for the treatment of symptomatic FAI. Recruitment will take place over 12 months and 120 patients will be randomised. The primary outcome measure is the Hip Outcome Score at 8 months post randomisation (6 months post intervention). Patients will be followed-up for 3 years and

the development of osteoarthritis will be assessed using conventional imaging, compositional MRI, and biochemical markers.

Text modified from:

- *Palmer AJR, Ayyar-Gupta V, Dutton SJ, Rombach I, Cooper C, Pollard TCB, Hollinghurst D, Taylor A, Barker KL, McNally EG, Beard DJ, Andrade AJ, Carr AJ, Glyn-Jones S. Protocol of Femoroacetabular Impingement Trial (FAIT): A Multi-Centre Randomised Controlled Trial comparing Surgical and Non-Surgical Management of Femoroacetabular Impingement. Bone Joint Res 2014 Nov;3(11):321-7. PMID: 25431439*

E.2 Protocol

E.2.1 Amendment History

Version 1.0: 01/03/13: Submission to Ethics Committee

Version 2.0: 14/06/13: Modification to timing of outcome measurements from post-intervention to post-randomisation

Version 3.0: 08/08/14: Addition of study sites and secondary outcome measures modified to exclude post-intervention MRI where this does not represent routine care

Version 4.0: 22/02/15: Based on interim data analysis trial sample size increased from 120 to 214 participants with extension of recruitment period from 31/07/15 to 31/07/16.

Appendix E-1 - FAIT Trial Registration Dataset

Study Title	A Randomised Controlled Trial of Surgical versus Non-Surgical Treatment of Femoroacetabular Impingement
Primary Trial Registry	ClinicalTrials.gov: NCT01893034
Date of Registration	14 th June 2013
Date of First Enrolment	29 th July 2013
Secondary Trial Registry	NIHR Clinical Research Network: UKCRN ID 14755
Study Status	Recruitment Complete: Study in Follow-Up
Study Design	Allocation: Randomised Intervention Model: Parallel Masking: Assessor Blinding
Health Condition Studied	Symptomatic Femoroacetabular Impingement
Sample Size	214 participants
Funding	Arthritis Research UK Royal College of Surgeons of England/Dunhill Medical Trust NIHR Oxford Musculoskeletal Biomedical Research Unit
Sponsor	University of Oxford
Chief Investigator	Mr Sion Glyn-Jones
Principal Investigator	Mr Antony Palmer
Contact	FAIT@ndorms.ox.ac.uk
Study Aim	Determine whether symptomatic femoroacetabular impingement is best managed with physiotherapy and activity modification or arthroscopic surgery for improvement of symptoms and osteoarthritis prevention.

Interventions	Active Comparator 1: Arthroscopic Hip Surgery
	Active Comparator 2: Physiotherapy and Activity Modification
Primary Outcome Measures	Change in Hip Outcome Score (HOS) 8 Months Post Randomisation Change in Radiographic Joint Space Width 38 Months Post Randomisation
Key Secondary Outcome Measures	Additional Patient Reported Outcome Measure Collection (sub-study) - Hip Outcome Score (HOS) - PainDETECT Pain Questionnaire (PainDETECT) - Hospital Anxiety and Depression Score (HADS) - Non-Arthritis Hip Score (NAHS) - Hip and Groin Outcome Score (HAGOS) - Oxford Hip Score (OHS) - International Hip Outcome Tool (iHOT33) Additional Measures of Osteoarthritis (selected centres) - Radiographic Kellgren-Lawrence Grade - Morphological MRI (Semi-Qualitative Scores, Cartilage Volume) - Compositional MRI (T2 mapping +/- T1rho) - Urinary and Serum Biomarkers Clinical Assessment - Range of Movement - Impingement Tests Health Economic Analysis - EQ-5D - University of California, Los Angeles (UCLA) Activity Score
Key Inclusion Criteria	Symptomatic Patients Age 18 – 60 Clinical and Radiographic Evidence of Femoroacetabular Impingement Competent to Consent
Key Exclusion Criteria	Previous Surgery to the Index Hip Established Osteoarthritis (Kellgren-Lawrence ≥ 2) Hip Dysplasia (Centre-Edge Angle < 20 degrees on AP Radiograph) Completion of Physiotherapy Programme Targeting FAI within 12 Months Co-morbidities that mean surgical intervention is not possible/safe

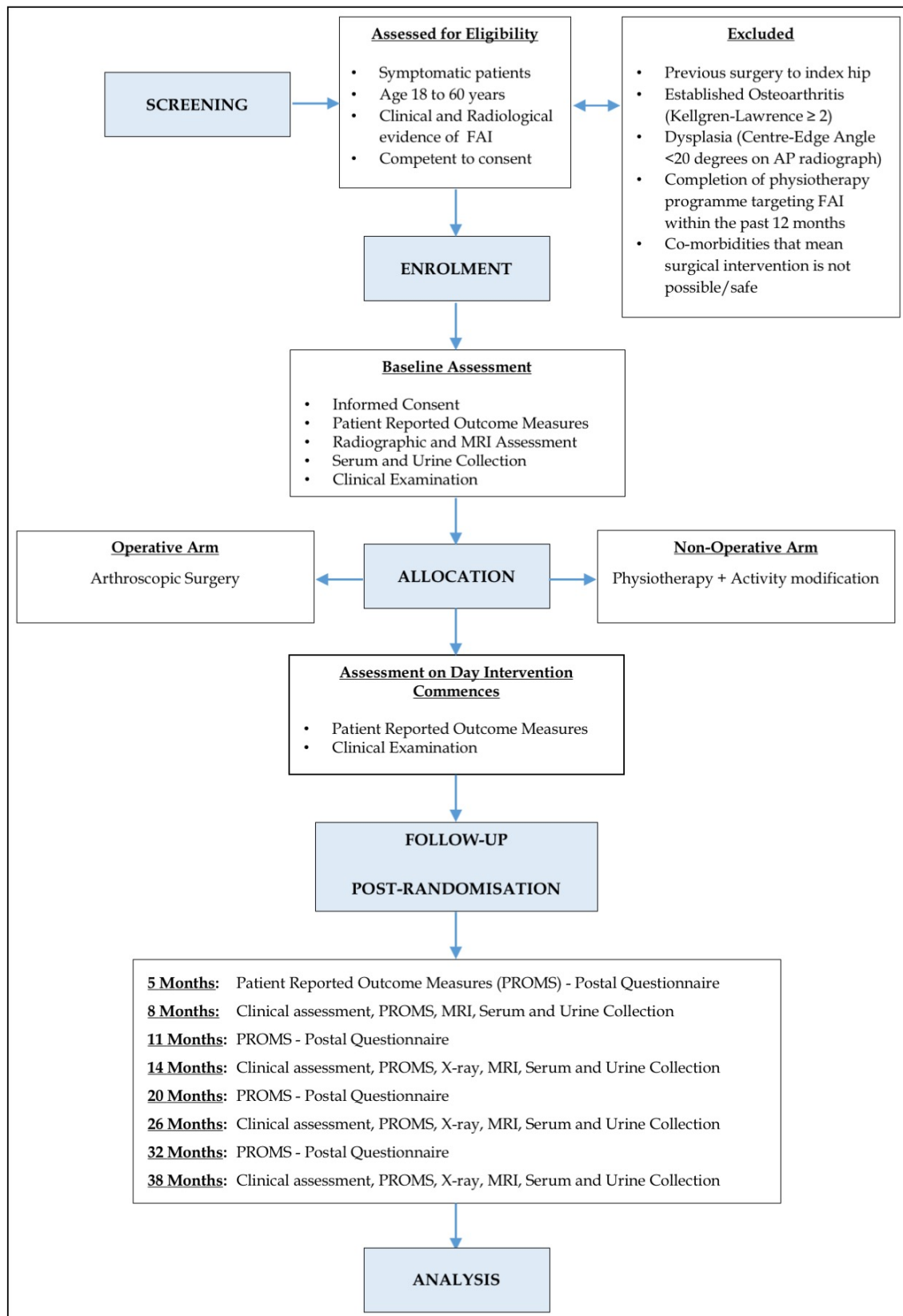
Appendix E - FAI Trial (FAIT) Protocol

Sites of Recruitment	Oxford University Hospitals NHS Foundation Trust Royal Berkshire Hospital NHS Foundation Trust Great Western Hospitals NHS Foundation Trust Cambridge University Hospitals NHS Foundation Trust Harrogate and District NHS Foundation Trust Wye Valley NHS Trust Weston Area Health NHS Trust
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Appendix E-2 - FAIT Study Assessments

Outcome Measure	Baseline	Intervention	Assess	Assess	Assess	Assess	Assess	Assess	Assess	Assess
	1	2	3	4	5	6	7	8	9	10
			5/12	8/12	11/12	14/12	20/12	26/12	32/12	38/12
Clinical Examination	X	X		X		X		X		X
PROMS	X	X (HOS)	X	X	X	X	X	X	X	X
Serum Collection	X			X		X		X		X
Urine Collection	X			X		X		X		X
Radiographs	X					X		X		X
MRI	X			X		X		X		X

Appendix E-3 - FAIT Patient Pathway



E.2.2 Background and Rationale

Femoroacetabular Impingement (FAI) describes abnormalities in the shape of the femoral head-neck junction (cam impingement) or acetabulum (pincer impingement). As a consequence of this abnormal morphology, when the hip flexes and internally rotates, the femoral head-neck junction abuts the acetabular rim resulting in labral damage and delamination of the adjacent cartilage²⁹¹. In a study of 2081 young healthy adults, 35% males and 10% females displayed cam morphology, and 34% males and 17% females displayed pincer morphology⁴⁴. In the short term, FAI can give rise to pain and disability, and in the long-term it increases the risk of developing osteoarthritis⁴¹³.

Despite the considerable prevalence of FAI morphology, only a proportion of individuals will develop pain or osteoarthritis, yet the condition is responsible for a significant burden of disease. Predictive values are dependent on the nature of the cohort, the method used to define the presence of FAI, and the length of follow-up. In an asymptomatic population, the relative risk of developing hip pain within four years in the presence of FAI morphology is 4.3 (95% CI 2.3 – 7.8) with a positive predictive value of 15.9%²⁹⁶. The positive predictive value for the development of osteoarthritis is estimated at 6-25% with longer follow-up times of 5⁴⁹ or 19 years²⁵⁷. It remains unclear whether pain secondary to FAI is a reliable predictor of future osteoarthritis. Refining the predictive models of pain and osteoarthritis in patients with FAI using diverse biomarkers is an active area of research, but low positive predictive values mean current clinical care must focus on treating current symptoms rather than preventing future disease. Nevertheless, FAI is a potentially modifiable cause of osteoarthritis, and cam lesions have been identified in greater than 50% patients undergoing total hip arthroplasty³¹.

There is great uncertainty as to how symptomatic FAI is best treated¹⁹⁰ and the principal two management options are physiotherapy with activity modification or surgery. Both modalities have been shown to improve symptoms in the short-term^{169,198,300,340,414,415}, however, there are no published studies to compare efficacy with each other or with sham procedures. Furthermore, it is not known whether treatment provides sustained symptomatic benefit in the long-term, and whether it delays or prevents development of osteoarthritis. Non-operative treatment of FAI aims to minimise impingement by the avoidance of activities that require repeated hip flexion and the modification of joint biomechanics through improving core stability and strengthening the external rotator and abductor muscle groups¹⁶⁹. Surgery can be performed open or arthroscopically to recontour the femoral neck or acetabular rim by burring away the impinging bone. Damage to the labrum or cartilage is also addressed.

FAI is an increasingly recognised condition and the number of surgical procedures performed in England to treat FAI has increased by 727% between 2002 and 2013²⁹³. A feasibility study demonstrated patient and surgeon equipoise and demand for a RCT comparing operative with non-operative treatment¹⁹⁰. The results of this feasibility study guided protocol design, which was drafted in accordance with the SPIRIT 2013 Statement⁴¹⁶.

E.2.3 Choice of Comparators

A chosen constraint to the comparators was that they must be deliverable on the National Health Service. Sham surgery was considered as a third treatment arm, however, it was felt this would make recruitment difficult. A survey of orthopaedic surgeons in Canada revealed only 24.8% supported a sham surgery control arm³⁴⁸. This study also reported that 49% surgeons employed physiotherapy as the first line of

treatment for FAI, and 62% considered failure of non-operative intervention as the primary indication for surgery³⁴⁸

E.2.3.1 Physiotherapy and Activity Modification

This represents routine care in many centres through clinician preference, available expertise, or local funding allowances. It describes a heterogeneous group of therapies, and a standardised treatment protocol for this study was agreed by a specialist panel based on their experience and current literature.

E.2.3.2 Arthroscopic Surgery

In England, FAI surgery is performed arthroscopically more than twice as frequently as an open approach³⁰² and studies show that it carries a lower complication rate with outcomes equal or better than alternatives¹⁸². Arthroscopic surgery was therefore adopted as the comparator, and low complication rates³⁴¹ make it an acceptable alternative to physiotherapy and activity modification.

E.2.4 Objectives

E.2.4.1 Primary Objectives

- i) To determine whether arthroscopic surgery is superior to physiotherapy and activity modification for improving symptoms in patients with symptomatic FAI.
- ii) To determine whether arthroscopic surgery is superior to physiotherapy and activity modification for preventing the development and progression of osteoarthritis in patients with symptomatic FAI.

E.2.4.2 Secondary Objectives

- i) Compare cost-effectiveness of physiotherapy and activity modification with arthroscopic surgery.
- ii) Evaluate performance of disease biomarkers (compositional MRI, urine and serum biochemical markers).

E.2.5 Trial Design

FAIT is an assessor-blinded multicentre superiority randomised controlled trial comparing physiotherapy and activity modification with arthroscopic surgery for the treatment of symptomatic FAI. Recruitment will be in parallel with 1:1 allocation.

E.2.6 Study Setting

Patients with clinical and radiological evidence of FAI will be recruited from NHS clinics in at seven hospitals in England that consist of both teaching hospitals and district general hospitals.

E.2.7 Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Symptomatic Patients	Previous surgery to index hip
Age 18 to 60	Established Osteoarthritis (Kellgren-Lawrence ≥ 2)
Clinical and Radiological Evidence of FAI	Hip Dysplasia (Centre-Edge Angle $< 20^\circ$ on Anteroposterior Radiograph)
Competent to Consent	Completion of physiotherapy programme targeting FAI within 12 months
	Medical conditions that preclude surgical intervention

Eligible patients will be aged 18 to 60 when individuals have reached skeletal maturity but the prevalence of osteoarthritis remains low. Patients will not be invited into the

study if they have radiographic evidence of established osteoarthritis (Kellgren-Lawrence ≥ 2) or hip dysplasia (centre-edge angle < 20 degrees) as these individuals are at greater risk of a poor surgical outcome⁴¹⁵. Additional exclusion criteria are previous surgery to the index hip and prior completion of a physiotherapy programme targeting their FAI within the last year to counter selection bias towards patients who have failed non-operative intervention. Medical conditions that prevent surgical intervention and contraindications to MRI are also exclusions, although patients will be offered continued participation in the study should contraindications arise during follow-up, for example, pregnancy. In such circumstances, imaging modalities that are contraindicated will be omitted for a particular visit.

E.2.8 Interventions

Study participants will be randomised in equal proportions to non-operative or operative intervention.

E.2.8.1 Non-Operative Intervention: Physiotherapy and Activity Modification

Participants will receive physiotherapy following a goal-based programme with up to eight physiotherapy sessions over a five-month period. During the initial assessment, goals will be agreed between the patient and physiotherapist based on the individual needs of the patient and their desired level of function. Sessions will be led by physiotherapists who have received training for this study to ensure treatment standardisation. The focus of this therapy is to strengthen core muscles groups and improve movement control to limit forceful impaction of the femoral neck against the acetabular rim. Patients will be encouraged to continue exercises at home and to refrain from activities that require the extremes of hip flexion, abduction and internal rotation (impingement position). Should participants achieve all of their physiotherapy goals within five months, they will be discharged and asked to continue their exercises and

activity modification in the community. There will be no physiotherapy sessions in the four weeks preceding follow-up appointments to ensure symptoms are stable when assessed.

E.2.8.2 Operative: Hip Arthroscopy

Participating surgeons perform over 100 hip arthroscopies each year and visit each other prior to commencing recruitment to ensure standardisation of technique. The procedure will be performed under general or spinal anaesthesia on a traction table. Hip morphology is assessed intraoperatively under arthroscopic vision and fluoroscopy. Bone that is seen to be causing impingement on flexing, abducting and internally rotating the hip will be excised with a burr. Damage to the labrum or articular cartilage will also be addressed. Labral tears will be repaired if possible using anchors or otherwise debrided. Articular cartilage damage will be debrided to a stable base, and in areas of full thickness loss, microfracture will be performed. Microfracture involves the creation of small holes in the subchondral bone to facilitate cartilage regeneration. Patients are discharged home once medically fit and after assessment by the Physiotherapy Team. They will be allowed to fully-weight bear immediately after surgery unless they received microfracture, when they will be required to touch-weight-bear for three weeks, partial-weight-bear for three weeks, and then fully-weight-bear. Participants will be asked to avoid high impact exercise for eight weeks unless they received microfracture, when they will be asked to avoid high impact exercise for 12 weeks. There is no restriction in the range of movement permitted post-operatively. Patients will be reviewed in the NHS clinic of their surgeon six weeks after surgery to monitor for any surgical complications, and further follow-up thereafter is with the study team.

Participants who undergo surgery will follow a routine physiotherapy programme post-operatively that focuses on rehabilitation and maintaining a functional range of movement. This is a different regime to that employed for the non-operative intervention. The number of sessions and duration of treatment will depend on individual patient requirements. Patients will be discharged once they have regained their desired level of function or their improvement has plateaued. There will be no physiotherapy sessions in the four weeks preceding follow-up appointments as per the non-surgical treatment arm.

E.2.8.3 Treatment Modification

The primary outcome is measured eight months post randomisation and crossover is not permitted before this assessment. Any time thereafter, if a participant feels they have not reached their goals and seek further intervention, they will be reviewed by a member of the recruiting surgical team and offered entry into the alternative treatment arm. Should a patient withdraw from the study, they will be referred back to the recruiting clinician for ongoing management.

E.2.8.4 Concomitant Care

Intra-articular steroid injections are not permitted after recruitment into the study as these may limit the ability to compare efficacy of the study treatment arms. All other concomitant treatments are permitted.

E.2.8.5 Management of Contralateral Hip

Patients frequently present with bilateral symptoms secondary to femoroacetabular impingement and the most symptomatic hip will be treated as the study index hip. Should a patient seek treatment for the contralateral hip while participating in the study, treatment and follow up care for this hip will be as per routine clinical care. Accordingly,

treatment for the contralateral hip will not commence until 12 months after commencing treatment for the index hip to allow adequate time for recovery from intervention. Where appropriate, treatment for the contralateral hip will be based on patient preference given that clinicians remain in equipoise with respect to treatment allocation. The only deviation from routine clinical care is that study questionnaires will be used in place of routine clinical pathway questionnaires at the study post intervention time-points. If follow up schedules for each hip fall within eight weeks of each other, these will be combined for a single assessment to lighten patient burden. Contralateral hip data collected up until follow up is complete for the index hip will be used in the data analysis for covariate adjustment.

E.2.9 Outcomes

E.2.9.1 Primary Objectives - Improvement of Symptoms

The primary outcome measure is change in the Hip Outcome Score (HOS)⁴¹⁷, which was specifically designed as an outcome instrument for hip arthroscopy and is considered the most reliable and valid measure of self-reported physical function in these patients⁴¹⁸. It comprises subscales for activities of daily living and sport, and this study is powered to detect a difference in activities of daily living. The primary outcome will be measured at eight months post-randomisation, equating to approximately six months after an intervention commences. This time point was chosen since: i) a clinically meaningful difference in the HOS is detectable six months after hip arthroscopy⁴¹⁹ ii) our feasibility study showed that 94% patients are happy to trial a treatment for six months, but no longer, without improvement in their symptoms¹⁹⁰ iii) this reflects current routine clinic appointment scheduling and increases clinical relevance. Evidence for reliability, validity, and responsiveness of patient reported outcome measures (PROMS) in FAI is limited⁴²⁰ and as secondary outcome measures the following additional PROMs will be

collected alongside the HOS: Non-Arthritic Hip Score (NAHS)²⁸⁵, International Hip Outcome Score (iHOT-33)⁴²¹, Hip and Groin Outcome Score (HAGOS)⁴²², and Oxford Hip Score (OHS)²⁸⁶. PainDETECT⁴²³ will be used to establish the nature and location of pain. At baseline, patients will be asked to complete an additional HOS to indicate the symptoms they expect to experience after treatment is complete.

E.2.9.2 Primary Objectives - Prevention of Osteoarthritis

Change in radiographic minimum joint space width (JSW) at 38 months post randomisation, hence approximately 36 months post intervention, is an additional primary outcome measure. Three-year follow-up is selected as responsiveness to change of this measurement improves significantly in studies exceeding two years⁴²⁴. Alternative measures of osteoarthritis may confer advantages over radiographic JSW⁶⁹, and secondary outcome measures will include radiographic Kellgren-Lawrence grading, cartilage morphology on MRI, and whole-joint semi-quantitative measures of osteoarthritis⁴²⁵.

E.2.9.3 Secondary Objectives – Health Economics

Information pertaining to the delivery of healthcare and the ability of patients to work will be collected from study questionnaires and medical records to establish the cost-effectiveness of the two treatments. EQ-5D⁴²⁶ and the Hospital and Anxiety Depression Scale (HADS)⁴²⁷ will be adopted as validated assessment tools.

E.2.9.4 Secondary Objectives - Evaluation of Disease Biomarkers

A number of novel biomarkers have been proposed for the evaluation of early osteoarthritis. These offer potential as tools to diagnose the earliest osteoarthritis when disease remains potentially reversible, and as measures of treatment efficacy within short timeframes, however, further validation is essential⁸. The MRI protocol for this

study includes T2 mapping and T1 Rho sequences that assess the biochemical composition of cartilage²⁰, and fasting serum and urine samples will be collected at study assessments to measure markers of cartilage metabolism²¹. Performance will be assessed through correlations with outcome measures from the primary objectives.

E.2.10 Participant Timeline

Study endpoints will be measured post randomisation, which will take place at the baseline assessment within four weeks of the initial clinic appointment (Appendix E-3). Intervention will start eight weeks after randomisation consistent with average NHS waiting times. The acceptable window for appointments is four weeks either side of the calculated date.

As a contingency, to ensure that outcome measures are assessed at an appropriate time point after intervention, if treatment is delayed and commences more than 12 weeks post randomisation, the assessment schedule will be shifted to a post-intervention timescale. This also ensures that follow-up coincides with routine hospital follow-up visits. The primary outcome measure HOS will continue to be collected eight months and 14 months post randomisation via postal questionnaire to allow comparison between assessment schedules.

The study is designed with regular follow-up to map symptom fluctuation⁴²⁸ and the trajectory of symptom improvement in this patient population. This information is valuable in the clinical setting when counselling patients and making management decisions.

E.2.11 Sample Size

This study is powered to detect a clinically important difference in the HOS in activities of daily living eight months after randomisation. Initial power calculations were

performed using data from published literature, but were modified based on the results of an interim analysis.

The published minimal clinically important difference is 9 points with a standard deviation of 14 at six months post-intervention⁴¹⁹. Using a statistical significance of 5% and a power of 90%, this gave a sample size of 51 patients in each arm, and accounting for a possible 15% loss to follow-up, 60 patients were required in each arm (total 120 patients). The effect measure is the difference in means. A sample size of 120 is also sufficient to detect a clinically relevant change in JSW at three years⁴²⁹, which is a co-primary outcome measure.

A blinded adaptive interim analysis revealed a standard deviation of 18 rather than 14 and a higher loss to follow-up than anticipated. Repeat calculations for a standard deviation of 18 give a sample size of 85 patients in each arm, and accounting for a possible 20% loss to follow-up, 107 patients are required in each arm (total 214 patients). Sample size was increased for Version 4.0 of the protocol.

E.2.12 Recruitment

Patients will be recruited from NHS clinics of participating centres. A member of the surgical team will introduce the trial to eligible patients, and if they would like further information, they will be introduced to the research nurse for more detailed discussion. Patients who opt-in will be given at least 48 hours to consider the study information before being contacted again by their preferred means to arrange a baseline assessment appointment. Baseline assessments will take place within four weeks of the initial approach. Consent and randomisation will take place at the baseline assessment and treatment will commence eight weeks later. On the day that intervention commences, clinical examination and collection of Patient Reported Outcome Measures will be repeated to enable evaluation of the stability of symptoms and signs.

E.2.13 Assignment of Intervention

All patients who provide consent and complete the baseline assessment will be randomised. Participants will be assigned either intervention with 1: 1 allocation through restricted randomisation with minimisation. Treatment groups will be balanced for:

- i) Age (<40 or ≥40 years)
- ii) Gender
- iii) Recruitment site
- iv) Baseline Activities of Daily Living Hip Outcome Score (HOS) subscale (<65 or ≥65)

The HOS threshold is derived from baseline scores in comparable studies^{184,419}. The randomisation algorithm is not available to any member of the research team.

Randomisation for all patients will be performed using a telephone system provided by the Oxford Clinical Trials Unit. The recruiting centre will then inform the participant of their allocation

E.2.14 Blinding

Assessments post randomisation will be conducted by an assessor blinded to treatment allocation. Participants will be asked not to disclose their treatment and will wear shorts to cover any scars. Due to the nature of the interventions, it is not possible to blind the participant or treating clinician. Data entry will be performed by staff members independent of the study team. Blinding will be maintained when performing assays of biochemical biomarkers and imaging study interpretation.

E.2.15 Data Collection

E.2.15.1 Clinical Assessment

Paper questionnaires will be completed by participants and the assessor will ensure there is no missing data. Clinical examination includes passive range of movement assessments measured with a goniometer, assessment of muscle strength, and special tests for impingement and labral pathology.

E.2.15.2 Serum and Urine Collection

Patients will have fasted since midnight. Venous blood samples (18ml) will be collected between 0900 and 1100 and allowed to coagulate, then centrifuged at 1500g for 10 minutes. Serum will be aliquoted and stored at -80°C within 2 hours of collection. Midstream urine (10ml) will be collected from the second void of the day and centrifuged at 1,500g for 10 minutes to remove sediment. Aliquots will be stored at -80°C within the Oxford Musculoskeletal Biobank (HTA License 1250).

E.2.15.3 Radiographs

A standing anteroposterior pelvis radiograph will be performed with the beam centred in the midline between the superior border of the pubic symphysis and a line connecting the anterior superior iliac spines. The feet will be internally rotated to 15 degrees and a calibration ball will be suspended below the pubic symphysis. Radiographs will be repeated if the obturator foramen index lies outside 0.7 and 1.4. A cross-table lateral radiograph will be performed with the beam centred parallel to the table and orientated 45 degrees to the index hip with the cross-hairs directed at the centre of the femoral head. The hip will be internally rotated to 15 degrees and filters used as required for excess soft tissue.

E.2.15.4 MRI Protocol

Sequences comprise three-dimensional morphological MRI sequences without arthrogram to assess the labrum, cartilage, and bone. Compositional MRI sequences will be used where available to include T2 mapping and T1 Rho as surrogate markers of early osteoarthritis^{113,430,431}.

E.2.15.5 Patient Retention

Participants will be reimbursed travel expenses for all appointments that are not routine.

E.2.16 Statistical Methods

Professional academic statisticians blinded to the study groups will conduct all analyses. Primary analysis will be based on the 'intention to treat' (ITT) population of all randomised participants regardless of their compliance with the protocol. Study analysis will take place in two stages: The first stage will take place after all participants have completed their eight month post-randomisation (or six month post intervention where treatment is delayed) assessment. The second stage of the analysis will take place once all follow-up is complete.

Linear regression analysis (ANCOVA) will be used to examine the differences between the two treatment arms in the HOS at eight months in a multivariate framework. The regression model will be adjusted for minimisation factors and relevant patient characteristics. Diagnostic checks will be performed to verify the model assumptions. Secondary outcome measures will be analysed using linear or logistic regression as appropriate with covariate adjustment. Subgroup analysis will include measures of osteoarthritis at baseline and at arthroscopy as studies suggest this to be an important predictor of outcome⁴³².

E.2.17 Monitoring

The Data Monitoring Committee (DMC) is independent of the research team and study sponsor and comprises a trial statistician, acting as the Chair, alongside an orthopaedic surgeon, physiotherapist, and patient representative (not a study recruit). This committee will review the unblinded interim analyses and inform the Trial Steering Committee (TSC) if it concludes that the outcome of one intervention has been shown, beyond reasonable doubt, to be different to the other with respect to either of the primary outcome measures and without unblinding the data. The TSC will decide whether to stop the trial early.

E.2.18 Harms

An adverse event will be defined as any untoward medical occurrence without regard for causality from study interventions. This data will be obtained from study questionnaires and medical notes and will be collected until follow-up is complete. A serious adverse event will be defined as any medical occurrence that results in death, threatens life, requires inpatient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability/incapacity. A serious adverse event will be reported to the Research Ethics Committee where in the opinion of the Chief Investigator the event was related to any of the research procedures and the type of event is not listed in the protocol as an expected occurrence. Recognised surgical complications include persistent or recurrent pain and stiffness, need for further surgery (e.g. recurrent labral tear, advanced osteoarthritis requiring arthroplasty), infection, thromboembolic events, neurovascular injury, genital/perineal bruising and swelling, and anaesthetic risks.

E.2.19 Trial Status

Recruitment commenced in July 2013 and finished in July 2016. The study is now in the follow-up phase and the final eight-month post-randomisation assessment is anticipated to take place in May 2017.