



Early Knee Osteoarthritis: Symptoms and Structure

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Abstract

Knee osteoarthritis (OA) is the commonest form of lower limb OA with a lifetime risk of over 40%. It is a disease characterised by symptoms such as pain and loss of function. In addition there are typical structural features on both radiographs and MRI. Knee OA represents a spectrum of disease, ranging from early preclinical cartilage change to established full thickness disease. Anteromedial knee OA is a particular phenotype of knee OA where disease is confined to the medial compartment. Whilst end stage arthritis is treated reliably with joint arthroplasty, those with early stage disease are treated with a variety of non- surgical interventions with varying success.

This thesis is concerned with understanding the disease of patients that have early radiographic changes but symptoms not controlled by conservative measures. Up to 150 of these patients a year present to the Nuffield Orthopaedic Centre, Oxford. They have been described as being in the “Treatment Gap”.

A series of validation studies were performed to determine the optimal method for diagnosing cartilage defects within the knee. The three commonest diagnostic methods were examined for their validity. Arthroscopic assessments of cartilage lesions demonstrated a moderate level of intra and inter observer reliability. In contrast, radiographs and MRI demonstrated high levels of reliability. When using MRI as a criterion standard, both radiographs and arthroscopic assessment were found to have poor accuracy. Based on the work in this thesis a formal definition of the cartilage changes exhibited in early knee OA was proposed.

A cross sectional cohort of 100 patients with the symptoms and radiological features of early knee OA were identified. Their pain and function profile was compared to two comparison groups of patients at the end stage of knee OA (defined by the need for partial or total arthroplasty). In up to 78% of individual cases those with early OA had pain and function profiles as bad as those with end stage disease. The cross sectional symptoms of early knee OA demonstrate a marked discordance with their mild radiographic changes.

The same cohort was extended to 125 patients. They were followed over one year with monthly PROM assessments to determine how symptoms change over time. 43% of patients experience a clinical improvement over 12 months, 31% experience a clinical deterioration and 26% remain unchanged. The range in OKS variation over 12 months was on average 12 points, with clinically

relevant variation occurring on 45% of monthly measurements. Patients with early knee OA can expect to experience considerable variation in their symptoms over 12 months and this must be considered when planning interventions.

A number of patients with early knee OA were noticed to demonstrate medial meniscal extrusion. Using data from the Osteo Arthritis Initiative (OAI) a nested case control study was designed to determine how the presence of meniscal extrusion in an otherwise normal knee affects the risk of developing knee OA over the next 48 months. This demonstrated an Odds Ratio of 3.5, suggesting that meniscal extrusion is a considerable risk factor for the development of OA. The presence of a knee injury or operative intervention to the index meniscus was shown to increase this risk.

Many phenotypes of OA are known to demonstrate familial aggregation. In an attempt to determine where the earliest structural changes occur in medial compartment knee OA, a cohort of patients selected only for their family history of the disease were developed. This cohort was compared to spouse controls for the presence of knee OA, as well as meniscal extrusion and long leg alignment. In addition, a functional analysis of their cartilage was performed. This cohort was not shown to be at increased risk of disease compared to controls. Discussion of the possible reasons for this finding is presented.

Early knee osteoarthritis is a considerable clinical problem. This thesis has aided the understanding of the condition by firstly defining the radiological description of these patients. Secondly, their cross sectional and longitudinal symptom profile have been described for the first time. In addition, the presence of an extruded meniscus has been demonstrated as a substantial risk factor for the disease. Finally, family history has not been demonstrated as a risk factor for the disease within the limits of the study described here. Future work has been proposed.

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Abbreviations

AMG Anteromedial Gonarthrosis, a synonym for AMOA

AMOA Anteromedial Osteoarthritis, a synonym for AMG

BMI Body Mass Index

HADS Hospital Anxiety and Depression Score

HTO High Tibial Osteotomy

ICOAP Intermittent and Constant Osteoarthritis Pain Score

KOOS Knee injury and Osteoarthritis Outcome Score

LLAA Lower Limb Anatomical Axis

LLMA Lower Limb Mechanical Axis

LOT-R Revised Life Orientation Test

NICE National Institute for Health and Clinical Excellence

NOC Nuffield Orthopaedic Centre

OA Osteoarthritis

OAI The Osteoarthritis Initiative

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OKS	Oxford Knee Score
SibKids	Second generation members of families with strong history of Knee OA
WBL	Weight Bearing Line

1. Introduction

1.1. Overview

Osteoarthritis (OA) is the most prevalent chronic joint disorder. The knee, hip and hand are the sites most commonly affected by the disease [1]. Knee OA is the most frequent form of lower limb OA [2]. It is estimated that 6% of those aged 30 years [3] and over and 15.2 % of those aged 45 years or over suffer from the condition, with a lifetime risk of 44.7% [4]. Whilst OA can exist throughout the knee joint, by far the commonest phenotype of knee OA is that of Antero Medial knee OA (AMOA). In AMOA, cartilage damage is confined to the anterior aspect of the medial compartment in the presence of an intact ACL. AMOA represents up to 70% of all patients with knee OA [5].

Knee osteoarthritis can be considered as a spectrum of disease, progressing from preclinical structural changes to established full thickness disease. The earliest symptoms of anteromedial knee arthritis can be treated in the primary care setting with paracetamol, anti inflammatory medication, bracing, weight loss and physiotherapy [6] [7] [8] [9]. These interventions, whilst successful in some patients, are known to have limited efficacy in others [10, 11, 12]. Following the failure of these modalities, the symptomatic patient may be referred to an orthopaedic surgeon for consideration of surgical intervention. In those with end stage knee OA, with pain and stiffness that has not responded to conservative measures and radiographs demonstrating bone on

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bone arthritis, knee arthroplasty [13],[14] is known to be a successful procedure. Over 80,000 are performed in the UK per year [15]. With 26 million UK residents over the age of 45 [16], 4 million adults in the UK have symptomatic knee OA but are not considered to be suitable for knee arthroplasty by either themselves, their GP or their orthopaedic surgeon. A proportion of these patients, in whom conservative management techniques are no longer providing symptom relief, but with disease not considered suitable for arthroplasty, have been previously described as being in the “Treatment Gap” [17]. A diagrammatic representation of the spectrum of knee OA and the treatment gap can be seen in figure 1.4.1 on page 31.

At the Nuffield Orthopaedic Centre, Oxford, at least 150 patients per year present to the knee surgery clinic with AMOA and knee pain, but with non full thickness cartilage loss [5], that is no longer responding to conservative primary care measures. It is these patients, with non end stage radiographic anteromedial knee OA and symptoms not controlled by conservative measures, that this thesis aims to investigate. Firstly, by describing their cross sectional and longitudinal symptom profile and secondly by identifying structural changes in their knee that predispose them to progression of disease.

Although successful management has been achieved in those affected with soft tissue injuries and end stage arthritis of the knee, the medical community is yet to achieve such success with early knee arthritis. Joint replacement is known to provide unreliable results in patients with non full thickness cartilage disease OA. [18]. Other non arthroplasty surgical interventions including HTO and cartilage regeneration procedures are similarly unpredictable or unsuitable in these patients [19, 20, 21, 22].

Problems exist with many of the current studies that attempt to investigate this group of patients. The diagnostic methods used to define the cohort of patients at recruitment to individual studies is varied. Whilst some focus on radiographic

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change, in others magnetic resonance imaging or intra operative direct vision cartilage assessment is used. Consequently it is difficult to compare the disease status of patients between studies.

Whilst pain related to knee OA is generally considered chronic it is known to fluctuate [23]. Clinically, physicians often notice that patients with OA experience episodes of recurrent pain or pain exacerbations over the course of the disease [24]. Although variation in symptoms is well recognised in those with end stage disease, no attempt has been made to understand the natural history of those with early disease. In addition there is no clear consensus on when to undertake interventions in patients at earlier stages of disease although symptom variation may clearly affect decision making. This means that studies compare interventions in patients who are at different clinical and radiological stages in their disease.

Currently there is no standard definition of these early radiographic knee OA patients, nor an understanding of their cross sectional and longitudinal symptom profile. Categorisation of patients is poor and this lack of attention to detail may in part account for the variability in results of the various surgical interventions.

A comprehensive understanding of early knee arthritis requires the identification of where the pre radiographic changes of disease occur before the development of symptoms, and anatomical abnormalities that predispose to progression.

To date, five key questions remain unanswered -

- How should we define this cohort of patients?
- What is the cross sectional symptom profile of these patients?
- What is the longitudinal symptom profile of these patients?
- Where in the knee do the earliest pre radiographic changes of disease occur?
- Does a strong family history predispose patients to developing these changes?

1. Introduction

Understanding these factors will allow musculoskeletal clinicians to accurately identify those patients with the disease, and those at risk of developing the disease. In addition, it will enable provision of evidence based advice about how symptoms may evolve in the long term, and on timings of interventions. In the future, it may allow the development of treatments that prevent the development of symptomatic disease.

1.2. Overall scope of the thesis

The scope of this thesis is firstly to define a cohort of patients with the syndrome of Early Radiographic Knee Osteoarthritis and describe their cross sectional and longitudinal symptom profile. Secondly, it is to identify radiological risk factors in those at high risk of developing the disease that may be potential bio markers or targets for interventions aimed at preventing disease progression.

1.3. Specific objectives

1. To create a strict definition of patients with early radiographic knee OA.
2. To determine the cross sectional symptomatic profile of those with early radiographic knee osteoarthritis at presentation to clinic.
3. To determine the variation in symptoms experienced by those with early radiographic knee osteoarthritis over a one year period.
4. To determine if extrusion of the medial meniscus plays a role in the development of early radiographic knee osteoarthritis.
5. To identify where the earliest radiological changes develop in those who are at risk of developing early radiographic knee osteoarthritis.

This will allow a body of evidence to be created that builds towards the clinical and radiological description of the medial compartment of the knee during its progression from a normal joint to end stage arthritis, i.e. as it “fails”.

1.4. Structure of thesis

This thesis is presented in the following chapters:

- Chapter 2 provides a literature review of the current research into early adult knee arthritis including definitions, classifications and treatment options and highlights areas in the literature that remain unexplored.
- Chapter 3 defines the term “early radiological knee osteoarthritis” (ERKO) for the use in this thesis. It does so by the use of six short studies that examine the role of radiographs, MRI and arthroscopy in the diagnosis of knee OA.

Chapters 4 and 5 explore the symptoms experienced by patients with ERKO.

- Chapter 4 reports a cross sectional study that describes the pain and function profile of those with ERKO at presentation to a dedicated orthopaedic knee clinic, and compares the symptom profile to patients with established knee arthritis awaiting arthroplasty.
- Chapter 5 reports a longitudinal study that explores the variation in symptoms experienced by those with ERKO over a 12 month period using validated patient reported outcome measures (PROMS).

Chapters 6 and 7 explore radiographic structural changes in those who are at risk of developing AMOA.

- Chapter 6 reports a clinical study that uses an established longitudinal cohort of patients, the Osteoarthritis Initiative (OAI), to develop a unique cohort of

1. Introduction

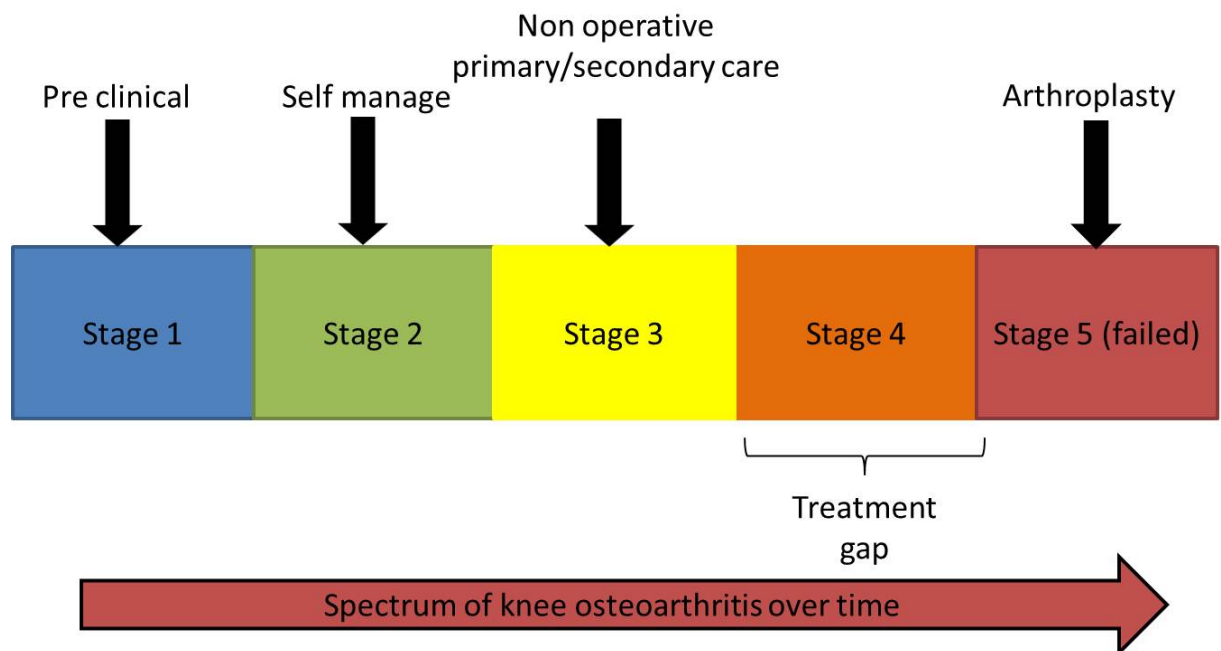
patients who do not have AMOA at recruitment but do develop AMOA over 48 months. These are used to examine the association of the extruded meniscus with the development of AMOA.

- Chapter 7 describes the development of a unique cohort of young patients at high risk of developing knee arthritis, the SibKids. Four clinical studies are reported. The first examines the vertical heritability of anteromedial knee arthritis. The second compares risk factors for AMOA, mechanical leg alignment and meniscal extrusion between SibKids and controls. The third compares structural MRI changes in the knee between SibKids and controls. In the final study a specialist MRI sequencing technique, T2 mapping, is used to attempt to identify where the earliest radiographic change of AMOA occurs in SibKids compared to controls.

Chapters 8, 9 and 10 summarise the important findings and conclusions presented in the thesis. They provide a clinical context for the work in this thesis and recommendations for work in the future.

1. Introduction

Figure 1.4.1.: The progression of knee osteoarthritis and the concept of the “treatment gap”. Patients may move both forwards and backwards along the spectrum.



2. Literature review

2.1. The knee.

The knee is a synovial joint consisting of the articulations of the femoral and tibial condyles, and the patella and the patella surface of the femur [25]. It is the largest joint in the body and its primary purpose is to allow effective and efficient placement of the foot during movement and gait.

2.1.1. Anatomical positions and planes.

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

2.1.1.1. The anatomical position.

A person in the anatomical position:

- Is standing upright or lying supine with head, eyes and toes directed anteriorly.
- Has upper limbs by the side with palms facing anteriorly.
- Has lower limbs together with the feet directed anteriorly [26].

2.1.1.2. The anatomical planes.

- The median plane (mid sagittal) is a vertical plane passing longitudinally through the body dividing it into right and left halves.
- The sagittal planes are vertical planes that pass through the body parallel to the median plane.
- The coronal planes are vertical planes that pass through the body at right angles to the median plane, therefore dividing the body into anterior and posterior sections.
- The horizontal planes (also referred to in this thesis as axial planes) are transverse planes that pass through the body at right angles to the sagittal and coronal planes, dividing the body into superior and inferior sections [26].

2.1.2. Knee anatomy.

The knee joint depends upon its bony articulations, ligaments, menisci, capsule and surrounding muscular attachments for both its stability and mobility.

2.1.2.1. Bony articulations.

The tibial plateau consists of two separate articular surfaces. The medial plateau is oval shaped and longer in the anterior posterior axis than the lateral plateau. The lateral tibial surface is smaller and more circular. The hyaline cartilage covered surface of the medial side does not extend beyond the margins of the medial plateau, whereas laterally the surface curves over the posterior margin of the plateau to allow for the greater movement of the lateral meniscus [27]. The medial tibial surface is concave whereas the lateral surface is convex. The lower end of the femur is formed of two condyles, separated by an intercondylar notch but joined anteriorly by

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the trochlea surface where the patella articulates. The curve of the femoral condyles is cam shaped in the sagittal plane and is flatter on the distal end of the femur and more curved on the free posterior margin of both condyles. The distal surface of the medial condyle tends to be narrower and longer than the lateral condyle.

2.1.2.2. Capsule.

The articular capsule is a thin, strong, fibrous and synovial membrane that surrounds the joint. It seals the joint space. It provides passive stability by limiting movements, and provides active stability via its proprioceptive nerve endings. It produces synovial fluid via its synovial lining [28]. The capsule attaches to the femur superiorly just proximal to the articular margins of the condyles and to the intercondylar notch posteriorly. It has a space on the lateral condyle to allow the tendon of popliteus to pass out posteriorly. On the tibia the capsule is attached around the articular margin of the plateau, except for where the tendon of the popliteus crosses the bone posteriorly.

2.1.2.3. Ligaments.

The capsule is strengthened by four intrinsic and one extrinsic ligament. The lateral collateral ligament (extrinsic) extends from the lateral epicondyle of the femur and attaches to the lateral surface of the head of the fibula. It remains extra articular. The popliteus tendon passes deep to the lateral collateral ligament and separates it from the lateral meniscus. The medial collateral ligament is a flat band that extends from the medial epicondyle of the femur to the medial condyle and superior part of the tibia. The deep fibres of this ligament are firmly attached to the medial meniscus. Postero laterally, the oblique popliteal ligament and arcuate popliteal ligament form part of a musculo ligamentous complex referred to as the postero lateral corner. [26]. Anteriorly, the capsule is strengthened by the patella ligament and on each side of

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the patella by the medial and lateral patella retinacula which arise from the vastus medialis and lateralis.

The cruciate ligaments are a strong “crossed” pair of ligaments that lie within the capsule of the knee joint but not within the synovial membrane. Their names derive from their tibial origins with the anterior cruciate ligament (ACL) attaching anterior to and between the intercondylar eminences. The femoral attachment is on the posteromedial aspect of the lateral femoral condyle [29]. The ACL has two anatomically distinct bundles, an anteromedial bundle that is tight in flexion and a posterolateral bundle that is tight in extension. The ACL includes prevention of backwards displacement of the femur on the tibia. In addition it limits extension of the lateral femoral condyle of the femur and causes medial rotation of the femur as it goes to full extension. The posterior cruciate ligament (PCL) originates anterolaterally on the medial femoral condyle and attaches to the posterior part of the tibia between the condyles and from the uppermost part of the adjacent posterior surface. The PCL is also composed of two bundles, an anterolateral portion that is tight in flexion and a posteromedial portion that is tight in extension. It acts to prevent the femur from sliding forwards off the tibial plateau.

2.1.2.4. Menisci.

The menisci, also known as the semi lunar cartilages, are crescent shaped and are triangular in cross section. The medial meniscus is more c shaped and the lateral meniscus is more circle shaped. They act to deepen the concavity of the tibial plateau facets, and assist in rotation of the knee, lubrication and nutrition. The menisci are attached at their ends (horns) to the intercondylar area of the tibia. The margins are attached to the fibrous capsule of the knee joint. The coronary ligaments are capsular fibres that join the margins of the meniscus to the tibial surface. Anteriorly the menisci are attached to each other by the transverse inter meniscal ligament. The

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menisco femoral ligaments, also known as the ligaments of Humphrey and Wrisberg, connect the posterior horn of the lateral meniscus to a location near the insertion site of the PCL on the medial femoral condyle [30]. The menisci are mobile during flexion, extension and rotation of the knee and act to increase the surface area between the tibia and femur, thus dissipating contact stresses [31]. A knowledge of the vascularisation of the adult meniscus is important for a knee surgeon. At maturity, the meniscus contains nerves and blood vessels in only the peripheral 10-25%. As a result, two distinct areas can be identified. An outer, vascularised and innervated region (red-red zone), and an inner, aneural avascular zone (white-white zone). The healing capacity of both regions is directly related to its vascularity, meaning the white region is susceptible to permanent post traumatic and degenerative lesions [32]. The collagen fibres of the menisci are arranged radially and longitudinally. The longitudinal fibres help dissipate hoop stresses in the meniscus, and the radial fibres allow the meniscus to expand under compressive forces and increase the contact area of the joint. The lateral meniscus is considerably more mobile than the medial meniscus, with twice the excursion of the medial side during knee range of motion and rotation [29].

2.1.3. Hyaline cartilage.

Hyaline (literal meaning “glass like”) cartilage coats the articular surface of synovial joints including the knee. It functions to distribute weight bearing forces and to provide lubrication. It is avascular, aneural, alymphatic and receives its nutrients via diffusion from the synovial fluid

2.1.3.1. Constituents of hyaline cartilage. [33]

- Cells (chondrocytes) - manufacture and maintain the extracellular matrix

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- Extracellular matrix
 - Fibres
 - * Collagen (type 2, 6, 9, 10, 11)
 - * Elastin
 - Ground substance
 - * Water
 - * Proteoglycans and Glycosaminoglycans (such as Aggrecan, hyaluronan)
 - Glycoproteins
 - Degredative enzymes (Matrix Metalloproteinases)
 - Extracellular ions

2.1.3.2. Histological structure. [34]

The structure of hyaline cartilage can be divided into four main layers. The uppermost superficial layer is made almost entirely of collagen, with the collagen and water concentration decreasing as the depth increases. Conversely, the proteoglycan concentration increases with depth.

1. Tangential layer (superficial zone). Here the chondrocytes are small and flattened parallel to the surface. The most superficial part, known as the lamina splendens, has no cells. Collagen fibres in the matrix of the tangential layer are very fine. They run parallel to the surface of the cartilage to allow resistance to shear stresses.
2. Transitional Layer: In this layer the chondrocytes are slightly larger, and there is an increase in proteoglycan concentration. Collagen fibres run obliquely. This

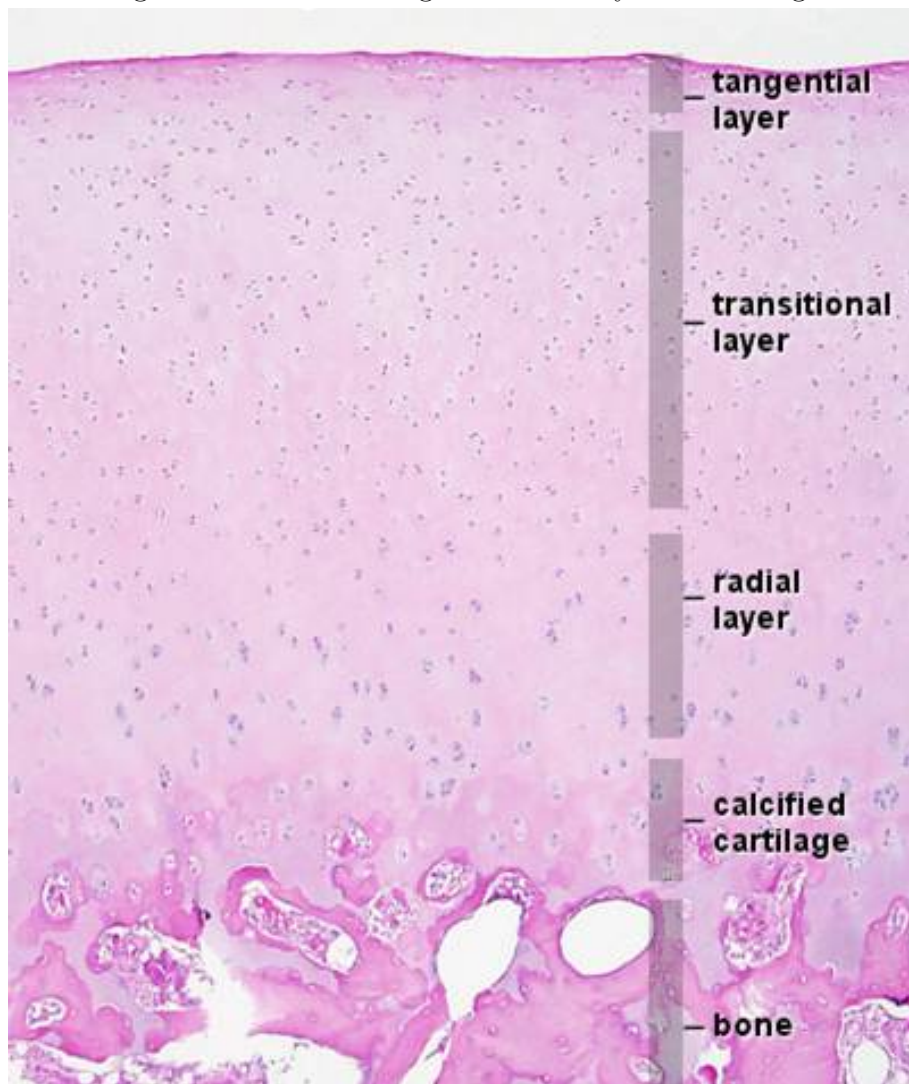
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zone forms the transition between the shearing forces of the superficial zone and the compressive forces in the deeper layers.

3. Radial Layer: This is the largest part of the articular cartilage. Here the chondrocytes form stacks of cells orientated perpendicular to the articulating surface. The course of the collagen fibres follows the orientation of the chondrocyte columns. These collagen fibres act to distribute load and resist compression.
4. Calcified cartilage layer: This rests on the underlying cortex of the bone. It anchors the cartilage to the underlying bone and forms a barrier to diffusion from blood vessels supplying the subchondral bone.

The “tidemark” is the boundary between the calcified and non calcified cartilage that is made visible by histological staining. It is cell free and represents a zone of calcification that migrates towards the surface of the cartilage with age. A histological slide of hyaline cartilage is shown in 2.1.1 on the next page, and is taken from www.lab.anhb.uwa.edu.au.

Figure 2.1.1.: A histological slide of hyaline cartilage



2.2. Osteoarthritis of the knee.

2.2.1. Epidemiology.

As described in section 1.1 on page 25, knee OA is the most frequent form of lower limb OA [2]. It is estimated that 6% of those aged 30 [3] and over and 15.2 % of those aged 45 or over suffer from the condition, with a lifetime risk of 44.7% [4]. It therefore represents a considerable burden on individual patients in terms of pain and

functional impairment, but also on society in terms of utilisation healthcare resources.

2.2.2. Definitions and classification.

Knee OA is characterised clinically by usage related pain and/or functional limitation. It is a common complex joint disorder showing focal cartilage loss, new bone formation and involvement of all joint tissues [35]. Structural tissue changes are reflected in the classical radiographic features of loss of joint space, sclerosis, osteophytes and cyst formation.

Perhaps surprisingly for such a common condition, no precise description and definition of osteoarthritis exists. The classification and diagnostic criteria remain a potent source of debate amongst researchers [36]. Reasons for this are numerous and include a lack of specific physical or laboratory findings and discrepancies between symptoms and the result of radiographic examinations. As a result, OA is frequently diagnosed by an overall clinical impression based on the patients age and history, location of the joint abnormality and radiographic findings.

2.2.2.1. ICD 10.

The ICD-10 is the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list by the World Health Organization (WHO). It provides codes for diseases and signs and symptoms, and allows effective communication between medical specialists. Chapter XIII, Blocks M00-M99 refers to diseases of the musculoskeletal system and connective tissue. Arthropathies are defined as disorders predominantly affecting peripheral joints and are again subdivided into infectious arthropathies, inflammatory arthropathies, arthrosis and other joint disorders. Therefore, arthrosis (a synonym for osteoarthritis or osteoarthritis) should be considered as a disease of the peripheral joints which is

not inflammatory or infective in origin. Gonarthrosis, or osteoarthritis of the knee, is coded as M17 and can again be subdivided as primary (idiopathic aetiology) or secondary (post traumatic or other identified cause), and whether it is unilateral or bilateral. No distinction is made between specific patterns of disease [37].

2.2.2.2. American College of Rheumatologists (ACR) criteria.

The ACR created their classification criteria for OA of the knee in 1986 using a Delphi method [38]. These were initially designed as six different algorithms and were felt to be impractical for practicing clinicians [39], and have since been revised and improved into two sets of criteria, the first based on clinical signs and the second based on clinical, laboratory and radiographic criteria. These are shown in figure 2.2.1.

Figure 2.2.1.: The ACR clinical classification criteria and the clinical plus radiographic criteria for osteoarthritis of the knee

1. Clinical

- a) The presence of articular knee pain for most days of the prior month, in addition to at least three of the following:
 - i. Crepitus on active motion.
 - ii. Morning stiffness of less than 30 minutes duration.
 - iii. Age >38 years.
 - iv. Bony enlargement of the knee.
 - v. Bony tenderness of the knee.
 - vi. No palpable warmth.

2. Clinical plus radiographic:

- a) Articular knee pain for most days of the prior month, plus radiographic evidence of osteophytes on joint margins in addition to one of the following:
 - i. Crepitus on active motion.
 - ii. Morning stiffness of less than 30 minutes duration.
 - iii. Age > 38 years.

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However, the original criteria have never been validated except for using the “clinical diagnosis of OA”. Importantly, these criteria do not specifically refer to articular cartilage damage, the predominant feature of OA. Wu et al have attempted to validate the ACR criteria against a surgical “Gold Standard” of arthroscopy [39], and suggested that, if arthroscopy is believed as the reference standard, the clinical criteria alone identify those patients with cartilage damage before any radiographic change whereas the clinical plus radiographic criteria identify knee OA patients with more severe cartilage damage.

EULAR, the European League Against Rheumatism, in a similar paper, performed a Delphi analysis of experts in 12 countries and developed ten propositions which they validated against two large prospective cohorts of patients known to have the disease in the UK and Denmark [35]. A principle finding of this study was the lack of an agreed single reference standard for the diagnosis of knee OA, and they therefore included research involving clinical, arthroscopic, radiographic and MRI reference standards. This has lead to the prioritisation in their research agenda on the development of internationally agreed criteria for the diagnosis of knee OA in clinical practice, clinical trials and epidemiological studies. They are yet to report the outcome of these. However, the presence of clinical symptoms, in particular pain that is usage related, will form a crucial part of these recommendations alongside suggestions on the most appropriate structural changes to include [40].

2.2.3. X ray descriptions of osteoarthritis.

Plain radiography, which is widely available, quick to perform and cheaper than other imaging modalities, has been the primary imaging modality for knee OA for many decades [36]. It detects the primary bony radiographic features of marginal osteophytes, joint space narrowing, subchondral sclerosis and subchondral cysts that

are well established in the medical lexicon. Radiographs have been used in the semi quantitative assessment of the severity of OA for many years with the Kellgren and Lawrence grade [41], Ahlback [42] and OARSI atlas [43] used most commonly.

2.2.3.1. Kellgren and Lawrence.

This classification system, which is used in the description of hand, hip and knee OA, uses the osteophytes, narrowing of joint space, and pseudocysts in the subchondral space as the key radiographic features. It divides the severity of disease into five grades

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

It is a widely used scheme [44][45][46] employed to define the presence or absence of structural changes of disease, with Grade 2 commonly being held as the threshold for the diagnosis of OA [47]. Problems with this system include its relative insensitivity to change and the importance of the osteophyte. In addition, interpretations of studies using this system must be done with care due to discrepancies in interpretations of the original paper [48]. Felson suggested a modification of KL grading to improve the sensitivity to change in longitudinal knee OA studies and suggested that OA be defined by a combination of joint space loss and definite osteophytes on radiography in a knee that did not have this combination on the previous radiographic assessment [49]

2.2.3.2. Ahlback.

This grading system, described later than that of Kellgren and Lawrence has fallen out of common use largely due to its insensitivity and the decrease in the proportion of patients who present with the most severe forms of radiographic disease due to the increased availability of surgical intervention. It consists of five grades:

- Grade I: Joint space narrowing (less than 3mm).
- Grade II: Joint space obliteration.
- Grade III: Minor bone attrition (0-5mm).
- Grade IV: Moderate bone attrition (5-10mm).
- Grade V: Severe bone attrition (>10 mm).

This system focuses on loss of medial joint space and is commonly held to be significantly less sensitive to change than the Kellgren and Lawrence grade [50]. It is therefore less commonly used in cross sectional and longitudinal studies into knee OA. In addition, although the reproducibility of this system appears to be high [51], the sensitivity and specificity have been found to be low when comparing radiographs to intra operative findings [52].

2.2.3.3. The OARSI Atlas grading system.

This radiological grading system, in response to criticism of other systems, grades osteophytes and tibio femoral joint space narrowing on a scale of 0-3 and also provides a grade per compartment. In addition, the presence or absence of medial attrition, lateral femoral sclerosis and medial tibial sclerosis are recorded. This system appears to be more sensitive to longitudinal change than the KL system [47], although the large number of readings required per joint and makes its use in large studies difficult

and time consuming. In addition, the application of the grading of individual features in the diagnosis of OA is difficult - since there is no clear guidance on which individual feature or combination of features should be used to diagnose OA [36].

2.2.4. Magnetic Resonance Imaging (MRI) in osteoarthritis.

Radiographs allow a 2 dimensional assessment of the bony configuration of the knee joint. However, staging of OA based on plain radiographic assessment has inherent inaccuracies. Firstly, the orientation of the knee at the time of image acquisition will affect the visualization of both the joint space and osteophytes [53]. Secondly, even with the standardisation of the radiographic technique, measurement of joint space loss has been shown to reflect changes in meniscal morphology and extrusion more accurately than cartilage loss itself [54]. In addition to being unable to view cartilage directly, other structures such as the ACL and synovium (amongst others) that may have important roles to play in the initiation and progression of OA are also not visible [55]. As a result of the limitations in the use of plain radiographs, the use of MRI in osteoarthritis of the knee has gained increasing momentum over recent years particularly in assessing diagnostic status, disease severity and in monitoring disease progression. Of particular interest is the use of MRI scanning to determine the presence of structural or functional change within the knee in those with knee pain but no radiographic changes present [56], [57], [58].

2.2.4.1. MRI to describe structural changes in knee OA.

Although not yet routinely used in clinical practice, MRI is increasingly becoming a key tool for the imaging of OA in clinical research. Based on the recognition of MRI's ability to detect structural changes not otherwise visible on radiographs, a consensus group from OARSI (Osteoarthritis Research Society International) has proposed an

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MRI imaging base definition of knee OA [59]:

1. Definite osteophyte formation and full thickness cartilage loss
2. One feature from 1) above and one of the following
 - a) Subchondral bone marrow lesion or cyst not associated with meniscal or ligamentous attachments
 - b) Meniscal subluxation/extrusion, maceration or degenerative (horizontal) tear
 - c) Partial thickness cartilage loss
 - d) Bone attrition

A number of quantitative scoring systems have been developed to evaluate the morphological characteristics of cartilage, in addition to those other intra and peri articular structures such as subchondral bone, menisci, osteophytes and synovium, in order to establish risk factors for symptoms and structural changes.

Structural change of cartilage lesions: ICRS and the modified ICRS grading system.

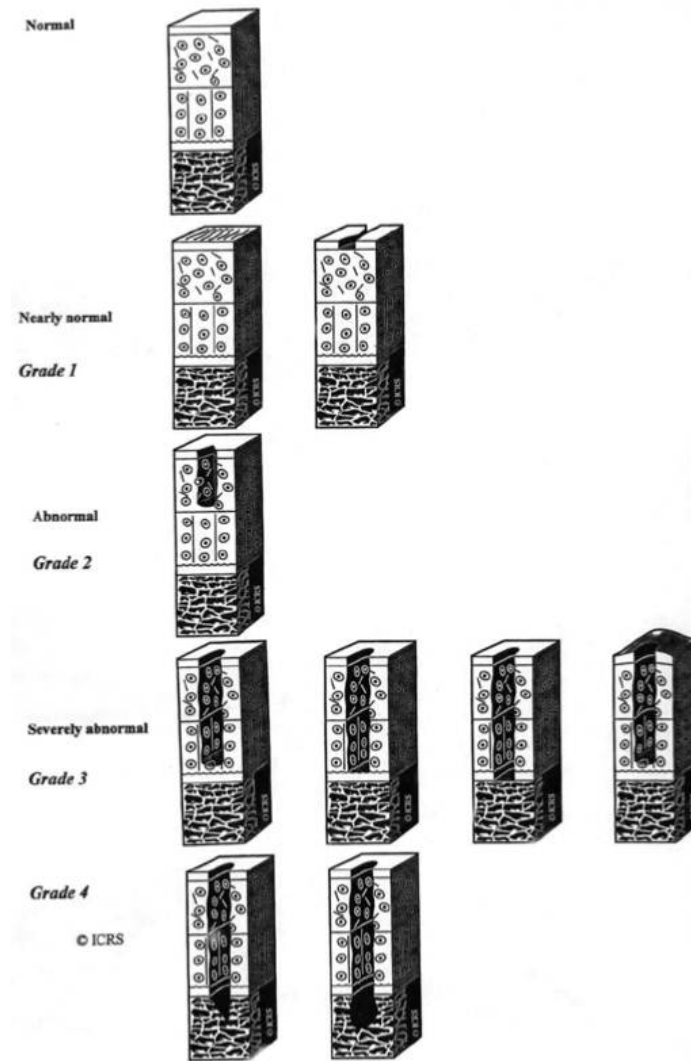
International Cartilage Repair Society grading system. This grading system, proposed in 2003 by Brittberg et al [60], and demonstrated in Figures 2.2.2 on the following page and 2.2.3 on page 48, was designed for use in both arthroscopic and MRI imaging. It focuses on the depth of the cartilage lesion as the primary measure of disease. It has been validated for reliability and reproducibility in both MRI and arthroscopy for both the initial assessment and for longitudinal assessment of cartilage change [61][62][63].

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Figure 2.2.2.: A description of the ICRS grading of cartilage lesions

- ICRS 0: Macroscopically normal cartilage without notable defects
- ICRS 1:
 - 1a: Intact surface but fibrillation and/or slight softening
 - 1b: Additional superficial lacerations and fissures are found
- ICRS 2: Defects extend deeper but involve <50% of cartilage thickness
- ICRS 3: Defects that extend through >50% of the cartilage thickness, through the cartilage but not through the subchondral bone plate
 - 3a: Deep defects that extend through >50% of the cartilage depth but not to the calcified layer.
 - 3b: Deep defects that extend through >50% of the cartilage depth to the calcified layer.
 - 3c: Deep defects that extend down to but not through the subchondral bone plate.
 - 3d: Blisters
- ICRS 4: Full thickness osteochondral defect.

Figure 2.2.3.: ICRS grading reproduced from Brittberg et al.



Modified ICRS grading. As a result of difficulties in the assessment of the subdivisions of the grades in the ICRS, Spahn et al [64] proposed a modified version of the grading system and demonstrated its validity and reliability against both infra read spectroscopy, MRI scan and arthroscopy. It is described below and a diagrammatic representation is given in figure 2.2.4 on the following page.

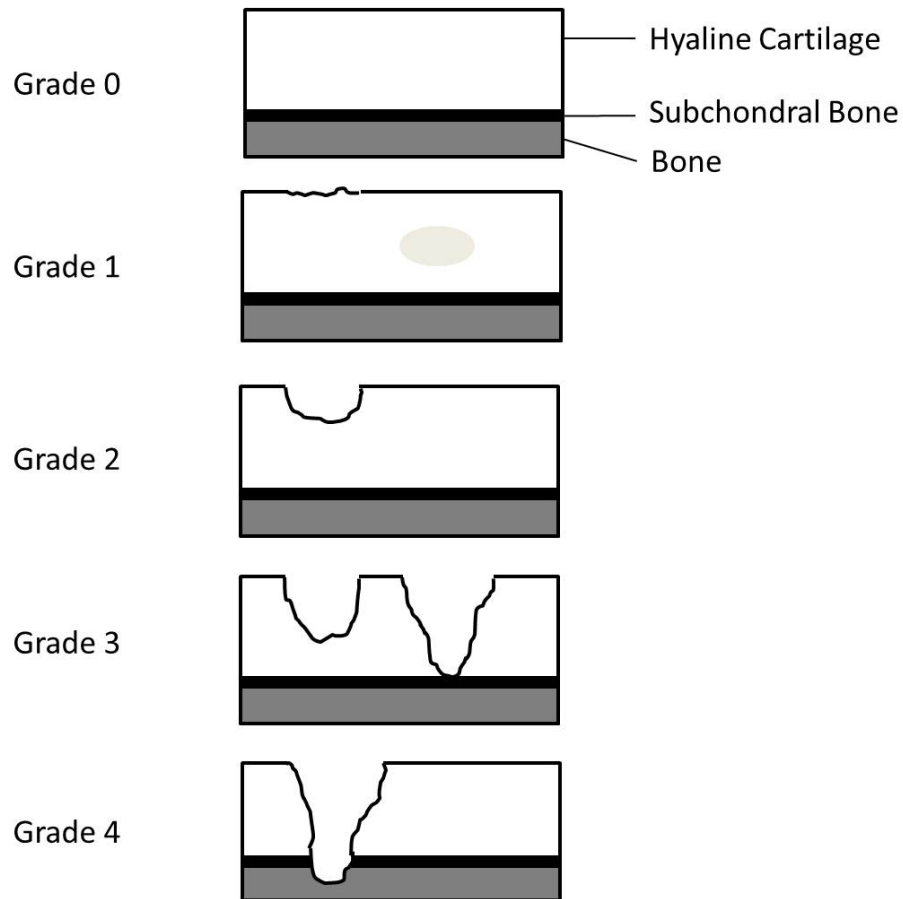
- Grade 0: Normal intact cartilage.
- Grade 1: Nearly normal. Focal signal intensity change +/- superficial fibrilla-

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tion.

- Grade 2: Abnormal. Lesions extending down to less than 50% of cartilage depth.
- Grade 3: Severely abnormal. Cartilage defects greater than 50% of total depth down to but not through subchondral bone.
- Grade 4: Severely abnormal. Full thickness cartilage loss with exposure of subchondral bone.

Figure 2.2.4.: Modified ICRS grading from Spahn et al.



Whole organ structural change - WORMS, BLOKS and MOAK.

WORMS. The Whole Organ MRI Score is a semi quantitative score that inspects the entire knee joint for changes associated with osteoarthritis. It was initially proposed and validated by Peterfy et al in 2004 [65]. In this system, fourteen specific independent articular features are analysed: cartilage signal and morphology, sub articular bone marrow abnormality, sub articular cysts, sub articular bone attrition, marginal osteophytes, medial and lateral meniscal integrity, anterior and posterior cruciate ligament integrity, medial and lateral collateral integrity, synovitis, loose bodies and periarticular cysts. Five of these features relate to the articular surface. The articular surfaces of the knee were therefore split into fifteen different regions.

1. The patella is separated into medial and lateral facet.
2. The femoral articular surface is divided into medial and lateral condyles with the trochlea groove considered part of the medial femoral condyle. The medial and lateral femoral regions are then split three regions.
 - a) Anterior, extending from the anterior-superior osteochondral junction to the anterior margin of the horn of the meniscus.
 - b) Central, extending from the anterior horn of the meniscus to the posterior capsular attachment of the posterior horn of the meniscus.
 - c) Posterior, extending from the postero horn of the meniscus to the posterior superior osteochondral junction.
3. The tibial plateau is also divided into medial and lateral, anterior, central and posterior portions.
4. The non articular portion of the tibial plateau beneath the spines is designated “Subspinous”.

Cartilage lesions are scored on an eight point system in this score.

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- 0 = normal thickness and signal.
- 1 = normal thickness but increased signal on T2 weighted images.
- 2.0 = partial thickness focal defect less than 1cm diameter.
- 2.5 = full thickness focal defect less than 1 cm in diameter.
- 3 = multiple areas of 2.0 defects or a 2.0 defect wider than 1cm but less than 75% of the entire region.
- 4 = Diffuse (>75%) partial thickness loss.
- 5 = multiple areas of 2.5 or a grade 2.5 greater than 1cm in diameter but less than 75% of the region.
- 6 = diffuse (>75% of the region) full thickness loss.

The maximum cartilage scores for the medial tibio femoral joint, lateral tibio femoral joint, patello femoral joint (ie the anterior portion of both femoral condyles and the medical and laterla facets of the patella) are 30, 30 and 24 respectively. The total for the entire knee cartilage surface is 84.

The Boston Leeds Osteoarthritis Knee Score (BLOKS). After identifying some limitations with WOMBS, particularly regarding the measurement of BML, the BLOKS score [66] was developed by members from the original WOMBS team. In this scoring system, there is increased focus on the role of Bone Marrow Lesions, and nine key features are scored: BML size, BML percentage area, percentage of lesion BML rather than cyst, Cartilage 1 (size and percentage loss of cartilage in full thickness lesions), Cartilage 2 (size and percentage loss at specified locations), Osteophytes, Synovitis, Effusion, Meniscal Extrusion, Meniscal Signal, Meniscus tear,

Ligaments and finally periarticular regions. Nine sub regions of cartilage are specified in this scoring system.

The WOMBS and BLOKS scoring systems are the commonest systems currently in use, and they both demonstrate good reliability and similar results in regard to prevalence and severity of cartilage loss. However, there are only two main studies that directly compare the two scoring systems and in neither study was either scoring system declared superior [67] [?].

Magnetic Resonance Imaging Osteoarthritis Knee Score (MOAKS). [68] This new semi quantitative image technique is currently being evaluated in the MeTeOR trial [69], and addresses concerns regarding both the WOMBS and BLOKS. In particular, changes have been made to the scoring of bone marrow lesions and the scoring of meniscal pathology. There is the addition of regional percentage change to the assessment of cartilage. However, due to the new nature of this scoring system it has not been validated yet for use in OA studies although it may well be the whole organ scoring system of choice in the future [47].

2.2.4.2. MRI description functional cartilage changes in knee OA - T2 mapping.

The T2 signal within hyaline cartilage reflects the interaction between water molecules and the surrounding macromolecules. It is highly sensitive to changes in the extracellular matrix. Increased interactions between water and macromolecules such as those of collagen lead to decreased T2 relaxation times. Thus T2 signal is sensitive to changes in hydration (indirectly reflected as collagen concentration) [70].

Whereas normal MR imaging allows subjective assessment of cartilage changes, quantitative T2 mapping provides objective data by generating a colour map representing the variations in relaxation times within cartilage. T2 mapping has been

shown to demonstrate sites of early stage degeneration (early disruption of the collagen matrix) in cartilage which appears as areas with higher T2 signal than normal cartilage. Compared with the T2 values mapped in normal hyaline cartilage, those found in osteoarthritic cartilage are more heterogeneous [55]. Although T2 maps can be used to differentiate normal areas of cartilage from areas of degeneration, there does not appear to be any linear relationship between T2 signal and osteoarthritis grade that could help differentiate mild from more advanced disease [71]. In addition, physical activity does seem to play an important role in T2 cartilage values, with recommendations that all weight bearing activity is ceased 30 minutes before quantitative T2 map acquisition is performed [72].

2.2.5. Arthroscopic assessment of hyaline cartilage lesions in knee osteoarthritis.

Damaged cartilage in osteoarthritis is a key finding in what is a multi-tissue disease that leads eventually to joint failure. Arthroscopy is considered by many to be the gold standard in the diagnosis and quantification of the severity of cartilage damage in knee OA [73]. It is an attractive proposition to surgeons as it allows a direct view of the lesion that is to be treated. However, problems with the method, such as its subjective nature, difficulties in visualisation of lesions due to surgical technique and its lack of suitability as a repeated assessment tool raises concerns over its use in the diagnosis of OA. In one survey of over 100 German surgeons, 52% stated they had difficulty in the differentiation between low-grade and high-grade cartilage lesions [74]. Oakley et al performed a cadaveric sheep study and concluded that only 36% of chondral surface was adequately assessed at arthroscopy and that significant pathological changes were missed, particularly in peripheral regions [75].

Multiple cartilage grading systems have been suggested [76, 77, 78, 79, 80, 81, 82,

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60]. They tend to specify the location, depth and size of the lesion as well as make a comment of the quality of the cartilage within the lesion itself. Two of the commonest, Outerbridge (See figure A.1.1 on page 276) and ICRS (see figure 2.2.3 on page 48) use a four point grading system and have been validated for their ability to assist in management decisions [83] [60]. The clinical benefit of arthroscopic grading systems for osteoarthritis is well established and lies in their ability to help guide focused management decisions. Individuals with advanced radiographic disease (Grade 3 or 4 lesions) with severe symptoms often require operative intervention whereas less advanced disease (Grade 1 or 2 lesions) will commonly be treated non-operatively depending on the patients symptoms. Furthermore, a difference of one grade (such as that between Grade 2 and Grade 3) can radically change an individuals' treatment protocol.

Interobserver reliability of cartilage lesions arthroscopically is generally held to be good. However, in a study of four surgeons in 19 patients assessing three grading systems (Collins, Outerbridge and FSA) intra and inter observer reliability were found to have kappa values of only 0.42-0.66 and 0.43-0.49 respectively. In particular, arthroscopy was felt to be inexact in the assessment of early cartilage lesions [84]. Similar findings were generated in later studies by Marx et al [85] and Lasmar et al [86].

Concern remains regarding the accuracy of arthroscopic assessment of cartilage lesions within the knee. To some extent, this reflects a recurring problem: there is no true "Gold Standard" in the assessment of cartilage lesions. In one study that used histopathology as the gold standard and compared it to arthroscopic assessment, Acebes et al [87] assessed 72 chondral lesions arthroscopically in patients prior to joint arthroplasty. The resected joint surfaces were then analysed histologically. They demonstrated moderate to good agreement (kappa 0.62 +/-0.1) with high agreement

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for lower grade scores. However, they stated that arthroscopy tended to overestimate chondral lesions for histological grades 3 and 4.

More commonly, MRI is compared directly to arthroscopic findings. Von Englehardt et al [62] compared the arthroscopic assessment of chondral lesions by two surgeons to 1.5T MRI assessment by a single observer. Whilst they observed that there was good inter observer agreement between the two surgeons, the intra observer agreement between MRI and arthroscopy was less good (Kappa 0.32-0.5). They concluded that diagnostic arthroscopy is essential for guiding treatment options in OA. A similar study by the same team concluded the same for 3T MRI [88]. In contrast to this, Bredella et al [89] compared MRI to arthroscopy in 130 knees and, using arthroscopy as the gold standard, determined that 64% of lesions were graded identically by both methods, with 90% being graded to within one grade. Similarly, Li et al [90] determined that MRI correlated accurately with arthroscopic assessment on 90% of occasions in their study of 138 knees. In a recent study of 16 patients using 3T MRI compared to arthroscopic assessment, the sensitivity, specificity, and accuracy of MRI were 54%, 92%, and 75%, respectively. Based on these findings, the authors concluded 3.0T MRI is as an invaluable noninvasive tool with good diagnostic value for assessing articular cartilage lesions of the knee, although it may not be as sensitive and accurate as previously reported [91].

In a comparison of 450 cartilage lesions assessed both arthroscopically and open during repair procedures, only 80% of lesions were assessed correctly on arthroscopy, with arthroscopic assessment consistently underestimating the true size of the lesion at open assessment [92].

Knee arthroscopy provides direct visualisation of intra-articular structures, particularly the meniscus, ACL, and articular cartilage surfaces, while not being as useful in the visualization of extra-articular structures such as the superficial medial collat-

eral ligament or lateral collateral ligament. Although MRI can certainly show both intra articular and extra-articular anatomy and pathology, it can be less useful than clinical examination in some patients such as those with ACL or posterior cruciate ligament (PCL) insufficiency [93]. Current questions over the use of arthroscopy as a diagnostic tool in the assessment of cartilage lesions remain. As MRI accuracy and resolution increases, it is likely to improve its cartilage assessment. Although arthroscopy remains thought of by many as the “Gold Standard” for the assessment of cartilage surfaces, this is not supported by the literature.

2.2.6. Risk factors for knee osteoarthritis.

Risk factors for the development of Knee OA can be considered as endogenous - innate to the individual and unchangeable, and exogenous - lifestyle factors and external influences that may increase the risk of developing the disease.

Obesity is one of the strongest and best established risk factors in knee OA [94] with an Odds Ratio for presence of disease of approximately 2.8 compared to those without obesity [95]. Women are known to have higher rates of knee OA than men, particularly after the age of 50 with female to male ratios varying between 1.5:1 and 4:1 [94]. As expected in a disease characterised by degenerative change across a number of tissues, the incidence of knee OA also increases with increasing age [96]. Family history and heredity play an important part in the risk of developing knee OA, demonstrated in twin studies and familial aggregation, as well as sibling risk studies. These are discussed in greater detail in section 2.4 on page 83.

Ethnic origin appears to have a role to play in the development of knee OA independent of cultural behaviours or activity levels. In the Beijing OA study, Chinese women were found to have a higher prevalence of radiographic knee OA (prevalence ratio 1.45, 95% CI: 1.31–1.60) and symptomatic knee OA (prevalence ratio 1.43, 95%

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CI: 1.16–1.75), compared to their western counterparts from the Framingham study [24].

Activity level is an important exogenous risk factor. Using data from the 1946 British Birth Cohort, Martin et al [97] analysed data from 2597 patients who were assessed for the presence of clinical knee OA at age 53. They demonstrated that men and women in manual occupations are more likely to develop knee OA, and that higher BMI is consistently associated with increased risk of developing knee OA. Men who, at ages over 40, are exposed to lifting and kneeling at work are again at increased risk of OA. These findings were replicated in a systematic review by Palmer [98] who confirmed the role of kneeling, squatting and lifting in increasing risk of developing knee OA. In an assessment of over 28000 individuals over the age of 50, leisure time activity level, in contrast, did not correlate with the development of end stage radiographic OA of the hip or knee over an 11 year period [99].

Knee injury is a strong risk factor for the development of knee OA. Acute injuries, such as meniscal injuries, cruciate ligament tears, fractures and dislocations, can result in an increased risk of OA development [94]. In addition to the direct damage of local tissues by the trauma, disruption of normal bio mechanics and altered load distribution within the joint also contribute to the subsequent increased OA risk. This risk is greater still if the subject has OA in another joint [96]. Mensical injury is discussed in more detail in section 2.2.6.1 on the following page.

The role of long leg alignment as a risk factor for the development of knee OA remains a subject of debate [100] [101]. Teichthal et al [102] performed a cross sectional x ray study in 121 adults with known knee OA and demonstrated that increasing varus knee alignment was associated with increasing risk of medial compartment joint space narrowing. However, data from the Framingham Study, comparing 110 incident OA knees to 356 control knees suggested that there is no difference in long leg alignment

between those with who develop knee OA and controls [103]. In a large study of 2664 knees from the Rotterdam Longitudinal Study over 6.6 years, an increasing degree of varus alignment at baseline was associated with not only the progression of OA over that time period but also with the development of knee OA [104].

Despite some cross sectional studies suggesting a link, there is little high quality evidence for the protective or risk role of alcohol and cigarette exposure in developing knee OA.

2.2.6.1. The meniscus and its role in the development of knee osteoarthritis.

The role of the meniscus (the anatomy of which is described in section 2.1.2.4) in the pathogenesis of osteoarthritis of the knee has been debated for some time. Loss of mensical function, whether due to trauma, degeneration or iatrogenic causes increases peak stresses and contact pressures at the articular surface by up to nine times their physiological normal [105]. Similar biomechanical studies demonstrated that the greater the loss of meniscal volume, the greater the increase in articular contact pressures [106] .

In human studies, meniscectomy [107] has been demonstrated to lead to increased rates of cartilage volume loss compared to controls (6.9% greater loss per year). Meniscal tears and damage in those with existing OA of the knee has been demonstrated to lead to increased cartilage loss over two years compared to those without [108] [109]. Other retrospective studies of knees with previously normal cartilage surfaces followed for the development of OA over time [110] [111] have established correlation between a history of meniscal injury and the development of OA. What is not clear from these studies, which tend to be small and retrospective, is whether the underlying injury that leads to the meniscal damage played a role in the development of the OA, or whether it is the loss of mensical function itself that leads to the disease. A key step in this debate was the demonstration that defunctioning the me-

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dial meniscus leads to the development of medial compartment OA in animal models [112]. In this study on ten mice, lesions reliably developed on the central weight bearing portions of the medial tibial plateau and the medial femoral condyle at 4 weeks post surgery. Subsequent prospective studies in larger groups of patients with no history of OA who undergo medial meniscectomy have confirmed these findings in humans [113] [114].

The development of cartilage degeneration and osteoarthritis following trauma or resective surgery to the medial meniscus is a well established phenomenon. However, the majority of cases of knee OA are idiopathic and degenerative with no history of trauma to the meniscus or intra articular surgery. Meniscal extrusion (subluxation) was first described as part of a case report into a multi ligamentous knee injury [115]. The link between joint space narrowing and meniscal extrusion in symptomatic knee OA was first explored by Gale et al [116] who performed a cross sectional observational study on 233 cases and 58 controls. They demonstrated that meniscal subluxation was strongly associated with symptomatic knee OA and suggested joint space narrowing was secondary to extrusion, not hyaline cartilage loss. There was no longitudinal follow up. They postulated that, upon extrusion, the meniscus fails to perform its primary function of distributing loads across the hyaline cartilage leading to increased contact pressures and therefore cartilage degeneration. These findings were replicated in a later study by the same team [54]. Stehling et al demonstrated the presence of meniscal extrusion was greater under loading in those with mildly to moderate degenerative medial compartments than in those without [117]. Again, the cross sectional nature of this study meant that they were unable to determine whether extrusion of the meniscus preceded the development of knee OA.

In a study of 31 knees resected prior to arthroplasty for severe OA, the meniscus was found to be extruded but intact in 84% of cases suggesting that the meniscus had

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extruded prior to the development of OA and degeneration of the medial compartment [118]. Lerer et al [119] demonstrated that 77% of those with degenerative medial compartments had mensical extrusion. In contrast, Puig et al. [120] found that meniscal extrusion was present in nearly 68% of all knees without the presence of knee OA in a cohort of patients who had no history of surgery to the menisci. In a cross sectional analysis of 40 knees of young athletes with no evidence of hyaline cartilage degeneration, 48% of knees demonstrated meniscal extrusion [?]. In a cross sectional study of 1527 subjects from the MOST cohort, Crema et al [121] demonstrated that both cartilage damage and knee malalignment were associated with the presence of meniscal extrusion, however, due to their study design they were unable to determine whether extrusion preceded or followed the cartilage damage. Similarly, in a cross sectional study of those with and without radiological evidence of knee OA, meniscal extrusion and decreased tibial coverage was found to be greater in those with OA [122]. We presently know little about the risk factors for degenerate mensical tears, the natural history of intra substance alteration; and the timing of meniscal damage (and consequentially extrusion) with regards to OA development [123]. What is unclear is whether degenerative extrusion of the meniscus leads to the development of knee OA or vice versa.

2.2.7. Symptoms of knee osteoarthritis.

Pain in knee arthritis is a well recognised symptom and in the majority of cases is the main indication for referral for arthroplasty or operative intervention [124] [125]. Typically of a dull or aching nature, the pain starts on initiation of movement and on activity. As the severity of the disease progresses, the frequency of the pain increases until it becomes continuous, often affecting sleep at night. Chronic OA joint pain is debilitating and influences patients functional and social activities as well as having

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effects on relationships and emotional well being[126].

In addition, patients will often complain of stiffness, limitations in range of movement and impairment in everyday activities. Other symptoms, such as crepitus and an increased sensitivity to cold or damp can also occur [40].

Despite the importance of pain in the OA experience, little attention has been paid in research terms to the nature of the pain and the variation in pain that individuals experience. In a study of 143 individuals with knee or hip OA confirmed on radiographs, Hawker et al [127] identified two types of pain, a persistent background aching pain, in addition to intermittent severe and intense pain that were clearly distinguishable by patients. The more intense but less frequent pain seemed to affect patients quality of life to a greater extent than the background pain. However, this study focused on individuals with more advanced disease and they were unable to comment on those patients with early OA. Whilst pain related to knee OA is generally considered chronic it is known to fluctuate [23]. Clinically, physicians often notice that patients with OA experience episodes of recurrent pain or pain exacerbations over the course of the disease [24]. Despite the importance of pain in OA, relatively little research has been done to better understand the determinants and potential consequences of different patterns of knee pain.

Gooberman-Hill et al [128], in a study of only 28 patients that required retrospective recall of joint pain, reported that joint pain among subjects with knee or hip OA is often intermittent and variable, and adaptation and avoidance strategies modify the experience of pain. As a result of methodological and logistical difficulties, however, few studies have been conducted to examine the dynamic relationship between risk factors and pain fluctuation. Paradowski et al [129] looked at patients 14 years post meniscectomy with and without radiographic changes of OA. Between the two groups there were no statistical differences between mean group scores over two

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years. However, within the groups, individuals scores for function and quality of life varied markedly over the two year period. They reported that one in three patients, irrespective of radiographic status, experienced a clinically relevant change in pain and function. In a second study by the same group looking at the same patients [130], they concluded that symptomatic, overweight and middle aged patients were most likely to experience variation in their symptoms over the time period.

In a study that attempted to identify how pain changes monthly in patients with knee OA, Neogi et al [23] looked at the prevalence of, and factors associated with, consistency of knee pain. They used questionnaire analysis of 2940 patients, and asked the nature of their pain on two occasions, one month apart. They demonstrated that patients with depressive symptoms and radiographic OA of KL2 or more were more likely to have constant pain than inconsistent pain. Those with inconsistent pain had less overall pain, improved function and improved strength compared to those with constant pain. In another study, Dieppe et al [131] using the Bristol OA 500, examined patients with established knee OA at two time points three years apart. Again, although the group means for pain and function varied little over the time period, within individuals it varied greatly, with some worsening, some staying the same and others deteriorating. A multivariate regression analysis did not allow prediction of the clinical outcome from any of the baseline figures they collected.

The LEAP study [132] utilized weekly telephone interviews over 12 weeks to assess the impact of fluctuations in knee or hip pain but did not stratify patients by OA severity. Fluctuations were frequent, observed in about 49% of individuals, and decreases in pain were associated with improved function, decreased work absenteeism, sleep disruption, and health care resource use.

A comprehensive understanding of temporal changes in knee pain and symptoms related to early knee OA, as opposed to established OA, is needed to understand

the pathophysiology of disease and impact of the disease. In addition, pain fluctuations may have impact for trial enrollment as treatment effects may be difficult to determine. In addition, there is evidence to suggest that frequency of knee pain is associated with an increased risk of joint replacement surgery over a 30 month period, independent of the severity of pain [133]. High quality longitudinal research is needed into knee pain and functioning to strengthen the evidence for changes in symptoms experienced over time [134].

2.2.8. Knee symptoms and correlation with radiographic findings.

Clinicians are known to use radiographs of the knee to aid in management decisions, in particular in consideration of arthroplasty [135]. This means that understanding the relationship between radiological findings and clinical symptoms is extremely important.

Substantial discord can exist between radiographic findings and reported levels of knee pain. It is estimated that 40% of individuals with knee OA on radiographs and MRI scan have no pain [136]. Many studies suggest no link between the severity of X ray changes clinical symptoms experienced by patients [137], [23]. Similar findings have been demonstrated with MRI [56],[138]. In a recent cross sectional study of 5000 patients from the Rotterdam study, Schiphof et al [139] demonstrated that although patients with all grades of radiographic OA had a range of symptoms, those with lower radiographic grade OA were less likely to report constant pain. In addition, increasing age was found to be protective for the extent of pain experienced from the knee, independent of severity of disease. This suggests that the perception of pain in OA knee is influenced by factors other than the degree of osteoarthritic joint damage and is likely to be multifactorial. As cartilage is aneural, structures such as the bone, synovium and soft tissue may be candidates as pain producers or

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mediators of pain within the joint.[140] In addition, central pain processing [141] and psychological elements such as depression and anxiety also play a key role in pain processing by individuals [142], with depression predicting a greater variation in day to day symptoms over time than anxiety [143].

Some of the radiographic symptom discordance in knee OA may in part be related to the fluctuating nature of knee pain, with studies in which knee pain is only assessed at one time point possibly misclassifying individuals with respect to their pain status. In a study of 2,210 patients that explored the relationship of a change in radiographic OA to the development of functional impairment within the same knee, White et al [144] demonstrated that the development of radiographic OA over 30 months lead to a 2 times higher incidence of severe functional impairment than in those who did not develop radiographic changes. In patients with known knee OA with radiographs that worsened over 30 months, there was a 2.8 times higher risk of developing severe functional impairment than in those with stable radiographic signs of OA. This potentially suggests that change in radiographic status over time rather than the severity of the changes themselves is a key factor.

Reasons for the discrepancy between changes and symptoms are likely to be multifactorial. Firstly, the way in which radiographic OA is defined will affect the number of cases being labeled as having the disease or not. Secondly, clinical symptoms may arise from structures other than the cartilage and subchondral bone, hence the way in which the clinical syndrome of OA is diagnosed radiologically will influence the link to radiographic changes [145]. Others have hypothesized that the inconsistency in the detection of an association might be caused by different definitions of OA, by different radiographic protocols, and by scoring methods for radiographic damage and symptoms [146].

Irrespective of the reasons for the discrepancies, if OA is to be considered as a

syndrome of pain and structural changes, clarity on definitions of the disease as well as a longitudinal consideration of symptoms does appear important.

2.2.9. The use of Patient Reported Outcome Measures

(PROMs) in assessing symptoms in knee osteoarthritis.

It is widely accepted that clinical trials and other evaluative studies should incorporate patients view about outcome and their symptoms [147]. This has lead to the development of a considerable number of questionnaires and instruments that are designed to measure health status, and health outcomes from the perspective of the patient [148]. There is consensus that patient-reported outcomes have additional value compared to clinical variables when evaluating patient health. The underlying principle is that pain, functional status and quality of life (QoL) can be better described by the patients themselves than by orthopedic surgeons [149]. In the past 20 years, there has been considerable growth in the number of knee instruments and rating scales designed to measure outcomes from the perspective of the patient. Only a few of these instruments have been evaluated for reliability, validity, and responsiveness. No instrument is currently universally applicable across the spectrum of knee disorders and patient groups. Clinicians and researchers looking to use a patient-based score for measurement of outcomes must consider the specific patient population in which it has been evaluated. In assessing the use of these tools, some novel terms are used. These are considered here and are taken from the website of the Patient Reported Outcomes Measurement Group at Oxford University [150].

- **Appropriateness** refers to the extent to which the tool content is appropriate to its particular application. PROMs must be used to measure the outcome they were designed to.
- **Acceptability** is the extent to which the instrument is acceptable to the pa-

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tients. Factors associated with acceptability include administration time, response rates and the level of missing data. In addition, features such as layout, language, appearance and legibility are also important.

- **Feasibility** relates to the ease of administration and processing of an instrument. Instruments that are difficult to administer and process may jeopardise the conduct of research.
- **Interpretability** refers to the meaningfulness of the score produced by the instrument. Within this definition, terms such as the Meaningfully Clinical Important Difference (MCID) i.e. the smallest change that is perceived to be beneficial by patients, become important.
- **Precision** relates to the number and accuracy of distinctions made by an instrument. There are a number of aspects to the issue of precision, which relate to methods of scaling and scoring items, and the distribution of items over the range of the construct being measured. The scaling of items within instruments has important implications for precision. The binary or 'yes' or 'no' is the simplest form of response category but it does not allow respondents to report degrees of difficulty or severity. The majority of instruments use Likert type scales such as: strongly agree, agree, uncertain, disagree, strongly disagree. Visual analogue scales appear to offer greater precision but there is insufficient evidence to support this and they may be less acceptable to respondents.
- **Reliability** concerns whether an instrument is internally consistent or reproducible. It also assesses the extent to which an instrument is free from measurement error. As the measurement error of an instrument increases, so does the sample size required to obtain precise estimates of the effects of an intervention.
- **Validity** is the extent to which an instrument measures what is intended. Va-

lidity can be assessed qualitatively through an examination of instrument content, and quantitatively through factor analysis and comparisons with related variables such as recent work that has been done on the Oxford Knee Score [151].

- **Responsiveness** refers to the measurement of important changes in health. Responsiveness is assessed by examining changes in instrument scores for groups of patients whose health is known to have changed. This may follow an intervention of known efficacy. Alternatively, patients may be asked how their current health compares to some previous point in time by means of a health transition question.

Commonly used measures of knee pain and function, the Oxford Knee Score (OKS), Knee Injury and Osteoarthritis Outcome Score (KOOS), Intermittent Constant Pain Score and Pain VAS are considered here for use later in this thesis.

2.2.9.1. The Oxford Knee Score.

The OKS is a short, 12 item questionnaire with 5 point score of 0-4 per item that was originally designed for patients undergoing total knee replacement (TKR). It attempts to reflect the patients assessment of their assessment of knee related health status and benefits of arthroplasty [152]. It is a patient completed questionnaire that uses a 4 week recall period for items. Scoring is simple and quick and takes approximately 5 minutes [153]. It has good patient acceptability, reliability, and face and content validity [154]. Although the OKS demonstrates good sensitivity and responsiveness to change no minimal clinically important difference (MCID) has been reported [153]. Recent work from the Nuffield Orthopaedic Centre suggests that it is valid for measuring long terms outcomes in early knee arthritis [155].

2.2.9.2. Knee Injury and Osteoarthritis Outcome Score.

KOOS [156] is a self reported outcome score that is used to measure patients opinion about their knee and associated problems over short and long term follow up. It is intended for young and middle aged patients with post traumatic arthritis as well as those with ligament and associated intra articular damage that may predispose to OA. It has five sub scales: Pain (frequency and severity) , Symptoms (stiffness, swelling, clicking and crepitus), Activities of Daily Living, Sport and recreation, and Knee related Quality of Life. There are 42 questions across the five sub scales, and answers are given on a 0-4 Likert scale. Scores are then totaled and transformed to a score out of 100 with 0 representing extreme problems and 100 representing no problems. It takes approximately 10 minutes to complete and is felt to have satisfactory acceptability and reliability with good face and construct validity [153]. Problems with the score include the use of a sports component in older patients, however, omitting this component limits the ability to detect changes in the more demanding activities following treatments. There is no known MCID reported.

2.2.9.3. Intermittent and Constant Osteoarthritis Pain Score.

ICOAP is a multidimensional OA specific tool designed to evaluate pain in people with hip or knee OA, including pain intensity, frequency, and impact on mood, sleep, and quality of life, independent of the effect of pain on physical function [127] . It is an 11 item scale that assesses two pain domains: a five item scale for constant pain and a six item scale for intermittent pain. All questions are constructed as Likert rating scales with 5 levels of response from 0-4. Sub scale and total scores are created by adding the totals and normalising to 100, with 0 representing no pain and 100 representing severe pain. It is felt to be very acceptable to patients with good content and face validity. In addition it has excellent reliability [157]. Although

no formal MCID has been reported, this score is unique in that it evaluates the multidimensional pain experience in OA.

2.2.9.4. Pain Visual Analogue Scale.

The Pain VAS is a self reported, uni dimensional measure of pain intensity that has been used in a wide variety of clinical settings [158]. It is a continuous scale comprised of a horizontal line 100mm long, anchored by 0 as “no pain” and 10 as “worst pain imaginable”. The following cut points have been recommended: No pain (0-4 mm), mild pain (5-44mm), moderate pain (45-74 mm) and severe pain (75mm and greater). It requires little training to administer and its acceptability is best amongst patients without cognitive difficulties. It is felt to have good construct validity, reliability up to 4 weeks in chronic pain and has also been demonstrated to be reliable [159]. Although there is no MCID for the Pain VAS in knee arthritis, in Rheumatoid Arthritis it is felt to be 11mm [160].

2.2.10. Patterns of knee arthritis and the importance of Antero Medial Osteoarthritis (AMOA).

Epidemiological studies show that knee osteoarthritis is not one uniform disease but rather affects the individual compartments of the knee joint; medial tibio femoral, lateral tibio femoral and patello femoral, to varying degrees [161]. In a study that looked at all knees referred to the knee clinic at the Nuffield Orthopaedic Centre, Bottomley et al. determined that the predominant pattern of disease was medial (62-70%), followed by bicondylar (19-27%), lateral (8-9%) and then isolated patellofemoral (2-3%) [5].

AMOA, also known as Antero Medial Gonarthrosis (AMG), is a distinct phenotype of knee osteoarthritis formally described in 1991 [?]. In this specific disease, the

articular cartilage in the medial compartment experiences degeneration, the lateral compartment remains unaffected and the anterior cruciate ligament remains intact. The arthritic lesion is located on the anteromedial quadrant of the tibio femoral joint. The cartilage erosion within the medial compartment begins in the anterior third of the tibial plateau leading to full thickness cartilage loss. At the posterior third of the medial tibio femoral joint, there is preservation of cartilage, and this region has been described as being macroscopically normal [?]. Between these regions there is partial thickness cartilage loss. When established AMOA is present, the use of unicompartmental knee replacement is an effective treatment option [162].

2.3. Early knee osteoarthritis.

Knee OA is a spectrum of disease with the end stage of structural change described as “bone on bone” arthritis. Recognising the disease as a spectrum, there has been an increasing interest in the earlier stages of disease as clinicians and scientists attempt to identify those who are at risk of developing the disease and prevent them from developing it, or prevent the progression of those with established earlier stage OA.

Many publications refer to “Early knee arthritis” in their title and methods. Variability remains in the description of how this diagnosis is obtained particularly with reference to MRI magnet strength and sequencing information used to report structural changes. Peat et al [57], performed a prospective study of adults aged over 50 with knee pain and no structural X ray changes at baseline and a control group without pain or X ray changes. At three years, X rays were repeated and those with pain at baseline had developed X ray changes in approximately 40% of cases. They noted that the false positive clinical diagnosis of knee OA probably represents a failure of the imaging modality to detect structural change. Therefore, as the accuracy of our imaging increases, so the accuracy of diagnosis will increase. Quatman

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et al [163] defined early osteoarthritis as the presence of articular lesions of Noyes arthroscopic grade 1, 2 and 2A in their systemic review of the correlation between MRI and arthroscopic assessment of the joint. In 2010 Javaid et al [56] performed a retrospective case control study using data from the MOST study. They identified a cohort of individuals without X ray changes who go on to develop knee symptoms over 15 months and compared them to a cohort with the same radiographic status but no knee symptoms. They identified significant cartilage, bone marrow lesions and osteophyte MRI changes in the pain group and determined that this group were “Pre OA”. No attempt was made to define those with “Early OA”. In a study of 174 patients over the age of 45 with no X ray changes of OA but painful medial compartments, Andro et al [164] determined that up to 38% of individuals had cartilage lesions and 41% had extruded menisci on 3T MRI. The biological aspects of early OA are addressed by Madry et al [165] in a comprehensive review. They define early OA based on histopathological findings and the depth of the hyaline cartilage lesions, irrespective of their horizontal extent. Any cartilage lesion including fibrillation and vertical fissures to the mid zone of the cartilage are included as Early OA, but delamination and excavation are excluded and count as Advanced OA irrespective of symptoms. In a review of the potential conservative measures available for knee OA, Kon et al [166] define early OA as “OA with no clear lesions or associated abnormalities requiring to be addressed surgically”. They do not confirm under what circumstances surgical treatment might be an option, but importantly it appears for this definition, the use of surgery would exclude a diagnosis of early knee arthritis.

The Check (Cohort Hip, Cohort Knee) study from the Netherlands is one of the few studies that refers to symptomatic early knee OA. In this prospective study of 1002 patients over 10 years, early knee OA is defined as pain or stiffness in the knee not severe enough to require a consultation with a clinician in addition to KL grade of 0-

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2. No MRI scan is required to assess the severity of cartilage lesions. This definition is used again in a later study published from this cohort [167]. In a randomised, double blinded control trial of Pulsed electromagnetic frequency treatment in early OA, Nelson et al [168] describe early knee OA as Pain VAS >4, knee pain for 3 months, and imaging studies that confirm articular cartilage loss. No description of the imaging modality used is described. No description if the severity of the cartilage lesions is made.

The only current attempt to formally classify and define early knee arthritis is that of Luyten et al [169]. They state that the diagnosis of early knee OA can be made based on clinical and imaging findings and that individuals should fulfill the following three criteria

- Pain in the knee.
- Standard radiographs Kellgren–Lawrence grade 0 or I or II (osteophytes only).
- At least one of the two following structural criteria
 - Arthroscopic findings of cartilage lesions.
 - MRI findings demonstrating articular cartilage degeneration and/or meniscal degeneration, and/or subchondral BML

Definitions of early knee OA remain variable. Classifications depending on clinical symptoms, X ray changes, MRI findings and histopathology all exist, but their remains a wide variation despite a use of the same term “Early OA”. This variation in terminology may account for some of the variation in outcomes seen in treatments offered for the condition. A comparison of treatment methods is possible only if both the symptoms and the structural changes of patients in each treatment group are comparable.

Recently there has been increased attention paid to this problem [170] . However, until a universally accepted definition of the condition exists, comparison of treatment strategies and outcomes will remain impossible.

2.3.1. Treatment strategies for early knee osteoarthritis.

The National Institute for Health and Care Excellence (NICE) guidelines on arthritis care emphasise a holistic approach to care, and encourage shared decision making. Their guidelines are based on non pharmacological, pharmacological and surgical interventions [?]. Because no single therapy is adequate in OA, most clinical guidelines for the disease agree that multi modal therapy is needed to optimise symptom control [171]. Importantly, there are no guidelines that focus on early OA management. As a result, this section of the literature review will highlight recent updates in treatment in light of early stages of knee OA.

2.3.1.1. Conservative - non pharmacological.

Conservative management of knee osteoarthritis is based upon a stepwise scheme allowing a combination of treatments to be used simultaneously.

Physical therapy. Physiotherapy is known to have limited efficacy in patients following knee arthroplasty [172] and evidence for the use of physiotherapy specifically in the treatment of early disease remains sparse [166]. Fransen et al [9] demonstrated that patients treated with either group or individualized physiotherapy regimes can experience relief of pain and functional improvement compared to those with no physiotherapy at all over an eight week period. This study did not stratify by disease severity nor did it provide long term follow up of pain scores. Devos-Somby et al, in a meta analysis of 17 studies, concluded that compared to controls, exercise regimes led to improvement in physical health (by self-report and direct measures) and in overall

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impact of OA. Perceived psychological health remained unchanged by the exercise programs [7]. McKnight et al [173] did report of the effect of a comparison of quadriceps strengthening and patient self management in 200 patients with Kellgren and Lawrence scores of 2 in patients aged between 35 and 60 and demonstrated improvement in pain and ADL that persisted over a 24 month period. In contrast to this, in a review of the role of aerobic activity in the prevention and symptom control of OA, Semanik et al [174] concluded that most trials focused on short-term interventions (6 months or less) and that improvements in pain relief and functional status attained during those aerobic interventions rarely lasted beyond 6 months as compliance with activity levels dropped off. The limited number of long-term trials were made difficult to analyse as they were affected by poor post intervention maintenance of treatment effects. Although little research has been performed into the role of physiotherapy in the treatment of early disease, a recent trial has been registered which promises to answer this question when it reports in 2014 [175].

Bracing. There are studies that have demonstrated bracing to be effective in the relief of pain from knee OA [8]. Bracing aims to reduce the biomechanical load in the affected compartment of the knee (corrective bracing), or improve symptoms by relieving what is often perceived as biomechanical instability (accommodation bracing) [176]. Although some studies report it to be effective, bracing is generally poorly tolerated by patients due to discomfort or skin complications such as blistering. There is some evidence that long term compliance with bracing for orthopaedic conditions is poor [177]. Although results for established OA are well reported, those with early OA are not well documented and no high quality studies have been found where long term outcomes are stratified by radiographic or structural severity of disease [178] [179].

Foot Orthoses/Apos therapy. An alternative to bracing, in that it aims to non-invasively alter the bio mechanics of the knee, Apos therapy has gained wide interest recently due to a prominent presence at many Orthopaedic academic meetings. El-baz et al [180] initially reported on this treatment in 2010, where the patient wears a corrective shoe for 30 minutes per day. In a comparative study to those receiving traditional early OA treatment published in 2013, Bar-Ziv et al demonstrated improved PROM outcomes in those undergoing the treatment although not change in radiographic outcomes. They stratified their patients by disease severity and concluded the best results occurred in KL2, however, the entire treatment group consisted of only 40 patients and the control group 16, meaning that subset analyses of these groups was limited by low numbers [181]. This promises to be an interesting treatment in the future, although its role in the long term management of early knee OA is yet to be determined.

Weight loss. The medical benefits of weight loss for obese patients are clear. Whilst it appears intuitive that weight loss should assist in relieving the symptoms of knee OA, the evidence for this amongst those patients without significant obesity is mixed [177] and tends not to be stratified by severity of disease [182]. In studies of those with OA undergoing bariatric surgery, post surgery OA WOMAC pain scores can be reduced by up to 51% at six weeks [183]. Importantly, these findings are independent of physical activity or muscle strength and demonstrate that knee pain relief can be achieved through weight loss alone in the severely obese. Again, these studies in those with established knee OA and high quality studies in those with early knee OA have not been performed.

2.3.1.2. Conservative - pharmacological.

Simple analgesics. There are numerous pharmaceutical agents, but physicians have to be aware of their efficacy, advantages, and adverse effects, in order to choose the most suitable one for each patient. Paracetamol is the first choice of oral analgesic and should be taken long term if useful to the patient. The main mechanism of action is the inhibition of enzyme cyclo oxygenase (COX). Non steroidal anti-inflammatory drugs (NSAIDs) are the most widely used oral therapy in treating the symptoms of OA. It is recommended that NSAIDs be administered to patients who do not get adequate pain relief with paracetamol. It has been recommended that NSAIDs can be administered topically as well as orally[6]. Some evidence is emerging that long term NSAID use can have a negative impact on cartilaginous tissue [166]. In addition, the gastrointestinal, renal and cardiac side effects of NSAIDs mean they should not be considered a definitive, long term treatment for OA, regardless of the severity of the disease [177]. Oral analgesics should be considered as part of an overall treatment plan in symptom control in early OA.

Slow acting drugs for early OA. Slow-acting drugs for OA (SADOA) are pharmacological treatment options that can be used for early OA, aiming to slowing the early stages of degeneration progression. Glucosamine is a precursor for glycosaminoglycans and is administered orally. Although industry sponsored studies have shown that glucosamine leads to an improvement in patient symptoms compared to placebo in those with early OA, a Cochrane review has concluded that there is minimal evidence for its efficacy compared to placebo. This has been confirmed by a large, multicentre randomised study that demonstrated neither an improvement in radiographic findings nor a clinically relevant improvement in pain and function following two years of treatment in those with KL 2 and 3 [184]. In contrast, a later meta analysis by Lee et al [185], demonstrated that at three years there was a small 0.25

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mm improvement in joint space narrowing in patients with osteoarthritis of KL2 or less. The clinical significance of this change in joint space remains unclear, particularly given the number of structures involved in the process of joint space narrowing. Glucosamine has not been recommended by NICE.

Chondroitin Sulphate (CS) belongs to the glycosaminoglycan group and is a major component of articular cartilage. Thoughts regarding its potential efficacy in knee OA revolve around its potential anti inflammatory activity in addition to a potential to stimulate proteoglycan and Hyaluronic acid synthesis. Multiple controlled trials since the 1980s have examined the use of oral CS in patients with symptomatic OA of the knee, but the benefits in terms of reduction of pain, improvement of functional disability and decrease in NSAID consumption is still controversial [186]. In addition, studies tend not to stratify arthritis based on their radiographic grade. In a well designed study on those with symptomatic knee OA (although stratified only on their medial joint space width and not by their radiographic grade) Kahan et al [187] demonstrated that over 2 years, those treated with Chondroitin demonstrated less pain (although only a VAS change of 6 points, and not on WOMAC scores) and a less rapid loss of joint space width than those treated with placebo. The role of chondroitin, in combination with glucosamine, will continue to stimulate debate. Their low side effect profile and studies that demonstrate it can reduce pain in symptomatic knee OA [188] mean that its use in an attempt to halt progression of knee OA is reasonable. Clearly, however, they are not the “silver bullet” that those who propose their use had hoped they would be.

Intra articular injections. Intra articular corticosteroid injections are widely used to manage OA pain in those with established disease who are reluctant to consider operative intervention. The use of corticosteroid is known to produce less pain and improved function compared to placebo. However, these results last only out to 4

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weeks and has been demonstrated in a Cochrane review on the topic [189]. The use of intra articular steroids in those with early disease, however, remains controversial due to the well described cytotoxic effect on cartilage in both in vitro and ex vivo studies [190] [191]. Consequently, they are rarely used in early disease patients despite the fact that no clinical studies specifically address OA progression after corticosteroid injection [166].

Hyaluronic acid (HA) is a glycosaminoglycan that provides joint lubrication and shock absorbency and forms an essential component of the proteoglycans of the extracellular matrix. Multiple commercially available versions of HA exist, however clinical trials do not indicate one preparation to be superior to another. A Cochrane review by Bellamy et al [189] looked at 76 trials of HA versus placebo, steroids or NSAIDS and determined that HA improved pain, function and global assessment at 5 to 13 weeks post injection suggesting a longer lasting effect than corticosteroids. However, Lundsgaards et al [192] in a study where 250 patients were randomized to HA or saline placebo and followed for six months, demonstrated no difference between the two groups in terms of pain or function. Baltzar et al [193] demonstrated similar findings in a three group trial that also looked at autologous serum injections. Consequently, the American Academy of Orthopaedic Surgeons do not recommend for or against the use of HA in osteoarthritis [194]. As yet, no high level studies have been completed on the effect of HA in early radiographic knee OA [170]. Intraarticular Hyaluronic acid administration is not recommended by NICE.

2.3.1.3. Joint preserving surgery: Extra articular and intra articular.

High Tibial Osteotomy. High Tibial Osteotomy (HTO) has been considered as a treatment option for medial knee OA for many years. Originally described by Jackson in 1961 [195], it gained increasing popularity following extensive work by Coventry [196, 197, 198]. HTO changes the mechanical axis of the lower limb by realigning the

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proximal tibia, thus altering the load distribution from the pathological to the normal compartment [199]. Recent improvements in plate technology have led to a renewed interest in the procedure, with opening wedge HTO performed more commonly than closing wedge HTO [22].

HTO is usually undertaken for “young” patients with established radiographic knee OA and severe symptoms in whom concerns regarding the activity levels and longevity have cautioned against the use of arthroplasty. The results of HTO in these patients remain clinically unpredictable and are known to deteriorate over time [200]. Hernigou et al [201] describe only a 45% 10 year excellent outcome in 93 knees and determined that those with LLMA of 186 to 186 experienced the least progression over that time. Yasuda et al in contrast describe a 63 % survivor ship at 10 years and determined that the optimal post-operative correction position in terms of improved clinical results was LLMA of 190 to 194 degrees [202]. In a meta analysis of outcomes of HTO over a 28 year period [203], HTO had a good to excellent result in 75.3% of patients after 60 months, and 60.3% after 100 months. The overall failure rate is described as 24.6% at 10 years. Reasons for these long term results included poor patient selection, inadequate internal fixation techniques and inaccuracy of alignment correction.

In those with early OA knee, less extensive studies have been performed. In a small study of patients younger than 25 with constitutional varus, Masrouda et al [204] report significant improvements in pain, but not function at three years. Radiographic findings pre and post op were not described and there was no long term follow up. In a 10 year study of HTO results in patients under the age of 50 [205], 70 per cent (thirty-six knees) were rated as good or excellent and 30 per cent (fifteen knees) were rated as fair or poor. There was no clear correlation between the quality of the result and the radiographic evidence of the severity of the arthritis preoperatively, the age

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of the patient at osteotomy, or the length of follow-up. The main indicator of good outcome was a good preoperative knee score. Similarly, Odenbring et al [206], in a small study of described an 11 year follow up of 28 patients under the age of 50 with a variety of radiographic grades of OA. In no cases had the radiographic grade progressed. However, only 22% of patients described themselves as satisfactory. In a long term follow up study of 50 patients [207], the radiographic OA grade of the knee joint significantly deteriorated at the mean follow-up of 17 years, but no statistical difference was observed regarding the preoperative severity of the radiographic knee OA between the satisfactory and the unsatisfactory group. The percentage of patients unhappy at 10 years was approximately 20%, similar to the number reported by Berman et al, who again declared that younger patients performed better than those greater than 50, but did not stratify outcome by radiographic severity [208]. Results in HTO appear to be variable, irrespective of pre operative radiographic status. Good quality studies on patient with early radiographic disease are not common. Reasons for variability are not clear, although accuracy of operative correction and timing of intervention are both likely to play a part.

Kine Spring. The Kine spring is an extra articular, extra capsular, subcutaneous surgical device that acts to reduce the loading across the medial compartment by up to 18 kg at full extension of the knee (therefore at the moment of heel strike) supposedly without increasing stresses across the medial compartment [209]. It does so by the use of a medial sided spring that acts across the joint with the use of two ball and socket joints. This device does not compromise the joint, theoretically meaning that removal or further non arthroplasty or arthroplasty procedures are easy to perform. Midterm results at 17 months of 99 patients indicate a mean decrease of approximately 24 points on the WOMAC pain score [210]. These results were better in those with mild rather than advanced medial degenerative change although

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of note only 18% of their cohort had KL 2 or less. Results with this device need longer follow up before conclusions can be made on its suitability for the treatment of early radiographic knee OA.

Arthroscopic lavage and debridement. The role of arthroscopy and washout in OA is controversial and focuses on the potential benefits of removal of inflammatory cytokines and debris in the synovial fluid. Two recent studies have demonstrated that it does not lead to benefits in those with OA compared to sham procedures at time points out to 24 months [211] [212]. Consequently, in patients without mechanical features and with early knee OA, arthroscopic assessment and lavage is not recommended by NICE.

Cartilage repair procedures. Cartilage repair procedures are of primary interest in the treatment of osteochondral or focal cartilage defects. They are not traditionally considered for use in treatment of OA, however it has become of increased interest in recent years due to its potential to provide pain relief and alter progression of degenerative disease. When considering the literature, it is important to make a clear distinction between osteochondral, or focal chondral lesions, and the degenerative lesions of osteoarthritis. In particular, early knee arthritis with non full thickness cartilage disease must be distinguished from “early onset “ knee arthritis, where full thickness lesions are present in young patients.

Arthroscopic drilling/micro fracture/abrasion arthroplasty. Arthroscopic drilling of full thickness chondral lesions is well established. It is of particular use in those with well localised and well shouldered (the surrounding cartilage is intact and diffusely damaged) lesions [213]. However, these full thickness lesions are by definition advanced OA. As micro fracture is not of use in those without full thickness lesions, it therefore has no indication in the treatment of early, or partial thickness disease.

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Although searches of the literature does reveal studies that refer to its use in early osteoarthritis, this tends to refer to the young age of the patient rather than to the severity of the disease within the joint itself [214].

Autologous chondrocyte implantation The disturbed joint homeostasis in a degenerative joint presents a challenging environment for cartilage repair. In autologous chondrocyte implantation evidence for its use in those with non full thickness cartilage lesions is minimal. In young patients with full thickness disease, the use of ACI again remains controversial. In this technique, the lesion is debrided until stable edges are encountered and then the base of the lesion is curettaged through the calcified layer. Chondrocytes are then implanted into the lesion with a variety of techniques [63]. A literature review indicates that although there are many studies on its efficacy in young patients with full thickness cartilage lesions [215] [216] [214] there are none that described its use in non full thickness cartilage disease.

Osteochondral autograft transfer (OAT) Focal chondral defects can be addressed with OAT which involves the harvesting and subsequent implantation of autologous osteochondral plugs in a single stage operation [217]. This technique is of interest in young adults with larges osteochondral defects [218][219]. Its use in early degenerative non full thickness cartilage lesions in the knee has not been described.

Osteochondral allograft Osteochondral allograft is a procedure similar to OATs but uses graft material from preserved cadaveric cartilage. Mosaicplasty is a generic term that covers OATs and osteochondral allografting. Osteochondral allografts have a well established role in in articular cartilage restoration and repair of focal defects [220] [221]. There has been an increasing interest in its use in full thickness degeneration in young athletes with osteoarthritis [222] [223], but again, it has not been described as a treatment for non full thickness early knee OA.

2.3.1.4. Joint replacement surgery.

Joint arthroplasty in the setting of early knee degeneration is not well described. However, Pandit et al [18] described a case series of 29 patients with non full thickness cartilage degeneration on the medial side of the knee that were operated on with unicompartmental knee replacement. At 2 years post operation, the non full thickness group had significantly worse PROMs and satisfaction scores than those with full thickness disease. In addition, the role of intervention in those with early knee OA is to alleviate symptoms sufficiently to delay arthroplasty and, in the young patient, the consequent need for at least one revision procedure [216].

2.3.1.5. Problems with current options.

Despite the growing interest in patients with early degenerative changes and the continuous innovation of industry in the development of new fashionable treatments, there remains no clear definition of where early OA begins and ends. Consequently, treatment pathways are poorly defined for those with early knee OA.

2.4. The genetics of knee osteoarthritis.

Genetic epidemiology is the study of genetic factors that influence the dynamics of diseases in populations [224]. Genetic risk factors can influence both the risk of OA and can also affect the outcomes of OA at various stages in the course of the disease. As such, genetic variation in such parameters as obesity, skeletal morphology, bone mass or synovitis may all play a role. Studies that influence our understanding of the role of genetics in OA can be split into broad groups:

Twin studies and family aggregation studies estimate the extent to which genetic variation determines the variation of that trait or heritability. In more specific ge-

netic studies, linkage analysis, candidate gene studies, meta analyses (to account for the large number of subjects required per study) and Genome Wide Association Studies have all been undertaken. These have identified genes associated with bone morphogenic protein, thyroid regulation pathway and apoptotic pathways associated with large joint osteoarthritis [225]. However, the odds ratios generated by the presence of these isolated loci are at best modest (OR 1.11 -1.21) [226].

2.4.1. Twin studies in knee osteoarthritis.

Classical twin studies enable investigators to quantify the environmental and genetic factors that contribute to a trait or a disease. In these studies, comparing identical twins for the presence of a trait or disease with non identical twins for the presence of a trait or disease allows a good initial estimate of how genetic variation determines the heritability of a disease. In a sequence of studies that looked at medial knee arthritis using a London based twin register, Spector et al demonstrated a 39% genetic influence on the incidence of radiographic and clinical knee OA, independent of known environmental or demographic confounders [227]. In a 7 year follow up of the same cohort, they demonstrated an ongoing genetic influence in the progression of specifically medial compartment knee OA [228]. Importantly, they used only women subjects and others have suggested that the genetic predisposition to OA may be greater in women than in men [229]. Twin studies have also demonstrated a genetic contribution to the volume of knee cartilage volume [230].

2.4.2. Familial aggregation studies in knee osteoarthritis.

Investigation of familial aggregation is used to indicate the disease risk for a relative of a patient compared with prevalence of a disease in the general population. In 1997, Chitnavis et al. [231] compared the prevalence of Hip and Knee replacement in the

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siblings of those who have had total joint arthroplasty to their spouses. They demonstrated a relative risk of 4.8 (95% CI 0.64 - 36.4) but were only able to comment on the risk of arthroplasty, not the presence or otherwise of OA. Neame et al. in a later study of 409 end stage knee OA patients, [232], demonstrated a heritability of radiographic knee OA in men of 0.78 and 0.49 in women after adjustment for confounders. In contrast to this, in the GARP study of sibling risk that looked at middle aged patients with familial osteoarthritis at multiple sites, familial aggregation of osteoarthritis was most striking for hand and hip but absent for the knee. This study utilised the ACR criteria for diagnosis the of OA and therefore no radiographs were performed [233]. The specific phenotype of anteromedial knee arthritis has been investigated by McDonnell et al [234]. Although this pattern of arthritis can be attributed to specific mechanical factors (there is specific wear lesion in the tibio femoral compartment with preservation of cartilage in other parts of the compartment) a relative risk of 3.21 was identified for the presence of symptomatic and radiographic knee OA in the siblings of those who have undergone unicompartmental knee arthritis. “Horizontal transmission “ of risk from sibling to sibling suggests that this particular type of knee OA has a substantial genetic component. The use of sibling studies to demonstrate horizontal risk is therefore well established. In studies of the hip, investigators have used family aggregation studies to look for vertical transmission of risk from parents to children. Using 49 families where there were affected female sibling pairs with hip OA diagnosed by arthroplasty [235], Spencer et al. identified 145 offspring and 119 control cases. If subjects had the presence of symptoms or signs of OA (joint pain, deformity, ROM changes, Heberdens nodes) they underwent radiographic assessment. If they declined radiographic assessment, the Heberdens nodes were used to declare a diagnosis of arthritis. They demonstrated a 3.5 times higher risk in the offspring of those with Hip OA compared to controls. In a five year follow up of this study,

Pollard et al [236] confirmed the initial findings of Spencer et al and determined that at 5 years, the Sibling Offspring had OR's of 4.7 (1.7-13.2) for the development of signs and radiographic change. The same team also confirmed the heritability of specific morphological features known to predispose to hip OA [237]. As yet, studies of the heritability of knee OA, in particular anteromedial knee OA, have not been undertaken.

Understanding the genetic contribution to OA has important clinical implications. Firstly, the identification of genes involved in disease risk can improve our understanding of the molecular mechanisms involved in the pathogenesis of OA. Secondly, by selecting sets of genetic variants associated with risk of disease or with progression of OA, it may be possible to define phenotypic subsets of OA.

2.5. Summary - what's next?

It is clear that the clinical syndrome of knee OA is a combination of both symptoms and structural changes. Knee OA is a spectrum, with full thickness knee OA representing the end stage of disease. Early knee arthritis is a term that is widely used in the literature but is poorly defined. It is important to distinguish between the young patient with full thickness disease, and the late middle aged patient with degenerative changes that have not yet manifested as full thickness cartilage lesions. It is this second group of patients that are of particular interest as they represent a cohort who are "progressing" to end stage disease.

A number of gaps exist within the literature. Firstly, the term early knee OA has not been clearly defined. Partly this is due to the lack of a criterion standard to assess diagnostic techniques against and therefore any method used for the assessment of structural change must be shown to be valid and reproducible. This is required to allow the formation of homogeneous cohorts. Secondly, a cross sectional and

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longitudinal symptom profile of patients with early radiographic knee OA has not been performed and this is required to develop a greater understanding of the natural history of patients in the early stages of the disease. Thirdly, a key risk factor for the development of knee OA, that of the role of meniscus, has not been adequately explored. Good quality longitudinal studies have not been performed on the role that the meniscus plays in the development of degenerative knee OA. Finally, the vertical heritability of anteromedial knee arthritis has not been determined.

3. Assessing structural changes in early radiographic knee osteoarthritis

3.1. Introduction.

Perhaps surprisingly for such a common disease, there is little consensus on a consistent description and definition of osteoarthritis with specific reference to the knee. The classification and diagnostic criteria remain a potent source of debate amongst researchers [36]. As a result of the lack of a single agreed reference standard for the diagnosis of knee OA, studies often make decisions to include clinical, radiographic, MRI and arthroscopic reference standards [35]. Consequently subjects recruited under the banner of “early knee arthritis” in clinical research are defined differently depending on which study is considered.

Osteoarthritis of the knee is a complex disease that affects many tissues within the joint. The radiographic manifestations of the disease include the well described x-ray features of loss of joint space, subchondral sclerosis, subchondral cysts and the presence of osteophytes [41]. However, the advent of more advanced imaging techniques have made it clear that associated findings such as bone marrow lesions,

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synovitis, meniscal degeneration amongst others, are also important. As such, classical orthopaedic thinking of the disease as purely a disease of cartilage degeneration and “wear and tear” is probably somewhat outdated [238]. Despite this, damage to cartilage does appear to be a marker of the severity of joint damage and progression. As the severity of the disease progresses (as determined by symptoms) the extent and location of cartilage damage in the knee changes and progresses [239]. Therefore, the use of cartilage damage as a marker of disease appears reasonable. However, problems do exist when using cartilage damage as a marker of OA severity. Radiographs, the commonest method of diagnosing OA, do not assess cartilage damage directly, and proxy assessment measures for cartilage damage such as loss of medial joint space have been demonstrated to be multifactorial in their causation [?]. More direct measures of cartilage damage, such as Magnetic Resonance Image scans, are expensive, less widely available and time consuming. In addition, concerns exist regarding MRI accuracy when compared to the “reference standard” of arthroscopy. Therefore, considerable debate regarding the best method of assessing cartilage damage remains.

An increasing number of clinical studies in the field of cartilage surface repair have revealed that several treatment approaches may be successful in improving clinical outcomes in the short and long term [63] [240]. Unfortunately, studies that include patients with painful cartilage defects do not always use homogeneous patient groups. In some patients there are isolated joint surface defects in otherwise normal joints, whereas other studies include patients with multiple defects, associated joint lesions and loss of joint homeostasis. In order to understand outcomes from clinical studies, and to allow clinicians to translate study results to their clinical practice, an improvement in the characterization of patients with early disease is clearly important. The ideal method of diagnosing early arthritis (i.e. the criterion standard against

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which new methods are measured) has not been established, and consequently there is a large variability in diagnostic techniques used to classify patients. This leads to difficulty comparing studies.

Knee arthritis is a combination of symptoms and structural changes within the knee. As described in section 1.1 this thesis is concerned with those patients who present to the knee clinic with AMOA having failed conservative management but without end stage OA. By definition, these patients will have experienced pain not controlled by simple painkillers, exercise and physiotherapy. The clinical criteria that patients must meet to allow inclusion in studies in this thesis are clear. However, the relevance of structural joint changes and the best method of assessing such changes is not. A pragmatic, reproducible and robust definition of “Early Radiographic Knee Arthritis” is required for two reasons. Firstly, to define the population of patients used in addressing questions in this thesis, and secondly, to allow findings of this work to be considered applicable to the general orthopaedic surgery community.

The overall aims of this chapter are firstly to determine the most reproducible and valid method of diagnosing early structural osteoarthritis, and secondly to define “early” structural OA on this basis.

Reliability refers to the reproducibility (or precision) of assessment data or scores over time or occasions [241]. A test is considered reliable if the same result is obtained repeatedly when the status it is measuring has not changed. Inter observer reliability (also known as inter rater reliability) refers to the degree to which different observers (or raters) give consistent estimates of the same phenomenon. Intra observer reliability (also known as test-retest reliability) indicates how stable responses obtained from the same observer are over time. In assessing intra and inter observer reliability, a kappa coefficient is used for categorical data, and the intra class correlation coefficient (ICC) for continuous data. The accuracy of a test refers to the proportion

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of correct diagnoses that the test makes, whereas the validity of a test refers to both the accuracy and the reliability of a test [242]. A “gold standard” is a test that is considered the definitive approach for diagnosing a disease [243]. Ideally, this test should neither fail to diagnose arthritis in people with arthritis, nor falsely label people without arthritis as having the condition. In the diagnosis of OA, arthroscopy is often considered the “gold standard”. It should, however, be more accurately be referred to as a criterion standard (a simile for clinical standard). A criterion standard, according to the AMA Manual of Style, represents the “diagnostic standard for a particular disease or condition, used as a basis of comparison for other (usually noninvasive) tests. Ideally, the sensitivity and specificity of the criterion standard for the disease should be 100%.” [244]. In the diagnosis of OA, postmortem histological analysis of cartilage lesions would represent the true “Gold standard”. However, this is clearly not possible in adults with early disease. Criterion standards such as X ray, Arthroscopy and MRI have increasingly come into use in clinical practice although there is a lack of consensus on which is the optimum technique to diagnose early structural cartilage changes.

The specific aims of this chapter are therefore to :

1. Assess the validity of the three main criterion standards for the assessment of the severity of structural damage in knee OA (Arthroscopy, X ray and MRI.)
2. Compare these three methods with each other in terms of their reproducibility and reliability.
3. To propose a definition of early structural knee OA to allow for recruitment into studies later in this body of work.

This chapter consists of six short studies.

3. Assessing structural changes in early radiographic knee osteoarthritis

- In the first study, the intra operative inter observer reliability of arthroscopy is assessed.
- In the second study, the intra and inter observer reliability and accuracy of assessment of intra operative images to diagnose the severity of cartilage lesions is assessed, to determine if this method of assessment can be reliably used to retrospectively identify patients with early knee osteoarthritis in the clinical setting.
- In the third study, the assessment of cartilage damage on MRI and its inter and intra observer reliability is determined, using a recognised and validated scoring system.
- In the fourth study, the most common radiographic grading system for knee OA is assessed for its inter and intra observer reliability using a recognised and validated grading system.
- In the fifth study, X ray and MRI are correlated to compare their assessment of cartilage damage severity.
- In the sixth study, arthroscopic assessment of cartilage lesions is compared to MRI assessment of cartilage lesions.

Finally, based on the validity studies of the criterion standards assessed in this chapter, a formal definition of early structural OA is proposed for further use in this thesis. In all studies advice on analysis was sought from a senior statistician from the Botnar Research Centre, Oxford.

3.2. Null hypotheses.

1. Knee arthroscopy cannot be used to reliably assess cartilage surface damage in knee OA.
2. Intra operative arthroscopic images cannot be reliably used to retrospectively identify those patients with early structural OA.
3. MRI cannot be used to reliably assess surface cartilage damage in the knee.
4. Plain radiographs cannot be used to reliably assess structural damage in OA of the knee.
5. There is no association between radiographs and MRI in their assessment of structural cartilage damage as a measure of OA severity
6. There is no association between MRI and arthroscopy in the assessment of structural cartilage damage in the knee.

3.3. Study 1 The inter observer reliability of arthroscopic cartilage grading.

3.3.1. Materials and methods.

Seven patients who presented to the Knee Clinic at the the Nuffield Orthopaedic Centre with knee pain and evidence of meniscal damage and hyaline cartilage degeneration on MRI were consented for arthroscopic assessment and debridement of the knee as part of their normal clinical treatment. At the time of surgery, two experienced arthroscopists (both consultant knee surgeons), who were responsible for the care of the patient were asked to assess the knee. Each surgeon was asked specifically to assess:

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- Six specific chondral regions of the knee (patella, trochlea, medial femoral condyle, lateral tibial condyle, lateral femoral condyle and lateral tibial plateau),
- For each region the surgeon was asked to rate the single worst lesion according to the modified ICRS grading system.

To ensure a good understanding of the grading system being used, prior to surgery each arthroscopist had been given a copy of the original paper by Brittberg et al [60] and a copy of the modified ICRS grading atlas as seen in figure 2.2.4 on page 49. Each observer was free to palpate the chondral lesions. Following surgery they were asked to record their findings on a knee assessment form (see appendix A.2.1 on page 277). Each observer was blinded to the results of the other. Results were collated and a cross tabulation was generated. A Kappa analysis of the results was performed to assess inter rater reliability.

3.3.2. Results.

Each observer recorded 42 regions of interest. The raw data for this study can be seen in table 3.1 on the next page. There is an overall perfect agreement in 25/42 observations (59.5%). The following levels were used in the interpretation of kappa [245, 246]:

<0: Less than chance agreement

0.01-0.2: Slight agreement

0.21-0.40: Fair agreement

0.41-0.6: Moderate agreement

0.61-0.80: Substantial agreement

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0.8-0.99: Almost perfect agreement

A linear weighted kappa [247] (to account for the greater difference between disagreement between a score of 1 and 4 than between 1 and 2) of 0.628 (SE 0.1056 $P < 0.00$) indicates a substantial level of overall linear agreement between two observers. Consultant surgeons agree on 60% of occasions based on these results.

Table 3.1.: Arthroscopic assessment correlation between two observers

		Observer 1					
	ICRS GRADING SYSTEM	0	1	2	3	4	Total
Observer 2	0	12	0	0	0	0	12
	1	3	7	1	2	0	13
	2	1	5	1	0	0	7
	3	0	0	4	3	1	8
	4	0	0	0	1	1	2
	Total	16	12	6	6	2	42

3.4. Study 2: An assessment of the reliability and accuracy of cartilage grading from intra operative images - another method of patient identification?

Determining intra observer reliability of arthroscopy, by repeated operative assessment of the same patient over three time periods by the same surgeon, is not possible from a clinical or ethical point of view. In addition, the use of arthroscopy in the treatment of knee OA is known to be limited [248]. Therefore, determining the intra observer reliability of arthroscopy is a challenge. As part of the arthroscopic procedure, the use of intra-operative ‘snap-shot’ photograph images has become commonplace. These digitally printed images provide a record of current lesion severity

when used at a later date (not necessarily by the original operating surgeon) in formulating a management plan, in conjunction with clinical examination and alternative imaging modalities. Whilst assigning a grade (0-4) of severity of cartilage damage to a photograph may appear intuitive, the validity of applying retrospective cartilage grading to intra-operative images has not been explored.

3.4.1. Materials and methods.

70 Orthopaedic surgeons, representing trainers (consultants), and higher surgical trainees (ST3-8) were selected from two independent surgical deaneries (Oxford and NE Thames) at their annual training days.

Sixteen intra-operative images representing a spectrum of cartilage damage were obtained from sequential, arthroscopic knee assessments. Standard arthroscopic technique was used via antero-lateral and antero-medial portals. Image collection was with the Smith and Nephew (London, UK) 660 High Definition Image Management System. All arthroscopic procedures were performed by a senior orthopaedic surgeon at the Nuffield Orthopaedic Centre (AJP). Digital images were professionally printed onto high quality IPRINT Digital Silk 170gsm white paper using an industrial laser printer (Canon CLC5100).

Inter observer reliability. Each surgeon assessed 16 images; 15 individual images plus a duplicate, rotated image (images 4 and 12). Each surgeon was asked to assign a grade of cartilage disease to each image. Surgeons were not required to use a specific scoring system, but were later asked to volunteer which scoring system they had chosen to use.

Intra observer reliability. Images 4 and 12 were the same image. However, rotating and inverting the image (so that it was upside down and a mirror image of itself)

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allowed a test - retest reliability assessment of the image to be performed in one sitting. In addition, at a time point 10 weeks following the initial assessment, ten of the surgeons were asked to repeat their assessment of all 16 images.

Accuracy - comparison to a reference standard. A “reference standard” score for each image was reached by consensus amongst three Consultant knee surgeons, using the original Outerbridge and ICRS descriptions (see figure A.1.1 on page 276, and figure 2.2.3 on page 48). The responses of each surgeon were then compared to the reference standard. Where no scoring system was selected, scores were compared to the Outerbridge reference standard, as this system was most commonly used.

3.4.1.1. Data analysis.

Inter observer reliability.

1. Utilising the data from all images and surgeons, Fleiss’ kappas [249] for multiple raters were calculated. To overcome problems associated with the use of multiple scoring systems, a sensitivity analysis was conducted using only the scores from those stating they had used the most common scoring system.
2. Using this restricted group of surgeons, each rating was recategorised into two groups, those graded less than three and those graded three or greater. This cut-point was chosen to reflect the generally accepted point at which surgery would be considered. Using these binary scores linear weighted kappas were calculated.

Intra observer reliability. Using data from images 4 and 12 (the same image, with 12 a rotated and inverted version of 4), linear weighted kappas were calculated to assess the level of intra-observer agreement. As this was a non-standard application

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of kappa, a Wilcoxon signed rank test was also used to assess whether the rating of image 4 differed significantly to image 12. Calculating the differences between the first and second score for each judge, ordinal regression was used to assess whether particular scoring systems or seniority of the surgeon was associated with increased reliability. To account for the concern that the use of different scoring systems may have affected the results a sensitivity analysis was performed using only the scores from those surgeons stating that they used the most common scoring system reported.

Accuracy.

1. Using the ratings from all participants who scored no image greater than 4, in line with the method selected for establishing the reference standard scores, a linear weighted kappa was calculated comparing the reference standard to each rating for each image from each surgeon.
2. To address the lack of independence between the scores, a percentage agreement to the reference standard was also established for the ten surgeons asked to re-rate all images in order to measure individual effectiveness.
3. The percentage of images for which all surgeons agreed with the reference standard was calculated.

3.4.2. Results.

The commonest grade of assessor was Consultant (n=26), with an even spread across training grades ST3-8 (see table 3.2 on the following page). A variety of grading systems were used. The majority of surgeons who stated a known scoring system used either Outerbridge/ modified Outerbridge scoring system (n=29) or the ICRS (n=5). Twenty of the assessors were unable to name the grading system used. Of

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Table 3.2.: Grade of surgeon assessors

Grade	N=
Consultant	26
ST8	4
ST7	9
ST6	5
ST5	9
ST4	8
ST4	9
Total	70

the remainder, seven other individual systems were used, including, inappropriately, both Ahlback and Kellgren and Lawrence (see table 3.3).

Table 3.3.: Cartilage grading systems used across 70 surgeons

Grading system	N=	%
Outerbridge	29	41
ICRS	5	7
Modified Collins	2	5
Ahlback	2	5
Other	8	11
No named system	24	32
Total	70	100

Inter observer reliability.

1. The Fleiss' kappa for multiple raters was 0.26. This demonstrates poor agreement between responses.
2. Inter observer reliability in the assessment of lesions as grade >3 or <3 . Using kappa for two outcomes and more than two raters an inter-rater agreement value of 0.57 was obtained. This indicates that there is at best, a moderate agreement amongst raters as to whether the cartilage lesion is greater or less than 3. As expected, those with particularly good agreement are those with particularly low (median=0 or 1) or particularly high (median=4) average scores.

Intra observer reliability - comparison of scores for image 4 and image 12. The Wilcoxon signed rank test did not indicate any significant differences between the two sets of scores ($z=-1.143$, $p=0.25$). Table 3.4 indicates that there is significant disagreement between scores for the same image. For example, only 20% of those scoring the image as grade 2 on the first trial restored it as grade 2 on the second trial, with 30% increasing their score to a 4 on the second viewing. This observation is strongly supported by a linear weighted kappa of 0.13. The data suggests that as perceived severity increases so does the repeatability with almost all (5 out of 8) of those scoring the image a 4 on the first reading re scoring it a 4 on the subsequent review. One person scoring the image a 5 on the first viewing scored the image a 3 on a subsequent viewing. However it is noted that Outerbridge is a scale from 0 to 4, and therefore the score of 5 should not have applied (this respondent stated that they were using the Outerbridge grading system). Regression based on seniority did not indicate that seniority affects repeatability.

Table 3.4.: Assessment of intra observer reliability via comparison of responses to image 4 and image 12

	Image 12 response						
		1	2	3	4	5	Total
Image 4 response	1	0	0	0	0	0	0
	2	0	2	5	3	0	10
	3	0	2	4	3	0	9
	4	0	1	2	5	0	8
	5	0	0	1	0	0	1
	Total	0	5	12	11	0	28

Intra observer reliability - comparison of scores for 10 surgeons over two viewings. Using Gauge R&R methods [250] to look at intra observer reliability between categorical data from multiple observers, intra observer reliability was poor with an average agreement of 45.6%, and with only 4 participants agreeing between ratings on at least 50% of occasions.

Accuracy (comparison to a gold standard).

1. Table 3.5 shows the spread of scores allocated by surgeons to images regardless of level of training, in relation to the reference standard. In the table, the reference standard is shown in bold and in the column marked reference standard. A calculation of a linear weighted kappa value of 0.49 indicates only moderate agreement of raters to the reference standard. It should be noted however that the use of kappa is not ideal since there are a number of images being rated by a number of different raters and therefore the scores are not independent.

Table 3.5.: Comparison between reference standard and surgeon assessment

Image number	Reference standard score	Scores allocated by surgeons				
		0	1	2	3	4
Image1	0	51	17	0	0	0
Image2	4	0	4	6	8	52
Image3	4	0	0	6	26	38
Image4	4	0	1	22	29	15
Image5	1	5	48	12	2	2
Image6	4	0	1	5	33	30
Image7	4	0	1	14	21	33
Image8	2	4	43	19	2	0
Image9	3	0	1	16	39	13
Image10	2	9	39	15	0	0
Image11	3	0	5	40	22	2
Image12	4	0	0	16	29	24
Image13	3	0	4	30	15	20
Image14	3	1	18	36	12	2
Image15	3	0	0	1	24	44
Image16	1	11	23	21	3	9

2. Individual effectiveness, which assesses agreement to the reference standard, was equally poor with agreement to the reference standard averaging 22.81%.
3. There were no occasions on which all surgeons agree for a given image, and in turn, no occasions on which all surgeons agree with the reference standard.

3.5. Study 3: Determining the reliability of a modified ICRS grading system in the MRI assessment of cartilage lesions.

3.5.1. Materials and methods.

The first ten knee MRI scans of patients with osteoarthritis of the knee referred to the knee clinic at the Nuffield Orthopaedic Centre in Oxford in October 2010 were obtained. The images were anonymised, and the images were transferred to DICOM viewing software (ONIS 2.4 Professional, Digital Core, Tokyo). The ICRS grading system for cartilage lesions, developed by the International Cartilage Repair Society [60], is a score measured on a scale of 0-4 with subsections in grade 1 and 3 (see Figure 2.2.3 on page 48 for details). A modified version of the ICRS grading has been proposed by Spahn et al [64].

A pictorial representation of the modified ICRS grading system was produced in agreement between an orthopaedic surgeon and an experienced musculoskeletal radiologist. The agreed modified grading system can be seen in Figure 2.2.4 on page 49.

Two observers were asked to report the single worst lesion seen in six regions in the knee (Patella, trochlea, medial tibial plateau, medial femoral condyle, lateral tibial plateau, lateral femoral condyle) using coronal and sagittal images, giving sixty observations for each observer.

An orthopaedic surgeon then graded the images on two further occasions one week apart, on each occasion blinded to his previous results. A high quality viewing screen was used to inspect the images (LG IPS234V, LG Corp, Seoul, South Korea). Results were recorded in an Excel spreadsheet and statistical analysis was performed using Stata (v12, Stata Corp, Texas, USA). A Linear weighted kappa [247] was used for

inter observer reliability and Fleiss' kappa [249] for intra observer reliability.

3.5.2. Results.

Interobserver reliability. The overall agreement was 97.5% (117/120 observations) with a kappa value of 0.93 (SE 0.093 $p < 0.00$) indicating almost perfect agreement. Disagreements in observations agreed only on three occasions. Twice disagreement occurred between grade 0 and grade 1, and on one occasion between grade 3 and grade 4.

Intraobserver reliability. Overall in 80% (48/60) of all cases there was agreement across all three readings. For the remaining 12 cases, the results from at least two of the readings were in agreement. In no cases did all three readings yield different results. The overall kappa value was 0.83 (SE 0.038 $p < 0.00$) again indicating almost perfect agreement.

3.6. Study 4: Determining the reliability of the Kellgren and Lawrence grading system in the radiographic assessment of severity of knee osteoarthritis.

The Kellgren and Lawrence grading system for knee arthritis [41] is a widely used assessment tool for the severity of knee OA that relies heavily on the presence of osteophytes in the diagnosis of OA. A validated atlas for the severity of osteophytes has previously been described by Bottomley [251]. As a training exercise prior to the main assessment, two orthopaedic surgeons reviewed ten weight bearing AP radio-

graphs in the presence of the original paper and the validated atlas. Consensus was reached on the grading of knee OA.

3.6.1. Materials and methods.

Fifty consecutive weight bearing AP radiographs of the knees of patients presenting to clinic in October and November 2010 with a diagnosis of osteoarthritis were then obtained and transferred to DICOM viewing software (ONIS 2.4 Professional, Digital Core, Tokyo). A high quality viewing screen was used to inspect the images (LG IPS234V, LG Corp, Seoul, South Korea). Two orthopaedic surgeons were separately asked to review each image and grade it according to the Kellgren and Lawrence reference paper on a score of 0-4. One surgeon then was then asked to grade the images on two further occasions one week apart, on each occasion blinded to his previous results. Results were recorded in an Excel spreadsheet and statistical analysis was performed using Stata, (v12, Stata Corp, Texas, USA). A Linear weighted kappa [247] was used for inter observer reliability and Fleiss' kappa [249] for intra observer reliability.

3.6.2. Results.

Inter observer reliability. The overall level of agreement was 94% with a kappa value of 0.8 (SE 0.096, $p < 0.00$) indicating a substantial level of agreement.

Intra observer reliability. In 72% (36/50) of the readings there was agreement across all three readings. For the remaining 14 cases, the results from at least two readings were in agreement. In no cases did all three readings yield different results. The overall kappa value was 0.745 (Se 0.046, $P < 0.00$) indicating substantial agreement.

3.7. Study 5: The validity of radiographs in the assessment of knee osteoarthritis and severity of cartilage damage using MRI as a criterion standard.

3.7.1. Materials and methods.

The first 50 patients with knee pain and a final diagnosis of early anteromedial knee OA that attended the knee clinic at the Nuffield Orthopaedic Centre in Oxford from January 2011 were identified from patient records. The standing AP radiographs and the 3T MRI scan of these patients were obtained. Those patients with a time of greater than 3 months (90 days) between acquisition of radiographs and acquisition of the MRI were excluded to eliminate the likelihood of significant change in gross cartilage morphology between these time points [252].

Both sets of images were exported to DICOM viewing software (ONIS 2.4 Professional, Digital Core, Tokyo). A high quality viewing screen was used to inspect the images (LG IPS234V, LG Corp, Seoul, South Korea). Both the Kellgren and Lawrence score and the Modified ICRS score are ordered categorical scoring systems which grade lesions from 0 (normal) to 4 (severe). The Kellgren and Lawrence score does not measure cartilage change, rather it assesses overall joint change within the knee. The purpose of this study was to determine if the Kellgren and Lawrence score correlates with the criterion standard (in this case, MRI). Each image was inspected by an orthopaedic surgeon trained in the modified ICRS and Kellgren and Lawrence grading system. On the radiographs the Kellgren and Lawrence score for the medial compartment was obtained. On the MRI scans, the single worst cartilage lesion in the medial compartment was noted. Results were recorded in an Excel spreadsheet

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and statistical analysis was performed using SPSS (v18.0.0, IBM, New York, USA). For the purposes of this study the MRI score was used as the reference standard. A Linear weighted kappa [247] was calculated.

3.7.2. Results.

Of the fifty patients, 13 had a gap of more than 90 days between the acquisition of their X ray and the acquisition of their MRI and were therefore discarded. Of the remaining patients, there was a mean difference in acquisition time of 47 days (range 0-78 SD 23.2).

Correlation between scores was poor. The overall agreement was 16.22% with a kappa of 0.124 (SE 0.05 P<0.00) indicating slight agreement at best. The raw data can be seen in table 3.6.

Table 3.6.: Association between Kellgren and Lawrence X ray grade and Modified ICRS MRI grade of the same knee

		X Ray KL grading					
MRI ICRS grade		0	1	2	3	4	Total
	0	0	0	0	0	0	0
	1	0	0	0	0	0	0
	2	6	3	1	0	0	10
	3	3	4	4	4	3	18
	4	0	0	3	5	1	9
Total		9	7	8	9	4	37

3.8. Study 6: The validity of arthroscopy in the assessment of knee arthritis and severity of cartilage damage using MRI as a criterion standard.

3.8.1. Materials and methods.

Seven patients with symptoms of meniscal damage and knee arthritis that presented to the knee clinic at the Nuffield Orthopaedic Centre, Oxford, were identified prospectively from January 2011. In each case MRI assessment indicated a meniscal lesion suitable for operative intervention and the patient was listed for arthroscopic assessment of the knee. One observer, trained in the ICRS grading system, assessed the chondral lesions in six areas of interest across the knee (Patella, trochlea, medial femoral condyle, medial tibial plateau, lateral femoral condyle, lateral tibial plateau) intra operatively. The single worse grade of cartilage lesion seen at arthroscopy was recorded on a knee assessment form as described previously (see appendix A.2.1 on page 277). In order to attempt to examine the relationship between arthroscopic findings and the MRI findings, the preoperative MRI scans of the same patients were anonymised (all name and demographic data was removed, leaving only the patient MRN - medical record number) and uploaded onto DICOM viewing software (ONIS 2.4 Professional, Digital Core, Tokyo). Images were then sorted by the MRN of each patient to increase the blinding of the assessor to the patient identity. A high quality viewing screen was used to inspect the images (LG IPS234V, LG Corp, Seoul, South Korea). The MRI scans were assessed by orthopaedic surgeon who assessed the same six regions of interest and scored the single worst cartilage lesion according to the ICRS grading system. Results were documented according to the patient MRN and

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recorded in an Excel spreadsheet. Statistical analysis was performed using Stata (v12, Stata Corp).

3.8.2. Results.

Forty two regions of interest were available for comparison. An overall linear weighted kappa value of 0.124 (SE 0.098 $P = 0.18$) indicated, at best, mild agreement between measures. Absolute agreement occurred in only 38% of occasions. This cross tabulation of MRI to arthroscopic scores is demonstrated in Table 3.7.

Table 3.7.: Association between MRI and arthroscopic assessment of cartilage lesions

ICRS MRI grade		ICRS arthroscopic grade					
		0	1	2	3	4	Total
	0	9	4	1	2	0	16
	1	6	5	2	2	0	15
	2	1	4	2	0	1	8
	3	0	1	0	0	1	2
	4	0	0	0	1	0	1
	Total	16	14	5	5	2	42

This table demonstrates that, on only 16 of 42 occasions does severity of disease assessed on MRI correspond precisely with assessment of the severity of disease arthroscopically. Even with grades 0 and 4 (ie no cartilage lesion, and full thickness cartilage lesions) the assessment correlated poorly. Arthroscopic assessment tended to overestimate the severity of lesions compared to MRI, with arthroscopy assessing 7 patients to have lesions of grade 3 or more, and MRI assessing only 3 to have lesions of grade 3 or more.

3.9. Discussion.

This chapter has examined the three main methods of assessing knee osteoarthritis, MRI, arthroscopy and radiography, and assessed both their reliability and validity.

3. Assessing structural changes in early radiographic knee osteoarthritis

The use of arthroscopy has long been hailed as the “Gold” or reference standard for OA. Study 1 and Study 2 assessed the reliability of arthroscopic assessment of cartilage lesions.

In Study 1 an intra operative assessment of the severity of chondral lesions was made by two consultant observers blinded to each others results. A two surgeon inter observer assessment of 42 regions of interest studied demonstrated a linear weighted kappa of 0.628. Although this is a substantial agreement, it is perhaps lower than one would expect for two experienced observers. This study suggests that, even amongst highly specialised arthroscopists who are specifically trained in the same cartilage grading systems, a cartilage lesion will be assessed as the same grade on only 59.5% of occasions. Consequently, the reliability of arthroscopy in the assessment of the severity of cartilage lesions (let alone the size or location which were not assessed here) must be questioned.

In the clinical setting, repeatability of arthroscopic assessment is not possible (i.e asking surgeons to scope patients knees at different time points to assess their chondral lesions) or practical due to the invasive nature of the procedure. Therefore in Study 2 an experiment was designed that assessed the use of intra operative digital pictures in the clinical outpatient setting. This demonstrated that surgeons use multiple different grading systems, potentially leading to diagnostic confusion in the post operative clinic setting. An assessment of the inter rater reliability using intra operative images was performed. A kappa analysis demonstrated poor reliability between observers using the same scale with a value of 0.26. Importantly, in assessing whether a lesion is greater or less than grade 3, a kappa of 0.57 demonstrated only moderate agreement. Using two separate methods of assessing intra observer reliability, the use of arthroscopic images in the assessment of cartilage damage has been shown to have poor reliability with a kappa value of only 0.13 and observers agreeing on the grade of

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cartilage lesion in only 45.6% of occasions. This study demonstrates the use of intra operative images to assess cartilage lesions is unreliable and has poor reproducibility.

Study 3 assessed the reliability of MRI assessment of cartilage lesions using the same grading system as studies 1 and 2 and demonstrated excellent levels of inter rater (kappa 0.93) and intra rater (kappa 0.83) reliability suggesting that MRI is a reliable method of assessing cartilage lesions.

Study 4 assessed the reliability of radiographs in assessing the severity of OA change within the knee as defined by Kellgren and Lawrence. Again, substantial levels of inter and intra observer reliability were observed (Kappa values of 0.8 and 0.75 respectively) meaning that radiographs, although assessing whole joint changes rather than cartilage lesions directly, is a reliable and reproducible assessment technique.

Studies 1 to 4 have therefore assessed the reliability of the three main criterion standards of assessing OA. They demonstrate that MRI has the greatest level of intra and inter observer reliability. Arthroscopy has generally good reliability, unless assessment of cartilage lesions is performed using intra operative images, rather than intra operative assessment itself.

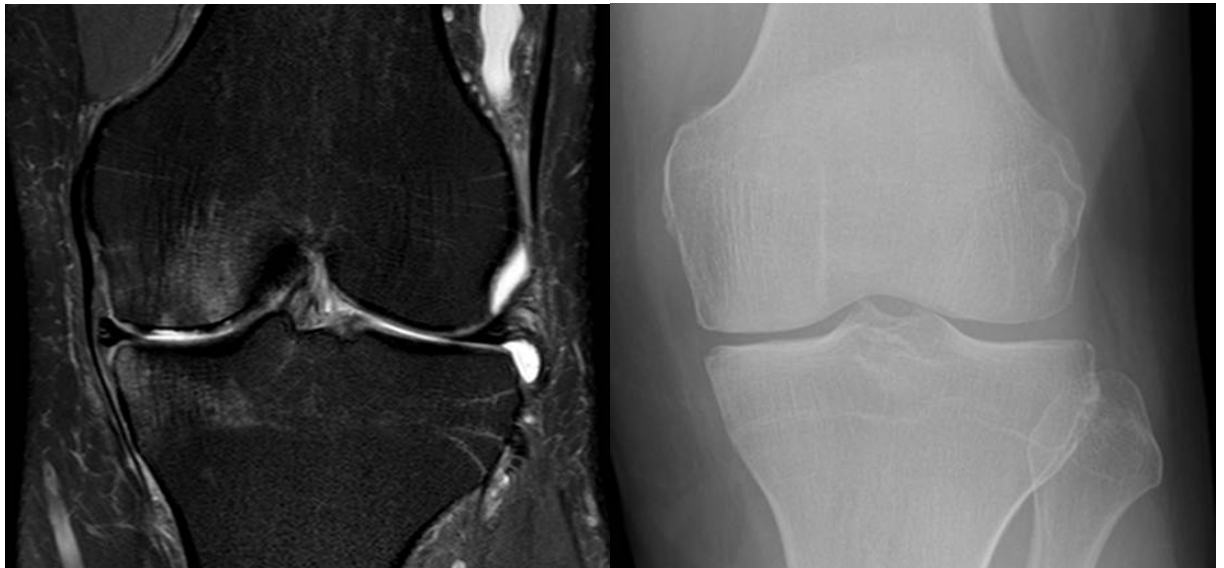
Studies 5 and 6 compared the validity of radiographs and arthroscopy to the most reliable criterion standard of MRI. Radiographs compare overall joint change, and MRI has been used in this chapter only to assess cartilage damage. However, in Study 5 an attempt was made to see if plain radiographs (which are cheaper, quicker and more readily available) can be used as a proxy for cartilage damage assessment on MRI. Correlation between MRI and X ray was very poor, with an overall kappa of 0.124. However, this study did demonstrate that patients with KL Grade 0 on X ray can have MRI cartilage lesions greater than 50% depth. As demonstrated in 9 cases, those with normal radiographs (KL0) can have significant partial thickness cartilage lesions on MRI. This finding was replicated in those with very early radiographic OA

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(KL1) where 7 had significant lesions. In patients with KL2 (the commonly used cut off for “Early OA”) three out of eight patients demonstrated full thickness disease. In only three cases did radiographs estimate the severity of OA as worse than MRI (KL4 on X ray and Modified ICRS 3 on MRI). Although MRI and the X ray are measuring different parameters (joint space loss and the presence of osteophytes vs morphological cartilage damage), it does indicate that radiographs tend to underestimate the severity of disease compared to MRI. This is what we might suspect from experience in clinical practice.

Examples of mild X ray changes with severe cartilage lesions on the medial femoral condyle are given in figure 3.9.1.

Figure 3.9.1.: T2 weighted coronal MRI of right knee demonstrating ICRS grade 3-4 lesion on medial femoral condyle and AP standing radiograph of same knee demonstrating KL 2 changes.



On the basis of this study, none of the patients with X ray changes of KL 0 or KL 1 had evidence of full thickness lesions on MRI. This suggests that patients with no OA on radiographs do not need an MRI to confirm a lack of full thickness cartilage damage. Three out of eight of those with KL 2 had full thickness lesions

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seen on MRI, indicating that, in patients with KL2 on their radiographs, an MRI is necessary to rule out evidence of full thickness disease. All knees with X ray changes of KL3 or more had MRI changes of Grade 3 or more. Five of the nine patients had full thickness lesions on MRI. In only 3 cases (8%) did the X ray over estimate the severity of OA compared to MRI. These findings indicate that, in the patient with a painful knee with no other cause for the pain, and demonstrating the very earliest X ray changes, an MRI is not necessary to rule out full thickness cartilage lesions, even if it is necessary to rule out other intra articular causes of pain. However, in those with KL2 or more, it is not possible to exclude full thickness cartilage lesions without MRI. This is an important finding as clinical decisions are made on the basis of the presence or otherwise of full thickness lesions.

In study 6, arthroscopic assessment of cartilage lesions was compared to MRI assessment of cartilage lesions using MRI as the criterion standard. The correlation between the two was poor with agreement occurring on only 38% of lesions, leading to a kappa value of 0.124.

The small numbers in these pilot studies mean that all conclusions must be drawn with caution. However, the work from this chapter demonstrates that, using the current scoring systems, arthroscopy exhibits poor reliability and compared to a criterion standard of MRI has poor accuracy. Therefore its use in the diagnosis of cartilage lesions is limited. Similarly, radiographs, although reliable, demonstrates poor validity when compared to MRI.

In contrast, MRI is reliable, non invasive, repeatable and has minimal side effects for the patient.

3.10. Conclusions and definition.

- Null Hypothesis 1 cannot be rejected. Knee arthroscopy cannot be used to reliably assess cartilage lesions in the knee.
- Null Hypothesis 2 cannot be rejected. Intra operative images cannot be reliably used to retrospectively identify those patients with early structural OA.
- Null hypothesis 3 is rejected and MRI is accepted as a reproducible method of assessing cartilage degeneration in the knee.
- Null hypothesis 4 is rejected and x rays are accepted as a reproducible method of assessing bony changes of early knee OA
- Null hypothesis 5 cannot be rejected. MRI correlates very poorly with X ray in the assessment of early knee OA.
- Null hypothesis 6 cannot be rejected. Whilst knee arthroscopy obtains satisfactory inter rater reliability across two observers, it correlates very poorly with MRI assessment of cartilage lesions.

In the absence of a consensus in the literature as to the definition of early knee OA, this chapter has explored the reliability of different criterion methods of assessing the thickness of cartilage lesions. As a non invasive, reproducible method of assessing cartilage lesions, MRI is clearly important, particularly in those with X ray changes of 2 or more. Although others may consider arthroscopy as a key way of assessing cartilage lesions, the studies reported here do not support this.

For the purposes of this thesis, early structural knee OA shall be defined as:

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X ray changes of KL of 0 or 1 in the absence of other intra articular causes for pain

OR

X ray changes of KL of 2 or more with no MRI evidence of full thickness cartilage lesions.

Previous work from this unit has indicated that some 150 patients per year present to the knee unit at the Nuffield Orthopaedic Centre, Oxford with non full thickness disease on radiographs. The severity of the symptoms that these patients have, in relation to those with more advanced disease is not known. In particular, what is the cross sectional pain and functional profile of these patients?

4. The demographic and cross sectional symptom profile of patients with early knee osteoarthritis.

4.1. Introduction.

In the previous chapter, a pragmatic definition of early radiographic knee arthritis was confirmed to allow the identification of a cohort to be studied further in this thesis. Work from the Nuffield Orthopaedic Centre [5] has suggested that 70% of patients with knee OA presenting to dedicated primary referral knee clinic have AMOA, and that of these, some 40% have Kellgren and Lawrence grade 2 or less on their radiographs. Thus, within one calendar year, at least 25% of all patients seen in clinic with knee arthritis are found to have non bone on bone AMOA on X ray. This corresponds to at least 150 patients per calendar year presenting to a three surgeon knee team.

If patients are not adequately clinically assessed it could be assumed that those with relatively mild radiographic findings will have mild clinical symptoms. How-

4. The demographic and cross sectional symptom profile of patients with early knee osteoarthritis.

ever, clinical experience suggests that this is not always the case [253]. Whilst some do indeed have lesser symptoms, a proportion of patients with early radiographic osteoarthritis can have severe clinical symptoms with debilitating pain and severe impairment of function. Thus whilst they may be considered on a structural basis to have an early radiographic grade of disease, due to pain and functional impairment their disease would be considered as symptomatically much more advanced. Whilst those with early radiographic OA are at the early stage of structural change, their symptoms appear on occasion to be as advanced as those with severe structural change (either uni or bi compartmental tibio femoral OA).

At present there is no formal data available to support this notion or to describe the pattern of OA symptom severity in these patients with early radiographic arthritis on presentation to the clinic. Understanding the clinical presentation of these patients is important not only to understand more about their natural history, but also to assist the clinician to identify these patients and potentially offer treatments to alleviate symptoms. In addition, with imaging increasingly being used as a screening tool to exclude patients from secondary care, determining the symptom profile of those patients with relatively mild structural change may help prevent patients being denied access to the secondary care they need.

4.2. Null hypotheses and aims.

Using the definition of structural early radiographic knee OA described in section 3.10 the following null hypotheses will be tested :

1. There is no difference in the Oxford Knee Score of patients with early radiographic knee OA compared to those with established full thickness symptomatic AMOA or tricompartmental OA.

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2. There is no difference in the pain score and functional impairment of patients with early radiographic knee OA patients and those with established full thickness symptomatic AMOA or tricompartmental OA.

As knee OA is recognised as a spectrum, an exploration of the overlap of scores between groups will be made, to determine whether those with early structural OA have well defined limits of symptoms or whether these symptoms are part of a continuum with an, as yet, unexplored level of overlap.

4.3. Materials and methods.

4.3.1. Study design.

A cross sectional case control study design was adopted comparing those with early structural change to those with advanced structural change. Knee OA represents a spectrum of disease. Full thickness AMOA requiring unicompartamental knee arthroplasty is considered the end stage of medial compartment OA [?]. Full thickness tricompartmental disease requiring total knee replacement is considered the end stage tricompartmental knee OA. In this study, the Cases of interest were defined as those with early structural disease and the symptoms that they experience. Patients undergoing TKA or UKA for full thickness cartilage loss have, by definition, severe structural disease. Consequently, those undergoing arthroplasty represent two “structural end stage” groups. As such, this study compares the symptom profile of those with mild structural change to the symptoms profile of those with severe structural change.

A sample size calculation was performed. Using data from a previous studies that described PROMs pain scores for those with OA grade KL2 and those undergoing TKA [254] [144], a standardized difference of 0.4 was determined. Using the Altman

4. The demographic and cross sectional symptom profile of patients with early knee osteoarthritis.

Nomogram, a Power of 0.8, and a p value of 0.05 a total sample size of 240 was calculated (80 in each group). The comparison groups were selected on 2:1 ratio of cases to controls. This was done to improve statistical power as per previous studies [255].

4.3.2. Cases (Early radiographic OA group).

The first 100 consecutive patients with structural early radiographic knee OA presenting to the knee service outpatient clinic at the Nuffield Orthopaedic Centre, Oxford, from December 2010 until August 2011 were prospectively identified on the basis of their radiographic changes. All met the symptomatic diagnostic criteria of early knee OA (Pain and stiffness within the knee associated with a failure of non operative treatments to control their symptoms). X ray and 3T MRI imaging of all cases was reviewed to confirm the absence of full thickness cartilage lesions. In this outpatient clinic, the Oxford Knee Score (OKS) is collected as part of routine clinical care prior to the consultation. Patients were excluded if they had any clinical and radiographic evidence of intra articular causes of knee pain other than osteoarthritis.

4.3.3. Comparison groups.

200 patients presenting to the pre-operative assessment clinic for unicompartmental knee arthroplasty (UKA group) and 200 patients presenting to the pre operative clinic for total knee arthroplasty (TKR group) were identified. By being placed on the waiting list, these patients had been assessed by an orthopaedic surgeon as having both symptoms and structural changes severe enough to warrant arthroplasty. Pre operative demographic data and Oxford Knee Score were collected as part of routine patient care within the Nuffield Orthopaedic Centre. The UKA group and TKR group preoperative radiographs were reviewed by a single observer (LJ) for confirmation of

4. The demographic and cross sectional symptom profile of patients with early knee osteoarthritis.

end stage, bone on bone disease. Eight patients presenting for UKA were found not to have bone on bone disease and were therefore excluded. This left a UKA group with 192 patients, and a TKR group with 200 patients.

4.4. Analysis.

The OKS, described in 2.2.9.1 on page 67, was calculated as a total score, and then was split to give a OKS pain domain score and an OKS function domain score. The split of the questionnaire into pain and function domains was performed after factor analysis of the questionnaire [151]. This allows the OKS to be used to describe more specific symptoms of osteoarthritis. Therefore, a comparison of pain and functional impairment, as well as overall score, can be performed. In this study, data collected prospectively as part of normal patient care at the Nuffield Orthopaedic Centre could be used to provide a greater level of information about the symptoms experienced by the comparison groups. Data was analyzed using PASW Statistic 18.0.0 (SPSS, IBM, New York, USA).

A one way analysis of variance [256] was performed to determine if there were differences in mean knee scores among respondents from TKR, UKA and early radiographic knee OA groups. Mean age, total OKS, OKS pain domain and OKS function domain were compared between groups. Higher OKS scores indicated a knee with less symptoms than those with a low OKS. In the OKS pain domain, higher scores indicated less pain. In the OKS function domain, higher scores indicated a better functioning knee.

Levene's test of homogeneity of variance [257] was used to determine whether the variance in scores was the same for all groups. If Levene's test for homogeneity of variance was not significant then an ANOVA was used. If Levene's test of homogeneity was significant then the assumption of homogeneity of variance was violated and

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the Robust Test of Equality of Means was used.

4.4.1. Further analysis.

Histograms of the frequency of individual total OKS, OKS pain domain and OKS function domain, were plotted to demonstrate the degree of overlap between TKR group, UKA group and early radiographic OA group, in terms of severity of symptoms.

Some patients with end stage radiographic knee OA may have been inappropriately listed for operative intervention on the basis of severe radiographic changes despite only having mild symptoms. To eliminate the possibility that the best functioning TKR group and UKA group patients may have been inappropriately listed, those patient with OKS greater than one standard deviation above the mean were removed from the TKR and UKA patient groups for this final section of the analysis.

4.5. Results.

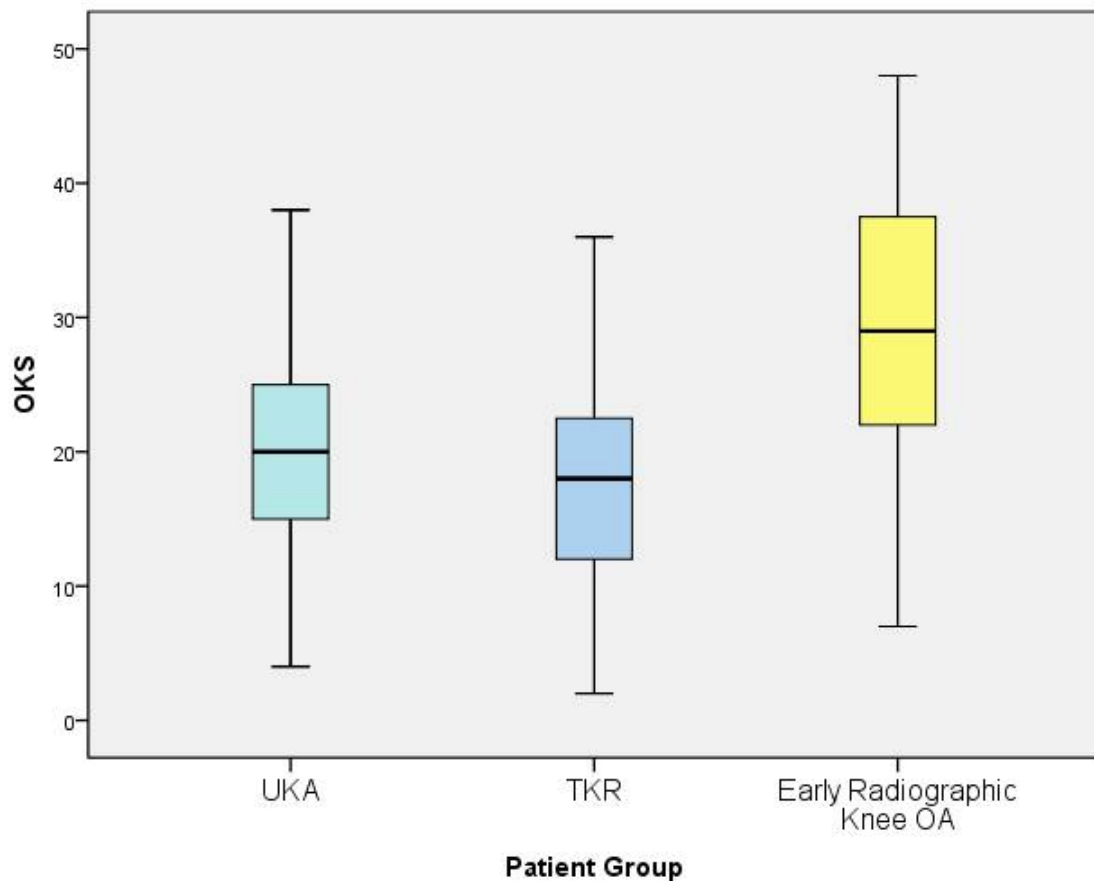
In the early radiographic OA group ($n = 100$) there 50 males and 50 females ($p=1.00$). In the TKR group ($n=200$), there were significantly more females than males (120 females (60%), 80 males (40%) $p<0.05$). In the UKA group ($n = 192$) there were 86 (44.8%) males and 106 females (55.2%) ($p=0.149$).

1. Comparison of age between early radiographic OA group, UKA group and TKR group indicated that the TKR (mean = 70.3, SD +/- 10.1) group were significantly older than UKA (mean = 67.1, SD +/- 9.9). Both UKA group and TKR group were significantly older than the early radiographic OA group (mean = 57.4 SD +/- 10.9).
2. A one way ANOVA for comparison of mean OKS between early radiographic

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OA, UKA and TKR groups indicated that as expected TKR OKS score was significantly worse (mean = 18.11, SD +/- 7.7) than both UKA (mean = 20.35, SD +/- 7.7) and early radiographic OA group (mean = 29, SD +/-9.139) as shown in Figure 4.5.1.

Figure 4.5.1.: Box and whisker plot comparing OKS between early radiographic knee OA group, TKR group and UKA group.



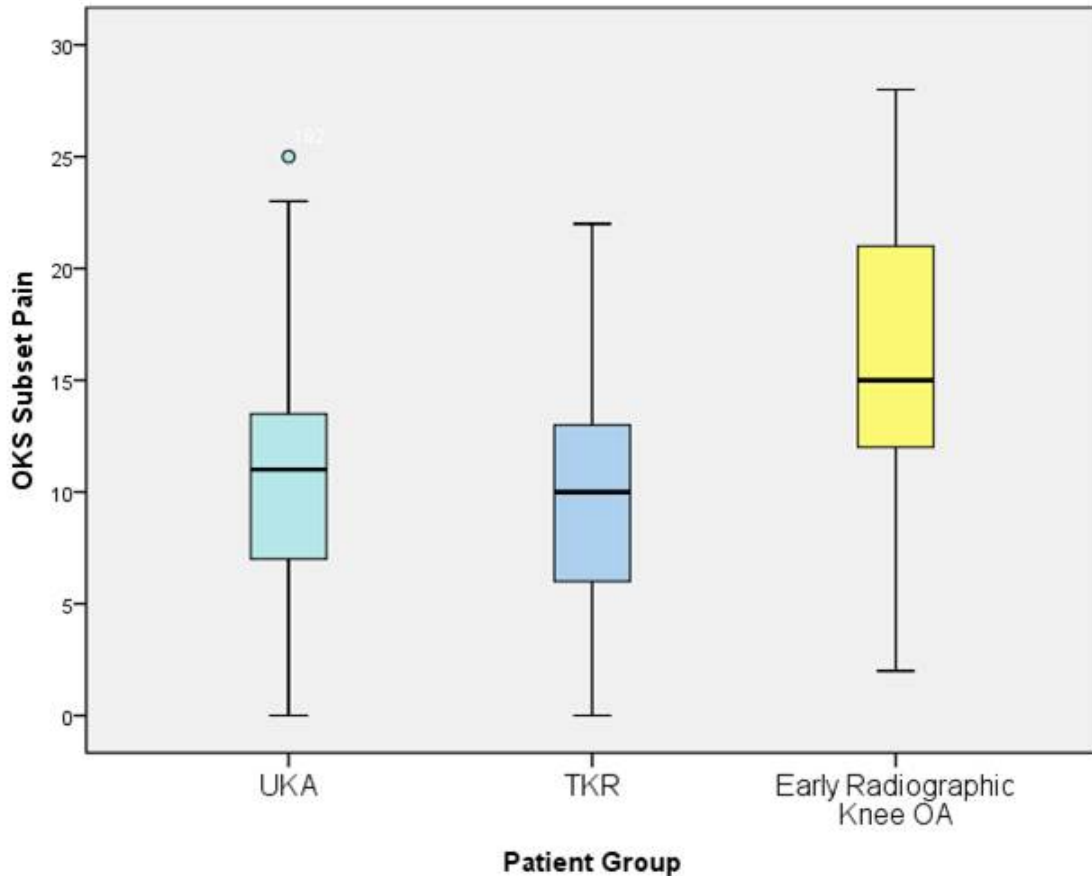
In addition, UKA group had worse scores than early radiographic OA group ($p = 0.00$).

3. A one way ANOVA for comparison of mean OKS pain domain score between early radiographic OA group, UKA group and TKR group indicated that there was no significant difference between UKA group (mean = 10.29, SD +/-

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4.7) and TKR group, (mean = 9.63 SD +/- 4.5), (p = 0.51) However, both UKA group , (p=0.00) and TKA group (p = 0.00) were significantly worse than early radiographic OA group (mean = 16, SD +/- 5.5) as shown in Figure 4.5.2.

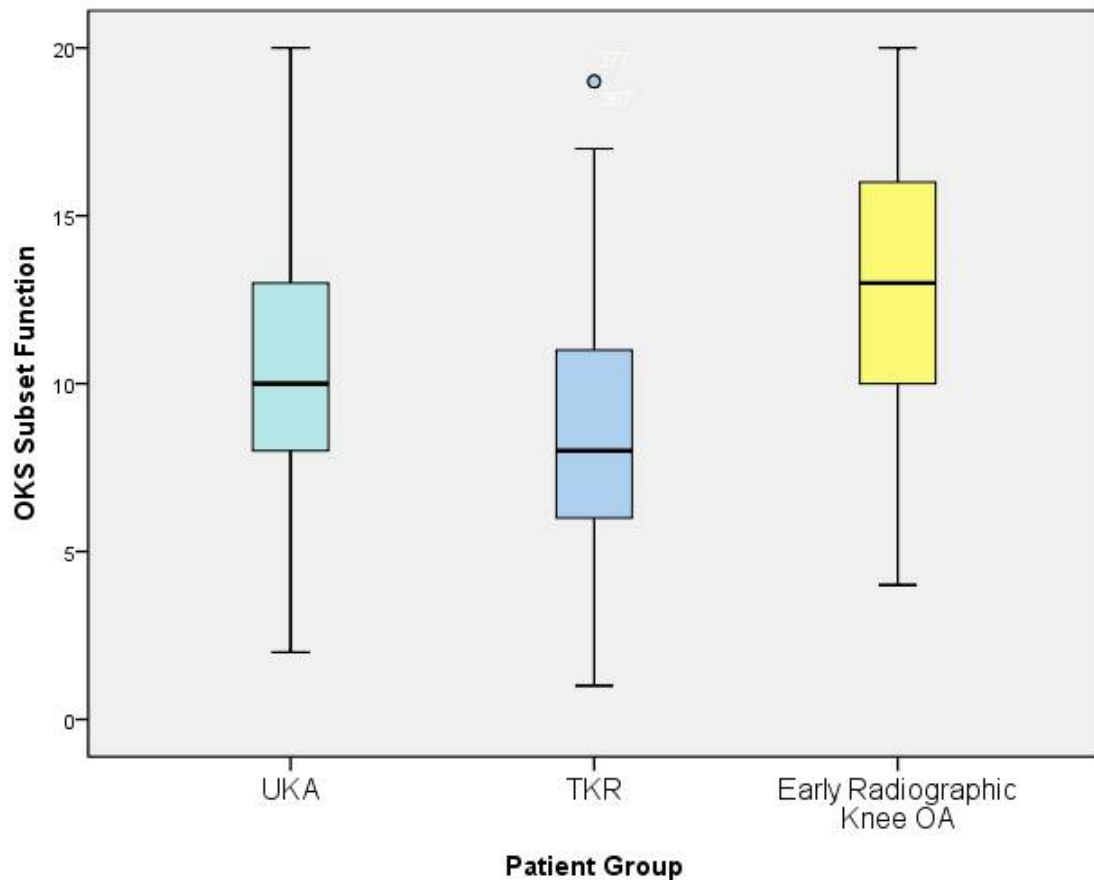
Figure 4.5.2.: Box and whisker plot comparing OKS pain domain scores between early radiographic knee OA group, TKR group and UKA group.



4. A one way ANOVA for comparison of mean Function scores between early radiographic OA group, UKA group and TKR group indicated that TKA group (mean = 8.56, SD +/- 3.7) was significantly worse than UKA group (mean = 10.16, SD +/- 3.73) (p = 0.00). Both were significantly worse than early radiographic OA group (mean = 13.21, SD +/- 4.21.) (p = 0.00) as shown in Figure 4.5.3.

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Figure 4.5.3.: Box and whisker plot comparing OKS function domain scores between early radiographic knee OA group, TKR group and UKA group



4.5.1. Further analysis results.

Histograms were plotted to demonstrate the overlap of total OKS scores, Pain domain scores and Function domain scores between the early radiographic OA group, the TKR group and the UKA group.

1. Whilst the means for the groups were different, the population profiles had substantial overlap.
 - For total OKS, 78% of individual patients with early radiographic OA had an OKS score equal to individual patients presenting for UKA, whilst 74%

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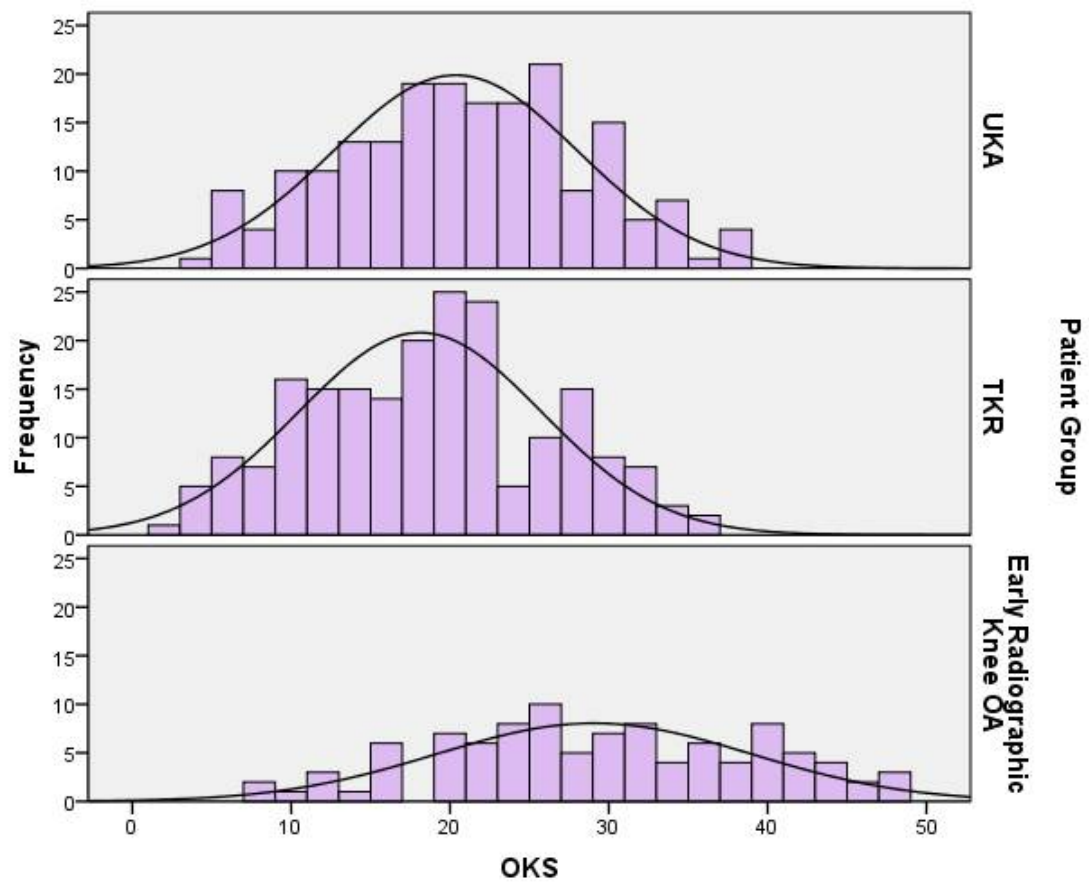
of individual patients with early radiographic OA had scores that equal to or worse than individual patients presenting for TKR (see Figure 4.5.4).

- For OKS pain domain scores, 95% of early radiographic OA group individual patients had pain domain scores equal to individual patients presenting for UKA and 83% of individual early radiographic OA group patients had scores equal to individual patients presenting for TKR (see Figure 4.5.5)
- For OKS function domain scores, 100% of early radiographic OA group individual patients had function domain scores equal to individual patients presenting for UKA and 95% of early radiographic OA group individual patients had scores that equal to individual patients presenting for TKR (see Figure 4.5.6)

2. Even if patients with scores one standard deviation greater than the mean OKS are removed from the TKR and UKA groups (to eliminate those highest performing preoperative patients - thereby removing from the analysis those who potentially may have been listed for arthroplasty inappropriately early), individual early radiographic OA patients have an OKS equal to 40% of individuals presenting for UKA and 29% of individuals presenting for TKR.

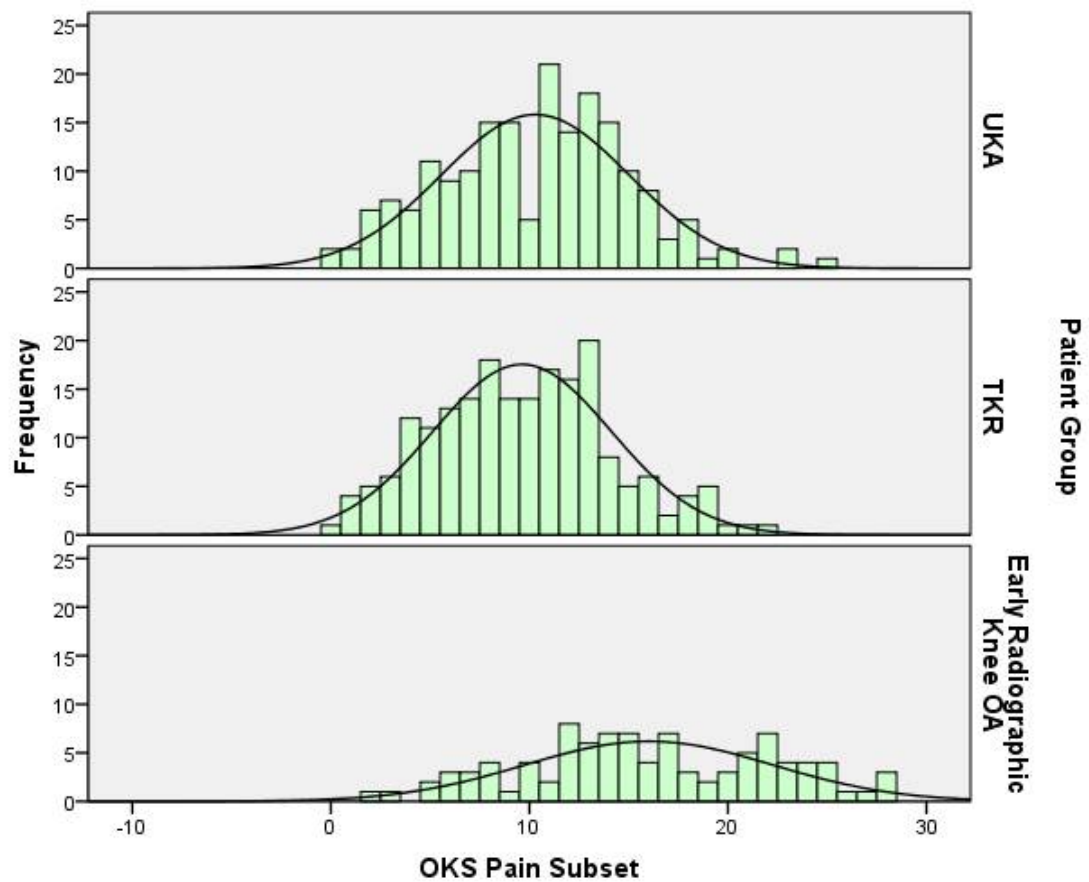
4. The demographic and cross sectional symptom profile of patients with early knee osteoarthritis.

Figure 4.5.4.: Histogram comparing OKS between early radiographic knee OA group, TKR group and UKA group.



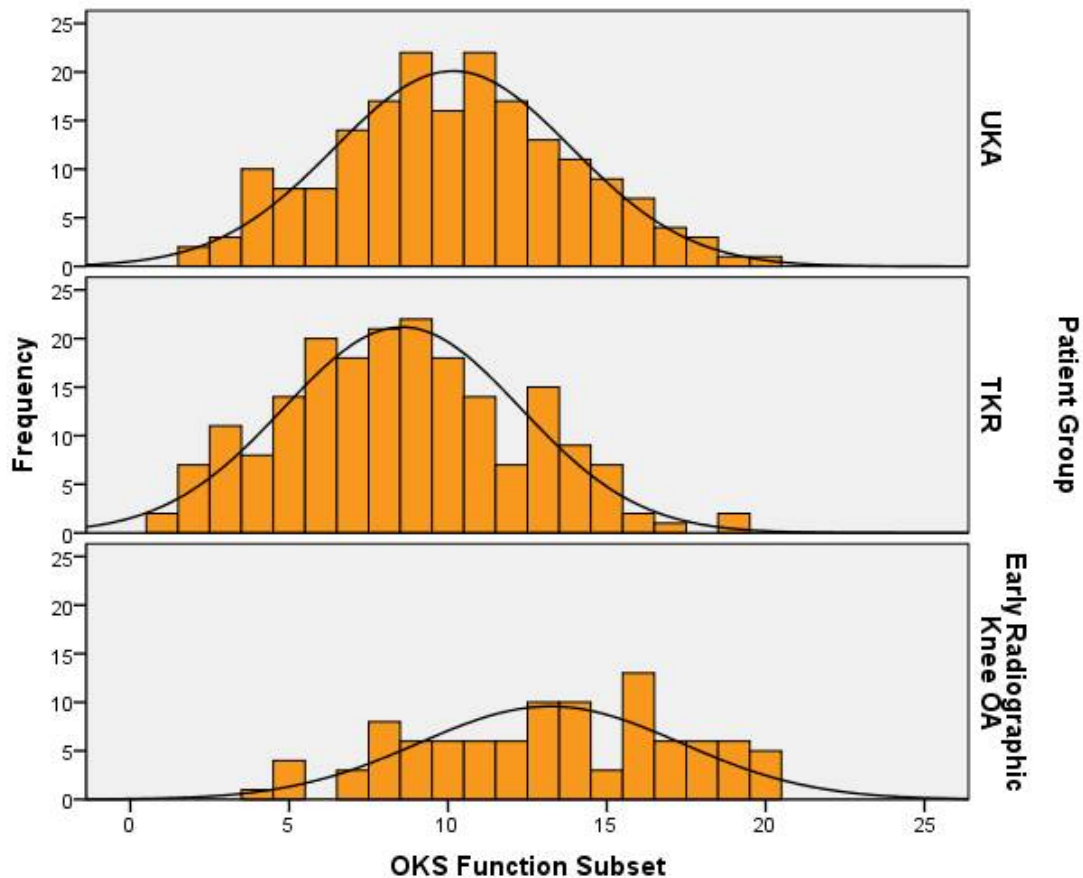
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Figure 4.5.5.: Histogram comparing OKS pain domain scores between early radiographic knee OA group, TKR group and UKA group.



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Figure 4.5.6.: Histogram comparing OKS function domain scores between between early radiographic knee OA group, TKR group and UKA group



4.6. Discussion.

This is the first time that an attempt has been made to characterise the cross sectional symptom, pain and function profile of patients with early structural anteromedial gonarthrosis.

The early radiographic OA group are typically younger than the TKA and UKA group patients. This may indicate that they are earlier in the disease process at presentation.

A comparison of the means for the groups indicate that the early radiographic OA

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group patients on average have significantly better OKS and have significantly less pain and better function than both the TKA group and UKA group patients. Again this is not unexpected if they are considered to be earlier in the disease process.

However, on further inspection of the spread of the scores, in up to 78% of individual cases their clinical knee scores suggest that if they had had worse structural changes then surgeons would consider established surgical interventions such as arthroplasty. This means that, in these individual patients, their pain and function (and overall OKS) is as bad as those with end stage disease. As knee arthritis represents a spectrum of disease, the variation in symptomatology in early radiographic knee OA group is greater than the variation in symptomatology in the other two groups. The heterogeneous nature of their symptom profile may account, in part, for the tendency for their symptoms, as a group, to be underestimated. This study indicates that, within the early radiographic OA group, a significant proportion have pain and functional impairment at presentation to secondary care as severe as those presenting with end stage structural change knee arthritis.

Whilst the discordance between radiographic findings and clinical symptoms is well established in those with severe arthritis [258] [259] an attempt to fully understand the clinical profile of these early radiographic knee OA patients has not been previously undertaken. Bedson et al [145] have described the discordance between the clinical and radiological findings in knee OA but did not stratify symptoms according to radiographic severity. Luyten et al [169] have attempted to classify the problem according to the occurrence of two episodes of pain lasting more than 10 days in one year, and radiological findings. Again, they did not describe the severity of pain or loss of function and there was no attempt to compare the pain to those patients with full thickness disease. The natural course of the clinical symptoms of knee pain leading to OA over a 12 year period was described by Thorstensson et al [260], but

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there was no comparison to those patients with established OA and groups were not stratified by radiographic severity. Those who have not progressed to advanced radiographic grade disease, but have symptomatic knee OA, have been previously termed “partial thickness OA”[141] and “early knee OA” [169, 40].

We suggest that these descriptors do not describe the disease in a useful way, and that patients should be considered on the basis of both their structural radiographic change and their clinical symptoms as described here.

This study demonstrates that, in terms of function, on an individual basis, in the early radiographic AMG group 100% had a function profile as bad as individuals in the UKA group and 95% had a function profile as bad as individuals in the TKR group. In terms of pain, on an individual basis, in the early radiographic AMG group 95% had a pain profile as bad as individuals in the UKA group and 83% had a pain profile as bad as individuals in the TKR group. Even having eliminated the highest performing preoperative patients (thereby removing those who may have been listed for arthroplasty inappropriately early), individual early radiographic OA patients had an OKS equal to 40% of individuals presenting for UKA and 29% of individuals presenting for TKR.

There are a number of limitations to this study. The Oxford Knee Score [152] was used to determine the overall severity of symptom, pain and functional impairment experienced by the early radiographic knee OA group. However, it may be that other pain and function scores would more accurately describe the nature of the symptoms experienced by patients. Similarly, the decision to operate on patients in the UKA group and the TKA group was used as a proxy for the severity of knee osteoarthritis (i.e. this was used to include patients in groups that were defined as “end stage” of disease). Preoperative radiographs were reviewed to ensure they had a preoperative diagnosis of KL 3-4, but despite this it may be that not all had full thickness disease

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at operation. In addition, the OKS was determined in preoperative clinic and may not reflect the symptoms on the day of surgery.

The message from this study is that those with early radiographic AMG often have very severe knee symptoms and that we should not dismiss them as “not ready for intervention” solely on the basis of their radiographs. Although it may be difficult to advise patients with these symptoms and radiological findings on the best course of treatment for their knee, this study provides clear evidence that their condition should not be dismissed as benign. More work is required to determine indications for and use of non arthroplasty treatments in non-full thickness OA [199]; there remain few guidelines for these joint preserving procedures and it is therefore difficult for surgeons to decide on or recommend optimal treatments. The non arthroplasty surgical procedures that are available for these patients will be selected on the pattern and distribution of cartilage damage, and thus the use of MRI appears to be prudent in the clinical assessment of patients with significant pain and loss of function with early grade disease on radiographs.

4.7. Conclusions.

- Null Hypothesis 1 is rejected. Those with early radiographic knee OA have on average a higher OKS (indicating a better functioning knee at presentation to secondary care) than those with end stage disease. However, despite this, inspection of overlap of scores indicates that up to 40% of individuals have pain as bad as those presenting for UKA and 29% as bad as those presenting for TKA.
- Null hypothesis 2 is rejected. Those with early radiographic knee OA had significantly less pain and functional impairment than those with partial early

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radiographic knee OA. However, functional impairment overlap between groups was greater than for pain, indicating that in these younger patients, functional impairment appears to drive their lower Oxford knee scores to a greater extent than pain.

- Patients with early radiographic knee OA demonstrate considerable overlap in the severity of their symptoms with those demonstrating end stage arthritis structural changes within the knee. Patients with early structural changes of arthritis in their knee should not be assumed by clinicians to have mild disease. In many cases their symptoms are as bad as those with end stage structural changes.

This chapter has examined the symptomatic profile of patients with early radiographic knee OA at presentation to knee clinic and therefore provides a “cross sectional” view of their symptoms. Interestingly 14 of the early radiographic knee OA patients had knee scores greater than 40, indicating a high functioning knee. At first glance this perhaps appears unsurprising, but as previously mentioned, to obtain referral to secondary care patients must have severe knee symptoms uncontrolled by conservative measures. Therefore, to see so many knees with no symptoms is unexpected. On discussion with patients they often report that their knee feels “better now than it did when I saw my GP” suggesting that the pain and functional impairment varies over time, or that patients are getting some spontaneous improvements (and therefore potentially exacerbations too) in their symptoms. In order to investigate this further the next chapter will investigate the natural history of these patients over a one year period, to explore how symptoms vary over time.

5. The longitudinal symptom profile of patients with early radiographic knee arthritis.

5.1. Introduction.

In Chapter 4 it was noted that a number of patients with knee OA present to the clinic with an OKS of up to 48 (the maximum score for this PROM). This appears counter intuitive - the indication for referral to clinic is knee pain and functional impairment and these patients apparently had no symptoms. These results may reflect an insensitivity of the OKS as a measurement tool of knee pain in early adult knee arthritis. However, recently published work suggests that this is not the case [155]. On discussion with these patients, it appears that a variation in symptoms was not uncommon. In some patients their pain had spontaneously resolved between referral and clinical consultation in the knee clinic. Studies of knee OA pain demonstrate that knee pain varies between patients in terms of both its nature and intensity [127] [261] [134]. However, the way in which symptoms change longitudinally has not been explored in great detail. Of the studies that look at patient reported outcome measures of pain over time in those with radiographic knee arthritis [129, 130, 262, 134], most

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describe the change in pain between two time points (typically recruitment and then at a fixed time point up to three years later). They do not describe the fluctuations in pain experienced by patients during this time period. A quantitative description of this variation over one year has not been previously explored in patients with early adult disease. The LEAP study [132], which investigated fluctuations in joint pain, looked at both hip and knee pain but only looked at fluctuations over a 12 week period. In addition, the authors did not stratify for severity of OA and had no radiographic criteria for inclusion. They demonstrated that patients demonstrated weekly variation in pain, and that improvements in pain correlated with improvement in activities of daily living, decrease in days off work, improved sleep and reduced healthcare usage.

An understanding of the longitudinal pain profile in early adult knee OA is important for two main reasons. Firstly, it will allow patients to understand how their symptoms might change over time. Secondly, for the surgeon managing the patient in clinic and potentially offering surgical interventions, an appreciation that variations in symptoms can occur may lead to the avoidance of surgery until a clearer pattern of the pain and its chronicity has been established. Understanding longitudinal pain profiles and timing interventions to optimise pain relief is a major goal of early OA treatment.

This chapter aims to understand how the pain and function profile of those with early radiographic OA changes over a one year period. In particular, variation in symptoms over a one year period and monthly during those 12 months are examined. In an attempt to predict the pattern of symptoms experienced by individuals, a multivariate analysis was performed based on demographic, mood, activity and lifestyle factors.

5.2. Null hypotheses.

1. Patients with early radiographic knee OA do not experience a clinically relevant deterioration in symptoms over 12 months.
2. Patients with early radiographic knee OA do not experience clinically relevant monthly variation in symptoms.

5.3. Materials and methods.

5.3.1. Ethical approval.

Ethical approval for this study was received from National Research and Ethics Committee South Central Oxford B (REC reference 11/SC/0050).

5.3.2. Study design.

This was a longitudinal observational cohort study with recruitment between June 2011 and May 2012 and data collection until May 2013. All patients who met the the study entry requirements and completed the informed consent process were sent questionnaires relating to their general health and knee symptoms on a monthly basis over a minimum 12 month period.

5.3.3. Patient recruitment.

The first 125 consecutive patients with early radiographic knee OA who matched the study inclusion criteria were prospectively identified and recruited from the Knee Service outpatient clinic at the Nuffield Orthopaedic Centre, Oxford, from June 2011 to May 2012. Standing anterior-posterior (AP) radiographs and 3T MRI imaging of the knee of interest was reviewed to confirm the absence of full thickness cartilage

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lesions. Patients were approached in clinic and asked if they would be interested in taking part in the study. If they agreed to being contacted then their address was taken and a patient information sheet and consent form was sent to them in the post. All 125 agreed to being contacted. If the patient returned the consent form then they were formally recruited to the study. Patients were sent a questionnaire pack on the first Wednesday of each month over a minimum of 12 month period. All questionnaires were sent out by LJ who also collated, recorded and analysed the data. They were asked to fill the forms in with reference to their knee in the previous month and then return the forms in a prepaid envelope to the the Principal Investigator (LJ). The contents of each pack is described in table 5.2 on page 137.

5.3.3.1. Inclusion criteria.

- Patient is willing and able to give informed consent for participation in the study.
- Male or female, aged 18 years or above.
- Underlying diagnosis of early radiographic knee OA, with symptoms not controlled with conservative measures.
- No current plan for operative intervention to the index knee.
- Considered able to complete the questionnaires unassisted.

5.3.3.2. Exclusion criteria.

The participant was excluded from the study if any of the following applied:

- Evidence of full thickness lesions on radiographs or MRI.
- Previous history of intra articular ligament reconstruction.

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- Unable or unwilling to participate.
- Awaiting, or planned arthroplasty.
- Non-English speaking (not all of the patient reported outcome measures have been validated for languages that are not English).

Patients were advised to undergo their normal hospital treatment protocol. This includes physiotherapy to improve quadriceps strength and function, and the use of common painkillers (non steroidal anti inflammatory medications, paracetamol, codeine). All participation in this study was voluntary and patients were not paid for their time.

5.3.3.3. Missing data.

If a patient did not return a questionnaire then they were contacted on two occasions by telephone by LJ. If they failed to return more than two months of questionnaires or indicated that they did not wish to take any further part in the study then they were removed from the study. Reasons for patients leaving the study were recorded and an exploration of their results was performed separately to the main cohort. A total of 102 patients completed 12 months of follow up. Not all patients returned all questionnaires at all time points. Of the 102 patients who completed the follow up, the total number of patients that returned a questionnaire at each individual time point is shown in table 5.1. Of note, only 50 patients were followed up to 18 months. All questionnaires were filled out by post and none over the telephone.

5.3.4. Assessment questionnaires.

Questionnaires were posted to subjects monthly based on the schedule in table 5.2 on the following page.

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Table 5.1.: Number of missing data points per month

Month	Total number of potential patients	Data missing in N patients	% missing data
0	102	3	2.94
1	102	8	7.84
2	102	4	3.92
3	102	6	5.88
4	102	8	7.84
5	102	16	15.69
6	102	15	14.71
7	102	13	12.75
8	102	11	10.78
9	102	9	8.82
10	102	11	10.78
11	102	10	9.8
12	102	15	14.71
13	102	25	24.51
14	102	29	28.43
15	102	33	32.35
16	102	37	36.27
17	102	46	45.1
18	102	44	43.14

Table 5.2.: Schedule for collection of demographic data and Patient Reported Outcome Measures.

Baseline questionnaires	Monthly questionnaires for a minimum of 12 months
Demographic questionnaire	
Oxford Knee Score (OKS)	Oxford Knee Score
Pain Visual Analogue Scale (VAS)	Pain Visual Analogue Scale
Intermittent Constant Pain Score (ICOAP)	Intermittent Constant Pain Score
Knee Osteoarthritis and Injury Outcome Score (KOOS)	Knee Osteoarthritis and Injury Outcome Score
Hospital Anxiety Depression Score (HADS)	Hospital Anxiety Depression Score
Revised Life Orientation Score (LOT-R)	

5.3.5. Data collation (entry into database).

A bespoke, secure, password protected Access database was designed to allow collation of data. Examples of the user interface for demographic data and monthly data collection are demonstrated in Figure B.1.1 and Figure B.1.2 on page 279 in section B.1 on page 278. Following collection, data was exported from Access to Excel (Microsoft Office 2012, Microsoft, Washington, USA) for data inspection and cleaning and then imported to STATA (v12, StataCorp, Texas, USA) for statistical analysis.

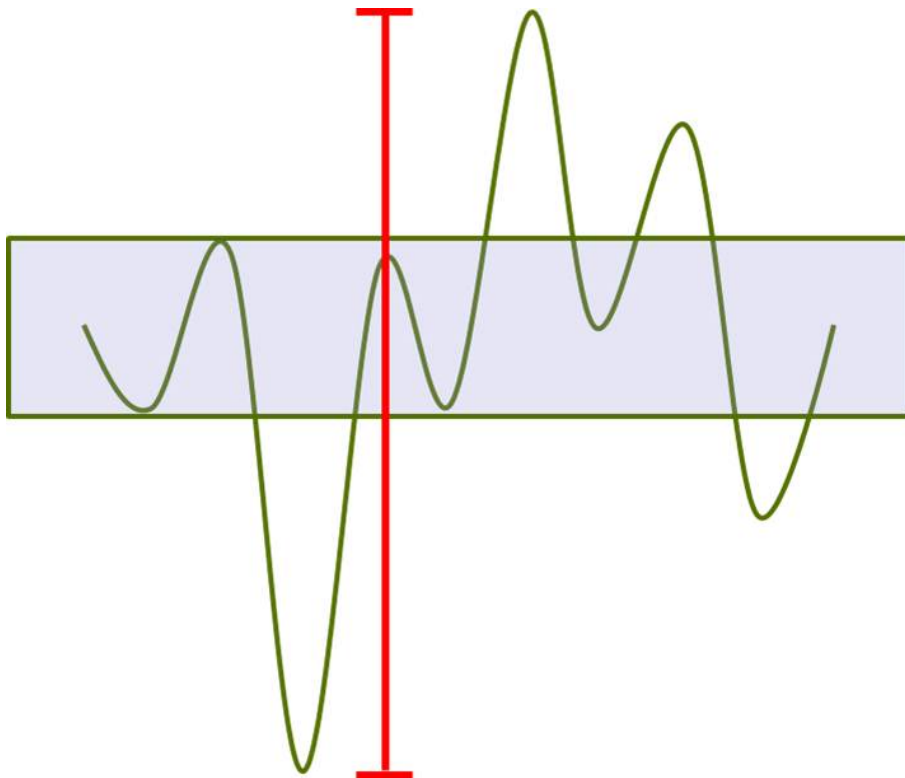
5.3.6. Analysis.

1. Baseline data were summarised descriptively for the entire study population.
2. Longitudinal symptom change between recruitment and 12 months: Overall change. Change in individual PROM scores between baseline recruitment scores and 12 months scores (two time points in total) were determined. Patients were grouped according to whether they improved (by 3 or more OKS points), worsened (by three or more OKS points), or stayed the same (varied by 2 or less points in either direction). Where the OKS data for months 0 and 12 were unavailable, the missing values were substituted with OKS data collected within a two month range of these target values on advice from a medical statistician. Missing data for month 0 was substituted using data from month 1 or, if that was unavailable, month 2. Similarly, missing data for month 12 was substituted with data from months 13, 11, 14 or 10, depending on availability. A comparison of the demographic profile of the improved, stayed the same, and worsened groups was performed.
3. Longitudinal monthly symptom fluctuations: Overall range of symptoms expe-

5. *The longitudinal symptom profile of patients with early radiographic knee arthritis.*

rienced over 12 months. The patient rated highest and lowest monthly pain and function scores recorded over 12 months were used to calculate the overall range in symptoms experienced during a one year period. This is represented in Figure 5.3.1.

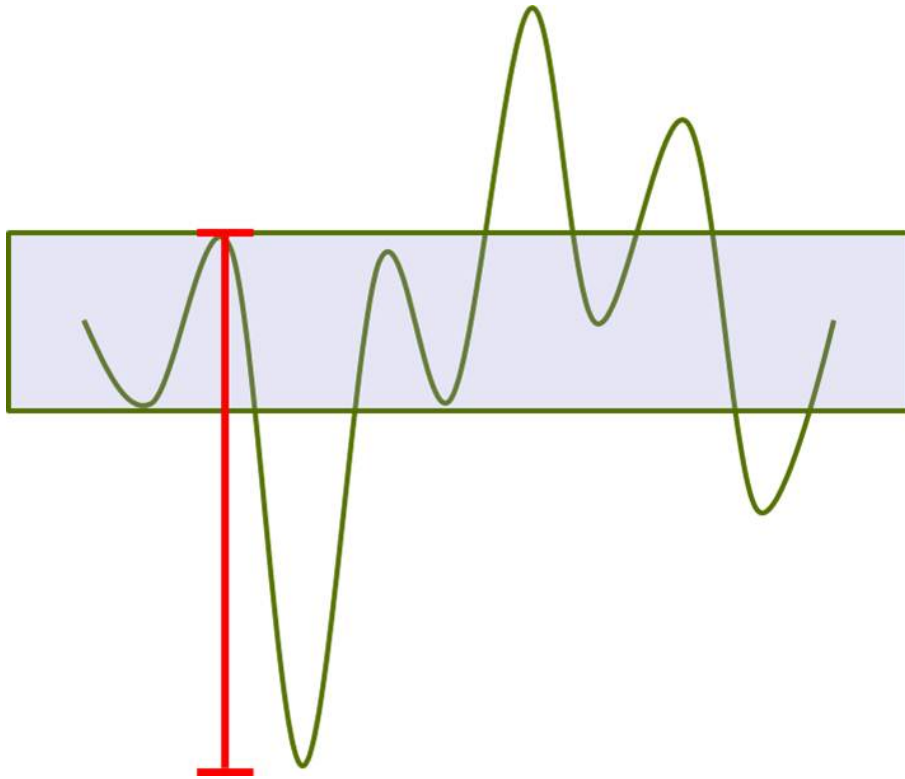
Figure 5.3.1.: Schematic representation of theoretical range of variation in symptoms over 12 months. The red line represents the difference between the highest and lowest PROMs score. The grey box represents the non clinically relevant change that occurs due to inherent variability in the score.



4. Longitudinal monthly symptom fluctuation: Maximum between month change. The maximum between month change was calculated by defining a change event as a difference in OKS of three or more points in either direction between two consecutive months and then determining that largest change for each individual over the 12 month period. This is represented in Figure 5.3.2.

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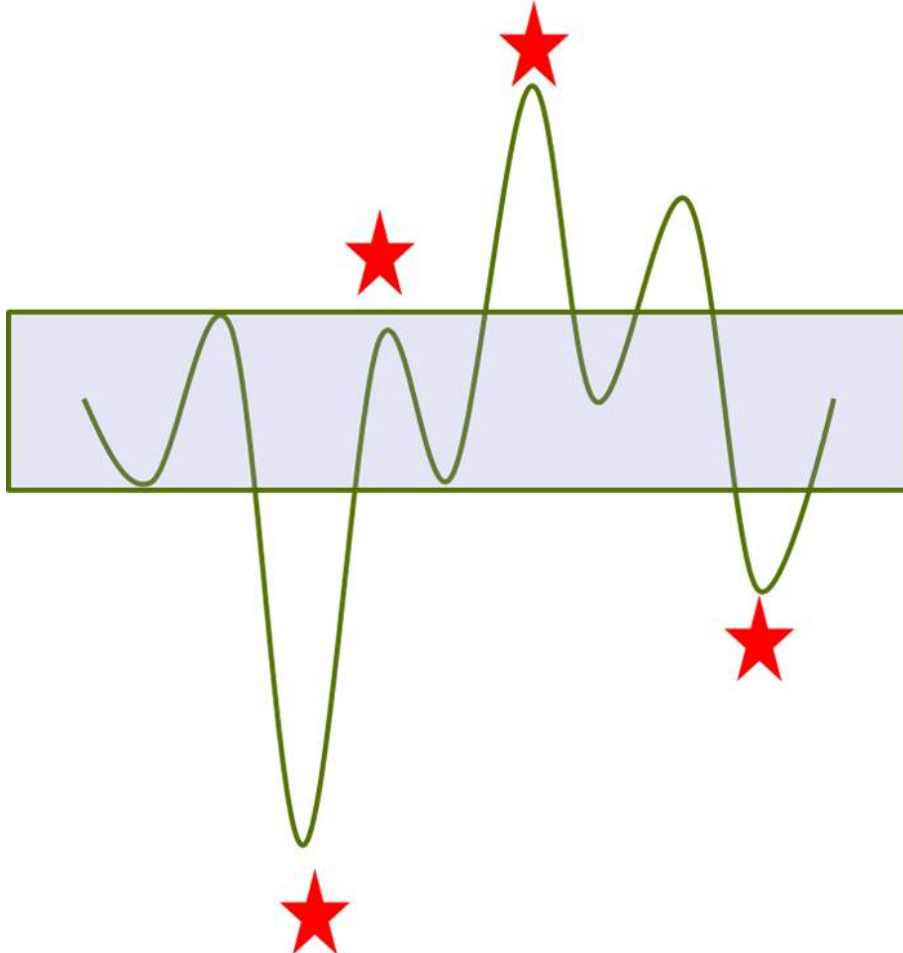
Figure 5.3.2.: Schematic representation of the maximum between month change in PROMs score between two consecutive months. The red line represents the change and the grey box represents the non clinically relevant change that occurs due to inherent variability in the score



5. The frequency of which patients experienced a clinically significant change in symptoms between two consecutive months during one year was also determined. This is the proportion of significant changes between two consecutive months out of all between months observations per patient. This is represented in Figure 5.3.3.

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Figure 5.3.3.: Schematic representation of the frequency of clinically significant change in PROMs score between two adjacent time points. The red stars represent months where the variation from the previous month was clinically relevant. The grey box represents the non clinically relevant change that occurs due to inherent variability in the score



6. Regression analysis. The relationship of change PROM score over one year and variation in PROM score on a monthly basis to other health outcomes and demographic data were explored using regression analysis. Following exploratory uni variate analysis, automatic model selection was used to establish a suitable model using relevant co-variates. A stepwise backwards selection method was then utilised, whereby the selection model starts with the full model, including all potential co-variates used in the exploratory analysis. Then, at each

5. *The longitudinal symptom profile of patients with early radiographic knee arthritis.*

iteration, the least statistically insignificant co-variate was excluded from the model, until only terms with a significance level of 0.05 or less were retained in the model.

5.4. Validation of measurement properties of patient reported measures.

Five different patient reported outcomes measures were collected on a monthly basis. Initial analysis of outcomes were performed on the Oxford Knee Score. The responsiveness of this score in early disease has recently been described by Harris et al [155]. Paired cumulative distribution function curves of the Oxford Knee Score against the other PROMs were plotted to visualise correlation in change of score over 12 months. Spearman's Rho were calculated to determine overall linear correlation. Change was calculated from month 0 (or 1,2 if 0 unavailable to month 12 (or 13,11,14,10 if 12 unavailable) as described previously. Scores were standardised, so that they all ranged from 0 to 100, with higher scores indicating better outcomes. ICOAP and KOOS subsets reversed to enable comparison of the amount of change between scores. Changes in the Oxford Knee Score at 12 months were highly correlated with the changes in the Pain Visual Analogue Scale (see figure 5.4.2 on the following page), Knee Injury Osteoarthritis Outcome Score Pain (see figure 5.4.2 on the next page), KOOS Quality of Life (see figure 5.4.3 on page 144), KOOS ADL (see figure 5.4.4 on page 144) and Symptoms Subset (see figure 5.4.5 on page 145) and the Intermittent and Constant Pain Score (see figure 5.4.6 on page 145). The results of this analysis demonstrate that the OKS measures change in the same way as the other scores and therefore all subsequent analysis was performed regarding the OKS alone.

5. The longitudinal symptom profile of patients with early radiographic knee arthritis.

Figure 5.4.1.: Paired Cumulative Distribution Function (CDF) curve of OKS vs Pain VAS

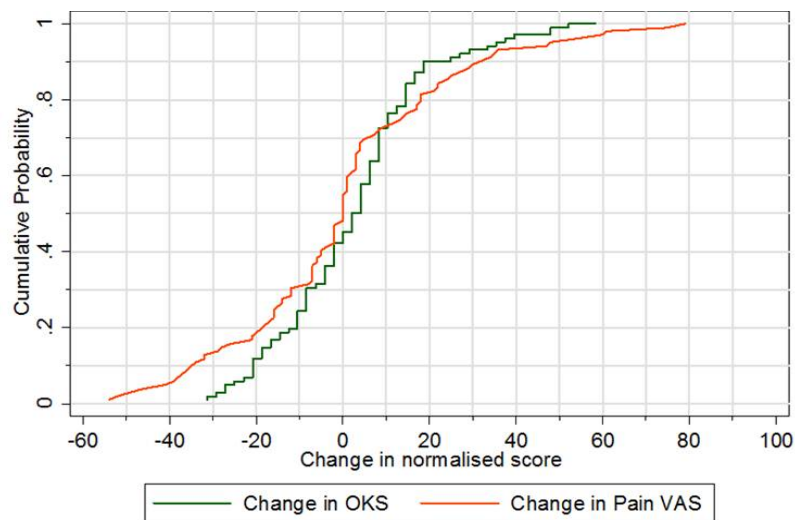
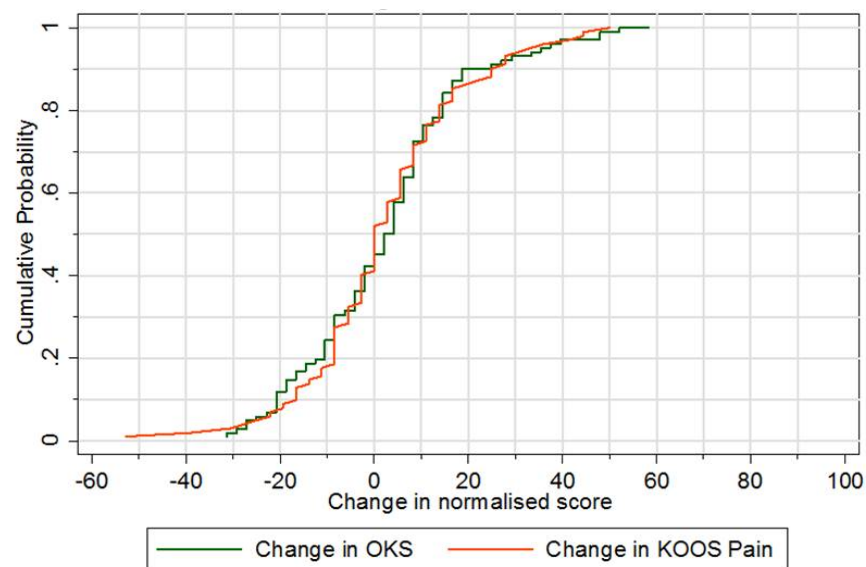


Figure 5.4.2.: Paired Cumulative Distribution Function (CDF) curve of OKS vs KOOS Pain subset



5. The longitudinal symptom profile of patients with early radiographic knee arthritis.

Figure 5.4.3.: Paired Cumulative Distribution Function (CDF) curve of OKS vs KOOS QoL subset.

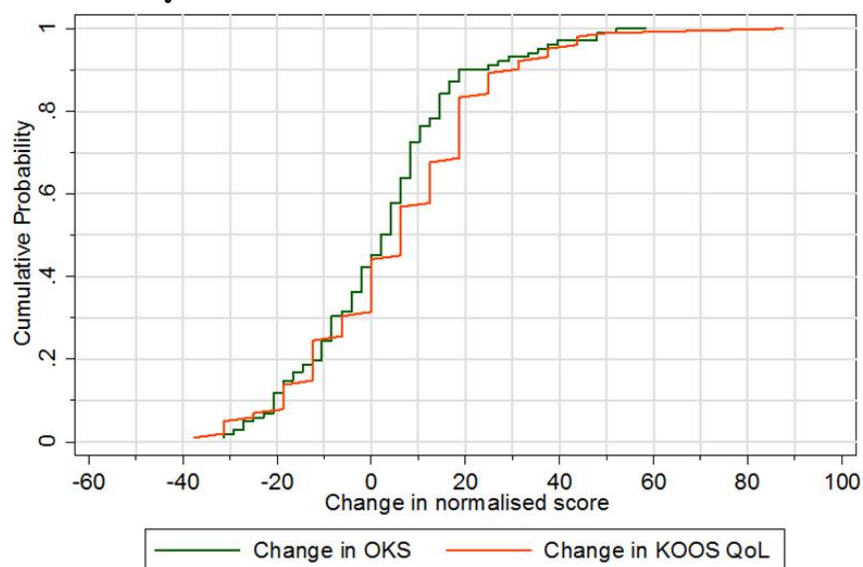
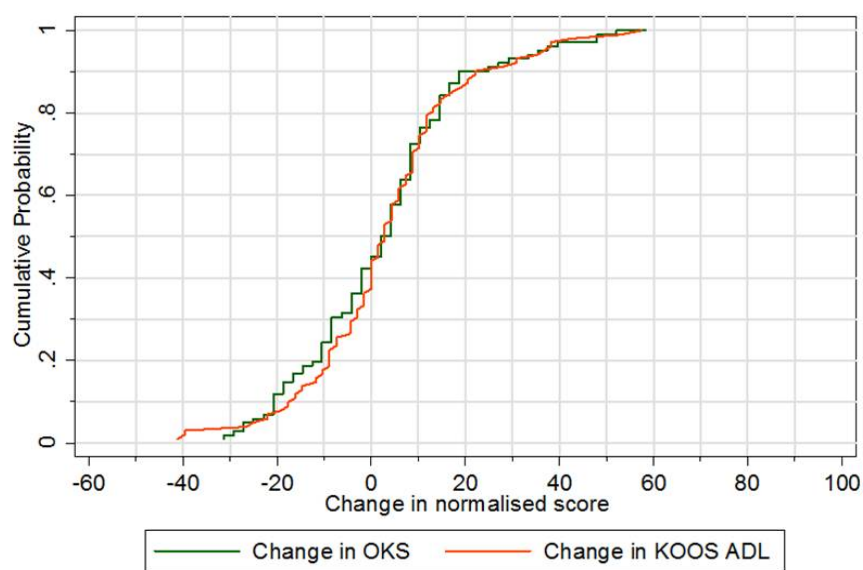


Figure 5.4.4.: Paired Cumulative Distribution Function (CDF) curve of OKS vs KOOS ADL subset.



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Figure 5.4.5.: Paired Cumulative Distribution Function (CDF) curve of OKS vs KOOS Symptoms subset.

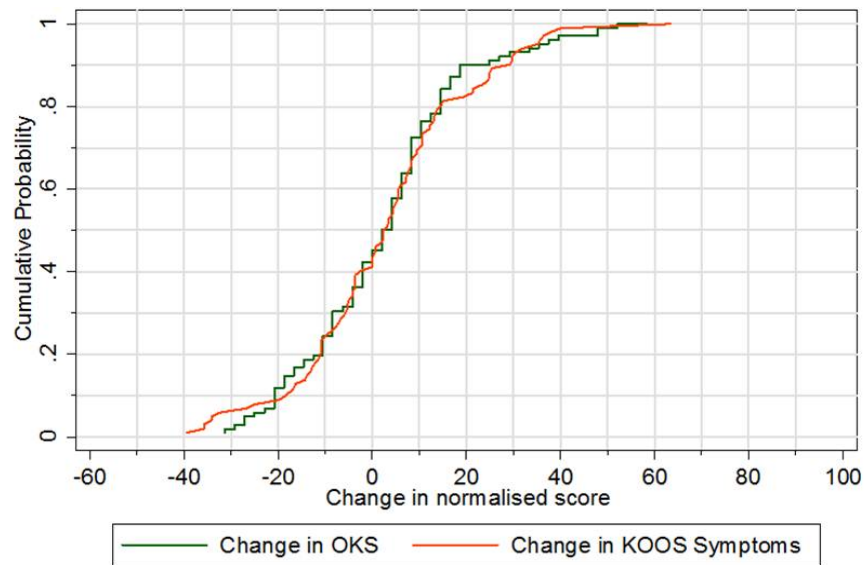
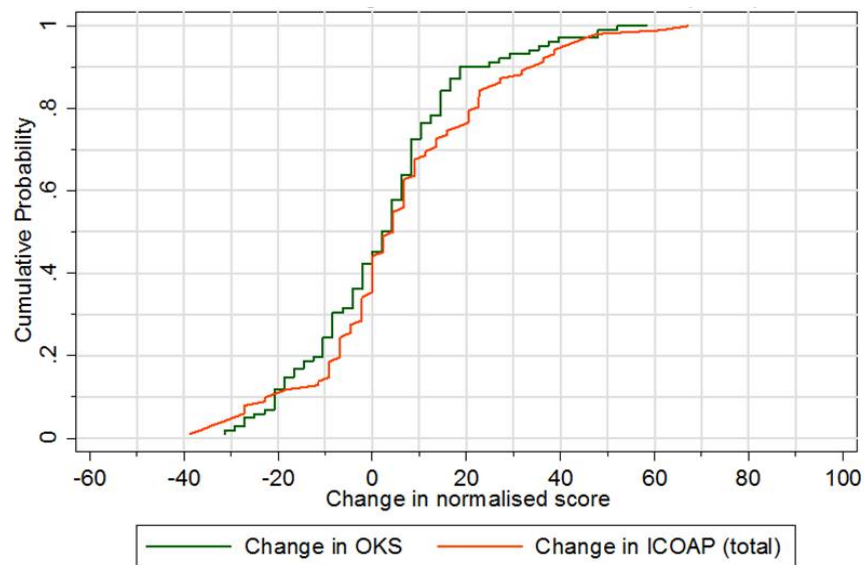


Figure 5.4.6.: Paired Cumulative Distribution Function (CDF) curve of OKS vs ICOAP



A Spearman's Rho was calculated to determine the correlation of change in PROMs with change in OKS. This demonstrates a good level of correlation between the change

5. *The longitudinal symptom profile of patients with early radiographic knee arthritis.*

in OKS over 12 months and the change in other PROMS over 12 months and is shown in table 5.3.

Table 5.3.: Table of Spearman's Rho of correlation of change in OKS with change in all other PROMs

	Spearman's Rho correlation with change in OKS
Pain VAS	0.78
ICOAP total	0.73
KOOS pain	0.76
KOOS QoL	0.62
KOOS ADL	0.75
KOOS Symptoms	0.64

5.5. Results.

5.5.1. Demographic data.

125 subjects were enrolled to take part in the study. Baseline demographic data is shown in table 5.4.

Table 5.4.: Baseline demographic data for entire cohort

		Number
Gender	Male	63 (50.4%)
	Female	62(49.6%)
Age		Mean 58.7 (SD 10.9)
Affected Knee	Right	63 (50.4)
	Left	62(49.6)
Height		Mean 169 cm (SD 9.6)
Weight		Mean 82.14kg (SD 17.95)
BMI		28.52 (SD 5.53)
Employment status	Unemployed	n = 4 (3.3%)
	Homemaker	n = 7 (5.6%)
	Non Manual	n = 66 (52.8%)
	Light Manual	n = 36 (28.8%)
	Heavy Manual	n = 12 (9.6%)
Smoking Status	Non Smoker	n = 111 (88.8%)
	Previous/Current smoker	n = 14 (11.2%)

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5.5.2. Longitudinal pain fluctuations.

5.5.2.1. Baseline and 12 months PROMS scores.

Mean PROM scores for the entire cohort from baseline and 12 month are shown in Table 5.5. Paired t tests were used to compare baseline and 12 months scores as the data was normally distributed. Statistically significant, although not clinically significant changes were seen in all PROMS other than Pain VAS between baseline and 12 months. Overall there was a improvement in mean scores were seen in OKS, Pain VAS, ICOAP (as a low score indicates less pain), HADS (a low score indicates less depression and anxiety) and all KOOS subsets.

Table 5.5.: Baseline and 12 month values of Patient Reported Outcome Measures.

PROM	Mean Baseline Score (SD)	Mean 12 Month Score (SD)	P value (paired samples t test)
OKS	30.0 (10.05)	32.0 (12.2)	0.04
Pain VAS	3.6 (2.6)	3.41 (2.83)	0.42
ICOAP	37.0 (25.14)	29.2 (25.5)	< 0.01
KOOS Symp- toms	58.7 (20.8)	63.2 (23.3)	0.01
KOOS Pain	58.9 (21.87)	63.4 (22.9)	0.02
KOOS ADL	64.9 (24.6)	70.8 (24.9)	< 0.01
KOOS Sport	40.55 (26.4)	46.5 (28.7)	0.02
KOOS QoL	41.0 (23.2)	49.3 (24.7)	< 0.01
HADS	11.6 (8.5)	9.7 (9.4)	< 0.01
LOTR	15.5 (5.12)	N/A	N/A

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5.5.2.2. Longitudinal symptom change between recruitment and 12 months .

Individuals scores at baseline and at 12 months were collated for all patients. Using the substitution method for missing data described in section 5.3.6, of the 125 patients in the dataset a baseline OKS was available for 124 patients and a 12 month follow-up for 102 patients (see table 5.6).

Table 5.6.: Data substitution required for 12 month follow up (to account for individual missing data values at 12 months)

Time from baseline to follow up (months)	Number
10	4
11	6
12	86
13	5
14	1

Depending on the magnitude of the change in OKS from baseline to month 12, patients were classified into the following categories: improving (≥ 3 points), no change (-2 to 2 points), worsening (≤ -3 points) (see table 5.7)

Table 5.7.: Patient categorisation into Improving, No change and Worsening categories.

Symptoms	Frequency
Worsening	31 (30.39%)
No Change	27 (26.47%)
Improving	44(43.14%)
Total	102 (100%)

Up to 43% of subjects we found to demonstrate a clinically relevant improvement in scores over 12 month period, 26% did not change and 30% demonstrated a deterioration in symptoms. A graphical representation of change in symptoms between baseline and 12 months is given in Figure 5.5.1, Figure 5.5.8, and Figure 5.5.9. In all groups, a wide variation in both baseline scores and magnitude of overall change can be seen.

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Figure 5.5.1.: Graph to demonstrate patients with no clinically relevant change in scores between two time points 12 months apart (baseline recruitment and 12 months).

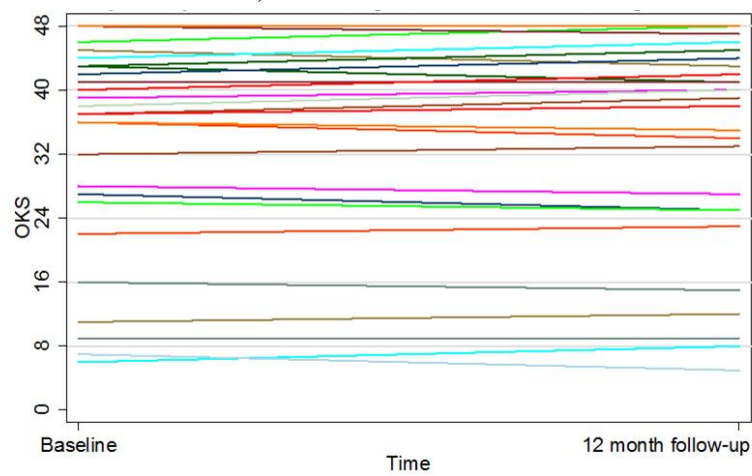
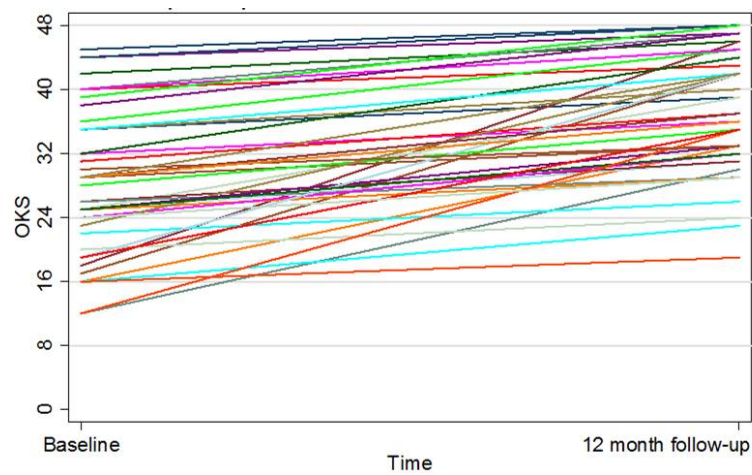
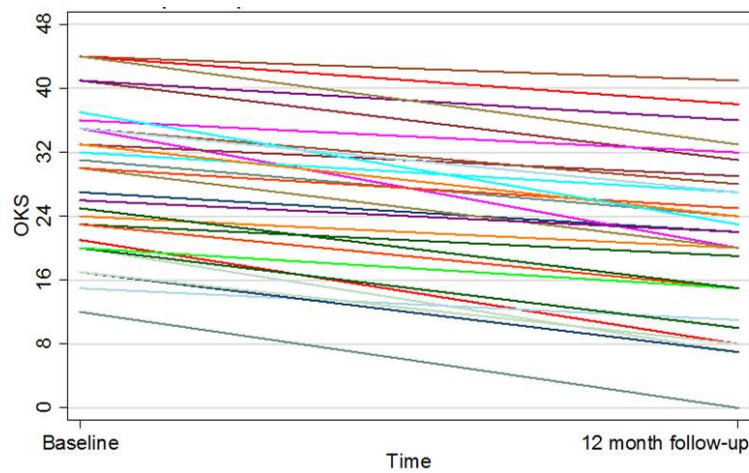


Figure 5.5.2.: Graph to demonstrate patients with clinically relevant improvement in scores between two time points 12 months apart (baseline recruitment and 12 months).



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Figure 5.5.3.: Graph to demonstrate patients with clinically relevant worsening in scores between two time points 12 months apart (baseline recruitment and 12 months).



A comparison of the baseline features of patients in the Worsening OKS group, No change OKS group and Improving OKS group was performed to determine if their presence in each group could be determined by baseline features. For continuous data a non parametric Kruskal-Wallis test was performed as the distribution within the groups were either too small to conclude normality or not normally distributed. For categorical data a chi-squared test of association (or Fisher's exact test if expected counts smaller than 5) was performed. Test results are demonstrated in table 5.5.2.2 and indicate that only the baseline KOOS symptoms value significantly differed between the three groups.

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Table 5.8.: Statistical differences between Worsening, No change and Improving categories by baseline variable.

Variable	p-value
Gender	0.66
Smoking status	0.98
Job	0.92
Affected knee	0.52
Age	0.71
Weight	0.80
Height	0.64
BMI	0.87
Baseline OKS (month 0)	0.10
Baseline OKS (months 0,1 or 2)	0.06
Baseline KOOS ADL	0.21
Baseline KOOS pain	0.14
Baseline KOOS sport	0.14
Baseline KOOS symptoms	0.04
Baseline ICOAP intermittent pain	0.14
Baseline ICOAP constant pain	0.12
Baseline HADS anxiety	0.31
Baseline HADS depression	0.11
Baseline HADS total	0.19
LOTR	0.33
Pain VAS	0.11

A detailed comparison of the baseline KOOS symptoms for the three groups indicates that those with higher median KOOS are more likely to be unchanged over 12 months than those with lower values of baseline KOOS symptoms.

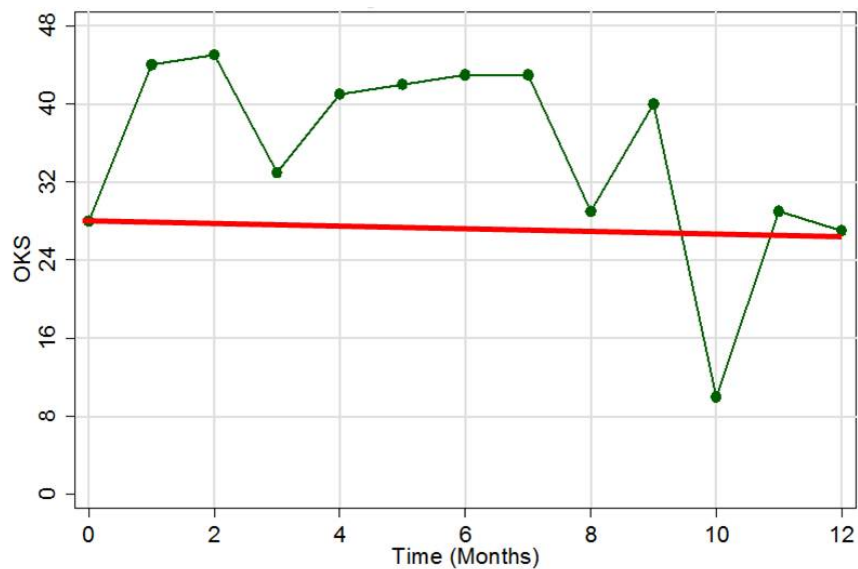
Table 5.9.: Comparison of baseline KOOS Symptoms between Worsening, Unchanged and Improving categories.

	Worsening (N = 30)	No change (N = 26)	Improving (N = 43)
Median	55.36	71.43	57.14
IQR	39.29 - 64.29	53.57 - 85.71	50 - 71.43
5th -95th percentile	25 - 85.71	21.43 - 100	28.57 - 89.29
Range	17.86 - 89.29	17.86 -100	14.29 - 92.86

5.5.2.3. Monthly variation in pain scores between baseline and 12 months..

The change in symptoms between baseline and 12 months (two time points) represent a simplified view of the symptom change demonstrated by patients. Examples of patients that according to the analysis given in section 5.5.2.2 would be classified as No change, Improving and Worsening groups are given in figure 5.5.4, figure 5.5.5, and figure 5.5.6. In each of these examples, there is considerable monthly variation in addition to the overall trend in symptoms over 12 months.

Figure 5.5.4.: Graph of the monthly OKS variation over one year of a patient with no clinically relevant difference between baseline and month 12 scores.



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Figure 5.5.5.: Graph of the monthly OKS variation over one year of a patient with a clinically relevant improvement between baseline and month 12 scores.

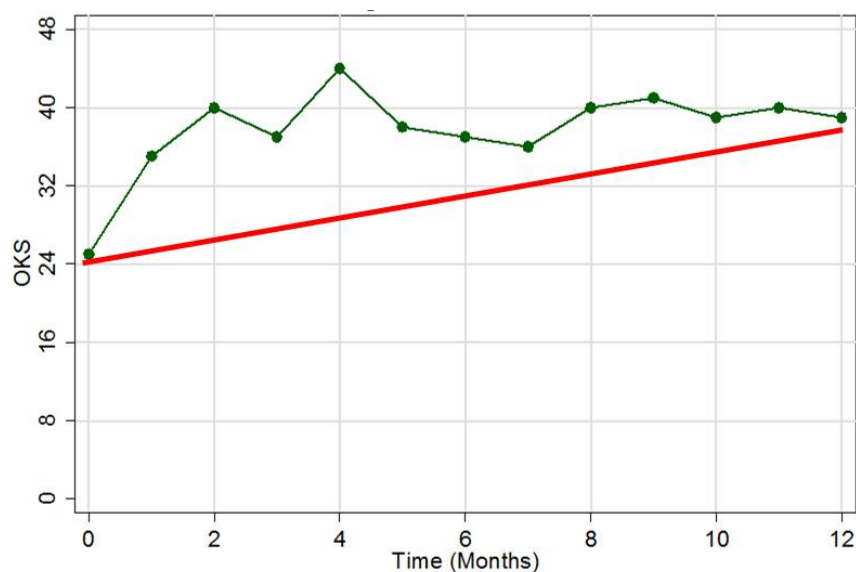
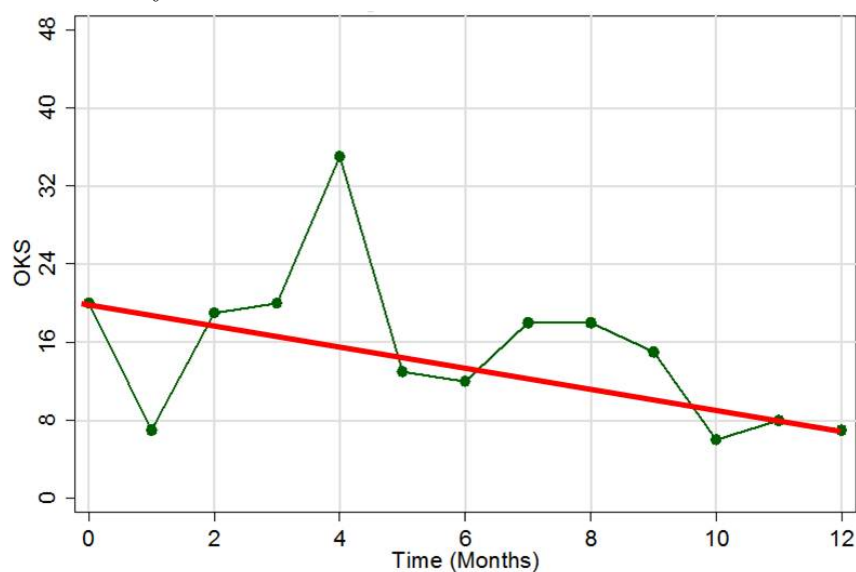


Figure 5.5.6.: Graph of the monthly OKS variation over one year of a patient with a clinically relevant deterioration between baseline and month 12 scores.

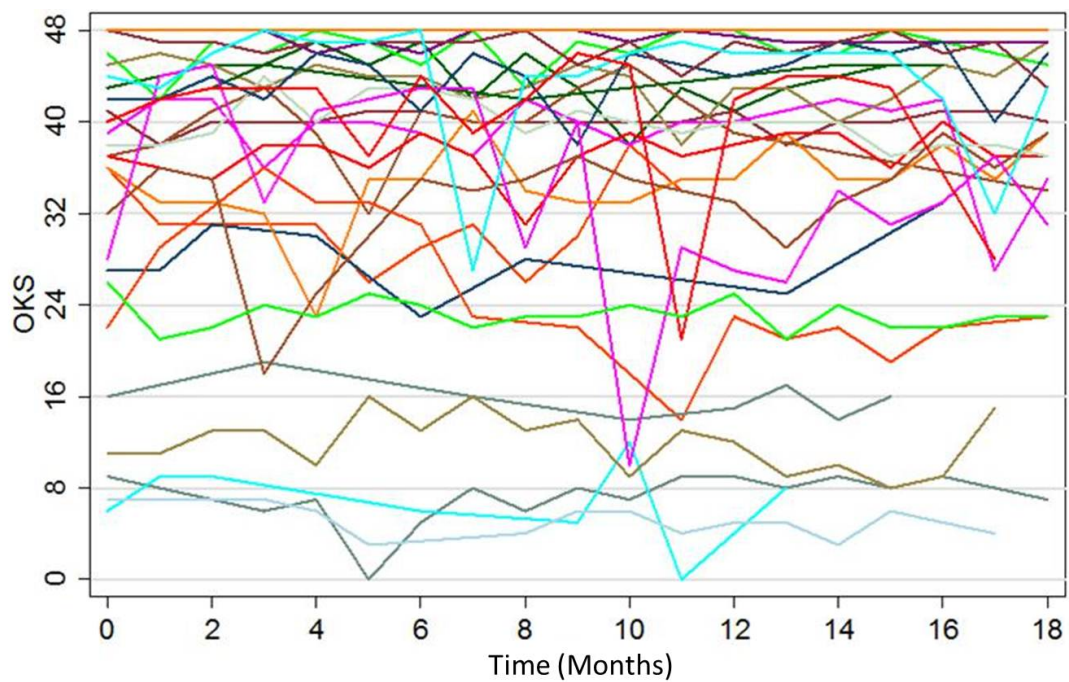


A straight line drawn between two data collection points 12 months apart poorly represents the change in symptoms demonstrated by these patients over 12 months.

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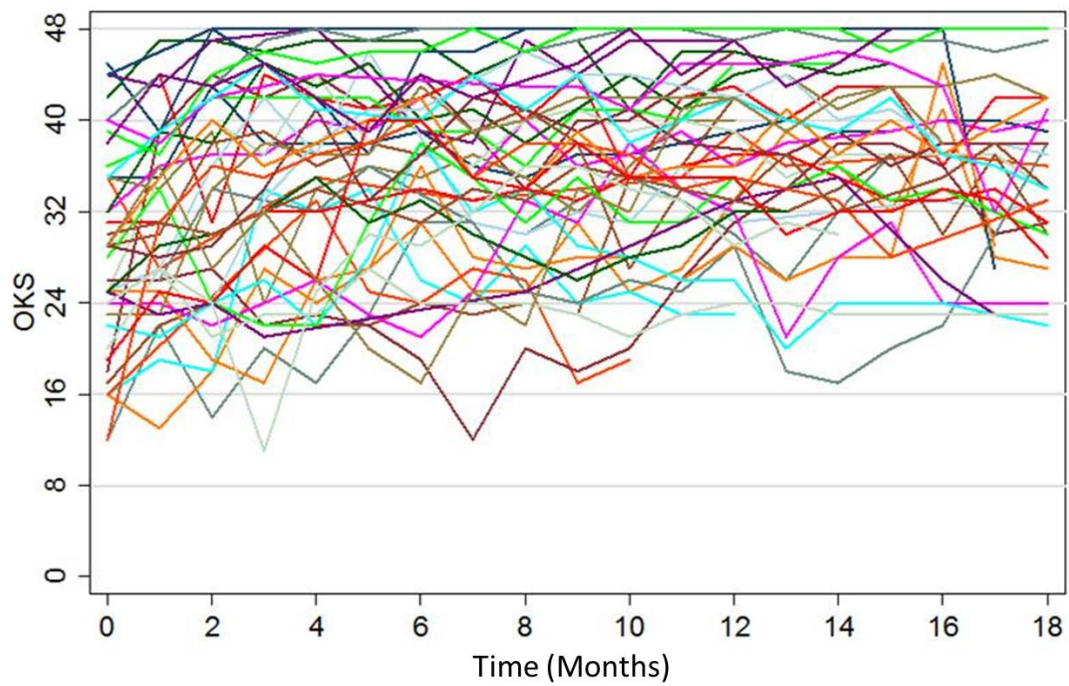
The monthly variation demonstrated by the subjects in the No change, Improving and Worsening categories is demonstrated in figure 5.5.7, figure 5.5.8 on the next page and figure 5.5.9 on page 156.

Figure 5.5.7.: Graph to demonstrate monthly variation in scores in patients who demonstrate no significant change between baseline and minimum 12 months.



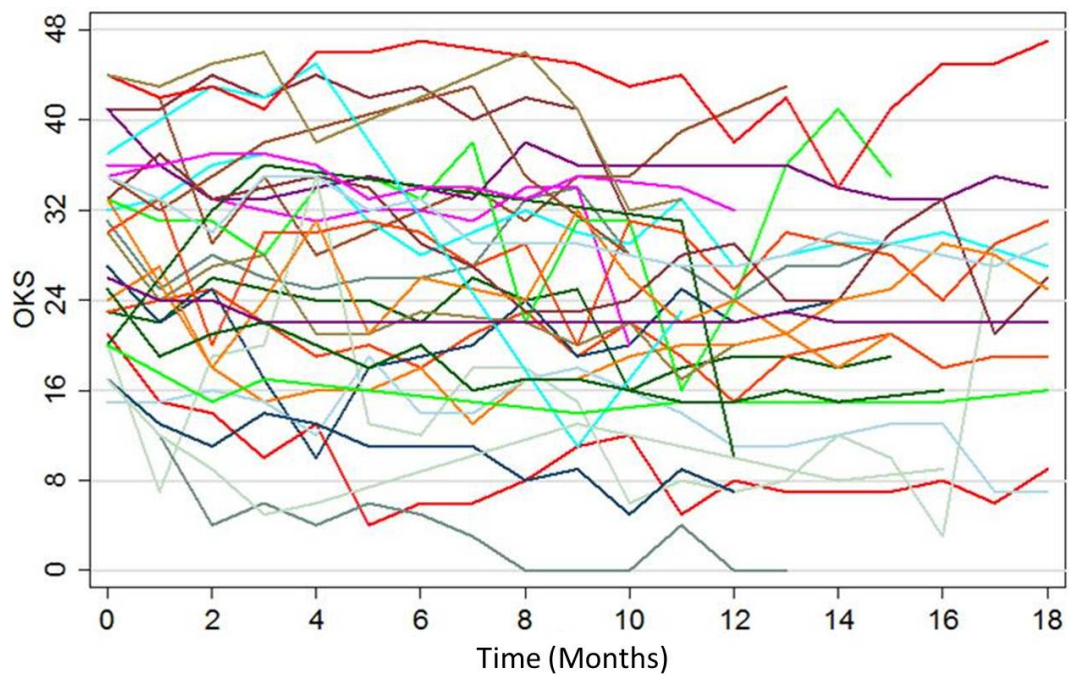
5. *The longitudinal symptom profile of patients with early radiographic knee arthritis.*

Figure 5.5.8.: Graph to demonstrate monthly variation in scores in patients who demonstrate significant improvement between baseline and minimum 12 months.



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Figure 5.5.9.: Graph to demonstrate monthly variation in scores in patients who demonstrate significant worsening between baseline and minimum 12 months.



Inspection of these graphs reveals monthly variation symptoms for patients in all groups.

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5.5.2.4. Range of symptoms experienced over 12 months.

Table 5.10.: Range of variation over 12 months, subdivided into categories based on overall pattern of symptoms

Range of OKS over 12 months	Total cohort	Improving group	No change group	Worsening group	Missing
Number	(N=125)	(N=44)	(N=27)	(N=31)	(N=23)
Median change	12	13.5	8	13	9
IQR	8, 17	10, 19.5	5, 13	10, 16	4, 13
5th/ 95th per- centiles	3, 28	7, 27	2, 25	5, 29	2, 34
Min, max	0, 48	6, 28	0, 35	4, 34	1, 48

Table 5.10 demonstrates that patients with early radiographic knee OA can expect to demonstrate a median total change in Oxford Knee Score of 12 points over 12 months. Patients whose overall symptom pattern symptoms is that of improvement demonstrate, on average, a larger range during the 12 months than those whose overall symptom pattern is one of worsening pain or of pain remaining the same. In this table, 23 patients are counted as missing. These patients are those where no baseline or follow up data were available as per the previously described time range.

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Table 5.11.: Maximum change in OKS between two consecutive months, subdivided into categories based on overall pattern of symptoms.

Maximum change in OKS	Total cohort	Improving group	No change group	Worsening group	Missing
	(N=125)	(N=44)	(N=27)	(N=31)	(N=23)
Median change	7	9	6	7	4
IQR	4, 10	7, 10.5	4, 9	5, 10	3, 8
5th/ 95th percentiles	2, 21	3, 16	2, 24	2, 21	1, 26
Min, max	0, 34	2, 21	0, 30	2, 22	0, 34

Maximum change in symptoms experienced between two months. Table 5.11 demonstrates that patients with early radiographic knee OA will experience a median change of 7 points between adjacent months at some point throughout the year. Patients whose overall symptom pattern is of improvement demonstrate, on average, a larger change between two consecutive months than those whose overall symptom pattern is of worsening pain or of pain staying the same. It can be seen that 23 patients were counted as missing as they did not have two months where consecutive data points were collected.

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5.5.2.5. Number of occasions when clinically significant variation is demonstrated between consecutive months.

Table 5.12.: The frequency of clinical significant change between two sequential months, subdivided into categories based on overall pattern of symptoms

Frequency of clinical change	Total Cohort	Improving group	No change group	Worsening group	Missing
Number	(N=125)	(N=44)	(N=27)	(N=31)	(N=23)
Mean	44.65 %	48.35 %	35.57 %	45.54 %	46.18 %
Median	41.67	50	37.5	41.67	46.43
IQR	28.57, 58.33	33.33, 60	16.67, 58.33	30, 58.33	20, 75
5th/ 95th percentiles	0, 83.33	16.67, 80	0, 75	0, 100	0, 100
Min, max	0, 100	0, 100	0, 75	0, 100	0, 100

As seen in Table 5.12, on approximately 45% of occasions individuals displayed a clinically significant change in symptoms between adjacent months with those demonstrating an overall improvement in symptoms having greater frequency of change than those with worsening or no change overall. In addition to the information displayed in Table 5.12, overall 11/125 or 8.8% of participants did not experience any significant change in OKS between two sequential months over the 12 months. Of these, 1/44 (2.27%) demonstrated an overall increase in OKS, 3/27 (11.1%) demonstrated no change in OKS and 2/31 (6.45%) demonstrated an overall decrease in OKS. In addition, 23 of the total patients were categorised as missing as they had insufficient data to categorise them into any of the change categories.

5.5.2.6. Validation of monthly variation.

If patients demonstrate significant monthly variation, then depending on when the end point of the study is defined will affect the category that the patient is placed

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into (Improving, No change or Worsening).

Take, for example, a patient with an OKS of 30 at recruitment, an OKS of 35 at month 11, an OKS of 26 at month 12, and an OKS of 30 at month 13. This patient will be classified differently depending where the arbitrarily defined end point of the study is placed. They would be classified into the Worsening group if the study ends at month 12, Improvement group if the study ends at month 11, and if at month 13 their OKS has changed to 30, they would be again recategorised into the No Change group. In order to explore further and address these concerns, 86 patients were followed to up to 15 months. Recategorising the data collected at Month 3 as Baseline, and Month 15 as Month 12, a sensitivity analysis was performed to see if there was significant movement between categories by subjects. Patients were reclassified into the change categories based on their change in OKS from month 3 (substituted by month 4,2,5,1 if not available) to month 15 (16, 14, 17,13). This is demonstrated in Table 5.13 .

Table 5.13.: Reclassification of subjects in to Worsening, No change, and Improving categories based on change between 3 months and 15 months.

Change over 12 months (Month 3- Month 15)	Frequency	%
Worsening	16	18.6
No Change	42	48.8
Improving	28	32.6
Total	86	100

A comparison of classifications when the same patients are considered from baseline - Month 12, and Month 3 to Month 15 is shown in Table 5.14. A kappa test for agreement following recategorisation demonstrates that patients remained within the same category in 48.24% of the time leading to a kappa value of 0.22, thus indicating moderate agreement at best.

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Table 5.14.: Cross tabulation of recategorisation between months 0-12 and months 3-15.

Change in OKS over 12 months (from 0-12)	Change in OKS over 12 months (from 3-15)				
		Worsening	No Change	Improving	Total
	Worsening	8	8	6	22
	No Change	4	16	5	25
	Improving	4	17	17	38
	Total	16	41	28	85

5.5.3. Regression analysis.

5.5.3.1. Attempt to predict range of change (uni variate analysis)

Using a stepwise backwards model selection with a significance level of 0.05 for a variable to remain in the model, the final model only includes the KOOS ADL and OKS baseline variables, indicating that the addition of other variables does not significantly improve the model fit. However, as the two PROMs in the final model are highly correlated to each other, they should not be included into the model simultaneously as this would cause problems with multicollinearity (i.e. the statistical model may produce inconsistent and unreliable results). OKS is selected to remain in the final model as its p-value in the uni variate model was more significant. The regression model predicting the range in the OKS over 12 months using baseline KOOS pain (and the corresponding quadratic term) explains 11% of the variation in the outcome around the mean (R^2 , coefficient of determination). Whilst there are statistically significant differences in the average range of OKS over time for different baseline OKS scores, only a small percentage of the variation can be explained by the model.

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Table 5.15.: Uni variate analysis to determine if any baseline characteristics are associated with overall change in OKS

Variable in model	Regression coefficient	95% CI	p-value	Non linear effect in Model?
Baseline OKS	-0.25	-0.38 - -0.11	0.00	Yes
Gender (male ref category)	0.26	-2.55 - 3.06	0.86	N/A
Age	-0.06	-0.2 - 0.08	0.40	No
BMI	0.08	-0.17 - 0.34	0.53	No
Smoker	-0.04	-4.49 - 4.41	0.98	N/A
Employment details				
Light manual:	1.69	-1.61 - 4.98	0.31	N/A
Heavy manual:	2.19	-2.81 - 7.19	0.39	N/A
Knee affected (left knee is ref. category)	-1.38	-4.17 - 1.42	0.33	N/A
Baseline ICOAP intermittent pain	0.09	0.03 - 0.15	0.003	No
Baseline ICOAP constant pain	0.07	0.02 - 0.11	0.01	No
Baseline KOOS pain	-0.11	-0.17 - -0.04	0.001	Yes
Baseline KOOS ADL	-0.07	-0.12 - -0.00	0.03	Yes
Baseline KOOS sport	-0.07	-0.12 - -0.022	0.005	No
Baseline HADS Depression	0.15	-0.19 - 0.48	0.38	Yes
Baseline HADS anxiety	-0.02	-0.37 - 0.28	0.89	No
Baseline LOTR	-0.10	-0.38 - 0.19	0.502	No

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5.5.3.2. Attempt to predict frequency of overall change (uni variate analysis).

Using an automatic stepwise model selection method, no co variates significant at the 0.05 significance level were identified. None of the observed data was useful in predicting or explaining the frequency (percentage) of significant changes in a patient's OKS over 12 months as they all had p values greater than 0.05 in the uni variate model.

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Table 5.16.: Regression analysis to attempt to predict the frequency of overall change (in either direction) over 12 months

Variable in model	Regression coefficient	95% CI	p-value	Evidence of non linear effect in Model?
Baseline OKS	-0.41	-0.85 - 0.023	0.06	No
Gender	-2.53	-11.52 - 6.45	0.58	N/A
Age	-0.23	-0.68 - 0.25	0.32	No
BMI	0.21	-0.59 - 1.02	0.60	No
Smoker	-3.59	-17.7 - 10.6	0.62	N/A
Employment details				
Light manual	0.96	-9.43 - 11.35	0.86	N/A
Heavy manual:	-9.78	-25.37 - 5.82	0.22	N/A
Knee affected (left knee is ref. category)	-1.21	-10.2 - 7.79	0.79	N/A
Baseline ICOAP intermittent pain	0.16	-.002 - 0.35	0.08	No
Baseline ICOAP constant pain	0.11	-0.05 - 0.27	0.17	No
Baseline KOOS pain	-0.18	-0.37 - 0.02	0.08	Yes
Baseline KOOS ADL	-0.16	-0.35 - 0.02	0.09	Yes
Baseline KOOS sport	-0.10	-0.27 - 0.06	0.21	No
Baseline HADS depression	0.98	-0.07- 2.03	0.07	No
Baseline HADS anxiety	0.85	-0.10 - 1.81	0.08	No
Baseline LOTR	-0.94	1.82 - -0.05	0.04	No

5.5.3.3. Attempt to predict overall change over 12 months.

The automatic stepwise model selection leaves the baseline KOOS ADL and the baseline OKS as the only significant exploratory variables in the model. However, these two variables were highly correlated (correlation coefficient = 0.9024), which can cause problems with multicollinearity. For this reason, only one of the variables was kept in the final model. Keeping only the baseline OKS in the model to predict the overall change in OKS over 12 months (model estimates above), the regression on the explanatory variable only explains approximately 4% of the variation around the mean of the outcome. It can be concluded that in this sample the baseline OKS is not a very useful predictor of the change in OKS over 12 months.

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Table 5.17.: Regression analysis to attempt to predict the overall change in OKS demonstrated over 12 months

Variable in model	Regression coefficient	95% CI	p-value	Evidence of non linear effect in Model?
Baseline OKS	-0.19	-0.37- -0.22	0.03	No
Gender	1.28	-2.09 - 4.65	0.45	N/A
Age	0.03	-0.14 - 0.21	0.72	No
BMI	-0.03	-0.33 - 0.27	0.83	No
Smoker	-0.37	-5.28 - 4.54	0.88	N/A
Employment details				N/A
Light manual	-0.6846154	-4.29 - 2.92	0.70	N/A
Heavy manual:	-3.88	-9.10 - 1.33	0.14	N/A
Knee affected (left knee is ref. category)	0.18	-3.21 - 3.56	0.92	N/A
Baseline ICOAP in- termittent pain	0.03	-0.036 - 0.11	0.32	No
Baseline ICOAP constant pain	0.039	-.023 - 0.10	0.23	No
Baseline KOOS pain	-0.04	-0.12 - 0.035	0.28	No
Baseline KOOS ADL	-0.0246689	-.0950649 .0457271	0.488	No
Baseline KOOS sport	-0.0701814	-0.1403628	0.027	No

5.5.4. Management of missing data.

Further details on the management of missing data can be seen in section B.2 on page 279.

5.6. Discussion.

This is the first study to examine the longitudinal symptom variation experience by patients with early structural knee osteoarthritis. It demonstrates that, between two time points over a 12 month period, approximately 25% of patients will experience no change in symptoms, 30% will get clinically relevant worsening of symptoms and 45% will experience clinically relevant improvement in symptoms. Patients also tend to experience variation from month to month, with a median range in symptoms in either direction experienced over the 12 months of 12 points on the OKS. In addition, patients experienced median change from month to month of 7 points on the OKS. 91% of patients experience a clinically relevant change in their symptoms between two consecutive months over a one year period. Only 9% do not. On average, patients experience a clinically relevant change between consecutive months on 45% of occasions. Regression analysis did not reveal that any key demographic, lifestyle or activity measurements that were collected as part of the study, could be identified as a significant predictor of either the change, frequency or range of change experienced by patients.

Other studies on the variability of symptoms experienced by patients with knee arthritis do exist. However, to our knowledge this is the only study that examines those with early radiographic knee OA on a monthly basis for 12 months. As part of the Bristol OA500 looking at those with established knee OA, Dieppe et al [131] reported on the change in knee OA symptoms over a 36 month period in 415 patients.

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Of these, 58% worsened, 21% remained unchanged and 21% improved. They did not inspect for monthly change over this time period. In a study over 2 years that looked at patients post knee meniscectomy, Paradowski et al [129] demonstrated that 16% improved, 72% remained unchanged, and 12% deteriorated. In a very thorough study of those with hip and knee osteoarthritis that were followed for their weekly variation in pain over three months, Hutchings et al [132] demonstrated that 49% of patients demonstrated a within week fluctuation in pain of 2 points or more on the WOMAC scale. Decreases in knee pain were associated with greater productivity and improved mood scores. The work in this chapter did not confirm this.

This study has a number of limitations. There was a drop out rate of 17%. However, as these patients did not have any characteristics in either their demographic or pain profiles that distinguished them from other members of our cohort, they were treated as missing at random. We monitored pain on a monthly basis. Although others have monitored pain more frequently than that, previous work from our unit [155] has demonstrated good stability of all the scores on a weekly basis. In addition, our methodology required patients to report their pain experienced over the preceding two or four weeks and therefore monitoring with any greater frequency would not have been appropriate given the validity of the scores. We used the questionnaires in this study due to their robust method of development and their recognised validity. It may be that the use of other tools may have been more appropriate. We did not monitor for or attempt to correlate with change in radiographic findings. Whilst this is a potential confounding, the radiographic requirements for recruitment into the study were strict, ensuring homogeneity of subjects. In addition this was a project that specifically aimed to explore symptom change. As demonstrated in our results, the time at which a patient enters and leaves the study dramatically affects which group (improving, unchanged, worsened) that they were categorised into. This study

5. The longitudinal symptom profile of patients with early radiographic knee arthritis.

had no intervention and therefore the “start” and “end” of the study were difficult to define and were arbitrarily determined by the referral pattern to clinic by the general practitioner. As shown in the results, altering the arbitrarily defined start and end point meant that 19 % (compared to 30%) worsened, 49% (compared to 25%) remain unchanged, and 33% (compared to 45%) improve. Nonetheless, the range and frequency of variation remain unchanged. Interestingly we were unable to determine any co variates that helped predict either the overall change, range of change, average change or frequency of change experienced by patients. This may represent a failure to include sufficient co variates in the model. Other co variates might include seasonal variation, effect of pain medications or change in activity over time and these factors should be included in further studies on this topic. All our patients underwent the standard treatment of pain relief, physiotherapy and weight loss advice for their knee, however their compliance with this may have been variable and we did not attempt to stratify for this. In the future, other studies should do so.

5.7. Conclusions.

1. The first null hypothesis is rejected. 20-30% of patients with early radiographic knee OA will experience a clinically relevant worsening of symptoms, 25-49% will remain unchanged and 33-45% of patients will experience a clinically relevant improvement of their symptoms over 12 months.
2. The second null hypothesis is rejected. 91% of all patients with early radiographic knee OA experience a clinically relevant change in symptoms between consecutive months over one year. In addition, patients can expect to experience a variation in symptoms on 45% of consecutive measurement points.

5.8. Future work.

Understanding the variation in symptoms experienced by patients is clearly important in both informing the patient as to how their symptoms will change over time, in addition to assisting the surgeons in timing their interventions. Currently, an increased number of patients are being recruited to this cohort which will be followed longitudinally for five years. In addition, longitudinal collection of radiographic and MRI assessment of structure will allow a longitudinal correlation of changes in structure to changes in symptoms.

6. The chronology of meniscal extrusion in the development of structural knee osteoarthritis.

6.1. Introduction.

In the previous two chapters, the cross sectional and longitudinal clinical profile of those with early radiographic knee OA was explored and described. Whilst the structural changes and the symptom profile associated with early knee OA has been elucidated, a number of questions remain about risk factors that lead to the initiation of disease. As part of the recruitment process for the work described in Chapters 4&5, patients underwent radiographic assessment of their knee, including MRI if necessary. It was noted that few patients without radiographic knee OA had evidence of extrusion of the medial meniscus. This is demonstrated in Figure 6.1.1. In contrast, patients with both early and end stage radiographic disease demonstrated the presence of meniscal extrusion in all cases (see Figures 6.1.2 and 6.1.3 for examples) Extrusion and subluxation of the meniscus are terms that should be considered synonymous.

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Figure 6.1.1.: A T1 weighted Coronal MRI Knee demonstrating no evidence of medial meniscal subluxation or medial compartment damage.



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Figure 6.1.2.: A T1 weighted Coronal MRI Knee demonstrating medial meniscal extrusion but no OA (cartilage defects or osteophyte formation) in the medial compartment.



Figure 6.1.3.: A T1 weighted Coronal MRI Knee demonstrating established medial compartment OA and medial meniscal extrusion



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The role of meniscal extrusion in the initiation of osteoarthritis has yet to be fully elucidated. The meniscus is an integral part of a complex bio mechanical system within the knee. It appears to have a key role in spreading loading forces across the hyaline cartilage. Damage to the meniscus, whether due to degeneration, tears, meniscal root avulsion or iatrogenic intervention by the overenthusiastic surgeon, can impair this function [263] [105]. The meniscus has been a common target of investigation for those who are attempting to determine the pathogenesis of osteoarthritis and has already been discussed earlier in this thesis (see section 2.2.6.1 on page 58). The majority of studies that explore the association between meniscal extrusion and the development of OA in humans are cross sectional and compare the extent of extrusion in those with established OA to those with normal knees [116][118] [264]. Others retrospectively identify those who have had meniscectomy and compares rates of radiographic OA to those who have not. Those studies that do attempt to follow patients prospectively have included only small numbers, short follow up and heterogeneous cohorts that might include mensical tears, meniscal degeneration and meniscal extrusion as markers of “meniscal damage”[109] [265]. In humans, it is not known whether meniscal extrusion or cartilage degeneration occurs first.

Commonly, meniscal extrusion is measured by identifying a fixed bony point in the knee on coronal MRI slices, usually the peak of the medial tibial spine [266], [121], [264], [267]. This bony landmark ensures that, when comparing scans taken on the same patient at different time points, the same anatomical location in the knee is being inspected. Once the medial tibial spine has been confirmed the horizontal distance between the most medial aspect of the tibia and the most medial aspect of the meniscus at this point is measured. An absolute extrusion distance of 3mm, or greater than 30% of the total meniscal width, is commonly used as the definition of an “extruded” meniscus [?][116][?]. Whilst others have used relative extrusion

distances [268], [269], and more categorical definitions such as “none”, “partial” and “complete” extrusion [121][270], it is clear that accurate measurement of extrusion is essential in determining the outcomes of research studies.

Other methods used for measuring meniscal extrusion include inspecting all coronal slices for the location of greatest extrusion and measuring the horizontal distance at that point [?][271], and segmenting the tibia and meniscus [272, 273, 122] to allow a 3D volumetric analysis. The advantages of performing measurements on an easily reproducible coronal slice include speed and reliability (in that the same anatomical location can be easily located on sequential scans). It is therefore a pragmatic method when a large numbers of scans need to be read. Other methods, such as segmenting the entire meniscus and analyzing the volume of meniscus that overlaps the edge of the tibial edge are not suitable in large cohorts due to the laborious nature of manual segmentation. Fully automated computerized segmentation, may in the future, make this viable [274]. The ideal location for measuring extrusion of the meniscus has not been determined.

This chapter reports the findings of two studies. In the first, common methods of assessing meniscal extrusion are assessed and validated. These methods are subsequently used to explore the role of meniscal extrusion as a risk factor for the development of knee arthritis.

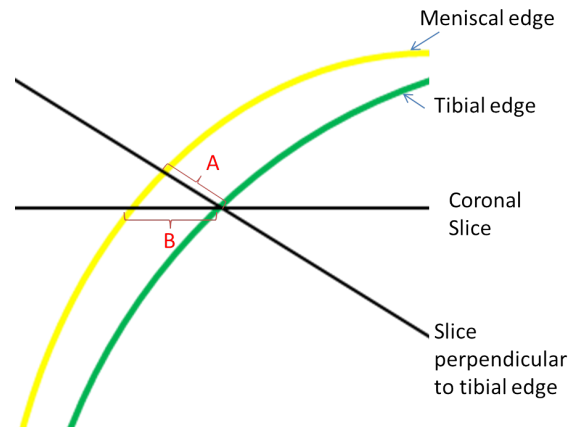
6.2. A validation study comparing methods of assessing meniscal extrusion.

Inspecting the meniscus for extrusion on the coronal slice that corresponds to the highest point of the medial tibial spine (MTS) means that menisci which are not extruded at that point, but are extruded further forward or further backwards, are

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labeled as “not extruded” (i.e. false negatives). Furthermore, measuring horizontal extrusion on coronal slices anterior and posterior to the mid line may artificially increase the “extrusion” as the approximately circular edges of the tibia and meniscus are not parallel here. This is demonstrated by line B in Figure 6.2.1. As the meniscus and the medial tibial plateau can be thought of as two semi circles overlying each other, in theory it would be more appropriate to measure true extrusion by determining the perpendicular distance between the edge of the tibia and the edge of the meniscus. This is demonstrated by line A in Figure 6.2.1. Concerns therefore remain

Figure 6.2.1.: Schematic representation of coronal slice compared to perpendicular slice through tibial edge



that the method used to measure meniscal extrusion affects the derived result. In addition, it is not known whether maximal meniscal extrusion occurs at the same part of the meniscus in all patients. Finally, and based on the two previous concerns, it is not known whether it is reasonable to measure meniscal extrusion at the level of the medial tibial spine in longitudinal cohorts.

In order to address these concerns and to determine the optimum method of measuring extrusion in large longitudinal cohorts, the following aims were identified for this study:

1. To determine

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- the AP location of maximal extrusion if the perpendicular distance between the edge of the tibia and the edge of the meniscus is estimated.

and to compare this to:

- the AP location of maximal extrusion on coronal knee slices using the horizontal distance between tibial edge and medial meniscal edge.
2. To determine if there is method dependent variation in the value of absolute meniscal extrusion measured by the two methods described in 1.
 3. To determine whether the amount of meniscal extrusion measured using the most common method in clinical trials (at the level of the medial tibial spine) correlates with the maximal meniscal extrusion measured using the two methods described in 1.
 4. To determine whether measuring meniscal extrusion at the level of the medial tibial spine is accurate in assessing the true maximal extrusion, and whether this method can therefore be used in larger studies.

6.2.1. Materials and methods.

High resolution 3T MRI scans (Philips Medical Systems International, B.V, Eindhoven, Netherlands) were obtained on 17 patients (17 knees) with early degenerative radiographic knee OA (Kellgren and Lawrence 2 or less). The geometry of each patient's tibia and meniscus were segmented using Mimics (v. 14.1, Materialise, Belgium) and exported as stereo-lithography (STL) files. Meniscal segmentation was performed in a manner previously validated by Bowers et al [275], using meniscal volumes calculated by surface integration.

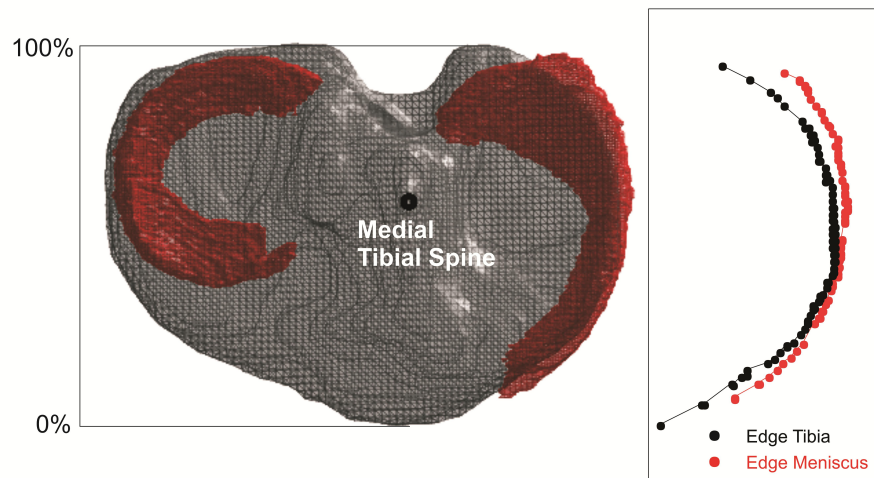
Coronal slices provided near perpendicular views for precise meniscal edge definition at the meniscosynovial rim. Accurate outlining was further aided by the high

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contrast between the low intra meniscal and high extra meniscal signal intensity on T2 weighted images. 3D Meniscal reconstructions were then obtained. These files were imported into MATLAB (R2010b, The MathWorks Inc., Natick, MA, USA) and medial meniscal extrusion was calculated using a custom routine.

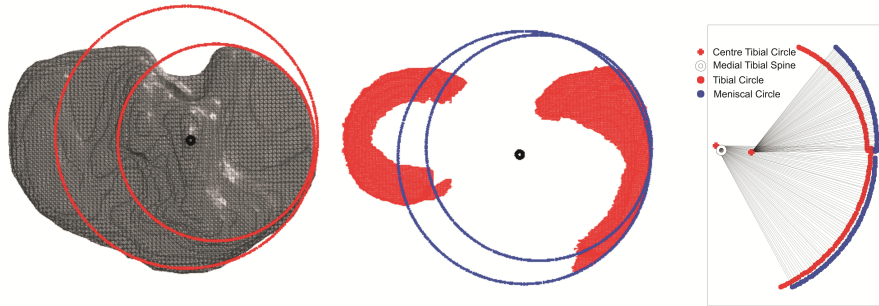
Firstly, the tibia and meniscus geometry were rotated to give a view down the longitudinal axis of the tibia . This was done by the user (LJ) selecting various points across the geometry in different planes. The breadth of the tibial plateau and the highest point (medial tibial spine) were then determined. Two methods were then employed to calculate extrusion. In the first method (Coronal Slices Method) measurements were carried out on slices at 1 millimetre intervals from the front to the back of the tibial plateau in the AP plane. Extrusion was calculated as the horizontal difference between the most medial edge of the meniscus and the tibia. To allow comparison of extrusion between patients, the position of the measurements were expressed as a percentage of the breadth of the tibial plateau i.e. 0% corresponded to the front (most anterior point of joint line) of the tibia, as well as in millimetres from the front of the tibia. The edges of both the meniscus and tibia were linearly interpolated to fill gaps caused by the scan slice thickness. A diagrammatic representation of this is shown in Figure 6.2.2.

Figure 6.2.2.: Segmentation of tibia and meniscus to demonstrate overlap between edges used to calculate meniscal extrusion in Coronal Slices Method.



In the second method (Circles Method) the position of the medial tibial spine was used to divide the tibia and meniscus into anterior and posterior portions. The points on the medial edge of the anterior and posterior tibia and meniscus were selected and circles were then fitted to these points. These four circles were used to estimate meniscal extrusion perpendicular to the medial edge of the tibia. Vectors were projected from the centre of the anterior and posterior tibial circles to corresponding points on the circumference of the circles fitted to the anterior and posterior portions of the meniscus. Extrusion was calculated by subtracting the radius of the tibial circles from the length of the vectors. The position of extrusion was expressed as both a percentage of the tibial breadth and a distance in millimetres from the anterior margin of the tibial joint line to allow a comparison between tibia of different sizes. A diagrammatic representation of this is shown in Figure 6.2.3. Theoretically, this represents the most accurate method of assessing meniscal extrusion.

Figure 6.2.3.: A diagrammatic representation of the circles fitted to meniscus and tibia to estimate perpendicular extrusion in Circles Method



6.2.1.1. Analysis.

Data from MATLAB was imported to SPSS for statistical analysis. Data was found to be non normally distributed and therefore non parametric tests were used. Wilcoxon signed rank tests for paired samples were used to compare the location of the maximal extrusion in the AP breadth of the tibia between the Circles and the Coronal Slices Method.

Friedman's ANOVA was used to compare maximal meniscal extrusion measured by the Circles Method, Coronal slices Method and the meniscal extrusion measured at the level of the Medial Tibial Spine.

A bi variate correlation analysis was used to determine whether the maximal meniscal extrusion measured using the Circles Method correlated more highly with the maximal meniscal extrusion measured using the Circles Method or the measurement at the level of the Medial Tibial Spine.

6.2.2. Results.

The mean AP tibial breadth was 52.9 mm (range 47.2-61.6 mm, st. dev. 3.58.) The highest point of the medial tibial spine was found at mean 29.8 mm (range 28-33

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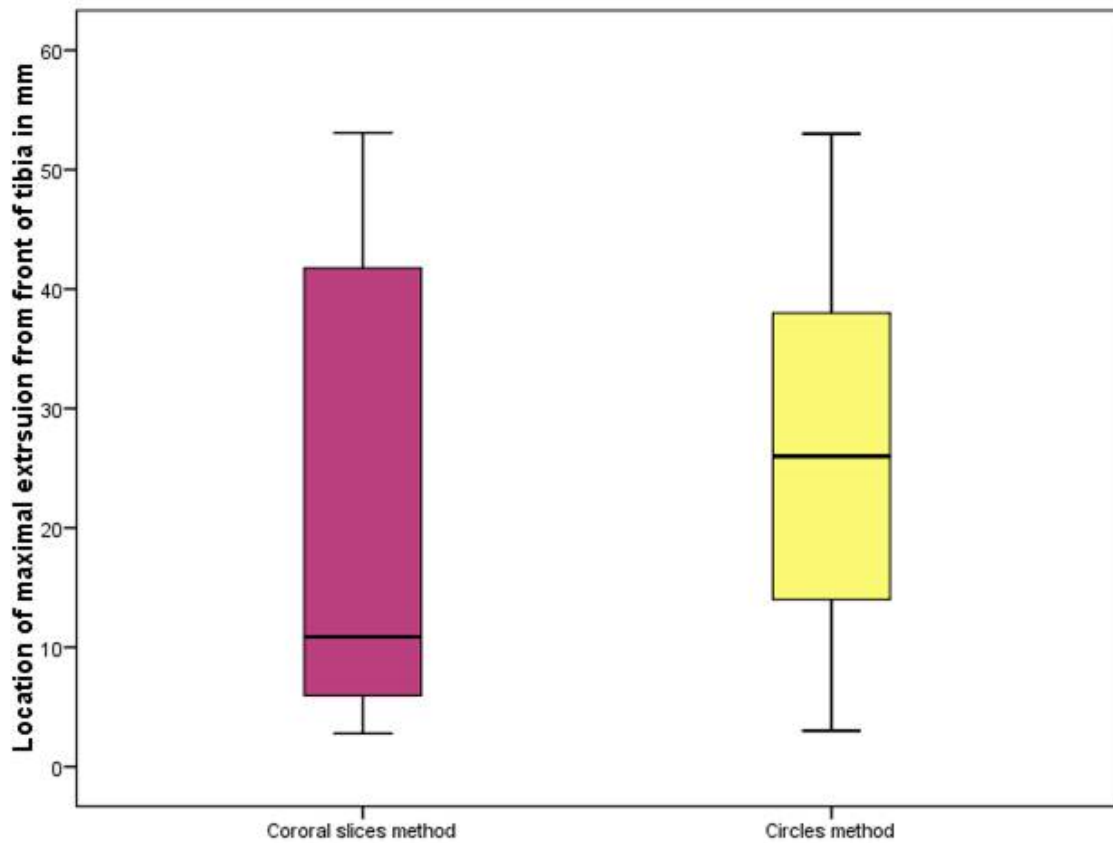
mm, st. dev. 1.7) from the most anterior point of the tibial plateau. On average, this corresponds to 56% of the AP distance breadth of the tibia.

Using the Coronal Slices Method the median maximal location of horizontal extrusion was found to be 10.8mm (range 2.78-53.08 SD18.2, mean 20.3mm) from the front of the tibial plateau, compared to 26mm (range 3-53, st. dev. 15.43, median 26.7mm) using the Circles Method. This is demonstrated in Figure 6.2.4. A Wilcoxon signed rank test for non-normally distributed data revealed a significant difference ($p=0.017$) between the two groups with the Coronal Slices Method consistently measuring the point of maximal meniscal extrusion to be anterior to that of the Circles Method.

This corresponds to a maximum meniscal extrusion occurring at median 21% (5-96 st. dev. 34.32 mean 38.2%) of the AP tibial breadth using the slices method, and median 48% (6-98 st. dev. 28.55 mean 50.17%) of the AP tibial breadth using the circles method. Again a Wilcoxon signed ranks test indicated a statistical significant difference between the two ($p= 0.021$).

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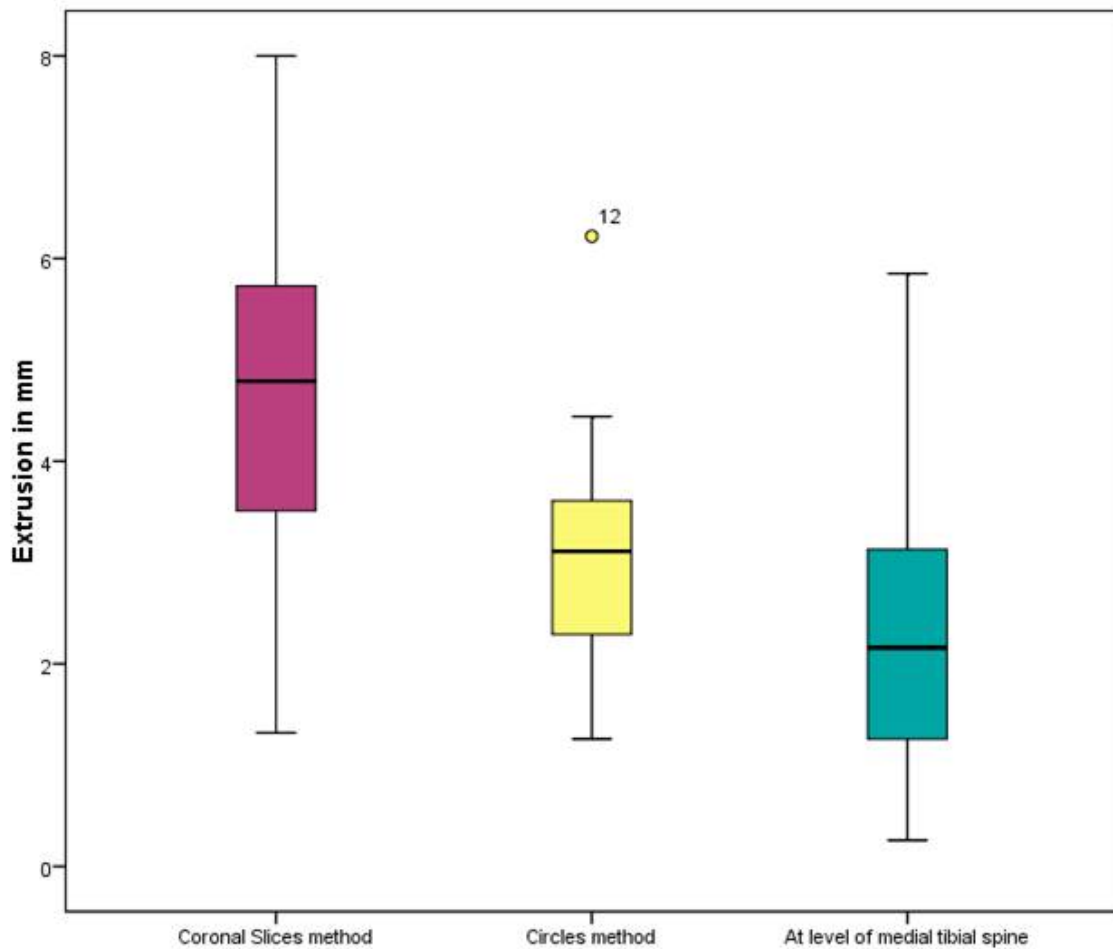
Figure 6.2.4.: Box and whisker plot comparing location of maximal meniscal extrusion in mm from front of tibia using two different methods



The median maximum meniscal extrusion was 4.79 mm (st. dev. 1.68 mean 4.69) when measured by the Coronal Slices Method, compared to 3.11 mm (st. dev. 1.23 mean 3.03) when estimated by the Circles Method. The median maximum meniscal extrusion measured on the slice corresponding to the highest point of the Medial Tibial Spine was 2.15 mm (st. dev. 1.51 mean 2.41). This is demonstrated in Figure 6.2.5.

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Figure 6.2.5.: Box and whisker plot comparing maximal absolute meniscal extrusion in mm using three methods

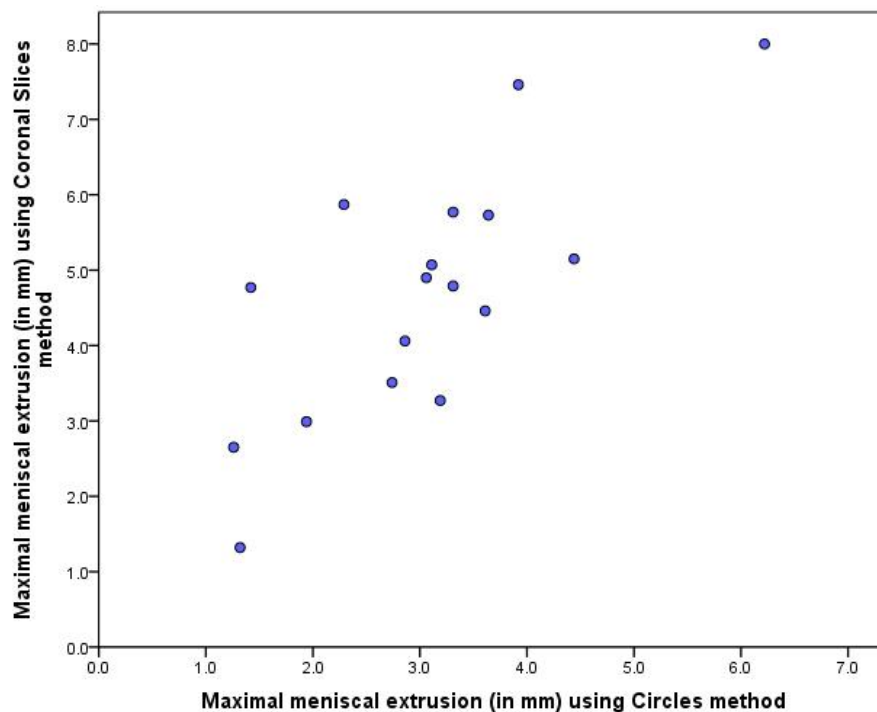


A Friedman's ANOVA for non-parametric data indicates that, using the Coronal Slices Method, the meniscal extrusion is measured as significantly higher than both the Circles Method (4.79 mm vs 3.11mm) and the slice corresponding to the highest point of the Medial Tibial Spine (4.79 mm vs 2.16mm) ($p=0.00$). In addition, the Circles Method estimates extrusion as significantly greater than the slice corresponding to the highest point of the Medial Tibial Spine (3.11 mm vs 2.16mm) ($p=0.00$).

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Bi variate correlation analysis of the maximum extrusion between measurement techniques indicates Spearman's rho correlation coefficients between the Circles Method and Coronal Slices Method of $r=0.705$ ($p=0.02$) (Figure 6.2.6), between the slice corresponding to the highest point of the Medial Tibial Spine and Circles Method of $r=0.723$ ($p=0.00$) (Figure 6.2.7), and between the slice corresponding to the highest point of the Medial Tibial Spine and Slices Method of $r= 0.529$ ($p=0.029$) (Figure 6.2.8).

Figure 6.2.6.: Correlation of maximal extrusion in mm comparing Circles method and Slices method.



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Figure 6.2.7.: Correlation of maximal extrusion in mm comparing MTS and Circles method.

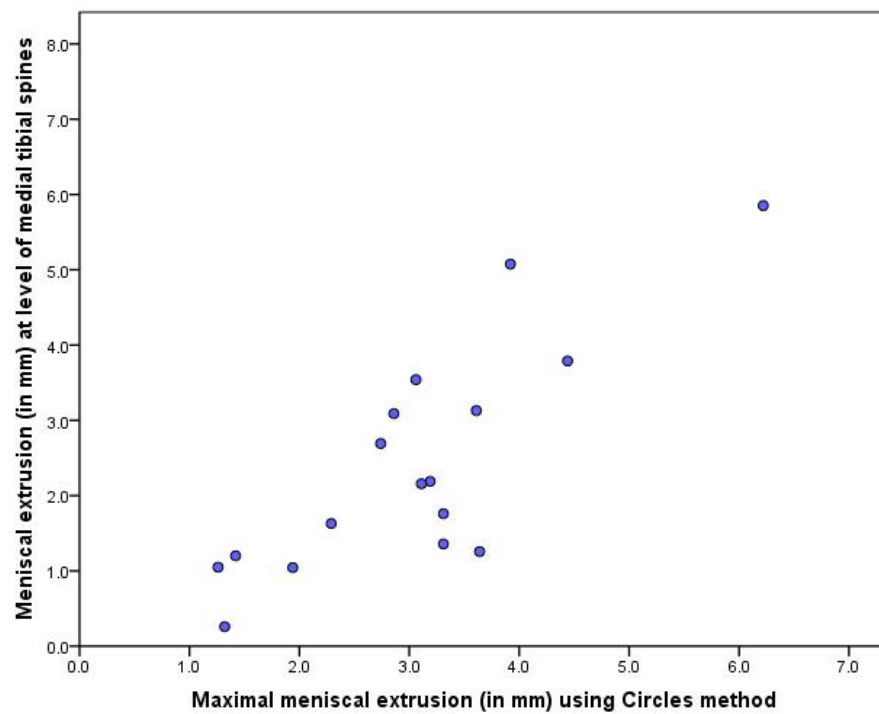
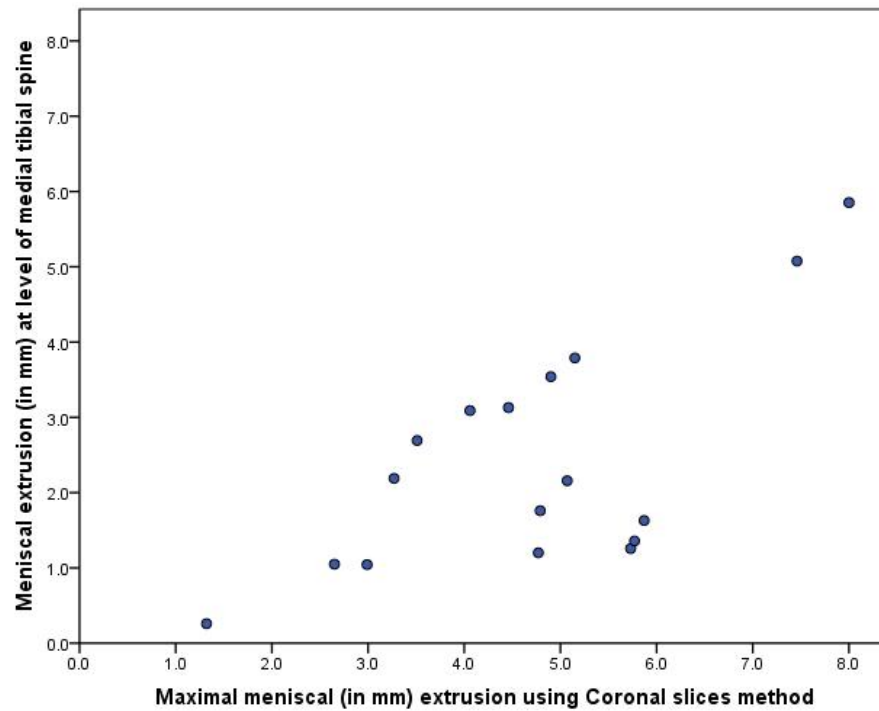


Figure 6.2.8.: Correlation of maximal extrusion in mm comparing MTS and Slices method.



6.2.3. Discussion.

This study, that compares different methods of measuring meniscal extrusion, demonstrates that maximum medial meniscal extrusion does not occur reliably in one location along the medial edge of the tibia (antero-posterior), irrespective of which measurement technique is used. The Coronal Slices method assessed the site of maximal meniscal extrusion to be on average at 38.2% of the AP breadth, with the Circles Method assessing it to be at 50.2 %. The average position of the Medial Tibial Spine was found to be at 56% of the AP breadth. The Circles Method (theoretically the most accurate method) therefore measures the location of maximal meniscal extrusion to be very close to the location of the MTS.

However, extrusion at the level of the Medial Tibial Spine was found to be on average significantly less than the maximal meniscal extrusion found by both the

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other methods for each individual. Dividing the tibia into anterior and posterior portions using this landmark ensured that the extrusion measured at this point using the circles method was perpendicular to the tibial edge. This represents the most reproducible way of performing the Circles Method on a coronal film. In all cases, the Coronal Slices Method overestimated maximal extrusion compared to the Circles Method due to the error described in figure 6.2.1. Furthermore, maximal extrusion estimated by the Circles Method showed better correlation with the horizontal distance measured on the coronal slice at the level of the Medial Tibial Spine than it did with the maximal extrusion measured using the Coronal Slices Method.

The literature reveals variation in the methods used to assess maximal meniscal extrusion. Crema et al. [121] in a study that looked at the association of meniscal tears, valgus mal alignment and cartilage damage with meniscal extrusion used the level of the medial tibial spine as their reference point. Wang et al. [270] performed MRI at 2 year intervals on 132 patients and measured extrusion at the anterior, middle and posterior horns. They did not state in their results where the extrusion occurred in each case or if the extrusion was measured at the same location on follow up scans.

The analysis of meniscal extrusion in the assessment of efficacy of meniscal transplant has gained increasing popularity in recent years. Many of these studies use the Coronal Slices Method to measure extrusion. Koh et al.[269] followed up 99 meniscal transplant patients over 32 months and on both MRI scans measured extrusion on the coronal slice where extrusion was felt to be maximal. They did not comment on whether the slice number was the same at both time points. Lee et al. [276] report on a case series of 43 patients who had undergone meniscal allograft transplantation and again measured extrusion on the coronal slice where it was felt to be greatest. They commented that maximal extrusion occurred in the body rather than the horns of the

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meniscus. Their 5 year radiographic follow up did not include MRI and sequential measurements were not taken. In a two year follow up of 37 meniscal allograft transplantation Ha et al. [271] again measured extrusion on the coronal slice at which it was felt to be maximal. They do not comment on the commonest site of extrusion.

This is the first time to our knowledge that different methods of measurement of meniscal extrusion have been directly compared in the same knee. Maximal meniscal extrusion as estimated by the Circles Method was consistently less than extrusion measured with the Coronal Slices Method that is commonly used. In addition, there was a high degree of correlation between the maximal meniscal extrusion using the Circles Method and the measurement of meniscal extrusion at the level of the Medial Tibial Spine. This study indicates that measuring meniscal extrusion at the level of the highest point of the Medial Tibial Spine has a strong association with the more labour intensive circles method.

There are limitations to this study. It is not longitudinal and it may be useful to determine whether the same coronal slice reliably measures the maximal extrusion over two time points in the same knee. The MRI scans were taken in a supine position and therefore the slices are not perfectly perpendicular to the axial plane. To allow direct comparison tibial plateau was reorientated and this may have led to errors in segmentation. Although others have used segmentation of menisci to estimate volumetric extrusion, the Circles Method employed in this study allowed a direct comparison with the Coronal Slices method that volumetric segmentation could not. The Circles Method theoretically is an optimal method of measuring true meniscal extrusion, however, it requires the tibia and the meniscus to be segmented. This makes it unsuitable for longitudinal datasets as manual segmentation is time consuming and requires specialist software. This study has demonstrated that using the coronal slice at the level of the Medial Tibial Spine correlates better with the

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Circles Method than the Coronal Slices Method does. Therefore, it represents a better method of assessing meniscal extrusion in longitudinal studies.

6.2.4. Conclusions.

Meniscal extrusion is under increased focus as the importance of the role of the meniscus in the pathogenesis of OA becomes clearer. This study demonstrates that, in a cross-sectional imaging study of knees, using coronal slices consistently overestimates the degree of extrusion in comparison to a method that estimates the perpendicular distance from the edge of the tibia to the most medial border of the meniscus. In addition it demonstrates that measurements taken from the coronal slice at the level of the medial tibial spine correlate closely with those taken perpendicular to the tibial edge.

Sequential assessment of extrusion is set to become increasingly important in both clinical assessment and longitudinal trials. We suggest that the assessment of extrusion at the level of the medial tibial spine is the most pragmatic method of extrusion assessment in this setting.

6.3. A study to determine the chronology of meniscal extrusion in the development of knee osteoarthritis.

The overall aim of this study was to determine how the presence of an extruded medial meniscus in a patient without medial knee OA influences the likelihood of the patient developing medial compartment OA over a 48 month period.

6.3.1. Null hypotheses.

1. Medial meniscal extrusion is not associated with the development of medial compartment knee OA over 48 months.
2. Medial compartment knee OA does not occur in the absence of an extruded medial meniscus.

6.3.2. Materials and methods.

The Osteo Arthritis Initiative (OAI) is a multicentre longitudinal prospective observational study of knee osteoarthritis that is run across four centres in the US and coordinated at the University of California, San Francisco School of Medicine. It has a stated overall aim to “develop a public domain resource to facilitate the scientific evaluation of bio markers for osteoarthritis as potential surrogate endpoints for disease onset and progression” (<http://oai.epi-ucsf.org/datarelease/StudyOverview.asp>). Briefly, this seven year project recruited 4796 men and women aged 45 to 79 between February 2004 and May 2006 and has since followed them prospectively with, amongst other observations, the collection of X rays and 3TMRI scans at yearly intervals. Initially this large cohort was split into three main groups;

1. Progression sub cohort: (n = 1389) These patients are known to have frequent knee symptoms (pain, aching or stiffness in or around the knee for at least one month during the past 12 months) and radiographic tibio femoral OA equivalent to Kellgren and Lawrence grade 2 or more on AP radiographs of the knee.
2. Incidence sub cohort: (n=3285) these patient do not have symptomatic knee OA in either knee, but they do have risk factors that put them at increased risk for developing knee OA during the study.
3. A reference or “non exposed” sub cohort (n=122).

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The OAI is an extremely valuable resource for the analysis of risk factors for progression to OA. However, personal discussion with John Lynch (the director of the OAI) indicated that the Progression, Incidence and Control groups were poorly defined and that these groups should largely be ignored when creating cohorts for radiographic assessment. Therefore, and as suggested, de novo cohorts were developed based on the presence of knee OA at baseline and at 48 months of follow up.

6.3.2.1. Study design.

A nested case control study design was selected to compare the effect of the exposure of interest (presence of meniscal extrusion at baseline) on Cases (those who do develop OA over 48 months) and Controls (those who do not develop OA over 48 months).

6.3.2.2. Subject identification.

LJ registered with the Osteo Arthritis Initiative and permission to use their data was obtained. The Kellgren and Lawrence grade of every knee within the OAI at recruitment and at 48 months was obtained from readings already performed by the OAI.

- Subjects with KL 0/1 at recruitment who progressed to KL2 or more at 48 months were allocated as “Cases” as they developed radiographic knee OA over the 48 month period.
- Subjects with KL 0/1 at baseline and KL 0/1 at 48 months were allocated as the “Control” as they did not demonstrate development of radiographic progression of OA over the 48 month period.

6.3.2.3. Sample size analysis.

Statistical sample size analysis was performed with the assistance of a medical statistician (Dr Andrew Judge, Botnar Research Centre, Oxford University). It was assumed that over 48 months, 6% of those with non extruded meniscus (ME-) would develop OA compared to 12% of those with an extruded meniscus (ME+). This was based on the results of a study performed by Englund et al [277], and was felt to be a conservative estimate (based on the increased length of follow up in our study).

A sample size calculation was performed. Using a 2-sample chi-squared test to detect a difference in the proportion of patients developing OA at 48 months of 12% (ME+) versus 6% (ME-), with 80% power, at a 5% level of significance (alpha), using a 2-sided test, and unequal group sizes in the ratio of 1 ME+ cases: 2 ME- controls, it was determined that 280 individuals with ME+ (Cases) and 560 individuals with ME- (Controls) were required.

6.3.2.4. Case selection and co-variate selection.

384 Cases were identified in the cohort who progressed from KL0/1 to KL2 or more over the 48 month period. All of these were included in the study.

562 controls who started at KL0/1 and remained at KL0/1 over the 48 month period of the study were identified. Assessment of the KL grade was done centrally by the radiologists at the OAI.

The total initial cohort size was therefore 946.

Exclusions. Cases were excluded if they had they had no baseline MRI scan ($n = 5$) or if they were determined to have isolated lateral disease ($n = 28$). The total sample size was therefore 913, with 354 Cases and 559 Controls.

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Co-variates. Co-variates of interest were age, gender and BMI. In order to be able to control for those with significant traumatic meniscal injury, a history of injury to the knee of interest and a history of surgery to the meniscus of the knee of interest were also selected as co-variates.

6.3.2.5. Image analysis.

The baseline MRI scans of the subjects in each cohort were obtained from the OAI and were inspected for the exposure of interest - the presence or absence of meniscal extrusion - using a strict protocol (see appendix C) Image analysis was performed by a single reader (LJ).

Figure 6.3.1.: A schematic summary of the nested case control design

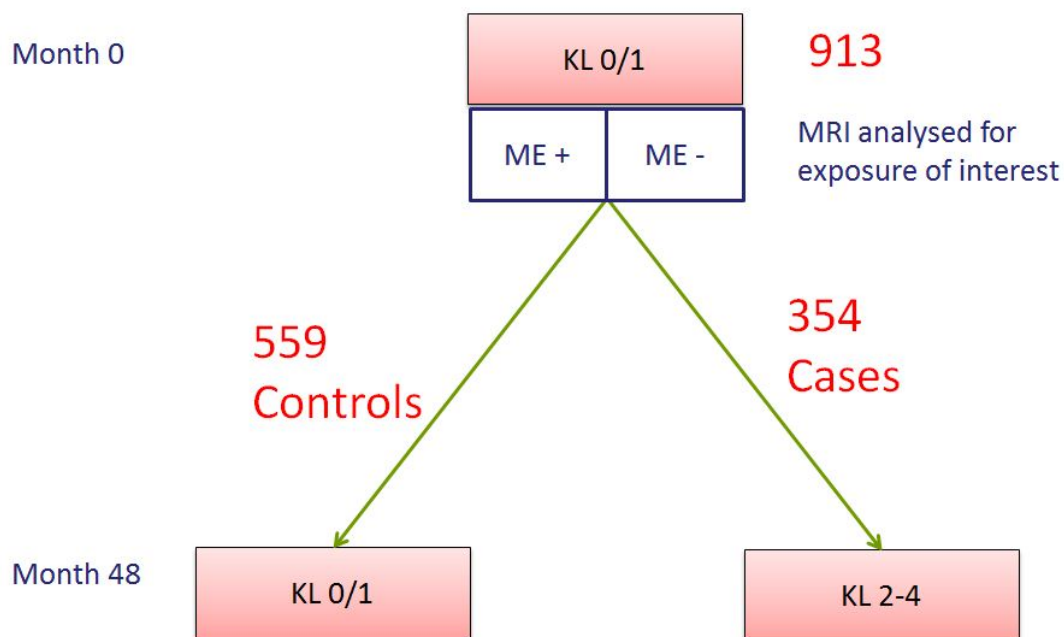


Image analysis was performed by a single observer (LJ) using the ONIS Professional v2.4 DICOM image viewer (Digitalcore Co Ltd, Tokyo, Japan) on an LG workstation.

The image selection was based on the highest point of the medial tibial spine excluding osteophytes. This method has been used in previous studies [266][121][264][267],

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and has been validated as the optimal position for assessing meniscal extrusion as part of this thesis in section 6.3.6.

Importantly, the long axis of the tibia was identified in each scan and extrusion was at all times referenced from this long axis. This allows a repeatable anatomical alignment axis point to be used from which to reference extrusion. This method of determining the long leg axis from short leg films has been validated previously and is a recognised technique in the analysis of films (in particular radiographs) from longitudinal cohorts [278].

The slice selected, the total meniscal width and the absolute extrusion were recorded on an Excel spreadsheet (Excel 2010, Microsoft, Washington, USA). This was then exported to SPSS (v18.0.0, IBM, New York, USA). The meniscus was deemed to be extruded if it was subluxed by more than or equal to 3mm from the medial border of the tibia as per previous studies [?][116][?]. Absolute values of meniscal extrusion were collected and then reclassified as “extruded” or “not extruded” accordingly to produce dichotomous data.

6.3.3. Validation of image selection.

6.3.3.1. Image selection.

Two orthopaedic surgeons, trained in the measurement of extrusion of the meniscus as per the described protocol (See Appendix C on page 283) assessed 25 3T MRI scans of the knee each consisting of, on average, 25 image slices (23-29 SD1.88). In total, 633 images were reviewed per observer, per sitting. On each occasion, blinded to each others assessment, the surgeon was asked to select which slice corresponded to the highest point of the medial tibial spine excluding osteophytes. The second observer (LJ) then reviewed the images a second time, one week later. A Kappa analysis was performed for ordered categorical data.

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Inter observer reliability. In 84% of cases the same slice was selected by both observers (Kappa 0.727 SE0.106 P=0.00) indicating substantial agreement. Importantly, in the 16% where the slice selection was not the same, the difference between two observers was never greater than one slice.

Intra observer reliability. In 95% of cases the same slice was selected on each viewing, (Kappa 0.938 SE 0.06 P=0.00) indicating almost perfect agreement. Importantly, in the 5% of cases where the slice selection was not the same, the difference in slice number selected at the two observation time points was never greater than one slice.

6.3.4. Statistical analysis.

Descriptive statistics were collated and a 2x2 table constructed. Subjects were classified firstly as cases or controls, and secondly according the presence of exposure of interest.

A Chi square test was performed for binary outcomes and a Odds Ratio was generated for the presence of meniscal extrusion leading to the development of OA.

6.3.5. Results.

913 knees MRI's were inspected (right = 451, left = 462) at both baseline and 48 months. The cohort contained 307 (33.6%) males and 606 females (66.4%). The average age was 60.7 years (45-78 SD 9.2) and the average BMI was 27.7 (17.6 -44.2 SD 4.7).

6.3.5.1. Presence of meniscal extrusion at baseline.

Of 913 normal subjects (i.e. no OA at baseline) 304 had extruded meniscus and 609 had non extruded meniscus. Those with an extruded meniscus were more likely to

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be male, have a greater BMI and to have a history of arthroscopy to the index knee.

A summary of the cohort demographics is provided in Table 6.3.5.1.

Table 6.1.: Demographics of entire cohort of patients with baseline MRI scan

Number	Entire Cohort 913	Extruded 304 (33.3%)	Non Extruded 609(66.7%)	P value
Age (years)	60.72	61.56	60.3	0.06
BMI	27.7	28.5	27.3	0.00
Gender				
Male	307	123 (40%)	184 (60%)	0.02
Female	606	181 (29.9%)	425 (70.1%)	
Injury to index knee				
Yes	191	71 (37.2%)	120 (62.8%)	0.2
No	722	233 (32.2%)	489 (67.7%)	
Scope to index knee				
Yes	21	14 (66.6%)	7(33.3%)	0.00
No	892	290 (32.5%)	602 (67.5%)	

6.3.5.2. Comparing Cases (those who progress to OA) to Controls (those who do not progress to OA).

Within the Cases (Those known to develop OA over the following 48 months) 178/354 (50.2%) had an extruded meniscus at baseline. Within the Controls (those known not to progress to OA over the following 48 months) 126/559 (22.5%) had an extruded meniscus at baseline.

178/304 (55%) with an extruded meniscus went on to develop OA over 48 months. 176/609 (28.9%) without an extruded meniscus went on to develop OA over 48 months.

The contingency 2x2 table can be seen in 6.2 on the next page.

A Pearson chi square test value of 75.107 ($p=0.00$) demonstrates a significant difference between Cases and controls ($p < 0.00$).

An Odds Ratio of 3.5 (95% CI 2.6-4.6) indicates the strength of the relationship between presence of meniscal extrusion and risk of developing OA at 48 months.

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Table 6.2.: Contingency table of presence of extrusion at baseline vs progression to OA at 48 month

Extruded?		Controls	Cases	Total
ME-	Count	433	176	609
	Expected Count	372.9	236.1	609.0
ME+	Count	126	178	304
	Expected Count	186.1	117.9	304.0
Total	Count	559	354	913

This tells us that the odds of developing OA within 48 months if meniscal extrusion is present is 3.5 times the odds of developing OA if meniscal extrusion is not present.

Controlling for the presence of a pre existing injury to the knee indicates that the odds ratio of developing OA over 48 months in the presence of meniscal extrusion without a knee injury is OR 3.3 (2.4-4.6). With a history of knee injury the OR increases to 4.1 (2.2-7.6). Controlling for the presence of previous arthroscopic surgery to the index knee indicates that the OR of developing OA over 48 months in the presence of meniscal extrusion without an operation to the index knee is OR 3.36 (2.5-4.5). With a history of arthroscopic surgery to the index meniscus the OR increases to 15 (1.3-167).

6.3.6. Validation of observer reliability in meniscal extrusion measurement.

Intra observer reliability. Following training and the development of the measurement protocol, one observer (LJ) measured the first 20 scans and documented the presence or absence of meniscal extrusion and the absolute extrusion of the medial meniscus on each scan.

- Kappa analysis for the binary extrusion of meniscus (ie extruded or not) indicated a kappa value of 1.00 (SE 0.00 p=0.00) indicating perfect agreement.

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- Single measures ICC for continuous data of extrusion distance was 0.921 (CI 0.811-0.968 $p=0.00$) indicating excellent agreement.

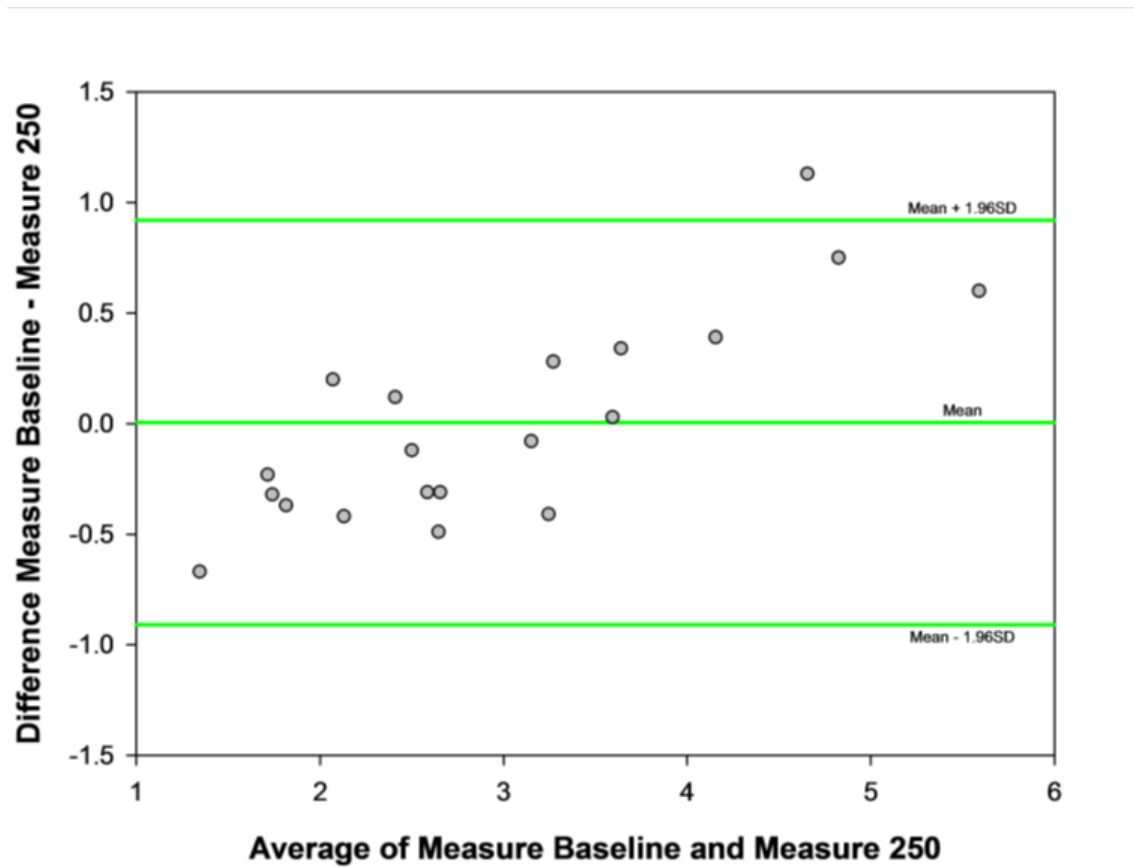
Inter observer reliability. A second observer underwent training in the use of the measurement protocol (described in Appendix C on page 283). Ten scans were read in conjunction with the author and consensus was reached on measurement. Following this, and blinded to the views of the first observer, the second observer read the first 20 scans and documented the presence or absence of meniscal extrusion and the absolute extrusion of the medial meniscus on each scan.

- Kappa analysis for the binary extrusion of meniscus (ie extruded or not) indicated a kappa value of 0.82 (SE 0.159 $p=0.00$) indicating substantial agreement.
- Single measures ICC for continuous data of extrusion distance was 0.884 (0.707-0.954) indicating excellent agreement.

Observer drift. Observer drift is the tendency, especially in lengthy research studies, for observers to become inconsistent in the criteria they use to make and record observations. This causes a decline in the reliability of the data collected [279]. To examine this tendency, following every 250 scans the first 20 scans were re read, blinded to the initial results. Although the ICC average measures for absolute meniscal extrusion was 0.991 (0.982 -0.996 $p=0.00$ - indicating excellent agreement), in response to the recognised shortcomings in ICC for continuous data, Bland Altman plots [280] were generated. The Bland Altman plot, also known as a difference plot, compares the results of two separate measurements of the same data. In this graphical method the differences in the results between the two measurements are plotted against the average of the two measurements. Horizontal lines are plotted at the mean difference between the two measurements and at the limits of agreement ($1.96 \times$ the SD of the differences).

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Figure 6.3.2.: Bland Altman plot comparing baseline measurement with measurements after 250 scans



Between baseline read and read 250. Figure 6.3.2 demonstrates an overall mean difference (bias) in measured distance of meniscal extrusion of 0.005mm with 95% CI of -0.91mm - 0.92mm. Therefore the overall agreement was very strong with only one outlier observation. This outlier was made during the baseline read.

Further Bland Altman plots for assessment of observer drift at the 500th, 750th and final readings are shown in Appendix C.4.

6.3.7. Validation of Kellgren and Lawrence score.

One potential criticism of this study is that those with KL1 have been labeled as not having OA. As discussed in Chapter 2, the Kellgren and Lawrence score is an

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insensitive tool for the assessment of OA cartilage lesions. On the advice of the OAI, KL 2 was used as the cutoff for the development of OA. However, using the data collected it is possible to reanalyse the data using KL0 as no OA and KL1 or more as presence of OA. Reclassifying the data in this way indicates that there were 670 knees available for study (ie had KL 0 at baseline). This includes 213 Cases (developed OA over the 48 months), and 457 Controls (did not develop OA over the 48 months). A 2x2 cross tabulation is seen in Table 6.3.

Table 6.3.: Contingency table of presence of extrusion at baseline vs progression to OA at 48 month if OA is defined as KL1 or more

Extruded?		Controls	Cases	Total
ME-	Count	362	133	495
	Expected Count	337.6	157.4	495.0
ME+	Count	95	80	175
	Expected Count	119.4	55.6	175.0
Total	Count	457	213	670
	Expected Count	457.0	213.0	670.0

The Pearson Chi square statistic of 20.6 was significant at $p < 0.01$ indicating an association between extrusion at baseline and development of OA at 48 months. A Odds Ratio of 2.3 (95% CI 1.6 - 3.3) indicates the strength of the relationship between presence of meniscal extrusion and risk of developing OA at 48 months. This tells us that the odds of developing OA within 48 months if meniscal extrusion is present is 2.3 times the odds of developing OA if meniscal extrusion is not present.

Therefore, although the association is weaker if KL 0 and KL1 are used for the definitions of normal and OA, there remains an association between the presence of extrusion and the development of OA.

6.3.8. Validation of meniscal extrusion cutoff.

The use of a cutoff point of 3mm as the definitive point for meniscal extrusion has, as mentioned, been used in many studies. In this study, we applied this convention. The mean extrusion overall was 2.64mm SD 1.02, (-1.58mm - 9.68mm). In the Cases, overall mean extrusion at baseline was 3mm (SD 1.08, range -1.21mm - 8.1mm). In the Controls, overall mean extrusion at baseline was 2.4 mm (SD 0.914, range -1.58 mm - 7.52mm). In those who were extruded at baseline, overall mean extrusion was 3.76mm (SD 0.744mm, range 3mm-8.1mm). In those who were not extruded at baseline, overall mean extrusion was 2.08mm (SD 0.61mm, range -1.58 - 2.98).

However, the use of 3mm is an arbitrary cutoff. Meniscal extrusion is likely to be a gradual event and therefore to address questions about how the amount of extrusion affects the OR of developing OA for a patient, the data was re analysed at levels of extrusion less and greater than 3mm.

6.3.8.1. Odds Ratio of OA if 2mm is used as the cutoff for extrusion.

The data described in section 6.3.5 was re analysed with the cutoff point for the binary description of “Extrusion” being redefined as 2mm. A Chi square test was re performed and the Odds ratio reclassified. A Contingency table was generated (Table 6.4).

Table 6.4.: Contingency table demonstrating presence of extrusion at baseline vs progression to OA at 48 month if meniscal extrusion is 2mm or greater

Extruded?		Controls	Cases	Total
ME-	Count	195	61	256
	Expected Count	156.7	99.3	256.0
ME+	Count	364	293	657
	Expected Count	402.3	254.7	657.0
Total	Count	559	354	913
	Expected Count	559.0	354.0	913.0

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Pearson Chi Square value of 36.2 ($p=0.00$) was significant indicating an association between the presence of a 2 mm extruded meniscus and the development of OA at 48 months. An Odds Ratio of 2.6 (95% CI 1.85-3.57) indicates the strength of the relationship between presence of meniscal extrusion and risk of developing OA at 48 months. This tells us that the odds of developing OA within 48 months if meniscal extrusion at 2mm is present is 2.6 times the odds of developing OA if meniscal extrusion is not present. Therefore, although the association is weaker if 2mm is used for the definitions of extrusion, there remains an association between the presence of extrusion and the development of OA.

6.3.8.2. Odds Ratio of OA if 4mm is used as the cutoff for extrusion.

The data described in section 6.3.5 was re analysed with the cutoff point for the binary description of “Extrusion” being redefined as 4mm. A Chi square test was re performed and the Odds Ratio recalculated. A 2x2 Contingency table was generated and is displayed in Table 6.3.8.2.

Table 6.5.: Contingency table demonstrating presence of extrusion at baseline vs progression to OA at 48 month if meniscal extrusion is 4mm or greater

Extrusion?		Control	Case	Total
ME-	Count	531	295	826
	Expected Count	505.7	320.3	826.0
ME+	Count	28	59	87
	Expected Count	53.3	33.7	87.0
Total	Count	559	354	913
	Expected Count	559.0	354.0	913.0

Pearson Chi Square value of 31.9 ($p=0.00$) was significant indicating an association between the presence of a 4 mm extruded meniscus and the development of OA at 48 months. An Odds Ratio of 3.8 (95% CI 2.37-6.08) indicates the strength of the relationship between presence of meniscal extrusion and risk of developing OA at 48 months. This tells us that the odds of developing OA within 48 months if meniscal

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extrusion at 4mm is present is 3.8 times the odds of developing OA if meniscal extrusion is not present.

It therefore appears that the OR of developing OA increases as the amount of extrusion increases.

6.3.8.3. Is the presence of Osteoarthritis always associated with the presence of meniscal extrusion?

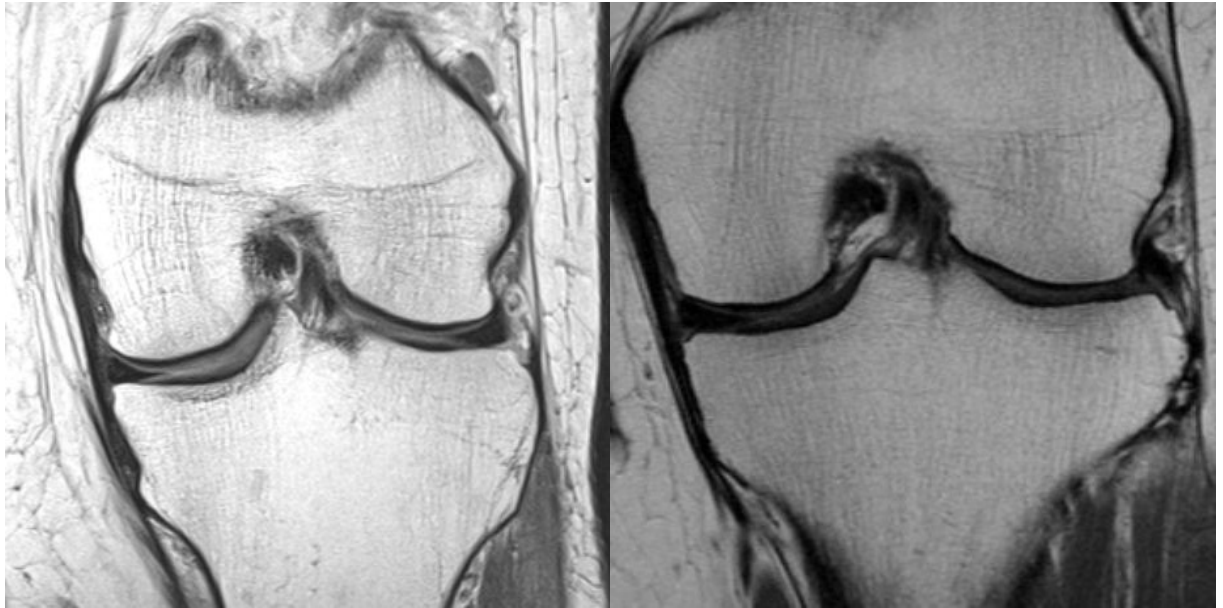
Of the 913 subjects with a recruitment scan in addition to baseline and 48 month X rays, 59 subjects had no follow up scan at 48 months. Of the 851 subjects that remained, 523 subjects did not go on to develop OA.

Of the 328 that went on to develop OA and had a 48 month scan, the mean meniscal extrusion was 4.3mm (SD 1.7mm range -0.9-11.5mm).

78/328 (23.8%) of individuals who developed OA did not have an extruded meniscus despite having X ray evidence OA (loss of joint space and osteophytes.) If extrusion is redefined as 2mm, then only 24 (7.3%) of people who develop OA do not have an extruded meniscus. This means that that an extruded meniscus is present in 92.7% of people who have arthritis (defined by as KL2). Therefore, it is possible to have OA without meniscal extrusion although it is uncommon.

Examples can be seen in Figure 6.3.3

Figure 6.3.3.: T1 weighted coronal MRI Knee of patients classified by OAI as having KL2, in the absence of meniscal extrusion



6.3.9. Discussion.

In this study in which the relationship between the presence of meniscal extrusion and the development of anteromedial knee OA is explored, the presence of meniscal extrusion in a radiographically normal knee has an Odds Ratio of 3.5 for the development of knee OA at 48 months.

Odds Ratios should be interpreted with care. An OR of 3.5 can be described as the ratio of the odds of developing OA if meniscal extrusion is present to the odds of developing OA if meniscal extrusion is not present.

The advent of large, multicentre prospective studies has meant that the meniscus has been studied in great detail in recent years. Ding et al prospectively followed 294 individuals over 2 years and determined that the presence of meniscal extrusion at baseline was associated with increased cartilage loss over 2 years although their study did not demonstrate an association when the presence of osteophytes (an important marker for OA) at baseline was controlled for [281]. Similarly, Sharma et al only

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examined individuals from their cohort who had a known presence of early OA at baseline, but were able to conclude that meniscal damage predicted cartilage loss. In a 24 months observational study of 152 women, cartilage loss was predicted by meniscal damage at baseline but again they failed to exclude those with established disease from their cohort at recruitment [282]. Englund's study using data from the Multicentre Osteoarthritis Study (MOST) [277] used a similar design to the study presented here. However, their follow up was only 30 months and they had a total cohort size of only 243. They were able to conclude that meniscal extrusion was present more in those who develop OA at 30 months than those who do not, but they provided Odds Ratios for meniscal damage only, not specifically for meniscal extrusion.

The study described in this chapter is, to our knowledge, the largest and longest nested case control study of its kind. It demonstrates that, having performed sensitivity analysis for different levels of extrusion and different classification of osteoarthritis, the presence of meniscal extrusion is a potent risk factor for the development of knee OA and that the odds ratio for progression over 48 months increases as the degree of baseline extrusion increases.

The study in this chapter has a number of limitations. Firstly, no information is offered on the presence of meniscal tears or the aetiology of meniscal extrusion. Instead, a regression analysis was performed to control for a history of surgery to the knee and significant history of injury to the knee. This decision was made for two reasons. Firstly the reason for the presence of an extruded meniscus does not need to be known in order to assess its presence. The meniscus is either extruded or not. Secondly, due to the time constraints on this project, it would not have been possible for a single observer to have accurately have read the meniscus for tears (including type, location and chronicity) in the time available.

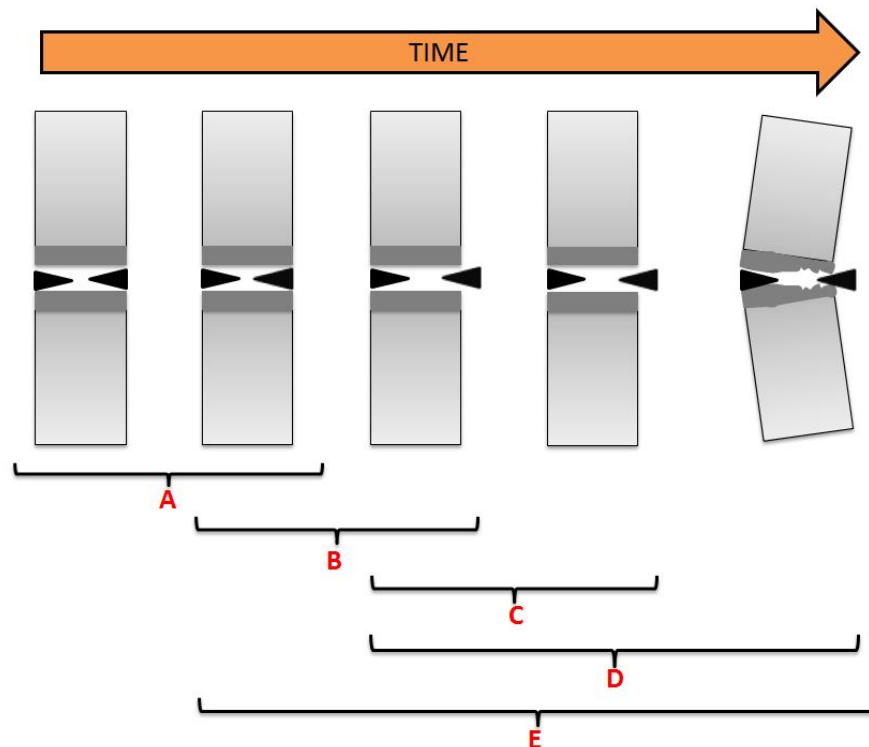
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A protocol was used to attempt to standardise the reading of the extrusion of the meniscus and the measurement technique has been validated against other, more labour intensive methods such as segmentation. The method selected to measure extrusion attempts to measure the single point of greatest extrusion. It is reasonable to assume that the total volume of mensical extrusion is a more important measure than a single maximal point of extrusion, and this should be a focus of work in the future.

By measuring extrusion at two time points, namely zero and 48 months, we are presuming that the presence of an extruded meniscus in an otherwise normal knee will lead to the development of OA over that time period. In reality of course, it may take much longer for the extruded meniscus to lead to the development of OA. Conversely, a non extruded meniscus in a normal knee may extrude and lead to significant degeneration in a shorter time period than this, thus meaning that potential cases are missed. A diagrammatic representation of this problem is shown Figure 6.3.4.

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Figure 6.3.4.: A proposed chronology of meniscal extrusion in the development of Knee OA



- A. Over 48 months the meniscus does not extrude.
- B. Over 48 months the meniscus does extrude but OA does not develop.
- C. The meniscus is extruded at baseline. At 48 months it has still not lead to the development of OA.
- D. The meniscus is extruded at baseline and leads to the development of OA at 48 months. This is what has been demonstrated in this study where those with an extruded meniscus at baseline have an OR of 3.5 of developing OA at 48 months.
- E. The meniscus is not extruded at baseline. Over the 48 month period the meniscus extrudes and OA develops rapidly.

Of note, mensical extrusion was not found to be present in all those with OA at 48 months. In this situation, problems with the definition of OA used in this study become clear. As demonstrated in Figure 6.3.3, these knees appear to be normal other than for a small medial joint line osteophyte. This osteophyte immediately causes the knee to be classified as KL2 despite the lack of evidence of any cartilage degeneration. Reasons for the existence of knee OA in the absence of meniscal extrusion are therefore

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that KL is an insensitive method of classifying OA, or that knee OA can develop prior to the extrusion of a meniscus even if that occurs only in 20% of cases as in this study. Proving causation between a risk factor and an outcome is difficult. Some authors suggest up to nine criteria need to be met [283]. It is clearly not the case that the meniscus is the only important factor in the development of knee OA, a condition known to be complex and multifactorial in its aetiology. A longer, prospective study with multiple MRI scans at perhaps yearly intervals might provide a better method of elucidating exactly how extrusion might precede OA development.

6.3.10. Conclusions.

- Null Hypothesis 1 is rejected. The presence of an extruded meniscus in a patient without OA is a significant risk factor for the presence of developing OA over the following 48 months.
- Null hypothesis 2 is rejected. Although causality cannot be determined from this study, it adds towards a body of evidence that highlights the importance of the meniscus structure and its integrity in the development of knee OA.

6.4. Future work.

This chapter used a novel approach in a unique cohort of patients without antero-medial knee OA, to attempt to determine the role of meniscal extrusion in the development of disease. Following the completion of this study, the OAI released data on X rays scores at 72 months. This means that it will now be possible to determine the Odds Ratio for developing the disease over a longer time period. This chapter has focused purely on radiographic risk factors for disease, and has not considered how patient symptoms such as pain may correlate with meniscal extrusion and this

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is certainly an area of interest. The cohort we have identified will allow this to be explored in some detail. The meniscus clearly appears to have a role to play in the development of OA, and it may also be of interest to determine how the change in extrusion over a 48 month time period affects the change in KL.

In using the OAI in this chapter we have retrospectively identified those who we know go on to develop the disease in an attempt to identify a key structural risk factor, the extruding meniscus. Prospectively following a large number of individuals, none of whom are certain to go on to develop OA, is an inefficient method of identifying risk factors for the development of OA. Disadvantages including the cost of acquisition of the images and the time taken to read and interpret them. In the next chapter, a unique cohort is developed based on a family history of disease. This should theoretically allow a more efficient method of studying risk factors for the disease in a group of individuals who are risk loaded.

7. A high risk cohort? The sibling offspring “SibKids”.

7.1. Introduction.

In the previous chapter, a large retrospective cohort was used to identify individuals who are known to go on to develop OA. This allowed the focused inspection of pre disease individuals for anatomical features that are not present in a control cohort who, by the same method, are known not to develop OA. As this retrospectively identified cohort of interest was nested within a larger prospective cohort, many individuals were required to be followed over time. Although knee OA is a common condition, in population studies large numbers of normal people have to be followed over many years to identify the 30% or so who develop the condition [231]. This is both expensive and time consuming. If it is possible to identify a group of younger patients who are at increased risk of developing the disease, prospective assessment of these patients would be more efficient, as less individuals would need to be followed over time to identify those who develop incident disease. In addition, the identification of the earliest changes of disease in those who are yet to develop symptoms would potentially be possible. Expensive, novel investigations could be targeted at these individuals rather than at a sample of the general population. This

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cohort would have other uses in studying the earliest stages of OA, such as developing reliable bio markers for the progression of disease or, similarly, in assessing and monitoring the efficacy of joint preserving non surgical interventions.

Studies that look at the influence of family history (sometimes labeled “genetic influence”) on the risk of siblings of those with end stage hip and anteromedial knee OA have been reported before [231] [234]. McDonnell et al [234] concluded that the siblings of those with full thickness anteromedial knee OA were at 3.14 times higher risk of having anteromedial knee OA themselves than age matched spousal controls. This suggests there is a horizontal transmission of risk between siblings that seems to be independent of lifestyle and environmental factors. Spencer et al [235] identified that this horizontal transmission of risk in hip arthritis is also transmitted vertically - with an increased risk of symptomatic and radiographic knee OA of 3.5 x that of matched controls in the offspring of those with end stage hip OA (this cohort have been named the “SibKids”).

The primary aim of familial aggregation studies in OA is to determine if there is a hereditary component to a specific phenotype of disease, thus allowing the early identification of “at risk” patients. The secondary aim is to determine how this increased risk manifests itself - demographic factors, or specific anatomical features. The vertical risk of developing disease has never been investigated in anteromedial knee arthritis before.

This chapter reports a study into familial risk in anteromedial knee OA. The primary aim of this study is to determine if the risk of developing anteromedial knee OA is transmitted vertically from parents to offspring. Although this cohort of patients may be at increased risk of developing the disease, it may be that they are too young to demonstrate the radiographic and symptomatic features of disease. Therefore, the second aim of this chapter is to determine whether SibKids demonstrate the presence

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of factors known to predispose to anteromedial OA in the future, namely meniscal extrusion on MRI (as demonstrated in the previous chapter) and varus malalignment on long leg films. Thirdly, as radiographic change is known to be insensitive compared to MRI, the WORMS score of the SibKids is compared to spouse controls. Finally, the fourth aim of this chapter is to determine, in those SibKids without structural MRI change or symptoms, whether examining specific regions of interest in their cartilage demonstrates functional preclinical change that may be a possible bio marker of early disease.

7.2. Null hypotheses.

1. The risk of developing AMOA is not transmitted vertically from parents to offspring.
2. The SibKids are not at risk of increased varus malalignment compared to spouse controls.
3. The SibKids do not have higher rates of meniscal extrusion compared to spouse controls.
4. There is no difference in the WORMS scores demonstrated by SibKids compared to those of spouse controls.
5. The SibKids do not demonstrate increased T2 signal in focused regions of interest compared to spouse controls.

7.3. Ethics committee approval.

Ethical approval for the generation, and clinical, radiographic and MRI study of SibKids and controls was obtained from NRES Committee South Central - Oxford

A (REC Reference 12/SC/0006) by LJ.

7.4. Materials and methods.

7.4.1. Cohort generation.

The development of the SibKids cohort took place in two stages. Firstly, symptomatic sibling pairs were identified. Secondly, the offspring of these symptomatic sibling pairs were recruited.

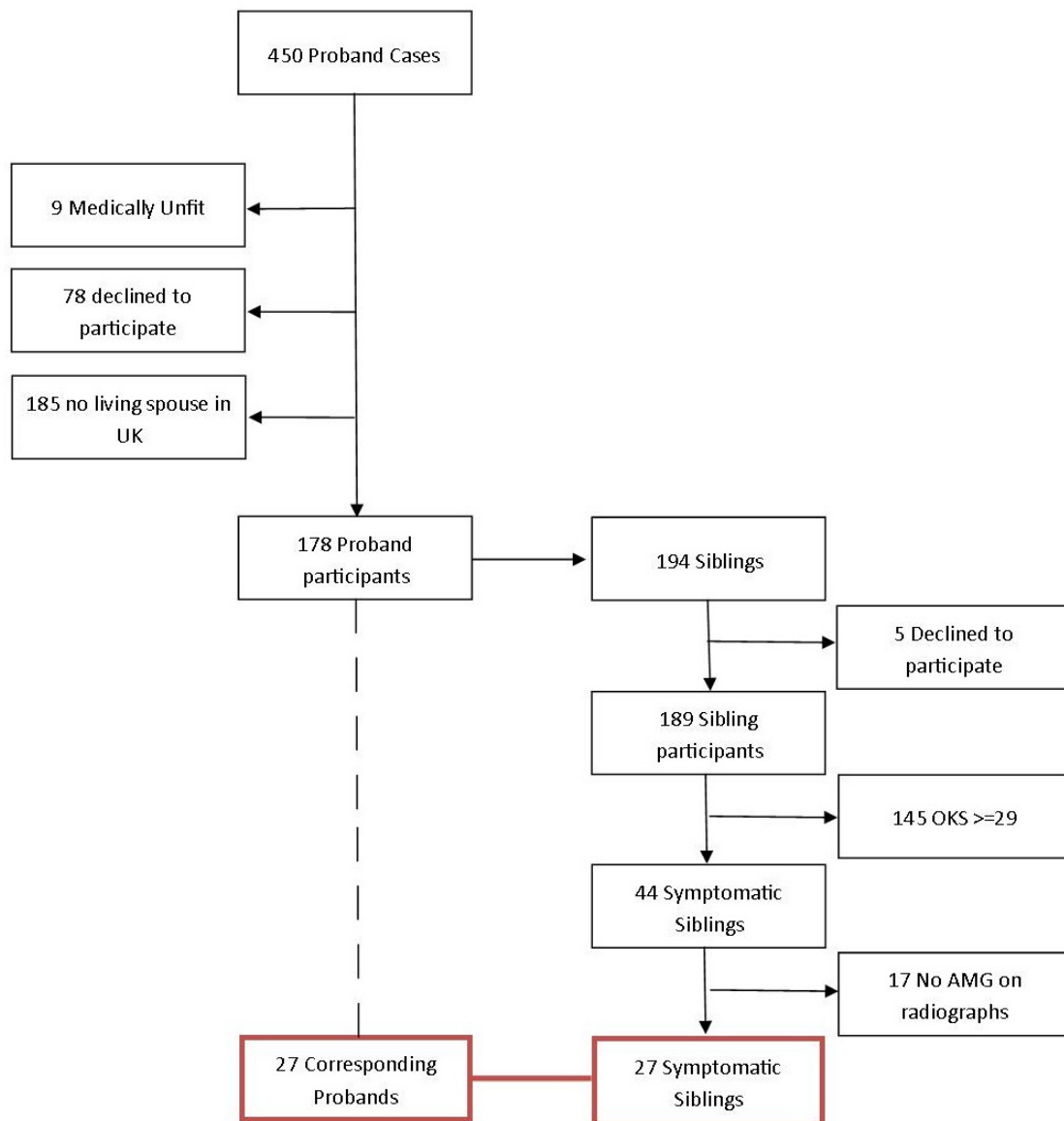
7.4.1.1. Identification of symptomatic sibling pairs.

This method has previously been described by McDonnell et al [234] who identified 16 symptomatic sibling pairs in their study. The same method was used in this study to increase the pool of symptomatic sibling pairs identified. A novel cohort of 450 patients with confirmed end stage anteromedial knee OA (had previously undergone Oxford uni compartmental knee arthroplasty) were identified from operative records. These patients were termed the Probands. The Probands were contacted and invited to take part in the study. If they agreed to take part they were recontacted for the details of all living siblings in the UK. The Proband Siblings were then sent an Oxford Knee Score. Those with an Oxford Knee Score of ≤ 29 were determined to be symptomatic and they were then invited for radiographic assessment of the knee. If the radiographic features of anteromedial knee OA were identified on the radiographs, then the sibling was determined to have symptomatic anteromedial knee OA. This sibling was then matched to its original Proband and together they form a Symptomatic Proband Sibling Pair (i.e. two siblings, both with the symptomatic and radiographic evidence of disease). Using this method 27 symptomatic Proband sibling Pairs were identified. The generation of this cohort and the reasons for exclusion are

7. A high risk cohort? The sibling offspring “SibKids”.

summarised in Figure 7.4.1.

Figure 7.4.1.: The generation of symptomatic Proband - sibling pairs

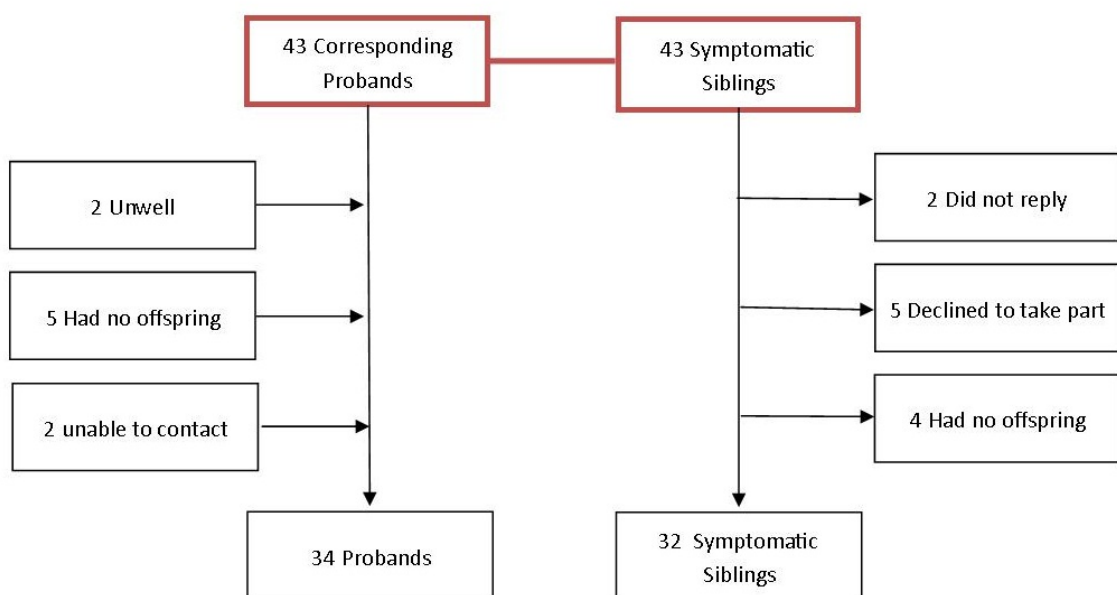


This new cohort of 27 symptomatic Proband sibling pairs was then combined with the 16 pairs previously identified by McDonnell et al [234] to generate a final group of 43 symptomatic Proband sibling pairs (86 individuals).

7.4.1.2. Identification of symptomatic sibling pair offspring (SibKids).

The 43 symptomatic Proband sibling pairs identified in section 7.4.1 were then contacted for the details of their offspring. A total of 34 Probands and 32 symptomatic siblings were willing to take part and had offspring. The exclusions from this group are demonstrated in Figure 7.4.2.

Figure 7.4.2.: Identification of symptomatic Probands and siblings available for inclusion in SibKids study



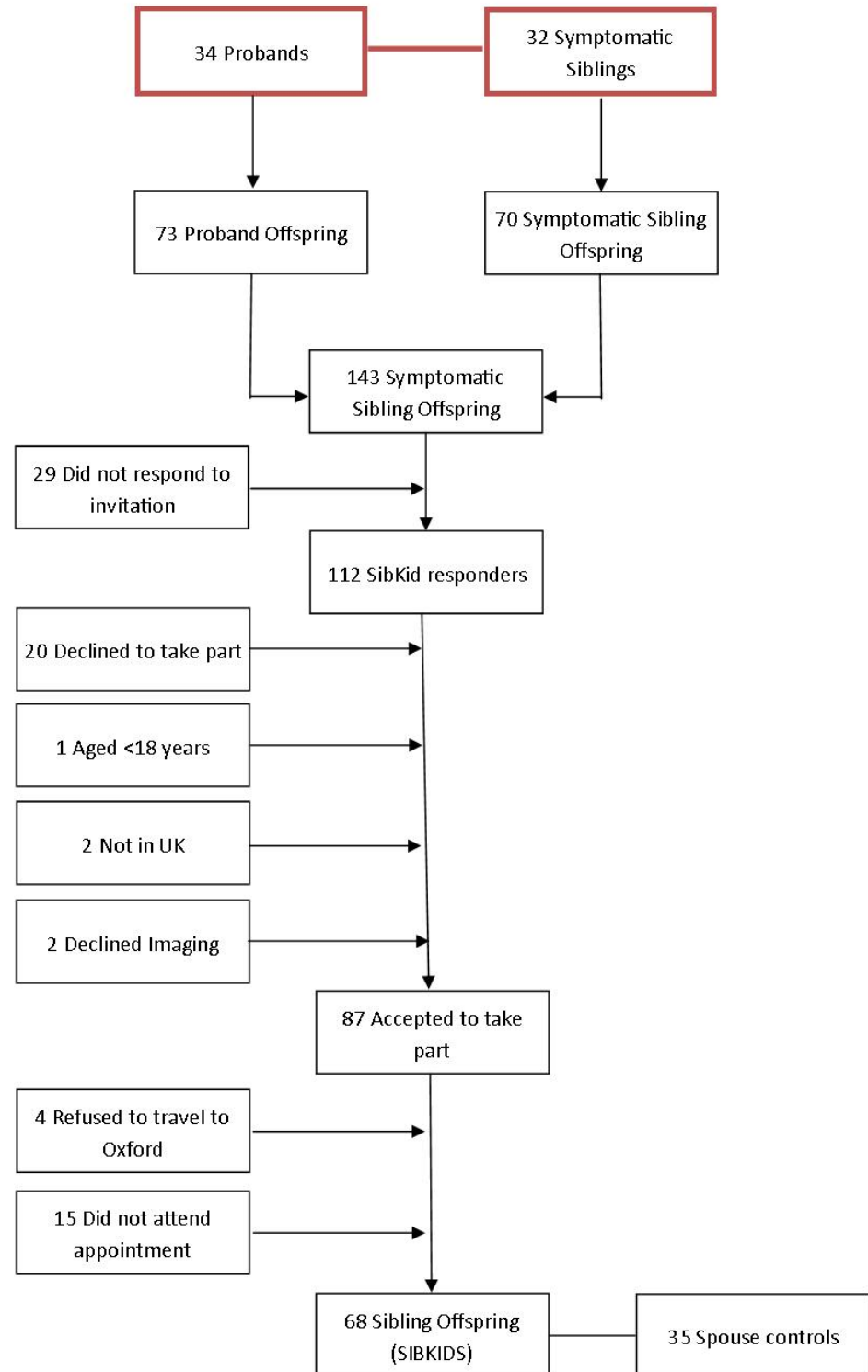
The Probands and siblings were contacted for the details of their offspring. The offspring (the SibKids) were then invited to take part in the study. It is important to emphasize that the SibKids were invited to take part on the basis of their family history only and not on the basis of their knee symptoms. At the same time as the SibKids were invited, their spouses were invited to act as controls. This method has been described previously in work from our unit [284]. Spouses were invited to take part because they are non related controls and share environmental factors

7. A high risk cohort? The sibling offspring “SibKids”.

with the cases. They were not recruited based on the absence of symptoms or on their medical history. Of the 143 SibKids identified by their parents as existing, 112 responded and, following further exclusions, 68 attended the investigation centre with 35 spouse controls. Generation of the SibKids cohort including details on exclusions is summarised in Figure 7.4.3.

7. A high risk cohort? The sibling offspring “SibKids”.

Figure 7.4.3.: Identification of SibKids and spouse controls



7. *A high risk cohort? The sibling offspring “SibKids”.*

Specific inclusion criteria for the SibKids cohort included:

- Participant is willing and able to give informed consent for participation in the study.
- Male or female, aged 18 years or above.
- The offspring of either a) Proband or b) a symptomatic sibling of a Proband with confirmed anteromedial osteoarthritis.

Specific exclusion criteria for the SibKids cohort included:

- Any form of arthritis of the knee other than anteromedial osteoarthritis.
- Any contraindication to MRI (such as cardiac stents, cardiac pacemakers, aneurysm clip, intra ocular metal fragments). This would preclude them from having MRI but not from having long leg radiographs.
- Pregnancy.

7.4.2. Clinical assessment.

68 SibKids and 35 spouse controls (103 total subjects) attended the clinical trials unit at the Nuffield Orthopaedic Centre in Oxford for inclusion in the study. All were assessed by an experienced Orthopaedic Fellow (LJ). Clinical assessment included obtaining a history and clinical examination with a proforma template to record the data in a standardized method. All participants were asked if they had had any previous surgery on their knees, hip or back and whether they took medications for pain related to these joints. Participants were specifically asked about their job status. A supine and standing clinical examination of both knees and hips was performed and height and weight was assessed. Participants were also required to complete two patient reported outcome measures. (Oxford Knee Score [152], and the Tegner

Activity Score [285]). Patients were then transferred to the Radiology department for radiographs and then MRI scans.

For practical reasons it was not possible to blind the assessor to the SibKid or spouse status of the participants, however, the clinical assessment was undertaken prior to the radiographic and MRI examination of the patients.

7.4.3. Radiographic assessment.

103 (68 SibKids, 35 spouses) subjects attended for radiographic assessment of the knee (total 206 knees). One patient refused to complete PROMs scores and in two further individuals a unilateral ACL reconstruction had taken place and therefore these knees were excluded although the contra lateral side of the same patient was not.

7.4.3.1. Plain radiographs for Kellgren and Lawrence score.

Subjects underwent standardised radiographic bilateral weight bearing AP and lateral of both knees to identify features of osteoarthritis. The protocol at the Nuffield Orthopaedic Centre dictates that the x ray beam is focused midway between both knees and at the level of the apices of the patella and the femoral condyles parallel to the cassette. Images were digitised and transferred from a DICOM Picture Archiving and Communication System (PACS, 2004; GE Healthcare, Little Chalfont, Bucks, UK) to ONIS v2.4 professional (DigitalCore, Tokyo). Images were anonymised and read by a single observer (LJ) for their Kellgren and Lawrence score. The observer was blinded to the SibKid/Spouse status of the subject who had been X rayed.

Validation. The intra and inter observer reliability for the Kellgren and Lawrence score has previously been described in section 3.6 on page 103.

7.4.3.2. Long leg radiographs for long leg alignment.

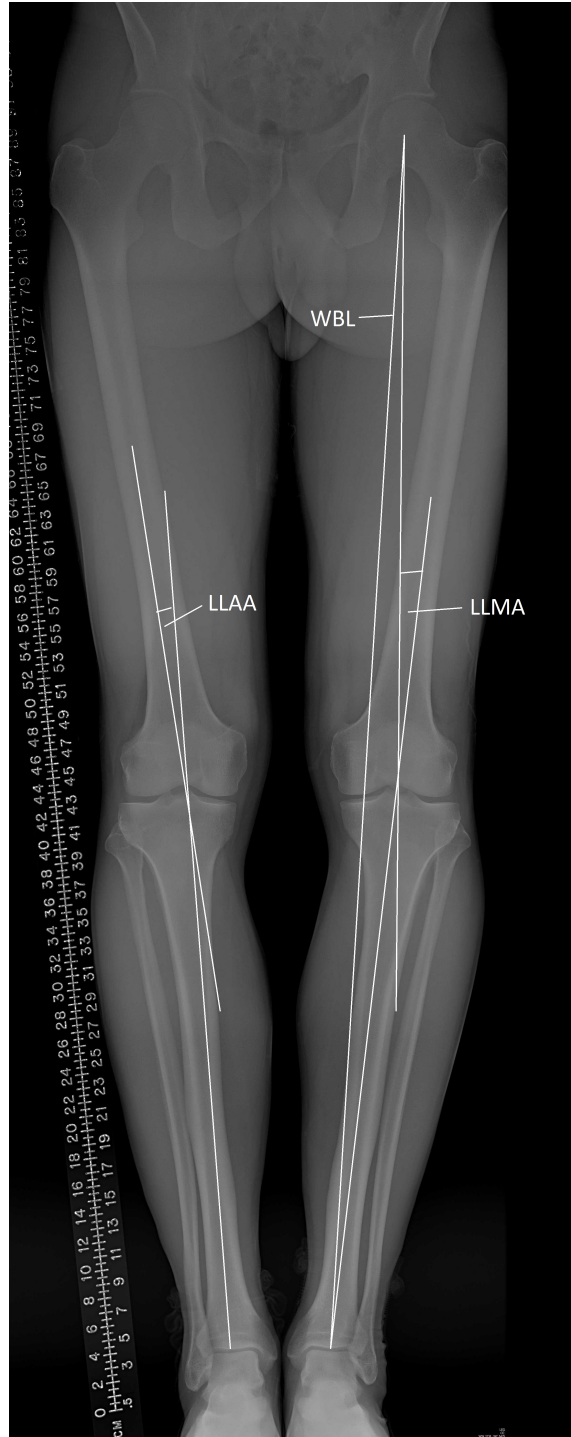
Subjects underwent standardised full limb standing AP radiographs of both lower limbs using a standardised technique. Digital radiographs were analysed using in-house software in MATLAB (7.9.0, The Mathworks Inc., Natick, USA). Based on the AP plane, this software allowed the user to identify the centre of the femoral head by fitting a circle to the femoral head; the centre of the ankle as the midpoint between the most medial and lateral points of the talar dome; and the medial and lateral extremities of the tibial plateau.

For the purposes of this study we considered the Lower Limb Mechanical Axis (LLMA) as the angle between the mechanical axis of the femur (a line drawn from the centre of the femoral head to the middle of the tibial spines) and the mechanical axis of the tibia (a line drawn from the middle of the tibial spines to the middle of the talus)[286]. This has been stated to vary between 0 to 2.20 degrees of valgus in normal adults [287], however more recent work has suggested that up to 32% of men and 17% of women have a constitutional valgus of 3 degrees or more[100]. The Lower Limb Anatomic Axis (LLAA) was considered as the angle between the femoral and tibial anatomic axis (physiologic range 5-7 degrees of valgus). The anatomical axis of the femur is a line connecting the midpoint of the femoral shaft width at the junction of the middle and distal thirds with the centre of the knee. The anatomical and mechanical axes of the tibia are co linear lines connecting the centre of the knee with the centre of the ankle. The weight bearing line (WBL) of the lower limb connects the centre of the hip to the centre of the ankle and represents the path of transmission of forces relative to the lower extremity. The LLMA, LLAA and WBL was derived for each limb as demonstrated in figure 7.4.4. The intersection of the WBL with the joint line was recorded as a percentage from medial to lateral across the tibial plateau. An Orthopaedic Fellow (LJ) analysed all the radiographs, using a 24 inch

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monitor (V243H, Acer Inc., Xizhi, Taiwan).

Figure 7.4.4.: Weight bearing line, lower limb anatomic axis angle, lower limb mechanical axis angle.



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Validation. To ensure the reliability of the single observer analysing the long leg radiographs, the same image was read on 10 occasions by the same observer, for the left and the right leg. This generated 24 observations per reading, a total of 240 for the reliability analysis. Intraobserver reliability studies were performed with a 95% confidence interval of 0.78 mm (SD 0.34) in each direction, based on the 12 landmarks/points of interest repeated 10 times for 1 left and 1 right knee. Intra class correlation coefficients using a two way fixed effects model for absolute agreement were 1.00 indicating excellent agreement.

7.4.3.3. MRI acquisition.

99 subjects (67 SIBKIDS and 32 spouses) presented for MRI acquisition. 2 declined due to claustrophobia, one had a history of aneurysm clips and on one occasion the MRI scanner failed. Due to financial constraints it was not possible to perform bilateral MRI of the knee and therefore if a patient stated that one knee was worse then this knee was investigated preferentially. If no knee was stated to be worse then the knee to be scanned was randomly allocated on a sequential basis by the Orthopaedic Fellow (LJ).

All knees were scanned with the use of a 3T scanner, (Acheiva 3.0T X series; Philips Healthcare, Eindhoven, Netherlands) and a transmit/receive eight channel phased array knee coil (Invivo coordination, Gainesville, Fl, USA.) The standard imaging protocol in our hospital includes Sagittal Proton density weighted SPAIR sequences (TR/TE: 8183/30, Flip angle 90 degrees, Slice thickness/Gap 2/0.2 mm, FH phase, Field of View (FOV) 15cm), mFFE Sagittal sequences (TR/TE 967/9, Flip angle 25, Slice thickness/Gap 3/0.3 AP phase, FOV 15cm), Axial Proton Density SPAIR sequences (TR/TE: 5919/50, Flip angle 90 degrees, Slice thickness/Gap 3/0.3 mm, RL phase, FOV 15cm), Sagittal T1 (TR/TE: 544/20, Flip angle 90 degrees, Slice thickness/Gap 2.5/0.8 mm, AP phase, FOV 15cm), and Proton Density SPAIR Axial

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sequences (TR/TE: 4809/50, Flip angle 90 degrees, Slice thickness/Gap 3/0.3 mm, FH phase). The approximate scan acquisition time was 30 minutes. In all cases the standard MRI protocol was acquired prior to the T2 map. The set up for the patient was as per the routine MRI protocol at the Nuffield Orthopaedic Centre. Briefly, the patient is supine with ankles supported on foam pads. The apex of the patella is placed in the centre of the coil. The leg is allowed to fall into a comfortable position and are then held in position with the use of foam pads. Following this a three plane localiser scan is obtained to ensure the correct position of the knee. In the coronal plane the slices are aligned with the back of the femoral condyle with the joint in the middle of the Field of View. The scan then proceeds posterior to anterior from the back of the femoral condyles and the popliteal artery to the middle of the patella anteriorly. In the sagittal plane the slices are angled along the ACL, along the middle of the notch and groove of the femur and then medially rotated by 15 degrees. In the axial plane two points of reference are used. Firstly, slices are aligned perpendicular to the patella femoral joint including the top of the patella and the insertion of the patella ligament. The joint is then positioned in the middle of the field of view and slices are secondarily referenced as perpendicular to the collateral ligaments using the coronal image.

7.4.3.4. MRI assessment for meniscal extrusion.

The MRI DICOM images were exported from PACS to ONIS 2.4 Professional and medial meniscal extrusion was measured as described in Appendix C on page 283.

Validation. Inter and intra observer reliability for measurement of meniscal extrusion has previously been described in Section 6.3.6 on page 197.

7.4.3.5. MRI assessment for WORMS scoring.

The T1, T2 coronal, sagittal and axial MRI DICOM images were exported from PACS to ONIS 2.4 Professional. An experienced Radiology Fellow, trained in the WORMS scoring technique read the images and scored them on a standardised proforma. The Radiology Fellow was not aware of the nature of the study and was blinded to the SibKid or Spouse status of the participants. As described in the original paper on WORMS scoring by Peterfy et al [65] and earlier in this thesis in section 2.2.4.1 on page 50, the following scores were compared between the SibKids and spouses:

1. Independent values for each feature in each of the three compartments in the knee (PFJ, MFTJ, LFTJ).
2. Cumulative surface feature (cartilage, marrow abnormality, sub articular cysts, bone attrition, osteophytes) score for each compartment.
3. Cumulative scores for each feature throughout the knee
4. A total combined score for the entire knee.

In addition, and in reference to the recognised increase in cartilage damage that occurs in the anteromedial portion of the medial tibial plateau in AMOA [?]:

1. Cartilage lesions in MTa, MTc, MTP and (MTa plus MTc) total were compared between SibKids and spouses

Validation. Two experienced musculoskeletal radiologists (one Consultant and one Fellow) were asked to read 5 MRI scans and to WORMS score each. Each reader was blinded to the SibKid/Spouse status of the scan in addition to the results obtained by the other reader. The second reader was asked to re read the same scans one week later blinded to his previous results.

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Intraobserver reliability: An ICC was calculated for the musculoskeletal radiology Fellow across two assessments of the same scans. This indicated a high level of agreement with an ICC of 0.98 (CI 0.978-0.985).

Interobserver reliability: In ICC was calculated for comparison of scores between the Fellow and the Consultant. This indicated a high level of agreement with an ICC of 0.94 (CI 0.928 - 0.95).

7.4.3.6. MRI T2 map for functional cartilage change.

T2 map creation. The T2 map protocol was performed approximately 30 minutes following the arrival of the subject in the 3T scanner in order to avoid the well established effect of recent weight bearing on the T2 status of the hyaline cartilage of the knee [72]. The imaging protocol for the acquisition of the T2Q MLE Sagittal images was TR/TE 3500/14, Flip angle 90, Slice thickness/Gap 3/0.3, FOV 15cm, AP Phase. T2 maps were created in a pixel wise fashion, with least-squares fitting according to the expected mono exponential decay with time constant T2. Using the Maximum Likelihood Estimation (MLE) option, correction for the Rician noise distribution of magnitude images at low SNR was also applied.

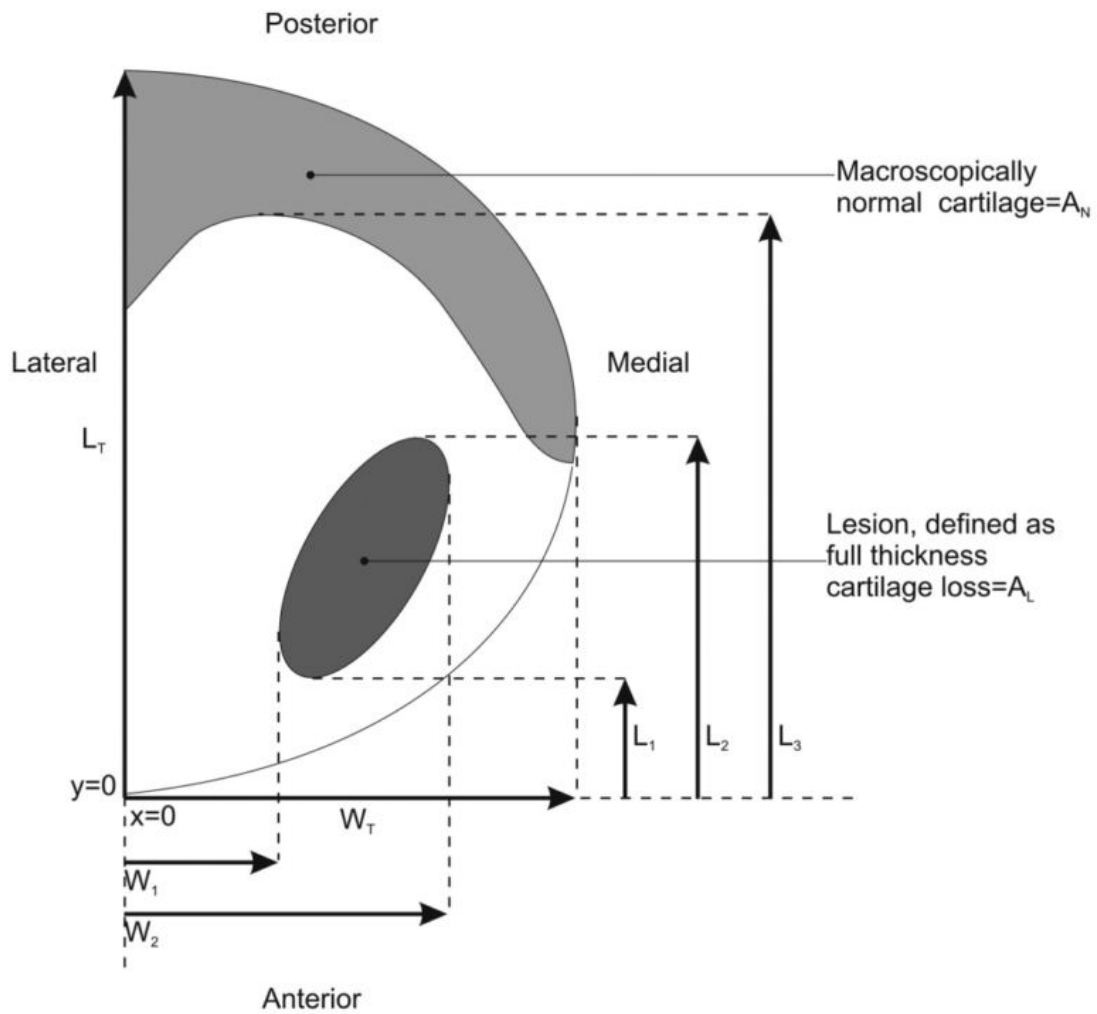
Identification of targeted region of interest (ROI) of knee cartilage. Due to time constraints it was not possible to manually segment each image slice on the femur and tibia. Therefore, a targeted region of interest (ROI) was identified based on where the earliest changes of disease might be expected to arise.

Rout et al [239], in a paper that correlates the pattern of cartilage damage in anteromedial knee OA and its relationship to the status of the anterior cruciate ligament, collected 90 specimens from patients undergoing uni compartmental knee arthroplasty at the Nuffield Orthopaedic Centre in Oxford. The surgical procedure for UKA is guided by instrumentation and is highly standardised. The vertical cut

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is made at the apex of the medial tibial spine and the medial tibial plateau is then removed as a single piece. The specimens were then photographed and then processed to identify where the changes of full thickness disease occurred. This is demonstrated in Figure 7.4.5

Figure 7.4.5.: A schematic of the medial tibial plateau in end stage AMOA reproduced with kind permission from Rout et al (2013).



Key areas demonstrated in this slide by Rout et al:

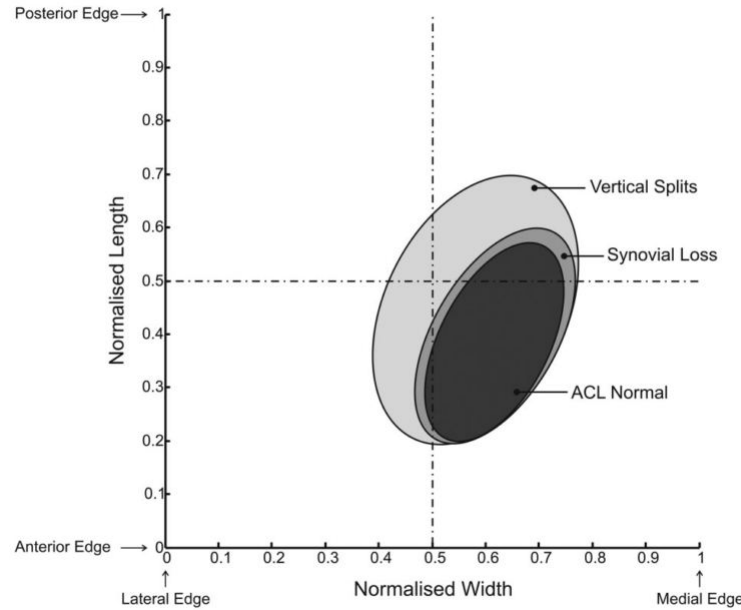
- AL = area of the lesion, expressed as a percentage of total medial tibial plateau area (AT).

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- AN = area of retained full thickness cartilage, expressed as a percentage of AT.
- L1 = distance in the antero-posterior direction, (along the y axis) between the anterior edge of the specimen and the anterior border of the lesion, expressed relative to total length of specimen (LT).
- L2 = distance in the antero-posterior direction between the anterior edge of the specimen and the posterior border of the lesion, expressed relative to LT.
- L3 = distance in the antero-posterior direction between the anterior edge of the specimen and the most posterior point of the transition zone; expressed relative to LT.
- W1 = distance in the medial-lateral direction between the lateral cut edge of the specimen and the start of the lesion expressed relative to total width of specimen (WT).
- W2 = distance in the medial-lateral direction between the lateral cut edge of the specimen and the end of the lesion expressed relative to WT.

Rout et al also demonstrate where the average lesions occur having normalised the measurement parameters to take into account variation in tibial plateau width between individuals. This is demonstrated in Figure 7.4.6 on the next page.

Figure 7.4.6.: Average location of cartilage lesions in end stage AMOA reproduced with kind permission from Rout et al (2013).



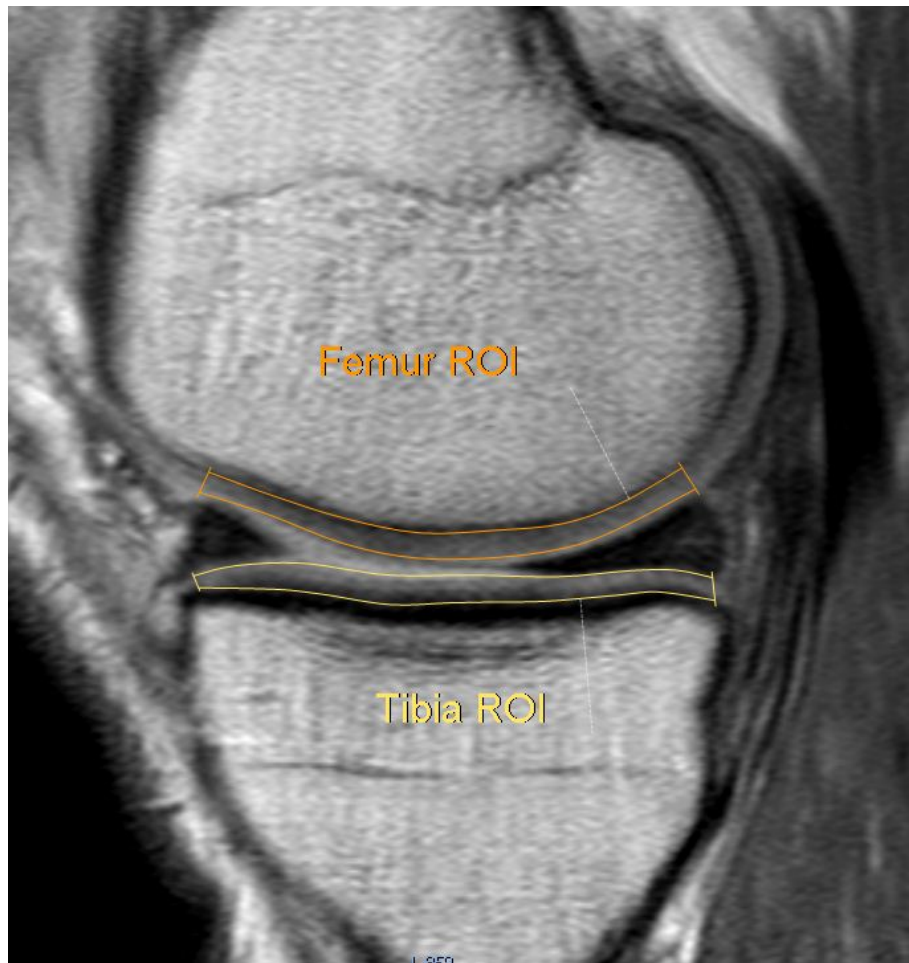
Analysing these images demonstrates that the centre of the full thickness lesion was found to be predominantly in the anteromedial quadrant of the tibia. The centre of the lesion was located at a point 60% of the width of the plateau in the coronal plane. The posterior border of the lesion at 60% of the tibial width was found to be at 50% of the AP distance of the tibia. Therefore, it was decided to inspect the T2 map at a slice corresponding to 60% of the width of the medial tibial plateau, and to split this slice into anterior (the location of theoretical damage) and posterior (which should be normal and therefore act as an internal “control” region). The protocol for identifying the slice to be analysed is described in Appendix D on page 294.

T2 map analysis. Quantitative T2 maps were analysed using a custom developed program (Philips Medical Workspot PII-SW11.1WIP, Philips Medical Systems Netherlands B.V). This software allows the user to view the MRI images as normal, but as part of the Cartilage Assessment package displays a proton intensified image

alongside a T2 colour map image as shown in Figure 7.4.8. The analysis took place as follows. In the first instance, the slice of interest, the identification of which was described in Section 7.4.3.6, was inspected. The software then allows the region of interest (ie the area of cartilage for which the T2 value is of interest) to be manually drawn. Both tibia and the corresponding area of cartilage on the femur were manually drawn. The femoral and tibial ROI were defined in the same way as by the WORMS scoring system [65]. The tibial cartilage ROI was defined as that area of cartilage from the anterior border of the anterior horn of the medial meniscus to the posterior border of the posterior horn of the medial meniscus. On the femur, the corresponding area of cartilage, ie that from the anterior border of the anterior horn of the medial meniscus to the posterior border of the posterior horn of the medial meniscus was identified as the ROI (see Figure 7.4.7).

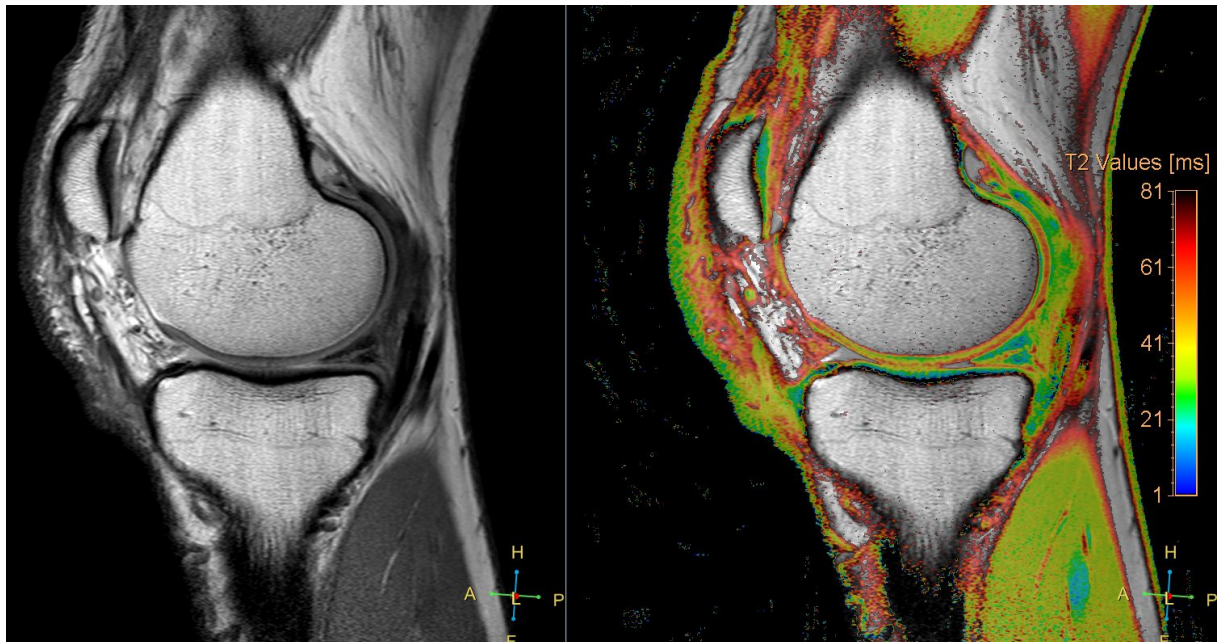
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Figure 7.4.7.: The tibial and femoral regions of interest.



The femoral portion of the patello femoral joint and the posterior region of the femur (that which corresponds to the posterior convexity and is found to articulate only in extreme flexion) were not included in the ROI in order to allow a focused comparison on areas of cartilage which were felt to most likely demonstrate cartilage degeneration. The observer was careful not to include joint fluid in the ROI and to distinguish cartilage from subchondral bone under two views: one a proton intensified image and one a T2 colour map (see figure 7.4.8 on the next page)

Figure 7.4.8.: Sagittal MRI scan slice demonstrating proton intensified map (left) and T2 colour map (right)



An absolute T2 value for both the femur and tibia ROI was generated. Each ROI was then split into anterior (A) and posterior (B) portions and a T2 value generated for both. The anterior portion of the femur and tibia felt to be most likely to represent the site of cartilage damage and the posterior portions felt most likely to be normal. Zone A and Zone B on the femur and tibia were then split into three layers of equal depth (superficial, intermediate and deep) [288].

The following values were compared between SibKids and spouse controls.

1. Absolute T2 values for entire ROI on tibia
2. Absolute T2 values for entire ROI on femur
3. T2 value in Zone A on tibia (superficial, intermediate and deep layers)
4. T2 value in Zone B on tibia (superficial intermediate and deep layers)
5. T2 value in Zone A on femur (superficial, intermediate and deep layers)

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6. T2 value in Zone B on femur (superficial, intermediate and deep layers)

Because one of the aims of this study was to determine whether SibKids had a relative increase in T2 signal in Zone A of the tibial and femoral ROI compared to Zone B, the ratio of T2 signal in Zone A to Zone B ($T2A/T2B$), and Zone A to the Total T2 for the ROI ($T2A/T2_{total}$) were created. This method of using individuals as their own “internal controls” has been used previously in SibKids studies [284]. Thus comparisons were made between SibKids and Spouse controls in terms of both absolute and relative values of T2 per region and zone.

7.4.4. Sample size and assessment.

Previous studies that look into the risk of developing anteromedial knee OA in the presence of significant family history have not been performed before and therefore there are no data to indicate what difference one may expect in the absolute and relative T2 map acquisitions between SibKids and spouses. A Total of 58 T2 maps is larger than most other studies [288], [289], [290] that look at T2 maps in knees, as well as family history SibKids studies that look at the risk of inheritance of hip OA [284].

7.5. Statistical analysis.

7.5.1. Vertical transmission risk using plain radiographs.

Chi squared values were used to analyse data in the contingency table and statistical significance was defined as a p-value of <0.05 . Risk estimates based on the presence of anteromedial OA in the SibKids versus the spouses were obtained using the following equation:

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Relative Risk = Percentage of SibKids with painful AMOA $\div$ Percentage of Spouses with painful AMOA.

7.5.2. Comparison of long leg alignment.

P-P plots and Kolmogorov Smirnov test indicated that the WBL, LLMA, and LLAA were all normally distributed so these data are reported as means with standard deviations. Differences between SibKids and spouse groups were compared with the use of independent samples T tests.

7.5.3. Comparison of meniscal extrusion.

Statistical analysis was performed as per section 6.3.4 on page 195.

7.5.4. WORMS for structural change in the knee.

P-P plots and Kolmogorov Smirnov test indicated that data was normally distributed. so these data are reported as means with standard deviations. Differences between SibKids and spouse groups were compared with the use of independent samples T tests.

7.5.5. T2 Map for functional change in cartilage without structural change.

P-P plots and the Kolmogorov Smirnov test indicated that all values of T2 and ratios of T2 were normally distributed so these data are reported as means with standard deviations. Differences between SibKids and spouse groups were compared with the use of independent samples T tests.

7.6. Results.

7.6.1. Patient demographics.

7.6.1.1. Entire cohort.

A total of 103 subjects (68 SibKids and 35 Spouses) attended the Nuffield Orthopaedic Centre for assessment.

- 102 completed the clinical assessment (67 SibKids and 35 spouses) One patient declined to give demographic data or be examined.
- All subjects underwent plain standing radiographs of the knee.
- 101 had technically acceptable Long Leg alignment films. (66 SibKids and 35 Spouses)
- 99 subjects completed MRI acquisition. (67 SibKids and 32 spouses). Two declined due to claustrophobia, one had a history of aneurysm clips and on one occasion the MRI scanner failed.
- 79 T2 Maps were created (54 SibKids and 25 Spouses). Of the 24 missing maps, in addition to the four that did not undergo scanning as previously described, 10 were lost from the scanner before reconstruction, 9 had significant movement artifact and a further one patient was unable to tolerate the scanner due to claustrophobia.

There were 68 SibKids and 35 spouses. 50.5% were male (n=52) and 49.5% were female (n=51). The mean age was 46.3 years (range 18.8-62.3, SD 8.33) and the mean BMI was 28.3 (range 18-51.9 SD 5.59). In 22.3% (n=23) the left knee was more painful, in 29.1% (n=30) the right knee was more painful, in 44.7% (n=46) neither knee had symptoms and in 2.9% (n=3) both knees were as bad as each other.

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Previous lower limb surgery, prevalence of low back pain, and occupation status are described in tables 7.1, 7.2 and 7.3.

Table 7.1.: History of previous surgery for entire cohort

Previous Surgery	Frequency	Percent
None	89	86.4
Arthroscopy	9	8.7
TKR	1	1.0
ACL	2	1.9
THR	1	1.0
Subtotal	102	99.0
Missing	1	1.0
Total	103	100.0

Table 7.2.: Frequency of low back pain for entire cohort

Presence of back pain	Frequency	Percent
No	85	82.5
Yes	17	16.5
Total	102	99.0
Missing	1	1.0
Total	103	100.0

Table 7.3.: Occupation status for entire cohort

Occupation	Frequency	Percent
Desk based	35	34.0
Not working	3	2.9
Light manual	37	35.9
Heavy manual	19	18.4
Homemaker	8	7.8
Subtotal	102	99.0
Missing	1	1.0
Total	103	100.0

7.6.1.2. Comparison of SibKid and spouse cohort demographics

The independent samples T Test demonstrated that there was no difference between the SibKid and spouse cohorts in terms of BMI, Activity Level and Oxford Knee

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Score for either knee. The SibKids were found to be significantly younger than the spouses (45.1 yrs vs 48.6 years $p=0.04$)

Table 7.4.: SibKid vs spouse demographics

		N	Mean	Std. Deviation	Std. Error Mean	Significance
BMI	SibKid	67	28.4	6.22	0.76	$p = 0.86$
	spouse	35	28.19	4.22	0.71	
Age	SibKid	68	45.12	8.77	1.06	$p = 0.04$
	spouse	35	48.61	6.97	1.18	
Left OKS	SibKid	67	45.27	4.76	0.58	$p = 0.27$
	spouse	35	44.06	6.01	1.01	
Right OKS	SibKid	67	44.43	5.24	0.64	$p = 0.57$
	spouse	35	43.74	6.69	1.13	
Tegner	SibKid	67	3.73	1.62	0.19	$p=0.23$
	spouse	35	4.11	1.28	0.22	

Pearson Chi squared test for independence of relationships between categorical variables indicates no significant difference between SibKids and spouse groups in terms of gender, or history of back pain. As occupation, history of previous knee surgery and knee affected contained values of less than ten in one or more cell of the contingency table, Fishers exact test was performed. This indicated no difference between SibKids or spouse groups in terms of occupation, history of previous surgery or knee affected.

7.6.2. Study 1 Vertical transmission of risk of symptomatic radiographic anteromedial knee arthritis.

A total of 206 standing AP knee X rays were obtained in 68 SibKids and 35 spouses. In one patient a TKR had been performed. The original X rays were obtained, which confirmed the presence of AMOA preoperatively and this patient was therefore coded as KL4 and considered to have had the presence of painful OA preoperatively. The two knees that had undergone ACL reconstruction were excluded as the absence of

an ACL, irrespective of reconstruction status, is known to predispose to development of knee OA [291]. Following the exclusion of two knees that had previous ACL reconstruction, 204 X rays were analysed in 68 SibKids and 35 spouses. One patient refused to complete PROMS data and therefore although radiographic OA was recorded in this patient, the presence or otherwise of painful radiographic OA was not able to be determined.

Radiographic AMOA was considered as the presence of KL 2 or more, and painful radiographic AMOA was considered as KL 2 or more with and OKS of 29 or less as per previous studies of this kind [234]. The presence of painful OA in either knee was compared between SibKids and spouse groups by means of a 2x2 contingency table and Pearson’s Chi Square test or Fishers Exact test depending on the number of values per cell in the table.

7.6.2.1. Analysis if OA is considered KL2.

Considering OA as KL2 or more in 103 subjects,

- 17 had radiographic OA in both knees.
- 23 had OA unilaterally (9 Right, 14 Left).
- 63 had no Radiographic OA in either knee.

Radiographic OA. A 2x2 cross-tabulation of SibKid/spouse status with the presence of radiographic OA in either knee is demonstrated in table 7.5. Pearson’s Chi Square test did not demonstrate a significant difference between groups ($p=0.862$).

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Table 7.5.: Cross tabulation of SibKid or spouse status vs presence of radiographic knee OA per subject

		Radiographic OA in Either Knee		Total
		OA not present	OA Present	
SibKid	Count	42 (61.7%)	26 (38.3%)	68 (100%)
Spouse	Count	21 (60%)	14 (40%)	35 (100%)
Total	Count	63 (61.2%)	40 (38.8%)	103 (100%)

If the presence of OA per knee is considered the cohort consists of

- 204 knees in total (101 Right, 103 Left)
- 135 SibKids knees (67 Right, 68 Left)
- 69 spouse knees (34 Right, 35 Left)

A 2x2 Cross-tabulation of SibKid or spouse status with the presence of radiographic OA per knee is demonstrated in table 7.6. Pearson’s Chi Square Test indicates that no significant difference between groups ($p=0.370$).

Table 7.6.: Cross tabulation of SibKid or spouse status vs presence of radiographic OA per knee

	Presence of OA per knee		Total
	OA not present	OA present	
SibKid	100 (74%)	35 (26%)	135(100%)
Spouse	47 (68.1%)	22 (31.9%)	69 (100%)
Total	147 (72%)	57 (28%)	204 (100%)

Symptomatic knee status. Symptom status (defined as OKS less than or equal to 29) was available on 202 knees in 102 patients (one patient had no PROMs data available, two right sided knees excluded due to ACL reconstruction).

- 6 subjects had symptoms in a total of seven knees.
- One patient had symptoms bilaterally

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- 5 had unilateral pain (R= 3 L = 2)

A 2x2 Cross-tabulation of SibKid/spouse status with the presence of symptoms in either knee is demonstrated in table 7.7. Fishers exact Test value of 0.410 indicates no significant different between groups.

Table 7.7.: Cross tabulation of SibKid or spouse status vs presence of pain (OKS <29) in either knee

	Presence of symptomatic knee		Total
	No pain	Pain	
SibKid	64 (95.5%)	3 (4.5%)	67 (100%)
Spouse	32 (91.4%)	3 (8.6%)	35 (100%)
Total	96 (94.1%)	6 (5.8%)	102 (100%)

A 2x2 Cross tabulation of SibKid/spouse status with the presence of pain per knee is demonstrated in table 7.8. Again, Fishers exact test value of 0.182 indicates no statistically significant difference between groups.

Table 7.8.: Cross tabulation of SibKid or spouse status vs presence of pain (OKS <29) per knee

	Presence of symptoms per knee		Total
	No Symptoms	Symptoms	
SibKid	130 (97.7%)	3 (2.3%)	133 (100%)
spouse	65 (94.2%)	4 (5.8%)	69 (100%)
Total	195 (96.5%)	7 (3.5%)	202 (100%)

Symptomatic Radiographic OA. Symptomatic radiographic OA, as defined by the presence of both a KL score of 2 or more and the presence of an OKS of 29 or less was present in 4 unilateral knees.

A 2x2 cross-tabulation of SibKid or spouse status with presence of symptomatic radiographic knee OA in either knee is demonstrated in table 7.9. Fishers Exact test value of 0.605 again indicates no difference in the risk of having painful radiographic knee OA between SibKids and spouses.

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Table 7.9.: Cross tabulation of SibKid or spouse status vs presence of symptomatic radiographic knee OA

	Symptomatic radiographic knee OA		Total
	No	Yes	
SibKid	65 (97%)	2 (3%)	67 (100%)
Spouse	33 (94.3%)	2 (5.7%)	35 (100%)
Total	98 (96.1%)	4 (3.9%)	102 (100%)

A 2x2 Cross tabulation of SibKid spouse status for the presence of symptomatic OA per knee is demonstrated in table 7.10. As expected, Fishers exact test of 0.607 reveals no difference between SibKids or spouses.

Table 7.10.: Cross tabulation of SibKid or spouse status vs presence of symptomatic OA per knee

	No symptomatic radiographic OA	Symptomatic radiographic OA	Total
SibKid	131 (98.5%)	2 (1.5%)	133 (100%)
Spouse	67 (97.1%)	2 (2.9%)	69 (100%)
Total	198 (98.1%)	4 (1.9%)	202 (100%)

7.6.2.2. Analysis if OA is considered KL1 or more.

Some investigators consider KL 0 as the absence of Radiographic OA and KL1 as the presence of the condition. The analysis above was therefore repeated having recoded the individuals as having the presence or absence of symptomatic radiographic OA on the basis of KL1 indicating the presence of disease.

Considering OA as KL1 or more in 103 subjects,

- 33 had radiographic OA in both knees.
- 31 had OA unilaterally (14 Right, 17 Left).
- 39 had no radiographic OA in either knee.

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Radiographic OA. A 2x2 Cross tabulation of SibKid/spouse status with the presence of radiographic OA in either knee is shown in table 7.11. Again the Pearson Chi square test did not indicate any difference between the two groups ($p=0.591$)

Table 7.11.: Cross tabulation of SibKid or spouse status vs presence of radiographic knee OA in either knee.

	Radiographic Knee OA in either Knee		Total
	OA not present	OA Present	
SibKid	27 (39.7%)	41 (60.3%)	68 (100%)
Spouse	12 (34.3%)	23 (65.7%)	35 (100%)
Total	39 (100%)	64 (100%)	103 (100%)

A 2x2 cross tabulation of SibKid or spouse status with the presence of radiographic OA per knee is shown in table 7.12. Pearson Chi Square approaches, but does not achieve significance at 0.067, indicating no statistically significant difference between SibKids and Spouses.

Table 7.12.: Cross tabulation of SibKid or spouse status vs presence of radiographic OA per knee

	No Radiographic OA	Radiographic OA	Total
SibKid	77 (57%)	58 (43%)	135 (100%)
Spouse	30 (43.5%)	39 (56.5%)	69 (100%)
Total	107 (52.4%)	97 (47.5%)	204 (100%)

Symptomatic Radiographic OA. Symptomatic radiographic OA, as defined by the presence of both a KL score of 1 or more and the presence of an OKS of 29 or less was present again in only 4 individuals unilaterally. Therefore, the analysis was exactly the same as that presented in table 7.7.

7.6.3. Study 2 comparison of long leg alignment between SibKids and spouses.

Long leg alignment films were obtained in 101 patients meaning 202 lower limbs were available for analysis.

For the entire cohort, the mean WBL position for crossing the tibial plateau was 45.6% (3-72.3, SD13.1), The Lower Limb Mechanical Axis was mean 0.96 degrees (Range -4.68- 10.74 SD 2.83) and the Lower Limb Anatomical Axis was Mean -4.4 degrees valgus, (range -10.2 - 3.66, SD 2.7).

An independent samples t test was conducted to compare the Lower Limb alignment of SibKids and spouse controls. The dependent variables, (Weight Bearing Line, Lower Limb Mechanical Axis and Lower Limb Anatomical Axis) were measured on a continuous scale. SibKids status was the independent variable. Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was generated. The results indicated that there was no difference in lower limb alignment between SibKids and spouse controls across these three measures and is demonstrated in Table 7.13.

Table 7.13.: Comparison of Lower Limb alignment between SibKids and spouses

		N	Mean	SD	SEM	P Value
Weight Bearing Line (%)	SibKid	132	45.19	13.69	1.19	0.53
	Spouse	70	46.43	12.14	1.45	
Lower Limb Mechanical Axis	SibKid	132	1.08	2.95	0.26	0.46
	Spouse	70	.77	2.59	0.31	
Lower Limb Anatomical Axis	SibKid	132	-4.37	2.74	0.24	0.84
	Spouse	70	-4.46	2.64	0.32	

7.6.4. Study 3: The incidence of meniscal extrusion in the SibKids

There was no incidence of primarily lateral degenerative disease and therefore no cases were excluded on this basis. In one subject there was no reconstruction of coronal images meaning assessment of extrusion was not possible. The total cohort size was therefore 98 with 66 SibKids and 32 spouses. The mean meniscal extrusion as previously defined for the entire cohort was 2.98mm (0.92-8.43 SD 1.36).

There was no difference between SibKids and spouses in terms of absolute meniscal extrusion as demonstrated in Table 7.14.

Table 7.14.: Comparison of absolute meniscal extrusion in mm between SibKids and spouses

		N	Mean	SD	SE Mean	P value
Absolute extrusion distance	Spouse	32	2.95	1.54	0.27	0.85
	SibKid	66	3.00	1.27	0.16	

If meniscal extrusion is defined as greater than 3mm extruded and a 2x2 table is constructed with a chi square analysis we can again see no difference between SibKids and spouses ($p=0.495$) (demonstrated in Table 7.15.) This lack of difference between groups persists if we define extrusion as 2mm ($p = 0.625$) (demonstrated in Table 7.16) or 4 mm ($p = 0.171$) (demonstrated in Table 7.17).

Table 7.15.: Cross tabulation of SibKid or spouse status vs presence of meniscal extrusion (when defined as 3mm)

	Extrusion defined as 3mm or more		Total
	Not extruded	Extruded	
Spouse	18 (56.25%)	14 (37.5%)	32 (100%)
SibKid	42 (63.6%)	24 (36.4%)	66 (100%)
Total	60 (61.2%)	38 (38.8%)	98 (100%)

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Table 7.16.: Cross tabulation of SibKid or spouse status vs presence of meniscal extrusion (when defined as 2mm)

	Extrusion defined as 2mm or more		Total
	Not extruded	Extruded	
Spouse	5 (15.6%)	27 (84.4%)	32 (100%)
SibKid	13 (19.7%)	53 (80.3%)	66 (100%)
Total	18 (18.4%)	80 (81.6%)	98 (100%)

Table 7.17.: Cross tabulation of SibKid or spouse status vs presence of meniscal extrusion (when defined as 4mm)

	Extrusion defined as 4mm or more		Total
	Not extruded	Extruded	
Spouse	26 (81.3%)	6 (18.8%)	32 (100%)
SibKid	60 (90.1%)	6 (9.9%)	66 (100%)
Total	86 (87.8%)	12 (12.2%)	98 (100%)

7.6.5. Study 4: A comparison of structural cartilage MRI

changes between SibKids and spouses: WOMS score.

7.6.5.1. Comparison of each feature in the three compartments in the knee.

The WOMS score for cartilage, bone marrow, cysts, attrition and osteophytes was calculated for each compartment. Mean values for SibKids and spouses was calculated and Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was computed. This indicated that there was no difference between the SibKids and spouses except for in the medial compartment where the spouses had a significantly greater osteophyte score than the SibKids. In addition, in the lateral compartment the spouses demonstrated a greater mean score in terms of attrition and osteophytes than the SibKids. This is demonstrated in Table 7.18.

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Table 7.18.: WORMS score comparison of each feature in each of the three compartments of the knee: SibKids vs spouses.

Compartment	Feature	SibKid or spouse	N	Mean	SD	SEM	P value
Patello femoral	Cartilage	SibKid	69	3.82	4.02	0.48	0.79
		Spouse	32	4.08	5.12	0.92	
	Bone marrow	SibKid	69	0.65	0.98	0.12	0.39
		Spouse	32	0.84	1.17	0.21	
	Cysts	SibKid	69	0.22	0.73	0.09	0.26
		Spouse	32	0.06	0.35	0.06	
	Attrition	SibKid	69	0.67	0.95	0.11	0.48
		Spouse	32	0.53	0.72	0.13	
	Osteophytes	SibKid	69	4.16	5.03	0.61	0.48
		Spouse	32	4.91	4.79	0.85	
Medial	Cartilage	SibKid	69	2.54	5.28	0.64	0.33
		Spouse	32	3.67	5.55	0.98	
	Bone marrow	SibKid	69	0.48	1.34	0.16	0.89
		Spouse	32	0.44	1.41	0.25	
	Cysts	SibKid	69	0.10	0.35	0.04	0.29
		Spouse	32	0.03	0.18	0.03	
	Attrition	SibKid	69	1.06	1.38	0.17	0.26
		Spouse	32	1.38	1.16	0.21	
	Osteophytes	SibKid	69	4.10	4.66	0.56	0.03
		Spouse	32	7.09	6.66	1.18	
Lateral	Cartilage	SibKid	69	1.37	2.79	0.34	0.95
		Spouse	32	1.41	2.97	0.53	
	Bone marrow	SibKid	69	0.39	1.02	0.12	0.70
		Spouse	32	0.31	0.74	0.13	
	Cysts	SibKid	69	0.10	0.46	0.06	0.67
		Spouse	32	0.06	0.35	0.06	
	Attrition	SibKid	69	1.86	1.13	0.17	0.04
		Spouse	32	2.38	1.26	0.22	
	Osteophytes	SibKid	69	3.06	3.74	0.45	0.02
		Spouse	32	5.69	4.03	0.71	

7.6.5.2. Comparison of cumulative surface feature (cartilage, marrow abnormality, sub articular cysts, bone attrition, osteophytes) score for each compartment.

The total WORMS score for each compartment was calculated. Mean values for SibKids and spouses were calculated and Levene’s test was conducted to evaluate

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homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was computed. This indicated that spouses demonstrated significantly worse mean scores for surface features in the lateral compartment than SibKids. This is demonstrated in Table 7.19.

Table 7.19.: WORMS score comparison of cumulative surface feature score for each compartment: SibKids vs spouses

Compartment	SibKid or spouse	N	Mean	SD	SEM	p value
Patello femoral	SibKid	69	9.51	9.65	1.16	0.66
	Spouse	32	10.42	9.28	1.64	
Medial	SibKid	69	8.28	11.09	1.34	0.09
	Spouse	32	12.61	13.07	2.31	
Lateral	SibKid	69	6.78	6.80	0.82	0.04
	Spouse	32	9.84	6.64	1.17	

7.6.5.3. Comparison of cumulative scores for each feature throughout the knee.

The cumulative score for each surface feature throughout the knee was calculated. Mean values for SibKids and spouses were determined and Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was computed. This indicated that there was no difference in the surface features between the two groups except for osteophytes which were more prevalent on average in the spouses than the SibKids. This is demonstrated in table 7.20 on the following page.

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Table 7.20.: WORMS score comparison between SibKids and spouses of cumulative scores for each joint surface feature

Feature total	SibKid or spouse	N	Mean	SD	SEM	P value
Cartilage	SibKid	69	7.72	9.87	1.19	0.49
	Spouse	32	9.16	9.54	1.68	
Bone marrow	SibKid	69	1.52	2.36	0.28	0.88
	Spouse	32	1.59	1.93	0.34	
Cysts	SibKid	69	0.42	1.05	0.13	0.18
	Spouse	32	0.16	0.52	0.09	
Attrition	SibKid	69	3.58	2.21	0.27	0.18
	Spouse	32	4.28	1.84	0.33	
Osteophytes	SibKid	69	11.32	12.49	1.50	0.03
	Spouse	32	17.69	14.23	2.51	

7.6.5.4. Comparison of combined total score for entire knee.

Total WORMS scores were calculated for each knee. Mean values for SibKids and spouses were calculated and Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was computed. This indicated that there was no difference in total WORMS scores between SibKids or spouses and is demonstrated in Table 7.21.

Table 7.21.: Comparison of total WORMS score between SibKids and spouses

	SibKid or spouse	N	Mean	SD	SEM	P value
WORMS	SibKid	69	26.59	26.89	3.24	0.12
	Spouse	32	35.53	26.16	4.62	

7.6.5.5. Comparison of cartilage lesions in anterior, central and posterior medial tibia regions, and medial and posterior femur.

As the SibKid cohort was developed from families with a history of antero medial knee arthritis, cartilage lesions in specific regions of the knee were determined. Specifically on the medial tibia, cartilage lesion totals in the anterior, central and posterior

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regions were calculated and compared between SibKids and spouses. On the medial femur, cartilage lesion totals in the central and posterior regions were calculated and compared between SibKids and spouses. In addition on the medial tibia the sum of the lesions in the anterior and central regions, felt to represent the site of antero-medial knee arthritis, were calculated and compared between SibKids and spouses. Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was computed. This indicated no difference in cartilage lesions between SibKids and spouses and is demonstrated in table 7.22.

Table 7.22.: WORMS score comparison of cartilage lesions in the anteromedial region of tibia and femur

Cartilage region	SibKid or Spouse	N	Mean	SD	SEM	P value
Medial tibia anterior	SibKid	69	0.38	1.27	0.15	0.63
	Spouse	32	0.52	1.46	0.26	
Medial tibia central	SibKid	69	0.51	1.41	0.17	0.32
	Spouse	32	0.84	1.89	0.33	
Medial tibia posterior	SibKid	69	0.26	1.09	0.13	0.72
	Spouse	32	0.34	1.10	0.19	
Medial femur central	SibKid	69	1.15	1.74	0.21	0.11
	Spouse	32	1.78	1.94	0.34	
Medial femur posterior	SibKid	69	0.24	0.73	0.09	0.73
	Spouse	32	0.19	0.59	0.11	
Medial tibia anterior plus tibia central	SibKid	69	0.88	2.59	0.31	0.42
	Spouse	32	1.36	3.06	0.54	

7.6.6. Study 5: A comparison of early functional cartilage change between SibKids and spouses: T2 mapping.

7.6.6.1. Comparison of tibial T2 values between SibKids and spouses.

An independent samples t test was conducted to compare the T2 values across different regions of the Tibia of SibKids and spouse controls. The dependent variables,

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(Total T2 Value, T2 Value of Zone A, T2 Value of Zone A Superficial, Intermediate and Deep layers, T2 Value of Zone B, T2 Value of Zone BS Superficial ,Intermediate and Deep Layers) were measured on a continuous scale. SibKid status was the independent variable. Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was computed. The results indicated that there was no difference in T2 values across any of the measures between SibKids and spouse controls and is demonstrated in Table 7.23 on the next page.

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Table 7.23.: A comparison of T2 values by region of tibia between SibKids and spouses

T2 Value		N	Mean	SD	SE Mean	t	DF	p value
Tibia T2 total	SibKid	47	69.61	13.45	1.96	0.63	69.00	0.53
	Spouse	24	67.77	6.45	1.37			
Tibia A	SibKid	47	68.38	15.08	2.20	0.45	69.00	0.65
	Spouse	24	66.91	7.01	1.43			
Tibia A Superficial	SibKid	47	85.17	20.09	2.93	0.18	69.00	0.86
	Spouse	24	84.40	8.56	1.75			
Tibia A Intermediate	SibKid	47	67.05	16.51	2.41	0.80	69.00	0.43
	Spouse	24	64.17	8.44	1.72			
Tibia A Deep	SibKid	47	52.48	11.65	1.70	0.47	69.00	0.64
	Spouse	24	51.25	7.75	1.58			
Tibia B	SibKid	47	70.71	14.00	2.04	0.83	69.00	0.41
	Spouse	24	68.08	9.58	1.95			
Tibia B Superficial	SibKid	47	85.89	18.07	2.64	0.52	69.00	0.61
	Spouse	24	83.79	11.70	2.39			
Tibia B Intermediate	SibKid	47	70.05	14.49	2.11	1.07	69.00	0.29
	Spouse	24	66.50	10.00	2.04			
Tibia B Deep	SibKid	47	54.49	12.73	1.86	0.62	69.00	0.54
	Spouse	24	52.70	8.48	1.73			

7.6.6.2. Comparison of femoral T2 values between SibKids and spouses.

An independent samples t test was conducted to compare the T2 Values across different regions of the femur of SibKids and spouse controls. The dependent variables, (Total T2 Value, T2 Value of Zone A, T2 Value of Zone A Superficial, Intermediate

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and Deep layers, T2 Value of Zone B, T2 Value of Zone B Superficial, Intermediate and Deep Layers) were measured on a continuous scale. SibKid status was the independent variable. Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was assumed. The results indicated that there was no difference in T2 Values across any of the measures between SibKids and spouse controls and are demonstrated in Table 7.24.

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Table 7.24.: A comparison of T2 values by region of femur between SibKids and spouses

T2 Value		N	Mean	SD	SE Mean	t	DF	p value
Femur T2 Total	SibKid	47	90.29	15.87	2.32	0.58	69.00	0.56
	Spouse	24	88.08	13.48	2.75			
Femur A	SibKid	47	82.83	17.42	2.54	-0.30	69.00	0.98
	Spouse	24	82.96	16.13	3.29			
Femur A Superficial	SibKid	47	100.95	19.60	2.86	-0.11	69.00	0.91
	Spouse	24	101.49	17.79	3.63			
Femur A Intermediate	SibKid	47	82.65	18.93	2.76	-0.02	69.00	0.99
	Spouse	24	82.72	17.77	3.63			
Femur A Deep	SibKid	47	68.69	17.51	2.55	0.07	69.00	0.94
	Spouse	24	68.38	16.37	3.34			
Femur B	SibKid	47	93.72	17.33	2.53	0.44	69.00	0.66
	Spouse	24	91.95	13.59	2.78			
Femur B Superficial	SibKid	47	108.98	20.43	2.98	0.79	69.00	0.44
	Spouse	24	105.24	15.55	3.18			
Femur B Intermediate	SibKid	47	94.57	17.53	2.56	0.83	69.00	0.41
	Spouse	24	90.99	16.32	3.33			
Femur B Deep	SibKid	47	78.75	16.82	2.45	0.05	69.00	0.96
	Spouse	24	78.55	16.63	3.40			

7.6.6.3. Comparison of T2 ratios (ROI zone A to ROI zone B) between SibKids and spouses.

As the region felt most likely to demonstrate early change was the anterior part of both the tibia and the femur, the T2 values of these regions were compared to the posterior parts of the same surface to create a “ratio” comparing a region suspected to be abnormal to a region suspected to be normal. This allows for normal variations in T2 signal between individual - each person therefore acts as their own internal control.

A independent samples t test was conducted to compare the ratio of T2 Values between SibKids and spouse controls. The dependent variables, (Tibia Zone A/Zone B, Tibia Zone A superficial layer/Tibia Zone B superficial Layer, Tibia Zone A Intermediate Layer/Tibia Zone B intermediate layer, Tibia Zone A Deep layer/Tibia Zone B Deep Layer, Femur Zone A/Zone B, Femur Zone A superficial layer/ Femur Zone B superficial Layer, Femur Zone A Intermediate Layer/ Femur Zone B intermediate layer, Femur Zone A Deep layer/ Femur Zone B Deep Layer) were measured on a continuous scale. SibKids status was the independent variable. Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was computed. The results indicated that there was no difference in ratio of T2 values across any of the measures between SibKids and spouse controls and are demonstrated in Table 7.25.

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Table 7.25.: A comparison between SibKids and spouses of T2 ratios by region of tibia and femur

T2 Value Ratio		N	Mean	SD	SE Mean	t	SF	Sig (2 Tailed)
Tibia A / Tibia B	SibKid	47	0.97	0.15	0.02	-0.70	69.00	0.49
	Spouse	24	0.99	0.15	0.03			
Tibia A Sup / Tibia B Sup	SibKid	47	1.00	0.17	0.03	-0.53	69.00	0.60
	Spouse	24	1.02	0.14	0.03			
Tibia A Int / Tibia B Int	SibKid	47	0.97	0.19	0.03	-0.30	69.00	0.77
	Spouse	24	0.98	0.17	0.03			
Tibia A Deep / Tibia B Deep	SibKid	47	0.98	0.20	0.03	-0.22	69.00	0.83
	Spouse	24	0.99	0.19	0.04			
Femur A / Femur B	SibKid	47	0.89	0.16	0.02	-0.47	69.00	0.64
	Spouse	24	0.91	0.17	0.04			
Femur A Sup / Femur B Sup	SibKid	47	0.94	0.15	0.02	-0.91	69.00	0.37
	Spouse	24	0.97	0.13	0.03			
Femur A Int / Femur B Int	SibKid	47	0.88	0.18	0.03	-0.85	69.00	0.40
	Spouse	24	0.92	0.21	0.04			
Femur A Deep / Femur B Deep	SibKid	47	0.88	0.18	0.03	-0.08	69.00	0.94
	Spouse	24	0.89	0.20	0.04			

7.6.6.4. Comparison of tibial T2 ratios (specific ROI zones to overall T2 value) between SibKids and spouses.

Further analysis was then performed creating ratios between the area of interest and the Total T2 value of the Tibia or Femur. This analysis, as an alternative to that seen above, controlled for variations between individuals in terms of their T2 signal, and used the overall T2 value of that particular surface as the denominator. A independent samples t test was conducted to compare the ratio of T2 Values between SibKids and spouse controls. The dependent variables, (Zone A/Tibia total, Zone A Superficial/Tibia total, Zone A Intermediate/ Tibia total, Zone A Deep/Tibia total, Zone B/Tibia total, Zone B Superficial/Tibia total, Zone B Intermediate/ Tibia total, Zone B Deep/Tibia total) were measured on a continuous scale. SibKids status was the independent variable. Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was computed. The results indicated that there was no difference in Ratio of T2 values across any of the measures between SibKids and spouse controls. This is demonstrated in table 7.26.

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Table 7.26.: Comparison of tibial T2 ratios between SibKids and spouses

T2 Ratio		N	Mean	SD	SE Mean	t	DF	p value
Tibia A / Tibia Total	SibKid	47	0.98	0.07	0.01	-5.31	69.00	0.60
	Spouse	24	0.99	0.07	0.02			
Tibia A Sup / Tibia Total	SibKid	47	1.22	0.12	0.02	-1.05	69.00	0.30
	Spouse	24	1.25	0.09	0.02			
Tibia A Int / Tibia Total	SibKid	47	0.96	0.10	0.01	0.43	69.00	0.67
	Spouse	24	0.95	0.09	0.02			
Tibia A Deep / Tibia Total	SibKid	47	0.76	0.09	0.01	-0.11	69.00	0.92
	Spouse	24	0.76	0.09	0.02			
Tibia B / Tibia Total	SibKid	47	1.02	0.08	0.01	0.80	69.00	0.43
	Spouse	24	1.00	0.08	0.02			
Tibia B Sup / Tibia Total	SibKid	47	1.24	0.13	0.02	0.08	69.00	0.94
	Spouse	24	1.24	0.12	0.02			
Tibia B Int / Tibia Total	SibKid	47	1.01	0.11	0.02	1.12	69.00	0.27
	Spouse	24	0.98	0.10	0.02			
Tibia B Deep / Tibia Total	SibKid	47	0.79	0.11	0.02	0.29	69.00	0.78
	Spouse	24	0.78	0.103	0.02			

7.6.6.5. Comparison of femoral T2 ratios (specific ROI zones to overall T2 value) between SibKids and spouses.

A independent samples t test was conducted to compare the ratio of T2 Values between SibKids and spouse controls. The dependent variables, (Zone A/Femur total, Zone A Superficial/Femur total, Zone A Intermediate/ Femur total, Zone A Deep/Femur total, Zone B/Femur total, Zone B Superficial/Femur total, Zone B Intermediate/ Femur total, Zone B Deep/Femur total) were measured on a continuous scale. SibKids status was the independent variable. Levene’s test was conducted to evaluate homogeneity of variance. Results of Levene’s test were not significant and therefore a t-statistic assuming homogeneity of variance was computed . The results, demonstrated in Table 7.27 indicate that there was no difference in Ratio of T2 Values across any of the measures between SibKids and spouse controls.

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Table 7.27.: Comparison of femoral T2 ratios between SibKids and spouses

T2 Ratio		N	Mean	SD	SE Mean	t	Df	p value
Femur A / Femur Total	SibKid	47	0.92	0.09	0.01	-1.06	69.00	0.29
	Spouse	24	0.94	0.10	0.02			
Femur A Sup / Femur Total	SibKid	47	1.12	0.12	0.02	-1.18	69.00	0.24
	Spouse	24	1.15	0.10	0.02			
Femur A Int / Femur Total	SibKid	47	0.91	0.12	0.02	-0.83	69.00	0.41
	Spouse	24	0.94	0.13	0.03			
Femur A Deep / Femur Total	SibKid	47	0.76	0.19	0.02	-0.57	69.00	0.57
	Spouse	24	0.78	0.12	0.03			
Femur B / Femur Total	SibKid	47	1.04	0.07	0.01	-0.45	69.00	0.65
	Spouse	24	1.05	0.09	0.03			
Femur B Sup / Femur Total	SibKid	47	1.21	0.11	0.02	0.32	69.00	0.75
	Spouse	24	1.20	0.19	0.02			
Femur B Int / Femur Total	SibKid	47	1.05	0.08	0.01	0.90	69.00	0.37
	Spouse	24	1.03	0.08	0.07			
Femur B Deep / Femur Total	SibKid	47	0.87	0.09	0.01	-0.71	69.00	0.48
	Spouse	24	0.89	0.10	0.02			

7.7. Discussion.

Prospective studies that follow cohorts of normal individuals in an attempt to identify early preclinical radiographic changes are expensive and time consuming due to the relatively low proportion of normal people who get Knee OA and the large variation in age of onset. This aim of the work presented in this chapter was to develop a cohort of individuals, who, on the basis of their family history, are potentially at high risk of developing AMOA. This unique cohort could therefore be followed over time to allow study of the earliest radiographic and clinical changes of OA. Similar studies of vertical risk have been performed in Hip OA and rotator cuff injuries, and AMOA is known to have an increased horizontal risk of transmission - siblings of those with end stage AMOA are 3.41 times more likely to have the disease than age matched spouse controls. An offspring risk study of this kind has not been attempted in AMOA before making this a unique study into the disease. Along with the vertical transmission of radiographic and clinical risk of disease, key risk factors known to predispose to the development of medial compartment OA, (meniscal extrusion and long leg alignment), were also investigated. 3T MRI structural changes in cartilage, along with functional cartilage T2 map in those without significant cartilage lesions were also investigated. The spouse controls were well matched to the SibKids other than their age, with the SibKids being on average 3.5 years younger than the controls at 45.1 years. Of interest, this is 12 years younger than the average age of the Early AMG patients presenting to knee clinic described in Chapter 4 on page 115. This study demonstrated that there was no statistical differences between SibKids and spouses in terms of the vertical risk of developing radiographic or painful radiographic AMOA. In addition, there was no difference between the two cohorts in terms of presence of meniscal extrusion or long leg alignment. Structural changes within the knee, as demonstrated by the WORMS score, did not differ between the two

7. *A high risk cohort? The sibling offspring “SibKids”.*

groups. Finally, using T2 mapping techniques, high risk regions of interest were inspected and compared between SibKids and spouses to determine whether there were functional, if not structural changes between the two groups. In none of the studies was any statistically significant difference found that indicated an increased functional deterioration in cartilage in SibKids compared to spouses.

Reasons for this lack of difference between the two groups deserves particular attention. The first and most striking observation is that potentially there is no difference between the two groups and AMOA does not demonstrate any vertical transmission of risk even in those with strong family histories of the disease. Certainly, our study has failed to demonstrate any evidence that would contradict this statement. This may represent either the truth, or it may represent a Type 2 error, a false negative finding. Our subjects were over 20 years younger than those with AMOA described by McDonnell et al [234], and 12 years younger than those described with early disease in previous chapters within this thesis. Whilst it has been estimated that 34% of the population over the age of 45 has OA of the knee [235], the lack of difference demonstrated may represent the fact that our SibKids are too young to demonstrate any changes of OA yet. Interestingly, although we might expect the SibKids to have higher incidence of OA than the normal population we would not expect them to demonstrate it at a younger age. They are theoretically at an increased risk of developing the disease, not at risk of developing a completely different phenotype of disease (i.e. younger onset than normal). In previous studies that have demonstrated vertical transmission of risk of hip OA, the ages of the SibKids have been 51.5 years [284] and 47.2 years [235]. In addition, this study had only 68 SibKids and 35 Spouses. Although this compares favorably with other studies, it may be that this study is underpowered. Spouse controls may also have a higher incidence of OA than might be expected in the normal population - those with knee problems may

be more motivated to take part in this study than those with normal knees.

A review of McDonnell’s original study indicated that, of 112 siblings identified, 16 had symptomatic AMOA (14.2%). Inspecting 7.4.1 on page 214 indicates that of 194 Proband siblings generated in our study, 27 had symptomatic AMOA (13.9%). Therefore, in the replication of the original study performed as part of the generation of the SibKids confirmed McDonnell’s findings, suggesting the horizontal transmission of risk of AMOA is a real phenomenon.

A five and then ten year follow up of the SibKids cohort with AP standing radiographs and 3T MRI scans should be performed to allow questions regarding horizontal transmission of risk to be clarified further.

7.8. Conclusions.

The following null hypotheses were proposed at the beginning of this chapter.

1. The risk of developing AMOA is not transmitted vertically from parents to offspring.
2. The SibKids are not at risk of increased varus malalignment compared to spouse controls.
3. The SibKids do not have greater propensity to meniscal extrusion compared to spouse controls.
4. The SibKids do not demonstrate worse WORMS scores than spouse controls.
5. The SibKids do not demonstrate increased T2 signal in focused regions of interest compared to spouse controls.

On the basis of the studies carried out in this chapter it has not been possible to reject any of these null hypotheses.

7.9. Future work.

The SibKid cohort remain an interesting group. Time will tell whether these individuals are at increased risk of developing OA compared to matched controls. Therefore, applications are currently underway to fund the follow up of these individuals at five and ten years from recruitment with radiographs as well as structural and functional MRI imaging. Ethical approval has been obtained to retain this novel cohort of individuals.

8. Assimilated thesis discussion.

This thesis has attempted to define and understand the clinical profile of early knee OA, and then explore two key factors in its development; genetic risk and meniscal extrusion. Specific discussion relating to each study is provided at the end of the respective chapters. Here an overview of the thesis is provided.

The lack of a clear definition of early knee osteoarthritis was a surprising gap in the literature. Distinguishing between young patients with full thickness cartilage degeneration, young patients with osteochondral lesions, and patients who are early on the spectrum of knee OA, irrespective of their age, is important. The “age of the knee” rather than the age of the patient, is the important factor in this context. In Chapter Three, diagnostic methods were compared and a definition of early structural knee OA was proposed.

X ray changes of KL of 0 or 1 in the absence of other intra articular causes for pain

OR

X ray changes of KL of 2 or more with no MRI evidence of full thickness cartilage lesions.

This formal definition of early structural knee OA has been provided on the basis of clinical validation studies and was used throughout the remainder of the thesis. Surprisingly, arthroscopy, long held as the surgeons choice in assessing cartilage le-

sions, performed poorly and was found to have, at best, moderate intra and inter observer reliability with a wide range of classification systems used by surgeons. Radiography was found to be insensitive to early change in disease compared to MRI which was demonstrated to have good inter and intra observer reliability. The lack of a recognised diagnostic gold standard casts a shadow over the assessment of these three diagnostic techniques. However, the non invasive, repeatable, non subjective nature of MRI with standardised scoring systems that have been demonstrated to have good reproducibility make it a sensible choice. The expanding role of MRI in the clinical assessment of OA looks set to continue.

In Chapter 4 the cross sectional symptom profile of patients with early structural knee OA was explored. As expected, those earlier on the spectrum of disease were younger than those with established full thickness disease. In addition the group mean for overall OKS and pain and function domains were less in the early disease cohort. However, the early disease cohort demonstrated a greater heterogeneity of symptoms than those with established disease. This heterogeneous nature may account in part for the tendency of their symptoms as a group to be underestimated. An exploration of the overlap in symptom profile between groups demonstrated that several patients in the early disease cohort had pain and function symptoms as bad as those in the established full thickness comparison groups. The importance of this finding is that it demonstrates the severity of the symptoms that patients with early structural change can experience. Their disease, although earlier on the structural spectrum of OA than those with full thickness lesions, can cause considerable impairment and pain. This emphasises not only the need for a greater overall understanding of the early stages of OA but also the importance of developing effective treatment strategies to help alleviate their symptoms. Criticisms with the design of this study include the choice of comparison groups, and the use of the Oxford Knee Score as assessment of the

patients overall symptoms.

In Chapter 5 the longitudinal symptom variation of the same cohort of patients demonstrated that 90% of patients demonstrate clinically significant variation in month to month symptoms over 12 months. Over the same period patients can expect a variation in OKS of twelve points with a mean between month variation of seven points. Overall between recruitment and month 12 of follow up, approximately one third improve, one third stay the same and one third will get worse over one year. Determining the optimal method of assessing clinical variation in symptoms is difficult. The lack of an intervention means that determining when to define the beginning and end of this study presents challenges. A pragmatic response to this would be to increase the length of follow up and report overall pattern of change at 1, 2 and 3 years of follow up. In addition to these concerns, the monthly measurement of symptom variation, performed here due to the pre existing validation of the PROMs, may not reflect the true frequency of symptom change. Addressing this is difficult as an increased frequency of questionnaire completion would be required and this may overburden the patients. Smaller studies of approximately one months duration with daily assessment of symptoms is one consideration, however no validated PROMS exists for this purpose. The pragmatic nature of this study meant that we did not ask patients to document their analgesia intake and thus we were not able to consider it as a co variate in the regression analysis. Other co variates of consideration for a future study should also include a monthly assessment of activity levels (perhaps with the use of acclerometers) as it is increasingly clear that younger patients will offer “battle through” pain when social or work situations demand it, leading to activity related pain and worsening in their PROMS scores.

The work in Chapter 6 and Chapter 7 moved away from the symptom profile of those with early radiographic knee OA and turned attention once more to struc-

ture. Firstly the role of the meniscus in the development of knee OA was explored. Meniscal extrusion in a patient with no radiographic changes of knee OA was found to confer an Odds Ratio of 3.5 of developing OA compared to those with no radiographic changes of knee OA and no extrusion. Even controlling for the presence of a significant knee injury or an operation to the index knee an Odds Ratio of 3.36 for the development of Knee OA over the coming 48 months was demonstrated. The presence of meniscal extrusion in the absence of injury or preexisting meniscectomy therefore confers significant risk of the development of knee OA. This study did not read the menisci for the presence of tears, due to time constraints. However, by controlling for knee injury and operation to the meniscus of interest, it was felt that only degenerative changes rather than traumatic changes would remain in the cohort. This study did not correlate pain with the presence of extrusion and this, with consideration to the findings of Chapter 5, is an important next step in understanding the development of knee OA in previously normal knees. As demonstrated in Figure 6.3.4 on page 207 inspecting MRI scans at only recruitment and 48 months means that patients who for example, extrude then develop OA within a two year period (e.g between month 6 and month 30) can be labeled incorrectly as those who develop OA at 48 months without having extrusion at baseline. Similarly, those who develop OA over a longer period such as 6 or 7 years, may be labeled as non progressors. A more complete study would inspect MRI scans at 6 month or yearly intervals for a longer time period. With 72 month follow up scans just having been released by the OAI, and available to researchers on this team, this may now be possible.

In an attempt to determine where the earliest changes of knee OA occur, Chapter 7 described the development of a cohort of patients selected for their strong family history of a particular phenotype of knee OA. Following the development of this cohort a number of further investigations were possible. Firstly, calculation of the

vertical transmission of family risk of the development of the disease was performed using radiographs. Secondly, those with the stronger family history were compared to controls for the presence of risk factors known to contribute to the development of knee OA: Activity, BMI, long leg alignment and meniscal extrusion. Finally, structural and functional changes in hyaline cartilage were examined to determine if there was a difference between those with family history and symptomatic controls. A strict protocol was used in the development of the cohort. Despite this, we did not demonstrate that SibKids had an increased risk of the development of symptomatic X ray changes of knee OA than controls. In addition, although the SibKids were younger than the controls, there were no other demographic differences. Similarly the SibKids did not differ from controls in terms of their long leg alignment or meniscal extrusion. WORMS scoring and T2 mapping did not indicate that SibKids had increased structural or functional changes in their hyaline cartilage compared to controls. Reasons for this lack of difference were discussed in detail at the end of chapter 7. As mentioned in the literature review, knee arthritis has been found by some to demonstrate strong familial linkages, but these findings have not been replicated by all investigators. It would be easy to conclude that this study enforces the latter view. This conclusion might be somewhat hasty as the SibKids investigated in this study were 12 years younger than the early knee OA cohort described in Chapters 4 and 5 and 3-5 years younger than previous hip joint SibKid cohorts. In addition, controls are likely to include a number of self selecting patients who had symptoms in their knees and wanted further investigation - leading to an over representation of symptomatic controls in those who agreed to attend for assessment. A five and ten year follow up of this cohort with radiographs and MRI will elucidate further the vertical risk of knee OA. On the basis of this study, it is not possible to conclude that anteromedial knee OA demonstrates any vertical heritability.

8. *Assimilated thesis discussion.*

Overall this study has demonstrated that MRI is the diagnostic imaging technique of choice in medial compartment OA, particularly in those with Kellgren and Lawrence changes greater than grade one where full thickness cartilage lesions are commonly encountered even in those with grade two disease. In addition it has demonstrated that meniscal extrusion is a potent risk factor for the development of medial compartment arthritis. The studies performed in this thesis have been unable to show that a strong familial history has a clear role as a risk factor for the development of the disease. Those who go on to develop early radiographic knee OA may experience pain and functional impairment as severe as those with more advanced radiographic changes, indicating that symptomatically they may often be more severe than expected from their imaging findings. Individuals with symptomatic early radiographic OA may expect to experience significant monthly symptom variation over a one year period.

9. Clinical relevance.

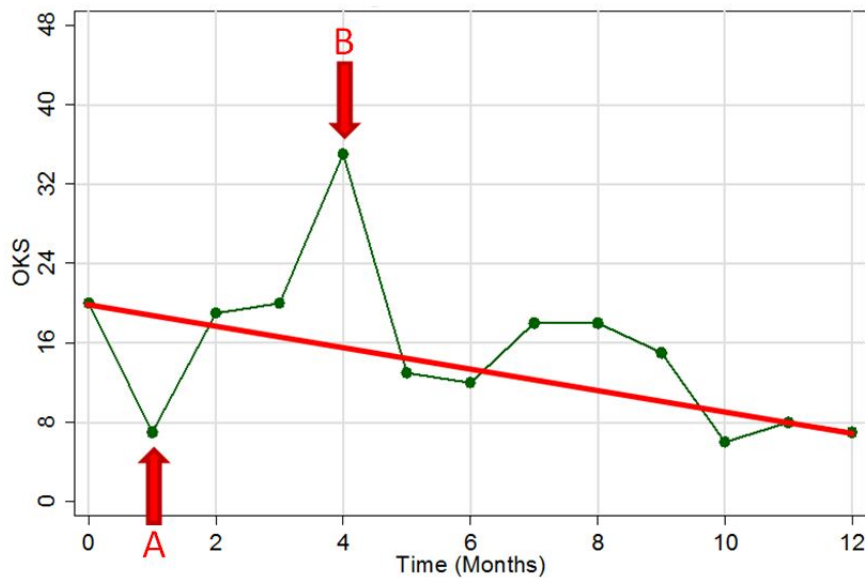
In performing clinical research it is easy to be so focused on process and scientific validity that the reason for the research, that of helping patients, can be lost. At all points the work in this thesis has tried to consider its findings in the context of the clinical encounter.

Chapter 3 demonstrates that radiographs can underestimate the severity of structural change within the knee, and that those with normal radiographs can demonstrate significant cartilage lesions. Thus, in the patient with a painful knee and no history of trauma and normal radiographs, an MRI scan is essential to accurately diagnose cartilage lesions. Whilst orthopaedic surgeons, with typical confidence, often declare that the only way to truly assess cartilage is to look at it directly through an arthroscope, work produced here does not confirm such a position. In particular, the use of arthroscopic pictures to allow surgeons to inform other surgeons of their findings is particularly unreliable and should be avoided. The results from an MRI are more reliable than that from arthroscopic assessment of cartilage and the latter should be avoided in those with nearly OA. Chapter 4 shows that those with early radiographic change can have severe symptoms - in 40% of cases as bad as those with full thickness disease. This is important for two reasons. Firstly, it allows a greater understanding of the disease - the surgeon confronted with an extremely painful knee with only mild MRI cartilage changes can be confident that he is not missing other pathology within the knee. Secondly, it draws attention to the difficulty these pa-

9. Clinical relevance.

tients experience and the need for effective interventions. Chapter 5 is potentially the most important piece of work in this thesis from the point of view of direct clinical applicability. Patients experience significant clinical variation over 12 months and therefore timing interventions is key. Operating on a patient during a peak of pain, when there overall tendency is to improve, may lead to a disappointing from the intervention. Similarly, as demonstrated in Figure 9.0.1, a patient who is getting worse over one year can demonstrate short term improvements. In this example, a patient with significant pain at time point A, deserving of arthroplasty, can improve to a near normal score of 36 some 3 months later at time point B. Therefore, a clinician who fails to appreciate this variation over time might either inappropriately list for arthroplasty at time point A, or discharge from clinic at time point B.

Figure 9.0.1.: Demonstration of how failure to appreciate symptom change over 12 months could lead to inappropriate timing of intervention.



Chapter 6 enables the clinician, when confronted with an MRI of a knee with an extruded meniscus but normal radiographs to be able to confidently assert that the odds of this patient developing radiographic OA over 48 months are 3.5 times that of a patient without an extruded meniscus. Further work on the correlation

9. Clinical relevance.

of this extrusion with pain will help elucidate the clinical profile of these patients further. In addition, Chapter 6 has validated the most appropriate site to measure meniscal extrusion on an MRI knee. This technique is therefore appropriate for use in longitudinal studies that may be undertaken into the role of an extruded meniscus in the pathogenesis of OA. The clinical relevance of Chapter 7 is, in truth yet to be determined. However, it currently suggests that family history has no proven role in the development of AMOA. In assessing a patients risk of developing knee OA, there is no evidence that the presence of AMOA in a parent confers risk in any way. Similarly, this study was not able to determine where the earliest changes of knee OA arise and therefore it was not able to shed any light on potential for prophylactic osteotomy or other preventative surgeries.

10. Where next for research into early radiological knee osteoarthritis?

Perhaps the most surprising aspect of conducting research into knee osteoarthritis has been the lack of consensus on the definition and diagnostic criteria of the condition. Despite attempts to deal with the problem, units around the world persist in driving forward trying to “cure” a condition that the musculoskeletal community as whole is yet to reach diagnostic consensus on. Irrespective of this, the lack of coordination in research strategies between units within the UK, let alone the rest of Europe or the US, means that valuable time and money, often raised by the charitable work of volunteers and patients, is wasted on duplicating work that others have already performed. Similarly, notable projects such as the OAI aside, academic rivalries between individuals and between units appear to prevent effective collaboration. There will be no “Alexander Fleming” in the history books of OA, and research centres must work together to make significant inroads into a problem that affects millions of individuals around the world.

Having considered the above, it appears to be increasingly clear that osteoarthritis of the knee is not a condition that can be cured or prevented. It is a condition that

10. Where next for research into early radiological knee osteoarthritis?

is inevitable, multifactorial in its causation and, despite an established influence of inflammation, primarily mechanical. A knee joint asked to perform millions of cycles over 80 years of human life will inevitably degenerate however well evolved it is for function. How then should research into the condition proceed (once consensus on definition and diagnosis has been reached)?

The studies performed in this thesis over the last 3 years emphasise the importance of the patient and their symptoms at the centre of the work we do as researchers as well as clinicians. There are two main elements to consider here. Firstly, pain as the key to the disease. Secondly the need for medical practitioners to avoid the temptation to classify patients into simplified, clumsy groups. They must instead return to individualised treatments.

A patient with early osteoarthritis does not present to clinic with an extruded meniscus or an ICRS Grade 3a cartilage lesion in their knee. They present to clinic with a knee that is painful. The pain stops them from playing with their child or going to work. Strangely, as surgeons, instead of trying to address the problem that the patient tells us they have, we try to treat a structural lesion we can see. We replace cartilage, microfracture bone and realign tibiae. Despite years of performing these operations, many small tweaks to techniques and many individual surgeons proclaiming their superiority over others, results remain almost uniformly underwhelming if the aim is to “cure” a patient of their symptoms. The finding of a statistically significant improvement in pain PROM scores after an operation, does not mean the patient has been cured. It means that they still have pain, just on the basis of a statistical test, less of it. “Statistics are needed to quantify differences that are too small to recognize through clinical experience alone [242] ”. Patients knees continue to hurt despite these research programmes. Bearing this in mind, perhaps it may be simpler and more fruitful for research programs to refocus attention into working out how to

stop joints from hurting. The processes involved here are likely to be peripheral and central, and large collaborations will be required across many disciplines. It would not involve the drive to image chondrocytes in greater and greater detail. The end point would be, perhaps, a peripherally applied minimally invasive knee intervention that can be performed in clinic. It would remove pain but preserve proprioception. Concerns regarding toxicity to chondrocytes, or loss of joint space, or bone attrition seem irrelevant if the knee is not painful. The need for eventual knee replacement will not be removed and the process of degeneration will continue as the patient moves along the spectrum. How many patients with advanced disease would elect for arthroplasty if their knee wasn't painful?

When analysing data from patients, their demographics, their femoral condyles, their weight and their activity levels, researchers routinely classify patients into groups. Classifications should be used only if they guide treatment or prognosis, yet increasingly they are used to simplify results and enable ease of communication of concepts. Unfortunately, patients are not machines that behave in the same way. This has been shown clearly in Chapters 4 and 5 of this thesis. Why then do we try to classify patients into groups and provide them with uniform treatments? When asked what they want from healthcare providers, patients want to be seen by the same doctor each time, they want to be listened to, and they want to be treated like an individual. Despite telling us this, we seem determined to go in the opposite direction and depersonalize their treatments. To develop thresholds, to stratify patients by their risk profile, and to develop protocols that mean patients all receive the same care as each other, irrespective of their need.

Patients tell us that their knees hurt. We need to listen to them and refocus our agendas. We need to develop well organised, open, collaborative research networks that move away from thinking of arthritis as a structural problem and returns to the

10. Where next for research into early radiological knee osteoarthritis?

task of making patients better. We need to stop knees from hurting.

A. Evaluation of cartilage defects.

A.1. Outerbridge grading system

Figure A.1.1.: The Outerbridge grading system for chondral lesions

Grade	Pathology
I	Softening and swelling of articular cartilage
II	Fragmentation and fissuring of articular cartilage affecting an area of less than 0.5 inches
III	Fragmentation and fissuring of articular cartilage affecting an area greater than 0.5 inches
IV	Cartilage erosion to bone

A.2. Knee cartilage assessment form

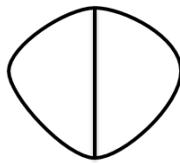
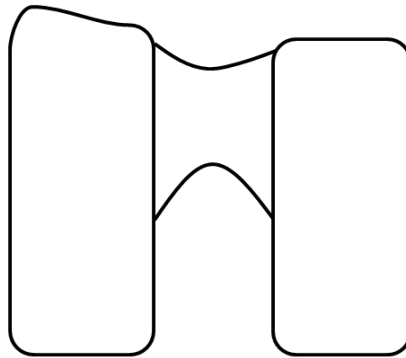
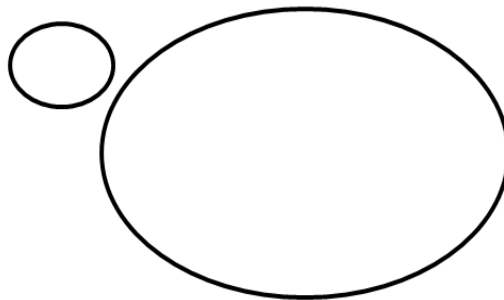
A. Evaluation of cartilage defects.

Figure A.2.1.: The Nuffield Orthopaedic Centre cartilage damage assessment form

Nuffield Orthopaedic Centre
cartilage damage assessment form

RIGHT KNEE

Patient Name:
DOB:
MRN:
Assessing Clinician:
Date of Assessment:



B. Longitudinal data analysis

B.1. Database interface

Figure B.1.1.: Screen shot showing demographic data entry interface for bespoke Access database.

Luke Jones (01)

Hospital number: 01 Date of entry: Date of exit:

Gender: Address: Date of exit:

Title:

Forename:

Surname:

Date of birth: Post code:

Telephone number:

Mobile number:

Knee affected: Weight/kg: Smoker?: No

Job type: Height/m: Pack years: 0

BMI:

Done	Month 11	Arthroscopy
Day 1	Month 12	Plain X-ray
Day 3	Month 13	Long leg X-ray
Day 5	Month 14	MRI
Month 1	Month 15	
Month 2	Month 16	
Month 3	Month 17	
Month 4	Month 18	
Month 5	Month 19	
Month 6	Month 20	
Month 7	Month 21	
Month 8	Month 22	
Month 9	Month 23	
Month 10	Month 24	

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Figure B.1.2.: Screen shot showing monthly PROMs data entry interface for bespoke Access database.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
OKS																	
Pain VAS																	
ICOAP																	
KOOS																	
KOOSQ																	
HADS																	
LOTR																	
SF																	
KPNOC																	
KSNOC																	
TEGNER																	

Done

OKS Total = N/A
Pain VAS = N/A
ICOAP 1 = N/A
ICOAP 2 = N/A
ICOAP Total = N/A
KOOS Total = N/A
KOOSQ Total = N/A
KOOSA Total = N/A
KOOSP Total = N/A
KOOSQ Total = N/A
HADS (Anxiety) = N/A
HADS (Depression) = N/A
LOTR = N/A

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NHS

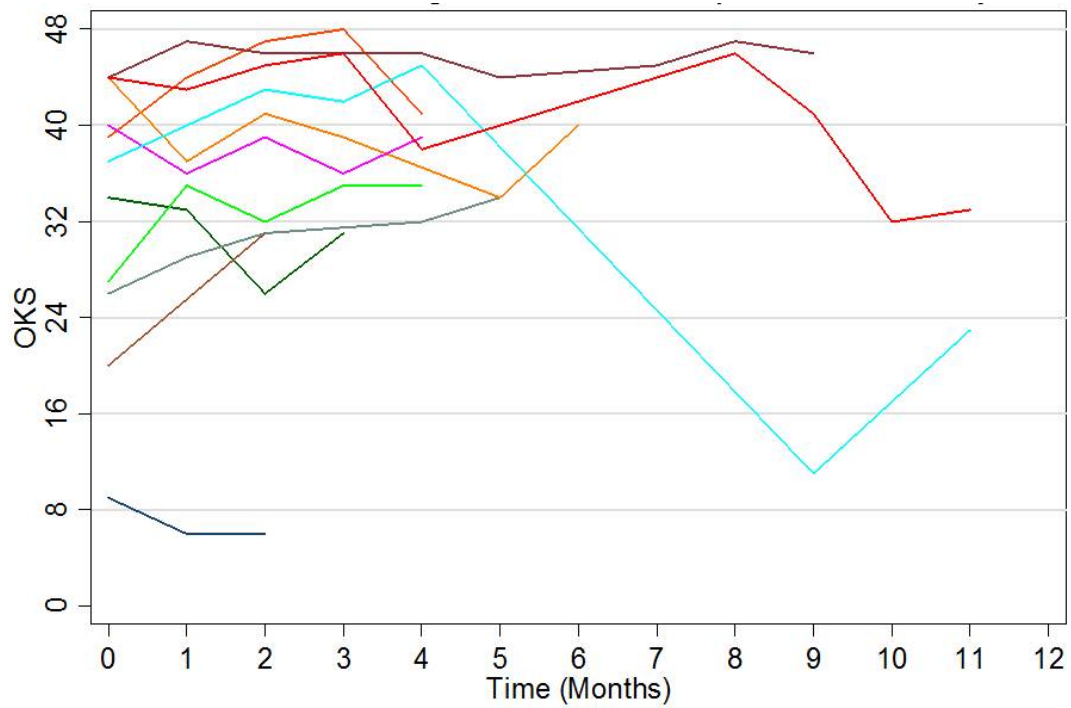
B.2. Management of missing data

In total, 21 patients (16.8%) left the study prior to completion of one year follow up. The mean length of follow up of these patients was 6.48 months (SD 3.08) and the mean recruitment OKS was 30.67 (SD 10.9). In total, 12 left as they were unwilling to take part in the study any further, 4 patients left the study as they had an arthroplasty, and 5 dropped out with no reason given.

Graphical representation of the symptom variation of these individuals is given in figure B.2.1 on the next page, figure B.2.2 on page 281, and figure B.2.3 on page 282.

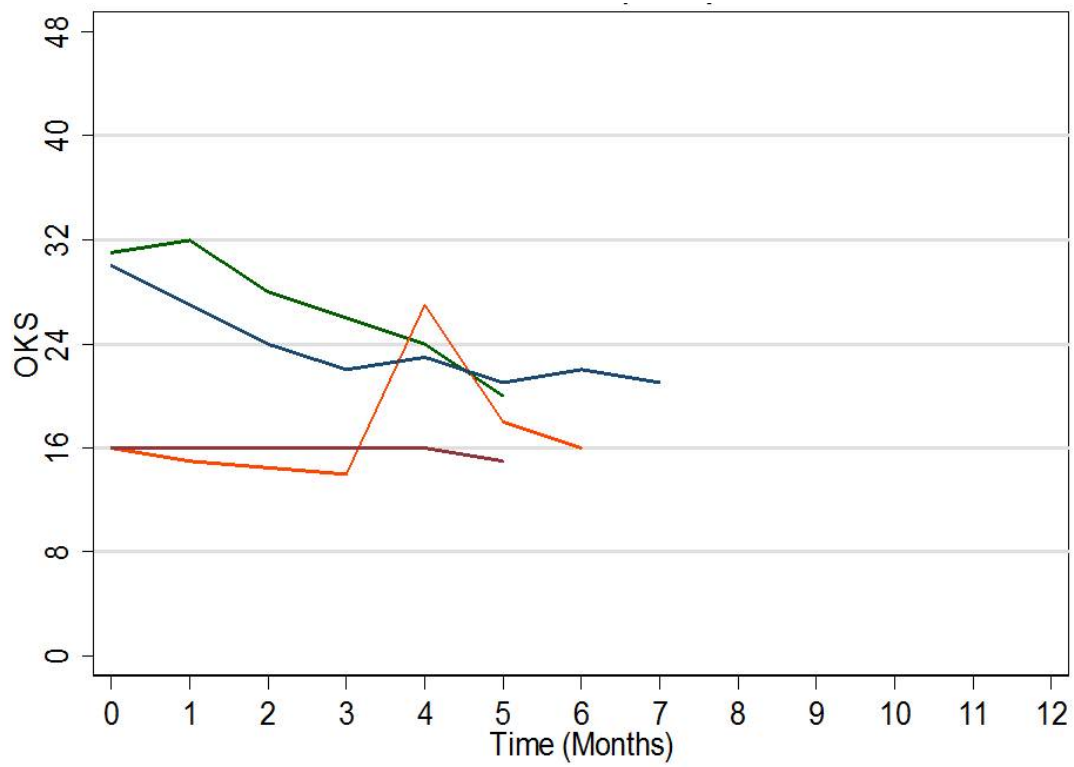
B. Longitudinal data analysis

Figure B.2.1.: A graph to demonstrate the change in symptoms over time in months experienced by patients who dropped out before 12 months of follow up had been completed - no longer wanted to take part.



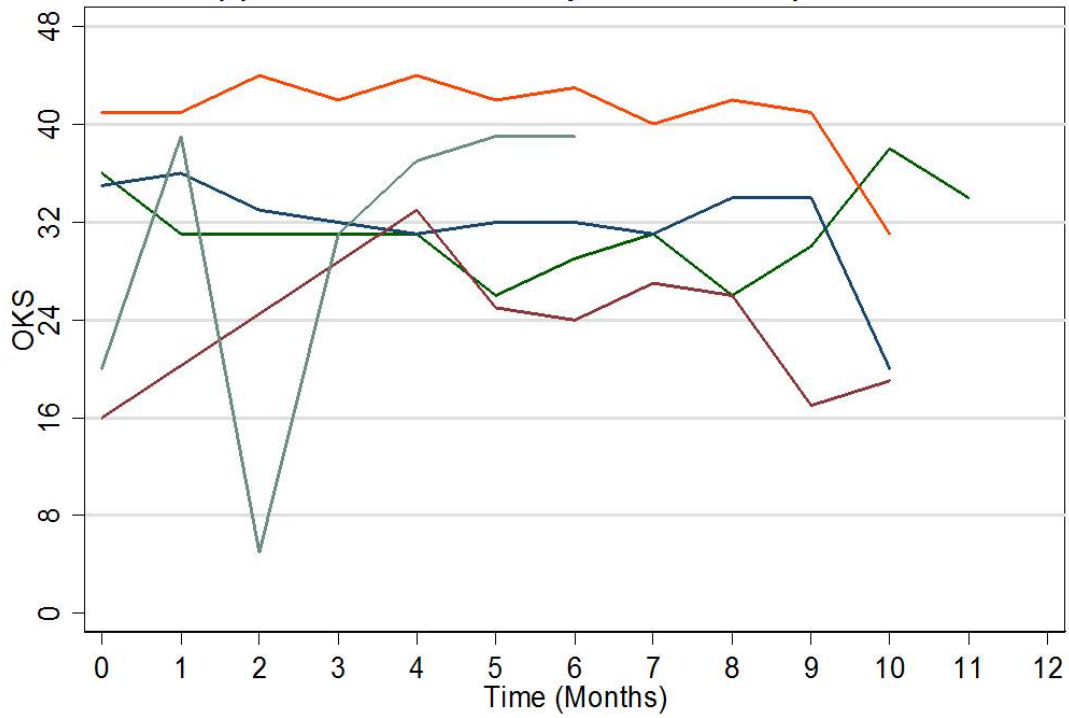
B. Longitudinal data analysis

Figure B.2.2.: A graph to demonstrate the change in symptoms over time in months experienced by patients who dropped out before 12 months of follow up had been completed - underwent arthroplasty.



B. Longitudinal data analysis

Figure B.2.3.: A graph to demonstrate the change in symptoms over time in months experienced by patients who dropped out before 12 months of follow up had been completed - no reason given for drop out.



No common trend was seen in the OKS of these individuals. Their baseline characteristics were not found to be different from those of the overall cohort and their data was therefore counted as missing completely at random. Their data was therefore excluded from the overall analysis without anticipating that this would introduce bias into our model.

C. Protocol for image measurements.

C.1. Set up

1. Open ONIS 2.4 Professional
2. Open Excel Data recording file
3. Select images in ONIS based on OAI reference number (XXXIX)
4. Open patient file and click “viewer”
5. From the “Tools” toolbar adjust the contrast until the menisci are clearly contrasted to the chondral cartilage, bone and deep MCL
6. Scroll through to identify the fibula. Confirm the contra lateral side is medial.
7. Scroll through to identify the highest point of the medial tibial spine and record this slice number (labeled “Instance” on the upper left hand side of the screen)

C.2. Determining longitudinal reference lines.

1. From the 2D Annotations box click the “Line” icon.
2. Draw a line along the joint line of the proximal tibia. This is done by identifying the most proximal and medial bony part of the tibia (that is not osteophyte)

C. Protocol for image measurements.

- and drawing a line from here to the most proximal and medial lateral part of the tibia as seen in C.3.1 on page 286.
3. From the 2D annotations box click the “select” tool.
 4. Click the line drawn in (2) and it turns yellow.
 5. Right click the line, go to “Actions” and select parallel
 6. The screen will now look like C.3.2 on page 286 .
 7. Select the distal line, then hover over it until the cross appears. Left click and drag the parallel down to the lowest part of the tibia on the scan. Adjust the width of the distal line so that it extends to the outside edge of the medial and lateral cortex as seen in C.3.3 on page 287.
 8. Now click the line that extends between the two parallel lines and drag it away to the edge of the screen so that it is out of the way C.3.4 on page 287.
 9. Select the proximal line, right click and select “split” . This cuts the line in half. Do the same with the distal line. See C.3.5 on page 288.
 10. From the 2D annotations box select “Line” and join the middle of the proximal line to the middle of the distal line to give you an approximation of the longitudinal axis of the proximal tibia as seen in C.3.6 on page 288. This line is the key line that all measurements are made relative to. It is important to draw this line accurately as we need to ensure that we make any meniscal measurements in the same way on both the initial and the follow up scan.

C.3. Measuring the meniscal extrusion

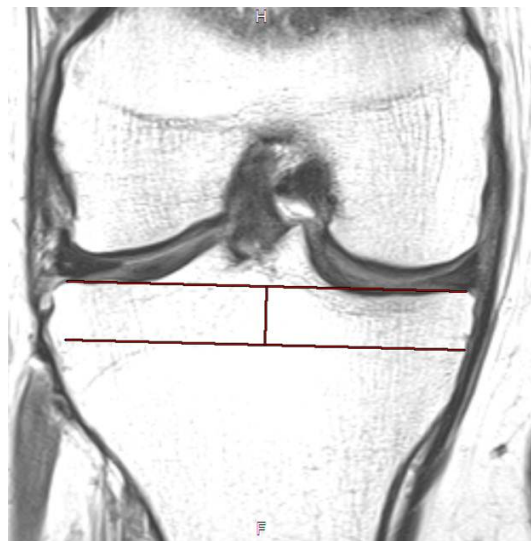
1. Select the longitudinal axis, right click, go to “Actions” and select parallel. Drag this parallel out to the inner(therefore most lateral) part of the medial meniscus see C.3.7 on page 289. This is line A.
2. Generate a parallel from line A and drag it out to the most medial border of the tibia excluding osteophytes (see C.3.8 on page 289– zoomed in). This is line B.
3. Generate a parallel from Line B and drag it out to the most medial border of the medial meniscus. (see C.3.9 on page 290 - zoomed in). This is line C.
4. Left click on the line that runs between A and B to select it. Right click, go to actions and then measure. The distance A-B will come up on the screen. This can be picked up and moved around. Do the same for the distance B-C (see C.3.10 on page 290)
5. Insert the measurements into the appropriate field in the Excel spreadsheet.
6. The spreadsheet has a formula inserted into it to determine the total meniscal width, the absolute meniscal extrusion (AME) and the relative percentage extrusion (RPE)

C. Protocol for image measurements.

Figure C.3.1.: Coronal T2 MRI knee demonstrating the joint line



Figure C.3.2.: Coronal T2 MRI knee demonstrating the generation of a line parallel to the joint line



C. Protocol for image measurements.

Figure C.3.3.: Coronal T2 MRI knee demonstrating the movement of a line parallel to the joint line as distal as possible



Figure C.3.4.: Coronal T2 MRI knee demonstrating the removal of the linkage bar between the joint line and its distal parallel



C. Protocol for image measurements.

Figure C.3.5.: Coronal T2 MRI knee demonstrating the midpoint of the joint line and the midpoint of the distal parallel line

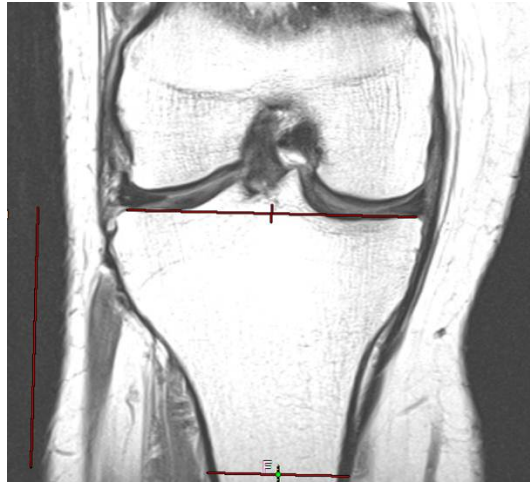


Figure C.3.6.: Coronal T2 MRI knee demonstrating the longitudinal axis of the proximal tibia



C. Protocol for image measurements.

Figure C.3.7.: Coronal T2 MRI knee demonstrating the lateral aspect of the medial meniscus: Line A

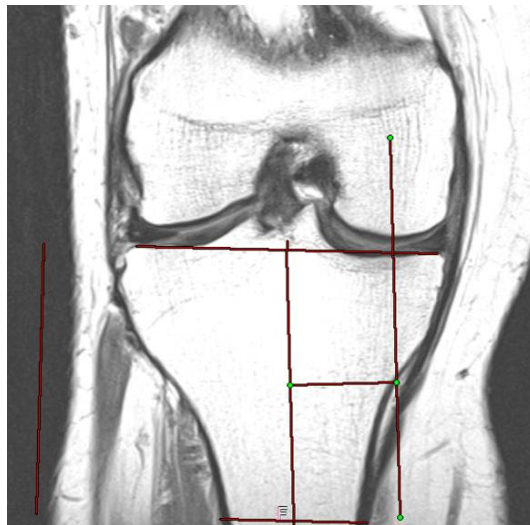
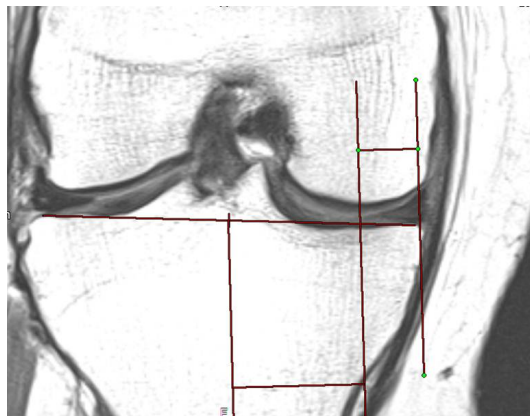


Figure C.3.8.: Coronal T2 MRI knee demonstrating the medial joint margin excluding osteophytes: Line B



C. Protocol for image measurements.

Figure C.3.9.: Coronal T2 MRI knee demonstrating the medial aspect of the medial meniscus: Line C

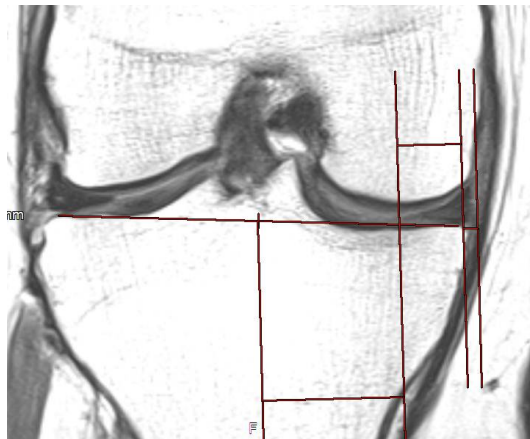
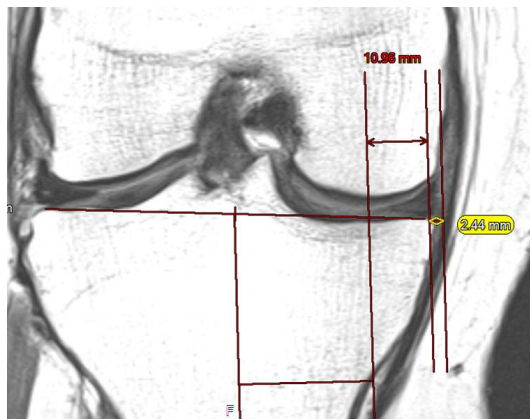
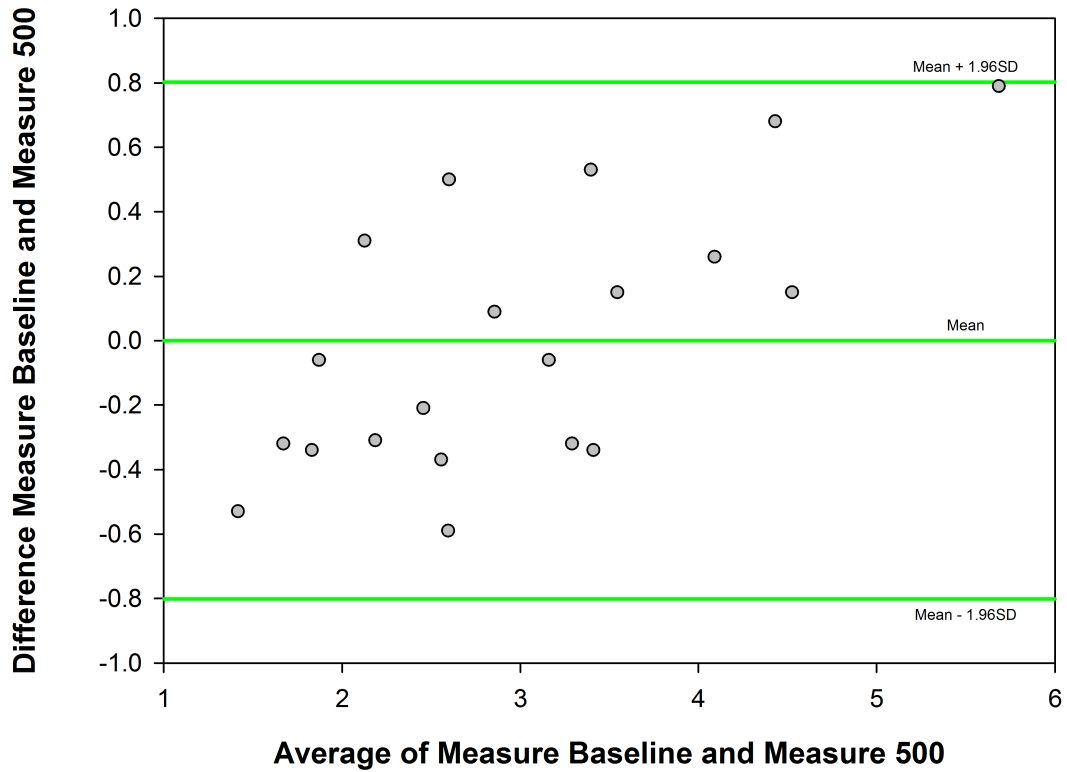


Figure C.3.10.: Coronal T2 MRI knee demonstrating the final meniscal extrusion distance. 2.44 mm in this example.



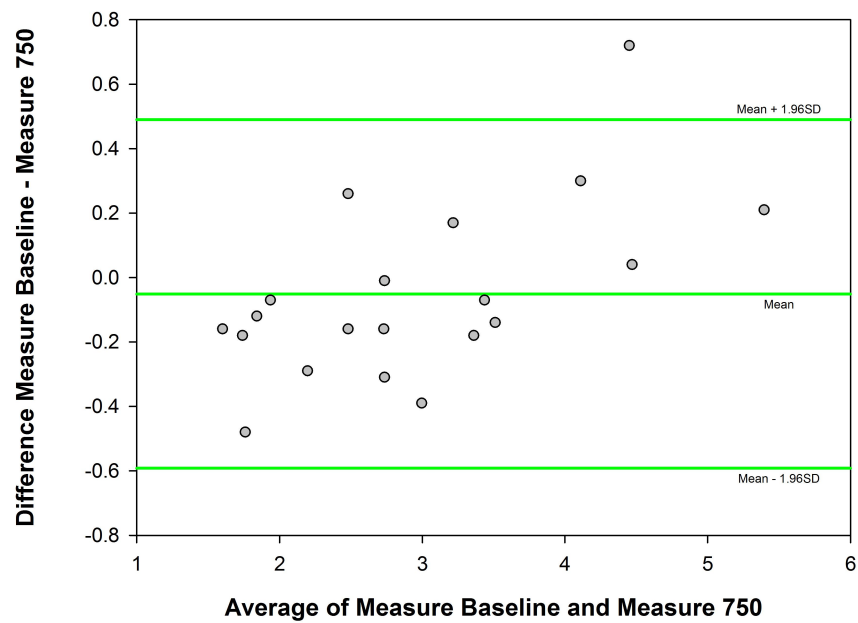
C.4. Bland Altman plots for observer drift during assessment of meniscal extrusion.

Figure C.4.1.: Bland Altman plot comparing baseline measurement with measurements after 500 scans



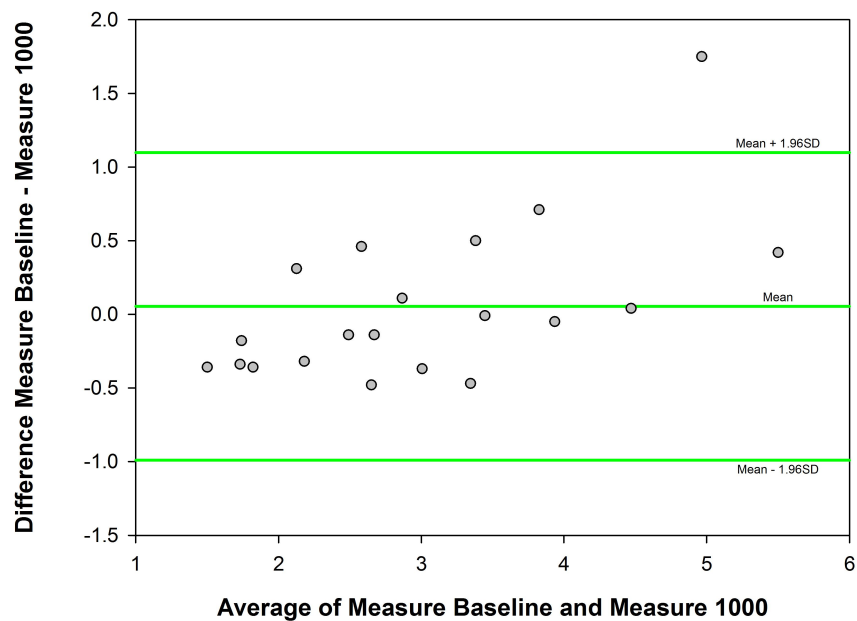
Observer drift between baseline reading and reading 500. Figure C.4.1 demonstrates an overall mean difference (bias) in measured distance of meniscal extrusion of 0.005mm (SD 0.4093) with 95% CI of -0.8mm - 0.8mm. On this occasion there were no outliers. However, a single reading did approach the upper limit of agreement.

Figure C.4.2.: Bland Altman plot comparing baseline measurement with measurement after 750 scans



Observer drift between baseline reading and reading 750. Figure C.4.2 demonstrates an overall mean difference (bias) in measured difference of meniscal extrusion of -0.05mm (SD 0.28) with 95% CI -0.59 - 0.49. There was a single outlier.

Figure C.4.3.: Bland Altman plot comparing baseline measurement with measurement after 1000 scans



Observer drift between baseline reading and reading 1000. Figure C.4.3 demonstrates an overall mean difference (bias) of 0.054mm (SD 0.533) with 95% CI -0.99-1.09. As can be seen from the graph although the general spread of score differences is very narrow, there is a single outlier.

D. Protocol for identifying the slice on T2 map that corresponds to region of interest.

1. Open ONIS Professional 2.4
2. Open Philips Medical Workspot (PII-SW11.1WIP Philips Medical Systems, Netherlands, B.V)
3. Open Excel file C:\Users\Luke\Documents\SIBKIDS\Analysis 2013\T2 Analysis\T2Map analysis.xlsx
4. In ONIS Professional 2.4
 - a) Read meniscal extrusion as described in protocol (Cross reference here)
 - b) Clear the annotations
 - c) Ensure you are on the coronal slice corresponding to the highest point of the medial tibial spine.
 - d) Redraw joint line
 - e) Click on joint line until it goes yellow.
 - i. Right click

D. Protocol for identifying the slice on T2 map that corresponds to region of interest.

- ii. Go to Actions
- iii. Click parallel
- f) Drag this line down as distally as possible
- g) Move central line away
- h) Split the top and bottom line.
 - i. Click on it.
 - ii. Right click.
 - iii. Clicking “split”.
- i) Draw a line between the two split points to represent the longitudinal axis of the tibia.
- j) From here, generate a parallel line and line this up to the highest point of the medial tibial spine.
- k) Measure the distance between the line generated in (j) and the most medial point of the tibia along the joint line drawn in (d).
- l) Once this line has been drawn split the line in two.
- m) This midpoint of the medial tibial plateau represents the 0.5 of the normalised width as described by Rout et al (2013).
- n) As noted by Rout et al, the central portion of the lesion generated in AMG lies at approximately 0.6 of the normalised width.
- o) Now click “view” then “split view horizontally”
- p) On the neighbouring image, bring up the T2 MLE map Sagittal image.
- q) A vertical corresponding line will now appear on the coronal image

D. Protocol for identifying the slice on T2 map that corresponds to region of interest.

- r) On the sagittal image scroll through and determine how many slices there are across the medial tibial plateau from the highest point of the medial tibial spine to the most medial part of the plateau.
- s) Identify the sagittal slice that is one slice medial to the midpoint of the medial tibial plateau.
- t) Record this number.

5. In Philips Medical Workspot

- a) In the Local Data section of the left hand panel scroll down to “User Selectable Repository
- b) Right click and then click the option “Open...”
- c) Select E: Elements
- d) Then open the file “SIBKIDS”
- e) Open the corresponding SIBKIDS named file.
- f) Open the DICOM file g. ST00000 usually corresponds to the MRI file.
- g) Within that, SE0000001 usually corresponds to the T2Q MLE images
- h) You may need to reload the whole viewing software before being able to open this.
- i) Right click on the image in the “series” box
 - i. Then click on “Cartilage assessment”
 - ii. The click “Cancel” when the debug notice pops up.
- j) Find the most medial part of the images.
- k) Scroll through until you reach the slice number you identified in 4(t).
- l) Turn attention to tibia first.

D. Protocol for identifying the slice on T2 map that corresponds to region of interest.

- i. Draw bone interface on left hand image and go from the front of the meniscus anteriorly to the back of the meniscus posteriorly.
- ii. Then do the same with the cartilage interface.
- iii. Record on the excel spread sheet
 - A. The overall Relaxation time and SD.
 - B. Then split the region into anterior and posterior and superficial/intermediate/deep.
 - C. Record these values in the excel spread sheet including the SD's n.
 - D. Then repeat for the femur

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