

The Role of Surgery in Early Osteoarthritis of the Knee

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Abstract

Early knee osteoarthritis (EKOA) is common, hard to treat and can be debilitating for symptomatic individuals. Whilst end-stage osteoarthritis is treated reliably with knee replacement surgery, such surgery is not routinely offered to those with less severe OA as it is associated with a poorer outcome. These patients are said to be in a 'treatment gap" and they are the primary focus of this thesis.

A series of large epidemiological studies were designed to clarify the natural history of symptomatic EKOA. A prospective cohort study including 1,634 symptomatic knees with EKOA found that malalignment was the most potent risk factor for structural progression. A subsequent study, which included a detailed assessment of lower limb alignment, established that this structural progression was driven by the alignment of the proximal tibia. Using semi-quantitive MRI analysis it was found that the increased structural progression seen in subjects with proximal tibia vara, was due to more full thickness cartilage loss in the central medial tibia. These are novel observations which have implications for future research as the alignment of the proximal tibia can be corrected with surgery.

Following this epidemiological description of EKOA, attention was turned to intervention and treatment. A systematic review of the literature identified moderate to very low quality evidence to support the role of surgery in treating symptomatic EKOA. A single-centre prospective cohort study for patients undergoing a novel neutralising high tibial osteotomy was established and excellent early (1yr) and mid-term (3-5 years) clinical outcomes are reported. A retrospective study was designed to investigate whether full thickness cartilage loss on magnetic resonance imaging, but not on plain film radiographs, is sufficient to warrant proceeding to unicompart-

mental knee arthroplasty (UKA). Outcomes for this cohort of patients were excellent, highlighting the usefulness of MR for the early identification of patients suitable for UKA.

In summary, this thesis has reported the natural history of symptomatic EKOA and identified proximal tibia vara as a potent risk factor for structural progression. The paucity of trials investigating subjects with this disease has been highlighted and surgical interventions which are safe and clinically effective have been identified. The direction of future research in this area has been proposed.

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Abbreviations

AIMS Arthritis impact measurement scales

AUC Area under curve

FFD Fixed flexion deformity

FNIH Foundation for the National Institutes of Health

HKA Hip knee ankle angle

ICC Intraclass correlation coefficient

JLCA Joint line convergence angle

KJD Knee joint distraction

KSS Knee society score

LI Lequesne index

LLR Long leg radiograph

mLDFA mechanical Lateral distal femoral angle

mLDTA mechanical Lateral distal tibial angle

mLPFA mechanical Lateral proximal femoral angle

AMOA Antero-medial Osteoarthritis

MPTA Medial proximal tibial angle

NNTB Number needed to treat for an additional benefical outcome

NNTH Number needed to treat for an additional harmful outcome

OR Odds ratio

PPV Positive predictive value

RCT Randomised controlled trial

ROC Receiver operating characteristics

RRR Relative risk ratio

SMD Standardised mean difference

TV+ Proximal tibia vara

TV- Non proximal tibia vara

VIF Variance inflation factor

WBA Weight-bearing axis

EKOA Early Knee Osteoarthritis

GEEs Generalised estimating equations

HKA Hip knee ankle angle

JSN Joint space narrowing

JSW Joint space width

NICE National Institute for Health and Clinical Excellence

OAI Osteoarthritis Initiative

OA Osteoarthritis

PSP Priority setting partnership

RxFT Radiographic Full Thickness

RxPT/MRI-FT Radiographic Partial Thickness/MRI Full Thickness

TKA Total Knee Arthroplasty

UKA Unicompartmental Knee Arthroplasty

1. Introduction

1.1. Overview

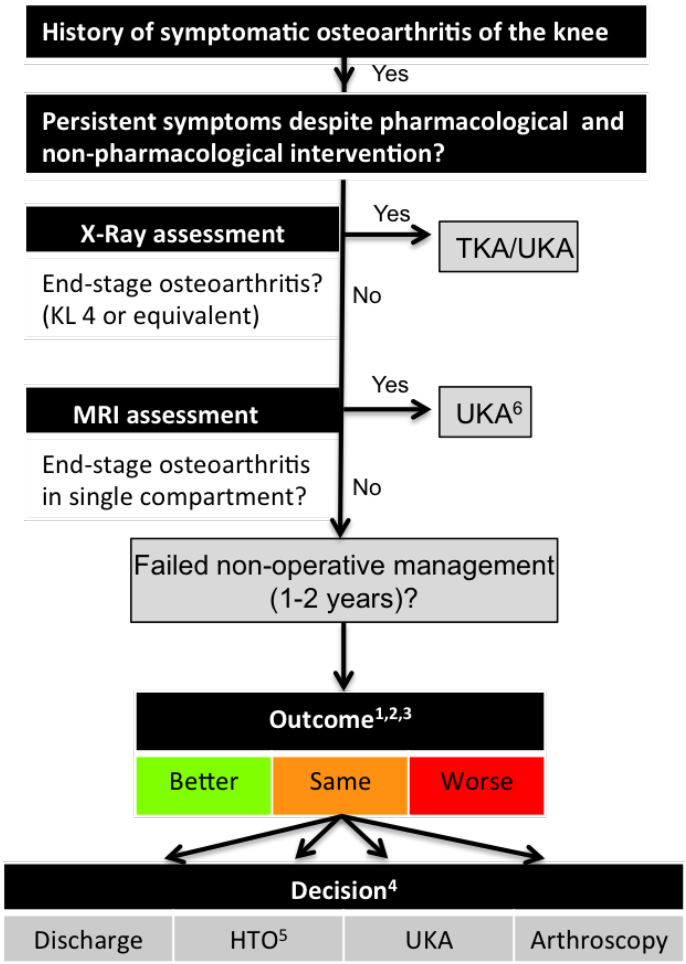
Osteoarthritis (OA) is a major health concern. It is the most common form of arthritis [1] and the lifetime risk of symptomatic knee OA in western populations has been estimated to be over 40% [2]. Osteoarthritis of the knee represents a continuum of disease from early cartilage thinning to full thickness cartilage loss, bony erosion and deformity. A cross-sectional study of primary referrals to a specialist knee clinic has shown that 62% of patients present with an antero-medial pattern of OA (AMOA) and that, of these subjects, less than 25% have advanced or 'bone on bone' disease [3]. This indicates that a significant burden of OA is caused by patients with only early to moderate structural pathology.

Many patients with early knee OA (EKOA) experience pain and dysfunction that is equal or worse than those patients with end-stage disease presenting for total knee arthroplasty (TKA) [4]. Whilst, end-stage osteoarthritis is treated reliably with replacement surgery in the form of total or unicompartmental knee arthroplasty (TKA/UKA) [5, 6], such surgery is not routinely offered to those with less severe OA as it is associated with a poorer outcome [7, 8, 9]. These patients are said to be in a 'treatment gap" [10] and this population is the primary focus of this thesis.

In order to bring together the available evidence and provide consistency of care to patients, a contemporary surgical pathway for EKOA is being developed at the

Nuffield Orthopaedic Centre. This pathway does not hold all the answers with regard to the management of early knee OA but instead seeks to provide a framework which can be used to identify areas where evidence is lacking or absent. The following thesis will inform this surgical pathway by answering critical questions which currently remain unanswered (figure 1.1.1). These questions were identified following the detailed literature review described in the next chapter.

Figure 1.1.1.: Contemporary surgical pathway for patients with early symptomatic knee osteoarthritis



1. What is the natural history of symptomatic EKOA with regard to symptom and structural progression and what factors influence this progression?

2. Are the factors that contribute to malalignment of equal importance when predicting progression in EKOA?

3. Do subjects with proximal tibia vara demonstrate a unique pattern of structural progression that explains the worsening joint space narrowing seen in varus malalignment?

4. In symptomatic EKOA, are any surgical interventions proven to improve outcomes for patients compared to non-surgical intervention?

5. Does a neutralising high tibial osteotomy improve clinical outcomes for patients with symptomatic EKOA?

6. Can MRI be used for the early identification of patients who are suitable for unicompartmental knee arthroplasty?

2. Literature review

2.1. The knee

The knee is a synovial joint that involves the distal femur, proximal tibia and patella. It is the largest joint in the human body and its purpose is to transmit weight and aid in foot placement during ambulation.

2.1.1. Anatomical features

Through a complex interplay of bony and soft tissue structures, the knee is provided stability and capable of a broad range of movements including; flexion–extension, internal–external tibial rotation, abduction-adduction, anterior-posterior displacement, medial-lateral joint space opening and compression-distraction [11]. This coaction of stability and movement facilitates motion.

Bony articulation The distal femur, proximal tibia and patella articulate to form three functional articular compartments; patello-femoral articulation, medial tibio-femoral articulation, lateral tibio-femoral articulation. The tibial plateau consists of a medial and lateral articular surface separated by a tibial spine. The lateral tibial plateau is smaller and more circular in shape. The medial tibial surface is concave in contrast to the lateral tibial surface which is convex [12]. The distal femur consists of a medial and lateral condyle. Anteriorly, the medial and lateral femoral condyles

are separated by the trochlea groove which articulates with the inner surface of the patella. Posteriorly, they are separated by the intercondylar fossa. The articular aspects of the femur, tibia and patella are lined with hyaline cartilage.

Capsule The knee joint capsule consists of dense fibrous connective tissue, lined with synovium, that forms a sleeve around the articulating bones to which it is attached. It seals the joint space and in so doing keeps lubricating synovial fluid, secreted from the synovium, in position [13]. Furthermore it provides passive stability by limiting movement and provides active stability via its proprioceptive nerve endings [13].

Ligaments The knee is stabilised by a series of ligaments which give stability to the joint capsule and provide proprioceptive feedback [14]. The anterior cruciate ligament (ACL) arises from the medial aspect of the lateral femoral condyle and has a broad insertion into the tibia anterior to the tibial spine. It prevents anterior translation of the tibia relative to the femur and consists of two bundles; an anteromedial bundle (tight in flexion) and a posterolateral bundle (tight in extension). The posterior cruciate ligament arises from the anterolateral aspect of the medial femoral condyle and inserts into the posterior aspect of the tibia. It prevents posterior translation of the tibia relative to the femur and consists of two bundles; posteromedial (tight in extension) and anterolateral (tight in flexion).

The lateral collateral ligament arises from the lateral epicondyle of the femur and inserts into the posterior aspect of the fibula head. It resists varus angulation of the knee and in combination with medial collateral ligament resists axial rotation of the knee. The medial collateral ligament arises from the medial femoral condyle and inserts into the medial aspect of the tibia. Further rotatory stability is provided by a complex of structures known as the posterolateral corner.

Menisci The knee joint contains a medial and lateral meniscus. The menisci are a pair of wedge shaped semilunar cartilages which are interposed between the femoral condyles and tibial plateaux. They are attached to the joint capsule by their thick convex-shaped peripheral rim and are connected to each other anteriorly by a transverse ligament [15]. The anterior and posterior meniscal horns are firmly attached to bone via insertional ligaments [16].

The menisci increase the contact area of the tibiofemoral joint significantly and in so doing the stresses on the tibial cartilage are reduced. The load distributing function of the menisci is made possible by their strong anterior and posterior entheses to bone which prevent the wedge shaped menisci from extruding from the joint during axial loading [16]. Menisci also play a role in shock absorption [17], joint stability [18], proprioception [19] and joint lubrication [20]. In the adult, a perimeniscal capillary plexus originating in the capsular and synovial tissues of the joint supplies the peripheral 10-25% of the menisci [21]. The healing capacity of the meniscus is directly related to this vascular supply; tears in the vascularised peripheral zone of the meniscal body have a greater healing potential than tears in the more avascular regions [22].

Hyaline Cartilage Articular surfaces of the healthy knee are covered in a layer of hyaline cartilage with a maximum thickness of approximately 4mm [23]. This thin layer of cartilage is devoid of blood vessels, nerves and lymphatics receiving its nutrient supply by diffusion from the surrounding synovial fluid.

Articular cartilage is composed of a dense extracellular matrix (ECM) with a sparse distribution of highly specialized cells called chondrocytes [24]. The ECM is principally composed of water, collagen, and proteoglycans [25]. The high water content together with the macromolecular framework gives the tissue its mechanical properties of stiffness and resilience [25]. The preservation of cartilage is reliant on maintenance

of this highly organised architecture.

Hyaline cartilage is divided into four discrete layers [25] :

- Tangential (superficial) zone: consists of a superficial acellular layer (lamina splendens) and a deeper layer which is densely packed with chondrocytes arranged parallel to the joint surface enabling it to resist sheer stresses
- Transitional zone: this layer has obliquely running collagen fibres and represents a transition from the superficial layer to the deeper layers.
- Radial layer: chondrocyte in this layer form columns which are perpendicular to the articular surface enabling it to resist compressive forces.
- Calcified cartilage layer: is a thin calcified cartilage layer that anchors the overlying cartilage to the underlying subchondral bone. A 'tide mark', visible on histological staining, distinguishes the calcified layer from the more superficial layers.

2.1.2. Anatomical planes

The description of anatomical planes in this thesis are as follows:

- Coronal plane: a vertical plane that divides the body into anterior and posterior sections
- Sagittal plane: a vertical plane that divides the body into right and left halves; at right angles to the coronal plane
- Axial plane: a transverse plane that divides the body into superior and inferior sections [26]

2.2. Lower limb alignment

2.2.1. Coronal alignment

In the coronal plane, lower limb alignment is categorised into three broad categories:

- Varus alignment: a 'bow-legged' deformity with the distal lower limb deviated towards the midline
- Valgus alignment: a 'knocked-knee' deformity with the distal lower limb deviated away from the midline
- Neutral alignment: no deviation of the distal lower limb

2.2.2. Sagittal alignment

Malalignment in the sagittal plane is a significantly different concept from that of malalignment in the coronal plane. The knee moves in the sagittal plane and as such compensates more readily for deformities in this plane [27]. Sagittal plane deformities include:

- Flexion/extension: flexion malalignment is present when the mechanical axis of the knee does not pass anterior to the centre of rotation of the knee and extension malalignment is present when the knee can be passively hyperextended more than 5 degrees (genu recurvatum) [27]
- Subluxation: anterior or posterior displacement of the tibia relative to the femur represents anterior or posterior subluxation, respectively [27].

2.2.3. Assessment of lower limb alignment

All long bones have both an anatomical and mechanical axis. The anatomical axis of a long bone refers to a line running parallel to the medullary canal. In contradistinction,

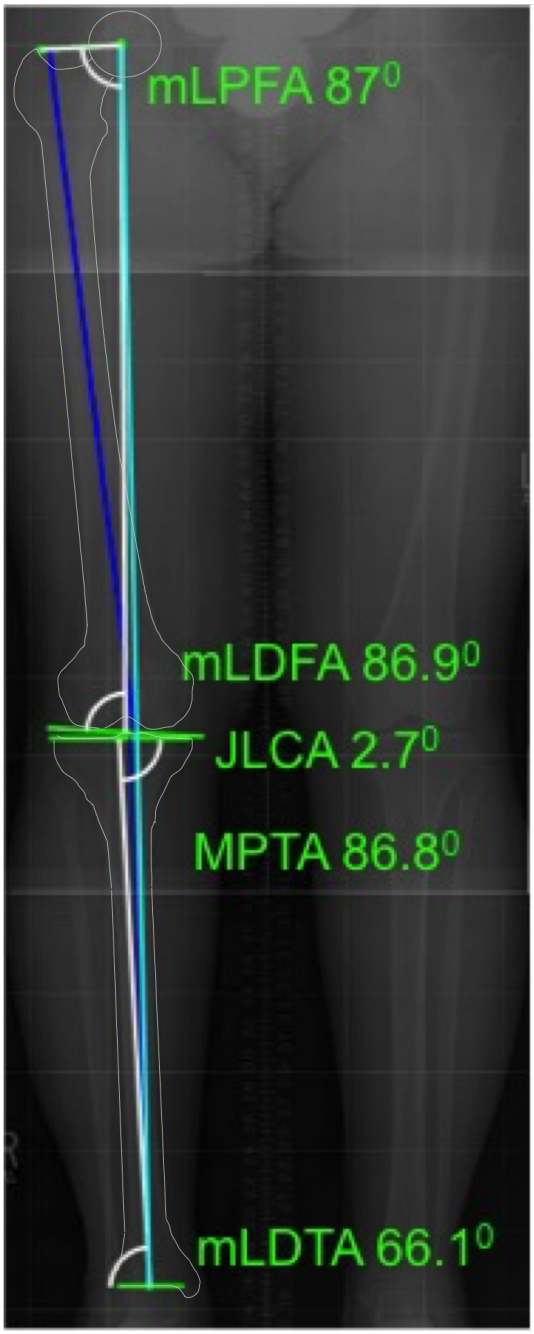
the mechanical axis refers to a straight line that joins the centre points of its proximal and distal articulating surfaces or the centre point of the adjacent joints [27]. For instance, the mechanical axis of the femur runs from the centre of the femoral head to the centre of the knee joint.

A variety of techniques can be used to assess lower limb alignment. Clinical assessment can be augmented with the use of calipers [28] or a goniometer. The latter has been shown to have reasonable correlation with alternative radiographic methods [29]. Due to the inherent straightness of the tibia, in the coronal plane the anatomical and mechanical axes of the tibia are often coincident, however, due to the femoral neck offset seen in the proximal femur it is not possible to accurately define the mechanical axis of the femur using this method. Similarly, the use of short leg knee radiographs allows an assessment of anatomical alignment but cannot accurately define the mechanical axis of the femur. Some studies have recommended a standardised correction in order to account for this offset [29, 30].

The accepted gold standard assessment of lower limb alignment is a standing anteroposterior long-leg radiograph (see figure 2.2.1). The weight-bearing axis (WBA) of the lower limb describes a line from the centre of the femoral head to the centre of the ankle (miculikcz line). Broadly speaking if this line passes through the medial compartment then the limb is in varus alignment, conversely, if it passes through the lateral compartment then the limb is in valgus. Alternatively, the hip knee ankle (HKA) angle can also be calculated to give an assessment of lower limb alignment. The HKA is calculated as the intersection of the mechanical axis of the femur and the mechanical axis of the tibia. A knee is defined as varus when HKA is more than 0° in the varus direction, valgus when it is more than 0° in the valgus direction, and neutral when it is 0° [31]. Alternatively, thresholds can be set to define varus (<-3°) and valgus (>3°) alignment [32].

Once the alignment of the lower limb has been established it is possible to determine the site of an underlying deformity by observing a significant deviation from the expected physiological values for individual alignment variables including; medial proximal tibial angle (MPTA), mechanical lateral distal femoral angle (mLDFA), mechanical lateral proximal femoral angle (mLPFA), mechanical lateral distal tibial angle (mLDTA) (see figure 2.2.1).

Figure 2.2.1.: Long leg radiograph illustrating the geometric alignment variables that contribute to overall lower limb alignment



The light blue line indicates the weight bearing axis (WBA). The white lines indicate the mechanical axis of the femur and the mechanical axis of the tibia. The dark blue lines indicate the anatomical axes of the femur and tibia. Values for the MPTA, mLDFA, mLPFA and mLDTA are highlighted in green. All measurements were taken using MediCAD© Classic Version 3.0.2.2 (Hectec GmbH, Germany). NB: The outline of the femur and tibia has been highlighted in white to aid interpretation of this figure.

2.3. Aetiology of lower limb malalignment

Several pathological processes have been attributed to lower limb deformity. Any process that causes interruption of the growth plate in youth can lead to a progressive malalignment (e.g. infection, trauma or tumour). Disorders of bone metabolism (e.g. secondary to vitamin D deficiency (rickets)) can also lead to lower limb deformity in the skeletally immature.

Blount described a progressive varus deformity of the proximal tibia observed in otherwise healthy children and adolescents [33]. Whilst the exact aetiology of this disease is unknown it is likely to be related to mechanical overload in genetically susceptible individuals with increased prevalence in children who walk early and those who are overweight [34]. Interestingly, the nature of the deformity seen in Blount's disease may vary depending on the age of onset. Patients with infantile tibia vara most commonly have a deformity isolated to the proximal tibia, however, distal femoral varus constitutes a substantial portion of the genu varum seen in children with late-onset disease [35].

It is important to note that lower limb malalignment does not necessarily indicate a pathological process. In a study of 250 asymptomatic healthy young adults as many as 32% of men and 17% of women had varus alignment (HKA >3°) [32]. The most important contributors to this 'constitutional varus' were the medial proximal tibial angle (MPTA) and the mechanical lateral distal femoral angle (mLDFA) [32]. The authors have subsequently noted that increased sports participation in youth is associated with varus alignment at the end of growth in males [36].

2.4. Geographical variations in lower limb alignment

As discussed in the previous section, a cross-sectional study including 250 asymptomatic healthy young adults from Belgium reported that as many as 32% of men and 17% of women had varus alignment (HKA >3°) [32]. Important contributors to this 'constitutional varus' alignment were the MPTA and the mLDFA, contributing 40.8% and 29.4%, respectively [32]. In Asian populations, constitutional varus alignment appears to be even more common. A cross-sectional study including 198 healthy participants demonstrated that varus alignment (HKA >3°) occurred in 34% of Indian and 35% of Korean participants (males 40%; females 28%) [37]. They compared their results to those obtained by Bellemans et al and determined that Asian adults have a a greater prevalence of tibia vara and femoral bowing when compared to Caucasian adults [37]. No study to date has reported on how geographical variations in lower limb alignment impact on the surgical interventions offered to patients within those communities.

2.5. Osteoarthritis of the knee.

2.5.1. Epidemiology

Worldwide musculoskeletal disorders account for 6% to 8% of all disability-adjusted life years, and osteoarthritis accounts for approximately 10% of this disease burden [38]. Osteoarthritis affecting the knee is common, with a global prevalence of radiographically confirmed symptomatic knee osteoarthritis estimated to be 3.8% [39], and a lifetime risk of symptomatic knee osteoarthritis in Western populations estimated to be over 40% [2]. In the UK, more people receive disability living allowance as a result of arthritis than for heart disease, stroke, chest disease, and cancer combined [40]. The prevalence of knee osteoarthritis increases with age [41] and is higher in

females [42].

2.5.2. Classification of knee osteoarthritis

There is currently no agreed definition for the diagnosis or classification of knee OA. In recognition of this the European League Against Rheumatism (EULAR) proposed evidence evidence-based recommendations for the diagnosis of knee OA. Using a systematic review of research evidence and expert consensus they determined that a purely clinical diagnosis of knee OA could be made according to three symptoms (knee pain, short-lived morning stiffness and functional limitation) and determination of three signs on examination (crepitus, restricted movement and bony enlargement) [43].

A revised version of the American College of Rheumatologists classification system for osteoarthritis has been validated for clinical use [44]. This system defines criteria for knee osteoarthritis based on clinical signs alone or a combination of clinical signs, laboratory investigations and radiological features:

- **Clinical** - Knee pain for most days of the prior month, in addition to three of the following:
  - Crepitus on active joint motion
  - Morning stiffness $\leq$ 30 minutes duration
  - Age $\geq$ 38years
  - Bony enlargement of the knee on examination
  - Bony tenderness of the knee on examination
  - No palpable warmth
- **Clinical plus radiographic**- knee pain for most days of the prior month, plus radiographic evidence of osteophytes on joint margins.

- **Clinical plus laboratory-** knee pain for most days of the prior month plus all three of the following:
  - Synovial fluid of osteoarthritis (at least 2: clear, viscous, WBC $<$ 2,000 cells/ml)
  - Morning stiffness $\leq$ 30 minutes duration
  - Crepitus on active joint motion

Whilst this is a useful algorithm for identifying people with knee osteoarthritis, it cannot reliably be extended to defining the severity or progression of disease. Furthermore, the requirement for pain to be present on most days in the previous month may capture a patient group with advanced disease and have poor sensitivity for patients with early or mild OA [45].

In epidemiological studies, subtle changes to the screening questions (e.g. Have you experienced pain, aching or stiffness in or around the knee on most days for at least one month **during the previous 12 months**?) can significantly affect the proportion of individuals identified with knee OA [46].

2.5.3. Radiological assessment of osteoarthritis

Several radiological grading systems have been introduced to try and provide an accurate and reproducible description of the structural changes seen in knee OA. They have the advantage of providing a scale upon which severity and progression can be measured.

2.5.3.1. Plain film classification

In general, the use of X-rays to grade OA relies on an assessment of one or more of the classical features of osteoarthritis; joint space narrowing, marginal osteophytes, subchondral bone cysts and subchondral cysts.

Kellgren and Lawrence (KL) Kellgren and Lawrence described a semi-quantitive assessment for OA that can be used for the hand, knee and hip [47]. It identifies radiographic features of OA including osteophytes, joint space narrowing, subchondral bone cysts and bony deformity and distinguishes disease severity using five grades:

- 0- None
- 1- Doubtful
- 2- Mild
- 3- Moderate
- 4- Severe

Grade 0 represents a definite absence of OA and grade 2 represents definite OA but of minimal severity [47] a threshold that has been used in several large epidemiological studies to investigating knee OA. Whilst this grading system has been widely adopted, significant variations and adaptations have been made to it in the literature [48]. As such care should be taken to confirm the exact definition used in any study concerning KL grade.

Ahlback Ahlback's classification for knee OA is based on radiographic evidence of joint space narrowing [49]:

- 0- None
- 1- Narrowing of the joint space (<3mm)
- 2- Obliteration of the joint space
- 3- Bone loss <5mm
- 4- Bone loss 5-10mm

- 5- Bone loss >10mm

This classification system has been shown to correlate well with KL grade [50], however, there is concern that the scoring system does not reliably differentiate between low and medium grades [51].

OARSI atlas grading The Osteoarthritis Research Society International (OARSI) published their original radiographic atlas of osteoarthritis in 1995 [52] and subsequently revised and updated it in 2007 [53]. The classification evaluates radiographic features of OA separately on a scale of 0-3 (mild, moderate, severe) in distinct locations on an AP radiograph:

- Marginal osteophytes- medial femoral condyle, medial tibial plateau, lateral femoral condyle, lateral tibial plateau
- Joint space narrowing- medial compartment, lateral compartment

Other radiographic features are also described as either absent or present; medial tibial attrition, medial tibial sclerosis, lateral femoral sclerosis. Despite the compartment-level data provided by this classification system it has not been shown to be superior to KL grade at either identifying the presence of OA or monitoring its progression [54].

Joint space narrowing Radiographic assessment of joint space narrowing has been widely used as a surrogate for cartilage thickness in knee osteoarthritis [55]. It is the only marker of structural progression currently approved by both the United States Food and Drug Administration (U.S. FDA) [56] and European Medicines Agency (EMEA) [57] for disease modifying drugs in phase 3 clinical trials. Detection of joint space narrowing is highly predictive of the risk of undergoing subsequent osteoarthritis related joint surgery including total knee arthroplasty [58].

An accurate assessment of joint space narrowing requires precise positioning of the proximal tibia and the X-ray beam [59]. Small errors in alignment lead to a significantly reduced sensitivity to detect joint space narrowing [60, 61]. As such thresholds for clinically relevant joint space narrowing vary depending on the protocol used to obtain the radiograph.

Despite its broad application as a marker for structural progression in knee osteoarthritis joint space narrowing has its limitations. As a marker for progression it is not specific to a particular tissue, but is associated with loss of cartilage thickness, meniscal position and meniscal integrity [62, 63]. Furthermore, since joint space narrowing progression is generally slow its use as an endpoint measurement requires long-term treatment periods (>1 year) and inclusions of large patient numbers [64].

2.5.3.2. Magnetic resonance (MR) imaging grade

Magnetic resonance (MR) imaging is a non-invasive imaging modality that allows for a detailed assessment of structures within the knee. It can be used to establish the presence of osteoarthritis, assess disease severity and monitor disease progression. MR can detect cartilage loss when none is evident on plain film radiographs and can be used to identify structural changes within the knee of a person with osteoarthritis symptoms but no radiographic changes [65, 66]. MR can be used to determine the extent and severity of cartilage injury in osteoarthritis of the knee [67] and is able to show full-thickness cartilage lesions that are not seen on plain film radiographs [68].

Direct, quantitative measurements of cartilage volume have demonstrated that early X-ray changes are associated with substantial reductions in cartilage volume (10-20%) [69] and that cartilage volume loss over 2 years is an independent predictor of the need for knee replacement [70]. However, there is some concern that quantitive MR assessments are poorly sensitive at detecting the focal cartilage loss seen in mild osteoarthritis and applying semiquantitative methods are superior [71].

A variety of semi-quantitive MR techniques have been reported. These systems divide the knee into subregions and individual tissue structures within each subregion are given a grade. Whole organ MRI score (WORMS) was the first to be described [72]. In response to some of its limitations the Boston Leeds osteoarthritis knee score (BLOKS) [73] was developed. In particular BLOKS takes a different strategy to measuring bone marrow lesions which appears to have a stronger association with pain severity [73]. Both methods have good cross-sectional reliability [74], however, both have strengths and weaknesses in terms of predicting cartilage loss [75]. Subsequently the MRI osteoarthritis knee score (MOAKS) was developed with the aim of combining the advantages of each scoring system [76]. The usefulness of semi-quantitative MRI outcomes has been verified in clinical trials [77] and recently strontium ranelate was reported to reduce the progression of BMLs in the medial tibiofemoral compartment described using semi-quantitive methods [78].

2.5.4. Patterns of knee osteoarthritis

Patterns of knee osteoarthritis are frequently described based on the identification of compartment involvement within the knee; patello-femoral, medial tibiofemoral and lateral tibiofemoral. A study of subjects referred to hospital with symptomatic knee OA revealed that 50% of people had combined patello-femoral and medial tibiofemoral OA [79]. However, gender differences occur with increased medial compartment OA in men compared to women [80].

White et al used the term 'antero-medial osteoarthritis' to describe a discrete phenotype of knee OA with the following features; articular cartilage erosion in the medial compartment to subchondral bone with erosion on the tibia restricted to the anterior and middle sections of the plateau, preservation of articular cartilage in the lateral compartment, intact anterior cruciate ligament and correctible varus

deformity.

Patterns of knee OA specific to EKOA are not widely reported and patterns of knee OA described using semi-quantitive (MRI) methods have not been described.

2.5.5. Symptoms in knee OA

Symptomatic osteoarthritis causes substantial physical and disability. The risk of functional disability attributed to knee osteoarthritis is equal to that attributable to cardiovascular disease and greater than that due to any other medical condition in elderly persons [81]. The prevalence of painful disabling knee osteoarthritis in people over 55 years is 10%, of whom one quarter are severely disabled [45]. The cardinal symptoms that suggest a diagnosis of OA have been described [82]:

- pain (typically described as activity related or mechanical; may occur with rest in advanced disease; often deep, aching and not well localised; usually of insidious onset)
- reduced function
- stiffness (of short duration, also termed "gelling")
- joint instability, buckling or giving way
- reduced movement, deformity, swelling, crepitus
- pain-related psychological distress

2.5.6. Outcomes in knee OA

A core set of four outcome measurements for use in Phase III clinical trial of knee OA have been reached by expert consensus (OMERACT III) [83]. They include; pain, physical function, patient global assessment and joint imaging (for studies >1yr).

The latter can be assessed using one of the classification systems discussed in section 2.5.3. The remaining core outcomes are frequently assessed using patient-reported outcome measurements (PROMs).

2.5.6.1. Patient reported outcome measures (PROMs)

In order to capture the range of symptoms and functional impairment that subjects with knee OA experience a broad variety of patient-reported outcome measures (PROMs) have been created. These have the advantage of including patient's subjective assessments of pain and symptoms which may more accurately reflect their quality of life than assessments made by a third party [84]. There are fundamental characteristics that an outcome measure must fulfil in order to be considered good [85]:

- **Reliability-** is the measuring instrument consistent, reproducible and free from random error?
- **Validity-** does the instrument measure what it purports to measure?
- **Responsiveness**- does the instrument detect changes over time that matter to patients?
- **Precision**- the ability of the measurement to reflect true changes or differences
- **Interpretability-** how meaningful are the scores that the instrument generates?
- **Acceptability-** is the instrument acceptable to patients ?
- **Feasibility-** is the instrument easy to administer and process?

WOMAC score The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a patient-reported assessment tool validated for use in subjects with osteoarthritis [86]. It assesses the three dimensions of pain, disability and joint stiffness in knee and hip osteoarthritis using a battery of 24 questions and is available in 5-point Likert, 100mm Visual Analogue and 11-box Numerical Rating Scale formats in over 100 languages [87]. The patient's response to each question produces a score that is then summed to derive an aggregated score for each dimension giving three sub scale scores (pain, stiffness and physical function) and a total score (WOMAC index) that reflects disability overall [88].

Oxford Knee Score The Oxford Knee Score (OKS) is a 12-item questionnaire designed for patients undergoing total knee arthroplasty[89]. Each item is scored from 0-4 with a low score denoting more severe symptoms [90]. In patients with early to moderate OA, it has been shown to be both reliable and responsive to the health state of the individual correlating highly with other patient reported outcome measurements [91]. Its use has been extended to evaluate outcomes in pharmacological studies [92] and other surgical interventions including osteotomy [93, 94].

2.5.7. The relationship between structural change and symptoms in knee OA

The previous sections have outlined the importance of pain as an indicator for both the presence and progression of knee OA. The structural determinants of pain and mechanical dysfunction in OA are, however, poorly understood [82]. Subjects with similar structural damage may experience very different levels of pain and approximately 50% of persons with structural changes consistent with OA are asymptomatic [95]. Patients with early to moderate OA frequently experience symptoms that are

as severe as those with end-stage disease [4]. The experience of pain is subjective and can be modified by several factors including age, gender [96] and psycho-social factors such as depression [97]. If these confounding factors are controlled for a strong structure-symptom association has been demonstrated in osteoarthritis of the knee [98] and subjects with early knee OA who demonstrate rapid radiological change (change of $\geq$2 KL grades in 4 or 5 years) experience a worsening of pain and function [99].

An important consideration is that structural progression is frequently measured using joint space narrowing as a surrogate marker for cartilage loss. However, articular cartilage is aneural and incapable of directly generating pain. There is a disconnect between the appropriate markers for structural progression and symptom worsening. In response to this various MRI features have been investigated to determine if they correlate more strongly with symptoms. MRI features, in pre-radiographic OA, have been shown to predict the onset of clinical symptoms [66] and are more likely to be found in painful than in the non-painful knees [100], Further studies have shown that bone marrow lesions [101], medial meniscal extrusion [102], exposed subchondral bone [103] and synovitis [101] are all associated with OA knee pain.

2.5.8. Risk factors for progression in knee OA

The identification of risk factors that predict the onset and progression of osteoarthritis has received a great deal of attention in the literature. Risk factors for both structural and symptom progression have been identified and are considered here separately.

2.5.8.1. Risk factors for structural progression

Several risk factors for structural progression in knee osteoarthritis have been reported in the literature. A recent systematic review reported that baseline patient characteristics with strong evidence for predicting knee OA progression were older age, presence of OA in multiple joints, varus deformity of the knee and radiographic features of OA at baseline [104]. By contrast female gender, former knee injury, quadriceps strength, smoking, running, and regular performance of sports are not predictive for progression of knee OA [105]. However, the literature is conflicted with regard to the effects of BMI, clinical/disease severity, leg length inequality and symptom duration [106]. Some of this conflict arises due to inconsistencies in the way patients are selected and outcomes are assessed across different studies. Subtle differences in methodology can lead to very different outcomes being observed [104].

Longitudinal cohort studies have demonstrated that malalignment at the knee is associated with both incidence and progression of knee osteoarthritis [107, 108, 31, 109]. Cerejo et al [110], reported a similar finding over 18 months in subjects with KL grade 2 and 3 OA at baseline, however, the effect of varus alignment on medial JSN progression was smaller for those subjects with KL grade 0/1 (n=54). The effect of malalignment on osteoarthritis is attributed to its unequal influence on loading of the knee joint. In cases of varus deformity, more load crosses the medial compartment, and in valgus (knock-knee) alignment, more load crosses the lateral compartment. As discussed in section 2.3 lower limb malalignment is not necessarily a pathological study and 'constitutional varus' is seen in a high proportion of healthy individuals [32]. Whilst the geometric variables that contribute to this alignment have been recognised their individual effects on structural progression have not been investigated.

The static, single plane model of mechanical loading maybe limited. Dynamic

assessments of knee loading have demonstrated that increase in the adduction moment during gait is associated with increased medial compartment loading [111] and that clinically observed varus thrust is associated with progression but not incidence of medial compartment OA [112]. A recent systematic review failed to show any evidence of a causal link between estimates of knee joint loading during walking and structural progression of knee OA [113].

2.5.8.2. Risk factors for symptom progression

Pain and functional status in hip or knee OA has been shown to deteriorate slowly, with limited evidence for worsening after 3 years of followup, however, older age, greater BMI and increased knee pain elevate the risk of deterioration of functional status during that time-period [114].

As previously discussed, pain is a subjective experience which can be modified by factors which are not related to pathology within the knee. Pain severity significantly increases with increasing persistence of depressed mood [97] and improved baseline mental health and social support have both been shown to reduce the likelihood of a poor functional outcome over 3 years in patients with established OA [115]. These findings are important as psychological well-being is potentially modifiable and, if addressed, could lead to clinical improvements in the patients experience of pain [97].

A subject's body mass index is also modifiable. Weight loss has been shown to improve patient-reported symptoms in established knee OA [116]. A logical explanation for this improvement is that patients who lose weight experience a reduction in the weight being transmitted through the knee leading to fewer symptoms. However, the effects of weight loss on joint loading have not been able to explain this improvement in symptoms [117] and malalignment (which leads to increased joint loading) has not been shown to be associated with symptom progression.

There is still wide ranging conflict in the literature regarding knee OA progression

[106] and the relationship between risk factors for structural progression and symptom worsening warrant further investigation.

2.6. Early knee osteoarthritis

Neither the American College of Rheumatology (ACR) criteria or European League against Rheumatism (EULAR) recommendations discussed in section 2.5.2 provide criteria for the diagnosis of early knee osteoarthritis (EKOA) [118]. In an effort to synthesise the available information regarding knee osteoarthritis, Luyten et al described early knee osteoarthritis based on clinical and imaging findings with the following three criteria:

1. Pain in the knee (at least two episodes of pain for 10 days or more in the last year)
2. KL grade 0, 1 or 2 (osteophytes only)
3. One of the following two structural criteria:
    a) Arthroscopic findings of cartilage lesions
    b) MRI findings demonstrating articular cartilage degeneration and/or meniscal degeneration, and/ or subchondral bone marrow lesions

This pragmatic approach to the diagnosis of EKOA has not been validated in the literature.

2.7. Treatment options for knee osteoarthritis

The following section outlines the principle surgical and non-surgical treatment options available for knee osteoarthritis regardless of severity. Where applicable the

evidence for use in early knee osteoarthritis is provided. Whilst many surgical procedures have been proposed for the treatment of EKOA their efficacy in patients with EKOA in comparison to non-surgical interventions has not been widely reported.

2.7.1. Economic considerations

Symptomatic osteoarthritis of the knee is a leading cause of disability among older adults [119]. Direct healthcare costs are considerable. One study, from France, estimated annual costs of treating hip and knee OA to be €3.5 billion with hospitalisation incurring costs in excess of €11,000 per patient with knee OA [120]. In addition to this there are indirect costs incurred by informal care givers and loss of employment through disability which may substantially outstrip the direct costs incurred by the healthcare provider [121]. Any proposed interventions for this condition have to be sufficiently clinically effective in order to offset the considerable socio-economic costs of this disease.

2.7.2. Non surgical treatment

National Institute for Health and Clinical Excellence (NICE) has produced guidelines for the management of patients with all grades of knee osteoarthritis (including EKOA). Initially, NICE recommends a period of conservative management during which time clinicians are to provide accurate information to patients regarding the nature of the condition, its progression and management options [122].

The European League Against Rheumatism (EULAR) have published recommendations for the non-pharmacological management of hip and knee OA [123]. Initially patients should receive education with regard to the diagnosis and then an exercise and weight loss (if appropriate) program tailored to the individual should be implemented. In addition advice regarding appropriate footwear, walking aids and home

adaptations should be considered.

A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) has expanded on these recommendations and provided recommendations for non-pharmacological and pharmacological management specific to knee osteoarthritis [124]. In the presence of knee malalignment the use of knee braces and foot orthoses have been recommended as they may be effective in decreasing pain and joint stiffness [125]. A step-wise approach to pharmacological therapy is then encouraged starting with paracetamol escalating to non-steroidal anti-inflammatory drugs (NSAIDs). Short-term weak opioids can be considered in addition to NSAIDs in recalcitrant cases on the basis that combination therapy in patients has been shown to be beneficial [126]. If these interventions fail then intra-articular injection can be considered.

2.7.2.1. Hyaluronic acid injection

Hyaluronic acid is an essential component of synovial fluid and its visco-elastic properties contribute help in joint lubrication [127]. It has been described as an effective treatment for knee OA with beneficial effects on pain and function observed at different post injection periods but especially 5 to 13 week post injection [128]. However, a more recent randomised trial in subjects with moderate to severe knee osteoarthritis (n=337), a course of five intra-articular injections of hyaluronan did not improve pain, function or other efficacy parameters 3, 6, 9 and 12 months after treatment [129].

2.7.2.2. Corticosteroid injection

Corticosteroids have been shown to provide short-term relief in symptomatic knee OA [130], however, there is little to support their efficacy with regard to long-term symptom improvement or structural progression. Furthermore, laboratory investigations

have shown that the combinations of certain types of steroids and local anaesthetics have a cytotoxic effect on articular chondrocytes [131]. This raised concerns in general about its use in the management of knee OA but in particular in the management of subjects with early knee OA.

2.7.3. Surgical treatment

2.7.3.1. Arthroscopy

Arthroscopy is a minimally invasive procedure that is offered to people with osteoarthritis of the knee. Generally, two small incisions are made in the front of the knee enabling the passage of a fiberoptic camera through one incision and surgical instruments through the other. Many surgical procedures can be performed using this technique and in the context of knee OA such procedures are generally intended to promote a smooth excursion of the knee joint surface. This may be achieved by washing debris out of the knee joint (irrigation), removing torn or irregular cartilage (debridement or chondroplasty), reconstituting a degenerate meniscus (meniscal repair/ replacement), or promoting cartilage growth in areas of deficiency (subchondral bone marrow stimulation or autologous chondrocyte implantation).

The exact mechanism by which a smooth joint surface relates to pain-free movement is unclear. Evidence for arthroscopic irrigation is poor, with a previous Cochrane review concluding no benefit for joint lavage when compared to sham surgery or no intervention [132]. The trials included in this review did not stratify results based on stage of osteoarthritis. A further Cochrane review found no significant benefit for arthroscopic debridement compared to sham surgery or arthroscopic irrigation [133]. Interestingly, the one trial in this review that reported improved outcomes in the arthroscopic debridement group involved people with single degenerative lesions, suggesting less extensive disease [134].

Cartilage repair techniques aim to restore a smooth articular surface. Loss of cartilage and exposure of the subchondral bone leads to crepitation and pain [135], therefore any efforts to reduce friction or cover the subchondral bone may improve this. Trials in this area have involved isolated full-thickness cartilage lesions representing an advanced cartilage lesion which may or may not have concomitant osteoarthritis.

The meniscus is responsible for increasing surface area of the knee and dissipating load through the knee joint. Meniscal injury causes symptoms by promoting inflammation and pain. Meniscal resection, either total or partial, has been used where the meniscus is irreparably damaged. However, there is growing concern over the effect of this operation, as it may in fact accelerate progression of osteoarthritis [136]. Meniscal repair is usually performed in the context of isolated injuries. Meniscal replacement in the form of cadaveric (allograft) or synthetic grafts is appealing with studies showing improved symptoms and function [137], however, randomised controlled trials investigating meniscal allograft are lacking.

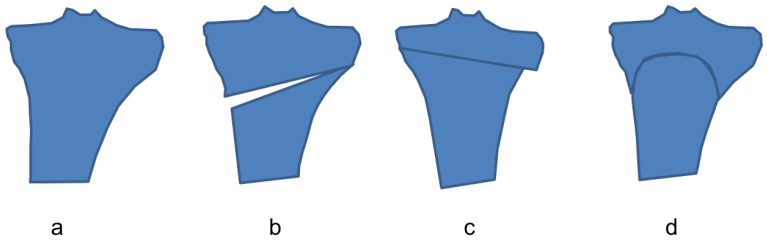
2.7.3.2. High tibial osteotomy

The basic principle of osteotomy surgery is to cut and re-shape bone in order to correct an underlying deformity. In the case of unicompartmental knee osteoarthritis the objective is to transfer weight bearing away from the compartment that is failing and shift it towards the compartment that has little or no pathology. Central to this is the concept that malalignment plays a pivotal role in both the incidence and progression of OA within the knee as discussed in 2.5.8.

A high tibial osteotomy (HTO) is the most widely recognised and practiced osteotomy for the treatment of medial compartment OA with associated metaphyseal varus deformity of the proximal tibia. Broadly speaking their are three methods that can be employed to achieve the desired correction. These include a closing wedge, an opening wedge and a dome osteotomy (figure 2.7.1). Traditionally, the objective of

surgery is to push the patient into valgus alignment and transfer weight-bearing into the disease-free lateral compartment. The objective being to reduce pain and slow progression of disease.

Figure 2.7.1.: Schematic diagram of the three broad categories of high tibial osteotomy for medial compartment osteoarthritis associated with metaphyseal tibia vara (a); opening wedge (b), closing wedge (c) and dome osteotomy (d)



The lateral closing-wedge HTO (CWHTO) was popularised by Coventry through his work at the Mayo clinic [138]. He secured his closed wedge with a staple and achieved good outcomes with 66% survival rate reported at 10yrs [139]. Subsequently, this has been the most widely reported and practiced surgical technique. Traditionally, a closing wedge osteotomy has been considered a more stable construct as the large surface area of cancellous bone contact means high rates of union can be expected. However, the procedure does have some inherent limitations. Once the wedge of bone has been resected the surgeon is committed to the osteotomy, whilst more bone could be resected it is not possible to lessen the osteotomy mid-procedure. The lateral approach to the knee joint leaves the common peroneal nerve vulnerable to injury and lateral ligament laxity may arise if the fibula head becomes elevated. A simultaneous fibula osteotomy or disruption of the proximal tibiofibular joint may be required to prevent this.

More recently, a medial opening-wedge HTO (OWHTO) has gained popularity. The approach is on the medial side of the knee avoiding injury to the common peroneal nerve and loss of tension in the lateral collateral ligament. It is also possible to

fine-tune the size of the correction once the osteotomy has been made. However, concerns have been raised over higher rates of non-union and morbidity associated with donor site pain from the iliac bone graft required to filled the defect [140]. Recent developments in surgical technique for opening wedge HTO have addressed many of these issues. In addition to a transverse osteotomy of the posterior tibia a second osteotomy can be performed in the coronal plane underneath the tibial tuberosity. This biplanar osteotomy provides rotational stability to the osteotomy [141]. Rigid fixation of the osteotomy allows for early mobilisation and high rates of union can be expected without the need for bone graft and with minimal slope change in the sagittal plane [141].

Lateral compartment OA with valgus deformity is a less common phenotype and consequently there are fewer studies supporting the use of osteotomy in this patient group. A distal femoral varus osteotomy (DFVO) is typically achieved using a medial closing wedge technique (review), however, a lateral opening wedge osteotomy can also be performed to correct the underlying deformity.

A combined distal femoral and high tibial osteotomy can be performed for medial compartment OA associated with varus alignment. This technique enables a large correction to be achieved without compromising joint line obliquity [142].

Osteotomy can be considered in combination with other joint preserving surgery including cartilage repair and meniscal transplant. Some have suggested that such regenerative procedures should not be considered unless the affected compartment has been effectively unloaded [143].

Patient Selection As with any orthopaedic procedure careful patient selection is key to a successful outcome. Advances in osteotomy are challenging the traditional concepts of an 'ideal' osteotomy patient. Favourable outcomes have been demonstrated in the young [144], the old [145], smokers [146] and those with a raised BMI

[146]. Patients should be made aware that although a return to sports is expected they will typically not recover their pre-pathology level of activity [147]. Traditionally, osteotomy surgery was reserved for end-stage 'bone on bone' unicompartmental osteoarthritis. However, in line with developments in surgical technique, the indications for this procedure are evolving. An expert panel from ISAKOS defined the criteria for a patient undergoing HTO for medial compartment osteoarthritis [148] (Table 2.1).

Table 2.1.: Selection criteria for high tibial osteotomy as defined by ISAKOS, 2005

Ideal	Possible	Not suited
Isolated medial joint line pain	Flexion contracture $< 15^0$	Bi-compartmental (medial and lateral) OA
Age (40-60yrs)	Age 60 -70yrs or <40yrs	Fixed flexion contracture $>15^0$
BMI < 30	ACL, PCL or PLC insufficiency*	Obese patients
High-demand activity but no running or jumping	Moderate patellofemoral OA	Meniscectomy in the compartment to be loaded by the
Malalignment $<15^0$	Wish to continue all sports	osteotomy
Metaphyseal varus; TBVA $>5^0$		
Full range of movement		
Normal lateral and patellofemoral compartment		
Ahlback grade I to IV		
No cupula		
Normal ligament balance		
Non-smoker		
Some level of pain tolerance		

*ACL, anterior cruciate ligament, PCL posterior cruciate ligament; PLC, Posterolateral corner.

An important consideration is not only the underlying deformity but the site of that deformity. Bonnin and Chambat reported superior clinical outcomes for pa-

tients undergoing osteotomy for medial OA for patients with a constitutional varus deformity of the proximal tibia. They proposed using the Tibia Bone Varus Angle (TBVA) to differentiate those patients with a congenital varus deformity from those with an acquired varus deformity [149]. Osteotomy in patients with a TBVA $>5^0$ was described as a curative procedure compared to those with a TBVA $<5^0$ in whom such surgery was felt to be a palliative measure [149]. The anatomy of the distal femur may also play a part in outcome for HTO surgery. An overly varus distal femur has been associated with recurrence of varus deformity following surgery [150]. However, a recent study has challenged these findings determining that that neither varus inclination of the proximal tibia or distal femur influenced long-term survival of HTO [151] over 10 years. Clearly, the importance of pre-operative alignment is conflicted in the current literature and the so to is the definition of an ideal osteotomy patient.

Planning the correction. Once the deformity has been established it is necessary to determine the desired correction point. Traditionally, for medial compartment OA associated with varus deformity, patients have been deliberately placed into a valgus position. Biomechanical studies have suggested that in a well-aligned limb (neutral) the majority of weight still passes through the medial compartment [152]. In the presence of an already failing compartment it is understandable that surgeons would want to transfer a greater proportion of the weight into the disease free lateral compartment by placing the patient into valgus. The so-called 'Fujisawa-point' has been widely adopted due to the superior results achieved when patients had a weight-bearing line positioned at approximately 62% of the medial-lateral tibial plateau width [153].

Once the desired correction has been determined it is possible to establish the size of the correction required using the pre-operative weight-bearing long leg radiograph. The two most commonly used techniques for planning the desired correction were

popularised by Dugdale [154] and Miniaci [155]. Several planning software packages are widely available which incorporate these techniques into a user friendly interface. Good inter- and intra-observer reliability has been demonstrated for many of these planning tools [156].

Outcome Osteotomy around the knee for the treatment of unicompartmental OA is a well-established and safe surgical procedure. It is, however, not without complication and understanding the benefits and risks of surgery is essential in order to enable patients to make an informed decision about whether or not to proceed.

The majority of the literature concerning outcomes from surgery concern closing wedge HTO. A systematic review of this procedure showed general complications for this procedure include venous thrombo-embolism (3.1%), infection (4.6%), neuromuscular complications (9.8%), intra-articular fracture (0-20%), delayed union (6.6%) and non-union (2.2%) [157]. Similar complications are seen in opening wedge HTO and, historically, there has been little to distinguish the two procedures with regard to adverse events and clinical outcome. However, using new techniques with stable fixation methods very low complication rates have been recorded. In a series of 262 opening wedge HTO procedures using the Tomofix® locking plate system, only two cases of delayed union and one case of deep infection were reported [158].

Survivorship of HTO is usually considered with regard to conversion to total knee replacement. A large registry based study including over 3,000 patients from Finland revealed an overall survivorship of 89% at 5yrs and 73% at 10yrs [159]. This study revealed poorer outcomes in female subjects and in those aged over 50yrs. Other studies have suggested that under-correction leads to reduced survivorship of HTO [139].

Details regarding distal femoral osteotomy are more limited. A review of DFO procedures estimated survivorship for a medial closing wedge DFO to be approxim-

ately 80% at 40 months dropping to 45% at 15yrs [160]. Importantly, a recent study showed that neither age or concomitant surgery (micro fracture) had a significant affect on patient reported outcome [161].

A previous Cochrane review concluded that although there was good evidence to support the fact that high tibial osteotomy (HTO) improves function and pain in people with osteoarthritis, there is significant heterogeneity of the clinical trials to date [162]. Patient selection, operative technique, and degree of correction have all been demonstrated to influence outcome [163, 140, 139]. Over-correction leads to a significant distortion of the local anatomy and has led to some concern over the survivorship of any future arthroplasty surgery should it be required. In particular UKA is contraindicated for patients who have previously undergone HTO [164]. Recently a more individualised approach has been advocated [165]. This uses the weight-bearing line to determine the desired correction point and suggests a modest (more neutral) correction for patients with less advanced OA. There is currently little evidence to support this more modest correction and no studies to date have reported results for a neutralising HTO in symptomatic EKOA.

2.7.3.3. Other load modifying procedure.

Chronic medial compartment joint-loading can be modified us- ing an extracapsular device. Devices such as the KineSpring® (Moximed Inc, Hayward, CA, USA) have been developed to partially absorb the load passing through the medial compartment without compromising the joint surface [166]. It is specifically indicated for medial compartment osteoarthritis and consists of a load absorber that can absorb a maximal load of 30 pounds in weight, with promising results in the short and medium term [166, 167].

Metallic interpositional devices are designed to remedy medial joint space narrowing caused by osteoarthritis; in so doing, a varus (bow-legged) knee can be placed into

a more neutral alignment [168, 169]. Such devices can be inserted using minimally invasive techniques and without the need for resection of underlying bone. Reports of high revision rates and unpredictable outcomes have raised concerns over these implants [170].

Knee joint distraction is a surgical technique that uses an external fixation device to separate the knee joint surfaces for a defined period of time. Joint distraction aims to reduce mechanical stresses on the joint surface, prevent further wear and tear of the cartilage, and allow chondrocytes to initiate repair [171]. One study has demonstrated both symptom improvement and cartilage repair using this technique [171], however, the exact mechanism by which cartilage regenerates under these conditions remains unclear.

2.7.3.4. Arthroplasty surgery

Total knee arthroplasty involves replacing the surfaces of the knee joint with artificial implants. The implants are usually made from a combination of metal alloy and high-density plastic, and require bone to be resected in order to accommodate them. Knee arthroplasty is an established technique for end-stage osteoarthritis, with good clinical outcomes described for both total and unicompartmental arthroplasty [172].

Unicompartmental knee arthroplasty (UKA) UKA involves replacing the surfaces of a single diseased compartment (medial, lateral, or patellofemoral), rather than the whole joint surface. Whilst lateral compartment [173] and patellofemoral compartment [174] arthroplasties have been investigated, the most common unicompartmental arthroplasty is medial. Broadly speaking the UKA can be divided in to 'fixed' or 'mobile' depending on the design of the bearing surface. Similar survival, function and complication rates have been published for both implant designs [175, 176].

Various advantages have been proposed for UKA over the more common total knee arthroplasty (TKA). These include a more rapid recovery, lower re-admission rates and reduced morbidity and mortality [5]. However, UKA is associated with a higher re-operation and revision rate [5]. Early results from an ongoing trial comparing UKA to TKA have described a modest improvement in outcome at 1 year for patients undergoing UKA compared to those undergoing TKA [177].

Patient selection for UKA In order to limit the need for revision and enhance the longevity of the prosthesis it is essential that appropriate inclusion criteria are consistently adopted. In 1989, Kozinn and Scott published a series of contra-indications for UKA:

- Age <60 yrs
- Non obese (<82 kgs)
- High patient activity level
- Rest pain (indicating a possible inflammatory arthritis)
- ROM <0-90^0
- Patello-femoral pain
- Exposed subchondral bone beneath the patella or in a weight-bearing area of the opposite compartment

It has been argued that these indications are too narrow with only 4% of knees suitable for arthroplasty surgery meeting the clinical and radiological standards described [178]. In particular the presence of radiographic patello-femoral OA and or anterior knee pain has not been shown to significantly affect outcome [179, 180].

Patient selection for mobile-bearing UKA Currently, patient selection for mobile-bearing UKA is based on radiographic criteria which is assessed using standing antero-posterior, valgus stress (in 20^{o} flexion), true lateral and skyline radiographs [181]. These include:

- bone-on-bone osteoarthritis (OA) in the medial compartment
- retained full thickness cartilage in the lateral compartment
- a functionally normal medial collateral ligament (MCL)
- a functionally normal anterior cruciate ligament (ACL)

In addition, severe damage of the PFJ with bone loss, grooving or subluxation should be excluded [179, 180]. The use of UKA is not routinely extended to those with less severe osteoarthritis, as it is associated with a poorer outcome [8, 7, 182]. Whilst there is evidence that some subjects with partial thickness cartilage loss do well [8] current radiographic criteria have not been able to distinguish between those who will and will not do well. No studies have attempted to use other imaging modalities in order to broaden the inclusion criteria for this intervention.

2.7.4. The treatment gap

Many patients with early radiographic knee arthritis have clinical symptom profiles equivalent to those with advanced "bone on bone" disease [4]. Many of these patients will continue to be symptomatic following a trial of conservative management. The role of surgery for such individuals is unclear. High tibial osteotomy may be beneficial in certain groups of individuals but current practices for this procedure are discordant and not widely available in the UK. Other surgical procedures have been reported but their efficacy in comparison to non-surgical interventions has not been investigated. Waiting for sufficient time to pass in order to demonstrate progression to "bone

on bone" arthritis and candidacy for arthroplasty surgery, potentially exposes the patient to a prolonged period of painful disability; 'the treatment gap' [10].

2.8. Synthesis of the literature

Early knee osteoarthritis is evidently common, hard to treat and can be debilitating for symptomatic individuals.

Identifying patients most likely to progress and those who are at low risk of progression enables resources into health care interventions and future research to be allocated appropriately [183]. Whilst a number of prognostic factors are associated with radiographic progression of knee OA including pain[105], meniscal extrusion [184] and genu varum [31, 108], it is not known which factor is the strongest predictor and it is hard to translate the available evidence directly to the clinical setting.

Varus alignment is common and is frequently seen in healthy individuals (32% of men and 17% of women) [32]. 'Constitutional varus' is a term that has been used to describe the varus deformity seen in healthy individuals and the most important contributors to this alignment are thought to be the medial proximal tibial angle (MPTA) and the mechanical lateral distal femoral angle (mLDFA) [32]. No study to date has looked at the role of these individual alignment variables on progression of knee osteoarthritis. The identification of such patient-based prognostic indicators is important as it enables clinicians to more accurately predict an individuals likelihood of disease progression and direct them to appropriate interventions [104]. For example, proximal tibia vara and distal femoral valgus are potential 'surgical targets' that can be corrected with a surgical intervention called an osteotomy.

There are several surgical procedures that target the structural changes seen in OA. These include arthroscopic and load-modifying procedures as well as arthroplasty surgery and novel surgical techniques (e.g. Kinespring TM). The current lit-

erature concerning osteoarthritis of the knee frequently takes an intervention-based approach. Where early osteoarthritis of the knee is considered there is often a focus on non-surgical/pharmacological management [185, 186, 187]. A systematic review of surgical intervention for EKOA to clarify whether surgery is superior to non-surgical intervention has not been done. As such it is not clear which, if any, of the available surgical modalities is the most effective treatment for patients with symptomatic EKOA.

The efficacy of arthroscopy has received significant attention in the medical literature. Whilst there are undoubtedly questions remaining regarding its role in EKOA, the trials based research required to compete with the exisiting literature is beyond the scope of this thesis. Knee distraction therapy is an interesting development in the management of EKOA, however, it is currently a niche surgical intervention with only one centre in Europe offering published reports on its efficacy [188]. It is not routinely practiced in the UK and as such implementing and assessing its usefulness within the context of this thesis was not possible.

A valgising high tibial osteotomy (HTO) is an alternative treatment option. Whilst outcomes from HTO surgery have been shown to be beneficial there is no agreement regarding patient selection or optimal correction point. Trials studying the efficacy of HTO suffer from marked heterogeneity [162]. Traditionally, surgeons have aimed to over-correct patients into valgus, the so-called 'fujisawa point' [153]. There is concern about the potential negative impact of this type of correction on subsequent arthroplasty, should it be required. Certainly, UKA is contra-indicated in patients who have previously undergone HTO [164]. More recently a conservative approach has been advocated [165]. It is not known whether this more neutral correction offers a significant benefit for patients with symptomatic EKOA. Clearly, well-designed, prospective trials with strict selection criteria and a consistent approach are greatly

needed.

As previously stated unicompartmental knee arthroplasty is not routinely offered to patients with EKOA. Waiting for sufficient time to pass in order to demonstrate progression to "bone on bone" arthritis potentially exposes patients with EKOA to a prolonged period of painful disability [10]. High tibial osteotomy may be considered in younger patients with an associated varus deformity, however, in older patients the role of UKA in the presence of radiographic partial thickness osteoarthritis remains unclear. A proportion of patients with EKOA on plain film radiographs will demonstrate full thickness disease on MRI. It is not known whether these findings are sufficient to warrant proceeding to UKA.

The James Lind Alliance is an independent non-profit making initiative which brings patients, carers and clinicians together in order to identify and prioritise clinical uncertainties regarding conditions and the effects of treatments [189]. This organisation has recognised EKOA as a condition which has significant uncertainty surrounding it. A priority setting partnership (PSP) was established by this group to identify critical unanswered questions regarding both the surgical and non-surgical management of this condition (http://www.jla.nihr.ac.uk/top-10-priorities; last accessed 1st Sept 2017). These questions that have been deemed important by clinicians, carers and most importantly patients, lend support to the research questions proposed in this thesis (see figure 1.1.1)

2.9. Overall scope of the thesis

The overall scope of this thesis is to assess the benefits and harms of early surgical intervention for the management of knee osteoarthritis. It will achieve this by describing the natural history of painful early knee osteoarthritis and identifying risk factors that pre-dispose to more rapid disease progression. It will establish the cur-

rent evidence for surgical intervention in this patient group and will report outcomes for patients who have undergone early surgery for this condition. In combination these studies will provide support for an evidence-based surgical pathway for patients with osteoarthritis of the knee and provide answers to key questions that have been proposed by clinicians, patients and their carers.

2.10. Specific objectives

1. To establish the prevalence of symptomatic and structural progression in painful early knee osteoarthritis and identify patient characteristics that are associated with a more rapid progression.

2. To establish the current evidence for surgical intervention in early knee osteoarthritis and report on surgical interventions that are safe and effective in this patient group.

2.11. Structure of thesis

The following chapters are presented in this thesis:

- Chapter 2 presents a focussed literature review of current research into osteoarthritis of the knee.

Chapters 3, 4 & 5 are epidemiological studies that describe symptom and structural progression in EKOA.

- Chapter 3 offers a detailed description of the natural history of symptomatic EKOA using data from the Osteoarthritis Initiative (OAI) a large prospective cohort of subjects from the United States of America. It outlines the preval-

ence of symptom and structural progression in EKOA and explores patient characteristics that predispose to this progression.

- Chapter 4 reports a further cohort study using data from the OAI. It takes a close look at the factors that contribute to lower limb malalignment and establishes whether or not they are of equal importance in predicting progression in EKOA.

- Chapter 5 explores the patterns of structural progression seen in subjects with EKOA. It uses semi-quantitive MRI analysis to identify whether the pattern of structural progression seen in EKOA varies in subjects with and without proximal tibia vara.

Chapters 5, 6 & 7 are concerned with providing evidence for early surgical intervention in osteoarthritis of the knee

- Chapter 6 describes a systematic review which follows the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards for reporting to assess the current evidence for surgical intervention for the management of symptomatic EKOA.

- Chapter 7 presents a prospective cohort study of patients with EKOA undergoing a neutralising HTO. Short-term (1yr) and mid-term (3-5yrs) outcomes for patients are reported and factors that contibrute to a good or poor outcome are discussed.

- Chapter 8 reports a retrospective study involving patients with radiographic partial thickness disease and a pre-operative MRI confirming full thickness cartilage loss (RxPT/MRI-FT) who have undergone unicompartmental knee arthroplasty. Outcomes for this cohort of patients are compared to a matched cohort of patients with radiographic full thickness disease (RxFT).

Chapter 9 outlines the key findings presented in this thesis and their implications on clinical practice. Recommendations for future work in this area are discussed.

3. Progression in Early Symptomatic Osteoarthritis of the Knee: a description based on data from the Osteoarthritis Initiative (OAI)

3.1. Introduction.

The preceding chapter has identified EKOA as common, hard to treat and debilitating for symptomatic individuals. Current best practice for this condition is not known with patients described as being in a 'treatment gap' [10]. The National Institute for Health and Clinical Excellence (NICE) has produced guidelines for the management of patients with all grades of knee osteoarthritis, including EKOA, which requires clinicians to provide accurate information to patients regarding the nature of the condition, its progression and management options [122]. This represents a significant challenge, particularly as many aspects of the natural history of knee OA remain unclear, unknown or are conflicted in the literature.

Whilst some predictors for the progression of established knee OA (KL grade $\geq$2) have been widely accepted (e.g. age, radiographic severity of OA, malalignment,

ACL rupture, baseline symptoms) the effects of other variables are inconsistently reported in the literature (e.g gender, BMI and baseline pain) [106]. It is not known if these predictors remain important in those symptomatic individuals with the earliest, radiographic changes (KL grade =1). A clear understanding of the predictors that make structural progression, symptom worsening or non progression more likely in individuals with symptomatic EKOA is necessary.

With this in mind a longitudinal study has been designed to identify predictors of progression and importantly non-progression in a cohort that reflect subjects in the 'treatment gap'. It will investigate the rates of symptom and structural progression and will describe patient characteristics that are associated with it. Furthermore, it will describe the influence of lower limb alignment on a subset of individuals within this cohort. The subsequent chapter will investigate the individual alignment variables that contribute to overall lower limb deformity and will determine if they are of equal importance with regard to structural and or symptom progression in EKOA. In so doing these two chapters will enable clinicians to provide patients with clear, consistent information regarding the natural history of symptomatic EKOA.

3.2. Aims.

- To describe the prevalence of symptomatic and structural progression in early symptomatic knee OA
- To identify risk factors that predict symptom and or structural progression in symptomatic EKOA
- To identify patient factors that are associated with non OA progression

3.3. Materials and methods.

The Osteoarthritis Initiative (OAI) is a multi-centre, longitudinal, observational cohort study focusing primarily on the natural history of knee OA [190]. Its publicly available archive allows a broad spectrum of clinicians to study a wide-range of radiographic, biochemical and genetic measurements as biomarkers and or potential surrogate endpoints for knee OA [190]. Since 2004, it has recruited 4,796 subjects, ages 45-79 yrs who either have or are at high risk of developing osteoarthritis. Within OAI, osteoarthritis is defined as "knee pain, aching or stiffness in or around the knee on most days "for at least one month" during the previous 12 months and definite tibiofemoral osteophytes seen on fixed flexion radiographs (equivalent to KL grade 2 or more). Based on this definition the whole OAI cohort has been divided into three groups:

- Progression cohort (n=1390): subjects who meet the criteria for knee OA at baseline in at least one knee
- Incidence cohort (n=3284): participants who do not meet the criteria for knee OA at baseline but who have risk factors for its development
- Control cohort (n=122): participants who do not meet the criteria for knee OA at baseline and who do not have risk factors for its development

Due to previously published discrepancies between peripheral and central site readings [191], baseline radiographic grades for participants within OAI were retrieved using datasets from central readers and the cohort assignment of each individual, defined by peripheral site readings, was ignored. For the purposes of this study a cohort of subjects was created de novo using datasets obtained at recruitment.

3.3.1. Study design

A longitudinal cohort study was designed to investigate the rates of symptom and structural progression seen in patients with symptomatic EKOA over 24 months. Analyses of baseline patient characteristics (co-variates) were performed in order to identify markers for progression in patients with symptomatic EKOA.

3.3.2. Study sample

JP registered with the OAI and with their permission obtained all relevant datasets (http://oai.epi-ucsf.org/datarelease/; search date 8th Jan 2016;). A EKOA cohort was identified and selected from the main OAI dataset. Eligible subjects for the EKOA cohort had at least one knee with a Kellgren Lawrence (KL) grade 1, 2 or 3 and symptoms in the same knee at recruitment. Symptoms were defined as knee pain, aching or stiffness: more than half the days of a month in the past year in the same knee. If a subject had two eligible knees then both knees were enrolled into the study. In order to be eligible for the study both clinical and radiographic outcomes at 24 months had to be available.

A subset of the EKOA cohort had values for lower limb mechanical alignment taken at 12 months; hip knee ankle angle (HKA). This EKOA + HKA cohort was analysed separately to evaluate the effect of mechanical alignment on OA progression. Twelve months from recruitment was the earliest time-point that any LLRs were performed. The HKA was determined from centralised readings and defined as the angle between the line through the centre of the femoral head and the centre of the knee and the line through the centre of the knee and the centre of the tibio-talar joint.

3.3.3. Outcomes

Outcomes were collected within the OAI at 24 months and included both structural and symptomatic markers of progression. This allowed sufficient time for progression to occur and also reflected a typical period of 'watch and wait' employed in a clinical setting before any surgical intervention is considered see Figure 1.1.1.

Symptom progression Symptom progression was defined as an increase in WOMAC score (symptom worsening) of >9 points at 24 months compared to baseline [192]. Subjects with severe symptoms at baseline (WOMAC >91 points) who could not progress by more than 9 points were defined as progressing if their symptoms were sustained (WOMAC>91 points) at 24 months. A total of 525 individuals (10.1%) had missing WOMAC scores from the whole OAI dataset at 24 months.

There is a risk that this definition of symptom worsening may reflect short-term fluctuations in disease activity rather than true symptom progression. A persistent deterioration in knee symptoms (WOMAC >9 points), from baseline to 12 months and then again from 12 months to 24 months was also investigated as a potential outcome for symptom progression.

Structural progression Several outcomes were used to describe structural progression in EKOA.

- Progression by $\geq$ 1 KL grade
- Progression to end-stage osteoarthritis (KL grade 4)
- Total knee arthroplasty
- Joint space narrowing progression in medial compartment (>0.7mm) [193]

Subjects who were unable to progress as their joint space was already too narrow at baseline (<1mm) were excluded from the study as their disease was too severe to be considered EKOA. Subjects who progressed to TKA at 24 months were assigned a Kellgren Lawrence grade of 5. These subjects were excluded from the cohort when assessing medial joint space narrowing. A total of 97 individuals (1.75%) had missing joint space narrowing scores from the whole OAI dataset at 24 month. In the OAI, the intraclass correlation for a repeat measurement by the same observer for the change in minJSW over 36 months in OAI knees was 0.96 and the weighted kappa for KL grade scoring was 0.75.

3.3.4. Variable selection

The OAI provides a wealth of information on subjects at recruitment (http://oai.epi-ucsf.org/datarelease/). Variables for this study were chosen to reflect information or investigations that are routinely available in an orthopaedic clinic setting. Variables of interest were selected *a priori* and included age, gender, BMI, number of co-morbidities, smoking status, race, employment status, previous history of knee surgery. Adjustments were made to some variables to facilitate their incorporation into the statistical models and subsequent interpretation. Employment status was converted from a categorical variable with 4 possible outcomes into a binary outcome (paid work vs not in paid work). Smoking status was converted from a categorical variable with four possible outcomes to a binary outcome (any smoking history vs no smoking history). Those with a positive smoking history included 112 current smokers and 607 ex-smokers. The majority of participants in the EKOA cohort self-reported their ethnic origin as black or white (97.1%). For this reason, the variable for race was simplified to a binary outcome (white vs non-white).

3.4. Analysis.

Baseline demographic variables were compared between the three groups; the whole OAI cohort, the EKOA cohort and the EKOA + HKA cohort. Significant differences were identified using chi-squared, independent samples t-test or Wilcoxon-Mann-Whitney tests depending on whether the variable of interest was categorical, parametric or non-parametric in nature.

Variables used to describe symptom and structural progression were compared at baseline and at 24 months using chi-squared, paired t-test or Wilcoxon-Signed rank test depending on whether the variable of interest was categorical, parametric or non-parametric in nature. This enabled a description of symptom and structural progression for the EKOA cohort as a whole.

Subjects demonstrating symptomatic and structural progression were identified and total counts were expressed as a percentage of the cohort as a whole. The outcomes for structural progression were assessed to determine which occurred most frequently and receiver operating characteristic (ROC) curves were used to identify which structural progression variable was more able to discriminate between those subjects with and without symptom worsening. This outcome (JSN) then became the indicator for structural progression in subsequent regression analysis.

All statistical analyses were performed using knee level data. Logistic regression models with generalised estimating equations (GEEs) were used to account for the potential correlation of observations that may arise from knees belonging to the same individual. Using this model the association between baseline variables and subsequent symptom or structural progression over 24 months was investigated. Each variable of interest (see 3.3.4) was added to the model in turn to assess its direct affect on the outcome of interest. Multivariate analysis, with all variables included, was then performed to explore and quantify the influence of these variable on OA progression.

All models were adjusted for baseline joint space width (JSW) and baseline WOMAC score. Relationships between predictor variables and outcome were expressed as Odds Ratios (OR) and a p -value <0.05 was considered statistically significant. The independent variables included in the model were tested for collinearity using the variance inflation factor (VIF).

The statistical approach described above reflects the fact that this study is trying to determine whether or not patient characteristics seen in an orthopaedic clinical setting lead to progression of osteoarthritis. More exhaustive predictive modelling involving all potential predictors and subsequent backward selection of the included variables was not undertaken. This data mining approach would have included many variables that may not be clinically relevant or freely available in a clinical setting in order to predict OA progression.

Not all subjects had baseline values for lower limb alignments; hip knee ankle angle (HKA). Those that did were were included in a 'EKOA + HKA' cohort. The regression model described above was repeated for this 'EKOA + HKA cohort' and data for HKA was incorporated into it.

All statistical analysis was performed using Stata 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

3.5. Results.

1,634 knees from 1,182 subjects were included in the study.

A subset of 993 knees from 699 subjects from within the EKOA cohort had values for lower limb alignment at 12 months (EKOA + HKA cohort).

3.5.1. Characteristics of the study population

Table 3.1 outlines the baseline characteristics of the three groups and any significant differences between them.

The EKOA cohort differed from the OAI cohort as a whole with a significantly higher BMI (p<0.001), fewer white subjects (p<0.001) and fewer subjects with no co-morbidities (p<0.001) observed in the EKOA cohort. Similar differences were observed in the EKOA + HKA cohort when compared to the OAI cohort. A significant difference in race was seen between the EKOA cohort and EKOA + HKA cohort was observed with fewer white subjects seen in the EKOA + HKA cohort (p=0.03).

Table 3.1.: Characteristics of the study cohorts

	OAI cohort (n=4,796)	EKOA cohort (n=1,182)	EKOA + HKA cohort (n=699)
Age (yrs) (mean)	61.2	60.9	60.7
Sex (% female)	58.5%	57.5%	56.9
BMI (kg/m^2) (mean, S.D.)	28.6, ±4.8	30, ±4.9*	30.1, ±4.8*
Race (% white)	79.1	71*	66.4*†
Co-morbidities (%none)	75.4	70*	70.4*
% employed	61.7	62.3	63.5
% smoker	6.6	6.8	7.5

*Indicates a significant difference in value compared to the OAI cohort (p = <0.05)
†Indicates a significant difference in value compared to the EKOA cohort (p = <0.05)

3.5.2. Symptom progression

The mean average WOMAC score for the EKOA cohort improved at 24 months (mean= 19.6, S.D 17.1) compared to baseline (mean= 23.1, S.D 17.3) (p <0.001). A

total of 268 subjects (16.4%) demonstrated symptom worsening (WOMAC>9 points) at 24 months compared to baseline. Figure 3.5.1 and 3.5.2 illustrates the improvement in WOMAC score seen at 24 months.

Very few individuals in this cohort demonstrated symptom progression from baseline to 12 months and again from 12 months to 24 months. Table 3.2 illustrates the total number of individuals who experienced a significant symptom worsening at 12 months, and subsequent progression from 12 months to 24 months (n=69). Due to the low occurrence of this outcome it was decided to use symptom worsening at a single time-point of 24 months.

Figure 3.5.1.: Kernel Density graph illustrating the distribution of WOMAC scores at baseline and at 24 months; EKOA cohort

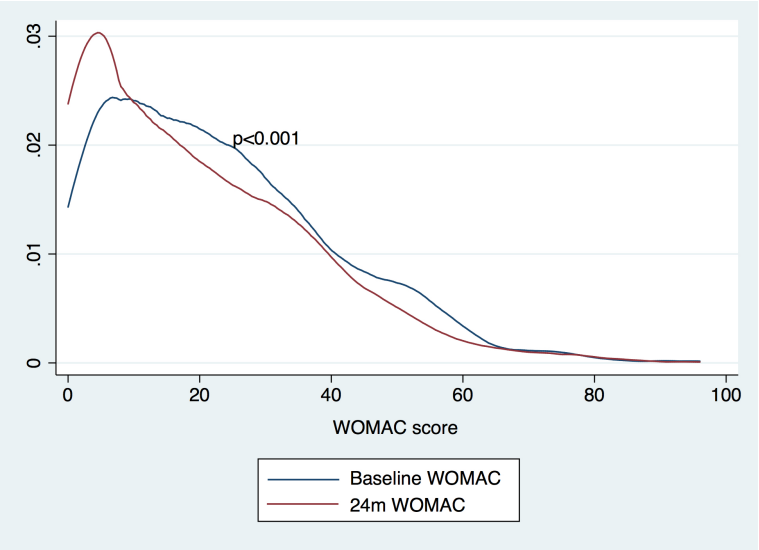
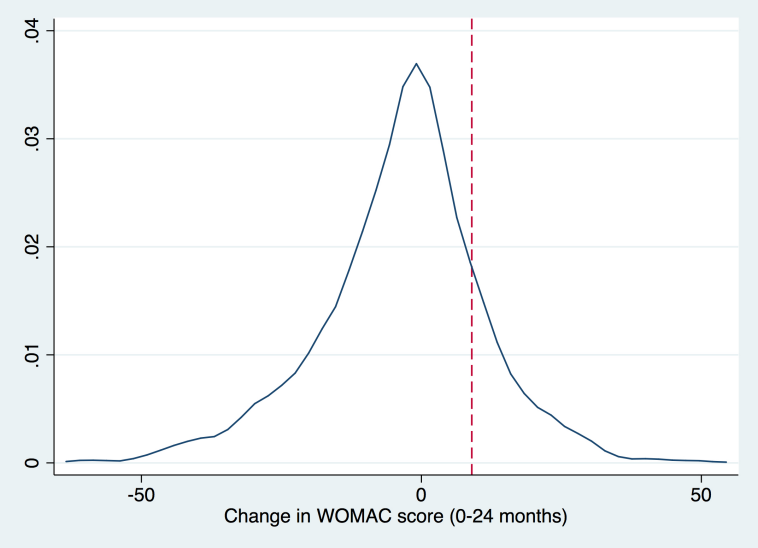


Figure 3.5.2.: Kernel Density graphs illustrating the distribution of change in WOMAC score from baseline to 24 months across the EKOA cohort



Legend: Dashed red line indicates the threshold for symptom worsening change in WOMAC= 9 points

Table 3.2.: Table showing knee level data for symptom worsening (WOMAC >9 points) from baseline to 12 months and from 12 months to 24 months; EKOA cohort

		Symptom worsening (12 months to 24 months)	
		No	Yes
Symptom worsening (baseline to 12 months)	No	1,056 (64.6%)	298 (18.2%)
	Yes	211 (12.9%)	69 (4.2%)

3.5.3. Structural progression

Structural progression was seen in the EKOA cohort over 24 months regardless of outcome measured; KL grade progression (p<0.001) and JSN progression (p<0.001). 15.4% of individuals progressed a KL grade ≥1. 16.4% of individuals demonstrated JSN progression of more than 0.7mm over 24 months. 1 in 20 individuals in the EKOA cohort progressed to end-stage osteoarthritis (KL grade=4) and 18 individuals (1.1%)

had a TKA in the index knee within 24 months of recruitment. Table 3.3 outlines the KL grade seen at 24 months compared to baseline scores.

Table 3.3.: Table of KL grades seen at recruitment and at 24 months; EKOA cohort

Baseline KL Grade		24 month KL Grade				
		1	2	3	4	5*
	1	200 73.53%	58 21.3%	13 4.8%	0 0%	1 0.37%
	2	0 0%	735 89.1%	80 9.7%	6 0.7%	4 0.5%
	3	0 0%	0 0%	558 83.4%	76 14.2%	13 2.42%

*KL Grade 5 represents those subjects who have undergone TKA

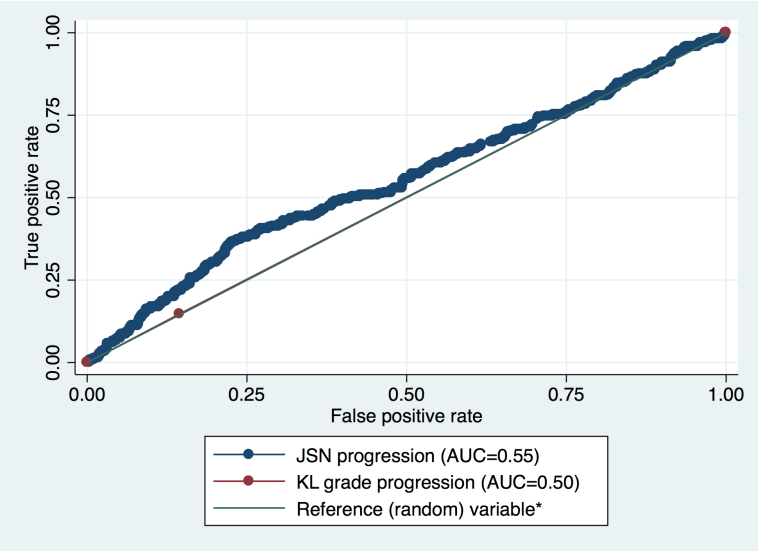
3.5.4. Symptom and structural progression

The majority of individuals showed neither symptom or structural progression (62.2%). Those that experienced a worsening of symptoms over 24 months frequently showed no structural change in terms of either KL grade (84.7%) or JSN (73.5%) progression. More individuals with JSN progression (22.3%) experienced symptom worsening at 24 months than those with KL grade progression (16.3%).

ROC curve analysis demonstrated that neither structural progression variable was good at discriminating those subjects with symptom worsening at 24 months (see figure3.5.3). However, the area under the cover (AUC) was greater for JSN progression (AUC=0.55) than for KL progression (AUC=0.50). The AUC of 0.50 seen for KL progression is equivalent to a completely random variable i.e. positive or negative KL grade progression is completely unrelated to the symptom worsening status of the individual. As such JSN progression was selected as the outcome for structural

progression for subsequent regression analysis.

Figure 3.5.3.: ROC curves illustrating the ability of each structural progression variable to classify those subjects with symptom worsening at 24 months; EKOA cohort



*The reference 'random' variable is equivalent to a variable that randomly assigns a symptom worsening outcome, equivalent to the toss of a coin and in this example equivalent to KL grade progression.

3.5.5. Symptom progression

Univariate analysis revealed several baseline variables that were significantly associated with symptom worsening over 24 months including; baseline WOMAC (p<0.001), gender (p=0.013), BMI (p=0.002), race (p=0.012) and employment status (p=0.029). The multivariate model demonstrated that only baseline WOMAC score (p<0.001) and BMI (p=0.009) had a significant affect on symptom worsening when all other variables remained constant. The effect of Gender, Race and Employment status were no longer significant.

In the multivariate model, the odds of symptom worsening by more than 9 points over 24 months were decreased by 4% for every one point increase on the baseline WOMAC score. The odds of symptom worsening by more than 9 points over 24

months were increased by 5% for every 1 unit increase in baseline BMI (kg/m^2). Table 3.4 and Table 3.5 summarise the results of the univariate and multivariate analyses for symptom progression.

Table 3.4.: Univariate regression analysis to assess the direct affect of each baseline variable on symptom worsening at 24 months (WOMAC >9points); EKOA cohort

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC*	0.971	0.959 - 0.984	<0.001
Baseline JSW	0.923	0.803 - 1.061	0.26
Age	1.011	0.990 - 1.031	0.31
Gender*	1.643	1.110 - 2.433	0.013
BMI*	1.063	1.022 - 1.106	0.002
Co-morbidities	1.211	0.986 - 1.487	0.07
Race*	1.719	1.124 - 2.627	0.012
Employment*	0.654	0.446 - 0.959	0.029
Smoker	1.085	0.746 - 1.579	0.67
Previous knee surgery	0.829	0.53 - 1.285	0.40

*Indicates $p<0.05$

Table 3.5.: Multivariate regression analysis to determine the influence of baseline variables on symptom worsening over 24 months; EKOA cohort

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC*	0.963	0.949 - 0.976	<0.001
Baseline JSW	0.963	0.835 - 1.111	0.604
Age	1.006	0.982 - 1.030	0.64
Gender	1.468	0.981 - 2.195	0.06
BMI*	1.054	1.014 - 1.098	0.009
Co-morbidities	1.125	0.912 - 1.387	0.27
Race	1.475	0.964 - 2.256	0.07
Employment	0.722	0.466 - 1.118	0.15
Smoker	1.078	0.742 - 1.568	0.69
Previous knee surgery	1.011	0.641 - 1.595	0.96

*Indicates $p<0.05$

3.5.6. Structural progression

Univariate analysis identified baseline WOMAC score was the only baseline variable associated with JSN progression over 24 months (p<0.001). This significant association was maintained in the multivariate model which demonstrates a 2% increase in the odds of developing structural progression (JSN>0.7mm) over 24 months for every 1 point increase in the baseline WOMAC score. The multivariate model also highlighted baseline JSW as a significant predictor of structural progression with the odds of JSN progression decreasing by 12% for every 1mm increase in joint space width at baseline. Table 3.6 and Table 3.7 summarise the results of the univariate and multivariate analyses for JSN progression.

Table 3.6.: Univariate regression analysis to assess the direct affect of each baseline variable on JSN progression at 24 months (>0.7mm); EKOA cohort

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC*	1.020	1.009 - 1.031	<0.001
Baseline JSW	0.907	0.792 - 1.038	0.15
Age	0.996	0.975 - 1.017	0.70
Gender	0.736	0.499 - 1.086	0.12
BMI	1.021	0.982 - 1.061	0.30
Co-morbidities	0.847	0.676 - 1.060	0.15
Race	0.906	0.592 - 1.388	0.65
Employment	1.235	0.835 - 1.825	0.29
Smoker	1.045	0.716 - 1.523	0.82
Previous knee surgery	0.957	0.621 - 1.475	0.84

*Indicates p<0.05

Table 3.7.: Multivariate regression analysis to determine the influence of all baseline variables on JSN progression over 24 months (>0.7mm); EKOA cohort

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC*	1.022	1.010 - 1.034	<0.001
Baseline JSW*	0.888	0.773 - 1.020	0.09
Age	1.004	0.980 - 1.030	0.73
Gender	0.718	0.478 - 1.080	0.11
BMI	1.024	0.984 - 1.067	0.24
Co-morbidities	0.836	0.663 - 1.055	0.13
Race	0.942	0.605 - 1.464	0.79
Employment	1.145	0.731 - 1.793	0.55
Smoker	0.994	0.677 - 1.459	0.98
Previous knee surgery	0.903	0.575 - 1.417	0.66

*Indicates $p<0.05$

3.5.7. Predicting Non-progressors

BMI at baseline was the only baseline variable to be associated with non-progression of OA at 24 months. The odds of not progressing decreased by 4% for every 1 unit increase in BMI (p=0.019) (see Table 3.8). This significant association persisted in the multivariate model (p=0.03) (see Table 3.9).

Table 3.8.: Univariate regression analysis to assess the direct affect of each baseline variable on subjects who do not progress over 24 months; EKOA cohort

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC	.9998481	0.991 - 1.009	0.973
Baseline JSW	1.083743	0.966 - 1.216	0.172
Age	.9961098	0.979 - 1.014	0.667
Gender	1.034576	0.747 - 1.432	0.838
BMI*	.9600685	0.929 - 0.992	0.016
Co-morbidities	1.003893	0.838 - 1.202	0.966
Race	.7847668	0.549 - 1.122	0.184
Employment	1.098386	0.793 - 1.522	0.573
Smoker	.9249244	0.673 - 1.271	0.630
Previous knee surgery	1.159889	0.804 - 1.674	0.428

*Indicates $p<0.05$

Table 3.9.: Multivariate regression analysis to determine the influence of all baseline variables on subjects who do not progress over 24 months

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC	1.003155	0.994 - 1.013	0.52
Baseline JSW	1.084364	0.963 - 1.22	0.18
Age	.994386	0.974 - 1.015	0.60
Gender	1.132151	0.805 - 1.591	0.48
BMI*	.9621964	0.930 - 0.996	0.03
Co-morbidities	1.062402	0.881 - 1.281	0.53
Race	.814945	0.563 - 1.179	0.28
Employment	1.086806	0.746 - 1.584	0.67
Smoker	.953212	0.691 - 1.316	0.77
Previous knee surgery	1.129283	0.770 - 1.656	0.53

*Indicates $p<0.05$

3.5.8. The effect of lower limb mechanical alignment on OA progression

Lower limb alignment had a significant association with JSN progression at 24 months ($p<0.001$). The odds of developing JSN progression of more than 0.7mm over 24 months decreased 19% for every 1 degree increase in HKA (less varus). A reciprocal relationship was seen in the odds of non-progression over 24 months which increased by 8.5% for every 1 degree increase in HKA ($p=0.008$). This association was maintained in multivariate analysis. No significant association between lower limb alignment and symptom worsening over 24 months was identified. Baseline WOMAC score continued to be significantly associated with JSN progression and symptom worsening over 24 months when HKA was incorporated into the model. BMI was no longer significantly associated with symptom worsening ($p=0.29$) or non-progression ($p=0.42$) when lower limb alignment was incorporated into the model. Table 3.10 and Table 3.11 outline the effects of lower limb alignment on OA progression.

Table 3.10.: Univariate regression analysis to assess the direct affect of lower limb alignment on OA progression over 24 months; EKOA + HKA cohort

Outcome of interest	Odds Ratio	95% CI	p-value
Symptom worsening (WOMAC >9 point)	1.038	0.976 - 1.104	0.24
JSN progression* (>0.7mm)	0.813	0.746 - 0.886	<0.001
No progression*	1.085	1.021 - 1.153	0.008

*Indicates $p<0.05$

Table 3.11.: Multivariate regression analysis including lower limb alignment; EKOA + HKA cohort

Outcome of interest	Variable	Odds Ratio	95% CI	p-value
Symptom worsening (WOMAC >9points)	Baseline WOMAC*	0.963	0.947 - 0.980	<0.001
	BMI†	1.03	0.977 - 1.081	0.29
JSN progression (>0.7mm)	Baseline WOMAC*	1.021	1.004 - 1.038	0.014
	HKA*	0.816	0.746 - 0.893	<0.001
No progression	HKA*	1.085	1.017 - 1.157	0.013
	BMI†	0.98	0.933 - 1.029	0.42

*Variables significantly associated with the OA progression outcomes at 24 months are included ($p<0.05$).

†BMI is no longer a significant predictor when HKA is included in the model

3.5.9. Collinearity of independent variables

The independent variables included in the multivariate model were tested for collinearity using the variance inflation factor (VIF). None of these variables had a VIF greater than 2 and the mean of the VIF scores was close to 1 representing inconsequential collinearity in the multivariate model [194]. The VIF scores for the

independent variables are summarised in table 3.12

Table 3.12.: Collinearity of the independent variables assessed using the variance inflation factor (VIF); EKOA + HKA cohort

Variable of interest	VIF
Baseline WOMAC	1.19
Baseline JSW	1.39
Age	1.42
Gender	1.27
BMI	1.15
Co-morbidities	1.07
Race	1.20
Employment	1.37
Smoker	1.04
Previous knee surgery	1.12
HKA	1.40
Mean VIF	1.24

3.5.10. Interaction between BMI and HKA

The finding that BMI was no longer significantly associated with symptom worsening (p=0.29) or non-progression (p=0.42) when lower limb alignment was incorporated into the model highlighted the possibility of a previously unseen interaction between alignment and BMI. The regression model was repeated to include an interaction term between these two variables. The model identified no significant interaction between the two variables (p=0.46)

3.6. Discussion.

This study has established the prevalence of disease progression in an EKOA cohort that reflects patients who find themselves in the treatment gap. The majority of individuals (62.2%) will experience no significant structural progression or symptom

worsening over 24 months. In terms of structural progression, joint space narrowing occurred more frequently than KL grade progression (JSN = 16.4%; KL grade= 15.4%) and was more commonly associated with symptom progression (JSN = 22.3%; KL grade = 16.3%).

Relatively few baseline patient characteristics predicted OA progression over 24 months. Predictors for symptom worsening included a low baseline WOMAC (less symptomatic knee) and high BMI. Predictors for structural progression included a reduced baseline JSW and a high baseline WOMAC score (more symptomatic knee). A low BMI was the only variable that was protective (i.e. predicted non-progression) over 24 months. The addition of lower limb alignment had a significant effect on the predictive models. Malalignment is a potent risk factor for OA progression with a more varus knee at greater risk of JSN progression and at lower risk of non-progression. BMI was no longer a significant predictor of either structural progression or non-progression when alignment was taken into consideration.

Multi-centre prospective cohort studies, such as the OAI, have enabled researchers to consider the factors that contribute to OA progression in detail. This study supports some of the existing literature and opposes other aspects of it. It also highlights some of the reasons why conflict in the literature may be present. The contradictory effects that baseline WOMAC score had on structural and symptomatic progression typifies the type of conflict that arises in the literature.

In their study of 354 individuals, Cooper et al, described baseline knee pain (pain in and around the knee for most days of at least one month over the past year) as a non-significant predictor of radiographic OA progression over 5 years [195]. A different study involving 236 participants found that pain severity (VAS) at baseline predicted subjects with a poor symptomatic outcome. This study divided baseline WOMAC scores into quintiles and defined symptom outcome based on movement or

stasis within these quintile groups over a three year period [115]. In doing so it is not clear how many subjects with a good or poor outcome had symptoms that simply reflected the status quo, similarly a small incremental change for a subject on the border of two quintiles could have led to a poor or good outcome but in real terms the subject may not have experienced any significant change in symptoms.

Clearly, predicting the effect of baseline symptoms on OA progression depends on numerous factors. The cohort of interest, the method of describing baseline knee symptoms and the definition of progression (symptoms or structure) will all have an effect on the studies conclusions. The study in this chapter used WOMAC to give a standardised assessment of baseline pain and function from which a clinically relevant threshold for symptom worsening was defined.

The finding that a high baseline WOMAC (more symptomatic knee) was associated with a lower risk of symptom worsening over 24 months may seem counter-intuitive. It is important to note that WOMAC scores improved for the whole EKOA cohort at 24 months. The OAI study recruited subjects with known OA or at high risk of its development. This definition was in part based on symptoms, furthermore, subjects for this EKOA cohort were selected-in based on their experiences of pain over the preceding 12 months, as such subsequent baseline WOMAC scores are likely to reflect an extreme measurement in terms of knee pain compared to the general population. This selected group are more likely to have a measurement that is closer to a true average as time progresses, this phenomenon is known as regression to the mean [196]. The counter-intuitive effect of baseline WOMAC on symptom worsening may represent a greater regression to the mean for subjects who had a high WOMAC score at baseline.

The finding that varus alignment is a potent risk factor for structural progression in the medial compartment has been validated within our cohort. The effect of mal-

alignment on structural progression has been reported before [31, 110, 197]. Sharma et al [31] studied 230 individuals and noted a 4-fold increase in the risk of medial JSN progression in the varus knee over three years. Cerejo et al [110], reported a similar finding over 18 months in subjects with KL grade 2 and 3 OA at baseline, however, the effect of varus alignment on medial JSN progression was smaller for those subjects with KL grade 0/1 (n=54). Using anatomical alignment from fixed-flexion AP radiographs, Brouwer et al [198] identified a stronger relationship between malalignment and the risk of development of OA in overweight subjects than in the non-overweight individuals and Driban et al noted that a greater coronal tibial slope was associated with incident accelerated knee osteoarthritis [199].

The study in this chapter has a number of limitations. A history of knee injury or ACL rupture was not included amongst the co-variates. The OAI does not hold specific information regarding ACL rupture, however, a history of ligament repair would have been included within the history of knee surgery variable. Whilst knee injury has been associated with incidence of knee OA there is no evidence to support its role in progression of established disease [200]. Univariate analysis revealed several factors that were were associated with symptom worsening (BMI, gender, race and employment status). The fact that all these become non-significant following further analyses highlights the importance of the multivariate model when drawing conclusions on potential predictors of OA progression. This potential confounding between variables of interest is only accounted for in the multivariate analysis which tests each variable in turn whilst controlling for the others. It is possible that other variables not accounted for in this study would have impacted on the results. Improved baseline mental health and social support have both been shown to reduce the likelihood of a poor functional outcome over 3 years in in patients with established OA [115]. However, whilst potentially important, these psycho-social variables

and the questionnaires used to quantify them are not routinely administered in an orthopaedic clinic setting and as such were excluded from the dataset.

Despite these limitations this study has many strengths. 1,634 knees from 1,182 individuals represents a large cohort of patients on which firm conclusions can be drawn. To our knowledge this is the first epidemiological study that has been designed to answer questions that specifically relate to a group of patients who represent a unique clinical problem i.e. those patients who find themselves in the 'treatment gap'. Reassuringly, over 24 months the majority of symptomatic patients with EKOA will experience no symptom worsening or structural progression and very few will progress to end-stage osteoarthritis (<1% of KL 1/2 subjects). Delaying surgery for these individuals is both reasonable and safe as their disease is likely to remain stable. Subjects with significant varus deformity and more moderate osteoarthritis (KL grade 3) are at an increased risk of progression to end-stage osteoarthritis over 24 months. An early discussion with these patients regarding surgical intervention in the form of an high tibial osteotomy would be reasonable but should be couched in terms of their overall risk of progression over the next 24 months. Surgery in the form of an osteotomy is a significant undertaking and whether or not such early intervention slows structural progression remains unknown.

Clearly, varus alignment has a very significant effect on medial compartment structural progression and valgus alignment is protective against this progression over 24 months. Whilst this is consistent with the previously published literature it is difficult to establish which subjects have an alignment that is 'constitutionally varus' and which subjects have an alignment that has been exacerbated by the presence of established OA. The next chapter will look at the component parts that contribute to lower limb alignment and identify which, if any, is the most important in terms of predicting structural progression.

3.7. Conclusions.

This study confirms that the majority of individuals with symptomatic EKOA do not show any progression of their OA over 24 months. Lower limb alignment has a significant influence on progression. More varus alignment predicts medial compartment progression and more valgus alignment predicts non-progression. Highly symptomatic individuals at baseline are at risk of structural progression but may not experience any symptom worsening over 24 months. This is reassuring for patients who are being counselled in the early stages of symptomatic knee osteoarthritis. More information is needed to understand the factors that contribute to varus deformity and whether they are all equally important in predicting progression of OA.

4. The site of varus deformity and its influence on knee OA progression

4.1. Introduction

The previous study demonstrated that varus deformity was a potent predictor of medial compartment structural progression in a group of individuals with symptomatic EKOA. As osteoarthritis progresses various factors will contribute to a worsening of lower limb alignment. Noyes et al, in their description of ACL deficient varus knees have referred to the inherent tibiofemoral osseous alignment and any concomitant intra-articular cartilage loss as a primary varus deformity [201]. As osteoarthritis in the medial compartment progresses this varus deformity is exaggerated by deficiency of the lateral soft tissue structures and eventually bony attrition.

The term 'constitutional varus' has been used to describe the varus deformity seen in healthy individuals [32]. As many as 32% of men and 17% of women had constitutional varus knees with the most important contributors to this varus deformity being the medial plateau tibial angle (MPTA) and the mechanical lateral distal femoral angle (mLDFA), contributing 40.8% and 29.4% to the overall alignment respectively [32]. These individual alignment variables, available from a long leg radiograph, are routinely measured within an orthopaedic clinical setting. The measurements rely

on bony landmarks and as long as bone integrity has not been compromised they should not be affected by the progression of osteoarthritis. As such they could be used to identify patients with constitutional varus alignment regardless of the stage of osteoarthritis [32]. No study to date has looked at the role of these individual alignment variables on the progression of osteoarthritis.

4.2. Aims

- To identify the individual alignment variables that contribute to lower limb alignment
- To identify which of these alignment variables predict symptom and/or structural progression in symptomatic EKOA

4.3. Materials & methods

An EKOA cohort of patients from the Osteoarthritis Initiative was created de novo in the previous chapter including 1,634 knees from 1,182 subjects. The same cohort forms the basis of this study.

4.3.1. Study design

A longitudinal cohort study was designed to investigate the rates of symptom and structural progression seen in patients with symptomatic EKOA over 24 months. This EKOA cohort was investigated in the previous chapter and a subgroup of individuals within it had an overall assessment of limb alignment performed at 12 months, EKOA + HKA cohort.

The following study takes subjects from the EKOA cohort and includes those

individuals that had a long leg radiograph available at any time-point, EKOA + LLR cohort. Measurements from long leg radiographs were analysed to identify the alignment variables that contribute to varus deformity. These alignment variables were then investigated to identify which of them contribute to varus alignment and which if any are causative of OA progression.

4.3.2. Study sample; EKOA + LLR cohort

Eligible subjects from the EKOA cohort had at least one knee with Kellgren Lawrence (KL) grade 1, 2 or 3 and symptoms in the same knee at recruitment. Symptoms were defined as knee pain, aching or stiffness: more than half the days of a month in the past year in the same knee. If a subject had two eligible knees then both knees were enrolled into the study. In order to be eligible for the study both clinical and radiographic outcomes at 24 months had to be available. To be included in this study, individuals had to have a long leg radiograph (LLR) with all landmarks clearly visible and available for analysis.

Eligibility for LLR Information regarding eligibility for LLRs within OAI is publicly available (https://oai.epi-ucsf.org/datarelease/SASDocs/flXR_KneeAlign_Descrip.pdf; last accessed 14th June 2017). The OAI did not perform LLRs on any individuals at recruitment. The Progression sub-cohort, within OAI, discussed in the previous chapter were all eligible for a single, weight-bearing AP radiograph of the lower limbs at 12 months. These individuals all had established OA at recruitment (KL grade 2 or more and symptoms). LLRs were performed at later time points in subjects who were eligible (KL grade 2 or more) but in whom a valid measurement had not been taken at the previous visit. Funding for acquisition of full-limb radiographs within OAI was obtained later for the incidence cohort and their long leg radiographs were acquired at the 24-month visit. Only one full-limb radiograph was acquired per per-

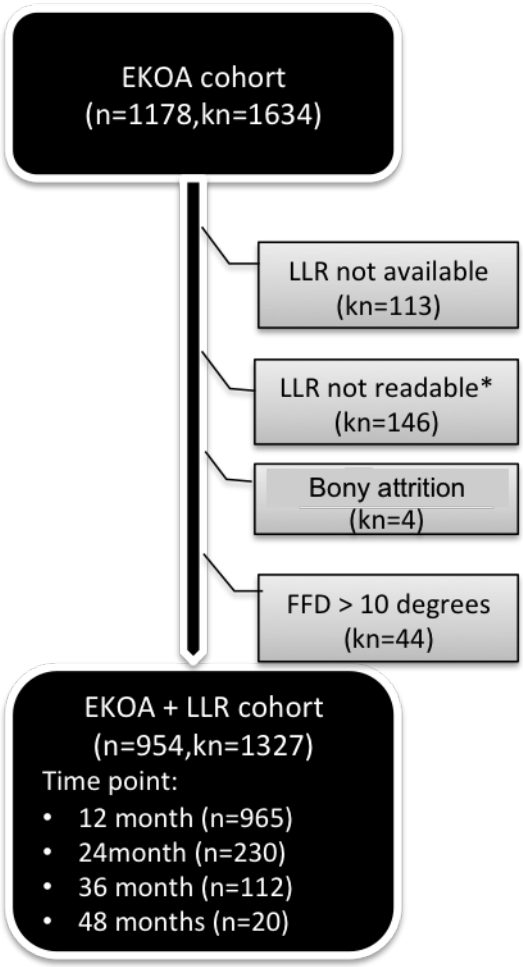
son unless the initial one was of poor quality. In order to maximise the sample size, LLRs for participants were retrieved for all time points and the LLR from the earliest time point available was studied. As such this group differ from the EKOA + HKA group from the last chapter who only had alignment measurements taken at 12 months.

Acquisition of LLR Information regarding the acquisition of LLRs within OAI is publicly available (https://oai.epi-ucsf.org/ datarelease/ operationsManuals/ RadiographicManual.pdf; last accessed 14th June 2017). LLRs were obtained from the five different sites using different X-ray machines at each site, however, a standardised approach was kept consistent across sites. Radiographs of the entire lower extremities were taken together in an upright weight-bearing position including complete visualisation of the femoral head and the talus of the foot. Participants placed their toes perpendicular to the film, the femoral epicondyles were kept parallel to the cassette and knees were kept fully extended whilst distributing the participants weight evenly.

Exclusion criteria for this study Subjects with a significant fixed flexion deformity (FFD>10 degrees) at recruitment were excluded. A small degree of rotation in individuals with a large FFD can significantly affect the accuracy of coronal alignment measurements [202]. Subjects who demonstrated progression of osteoarthritis on their LLR such that boney deformity was present on either the tibial plateaus or femoral condyles were excluded. This may have arisen if their LLR was performed long after they were recruited into the study. Such boney deformity would potentially over-estimate alignment measurements. For example, bony attrition of the medial tibial plateau would decrease the medial plateau tibial angle making it more varus [203]. Similarly, subjects were excluded if a THR or TKR was present on the LLR as their presence would have significantly altered the alignment of the lower limb.

Figure 4.3.1 outlines the availability of LLRs for subjects within the cohort and the time point from which they were taken.

Figure 4.3.1.: Flow diagram outlining the availability of LLRs from the original EKOA cohort



*Bony landmarks not visible (kn=117), Arthroplasty in situ (kn=27)

4.3.3. Outcomes

Symptom progression Symptom worsening was defined as an increase in WOMAC score (symptom worsening) of >9 points at 24 months compared to baseline [192]. Subjects with severe symptoms at baseline (WOMAC >91 points) who could not progress by more than 9 points were defined as progressing if their symptoms were

sustained (WOMAC>91 points) at 24 months.

Structural progression Structural progression was defined as Joint space narrowing (JSN) progression in the medial compartment (>0.7mm) [193]. Subjects who were unable to progress as their joint space was already too narrow at baseline (<1mm) were excluded from the study as their disease was too severe to be considered EKOA.

4.3.4. Variable selection

Variable selection was the same as for the previous chapter. These included age, gender, BMI, number of co-morbidities, smoking status, race, employment status, previous history of knee surgery. In addition mechanical alignment variables were obtained and included in the analysis.

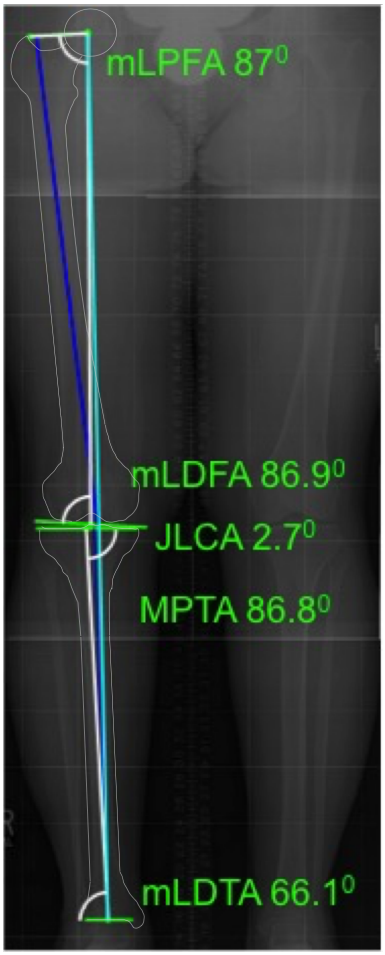
Alignment variables All available LLRs were viewed as Digital Imaging and Communications in Medicine (DICOM) files and analysed using the Osteotomy module within Medicad® Classic (Hectec GMBH). This landmark-based surgical planning software is well described in the literature [204, 205, 206]and is known to have high inter-rater reliability [156]. It generates mechanical alignment measurements including weight-bearing axis (WBA), mechanical Lateral Proximal Femoral Angle (mLPFA), mechanical Lateral Distal Femoral Angle (mLDFA), Medial Proximal Tibial Angle (MPTA), mechanical Lateral Distal Tibial Angle (mLDTA) and medial Joint Line Convergence Angle (JLCA_med) see figure 4.3.2. Alignment variables were retrieved for all individuals.

Observer Reliability A single observer (JP) reviewed all the LLRs in the cohort. Intraclass correlation coefficients (ICCs) were performed on readings of the first 20 limbs performed by the same observer (JP) at different time points across the study

(intra-observer reliability) and by another orthopaedic registrar trained in the use of Medicad® Classic (Hectec GMBH) (inter-observer reliability). Observer drift describes a tendency for observers to become less consistent as time progresses. To identify any evidence of this phenomenon, ICCs were repeated for readings of these 20 limbs made after the first 100, 200 and 500 LLR readings were completed.

Variables used to describe symptom and structural progression were compared at baseline and at 24 months using chi-squared, paired ttest or Wilcoxon-Signed rank test depending on whether the variable of interest was categorical, parametric or non-parametric in nature. This enabled a description of symptom and structural progression for the EKOA + LLR cohort as a whole. Subjects demonstrating symptomatic and structural progression were identified and total counts were expressed as a percentage of the cohort as a whole.

Figure 4.3.2.: Medicad® Classic (Hectec GMBH) was used to acquire alignment variables for individuals within the EKOA + LLR cohort



Mechanical alignment measurements included weight-bearing axis (WBA), mechanical Lateral Proximal Femoral Angle (mLPFA), mechanical Lateral Distal Femoral Angle (mLDFA), Medial Proximal Tibial Angle (MPTA), mechanical Lateral Distal Tibial Angle (mLDTA) and Joint Line Convergence Angle (JLCA). The light blue line indicates the Weight-bearing Axis expressed as a percentage of the medial-lateral tibial plateau (35.3% in this plan). NB: The outline of the femur and tibia has been highlighted in white to aid interpretation of this figure.

4.4. Analysis

Baseline demographic variables were compared between the whole OAI cohort, the EKOA cohort described in the last study and the EKOA + LLR cohort for this study.

Significant differences were identified using chi-squared, independent samples t-test or Willcoxon-Mann-Whitney tests depending on whether the variable of interest was categorical, parametric or non-parametric in nature.

All statistical analysis was performed using Sata 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

4.4.1. Alignment variables

4.4.1.1. Association of alignment variables

Pearson correlation tests were performed to determine whether the alignment variables were independent of each other or whether significant linear relationships were present between them. Pearson correlation cannot account for the influence of more than one knee from the same individual and as such one knee was selected at random for each individual. A separate test was performed to identify any correlation between Joint space narrowing (JSN) and medial Joint line convergence angle (JLCA_med) as an increase in one of these measurements should lead to a reciprocal decrease in the other. If a variable showed a strong and significant correlation with another variable then a single variable was chosen and included in the final multivariate model. Further statistical analyses were performed using generalised estimating equations (GEEs) to determine whether differences in alignment variables seen by gender or baseline KL grade.

4.4.1.2. Alignment variables that predict overall alignment (e.g. valgus or varus).

The hip knee ankle angle (HKA) was converted to a binary outcome to separate those with valgus alignment (HKA>0°) and those with varus alignment (HKA<0°). GEEs were then used to identify which alignment variables predicted whether or not a sub-

ject was in varus or valgus alignment. Standardised coefficients were then calculated to enable an assessment of how many standard deviations the HKA changed, per standard deviation increase in the alignment variable. In doing so, it was possible to determine which of the individual alignment variables, if any had the greatest effect on the HKA.

4.4.1.3. Alignment variables and their effect on progression

Using GEEs the association between baseline variables and subsequent symptom or structural progression over 24 months was investigated. Each variable was added to the model in turn to assess its direct affect on the outcome of interest. Multivariate analysis, with all variables included, was then performed to explore and quantify the influence of these variable on OA progression. All models were adjusted for baseline joint space narrowing (JSN) and baseline WOMAC score. Relationships between predictor variables and outcome were expressed as Odds Ratios (OR) and a p -value <0.05 was considered statistically significant. The independent variables included in the model were tested for collinearity using the variance inflation factor (VIF). This statistical approach is consistent with the previous chapter. The statistical model is being used in this instance to explain the effect of lower limb alignment on OA progression described in the previous chapter.

Subsequently, outcome groups were determined based on symptomatic worsening (WOMAC >9 points) and structural progression (JSN >0.7mm). Multinomial regression was then performed to determine the effect of predictor variables on the likelihood of an individual progressing to one of three outcome groups compared to the likelihood of progressing to a fourth referent group:

1. Super control (non-progressor) - no symptom worsening and no structural progression at 24 months (referent group)

2. Structural progressor - no symptom worsening but structural progression at 24 months

3. Symptom progressor- symptom worsening but no structural progression at 24 months

4. Super progressor- symptom worsening and structural progression at 24 months

Results were expressed as relative risk ratios (RRR) and p- values of <0.05 were considered statistically significant.

4.5. Results

955 individuals with 1,329 knees were included in the study.

4.5.1. Observer reliability

Excellent intra-observer reliability was demonstrated with Intraclass correlation coefficients >0.90 for all alignment variables measured at baseline compared to those measured after the 1st 100 readings. There was no evidence of any observer drift with ICCs being maintained at >0.80 after the 1st 200 and 1st 500 readings were performed. Excellent inter-observer reliability was also demonstrated. Table 4.1 summarises the ICC results for the LLR readings.

Table 4.1.: ICCs were performed to assess intra- and inter-observer reliability for the alignment variables

	Intra-observer reliability			Inter-observer
	1st 100 readings	1st 200 reading	1st 500 readings	2nd Reader
mLPFA	0.965	0.968	0.977	0.957
95% CI	0.866, 0.991	0.921, 0.987	0.934, 0.991	0.892, 0.983
mLDFA	0.991	0.987	0.986	0.984
95% CI	0.967, 0.998	0.967, 0.995	0.965, 0.994	0.960, 0.994
MPTA	0.985	0.980	0.981	0.924
95% CI	0.940, 0.996	0.801, 0.994	0.811, 0.995	0.811, 0.970
mLDTA	0.950	0.983	0.953	0.926
95% CI	0.806, 0.988	0.957, 0.993	0.873, 0.982	0.814, 0.971
JLCA_med	0.933	0.806	0.921	0.782
95% CI	0.726, 0.983	0.477, 0.920	0.687, 0.973	0.406, 0.917
WBA	0.999	0.998	0.998	0.997
95% CI	0.994, 1.000	0.996, 0.999	0.996, 0.999	0.966, 0.999

4.5.2. Characteristics of the study population

The EKOA + LLR cohort had a significantly higher BMI, had fewer white subjects and more co-morbidities than the entire OAI cohort. They had similar baseline characteristics to the EKOA cohort from the previous chapter with no significant differences observed between them for the variables recorded. Table 4.2

Table 4.2.: Characteristics of the study cohorts

	OAI cohort (n=4,796)	EKOA cohort (n=1,182)	EKOA + LLR cohort (n=955)
Age (yrs) (mean)	61.2	60.9	60.7
Sex (% female)	58.5%	57.5%	57%
BMI (kg/m^2) (mean)	28.6	30*	29.9*
Race (% white)	79.1	71*	69.8*
Co-morbidities (%none)	75.4	70*	70.5*
% employed	61.7	62.3	63.6
% smoker	6.6	6.8	7.2
KL grade (%)		1= 17% 2= 50% 3= 33%	1= 17% 2= 50% 3= 33%

*Indicates a significant difference in value compared to the OAI cohort (p<0.05)
†Indicates a significant difference in value compared to the EKOA cohort (p<0.05)

4.5.3. Associations between alignment variables

Table 4.3 summarises the correlations observed between the alignment variables. A small but statistically significant positive correlation was observed between the mechanical Lateral Distal Tibial Angle and mechanical Lateral Proximal Femoral Angle (p<0.001). Small but statistically significant negative correlations were observed between JLCA_med and mLDFA and MPTA. A similarly small but weakly positive relationship was observed between JLCA_med and mLDTA. Due to the multiple significant correlations observed between JLCA_med and other alignment variables it was decided to exclude JLCA_med from the multivariate model.

Table 4.3.: Pearson correlation demonstrating the strength and direction of association that exists between the alignment variables

	mLPFA	mLDFA	MPTA	mLDTA	JLCA_med
mLPFA	1.00				
mLDFA	0.05	1.00			
MPTA	0.05	0.05	1.00		
mLDTA	0.10	0.07	0.00	1.00	
	p=0.002	p=0.04			
JLCA_med	0.05	-0.09*	-0.13*	0.07*	1.00
		p=0.006	p<0.001	p=0.03	

*p-values given for statistically significant (p=<0.05) correlations

4.5.4. Alignment variables by gender

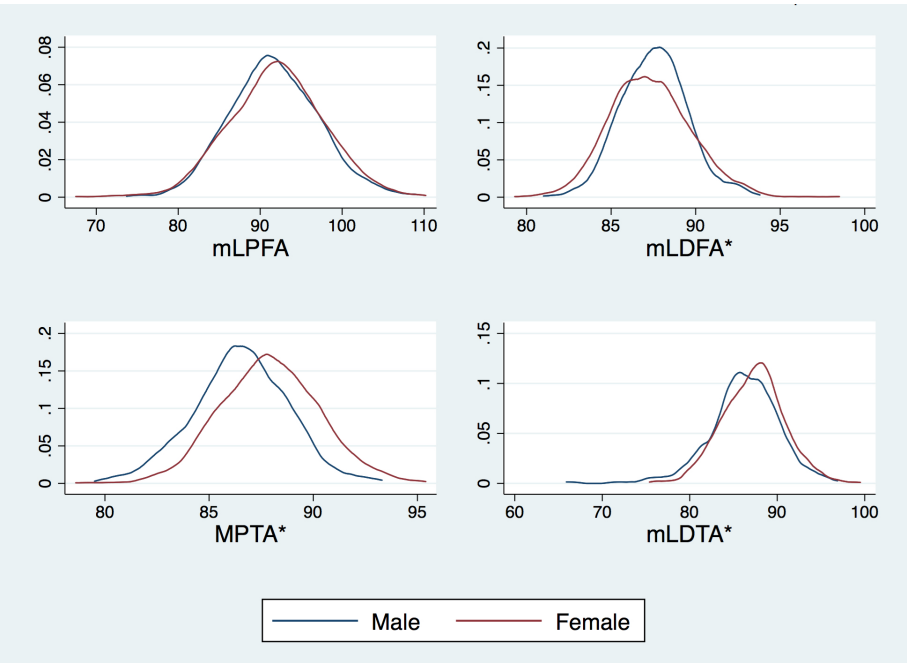
A significantly smaller, more varus, MPTA was observed amongst male subjects (Male avg. = 86.6°, Female avg. = 87.9°; p=<0.001). Males also demonstrated a significantly greater mLDFA i.e. more varus, than females (Male avg. = 87.5°, Female avg. = 87.3°; p= 0.04). A significantly smaller mLDTA was seen in males (Male avg. = 86.2°, Female avg. = 87.3°; p=<0.001). There was no significant difference in mLPFA seen by gender (p=0.24). Table 4.4 summarises the differences observed for the alignment variables by gender. Kernel density graphs in Figure 4.5.1 summarises the differences seen by gender for the alignment variables measured.

Table 4.4.: Table outlining the difference in alignment variables observed by gender

	All (n=1327)		Males (n=535)		Females (n=792)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
mLPFA	91.9°	5.7	91.8°	5.4	92.0°	5.8
mLDFA	87.4°	2.2	87.5°	2.0	87.3°*	2.4
MPTA	87.4°	2.4	86.6°	2.3	87.9°*	2.4
mLDTA	86.8°	3.8	86.2°	4.0	87.3°*	3.5
jlca_med	1.2°	1.8	1.3°	1.6	1.1°	1.9

*Indicates a significant difference by gender (p<0.05)

Figure 4.5.1.: Kernel density plot graphs illustrating the differences in alignment variables observed by gender



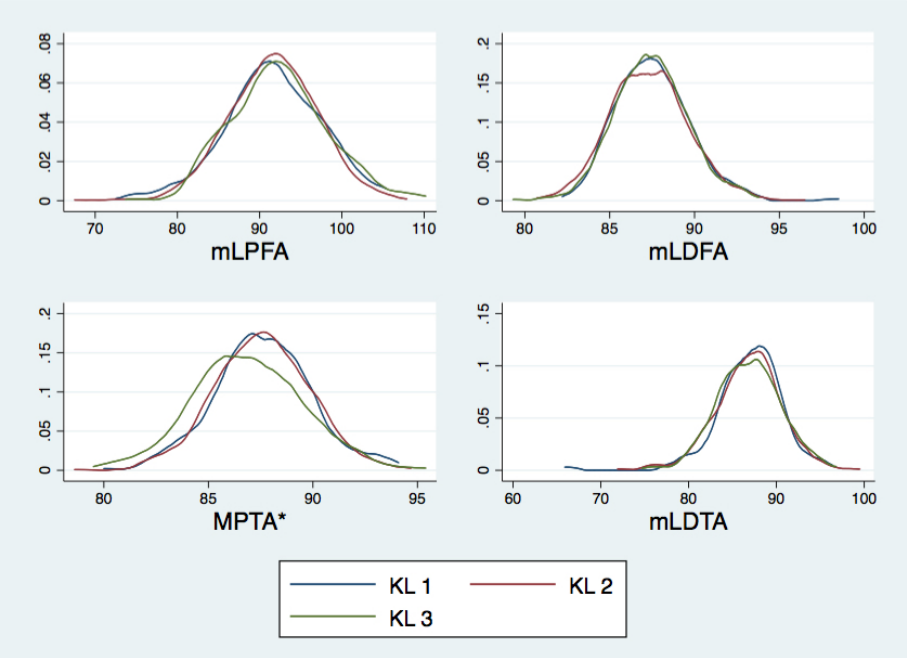
*p=<0.05

4.5.5. Alignment variables by baseline KL grade

Subjects who had a KL grade of 3 at baseline demonstrated a smaller, more varus MPTA than those who were KL grade 1 (KL 3 avg. = 86.9°, KL 1 = 87.6°; p=0.003). The remaining alignment variables were not significantly different when compared by

baseline KL grades of the subjects. Figure 4.5.2 illustrates the relationship between the alignment variables and baseline KL grade.

Figure 4.5.2.: Kernel density plot graphs illustrating the differences in alignment variables observed by baseline KL grade



*p=<0.05

4.5.6. Alignment variables that predict valgus and varus alignment

Three of the four alignment variables, mLDFA, MPTA and mLDTA predicted both varus and valgus alignment. mLPFA did not significantly influence lower limb alignment. Standardised co-efficients revealed that the scale of effect on varus and valgus alignment was similar for both MPTA and mLDFA. A summary of the lower alignment variables and their influence on HKA is given in Table 4.5.

Table 4.5.: Table outlining the influence of alignment variables on overall alignment

Alignment	Predictor	Odds Ratio	95% CI	p-value	Standardised co-efficient
Varus	mLPFA	1.03	0.989 - 1.078	0.15	0.02
	mLDFA*	3.63	2.571 - 5.123	<0.001	0.58
	MPTA*	0.23	0.155 - 0.340	<0.001	-0.60
	mLDTA*	1.11	1.036 - 1.191	0.003	0.03
Valgus	mLPFA	0.97	0.931 - 1.015	0.20	-0.005
	mLDFA*	0.27	0.187 - 0.391	<0.001	-0.58
	MPTA*	4.44	2.913 - 6.767	<0.001	0.61
	mLDTA*	0.90	0.844 - 0.970	0.005	-0.03

*p=<0.05

4.5.7. Variables that predict symptom worsening

None of the alignment variables predicted symptom worsening at 24 months. Predictors of symptom worsening (WOMAC >9 points) at 24 months included WOMAC score (p<0.001) and BMI (p=0.014) at recruitment. For every one unit increase in baseline BMI the odds of developing worsening knee pain at 24 months increased by 6%. For every one unit increase in baseline WOMAC the odds of developing worsening knee pain at 24 months decreased by 3%. A summary of the univariate analysis is given in Table 4.6 and a summary of the multivariate analysis is given in Table 4.7. This confirms the findings of the previous study.

Table 4.6.: Univariate regression analysis to assess the direct affect of each alignment variable on symptom worsening at 24 months (WOMAC >9points)

Alignment variable	Odds Ratio	95% CI	p-value
mLPFA	1.022	0.987 - 1.058	0.23
mLDFA	0.937	0.859 - 1.023	0.15
MPTA	1.065	0.983 - 1.153	0.12
mLDTA	1.023	0.971 - 1.078	0.40

Table 4.7.: Multivariate regression analysis to determine the influence of all baseline variables on symptom worsening over 24 months

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC*	0.965	0.950 - 0.981	<0.001
Baseline JSN	0.946	0.795 - 1.125	0.53
Age	0.988	0.961 - 1.017	0.41
Gender	1.458	0.897 - 2.367	0.13
BMI*	1.059	1.012 - 1.109	0.01
Co-morbidities	1.098	0.862 - 1.398	0.45
Race	0.762	0.469 - 1.239	0.27
Employment	0.628	0.377 - 1.045	0.07
Smoker	1.254	0.818 - 1.922	0.30
Previous knee surgery	1.187	0.702 - 2.00	0.52
mLPFA	1.025	0.988 - 1.064	0.18
mLDFA	0.920	0.836 - 1.013	0.09
MPTA	1.048	0.957 - 1.149	0.31
mLDTA	1.016	0.959 - 1.075	0.59

*p=<0.05

4.5.8. Variables that predict structural progression

The only variable that predicted structural progression at 24 months (JSN >0.7mm) was MPTA. The odds of JSN progression occurring at 24 months decreased by 21% for every one unit increase (more valgus) in MPTA *(p<0.001)*.

Table 4.8.: Univariate regression analysis to assess the direct affect of each alignment variable on structural progression over 24 months (JSN >0.7mm)

Alignment variable	Odds Ratio	95% CI	p-value
mLPFA	1.019	0.979 - 1.060	0.35
mLDFA	1.028	0.933 - 1.134	0.57
MPTA*	0.808	0.733 - 0.889	<0.001
mLDTA	1.029	0.971 - 1.091	0.33

*p=<0.05

Table 4.9.: Multivariate regression analysis to determine the influence of all baseline variables on structural progression over 24 months (JSN >0.7mm)

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC	1.010	0.996 - 1.024	0.16
Baseline JSN	1.064	0.890 - 1.274	0.50
Age	1.009	0.979 - 1.041	0.56
Gender	1.179	0.702 - 1.981	0.53
BMI	1.021	0.973 - 1.073	0.39
Co-morbidities	0.878	0.664 - 1.161	0.36
Race	1.145	0.670 - 1.956	0.62
Employment	1.218	0.701- 2.116	0.49
Smoker	1.299	0.817 - 2.063	0.27
Previous knee surgery	0.968	0.556 - 1.686	0.91
mLPFA	1.018	0.978 - 1.060	0.39
mLDFA	1.050	0.948 - 1.164	0.35
MPTA*	0.791	0.710 - 0.882	<0.001
mLDTA	1.021	0.961 - 1.084	0.50

*p=<0.05

4.5.9. Collinearity

The independent variables included in the multivariate model were tested for collinearity using the variance inflation factor (VIF). None of these variables had a VIF greater than two and the mean of the VIF scores was close to one representing inconsequential collinearity in the multivariate model [194]. The VIF scores for the independent variables are summarised in table 4.10

Table 4.10.: Collinearity of the independent variables assessed using the variance inflation factor (VIF)

Variable of interest	VIF
Baseline WOMAC	1.21
Baseline JSW	1.21
Age	1.47
Gender	1.28
BMI	1.16
Co-morbidities	1.17
Race	1.20
Employment	1.37
Smoker	1.04
Previous knee surgery	1.13
mLPFA	1.05
mLDFA	1.09
MPTA	1.21
mLDTA	1.08
Mean VIF	1.18

4.5.10. Multinomial regression; univariate analysis

The cohort was split based on the four possible outcome groups. The majority of individuals were in the no progression group (69.1%). This group was the referent group from which the RRR of a theoretical subject falling into one of the remaining three groups was calculated. The number of individuals in each outcome group is summarised in Table 4.11.

Table 4.11.: Number of individuals within each outcome group

	n	%
No progression	917	69.1%
Symptom worsening	158	11.9%
Structural progression	195	14.7%
Symptom and structural progression	57	4.3%

Univariate analysis was performed on each of the alignment variables in turn to

assess their direct affect on determining an individuals outcome group. MPTA had a significant but opposing effect on the relative risk of being in both the symptom worsening (p=0.036) and structural progression groups (p<0.001). For every unit increase in the MPTA (more valgus), the relative risk of being in the symptom worsening group increased by a factor of 1.09 and the relative risk of being in the structural progression decreased by a factor of 0.86 relative to the referent group. A summary of the results is given in table 4.12.

Table 4.12.: Univariate multinomial regression analysis to the direct affect of alignment variable predicting a subjects outcome group relative to the no progression group (referent group)

Outcome group	Variable of interest	RRR	95% CI	p-value
Symptom worsening	mLPFA	1.02	0.995 - 1.063	0.09
	mLDFA	0.95	0.864 - 1.04	0.26
	MPTA*	1.09	1.005 - 1.179	0.036
	mLDTA	1.02	0.968 - 1.069	0.51
Structural progression	mLPFA	1.01	0.986 - 1.043	0.32
	mLDFA	1.05	0.982 - 1.131	0.15
	MPTA*	0.86	0.801 - 0.921	<0.001
	mLDTA	1.01	0.961 - 1.058	0.73
Symptom and structural progression	mLPFA	1.01	0.950 - 1.070	0.78
	mLDFA	0.94	0.836 - 1.052	0.27
	MPTA	0.91	0.807 - 1.033	0.15
	mLDTA	1.06	0.968 - 1.153	0.22

*p=<0.05

4.5.11. Multinomial regression; multivariate analysis

4.5.11.1. Symptom worsening group (n=158)

Only baseline WOMAC had a significant effect on the risk of being in the symptom worsening group relative to the referent group. For every unit increase in the baseline WOMAC, the relative risk of being in the symptom worsening group, relative to the

referent group, is expected to decrease by a factor of 0.98 if the remaining variables in the model are held constant.

4.5.11.2. Structural progression group (n=195)

Baseline WOMAC and MPTA had significant but opposing effects on the risk of being in the structural progression group relative to the referent group. For every unit increase in the MPTA (more valgus), the relative risk of being in the structural progression group, relative to the referent group, is expected to decrease by a factor of 0.86. For every unit increase in the baseline WOMAC, the relative risk of being in the structural progression group, relative to the referent group, is expected to increase by a factor of 1.01.

4.5.11.3. Symptom and structural progression group (n=57)

Baseline WOMAC, MPTA and gender had significant but opposing effects on the risk of being in the symptom and structural progression group relative to the referent group. For every unit increase in the MPTA (more valgus), the relative risk of being in the symptom and structural progression group, relative to the referent group, is expected to decrease by a factor of 0.86 if the remaining variables in the model are held constant. For every unit increase in the baseline WOMAC, the relative risk of being in the symptom and structural progression group, relative to the referent group, is expected to decrease by a factor of 0.97 if the remaining variables in the model are held constant. For female participants, the relative risk of being in the symptom and structural progression group, relative to the referent group, is expected to increase by a factor of 2.7 if the remaining variables in the model are held constant.

Table 4.13.: Multivariate multinomial regression analysis to determine the influence of all the variables of interest on predicting a subjects outcome group relative to the no progression group (referent group)

Outcome group	Variable of interest	RRR	95% CI	p-value
Symptom worsening	Baseline WOMAC*	0.979	0.967 - 0.991	0.001
	Baseline JSN	1.012	0.864 - 1.184	0.89
	Age	0.996	0.972 - 1.021	0.76
	Gender	1.083	0.705 - 1.663	0.72
	BMI	1.042	0.999 - 1.086	0.06
	Co-morbidities	1.087	0.893 - 1.323	0.41
	Race	0.830	0.535 - 1.286	0.40
	Employment	0.668	0.430 - 1.039	0.07
	Smoker	1.214	0.831 - 1.775	0.32
	Prev. knee surgery	1.166	0.748 - 1.818	0.50
	mLPFA	1.026	0.991 - 1.063	0.15
	mLDFA	0.945	0.861 - 1.038	0.24
	MPTA	1.076	0.986 - 1.174	0.10
	mLDTA	1.002	0.952 - 1.055	0.93
Structural progression				
	Baseline WOMAC*	1.013	1.002 - 1.024	0.02
	Baseline JSN	1.086	0.934 - 1.263	0.28
	Age	1.013	0.992 - 1.035	0.22
	Gender	0.897	0.624 - 1.291	0.56
	BMI	1.003	0.969 - 1.038	0.87
	Co-morbidities	0.934	0.770 - 1.134	0.49
	Race	1.071	0.715 - 1.604	0.74
	Employment	1.198	0.791 - 1.813	0.40
	Smoker	1.229	0.865 - 1.747	0.25
	Prev. knee surgery	0.981	0.647 - 1.488	0.93
	mLPFA	1.014	0.986 - 1.044	0.32
	mLDFA	1.074	0.995 - 1.160	0.07
	MPTA*	0.856	0.795 - 0.921	<0.001
	mLDTA	1.000	0.952 - 1.049	0.99
Symptom & structural progression				
	Baseline WOMAC*	0.972	0.953 - 0.992	0.005
	Baseline JSN	0.918	0.667 - 1.263	0.60
	Age	0.985	0.945 - 1.027	0.48
	Gender*	2.657	1.263 - 5.589	0.01
	BMI	1.055	0.996 - 1.117	0.07
	Co-morbidities	0.933	0.679 - 1.281	0.67
	Race	0.891	0.461 - 1.722	0.73
	Employment	0.802	0.383 - 1.682	0.56
	Smoker	1.318	0.740 - 2.349	0.35
	Prev. knee surgery	1.176	0.551 - 2.510	0.68
	mLPFA	1.011	0.953 - 1.073	0.72
	mLDFA	0.950	0.834 - 1.082	0.44
	MPTA*	0.860	0.752 - 0.983	0.03
	mLDTA	1.051	0.956 - 1.155	0.30

*p=<0.05

4.5.12. Further analysis

Higher baseline KL grade was associated with a smaller, more varus, MPTA. Baseline KL grade was not included in the statistical model as it has a significant correlation with baseline JSN (Pearson Correlation = -0.4; p=<0.001). In order to ensure that the predictive effects of MPTA are not the result of an unseen interaction between MPTA and baseline KL grade the models were repeated with baseline KL grade exchanged for baseline JSN in the multivariate model for structural progression (see appendix A). The predictors of structural and symptom progression seen in the above results sections remained stable following this adjustment.

Symptom worsening was predicted by BMI. The previous chapter demonstrated a similar finding, however, the effect of BMI on symptom worsening was no longer significant when alignment (HKA) was included in the model. In order to ensure that the predictive effects of BMI in this study were not the result of an unseen interaction with overall alignment, the multivariate model was repeated with HKA included in the model instead of the geometric variables (mLPFA, mLDFA, MPTA and mLDTA). The effects of BMI on symptom worsening remained stable following this adjustment (see appendix A)

4.6. Discussion

This study is the first to look at individual geometric variables that constitute varus deformity and how they influence progression of disease in symptomatic EKOA. Several factors contribute to both valgus and varus alignment (mLDFA, MPTA and mLDTA), however, only the MPTA had a significant effect on structural progression. The odds of JSN progression occurring at 24 months decreased by 21% for every one degree increase (more valgus) in MPTA (p<0.001). Multinomial regression identified

that for a similar increase in MPTA the relative risk of being in the symptom and structural progression group and the structural progression group, relative to the referent group, decreases by a factor of 0.86.

A high baseline WOMAC was associated with a reduced odds of symptom worsening at 24 months. This finding is consistent with the results from the previous chapter and the reasoning behind it has been discussed before.

Multinomial regression analysis identified female participants as having an increased relative risk of being in the symptom and structural progression group, relative to the referent group. This is the only analysis, in this study, that has described gender as being a significant predictor of outcome at 24 months. It is important to note that symptom and structural progression was a relatively rare outcome (n=57) as such whilst the effect of gender is an interesting observation it should be interpreted with caution.

Cooke et al, compared the alignment of 127 patients with symptomatic varus osteoarthritis to 75 varusly aligned healthy individuals [207]. Significant differences were observed in distal femoral geometry between the two groups leading the authors to conclude that it was distal femoral alignment that drove the development of medial compartment osteoarthritis. This cross-sectional study did not have follow up data from which to confirm this finding and it is not supported by our study. Our study confirmed that mLDFA, MPTA and mLDTA were associated with varus malalignment, however, it is only the MPTA that is driving structural progression in EKOA.

By contrast, in the description of 'constitutional varus' provided by Bellemans et al the greatest contributor to varus deformity was MPTA [32]. Other contributors included the mLDFA, physical activity level in youth, femoral bowing and a more varus medial neck-shaft angle. This study describes lower limb varus deformity as

a non-pathological state that occurs frequently in young healthy individuals and it does not describe whether this constitutional varus deformity leads to incidence or progression of OA.

As discussed in the previous chapter several studies have reported on varus malalignment and its potent effects on structural progression in knee osteoarthritis [31, 110, 197, 198]. Our study supports this literature and in addition makes an important novel observation. Of the factors that contribute to varus deformity only the MPTA had a significant effect on structural progression in the medial compartment. In addition MPTA was the only alignment variable that increased the relative risk of an individual being in the structural progression group.

This study has some important limitations. Whilst the individual alignment variables did not correlate strongly with each other, a small but statistically significant interaction was observed between the distal tibial angle (mLDTA) and both the proximal femoral angles (mLPFA) and distal femoral angles (mLDFA). This unexpected interaction is unlikely to impact significantly on the results, an assertion which is supported by the low VIFs seen throughout all the statistical models.

The acquisition of long leg radiographs with the feet perpendicular to the film may have affected the accuracy of the alignment measurements recorded. In the presence of external or internal tibial torsion, such positioning would result in the patellae pointing inward or outward and may lead to an under- or over-estimation of any angular deformity. Positioning the limb with the patella or tibial tuberosity facing forward may have overcome this problem.

The exclusion of certain variables could be a potential source of bias. Subjects with a fixed flexion deformity (FFD) of more than 10 degrees were excluded from the study. A high FFD may in itself be associated with progression and by excluding this variable we may have biased the sample towards a risk group that is not related

to FFD. The study also dropped medial joint line convergence angle (JLCA_med) from the statistical analysis. JLCA_med is essentially a composite angle that reflects the MPTA, mLDFA and the medial JSW (see figure 4.3.2). As a composite of these angles it would not be appropriate to include it in the multivariate model as it could lead to unstable estimates of the regression co-efficients for the remaining variables.

The participants in this study were selected to reflect patients who find themselves in the treatment gap. The average age of the EKOA + LLR cohort was 60.7yrs and the mean MPTA was 87.4°(± 2.4), similar to that reported in a healthy population described by Bellemans et al (87.04°(± 2.07)) [32]. Younger age patients (<45yrs) are not represented in this study and whilst some severe varus deformity will be present the cohort as a whole shows very little variation in alignment. By contrast, a prospective study of individuals undergoing high tibial osteotomy with an average age of 47.5yrs had a mean proximal tibial angle of 81.44°(± 4.51) [208]. Rates of progression in these younger patients with more severe proximal tibia vara would be of interest and has not been fully delineated by this study.

Despite these limitations this study has many strengths. The study population is large (n= 955; kn=1,329) and the statistical analysis was established *a priori*. The finding that varus alignment leads to worsening medial JSN is not new, however, confirming the effects of this predictor was essential and needed to be done before any analysis of the discrete alignment variables could be considered. Cohort populations are unique. Differences in population characteristics, recruitment methods and the method by which investigations are obtained could all have an impact on the outcomes observed. The approach to statistical modelling can also have a significant effect on the interpreted results. Replicating the effects of alignment on structural progression in this cohort is an important validatory step for the statistical model used and substantiates the subsequent conclusions drawn with regards to MPTA.

Proximal tibial alignment has clinical relevance. In the context of varus deformity the proximal tibia can be corrected with a surgical intervention such as an osteotomy. Bonnin and Chambat reported superior clinical outcomes for patients undergoing osteotomy for medial OA for patients with a constitutional varus deformity of the proximal tibia [149]. The study described in this chapter supports the use of a high tibial osteotomy in the presence of proximal tibia vara as it is this deformity that is driving structural progression over 24 months.

The definition of structural progression described in this chapter has been restricted to medial JSN. This is a reliable marker for cartilage thickness in the medial compartment in the presence of OA [55]. However, the meniscus also occupies space in the medial compartment and it also accounts for a substantial proportion of the change in JSN seen in OA progression [62]. It is not known whether the increased medial JSN seen with proximal tibia vara is caused by a deterioration of the meniscus, of the cartilage or both. Subjects with proximal tibia vara may simply experience a more rapid deterioration of these structures, however, the worsening JSN seen over 24 months may reflect a specific pattern of structural damage that is unique to this phenotype. The pattern of structural progression seen in subjects with EKOA with and without proximal tibia vara will be considered in the next chapter.

4.7. Conclusions

This study has confirmed that whilst malalignment is a significant predictor of structural progression in EKOA it is specifically the alignment of the proximal tibia that drives this phenomenon. The odds of JSN progression occurring at 24 months decreased by 21% for every 1 unit increase (more valgus) in MPTA ($p<0.001$). Other factors that appear to contribute contribute to varus alignment (i.e. mLDFA and mLDTA) do not appear to have a significant association with structural progression.

5. Patterns of structural progression seen in EKOA subjects with proximal tibia vara

5.1. Introduction

The previous chapter made the novel observation that specifically varus alignment of the proximal tibia was associated with medial JSN progression over 24 months. It is not known whether this increased structural progression is the result of meniscal degradation or cartilage thinning or a combination of the two. Subjects with proximal tibia vara may experience the same, but accelerated, pattern of OA progression as non-tibia vara subjects, however, they may experience a pattern of structural progression that is unique to their alignment phenotype. Identifying unique structural changes in OA progression could enable a more targeted therapeutic approach for the management of EKOA.

Semi-quantitive assessment of knee MRI offers a detailed assessment of knee osteoarthritis that is reliable [76] and can be used to assess both the presence of OA [209, 74] and evaluate its progression [75]. Commonly used scoring systems divide the knee into multiple subregions and then describe the appearance of structures (i.e.

cartilage, osteophytes, bone, meniscus) within each subregion. This enables points of significant structural damage to be localised to specific regions within the knee. Semi-quantitive MRI analysis of subjects with EKOA could, therefore, be used to determine whether the increased medial joint space narrowing seen in subjects with proximal tibia vara is due to differences in structural and subregional progression which is unique to their alignment.

5.2. Aims

To establish whether worsening medial joint space narrowing observed in subjects with proximal tibia vara can be explained by the pattern of structural progression.

5.3. Material and Methods

The purpose and design of the Osteoarthritis Initiative (OAI) cohort has been discussed in the previous two chapters. Within OAI, a nested case–control study was developed with the expressed purpose of identifying biomarkers for OA progression and assessing the responsiveness of imaging and biochemical markers relevant to knee OA. This group of participants forms part of the Foundation for the National Institutes of Health (FNIH) OA Biomarkers Consortium project and was funded by the FNIH a not for profit charitable organisation. Full details of the study can be found on the OAI website (https://oai.epi-ucsf.org/datarelease/docs/FNIH/OaBioFnihDataOverview.pdf; last accessed 14th June 2017) and it has been referenced in several published scientific articles on knee OA progression [210, 211, 212, 213, 214, 193, 215] .

FNIH OA Biomarkers Consortium project The FNIH study included 600 participants with at least one knee with a KL grade of 1, 2 or 3 at baseline and availability at baseline and 24 months of knee radiographs, knee MRI, stored serum and urine specimens and clinical data. The purpose of this case-control study was to identify potential biomarkers at baseline that might be sensitive to OA progression.

Radiographic progression Radiography of both knees was performed at all clinic visits using a non-fluoroscopic fixed flexion protocol (SynaFlexor, Synarc, Newark, California, USA) and images were read centrally using automated software [216]. Radiographic progression was defined as a decrease in medial minimum joint space width of $\geq$0.7 mm from baseline to any of three possible time-points; 24, 36 or 48 months.

Symptom progression Knee pain was assessed using the WOMAC pain sub-scale. Pain progression was defined as a persistent increase from baseline to 24, 36 or 48 months of $\geq$9 points at $\geq$2 time-points based on the literature for a minimum clinically important difference for pain worsening [192, 217].

Outcome groups A pre-determined number of index knees, one knee per subject, were selected based on four possible outcome groups. The knees selected for the 4 outcome groups were frequency matched, with data stratified by K/L grade (grade 1, 2, or 3) and BMI:

- X-ray and pain progression (n=194)
- X-ray only progression (n=103)
- Pain only progression (n=103)
- No progression (n=200)

Exclusion criteria Exclusion criteria include:

- Ceiling effect for observed outcomes; baseline medial JSW <1.0mm, baseline WOMAC >90
- Total hip or knee arthroplasty during the study period
- Structural or pain progression occurring within 12 months
- Outcomes between knees of the same subject are inconsistent
- Knees with predominantly lateral compartment joint space narrowing at baseline

Semi-Quantitative Scoring of Knee MRI; MOAK score MRI acquisition was performed using the same 3T MRI system (Trio, Siemens Healthcare, Erlangen, Germany) at the four OAI clinical sites [218] for all subjects in this study group at baseline and 24 months. Scores relating to cartilage and medial meniscal pathology were the focus of this study. Two musculoskeletal radiologists, blinded to clinical data and case–control status, read the baseline and 24 month with knowledge of the chronological order of the scans [219].

MOAK scores cartilage morphology in 14 subregions within the knee on a 4 point scale based on the percentage of the surface area of the subregion affected by the lesion(s) and the percentage of the subregion that is affected by full thickness cartilage loss [76]. The overall score for cartilage morphology is given as a single number with the number before the decimal point referring to surface area loss and the number after the decimal point referring to full thickness loss (see table 5.1). If a lesion spans more than one subregion, the lesion needs to be scored in all involved subregions.

In order to increase the sensitivity of semiquantitative readings in detecting longitudinal change [220] a within grade change for MRI cartilage morphology has been included in the follow-up scores for OAI. While scoring of within grades will increase

numbers of subregions and compartments showing change, it is unknown if these recorded changes are meaningful [220]. For the purposes of this study within grade changes were excluded and a full grade change had to be evident in order to be included.

Table 5.1.: MOAK scores for MRI cartilage morphology

Percentage of surface area affected by cartilage loss within the subregion	Percentage of full-thickness cartilage loss within the subregion
0: none	0: none
1: <10% of the surface area	1: <10% of surface area
2: 10-75% of the surface area	2: 10-75% of surface area
3:>75% of the surface area	3:>75% of surface area

MOAK scores the medial meniscus for both morphology and the presence of extrusion. Abnormalities of meniscal morphology are scored in three distinct regions (anterior, body and posterior) using eight descriptive terms:

- 0: normal meniscus
- 1: signal abnormality that is not severe enough to be considered a meniscal tear
- 2: radial tear
- 3: horizontal teal
- 4: vertical tear
- 5: complex tear
- 6: partial maceration
- 7: progressive partial maceration (only used for follow-up visit scores)
- 8: complete maceration

Meniscal extrusion is scored separately for both medial and anterior extrusion [76] (Grading for extrusion: Grade 0: <2mm; Grade 1: 2 to 2.9mm, Grade 2: 3-4.9mm; Grade 3: >5mm).

5.3.1. Study design

A longitudinal observational study was designed, using subjects from the FNIH study group, to investigate whether the increased medial joint space narrowing seen in subjects with proximal tibia vara reflects a sui generis pattern of structural progression.

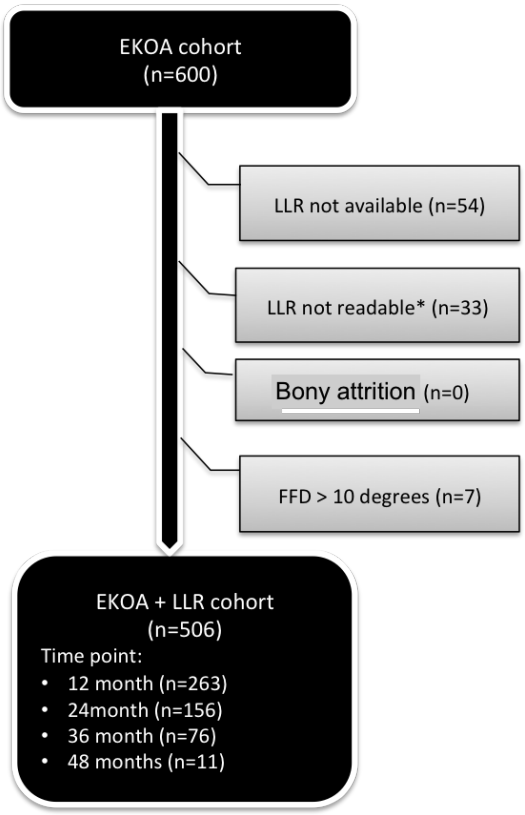
5.3.2. Study sample

As previously discussed the FNIH study group was designed as a case-control study. Subjects were pre-selected based on their outcome at 24 months and divided into cases (those with symptom and structural progression) and controls (those with no progression, symptom progression or structural progression) in order that a biomarker at baseline could be investigated to see if it was associated with one of these outcome groups. The following study is not trying to establish a temporal relationship between proximal tibia vara and outcome using this model. This has already been achieved in the previous chapter. However, the FNIH group contain a unique group of participants with early to moderate OA (KL grade 1, 2 or 3), like those from the previous chapter, who had MOAKS assessment performed at baseline and 24 months. This detailed imaging modality would enable any variations in structural progression to be seen, if present, in subjects with proximal tibia vara.

Initially, the OAI datasets were interrogated to establish the number of individuals within the FNIH study group that had LLRs performed at 12-month, 24-month, 36-month or 48- month time-points (n=546). Subjects were excluded if a fixed flexion deformity of more than 10 degrees was present (n=7). Figure 5.2 outlines LLR

availability, reasons for exclusion and time-point at which the images were taken.

Table 5.2.: Flow diagram outlining the availability of LLRs from the FNIH cohort



*Landmarks not visible n=29; arthroplasty visible n=2; rotated film n=1; trauma n=1

Subjects were defined as having proximal tibia vara (TV+) if they had an MPTA >1 standard deviation towards varus from the mean value described in a healthy individual [32]. This value was adjusted according to gender, reference values are given in table 5.3.

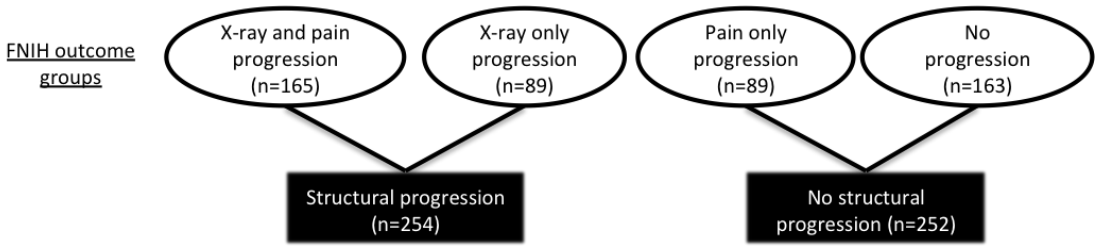
Table 5.3.: Reference values for defining proximal tibia vara in healthy individuals according to gender

	MPTA*	Proximal tibia vara (TV+)
Male	86.50^0, $\pm$ 2.17	MPTA $< 84.33^0$
Female	87.58^0, $\pm$ 1.82	MPTA $< 85.76^0$

*mean, S.D

The FNIH study group were divided based upon the outcome upon which they had been selected. The previous two chapters demonstrated that proximal tibia alignment was a strong predictor of structural progression but not symptom progression. As a consequence, outcome groups from the FNIH study were merged based on medial JSN progression at 24 months alone (see figure 5.3.1). This meant that the effects of proximal tibia vara on structural progression would be considered separately in subjects who demonstrated structural progression at 24 months and in those who did not.

Figure 5.3.1.: Flowchart illustrating the selection of outcome groups based on structural progression alone



5.3.3. Outcomes

Cartilage MOAK scores for cartilage morphology were separated to give an individual score for percentage surface area affected by cartilage loss (%SA) and for percentage of full thickness cartilage loss (%FT). Baseline MOAK scores were recorded to identify the distribution of cartilage scores within the sample population. For both %SA and %FT a change score was calculated as a binary outcome (any worsening versus no worsening of score) from baseline to 24 months.

Cartilage morphology outcomes were recorded for each of the 14 subregions of the knee.

Medial Meniscus Medial meniscal morphology scores were condensed into three groups; grades 0 and 1 (reference), grades 2–5 (tears), and grades 6–8 (maceration) [215]. A change score was calculated as any worsening in meniscal morphology from one group to the other (i.e. reference to tear, reference to maceration, or tear to maceration) [215]. Change in medial meniscal extrusion was considered separately for anterior and medial extrusion and was categorised as any worsening versus no worsening of extrusion grade.

Subjects who were unable to progress because they had already experienced a maximum meniscal morphology (n=132) or extrusion score (n=42) at baseline were included as progressors.

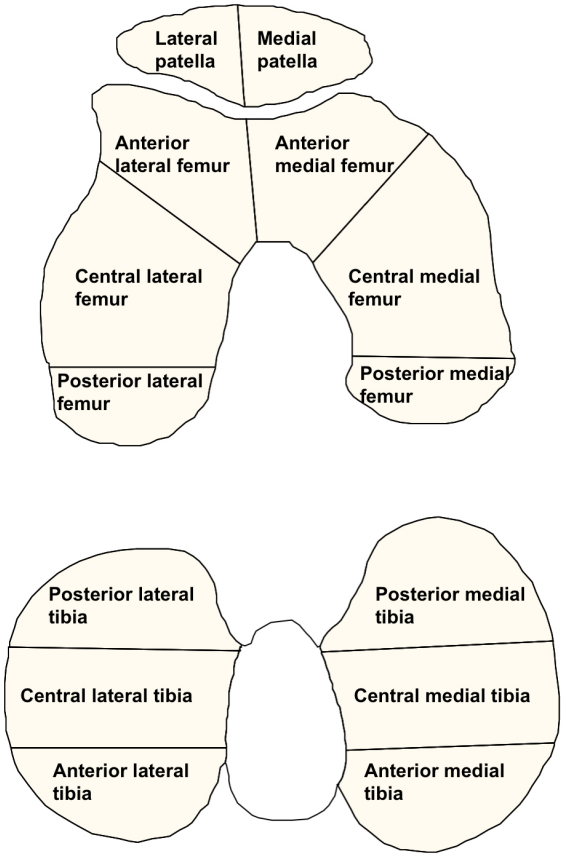
5.3.4. Knee maps

Semi-quantitive MOAK scores for cartilage morphology are completed for 14 subregions within the knee. Each individual subregion has 10 possible cartilage scores. With thousands of possible permutations of cartilage morphology for any single individual, characterising between group differences presents a significant challenge. Comparing each subregion in turn leads to problems associated with multiple statistical testing, whilst generating statistical models that account for subregion level data would necessitate large group numbers in order to make meaningful conclusions. Consequently, statistical approaches for semi-quantitive MRI scoring usually requires the raw data to be condensed. This can be done by grouping the subregions [221, 222, 223]or by grouping the cartilage morphology scores [215]. With any of these methods there is a consequent loss of information.

With this in mind, knee maps, were developed to illustrate the cartilage morphology scores seen at baseline and the change in cartilage score observed over 24 months. This approach uses spatial mapping software (spmap) within Stata 13.1 (StataCorp.

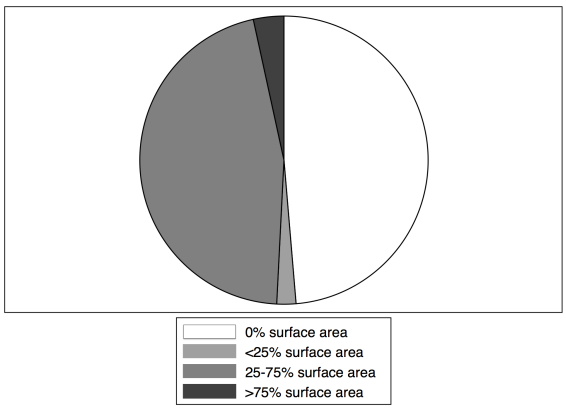
2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) to project MRI cartilage morphology scores onto the corresponding subregion. In order to do this a map of the knee was developed with subregions analogous to those used in the MOAK scoring system (see figure). Separate knee maps were developed for %SA and %FT scores.

Figure 5.3.2.: Knee map outlining the subregions of the knee which correspond to those used in the MOAK scoring system



Baseline cartilage morphology A pie chart was projected onto each subregion to illustrate the distribution of baseline cartilage scores within that subregion. An example pie chart demonstrating %SA scores for the whole cohort for a single subregion (central medial tibia) is given in figure 5.3.3.

Figure 5.3.3.: Pie chart illustrating the proportion of participants within each grade of %SA MOAK score for a single subregion (central medial tibia)



Change in cartilage score The number of individuals who showed a worsening of cartilage score at 24 months were calculated and expressed as a percentage for each subregion. Thresholds were set to illustrate between group differences in the proportion of individuals that progressed and the subregion was given a colour that reflected the different thresholds; 0% (dark blue) , 1-10% (light blue), 10-20% (green), 20-30% (yellow) >30% (red). Subjects who were unable to progress because they had already experienced a maximum cartilage score at baseline were included as progressors.

5.4. Analysis

Descriptive differences in the knee maps between subjects with proximal tibia vara and those without form the primary outcome of this study. Statistical analysis was then performed to identify whether any observed differences were statistically significant. All analyses were performed separately for subjects who demonstrated structural progression at 24 months and for those who did not.

Cartilage In order to determine whether any observed differences in the knee maps were significant statistical analyses were applied to the raw data. The proportion of individuals who progressed with regard to %SA and %FT cartilage score was compared between subjects with proximal tibia vara (TV+) and those without (TV-) 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.

Medial meniscal morphology and extrusion The proportion of individuals who progressed with regard to meniscal morphology and meniscal extrusion was compared between TV+ and TV- subject by means of a 2x2 contingency table. Each subregion of the meniscus was investigated in turn for morphology (anterior, body and posterior) and extrusion (anterior and medial).

Baseline meniscal morphology and extrusion scores were compared for corresponding subregions (anterior & body/medial) to explore the relationship between these two variables. The significance of these relationships was confirmed using Pearson's chi-squared test.

Subjects who were unable to progress in any outcome category because they had already experienced a maximum severity score at baseline were included as progressors in the final analysis.

5.5. Results

A total of 506 participants had a single knee with semi-quantitive MOAK scores and a LLR available for analysis. The structural progression group had 254 subjects and the non structural progression group had 252 subjects. These groups are considered separately below.

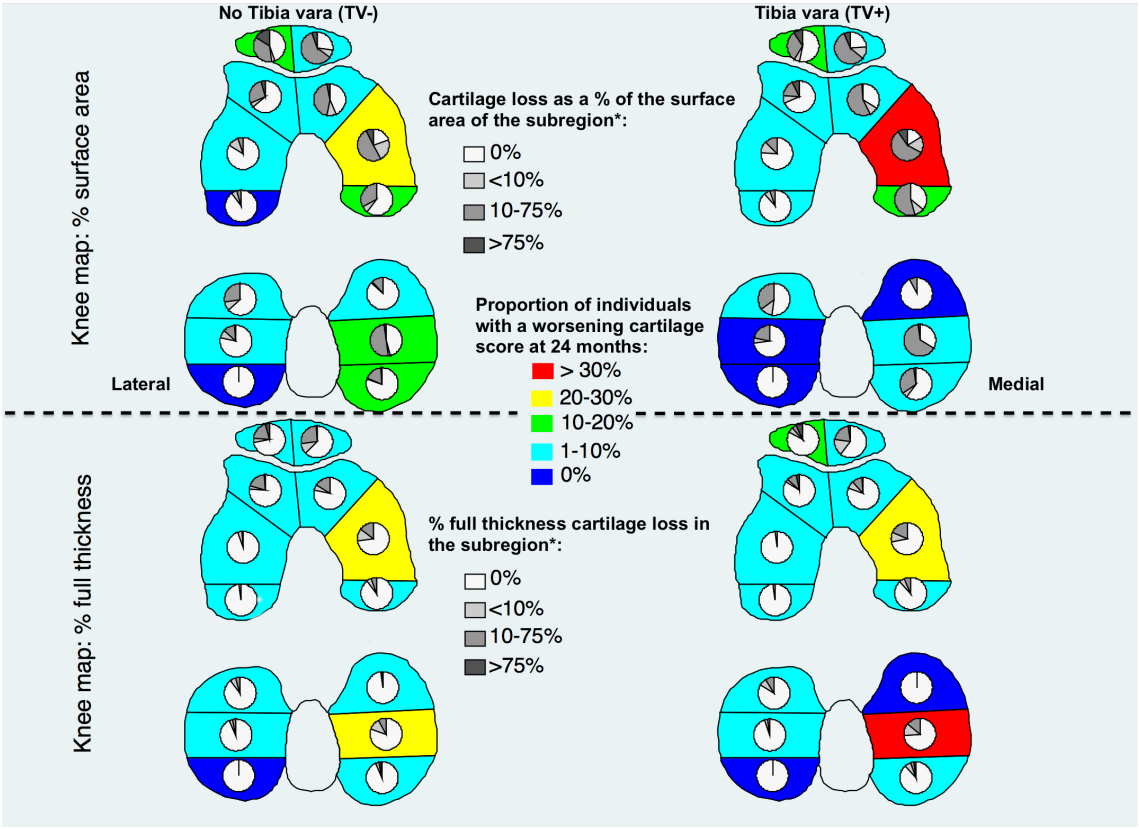
5.5.1. MOAK cartilage score

Knee maps Figure 5.5.1 and figure 5.5.2 illustrate the differences in MOAK cartilage scores observed between subjects with and without proximal tibia vara at baseline and their subsequent progression over 24 months.

In the structural progression group, differences in the proportion of individuals demonstrating %SA progression between those subjects with proximal tibia vara and those without were observed in 6 subregions. In the same group differences in the proportion of individuals demonstrating %FT progression were observed in three subregions. A greater proportion of full thickness cartilage progression was seen in the central medial tibial compartment in TV+ subjects (>30%) compared to TV- subjects (20-30%). In contradistinction a greater proportion of %SA progression was seen in two medial tibial subregions (central and anterior) in TV- subjects (10-20%) compared to TV+ subjects (1-10%). A single subregion in the central medial femur showed greater %SA progression in subjects with proximal tibia vara (>30%) than those without (20-30%).

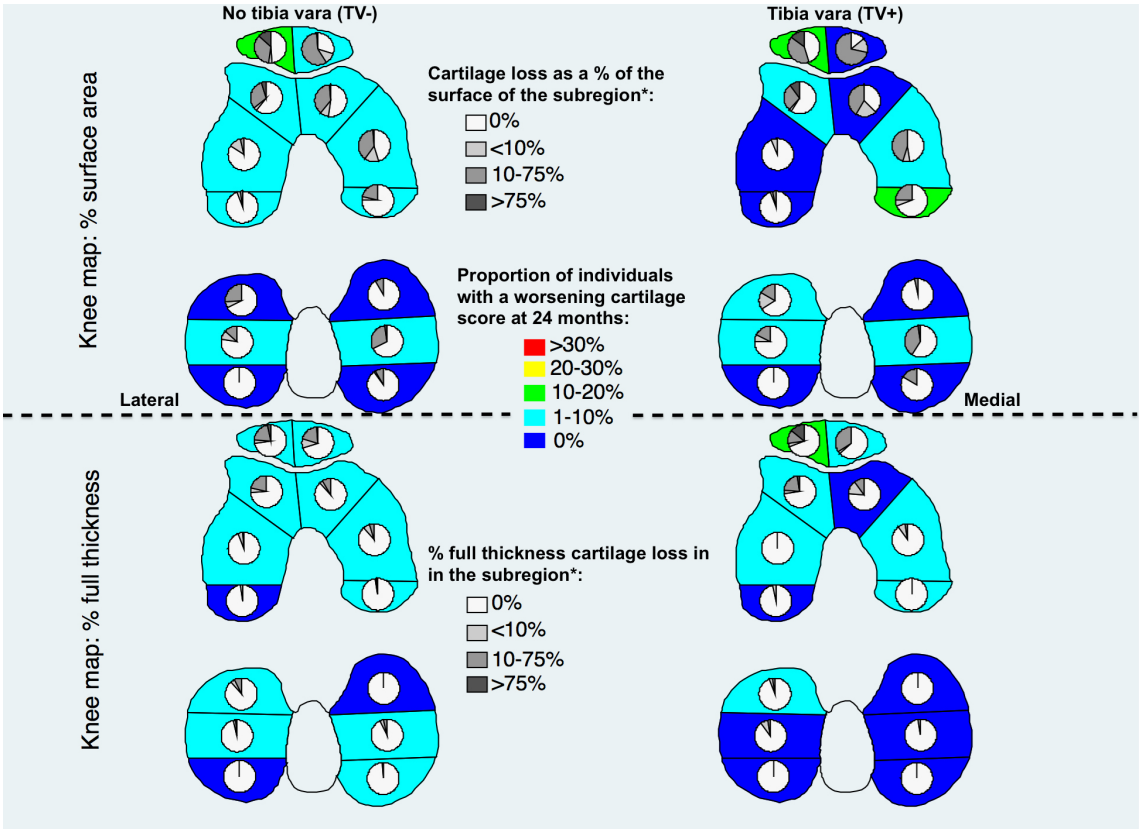
In the non-progressor group, differences in the proportion of individuals demonstrating % SA progression between those subjects with proximal tibia vara and those without were observed in 5 subregions. In the same group differences in %FT progression were observed in 5 subregions. The majority of these subregion differences (9 out of 10) reflected the 0% to 1-10% thresholds.

Figure 5.5.1.: Knee maps illustrating the baseline cartilage MOAK scores and subsequent progression over 24 months; structural progression group



*Pie charts illustrate the proportion of participants within each grade of cartilage score for a single subregion

Figure 5.5.2.: Knee maps illustrating the baseline cartilage MOAK scores and subsequent progression over 24 months; non progressor group



*Pie charts illustrate the proportion of participants within each grade of cartilage score for a single subregion

5.5.2. Analysis of subregion data

Structural progression group 2x2 contingency tables revealed that none of the subregion variations observed in the knee maps for the structural progression group were statistically significant. Whilst there was a trend towards subjects with proximal tibia vara having more %FT cartilage progression in the central medial tibia but this was not statistically significant (p=0.18). Table 5.4 summarises the rates of progression observed in TV- and TV+ subjects within the structural progression group. The p-values for the 2x2 contingency tables performed on subregions with observable difference on the knee maps are also provided.

Table 5.4.: Summary table comparing rates of progression within each subregion for TV- (n=196) and TV+ (n=58) individuals; structural progression group

Subregion	Rate of Progression		Subregion	Rate of Progression	
Medial patella	% SA	% FT	Central medial tibia	% SA	% FT
TV-	11(6%)	15(8%)	TV-	28(14%)	47(24%)
TV+	1(9%)	2(3%)	TV+	5(9%)	19(33%)
			p-value		0.18
Lateral patella	% SA	% FT	Posterior medial tibia	% SA	% FT
TV-	40(20%)	9(5%)	TV-	9(5%)	3(2%)
TV+	8(14%)	3(5%)	TV+	0(0%)	0(0%)
p-value*		0.45	*p*-value	0.22	0.46
Anterior medial femur	% SA	% FT	Posterior lateral femur	% SA	% FT
TV-	8(4%)	2(1%)	TV-	0(0%)	2(1%)
TV+	4(7%)	3(5%)	TV+	1(2%)	4(7%)
			p-value	0.23	
Anterior lateral femur	% SA	% FT	Central lateral femur	% SA	% FT
TV-	11(6%)	5(3%)	TV-	2(1%)	3(2%)
TV+	5(9%)	0(0%)	TV+	3(5%)	4(7%)
Posterior medial femur	% SA	% FT	Anterior lateral tibia	% SA	% FT
TV-	39(20%)	17(9%)	TV-	0(0%)	0(0%)
TV+	8(14%)	6(10%)	TV+	0(0%)	0(0%)
Central medial femur	% SA	% FT	Central lateral tibia	% SA	% FT
TV-	41(21%)	48(25%)	TV-	8(4%)	6(3%)
TV+	12(21%)	15(26%)	TV+	0(9%)	2(4%)
p-value	0.62		*p*-value	0.22	
Anterior medial tibia	% SA	% FT	Posterior lateral tibia	% SA	% FT
TV-	21(11%)	13(7%)	TV-	2(1%)	4(2%)
TV+	5(9%)	5(9%)	TV+	1(2%)	4(7%)
p-value	0.53				

*p-values were only calculated for those subregions with observed differences on the knee maps

No structural progression group 2x2 contingency tables revealed a statistically significant between group difference in %SA progression in a single subregion. Significantly more individuals with proximal tibia vara (10-20%) demonstrated %SA progression than those without (1-10%) (p=0.004). No other observed between group differences were statistically significant. Table 5.5 summarises the rates of progression observed in TV- and TV+ subjects within the non-progression group. The p-values for the 2x2 contingency tables performed on subregions with observable difference on the knee maps are also provided.

Table 5.5.: Summary table comparing rates of progression within each subregion for TV- (n=223) and TV+ (n=29) individuals; non progression group

Subregion	Rate of Progression		Subregion	Rate of Progression	
Medial patella	% SA	% FT	Central medial tibia	% SA	% FT
TV-	9(4%)	16(7%)	TV-	4(2%)	5(2%)
TV+	0(0%)	2(7%)	TV+	1(3%)	0(0%)
p-value*	0.6		*p*-value		0.54
Lateral patella	% SA	% FT	Posterior medial tibia	% SA	% FT
TV-	38(17%)	8(4%)	TV-	0(0%)	0(0%)
TV+	5(17%)	0(0%)	TV+	0(0%)	0(0%)
p-value		0.25			
Anterior medial femur	% SA	% FT	Posterior lateral femur	% SA	% FT
TV-	5 2%)	5(2%)	TV-	3(1%)	1(0.5%)
TV+	0 0%)	0(0%)	TV+	0(0%)	0(0%)
p-value	0.54	0.54	*p*-value	0.69	
Anterior lateral femur	% SA	% FT	Central lateral femur	% SA	% FT
TV-	17 8%)	9(4%)	TV-	9(4%)	6(3%)
TV+	3 10%)	1(3%)	TV+	0(0%)	1(3%)
			p-value	0.32	
Posterior medial femur	% SA	% FT	Anterior lateral tibia	% SA	% FT
TV-	6(3%)	7(3%)	TV-	0(0%)	0(0%)
TV+	5(17%)	3(10%)	TV+	0(0%)	0(0%)
p-value	0.004				
Central medial femur	% SA	% FT	Central lateral tibia	% SA	% FT
TV-	14(6%)	15(7%)	TV-	6(3%)	5(2%)
TV+	2(7%)	2(7%)	TV+	2(7%)	0(0%)
			p-value		0.54
Anterior medial tibia	% SA	% FT	Posterior lateral tibia	% SA	% FT
TV-	1(0.5%)	4(2%)	TV-	1(0.5%)	4(2%)
TV+	0(0%)	0(0%)	TV+	1(3%)	1(3%)
p-value		0.61	*p*-value	0.22	

**p*-values were only calculated for those subregions with observed differences on the knee maps

5.5.3. Meniscus progression

Meniscal extrusion and morphology An association was observed between the grade of tear in the body of the meniscus and the presence of medial meniscal extrusion. More severe tears were associated with a more extruded meniscus. A similar relationship was not observed for the anterior aspect of the meniscus. The relationship between baseline medial meniscal extrusion and morphology is summarised in table 5.6.

Table 5.6.: Summary tables illustrating the relationship between baseline medial meniscal extrusion and morphology

	Medial meniscus extrusion grade (medial)				
		0	1	2	3
Meniscal morphology grade (body)	0	145(42%)	98(28%)	76(22%)	26(8%)
	1	16(26%)	17(28%)	24(39%)	4(7%)
	2	13(13%)	29(29%)	40(40%)	17(17%)
p-value*					<0.001

	Medial meniscal extrusion grade (anterior)				
		0	1	2	3
Meniscal morphology grade (anterior)	0	316 (65%)	78 (15%)	93 (19%)	3 (1%)
	1	2(40%)	1(20%)	2(40%)	0(0%)
	2	4(36%)	4(36%)	3(27%)	0(0%)
p-value					0.41

*Pearson's chi-squared test

Meniscal morphology In both outcome groups, the proportion of individuals who had progression of their medial meniscal tears over 24 months was similar in subjects with and without proximal tibia vara. No statistically significant differences were observed between the two groups.

Meniscal extrusion In both outcome groups, the proportion of individuals who had progression of their medial meniscal extrusion over 24 months was similar in subjects with and without proximal tibia vara. No statistically significant differences were

observed between the two groups.

Table 5.7 and table 5.8 summarise the rates of progression for TV- and TV+ individuals.

Table 5.7.: Summary table comparing rates of progression within each meniscal subregion for TV- and TV+ individuals; structural progression group

Subregion		Meniscus progression	
Anterior	n	Morphology	Extrusion
TV-	196	10 (5%)	23 (12%)
TV+	58	3 (5%)	7 (12%)
p-value		1.0	1.0
Body/Medial	n	Morphology	Extrusion
TV-	196	66 (34%)	75 (38%)
TV+	58	23 (40%)	25 (43%)
p-value		0.4	0.51
Posterior	n	Morphology	Extrusion
TV-	196	75 (38%)	
TV+	58	21 (36%)	
p-value		0.78	

Table 5.8.: Summary table comparing rates of progression within each meniscal subregion for TV- and TV+ individuals; non progression group

Subregion		Meniscus progression	
Anterior	n	Morphology	Extrusion
TV-	223	4 (2%)	1 (0.5%)
TV+	29	0 (0%)	1 (3%)
p-value		0.61	2 (1%)
Body/Medial	n	Morphology	Extrusion
TV-	223	40 (18%)	15 (7%)
TV+	29	9 (31%)	2 (7%)
p-value		0.09	17 (7%)
Posterior		Morphology	
TV-	223	34 (15%)	
TV+	29	7 (24%)	
p-value		0.17	

5.6. Discussion

This study used semi-quantitive MRI analysis to describe differences in the patterns of structural progression observed between subjects with proximal tibia vara (TV+) and those without (TV-). Progression of meniscal tears and extrusion was remarkably similar in TV+ and TV- subjects, suggesting that the increased medial joint space narrowing seen in the previous chapter was due to differences in cartilage progression. The knee maps illustrate a pattern of cartilage progression that could explain the increased medial joint space narrowing seen in TV+ subjects. In the structural progression group, an increased proportion of TV+ individuals demonstrated %FT progression in the medial central tibia indicating an intense focal degradation of cartilage over 24 months. The reciprocal finding that TV- subjects had more surface area (%SA) progression in the same subregion and the adjacent subregion (anterior medial tibia) suggests these subjects experience a more diffuse but less severe de-

gradation of cartilage within the medial compartment. A similar finding was not seen in the non progression group. In this group a significantly greater proportion of TV+ individuals experience %SA progression in the posterior medial femur subregion (p=0.004). This finding highlights the fact in the absence of radiographic joint space narrowing significant progression can still occurs in the medial compartment and this progression is more severe in TV+ subjects.

Patterns of knee osteoarthritis have been described before. Antero-medial osteoarthritis describes the relative sparing of the posterior tibial cartilage seen in end-stage medial compartment OA when the ACL is intact and has been reported using histological specimens [224, 225]. The knee maps in this chapter support the finding of very little cartilage damage in the posterior medial tibia at baseline and also very little structural progression in this region.

Using MRI, Cicuttini et al performed a longitudinal study in subjects with KL grade 1,2,3 knee osteoarthritis and identified an association between varus alignment and reduced cartilage volume in the medial compartment over 24 months [226]. In this study, cartilage volume loss was more significant in the femur than the tibia. Similar findings were reported in a cross-sectional study of subjects with end-stage osteoarthritis, however, varus alignment was more strongly correlated with cartilage volume loss in the tibia than the femur [227]. Varus malalignment has also been associated with medial tibiofemoral compartment cartilage loss defined using semi-quantitive scoring in the form of WORMS [228]. None of these studies reports on subregional variation in cartilage thickness.

A further study using quantitive assessment of cartilage volume and thickness divided the medial compartment into 8 subregions [229]. In the medial tibia, there was a highly significant difference in the rate of change between the subregions (P < 0.001), with the central and external subregions showing the highest rates of pro-

gression over an average of 26.6 months [229]. These subregion variations, also seen in the knee maps presented in this chapter, are lost when data is grouped to give compartment or knee-level outcomes and caution should be taken before grouping data in this way.

Several studies have identified varus alignment as being associated with medial meniscal pathology. Specifically, a varus mechanical axis angle has been associated with a 3.3-fold increase in medial meniscal posterior root tears [230] and is more commonly associated with medial meniscal root tears accompanied by posterior horn tears in end-stage OA [231]. The latter study reported that their findings were not extended to those subjects with proximal tibia vara leading the authors to conclude that it was overall alignment that conferred the greater influence on meniscal tear pattern. A cross-sectional study of over 2,000 participants reported prevalent varus alignment was significantly associated with prevalent medial meniscal extrusion [232]. The study presented in this chapter does not support these findings, however, it specifically looked at progression of meniscal tears and extrusion as opposed to cross-sectional prevalence. It may be that the follow-up period of 24 months was too short to evaluate the risk conferred by malalignment on meniscal pathology or it may be that the risk conferred by malalignment is specific to overall alignment and is not related specifically to proximal tibia vara.

This study has several limitations inherent to it. A prospective cohort study would be a preferable study design in order to evaluate differences in structural progression between subjects with proximal tibia vara and those without. The study in this chapter took subjects who had been pre-selected based on known OA outcomes and then attempted to describe their structural progression prospectively over 24 months. These participants are a highly selected group and there is a danger that they do not adequately reflect the population from which they were taken. Attempts were made

to mitigate this by separating the subjects based on the medial joint space narrowing as this is known be associated with proximal tibia vara. In doing so, the study group was effectively split into two halve which may have led to the study being underpowered.

The use of arbitrary thresholds within the knee maps to categorise progression groups may have led to differences being observed which simply reflect values that are either side of a threshold. Similarly, subregions with real differences in the raw data may have been overlooked if those differences were within the boundaries of a single threshold.

Despite these limitations there are strengths to this study. The knee maps have enabled a large amount of data to be compared simultaneously between two groups. Variations in baseline cartilage morphology and subsequent progression can be interpreted within each individual subregion and where differences are observed statistical analysis can be performed. With 14 subregions and two cartilage scores for each subregion a total 28 statistical tests would have been applied to the raw data for each of the two outcome groups. Following the knee maps this was reduced to 8 subregions in the structural progression group and 11 subregions in the non-progressor group, reducing the risks associated with multiple testing.

5.7. Conclusions

This chapter has used the MOAK scoring system to develop a novel method for illustrating structural progression in EKOA. It has been able to identify a unique pattern of structural progression in subjects with EKOA who demonstrate medial joint space narrowing over 24 months; TV+ subjects experiencing more focal full thickness cartilage progression in the central medial tibia and TV- subjects experiencing more diffuse surface area damage but less full thickness disease. Greater participant numbers with

subjects who are not selected based on pre-determined outcomes are required in order to establish the validity of these novel observations.

6. Surgical interventions for early structural knee osteoarthritis: a systematic review of the literature

6.1. Introduction

The previous chapters have detailed the natural history of symptomatic EKOA and identified factors associated with symptom worsening and structural progression. With the description of the condition and a greater understanding of the patterns of progression complete for EKOA, attention can be turned to intervention and treatment.

The previous chapters observed that whilst progression in EKOA does occur over 24 months, it is not common. It is, therefore, essential that any proposed surgical intervention for patients with symptomatic EKOA is carefully considered and done in light of the available evidence. Indeed, the James Lind Alliance, a patient-driven enterprise that works to prioritise unanswered questions about the effects of treatments, has highlighted the outcome of arthroplasty and non-arthroplasty surgery in this patient group as a critical research area (http://www.jla.nihr.ac.uk/top-10-priorities; last accessed 1st Sept 2017).

The current literature concerning osteoarthritis of the knee frequently takes an intervention based approach. Many studies do not stratify their results based on the severity of the disease at baseline or recruitment. Where early osteoarthritis of the knee is considered, there is often a focus on non-surgical or pharmacological treatments [185, 186, 187]. The following systematic review will assess the benefits of harms of surgical intervention in an effort to drive the direction of future research for this hard-to-treat patient group.

The protocol for this review has been developed under the guidance of the Cochrane Musculoskeletal group. The final protocol has been published on their database of systematic reviews [233].

6.2. Objective

To assess the benefits and harms of surgical intervention for the management of early structural knee osteoarthritis.

6.3. Materials and methods.

This systematic review will be conducted according to the guidelines recommended by the Cochrane Musculoskeletal Group Editorial Board [234].

6.3.1. Types of studies

Only randomised controlled trials (RCTs) and quasi-randomised controlled trials have been included. Studies reported as full text, those published as abstract only, and unpublished data were considered and there was no language restriction.

6.3.2. Types of participants

Adults (18 years of age and older) with a diagnosis of early structural knee osteoarthritis defined as the presence of pain and one of the following features:

Radiographic Kellgren-Lawrence grade 1, 2, 3 or equivalent.

MRI Cartilage degradation but minimal full-thickness loss (< 10% of surface area or < 1 cm) e.g. Boston Leeds Osteoarthritis Knee Score (BLOKS) cartilage morphology [73]:

- Extent of full-thickness loss (full-thickness loss score):
  - Grade 0: none
  - grade 1: <10%
- Per cent of subregion surface area affected by cartilage loss (any loss score):
  - grade 1: < 10%
  - grade 2: 10% to 75%
  - grade 3: > 75%

or any equivalent MRI scoring system such as MOAKS [76] or WORMS [209].

Arthroscopy Cartilage degradation but no more than one isolated full-thickness defect e.g. International Cartilage Repair Society (ICRS) score (ICRS 2000):

- grade 1: soft indentation
- grade 2: lesions extending down to < 50% of cartilage depth
- grade 3: cartilage defects extending down > 50% of cartilage depth (A) as well as down to calcified layer (B)

or any equivalent arthroscopic scoring system

Exclusion criteria Participants with the following co-morbidities/ characteristics were excluded:

- asymptomatic individuals
- end-stage osteoarthritis full-thickness cartilage loss (> 1 cm) or bony deformity (Kellgren-Lawrence grade 4), or both
- history of trauma, inflammatory arthropathy, metabolic bone disease or rheumatoid arthritis

If a trial included a subgroup of participants with EKOA (as defined above), and these results were reported separately from those with non-early osteoarthritis, then the data that related to EKOA was extracted. In the event that a trial appears to have a subgroup of participants with EKOA but has not reported their results separately, then attempts were made to contact the authors of the trial to ask them to provide the data for the EKOA subgroup.

6.3.3. Types of interventions

This study will take a disease based approach in order to assess the effectiveness of any surgical intervention employed in the management of symptomatic EKOA. Broadly speaking, such interventions fall under three categories; arthroscopic procedures, load-modifying procedures; arthroplasty surgery. A detailed description for these interventions and the evidence for them can be found in section 2.7.3.

6.3.3.1. Arthroscopic procedures

Arthroscopy is a minimally invasive procedure that is offered to people with osteoarthritis of the knee. Generally, arthroscopic procedures are intended to promote

a smooth excursion of the knee joint surface. This can be achieved by employing several different techniques:

- Irrigation; washing debris out of the knee joint
- Debridement or chondroplasty; removing torn or irregular cartilage
- Meniscal repair/ replacement; reconstituting a degenerate meniscus
- Cartilage regeneration; promoting cartilage growth in areas of deficiency (e.g. subchondral bone marrow stimulation or autologous chondrocyte implantation).

6.3.3.2. Load-modifying procedures

Load-modifying procedures for osteoarthritis of the knee joint aim to offload the diseased region of the knee joint. This can be achieved in a number of ways:

- High tibial osteotomy; cutting and re-shaping the peri-articular bone to shift the weight-bearing region of the knee to the disease free region
- Extracapsular device; to partially absorb the load passing through the medial compartment (e.g. KineSpring®, Moximed Inc, Hayward, CA, USA)
- Interpositional device; to remedy medial joint space narrowing caused by osteoarthritis and correct the intra-articular varus deformity bringing the leg into a more neutral alignment [168]
- Knee joint distraction (KJD); to reduce mechanical stresses on the joint surface [171].

6.3.3.3. Arthroplasty surgery

Knee replacement surgery is an established technique for end-stage osteoarthritis, with good clinical outcomes described for both total knee replacement and partial

knee replacement. However, the use of arthroplasty surgery is not routinely extended to those with less severe osteoarthritis, as it is associated with a poorer outcome [9, 7, 8]

6.3.4. Types of comparators

This systematic review considered the following comparisons:

- Trials comparing ANY type of surgical intervention (see Description of the intervention) with ANY non-surgical intervention (for example sham surgery, physiotherapy, bracing, non steroidal anti-inflammatory drugs, orthotics) in people with early structural knee osteoarthritis.
- Trials comparing ANY surgical intervention with ANY injectable therapy (for example steroid, hyaluronic acid, and regenerative therapies: stem cell therapy, platelet rich plasma, platelet lysates, prolotherapy).
- Trials comparing ANY surgical intervention with ANY OTHER type of surgical intervention.

Trials that compared the effect of a surgical intervention with or without ANY co-interventions were also included if the intervention and the co-intervention took place at the same time.

6.3.5. Types of outcome measures

Outcomes were based on a core set of outcome measures recommended for knee osteoarthritis and developed by consensus at OMERACT III [83]:

1. Pain with a hierarchy of 11 levels (when more than one is reported, the highest on the list will be used):

a) Pain overall

b) Pain on walking

c) Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain sub-scale

d) Pain on activities other than walking

e) WOMAC global scale

f) Lequesne osteoarthritis index global score

g) Other algofunctional scale

h) Patient's global assessment

i) Physician's global assessment

j) Other outcome

k) No continuous outcome reported

2. Physical function with a hierarchy of eight levels (when more than one is reported, the highest on the list will be used):

a) Global disability score

b) Walking disability

c) WOMAC disability sub-score

d) Composite disability scores other than WOMAC

e) Disability other than walking

f) WOMAC global scale

g) Lequesne osteoarthritis index global score

h) Other algofunctional scale

3. Radiographic joint structure changes according to the given hierarchy (the first two outcomes, minimum joint-space width and median joint-space width, are used most often):
    a) Minimum joint-space width
    b) Median joint-space width
    c) Semi-quantitative measurement
4. Quality of life
5. Short-term serious adverse effects from trials
6. Re-operation rate or conversion to total knee replacement (indicating failure of the primary intervention)
7. Withdrawals due to adverse events

If multiple time points are reported, we will group them into short- (less than one year), intermediate- (one to three years), and long- term (greater than three years) follow-up.

6.3.6. Search strategy

Search strategies were developed in conjunction with the Cochrane Musculoskeletal group. Electronic searches were performed of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE. Searches were also performed of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (www.who.int/ ictrp/en/). Databases were searched from their inception up until 7th June 2016 when the searches were run. There were no language restrictions. See Appendix B for the MEDLINE, CENTRAL and EMBASE search strategies.

Reference lists of all included studies were searched for additional studies. Relevant manufacturers' websites for trials information and contact individuals or organisations where also searched. PubMed was interrogated for errata or retractions from the included studies (www.ncbi.nlm.nih.gov/pubmed)

6.3.7. Data collection

6.3.7.1. Selection of studies

Studies were screened and data was extracted using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org).

Duplicate studies were identified and removed. Initially, the titles of all retrieved studies were screened by JP and one other reviewer. They were then coded with a 'yes', 'no' or 'maybe' for inclusion in the review. A full text review of these studies was then performed by JP and one other reviewer and studies were again coded 'yes', 'no' or 'maybe' for inclusion in the review. All disagreements were resolved through discussion.

Data was extracted by JP and double checked by a second reviewer. If more than one outcome measure was reported in a trial, a single outcome was prioritised based on the hierarchy of major outcomes listed above in section 6.3.5. Where both final values and change from baseline values were reported for a given outcome, the final value was extracted; if both unadjusted and adjusted values for the same outcome were reported, then the unadjusted value was extracted. Data was transferred into Review Manager (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

6.3.7.2. Assessment of Risk of Bias

Risk of bias was assessed according to the following domains:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Major baseline imbalance
8. Differences in rehabilitation

Sources of bias were graded high, low, or unclear risk and summarised in a 'Risk of bias' table. When considering treatment effects, the risk of bias for the studies that contributed to that outcome were taken into account.

6.3.7.3. Measuring treatment effect

Continuous data was analysed as mean difference or standardised mean difference (SMD), depending on whether the same scale was used to measure an outcome, with corresponding 95% confidence intervals. Data was presented as a scale with a consistent direction of effect across studies.

For dichotomous outcomes the event rates were very low, as such the number needed to treat for an additional harmful outcome (NNTH) and the number needed to treat for an additional beneficial outcome (NNTB) could not be calculated. The absolute risk difference could also not be calculated as there were no between-group differences for dichotomous outcomes.

For continuous outcomes, the absolute benefit was calculated as the improvement in the intervention group minus the improvement in the control group and the relative

difference in the change from baseline was calculated as the absolute benefit divided by the baseline mean of the control group.

6.3.7.4. Unit of analysis issues

If multiple time points were reported, they were grouped into short- (up to one year), intermediate- (one to three years), and long- term (greater than three years) follow-up. Where multiple time points with a group were reported, then data was extracted that related to the later time point (for example if one trial reports outcomes at six months and one year, we extracted the one-year results only).

6.3.7.5. Missing data

Trial investigators were contacted to obtain any missing numerical outcome data. Where possible, missing standard deviations were imputed from other statistics such as standard errors, confidence intervals, or P values, according to the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions [235]. If standard deviations could not be calculated then they were imputed (for example from other studies in the meta-analysis).

6.3.7.6. Assessment of heterogeneity

Clinical and methodological diversity in terms of participants, interventions, outcomes, and study characteristics for the included studies was performed by visual inspection of the forest plot for obvious differences in results between the studies, and by using the I2 and Chi2 statistical tests. As recommended in the Cochrane Handbook for Systematic Reviews of Interventions [235], the interpretation of an I2 value of 0% to 40% might 'not be important'; 30% to 60% may represent 'moderate' heterogeneity; 50% to 90% may represent 'substantial' heterogeneity; and 75% to 100% represents 'considerable' heterogeneity.

6.3.7.7. Data synthesis

Meta-analyses were performed when the treatments, participants, and the underlying clinical questions were similar enough for pooling to make sense. Data was analysed separately for each of the three main comparisons: surgical intervention versus non-surgical intervention, surgical intervention versus injectable therapy, and surgical intervention versus other surgical intervention.

There was significant clinical heterogeneity between participants across different trials. As such, a random-effects model was used for the meta-analysis.

6.3.7.8. Quality of evidence

The quality of evidence of included studies was reviewed by JP and a second reviewer using GRADEpro Guideline Development Tool (McMaster University, 2015, Evidence Prime, Inc.; available from gradepro.org. Five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) were used to assess the quality of evidence. Decisions to down- or up-grade the quality of studies are explained in section 6.4.8; effects of interventions.

6.4. Results

A total of 5 studies involving 568 subjects were selected for this review.

6.4.1. Results of the search

The search strategy retrieved 14,592 citations from the following databases:

- Cochrane Central Register of of Controlled Trials, CENTRAL (3,467 citations),
- OVID MEDLINE (6,532 citations) and

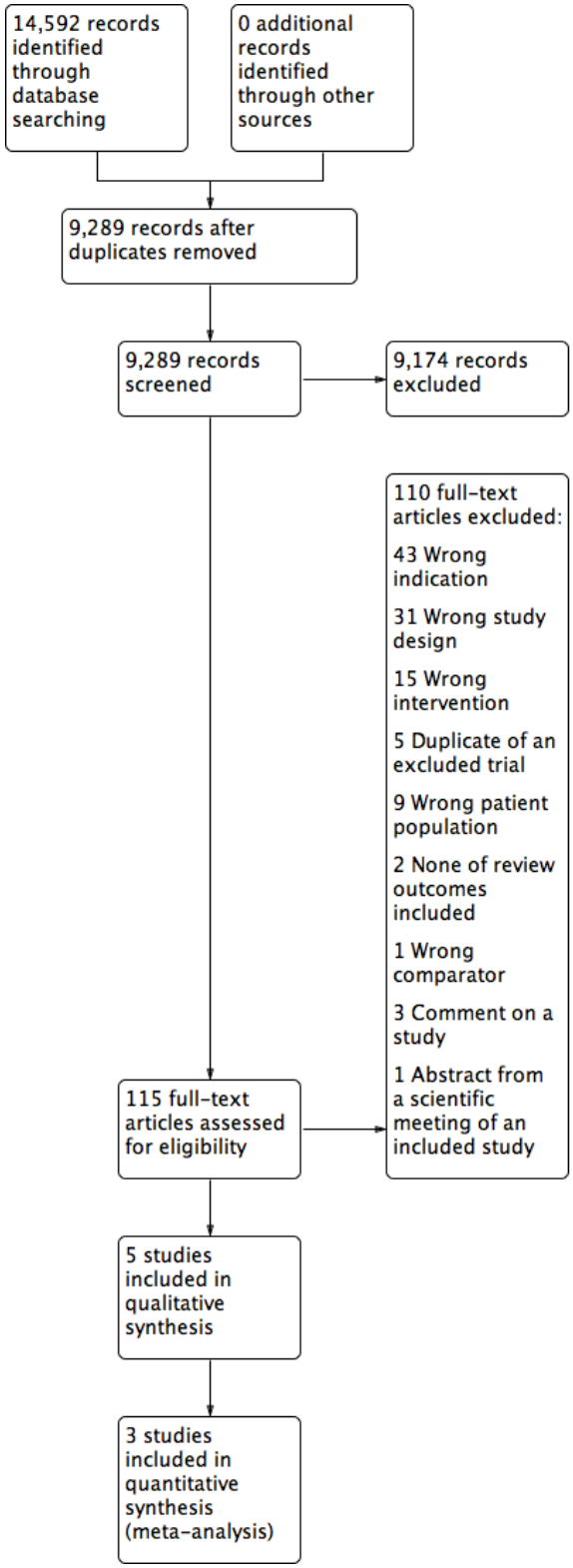
- OVID EMBASE (4,593 citations).

A total of 5,300 duplicate studies were identified, leaving 9,289 potentially eligible citations. After title and abstract screening a total of 115 full reports were retrieved. After full text screening 5 reports were included and 110 reports were excluded from this review (see Figure 6.4.1, PRISMA diagram). One ongoing trial was identified from clinicaltrial.gov but it is still actively recruiting and not due for completion until 2019.

Full details of the search strategy and results are given in Appendices B.1, B.2 and B.3.

All available data for four of the included was extracted from published reports (Chang 1993 [236]; Forster 2003 [237]; Katz 2013 [238]; Saeed 2015 [239]). Following communication with the contact author, one study provided data that was refined to meet our inclusion criteria (VanDerWoude 2016 [188]. Details of this adjustment are discussed in characteristics of included studies (section 6.4.2). All studies were published in English. No errata or retractions were identified.

Figure 6.4.1.: Study flow diagram illustrating the number of studies identified, included and excluded, and the reasons for exclusions



6.4.2. Characteristics of included studies

The five included studies were randomised parallel-group controlled trials. Pre-published protocols were available for two of the trials (VanDerWoude 2016 [188]; Katz 2013 [238]).

The studies reported results on a total of 566 participants.

Chang et al, randomised 34 participants, across two hospitals in the US, to two groups and reported results for 32 [236]. The study population was largely older females with moderate symptomatic osteoarthritis (mean age 62.7yrs; 72% female). Subjects with Kellgren-Lawrence (KL) grade 4 radiographic changes were excluded.

Forster et al, randomised 38 participants, across two hospitals in the UK, to two groups and reported results for 32 [237]. Their study population with a mean age of 61.4yrs. They did not report the distribution of gender. All subjects had symptomatic osteoarthritis with some residual joint space on weight-bearing radiographs (equivalent to KL grade<4)

Katz et al, randomised 351 participants, in blocks of varying sizes, to two groups and reported results on 320 participants [238]. This multi-centre trial was conducted across seven separate tertiary referral centres in the US. The study population was largely older males (mean age 58.2yrs; 28.5% female) with MRI confirmed meniscal tears. All subjects had evidence on knee MRI of osteophytes or full-thickness cartilage defect; or plain radiographic evidence of osteophytes or joint space narrowing. Patients with KL grade 4 were excluded.

Saeed et al, performed a single centre study in Pakistan and randomised 120 participants and reported results for all [239]. The study population was largely older females (all subjects >40yrs; 81.7% female) and subjects with KL grade 2 or 3 were included.

VanDerWoude et al randomised 69 patients in blocks of 6 at a ratio of (control

2:1 intervention) across two sites in the Netherlands [188]. The study population that was largely older males (mean age 50yrs; 35.8% female). The published report included participants with severe osteoarthritis (KL grade 4). In order to meet the inclusion criteria for this review a refined dataset (without KL grade 4 subjects) was obtained from the corresponding author and results for 62 participants were obtained.

6.4.3. Interventions

6.4.3.1. ANY type of surgical intervention versus ANY non-surgical intervention

Katz et al compared a surgical intervention (arthroscopic partial meniscectomy) with a non-surgical intervention (physical therapy) [238].

6.4.3.2. ANY type of surgical intervention versus ANY injectable therapy

Three trials compared a surgical intervention against injectable therapy (Chang 1993 [236]; Forster 2003 [237]; Saeed 2015 [239]). Chang et al compared arthroscopic surgery (debridement ± synovectomy ± chondroplasty) to closed-needle joint lavage. Forster et al compared arthroscopic surgery (washout ± debridement) to hyaluronic acid injection (five intra-articular injections of 20mg Hyalgan at 1-week intervals). Saeed et al compared arthroscopic surgery (debridement) to hyaluronic acid injection (five intra-articular injections of hyaluronic acid at 1-week intervals). Dose of hyaluronic acid not described.

6.4.3.3. ANY type of surgical intervention versus ANY OTHER surgical intervention

VanDerWoude et al compared a surgical intervention (high tibial osteotomy) with another surgical intervention (knee joint distraction)[188].

6.4.4. Outcomes

All studies reported at least one major outcome described in our protocol. All outcomes that related to knee pain and or physical function used at least one validated instrument. When a study provided data on more than one pain or physical function scale, we used the hierarchy described in our protocol to select a single outcome from each domain.

6.4.4.1. ANY type of surgical intervention versus ANY non-surgical intervention

Katz et al assessed pain using the pain section within the Knee injury and Osteoarthritis Outcome Score (KOOS) and function using the physical function scale of the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) [238]. Serious adverse events, conversion to total knee replacement and withdrawals from the study were also reported. Radiographic structural progression was not reported.

6.4.4.2. ANY type of surgical intervention versus ANY injectable therapy

All three studies in this subgroup included a pain outcome (Chang 1993 [236]; Forster 2003 [237]; Saeed 2015 [239]). No study reported radiographic structural progression. Chang et al reported the pain and function domains of the Arthritis Impact Measurement Scales (AIMS). A Visual Analogue Scale of Well-being was used to assess Quality of Life outcome at 12 months [236]. Serious adverse events, conversion to total knee replacement and withdrawals from the study due to adverse events were not reported.

Forster et al used the Visual Analogue Scale (VAS) to assess pain outcomes [237]. They reported the Lequesne Index (LI) and the functional component of the Knee Society Scoring (KSS) system to assess functional outcomes. The control and in-

tervention groups were not matched at baseline for the KSS function score with the intervention group having poorer function. As such the LI, for which the groups were matched, was selected as the functional outcome for the study. Conversion to total knee replacement was reported. Serious adverse events and withdrawals from the study due to adverse events were not reported.

Saeed et al used the pain component of the Knee Society Scoring System as their primary outcome [239]. The study also reported no loss to follow up from the point of randomisation and no significant adverse events. Outcomes related to function, quality of life and conversion to TKR were not included.

6.4.4.3. ANY type of surgical intervention versus ANY OTHER surgical intervention

VanDerWoude et al provided our review with an amended dataset which contained results for participants relevant to our study [188]. Several outcomes were reported that related to pain and function. According to our hierarchy of outcomes, the Visual Analogue Scale and WOMAC were selected for pain and function respectively. A radiographic structural progression outcome was included (minimum Joint Space Width). The EQ-5D index (0-1, 1 being the best) was used to assess improvement in quality of life. Serious adverse events, withdrawals due to adverse events and re-operation rates were reported.

6.4.4.4. Timing of outcome assessment

None of the included studies reported outcomes beyond 12 months. In accordance with the published protocol, all outcomes were considered at the longest time-point reported within this early outcome period (see subsection 6.3.7.4). Four studies reported outcomes at 12 months (Chang 1993[236]; Forster 2003 [237]; Katz 2013 [238]; VanDerWoude 2015 [188]) and a single study reported outcomes at 6 months

(Saeed 2015 [239]).

6.4.5. Risk of bias in included studies

A summary of the risk of bias observed across the five studies is given in figures 6.4.2 and 6.4.3.

6.4.5.1. Allocation concealment

Three studies mentioned a randomisation element to the study but did not describe the randomisation process leading to an unclear risk of selection bias (Chang 1993 [236]; Forster 2003 [237]; Saeed 2015 [239]). Both Katz et al and VanDerWoude et al used computer generated randomisation methods (low risk of bias). Sealed envelopes were used in two studies (Chang 1993 [236]; Forster 2003 [237]). Chang et al did not explicitly state the use of envelopes in their study, however, they reference another study in their methodology section which outlines in more detail the randomisation process [240]. The remaining studies did not report a method of allocation concealment (unclear risk) (Katz 2013 [238]; Saeed 2015 [239]; VanDerWoude 2016 [188]).

6.4.5.2. Blinding

All studies were considered high risk of performance bias as in all cases participants and personnel were not blinded to the treatment allocation. In order to accurately describe the risk of detection bias we grouped outcomes, where necessary, according to whether the patient reported the outcome (subjective outcome) or an independent assessor recorded the outcome (objective outcome). Subjective outcomes were considered to be high risk of bias in all cases as the participant reporting the outcome were aware of their treatment allocation (Chang 1993 [236]; Forster 2003 [237];

Katz 2013 [238]; Saeed 2015 [239]; VanDerWoude 2015 [188]). VanDerWoude et al assessed structural progression using an assessor "blinded to the order of acquisition" [188]. The presence or absence of a metal plate from those that underwent osteotomy would have made it clear which group the participant had been randomised. However, private correspondence with the authors of this study confirmed that the radiographic assessments were made by non-clinical staff who were unaware of the relevance of the metal plate (low risk) and performed in accordance with their previously published KIDA protocol [241].

6.4.5.3. Incomplete outcome data

All studies were considered to be low risk for attrition bias. One study reported no loss to follow-up following randomisation (Saeed 2015 [239]). The remaining studies experienced losses to follow-up that were small and similarly sized in each treatment arm (Chang 1993 [236]; Forster 2003 [237]; Katz 2013 [238]; VanDerWoude 2015 [188].

6.4.5.4. Selective reporting

Two studies demonstrated outcomes that were consistent with pre-published protocols (Katz 2013 [238]; VanDerWoude 2015 [188]) and therefore at low risk of reporting bias. Both Chang et al and Forster et al described acceptable and expected outcomes using validated instruments to assess both knee pain and function (low risk of bias) [236, 237]. Saeed et al reported the Knee Society Pain Score as the single outcome of interest, however, in their methodology they discuss the use of Knee Society Score to assess range of motion, function and stability [239]. These are not included in the analyses suggesting a high risk of reporting bias.

6.4.5.5. Other sources of bias

No other sources of bias were identified in two studies (Chang 1993 [236]; Saeed 2015 [239]). Selection bias due to differences in important baseline prognostic indicators was present in two studies (Forster 2003 [237]; VanDerWoude 2015 [188]). The functional scores in the arthroscopy were significantly worse pre-intervention in the study by Forster et al. A significant difference in female gender between the HTO group and the knee joint distraction group (41% vs. 29 %) was observed in the study by VanDerWoude et al. The study by Katz et al was also at high risk of further selection bias. Only 26% of eligible patients were enrolled which may have been due to both patients' preferences and selective enrolment by the surgeon [238]. There was also a high rate of cross-over in this study with 30.2% of patients assigned to physical therapy crossing over to arthroscopy within 6 months of the study start time [238].

Figure 6.4.2.: Risk of bias graph; including judgements about each risk of bias item presented as percentages across all included studies.

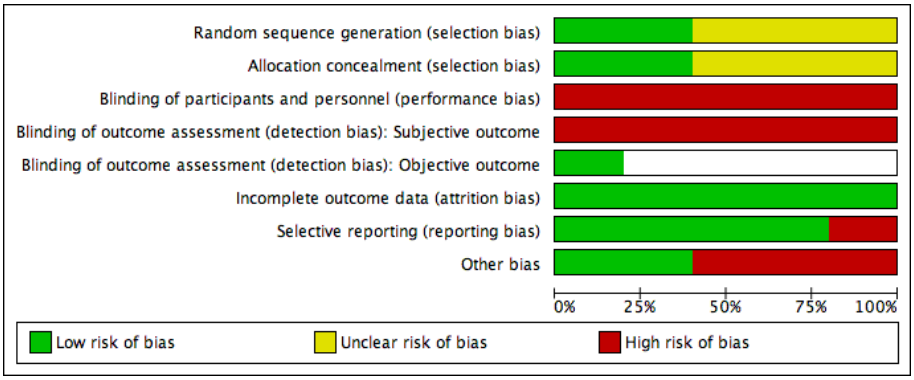
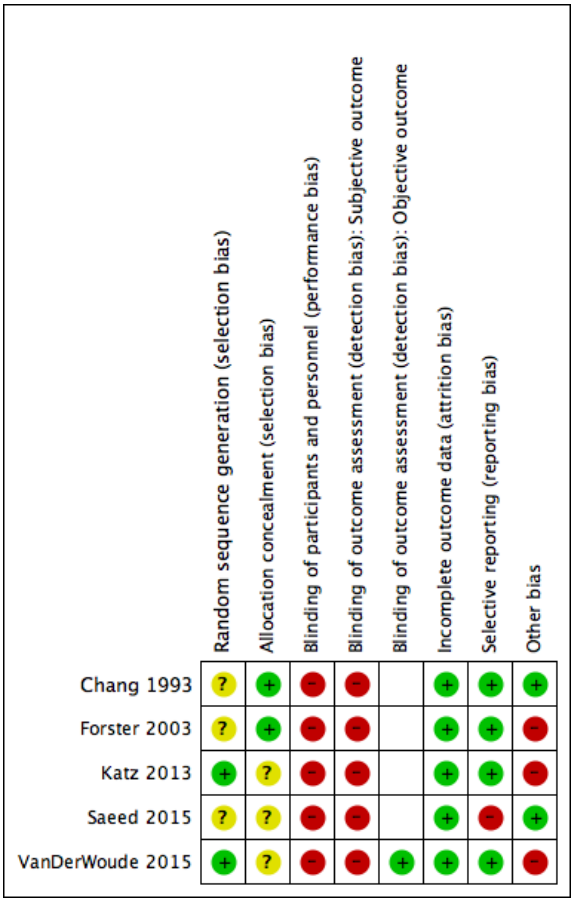


Figure 6.4.3.: Risk of bias summary; including judgements about each risk of bias item for each included study.



6.4.6. Characteristics of excluded studies

Full text reviews were performed on 115 studies and 110 were excluded from the review (see figure 6.4.1). Reasons for exclusion were as follows; wrong indication (n=43): wrong study design (n=31), wrong intervention (n=15), duplicate of an already excluded study (n=5), wrong patient population (n=9), none of the review's outcomes measured (n=2), wrong comparator (n=1), comment on a study/erratum (n=3), abstract from a scientific meeting for an included study (n=1).

Corresponding authors for trials were contacted if some, but not all, their participants appeared to fit our inclusion criteria to see if they would provide an amended dataset which included only those participants relevant to our review [242, 243, 140, 244, 245, 246, 247, 248, 249, 250]. None of these studies provided amended datasets. Full references for the excluded studies are given in appendix C.

6.4.7. Characteristics of ongoing studies

Searches of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform revealed one trial which met the inclusion criteria for our review. This trial is still actively recruiting and not due for completion until 2019. Details of this study are available in appendix D.

6.4.8. Effects of interventions

6.4.8.1. ANY type of surgical intervention versus ANY non-surgical intervention

Katz et al compared arthroscopic partial meniscectomy (APM) to physical therapy (PT). Due to the high risk of performance and detection bias and the high rate of cross-over from the control group to the intervention group the quality of evidence

for this study was considered to be low [238].

Pain Both groups demonstrated improved KOOS pain scores at 12 months (Mean score APM= 19.1 [16.4 to 21.9]; PT=19.3 [16.6 to 22.0]) compared to baseline scores. However, there was no observed between-group difference in the 12 month pain score (Standardised mean difference (SMD)= -0.4 [-4.8 to 4.0]).

Function Both groups demonstrated improved WOMAC physical-function scores at 12 months (Mean score APM= 13.7 [11.2 to 16.2]; PT= 14.5 [12.0 to 16.9]) compared to baseline scores. There was no observed between-group difference in function score (SMD at 12 months= 0.7 [-3.5 to 4.9]).

Other No significant between-group differences in the frequency of serious adverse events was noted (APM n=3; PT n=2). No significant differences were observed in the number of individuals who underwent conversion to total knee replacement within 12 months (APM n=5; PT n=3). Two subjects died and were withdrawn from the study (APM n=1; PT n=1).

6.4.8.2. ANY type of surgical intervention versus ANY injectable therapy

Three studies compared a surgical (arthroscopic) intervention to an injectable therapy (Chang 1993 [236]; Forster 2003 [237]; Saeed 2015 [239]). All studies had a high risk of detection and performance bias and were considered to be of low quality. The study by Saeed et al was also at high risk of reporting bias, had significant deficiencies in the way the data was reported and reported a markedly different outcome than the other two studies. As such outcomes that included this study were considered very low quality.

Pain Using the pain sub-scale of the AIMS, Chang et al observed no improvement in either group at 12 months compared to baseline. No between group difference was observed at 12 months (SMD at 12 months= 0.15 [-0.55, 0.85]). Forster et al used VAS to assess pain outcomes. The Standard Deviation (SD) was not reported and could not be provided by the authors. As such the SD was imputed from another study included in this review (VanDerWoude 2015). No between group difference was observed at 12 months (SMD at 12 months = 0.00 [-0.69 to 0.69]). The data presented in the study by Saeed et al had to be re-shaped in order to obtain a mean and standard deviation for each group. The study used the Knee Society pain score and reported clinical improvement in both groups at 12 months. A between group difference was reported in the pain score at 12 months; with the control group experiencing less pain at 12 months (SMD at 12 months = 0.92 [0.54, 1.30]) [239]. There was marked heterogeneity between these three trials (I^2= 73%). As such we used a random effects model to pool the data. No between-group difference was observed in the pain score at 12 months was observed in (SMD at 12 months= 0.41 [-0.23, 1.05]).

Function Using the physical function sub-scale of the AIMS, Chang et al observed an improvement in function at 12 months. There was, however, no between group difference in the 12 month functional score (SMD at 12 months = -0.26 [-0.96, 0.45]. Forster 2003 used the Lequesne index (LI) to report functional outcomes. The SD was not reported and could not be provided by the authors. An SD could not be imputed from another study included in this review. As such an SD was imputed using a peer-reviewed article that included patients with symptomatic knee osteoarthritis [251]. Both groups reported improved function at 12 months but there was no between-group difference observed at 12 months (SMD at 12 months= 0.56 [-0.15, 1.27]). The pooled data of these two studies demonstrated no between-group difference in patient

reported function at 12 months (SMD 0.15 [-0.65, 0.95]).

Other No between-group differences were reported for the single study (Chang 1993 [236]) that reported a quality of life outcome (VAS well- being) (SMD at 12 months 0.09 [-0.61, 0.79]). Forster et al reported no significant difference in conversion to TKR at 12 months (arthroscopy n=1, hyalgan injection n=2) [237]. Saeed et al reported no serious adverse event or withdrawals from the study for either group [239]. The remaining two studies did not comment on serious adverse events or withdrawals from the study due to adverse events.

6.4.8.3. ANY type of surgical intervention versus ANY OTHER surgical intervention

VanDerWoude et al compared two types of surgical intervention; knee joint distraction (KJD) versus high tibial osteotomy (HTO). The study was at high risk of performance bias. Subjective outcomes were at high risk of detection bias (low quality), however, the authors had attempted to mitigate risk of detection bias for objective outcomes including structural progression (moderate quality).

Pain Both groups had less pain at 12 months using the VAS pain outcome. There was no significant between-group difference in the pain score at 12 months (SMD at 12 months= 0.36 [-0.17, 0.89]).

Function Using the WOMAC function score, both interventions led to an improvement in these scores at 12 months compared to baseline. No between-group differences were observed in function at 12 months (SMD=-0.23 [- 0.76, 0.30]).

Other No between group differences were observed at 12 months using the EQ5D outcome (SMD =0.37 [-0.20, 0.94]). No between-group differences were observed for

structural progression (SMD= -0.37 [-0.94, 0.20]). No participants in either group experienced a serious adverse event, a withdrawal due to an adverse event, a return to theatre or conversion to TKR.

Figure 6.4.4.: Forest plot of comparison: Early pain outcomes (6-12 months).

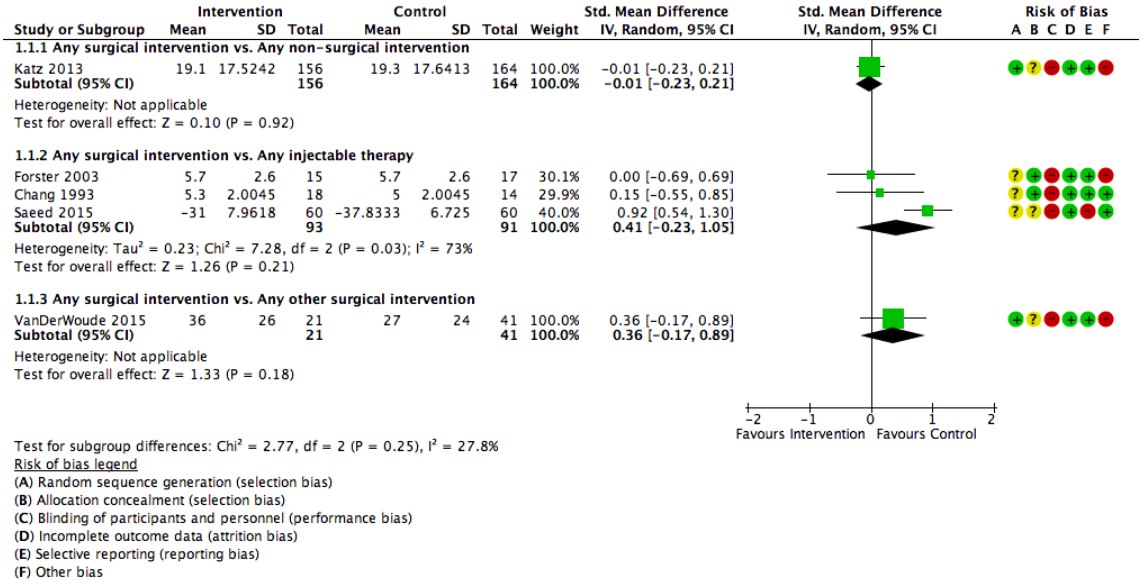
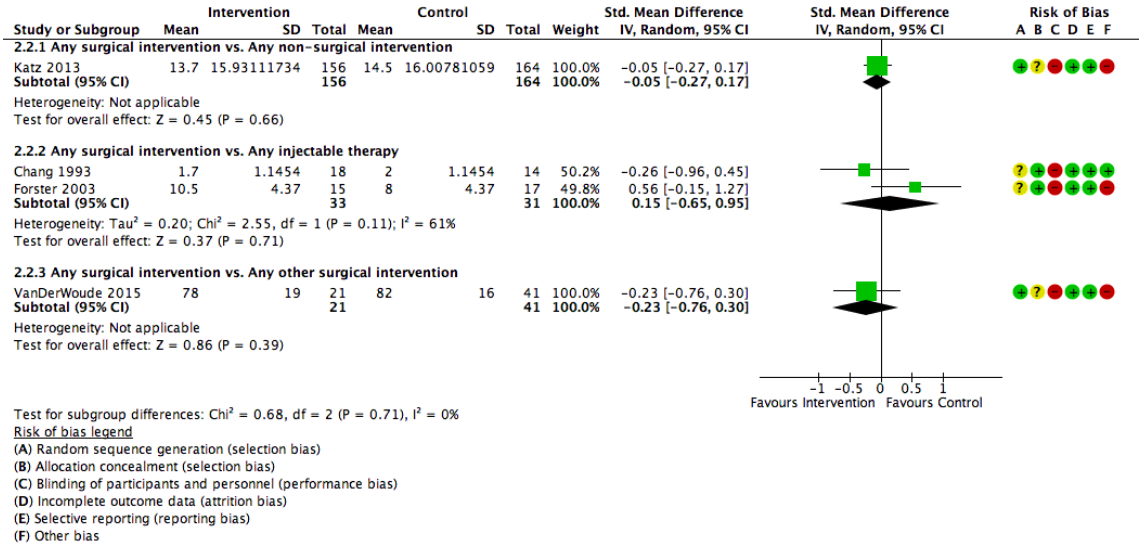


Figure 6.4.5.: Forest plot of comparison: Early functional outcomes (6-12 months).



6.5. Discussion.

6.5.1. Summary of main results

The objective of this review was to assess the benefits and harms of surgical intervention for the management of early structural knee osteoarthritis (EKOA). The definition of EKOA was deliberately kept broad and included symptomatic patients in whom osteoarthritis had been confirmed but excluded people with diffuse full-thickness disease who would be considered suitable for arthroplasty surgery. Despite this broad inclusion criteria our search yielded only 5 trials involving 568 participants. All the trials compared a surgical intervention with either a non-surgical intervention (Katz 2013 [238]), an injectable therapy (Chang 1993 [236]; Forster 2003 [237]; Saeed 2015 [239]) or another surgical intervention (VanDerWoude 2016 [188]). No trial included a sham control group. No trial reported results beyond one year.

Within-group comparisons showed short-term improvements in knee pain and function could be achieved regardless of intervention [236, 237, 238, 239, 188]. The patient reported pain and functional profiles, however, were not significantly different when between-group comparisons were made. When comparing surgical intervention and non-surgical intervention there was low quality evidence, from one trial, indicating no difference between the two groups in patient-reported pain and function at 1 year (Katz 2013 [238]. When comparing surgical intervention and injectable therapies there was very low quality evidence, from three trials, indicating no between-group difference in patient-reported pain at 6-12 months (Chang 1993 [236]; Forster 2003 [237]; Saeed 2015 [239]). When comparing surgical intervention and injectable therapies there was low quality evidence, from two trials, indicating no difference between the two groups in patient-reported function at 1 year (Chang 1993 [236]; Forster 2003 [237]). When comparing one surgical intervention to another surgical intervention

there was low quality evidence from one trial, indicating no difference between the two groups in patient-reported pain and function at 1 year VanDerWoude 2016 [188]. Serious adverse events were reported in three of the included studies (Katz 2013 [238]; Saeed 2015 [239]; VanDerWoude 2016 [188]). Adverse events following surgery are infrequent but potentially serious. There is insufficient evidence provided in this systematic review to define the risk of a serious adverse event occurring and reporting of adverse events related to surgery in future studies is strongly recommended.

Despite an extensive search, this systematic review has not been able to find any robust evidence to support surgical intervention in the management of early to moderate symptomatic osteoarthritis of the knee. The included studies, are generally small, heterogenous and suffer significant biases. As such there is also insufficient evidence to firmly oppose the use of surgery in this patient group.

6.5.2. Overall completeness and applicability of evidence

As previously discussed, the available evidence in the included studies is small, heterogeneous and insufficient to draw any firm conclusion to support or oppose the use of surgical intervention in the management of early knee osteoarthritis (EKOA). The definition of EKOA used in this review was based on radiographic findings and or a description of mild to moderate cartilage degradation. One could argue that a degenerate meniscal injury in the absence of trauma marked the onset of knee osteoarthritis regardless of whether or not the cartilage surface remained intact. Trials reporting on treatment of degenerate meniscal injuries that actively excluded subjects with osteoarthritis were not included in this review. Furthermore, only very small full-thickness cartilage lesions were considered in this review in attempt to exclude patients with diffuse full-thickness disease who would be eligible for arthroplasty surgery. Trials investigating cartilage regeneration procedures involving larger

full-thickness defects either in the presence or absence of osteoarthritis were excluded.

Of the five included studies, four investigated an arthroscopic procedure [236, 237, 238, 239]. Chang et al investigated arthroscopic debridement including meniscal resection where necessary [236]. Forster et al primarily performed an arthroscopic washout, however, debridement was performed where necessary [237]. Katz et al investigated arthroscopic partial meniscectomy using a standardised approach which allowed for the excision of loose fragments of cartilage and bone where necessary [238]. Saeed et al did not describe the extent or nature of the arthroscopic debridement undertaken in their study [239]. Clearly, within the studies involving arthroscopic surgery there is marked heterogeneity in the type of procedure performed both within the same study and between different studies.

VanDerWoude 2015 compared two surgical procedures; knee joint distraction and high tibial osteotomy [188]. There were no trials found comparing either of these interventions to a sham or non- surgical control group. There are several surgical procedures for which no reported randomised trials were found:

1. Cartilage regeneration procedures
2. Interpositional arthroplasty
3. Meniscal repair or transplant
4. Extracapsular load modifying devices (e.g. KineSpring® (Moximed Inc, Hayward, CA, USA))
5. Knee replacement surgery (e.g. total knee replacement, partial knee replacement)

Finally, osteoarthritis is a chronic condition and the follow-up period for studies included in this review was too short (6-12 months) to be able to make any conclusions

regarding the long-term outcomes for a chronic disease such as knee osteoarthritis. It is not possible to draw any conclusions from this review on the long-term efficacy of surgery in early knee osteoarthritis in terms of progression of symptoms or pathology.

As discussed earlier, several several study groups were contacted to see if they could provide amended data that included only those participants relevant to our trial. The inclusion of this data may well have led to the opportunity of pooling more data and drawing more robust conclusions. We identified one ongoing study that appears to fit the inclusion criteria for our review, however, this study is still recruiting and will not be completed until 2019 (see appendix D).

6.5.3. Quality of the evidence

The quality of this review is limited by the small number and high degree of heterogeneity in the included studies. Only two studies adequately described the randomisation process(Katz 2013 [238]; VanDerWoude 2016 [188]) and only two studies adequately described the used of sealed envelopes to conceal the treatment allocation (Chang 1993 [236]; Forster 2003 [237]. The quality of evidence ranged from moderate to very low depending on the included study and the outcome of interest. In all studies, participants were aware of their treatment allocation and the majority of outcomes were patient-reported in nature. As such the risks of performance and detection bias were high in all included studies. Only one study, was able to blind assessors for an objective outcome (radiographic structural progression)(VanDerWoude 2016 [188]).

Katz et al, investigated the role of arthroscopic partial meniscectomy for treating degenerative meniscal tears. This study contributed 330 of the however high rate of cross-over in this study with 30.2% of patients assigned to physical therapy crossing over to arthroscopy within 6 months of the study start time [238]. Outcomes were, however, reported on an intention to treat basis meaning that almost a third of

the outcomes in the physical therapy had actually undergone arthroscopic surgery. Saeed et al, reported on arthroscopic debridement versus hyaluronic acid injections and due to several methodological flaws was at high risk of detection, performance and reporting bias [239]. The authors concluded that the group receiving injectable therapy improved more than the arthroscopy group at 6 months, however, they failed to identify or report if this difference was significant. The outcome of this study was markedly different to the other two studies comparing surgical intervention vs. injectable therapy (Chang 1993 [236]; Forster 2003 [237]) and the results should be interpreted with caution. Given the low quality of evidence presented in this review, future studies if well-designed may have a significant impact on the confidence taken from the observed treatment effects.

6.5.4. Potential biases in the review process

This review was performed in accordance with the published protocol [233]. The search strategy was broad and comprehensive with no language barrier. As such the risk of missed trials is likely to be small but cannot be completely eliminated. The corresponding authors for trials were contacted if some but not all their participants appeared to fit our inclusion criteria. The inclusion of data from these trials would have provided more data which may have allowed for more robust meta-analysis and or led to more solid conclusions being drawn. It is possible that other studies would have been able to distinguish their participants by severity of osteoarthritis, however, if this was not clearly outlined in the abstract or results tables then the studies were not contacted. The use of SMDs as a common measure of effect size was necessary as all of the included studies used different instruments to assess the same outcome domains. Differences in the responsiveness of each outcome instrument may invalidate this statistical approach.

6.6. Future work

This systematic review has highlighted key deficiencies in the literature regarding the surgical management of early knee osteoarthritis. An awareness of this patient group as being distinct from those patients with end-stage or no osteoarthritis is necessary if these deficiencies are to be rectified. Subjects with end-stage osteoarthritis should not be grouped with subjects with relatively minor degenerative changes unless there is a clear and justifiable reason for doing so. In such instances, post-hoc analysis of the effect of grade of osteoarthritis on outcome frequently leads to a loss of statistical power and failure to make firm conclusions.

The biases seen in our included studies can be mitigated by clearly stating both the method of randomisation and concealment. Blinding participants is generally not possible unless a sham type procedure is being proposed. However, objective outcomes including structural progression lend themselves to blinding. The challenges associated with patient preference and cross-over will need to be anticipated when designing trials and interpreting their results. Adverse events need to be clearly reported so that potential harms of surgical intervention can be easily identified. Well-designed large trials are required to determine the efficacy of commonly practiced surgical procedures in this patient group. These interventions are not without risk and at present the evidence to support their use is of poor quality. There has been no sham trials for this condition and only one trial that compared surgical intervention with physical therapy (Katz 2013 [238]). There has been no trials reporting outcomes beyond 12 months.

6.7. Conclusion

This review has identified moderate to very low quality evidence from five trials involving 568 participants. Surgical intervention led to short-term (6-12 months) improvements in pain [236, 237, 238, 239, 188] and function [237, 238, 188] that were non-superior to physical therapy or injectable therapy. Knee joint distraction and high tibial osteotomy led to short-term improvements (12 months) in pain and function but neither intervention was superior to the other [188]. There is insufficient evidence provided in this systematic review to define the risk of a serious adverse event associated with surgical intervention for this condition. This review has not been able to comment on the effects of surgical intervention in this patient group beyond 12 months.

7. Outcome and Risk for a Neutralising High Tibial Osteotomy in the Varus (early OA) Knee.

7.1. Introduction

Osteoarthritis (OA) of the knee is a major health concern with over 6 million people in the UK suffering from painful osteoarthritis in one or both knees [252]. Work done in our unit has demonstrated that up to 78% of patients with early to moderate knee OA have pain and functional profiles equivalent to those with end-stage disease [4]. Whilst effective in those with full-thickness disease, arthroplasty surgery is not routinely offered to those with less severe OA as it is associated with a poorer outcome [8, 7, 9]. These patients, with symptomatic partial thickness osteoarthritis, represent a 'treatment gap' where management options are limited [10]. Indeed, the previous chapter highlighted the fact that, whilst many surgical interventions are available, there are very few trials investigating subjects with symptomatic EKOA. It is beyond the scope of this thesis to consider each of these interventions in turn.

The efficacy of arthroscopy has received significant attention in the medical literature. Whilst there are undoubtedly questions remaining regarding its role in EKOA, the trials based research required to compete with the exisiting literature is beyond the scope of this thesis. Knee distraction therapy is an interesting development in the management of EKOA, however, it is currently a niche surgical intervention with only one centre in Europe offering published reports on its efficacy [188]. It is not routinely practiced in the UK and as such implementing and assessing its usefulness within the context of this thesis was not possible.

A valgising high tibial osteotomy (HTO) is an alternative treatment option. Advances in surgical techniques and an improved understanding of biomechanical principles around the knee have brought osteotomy surgery into the modern age. In particular, low profile plates with high tensile strength have enabled medial opening wedge HTOs to be performed with low complication rates and early mobilisation [253].

Typically, surgeons have aimed to over-correct patients into a valgus position in an attempt to offload the diseased compartment. Fujisawa [153] described a point at 30-40% of the width of the lateral compartment. This equates to a point 65-70% of the total medial-lateral tibial plateau width (Weight-bearing axis; WBA) the so-called 'fujisawa point'. The principle is to transfer the load passing through the knee from the failing medial compartment to the disease free lateral compartment. Early reports suggested that such a technique afforded both improved symptoms [139] and reduced cartilage degeneration [153]. However, over-correction leads to a significant distortion of the local anatomy and has led to some concern over the survivorship of any future arthroplasty surgery should it be required. In particular UKA is contraindicated for patients who have previously undergone HTO [164].

Despite advances in the field of osteotomy, the optimal correction point has not

been established. Recently, an individualised approach to surgical correction has been advocated bringing the desired correction point closer to neutral depending on the severity of OA at baseline [165]. There is currently, a paucity of evidence to support such a strategy. Since 2011, the knee service at our institution has been offering a neutralising (WBA=50%) medial opening wedge high tibial osteotomy to a specific group of patients with early knee osteoarthritis. The selection criteria are as follows:

- Early to moderate medial osteoarthritis of the knee (Kellgren-Lawrence 1, 2 or 3)
- A weight-bearing axis (WBA) running through the medial compartment of the knee that could be corrected to neutral using an opening wedge HTO without compromising joint line orientation
- Pain and dysfunction for more than 2 years
- No osteoarthritis affecting the lateral compartment

7.2. Aims

- To establish the early and medium-term functional outcomes of patients with early to moderate varus osteoarthritis undergoing a neutralising osteotomy.
- To identify risk factors that influence outcome.

7.3. Materials and methods.

7.3.1. Study design

Ethical approval was granted for a single-centre prospective cohort study and for permission to retrospectively include patients who had undergone an HTO prior to

the study start date (London Bloomsbury REC, ref: 15/LO/0701). These subjects had information prospectively gathered in the hospital-setting and permission was granted to transfer the data to the research laboratory.

7.3.2. Study sample

All subjects who fulfilled the above selection criteria and underwent a neutralising high tibial osteotomy were enrolled in the study. If a subject had undergone an osteotomy on both lower limb then data from the first knee to have the osteotomy was included. As such each subject contributed one limb only for analysis. Demographic details were obtained from a standardised patient survey given to all patients undergoing surgery in our department. These details include; age, gender, BMI, smoking status and employment.

7.3.3. Surgical technique

The surgical technique was standardised for all patients. A medial opening wedge HTO was performed using a biplanar technique [141] and the position was secured using a Tomofix™ (Depuy Synthes) plate without bone graft. An opening gap was planned pre-operatively using the measurement tools on our local Picture Archiving and Communication System (PACS) (Insignia Medical Systems Ltd, UK) and the technique described by Miniaci [155]. The aim was to achieve a WBA of 50% but a post-operative correction error of 10% either side of neutral was considered acceptable. Alignment was assessed intra-operatively using an alignment rod running from the centre of the hip to the centre of the ankle. A neutral position was determined as the point at which the alignment rod passed through the centre of the tibial spines. At 1 year, or once bony union had been confirmed, all subjects are offered removal of metalwork as a day case procedure. All procedures were carried out by a specialist

consultant knee surgeon (AJP, WJ).

7.3.4. Radiological Analysis

All patients had bilateral standing long-leg radiographs (LLRs) taken pre-operatively. Patients were positioned centred on a wall stand with their patellae facing forward and a ruler taped to the leg for calibration. Automatic exposure chambers ensure consistent radiographic images with the focus film distance set at 180cm. All radiographs were made using the GE Definium model 8000 (GE Healthcare), which automatically tracks down the lower limb using pre-defined anatomical landmarks. The resulting images are then stitched together to produce a single image, which includes both lower limbs. Radiographs were transferred as Digital Imaging and Communications in Medicine (DICOM) files from the Picture Archiving and Communications System (PACS version) into MediCAD® (Hectec GmbH, Germany). The same technique was used to assess post-operative alignment once the patient was fully weight bearing. As discussed in section 4.3.4 this software generates mechanical alignment measurements including weight-bearing axis (WBA), mechanical Lateral Proximal Femoral Angle (mLPFA), mechanical Lateral Distal Femoral Angle (mLDFA), Medial Proximal Tibial Angle (MPTA), mechanical Lateral Distal Tibial Angle (mLDTA) and medial Joint Line Convergence Angle (JLCA_med) see figure 4.3.2.

This planning software was used retrospectively to assess alignment and was not part of our pre-operative planning.

7.4. Outcomes

Primary outcome

- Change in Oxford Knee Score (OKS) from pre-operative score to score at 1 year

(short-term)

Secondary outcomes

- Change in OKS from pre-operative score to score at 3-5yr (mid-term)
- Patient satisfaction at 1 year: a five level likert scale was used to answer questions relating to patient-reported satisfaction (How would you describe the results of your operation? excellent, very good, good, fair, poor)
- Patient transition at 1 year: A five level likert scale was used to answer questions relating to patient-reported transition (Overall how are the problems now in the knee on which you had surgery, compared to before your operation? much better, a little better, about the same, a little worse, much worse)
- Surgical accuracy: [post-operative WBA – intended WBA (50%)]. Under-corrections were converted to a positive integer to enable surgical accuracy to be reported as a deviation from neutral with lower values representing greater accuracy [254]
- 5 year survival: end-point defined as revision of the osteotomy
- Post-operative complications including; non-union, infection, venous thromboembolism and revision surgery

7.5. Variable selection

Variables that may influence outcome were selected *a priori* and included age, gender, BMI, smoking status and pre-operative mechanical alignment measurements including WBA, mLPFA, mLDFA, MPTA, mLDTA and JLCA_med). Two new variables

(surgical accuracy and size of correction) were generated using the weight-bearing axis (WBA) value:

- Surgical accuracy: [post-operative WBA – intended WBA (50%)]
- Size of correction: [post-operative WBA – pre-operative WBA]

7.6. Statistical Analysis

The mean and standard deviation (SD) were determined for all the variables measured.

Wilcoxon-signed rank repeated measures test, for non-parametric data, was used to describe the difference between pre-operative and 1yr Oxford knee scores (OKS), pre-operative and 3-5yr score and 1yr score to 3-5 year score.

Univariate regression analysis assessed the direct affect of independent variables (see section 7.5) on patient reported outcome (change in OKS), controlling each time for pre-operative OKS. These variables included both patient-specific variables (age, BMI, smoking status, gender) and surgery-specific variables (operating surgeon, size of correction, surgical accuracy and pre-operative alignment measurements; mLPFA, mLDFA, MPTA, mLDTA, JLCA_med). Multivariate regression analysis was then used to explore and quantify the influence of these baseline variables on the change in OKS. A similar model was used to determine if any pre-operative variables were associated with surgical accuracy, however, the model for surgical accuracy did not include or control for baseline OKS. These variables again included both patient-specific variables (age, BMI, KL grade, pre-operative OKS) and surgery-specific variables (operating surgeon, size of correction and pre-operative alignment measurements). Gender was not included in the multivariate statistical model as there was insufficient variability for this observation (female; n=1).

Ordered logistic regression was used to identify if any of these independent variables predicted outcome with regard to transition and satisfaction questions and the results were expressed as odds ratios.

P-values of <0.05 were considered to be significant. All statistical analyses were performed using Stata/IC 13.1 (©StataCorp, 2013).

7.7. Regression diagnostics

Regression diagnostics were performed on the multivariate regression models. The normality of residuals was checked using the Shapiro-Wilk test. The variance inflation factor (VIF) was calculated for each of the patient-specific and surgery-specific variables to identify any evidence of collinearity. A VIF greater than 10 was considered sufficient to warrant further investigation.

The ordered logistic regression models were tested to ensure that the relationship between the possible outcome categories for transition and satisfaction were constant. This 'proportional odds assumption' was tested using a likelihood ratio test and a p-value >0.05 indicated that the proportional odds assumption had not been violated.

7.8. Results

32 patients (31 males, 1 female) with early anteromedial knee arthritis underwent medial opening wedge high tibial osteotomies using a Tomofix® fixation device. All subjects were recruited into the study.

7.8.1. Characteristics of the study population

The mean age was 44.9 (range: 33-57) years and BMI was 29.6 (20.9-36.5). 47% described their employment as heavy manual labour and 38% were smokers. 40% of

patients had taken time off work due to the symptoms in their knee. A summary of patient characteristics is given in table 7.1.

Table 7.1.: Characteristics of the HTO cohort

Characteristic	
Mean age (range)	45 (33-57)
Gender	M = 31 F = 1
Mean BMI (range)	29.1 (20.9-36.5)
OA grade	KL 1= 10% KL 2 = 74% KL 3= 16%
Occupation	Heavy manual= 46.9% Light manual= 28.2% Non manual= 21.9% Unemployed= 3%
Smoker	63%

7.8.2. Change in Oxford Knee Score

7.8.2.1. 1 year (short-term)

All patients had OKS recorded pre-operatively and at 1 year post-operatively. Pre-operatively, mean OKS was 23.1 (10-41). At 1yr post HTO the mean OKS was 37.6 (9-48) giving a mean change of 15.3 points on the Oxford Knee Score (p<0.001) (see figure7.8.1). Three patients suffered deterioration in knee symptoms -2, -4 and -7 points. The three patients with deterioration in OKS at 1yr had a post-operative WBA of 44.6%, 55.8% and 78.2% respectively.

Univariate analysis revealed that a lower pre-operative OKS predicted a higher change in OKS at 1yr (p=0.04). No other surgery-specific or patient-specific variable was associated with change in OKS at 1yr (see Table 7.2).

Table 7.2.: Univariate regression analysis exploring the direct influence of patient-specific and surgery-specific variables on change in OKS at 1yr

Variable	Co-efficient	95% CI	p-value
Baseline OKS*	-0.519	-1.02 – -0.016	0.043
Age	0.259	-0.34 – 0.86	0.38
Gender	2.60	-18.44 – 23.65	0.8
BMI	-0.20	-1.12 – 0.73	0.67
Smoking status	5.23	-2.25 – 12.72	0.16
mLPFA	-0.37	-1.17 – 0.43	0.36
mLDFA	1.47	-0.65 – 3.58	0.17
MPTA	1.99	-0.11 – 4.08	0.06
mLDTA	-0.09	-0.76 – 0.58	0.79
JLCA_med	0.83	-1.42 – 3.09	0.45
Size of correction	-0.12	-0.39 – 0.15	0.37
Surgical accuracy	-0.10	-0.61 – 0.41	0.69
Surgeon	0.44	-6.85 – 7.73	0.90

*$p<0.05$

Multivariate regression revealed that the pre-operative mLDFA was associated with change in OKS at 1 year (p=0.04). For every one degree increase in the mLDFA (more varus) the change in OKS at 1 year is predicted to increase by 3 points, holding all other variables constant. No other surgery-specific or patient-specific variable was associated with change in OKS at 1 year. The direct association between pre-operative OKS and change in OKS at 1yr was not significant when the remaining variables were included in the statistical model (p=0.13). Table 7.3 gives the results for the multivariate analysis.

Table 7.3.: Multivariate regression analysis exploring the influence of patient-specific and surgery-specific variables on change in OKS at 1yr

Variable	Co-efficient	95% CI	p-value
Baseline OKS	-0.43	-1.07 – 0.20	0.17
Age	0.24	-0.56 – 1.04	0.54
BMI	-0.35	-1.33 – 0.63	0.46
Smoking status	2.03	-7.78 – 11.84	0.67
mLPFA	-0.12	-0.99 – 0.75	0.78
mLDFA*	3.15	0.24 – 6.05	0.04
MPTA	1.89	-1.13 – 4.91	0.21
mLDTA	0.08	-0.81 – 0.65	0.83
JLCA_med	1.59	-1.15 – 4.34	0.24
Size of correction	-0.16	-0.65 – 0.32	0.49
Surgical accuracy	-0.28	-0.85 – 0.30	0.33
Surgeon	-0.21	-9.92 – 9.50	0.96

*$p<0.05$

It was not possible to reject the hypothesis that the residuals for the multivariate model were normally distributed (Shapiro-Wilk test; p=0.17). The mean VIF for the variables included in the multivariate model was 1.78 and no variable had a VIF greater than 10 (see Table 7.4). This indicates that the model assumptions for normality of residuals and collinearity have not been violated.

Table 7.4.: Collinearity of the independent variables included in the multivariate model change in OKS at 1yr; assessed using the variance inflation factor (VIF)

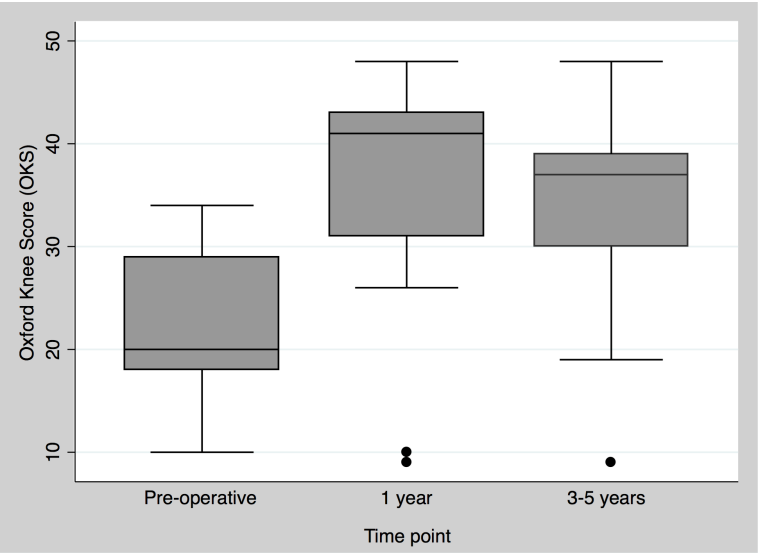
Variable of interest	VIF
Baseline OKS	1.63
Age	1.83
Gender	1.97
BMI	1.19
Smoking status	1.84
mLPFA	1.32
mLDFA	1.87
MPTA	2.13
mLDTA	1.27
JLCA_med	1.55
Size of correction	3.36
Surgical accuracy	1.39
Surgeon	1.92
Mean VIF	1.78

7.8.2.2. 3-5 year (mid-term)

Six subjects had not reached the minimum three year post-operative period to be included in the mid-term outcome analysis. One subject was eligible for inclusion but was lost to follow-up. A total of 25 subjects were available for follow-up. The mean follow-up for mid-term outcome results was 3 years 11 months from the time of surgery (Range; 3years 0 months to 5 years 5 months).

At 3-5yr post HTO the mean OKS was 34.8 (9-48) giving a mean change of 12.6 points on the Oxford Knee Score ($p<0.001$) (see figure 7.8.1). This reduction in mean OKS at 3-5 years compared to 1yr was not statistically significant ($p=0.15$).

Figure 7.8.1.: Box plot graph demonstrating Oxford knee scores at baseline, 1yr and 3-5 yrs



Two patients suffered a deterioration in knee symptoms -3 and -5 points. The two patients with deterioration in OKS at 3-5yrs had a post-operative WBA of 61% and 78.2% respectively.

Univariate analysis revealed that a lower pre-operative OKS predicted a higher change in OKS at 3-5yrs (Coefficient = -0.57; 95%CI -1.11 – -0.021; p=0.04). No other surgery-specific or patient-specific variable was associated with change in OKS at 1yr.

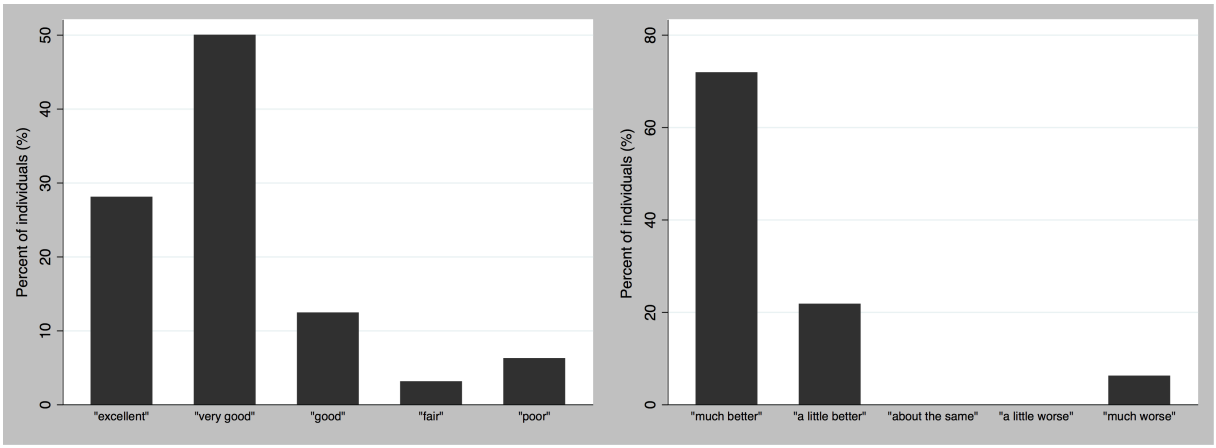
Multivariate regression revealed that no surgery-specific or patient-specific variable was associated with change in OKS at 3-5 years. A more varus distal femoral angle was not associated with improved OKS at 3-5 years (Coefficient = 1.39; 95% CI -2.84 – 5.63; p=0.49).

7.8.3. Patient satisfaction and transition

The majority of patients described their outcome from surgery as either “good” (13%) “very good” (50%) or “excellent” (28%) (figure 7.8.2) 1 year after surgery. Only 3

subjects described their outcome as fair or poor. Similarly, 94% of subjects described the condition of their knee as “much better” (72%) or a “little better” (22%) than it was pre-operatively (Figure 7.8.2).

Figure 7.8.2.: Bar graphs demonstrating patient satisfaction and transition score at 1 year



Ordered logistic regression revealed that pre-operative mLDFA was associated with an improved satisfaction score at 1 year (p=0.04). For every one unit increase in pre-operative mLDFA (more varus) the odds of a poor outcome versus the combined remaining outcome groups (excellent, very good, good, fair) were 0.51 times lower, given the other variables are held constant. Table 7.5 summarises the relationship between pre-operative mLDFA and satisfaction score. No other surgery-specific or patient-specific variable was associated with patient satisfaction or transition at 1 year (Table 7.8.3).

The ’proportional odds assumption’ was not violated in either ordered logistic regression model with the likelihood ratio test indicating proportionality of odds across outcome categories (satisfaction p=0.18; transition p=0.69).

Table 7.5.: Summary of pre-operative mLDFA and 1 year satisfaction score

Satisfaction Score	pre-operative mLDFA(^{0})	
	n	Mean (S.D)
Excellent	9	89.34 (1.09)
Very good	16	88.23 (1.70)
Good	4	88.03 (2.74)
Fair	1	86.8
Poor	2	88.15 (0.07)

Table 7.6.: Multivariate regression analysis exploring the influence of patient-specific and surgery-specific variables on change in OKS at 1yr

Variable	Satisfaction score			Transition score		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Baseline OKS	0.99	0.87 −1.13	0.88	0.92	0.78 − 1.09	0.34
Age	0.93	0.78 − 1.10	0.39	0.88	0.71 − 1.09	0.25
BMI	1.08	0.87 − 1.34	0.49	1.04	0.81 − 1.33	0.76
Smoking status	1.41	0.25 − 13.09	0.76	0.80	0.07 − 8.93	0.86
mLPFA	1.11	0.91 − 1.35	0.29	1.06	0.85 − 1.32	0.62
mLDFA*	0.51	0.27 − 0.98	0.04	0.92	0.46 − 1.87	0.82
MPTA	0.56	0.26 − 1.20	0.14	0.60	0.27 − 1.36	0.22
mLDTA	1.09	0.94 − 1.27	0.27	1.08	0.88 − 1.32	0.45
JLCA_med	0.64	0.35 − 1.18	0.15	0.79	0.38 − 1.64	0.52
Size of correction	0.96	0.86 − 1.07	0.45	0.91	0.80 −1.03	0.15
Surgical accuracy	1.07	0.95 − 1.21	0.27	1.11	0.98 − 1.27	0.11
Surgeon	0.57	0.07 − 4.48	0.59	4.20	0.33 − 54.12	0.27

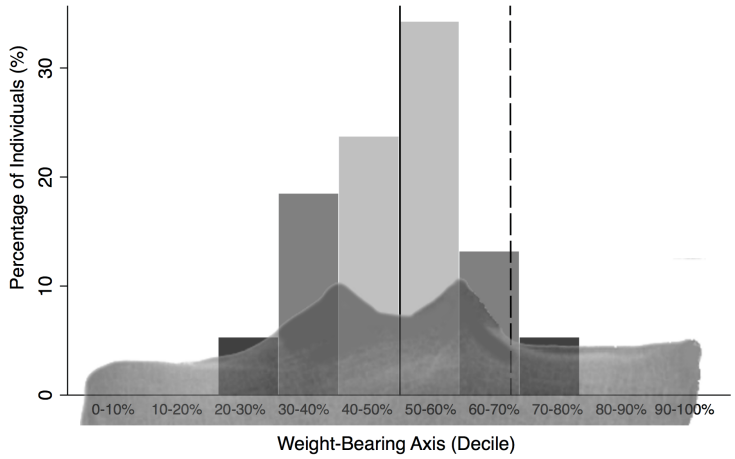
*p<0.05

7.8.4. Surgical Accuracy

All patients had imaging available for analysis including both pre and post-operative full-length radiographs. No patient was more varus following surgery. 56% of patients were within 10 percentage points of the planned neutral alignment of 50% (see figure 7.8.3). 6 knees were over-corrected (post-operative WBA >60%). 8 knees were under-corrected (post-operative WBA <40%). Outliers, in terms of surgical accuracy, had a mean change in OKS of 16 (over-corrected patients, n=6) and 19 (under-corrected

patients, n=8).

Figure 7.8.3.: A bar graph demonstrating surgical accuracy for the neutralising HTO



Note: The post-operative weight-bearing axes (WBA) for the whole cohort group are displayed and have been grouped into deciles. A tibial plateau has been superimposed onto the graph to illustrate the desired correction point (WBA = 50%; solid black line) and Fujisawa point (WBA=65-70%; dashed black line).

The univariate and multivariate models revealed that no surgery-specific or patient-specific variable was associated with surgical accuracy (see table 7.8.4).

Table 7.7.: Multivariate regression analysis exploring the influence of patient-specific and surgery-specific variables on surgical accuracy

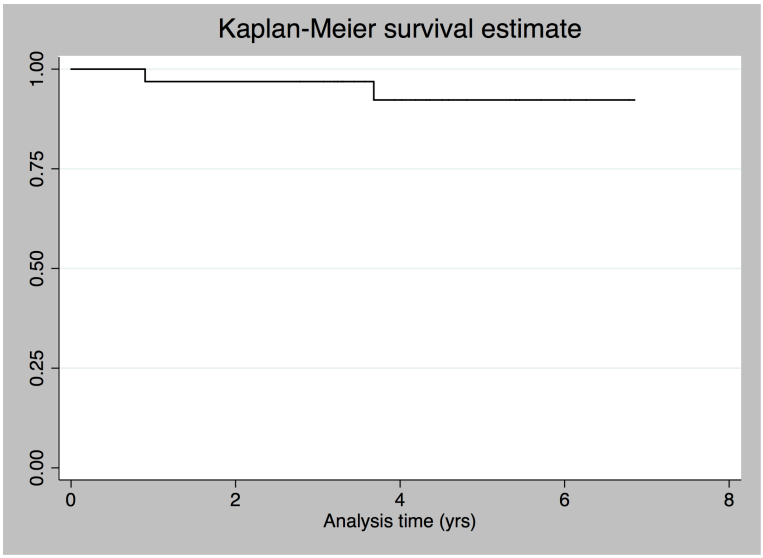
Variable	Co-efficient	95% CI	p-value
Age	0.18	-0.43 – 0.80	0.54
BMI	.0262399	-0.75 – 0.81	0.95
Smoking status	-1.346058	-8.63 – 5.93	0.70
mLPFA	.3595247	-0.27 – 0.99	0.25
mLDFA	1.7223	-0.45 – 3.89	0.11
MPTA	-.8047001	-3.11 – 1.50	0.48
mLDTA	.0864006	-0.49 – 0.66	0.871
JLCA_med	.8409601	-1.27 – 2.95	0.76
Size of correction	-.1358435	-0.49 – 0.22	0.42
Surgeon	4.59533	-2.85 – 12.04	0.21

7.8.5. 5yr Survival

The mean follow-up for the HTO cohort is currently 4 yrs 5 months (Range; 2yrs 9 months to 6yrs 10 months).

One patient had their HTO revised to a medial unicompartmental knee arthroplasty at 3yrs 8months. One patient had their HTO revised to an Ilizarov frame 11 months following the initial surgery. A Kaplan-Meier survival graph was constructed (see figure7.8.4) and 5 year survival for a neutralising high tibial osteotomy was estimated to be 93% (95%CI $0.75 - 0.98$).

Figure 7.8.4.: Kaplan-Meier survival graph for a neutralising HTO (n=32)



7.8.6. Post-operative complications

One patient experienced a non-union with failure of the plate. This required revision with an Ilizarov frame. One patient was treated, by their GP, for a superficial infection with oral antibiotics.

7.9. Discussion.

Our study demonstrates that a neutralising high tibial osteotomy offers significant symptom relief at 1 year (average change in OKS = 15.3 points) and up to 3-5 years (average change in OKS = 12.6 points) for patients with symptomatic early to moderate osteoarthritis in a varus knee . Our cohort of patients demonstrates high levels of satisfaction with over 90% of individuals describing their outcome as good, very good or excellent. As expected, a low pre-operative OKS predicted a higher change in OKS at 1yr (p=0.04). Those subjects with a higher pre-operative OKS have less scope for improvement. A more varus distal femoral angle (mLDFA) was associated with a greater change in OKS at 1 year (p=0.04) and increased patient satisfaction (p=0.04). No other independent variables measured at baseline or at follow-up were predictive of a successful outcome whether that be in relation to change in OKS, surgical accuracy or satisfaction and transition scores. In other words the success of surgery was independent of patient characteristics including age, BMI and pre-operative alignment. Furthermore good patient-reported outcomes from surgery were independent of surgical factors including surgical accuracy and size of correction. One major complication was observed. This gentleman experienced a non-union with plate failure and tibial plateau fracture. He has since undergone a revision osteotomy with Ilizarov frame. He describes his outcome from surgery as “good” and the symptoms in his knee as “a little better” than what they were pre-operatively.

The outcomes seen in this cohort reflect a significant improvement in patient reported symptoms (p<0.001). A fact supported by the high satisfaction and transition scores seen at 1yr (figure 7.8.2). The use of the Oxford Knee Score in the context of outcomes from a medial opening wedge high tibial osteotomies has been reported in other studies. Goshima et al aimed to correct individuals into a more traditional

valgus position (WBA 65-70%) and reported a mean post-operative OKS of 41 in 23 patients [93]. A large retrospective cohort of over 380 subjects undergoing a similar osteotomy reported a mean post-operative OKS of 43 [94]. Neither study reports pre-operative OKS. Given the influence of pre-operative OKS on change in OKS it is not possible to directly compare these outcomes to those described in this study.

Both studies included all grades of OA and reported medium-term follow up results (>2yrs post-op). Our study has reported short and mid-term OKS in a group of patients with early to moderate OA (KL1,2,3) who had been symptomatic for at least two years prior to being considered for surgery. Such chronicity of knee symptoms may have captured a group of individuals with more severe pain, which in turn may have had a bearing on outcome. Analysis of the post-operative long leg radiographs revealed that 56% of subjects were corrected to within 10 percentage points of the planned neutral alignment. This left 42% of subjects outside the range of neutral (19% over-corrected, 25% under-corrected). The mean post-operative WBA was 49.8% (S.D 11.9). Surgical accuracy is rarely reported in osteotomy studies. A recent systematic review showed a wide reported range of accuracy with 10-37% of individuals being outside an acceptable range, analogous to ours, albeit around a more valgus value [206]. Techniques have been described to improve surgical accuracy including computer-guided navigation [206] personalised cutting jig [255]. However, these add costs to the procedure, are not widely available and their role in improving patient-reported outcomes are not well reported.

Trials investigating outcomes for high tibial osteotomy suffer from marked heterogeneity [162]. Surgical techniques vary and many historical papers focus on closing wedge HTO. The medially-based opening wedge osteotomy utilised in this study offers many advantages. Unlike the closing-wedge technique the lateral structures of the knee are avoided and adjustments can be made to alignment intra-operatively

after the bone cuts are made. Subsequent rigid fixation enables early mobilisation whilst ensuring bone healing without loss of correction [141]. Several factors have been shown to influence outcome for high tibial osteotomy. Gender, body mass index, duration of surgery, gap filling, gap size in millimetres, experience level of the attending surgeon, length of inpatient stay and the intake of pain medication were significantly associated with the 2–5-year functional outcome in the previously mentioned study [94].

Varus deformity of the proximal tibia has been identified in chapter 4 as a potent predictor of structural progression in symptomatic EKOA. However, the acquisition of long leg radiographs in the OAI cohort was different to this study. The OAI cohort had long leg radiographs performed with their feet facing forward. In the presence of external or internal tibial torsion, such positioning would result in the patellae pointing inward or outward and may lead to an under- or over-estimation of any angular deformity. Positioning the limb with the patella or tibial tuberosity facing forward, as was done for the HTO cohort should have overcome this problem and as such making direct comparisons between the two cohorts should be done with caution.

Varus deformity of the proximal tibia has also been described as a predictor of successful osteotomy surgery. Bonnin et al, reported that osteotomy for individuals without inherent tibia vara was a palliative procedure that did not offer reliable, long-term clinical benefit whereas patients with tibia vara (Tibia Bone Varus Angle >50) could expect long-term improvement from the procedure [149]. However, other studies have contradicted this claim and found no association between the pre-operative boney geometry around the knee (MPTA, mLDFA) and survival outcome for high tibial osteotomy[151]. Our study was not able to support this finding. We found a relationship between a more varus distal femoral angle (mLDFA) and a greater change

in oxford knee score at 1 year (p=0.04). This finding was subsequently supported by the fact that an increased mLDFA (more varus) was associated with improved satisfaction 1 year following surgery (p=0.04). However, this relationship was not maintained in the mid-term. A more varus distal femoral angle was not associated with improved OKS at 3-5 years (Coefficient = 1.39; 95% CI -2.84 − 5.63; p=0.49).

There are several limitations inherent to this study. Our cohort is small with only 32 patients each contributing a single limb for analysis. Whilst this has been able to show good treatment response for the group as a whole it may lead us to falsely interpret the influence of individual variables on outcome. The cohort also has no comparator group who either underwent no surgery or were managed with the same technique but with the objective to place the patient into valgus. The results from this novel study certainly lend support to the value of future trials of that nature.

The OKS was originally developed to assess improvement after arthroplasty surgery. The extended use of OKS has been validated in patients with symptomatic knee OA who do not undergo arthroplasty [4]. In patients with early to moderate OA, it has been shown to be both reliable and responsive to the health state of the individual correlating highly with other patient reported outcome measurements [91]. However, following HTO many patients are able to participate in strenuous sports on a regular basis [147]. Some may argue that the OKS is not able to capture the high levels of activity achieved by these individuals and may introduce a ceiling effect. Although this did not appear to be the case in our study with only 1 patient reaching the maximum 48 points, alternative assessments such as the Tegner activity score [256] may have better differentiated high performing individuals from those whose functional limitations are being masked by low levels of activity. More recently, a patient-reported outcome measure of activity and participation (the OKS- APQ) has been developed to supplement the Oxford knee score and to try and address the is-

sues raised by younger more active patients [257]. The participants in our study had been recruited prior to the release of this supplemental questionnaire and to date its use in early to moderate osteoarthritis has not been validated.

Despite these limitations our study has many strengths. It is the first to report outcomes for a neutralising medial opening wedge high tibial osteotomy. Furthermore we have clearly defined patient selection criteria and a consistent surgical approach. This standardisation means you can more closely evaluate the effects of other variables of interest on a homogenous group. At present osteoarthritis of the knee is a progressive disease for which our best surgical option, in the form of arthroplasty, is only offered at the end-stage of the disease process. The patients described in this study are young, working-age individuals who are severely limited by knee pain. Many have had to take time off work due to the symptoms in their knee. Osteotomy offers a real clinical benefit and in some patients maybe curative. Our strategy has been to use a neutralising osteotomy and our study has shown that such a procedure offers significant symptom relief with high levels of patient satisfaction in the short and mid-term. Traditionally, the goal of osteotomy has been to over-correct patients into valgus with many early studies demonstrating improved symptoms and survivorship when such a technique is employed [153, 258, 139]. However, the origins of this practice pre-dates arthroplasty surgery, which has subsequently revolutionised the field of orthopaedic knee surgery. It is important to consider the potential need for future TKA when considering a patient for HTO. Some concern has been raised regarding high revision rates for total knee arthroplasty subsequent to a valgising osteotomy [259]. Furthermore, valgus alignment, leading to lateral compartment overload, has been considered causative of high failure rates in UKA post HTO [164] leading to it being considered an absolute contra-indication. More recently, an individualised approach has been suggested with a more conservative correction proposed for those

with less severe OA (WBA 55-60%) [165]. There is little prospective evidence in the literature to support this strategy. As surgeons it is important to consider the next surgical step when performing any surgical procedure. A more modest correction should negate the difficulties associated with arthroplasty in this group of patients should the need arise in the future. However, some may argue that the modest correction will precipitate the need for revision sooner. Long-term follow-up of this patient group is the only way to provide answers to these important issues regarding outcome from a neutralising high tibial osteotomy.

7.10. Conclusions

Early results from this prospective cohort study demonstrate that patients with early medial compartment OA and varus deformity can expect, on average, an improvement in Oxford Knee Score of 15 points at one year following a neutralising HTO. This data is useful to knee surgeons considering HTO for those patients who find themselves in the treatment gap. More work is required to identify the factors that predict a poor or good outcome in this patient group.

7.11. Future work

Continued prospective recruitment of patients into this group will enable more robust conclusions to be drawn with regard to the factors that are associated with outcome. In addition longer term follow-up of the existing cohort will enable more detailed survival analysis to be determined. Importantly, those subjects who go on to have arthroplasty surgery need to be monitored to see if a neutralising HTO affords improved survival of the prosthesis compared to a valgising HTO. This is particularly important with regard to UKA which is currently contra-indicated in patients who

have previously undergone HTO surgery. Finally, future studies will need to compare the outcomes from a neutralising osteotomy to those achieved with a traditional valgising osteotomy.

8. The Outcome of Unicompartmental Knee Arthroplasty in Patients with Partial Thickness Disease on Plain Radiograph: the importance of MRI.

8.1. Introduction

In chapter 5 the knee maps (see figure 5.5.1 and figure 5.5.2) demonstrate that some subjects with EKOA (KL grade 1-3) on plain film radiographs have full thickness disease evident on MRI. The role of surgical intervention for such individuals has not been defined in the literature.

Unicompartmental knee arthroplasty surgery is typically recommended on the strength of plain film radiographs [181]. Symptomatic patients with demonstrable bone on bone medial compartment osteoarthritis do well following medial unicom-

partmental knee arthroplasty (UKA) [224]. They can expect a marked improvement in patient-reported outcomes measures (PROMS) [260] and good long-term survivability [5]. However, high rates of failure have been demonstrated in patients who only have EKOA, defined as partial thickness cartilage loss affecting the medial compartment [8, 7, 261].

As the knee maps in chapter 5 confirm, limiting investigation to plain radiographs could lead to patients being diagnosed with EKOA that in reality have full thickness cartilage loss. Waiting for sufficient time to pass in order to demonstrate progression to "bone on bone" arthritis potentially exposes the patient to a prolonged period of painful disability; the 'treatment gap' [10].

At the Nuffield Orthopaedic Centre, MR has been used as part of the routine investigation of radiographic partial thickness (RxPT) knee OA. This identifies a subgroup of patients with RxPT knee OA in whom MR demonstrates full thickness disease (RxPT/MR-FT) (see figure 8.1.1). It is not known whether these findings are sufficient to warrant proceeding to UKA.

Figure 8.1.1.: Description of knee osteoarthritis based on radiographic and MRI findings

KL Grade	MR Findings	Description of Knee Osteoarthritis
1  2 	No Full thickness cartilage loss	Radiographic Partial Thickness & MRI Partial Thickness (RxPT/MRI-PT)
3 	Full thickness cartilage loss	Radiographic Partial Thickness & MRI Full Thickness (RxPT/MRI-FT)
4 	Not indicated unless concern over co-existing pathology (e.g. ACL integrity, OA in remaining compartments).	Radiographic Full Thickness (RxFT)

8.2. Objectives

- To determine the usefulness of MRI in the early identification of subjects who are suitable for unicompartmental knee arthroplasty.

8.3. Materials and methods.

8.3.1. Study design

The institutional database at the Nuffield Orthopaedic Centre contains detailed information on subjects undergoing UKA since 2012 (n=325) under the care of three consultant surgeons (AJP, WJ, AJP). Local permission was granted to retrospectively link this dataset with the United Kingdom's government led Hospital Episode Stat-

istics datasets including Patient-Reported Outcome Measurements (HES-PROMS).

8.3.2. Surgical pathway

The specialist knee service at the Nuffield Orthopaedic Centre (AJP, WJ, NB) offers unicompartmental knee arthroplasty to patients with severe 'bone on bone' antero-medial osteoarthritis on plain film radiographs (AP, lateral, skyline), an intact ACL, retention of full-thickness cartilage in the lateral compartment. In addition significant patello-femoral joint involvement in the form of lateral patellar bone loss and grooving should be excluded [180].

In symptomatic patients who fail to demonstrate 'bone on bone' antero-medial OA on plain film radiographs, MRI is used to confirm the diagnosis and assess severity. If full-thickness cartilage loss, with exposed bone, is present on the weight-bearing surface of either the femur, tibia or both the patient is considered suitable for unicompartmental knee arthroplasty.

8.3.3. Power calculation

The difference in Oxford Knee Score between subjects with partial thickness cartilage loss and subjects with full thickness cartilage loss has previously been calculated to be 3.9 ($\pm$ 9) at 1 year [182]. Therefore, with a statistical significance set at 0.05 and a power of 0.8, a total of 134 participants is required (67 in each group) to detect a between-group difference of 3.9 points.

8.3.4. Analysis of plain film radiographs

All pre-operative radiographs of subjects within the NOC dataset were reviewed by a single orthopaedic surgical registrar (JP) and given a KL grade. Those with KL grade 1, 2 or 3 were considered to have radiographic partial thickness (RxPT) disease with

evidence of a preserved joint space on the medial side. Those with KL grade 4 were considered to have radiographic full thickness disease (RxFT) with no preservation of joint space on the medial side.

The first twenty subjects had their radiographs assessed by another senior orthopaedic surgical registrar (AA) allowing intra-observer reliability for KL grade to be measured. A single assessor (JP) then re-reviewed the images 6 weeks following the initial assessment to allow inter-observer reliability to be recorded.

8.3.5. Study sample

A total of 61 subjects had radiographic partial thickness disease (RxPT) with a preserved joint space on the medial side equivalent to Kellgren Lawrence 2/3 [47]. A pre-operative MR was performed prior to surgery in all RxPT cases and patients were listed for surgery following assessment of the MR. The final decision to proceed to UKA was made intra-operatively once the full-thickness nature of the disease had been confirmed along with the integrity of the ACL and relative preservation of the lateral compartment. Since 2012, no subject listed for a UKA on the strength of their MR findings were deemed unsuitable for this procedure at the time of surgery.

A matched control group was selected from the remaining subjects (n=61). These subjects all demonstrated radiographic full thickness (RxFT) disease pre-operatively and were matched according to age, gender, pre-operative OKS, grade of surgeon (Consultant or SpR/Fellow) and number of co-morbidities. Oxford Knee Scores were retrieved pre-operatively and at 6 months following surgery together with patient-reported satisfaction (*How would you describe the results of your operation?*) and transition (*Overall how are the problems now in the knee on which you had surgery, compared to before your operation?*) scores via the HES-PROMS datasets.

8.3.6. Review of operative record

The operation notes were reviewed for all the RxPT cohort to confirm the intra-operative findings. The description of the medial compartment given in the operation note was viewed as the gold standard description for the state of the cartilage.

8.3.7. Analysis of MR imaging

A consultant musculoskeletal radiologist (SO) retrospectively reviewed the MRI images for all subjects in the RxPT group to determine three radiological questions:

- Is there antero-medial osteoarthritis?
- Is there exposed bone on the weight-bearing portion of the medial femur*?
- Is there exposed bone on the medial tibial plateau?

*any part of the distal femur that does not articulate with the patella

8.4. Statistical analysis

The mean standard deviation and range was calculated for all variables tested. Baseline demographic variables were compared between the two groups using chi-squared, independent samples t-test or Wilcoxon-Mann-Whitney test depending on whether the variable of interest was categorical, parametric or non-parametric in nature.

Weighted Kappa co-efficients were calculated to measure inter-observer and intra-observer agreement for the assessment of KL grade.

Independent samples t-test was used to compare the means of the change in oxford knee score ($preoperativeOKS - postoperativeOKS$) at 6 months. A Wilcoxon-Mann-Whitney test was performed to compare the pre-operative and post-operative Oxford

Knee Scores. and to compare the differences in responses between the two groups for the questions related to satisfaction and success of the procedure.

The retrospective MR analysis was used to determine the sensitivity, specificity and positive predictive value (PPV) of MR compared to the intra-operative record (gold standard).

All statistical tests were performed using Stata 13.1 (StataCorp).

Patients were matched for age, gender, grade of surgeon, number of co-morbidities and pre-operative OKS using software within Stata 13.1 (StataCorp).

8.5. Results

The two groups were matched for age, gender, number of co-morbidities, grade of surgeon and pre-operative OKS (table 7.1).

Table 8.1.: Demographic details of the two matched groups

	Radiographic Partial Thickness/ MR Full Thickness Group (RxPT/MR-FT)	Radiographic Full Thickness Group (RxFT)
Mean Age (yrs)	62.8 (∓9.9)	62.9 (∓6.1)
Gender (%Female)	77%	77%
No. of co-morbidities	0-1 = 33 2-3 = 24 ≥4 = 4	0-1 = 31 1-2 = 27 ≥4 = 3
Grade of Surgeon	Consultant= 30% SpR/Fellow= 70%	Consultant= 39% SpR/Fellow= 61%
Baseline OKS	Mean= 21 (Range= 5 - 40)	Mean= 21.6 (Range= 8 - 37)
KL Grade	Grade 2 = 4 Grade 3 = 57	Grade 4 = 62

8.5.1. Observer agreement

The inter-observer reliability for KL grade, given by the Kappa co-efficient, was 87.5% indicating very good agreement between the two observers. The intra-observer reliability was 92.5% again indicating very good agreement by the same observer at two different time-points.

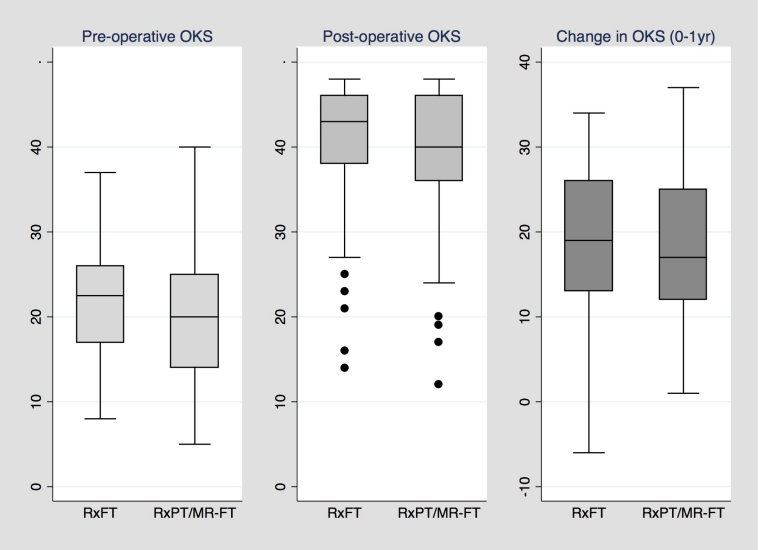
8.5.2. Operative record

54 subjects had full thickness cartilage loss on both the femur and tibia. 6 subjects had full thickness cartilage loss noted on the femur only. One subject had full thickness cartilage loss noted on the tibia only.

8.5.3. Patient reported outcomes

The mean OKS improved significantly in both groups ($p<0.001$) from pre-operative (RxFT=21.7; RxPT/MR-FT=20.9) to 6 months post-operatively (RxFT=40.5; RxPT/MR-FT=38.8) (figure 8.5.1). There was no significant difference ($p=0.48$) in the mean change in OKS between the two groups (RxPT=18.9; RxPT=17.8).

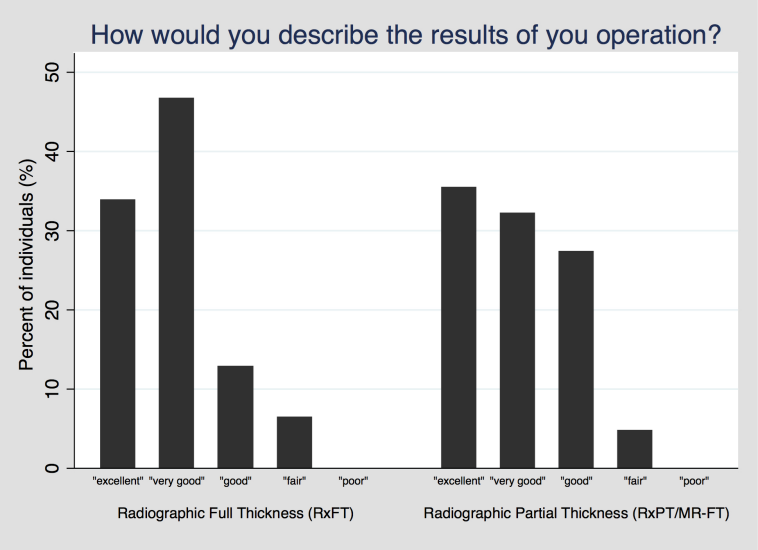
Figure 8.5.1.: Box Plot Graph illustrating the change in Oxford Knee Score (OKS) seen in the two groups (Radiographic Full Thickness RxFT, Radiographic Partial Thickness/MR Full-thickness RxPT/MR-FT) following UKA.



Note: Both groups showed significant improvement in OKS following surgery (P=<0.001).

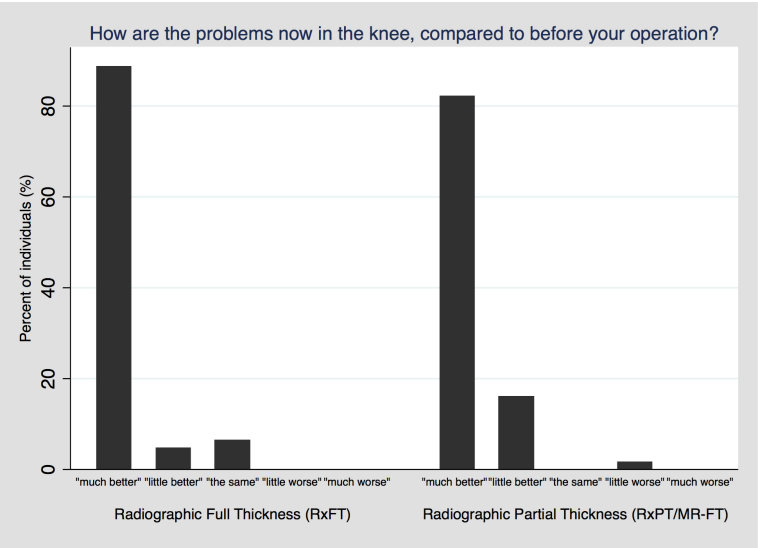
In the RxFT group, 93.5% of subjects reported an "excellent", "very good" or "good" outcome which was not significantly different to 95.1% of subjects in the RxPT/MR-FT group (p=0.53) (figure 8.5.2). No subjects in either group reported a "poor" outcome. Similarly, there was no significant difference in the number of subjects reporting outcomes that were "much better" or "a little better" when asked about the success of their operation (RxFT = 93.6%; RxPT/MR-FT=98.2%) (p=0.38) (figure 8.5.3). Again no subjects reported being "much worse" following surgery.

Figure 8.5.2.: Bar chart illustrating patient reported satisfaction for those subjects with radiographic full thickness disease (RxFT) and those with radiographic partial thickness and MR full thickness disease (RxPT/MR-FT).



Note: No subject reported a "poor" outcome following surgery.

Figure 8.5.3.: Bar charts illustrating patient reported transition score for those subjects with radiographic full thickness disease (RxFT) and those with radiographic partial thickness and MR full thickness disease (RxPT/MR-FT).



Note: No subject reported being "much worse" following surgery.

8.5.4. MR analysis

Fifty five patients had radiological findings consistent with degenerative antero-medial osteoarthritis. Six patients (9.8%) had radiological signs consistent with osteonecrosis or insufficiency fracture.

Forty five patients had MR evidence of exposed bone on both the femur and tibia. Eight patients had MR evidence of exposed bone on the femur only. Three patients had MR evidence of exposed bone on the tibia only. Five patients had no MR evidence of exposed on the femur or tibia. The sensitivity, specificity and positive predictive value for MR compared to the operative record are given in tables 8.2 and 8.3.

Table 8.2.: Performance of MR at determining exposed bone on the femur compared to the operative record (gold standard)

Exposed bone/ full thickness cartilage loss femur?			
		MR report	
		Yes	No
Operative record	Yes	52	8
	No	1	0
Sensitivity		86.7%	
Specificity		0%	
Positive predictive value		98.1%	

Table 8.3.: Performance of MR at determining exposed bone on the tibia compared to the operative record (gold standard)

Exposed bone/ full thickness cartilage loss tibia?			
		MR report	
		Yes	No
Operative record	Yes	47	8
	No	1	5
Sensitivity		85.5%	
Specificity		83.3%	
Positive predictive value		97.9%	

8.6. Discussion.

This study demonstrates that in patients with radiographic partial thickness medial compartment OA of the knee (KL grade 2, 3) and MR confirmed full thickness cartilage loss (RxPT/MR-FT), Oxford medial UKA can reliably achieve excellent 6-month patient-reported outcomes equivalent to those of a matched cohort of subjects that demonstrate radiographic full thickness disease (RxFT) (mean change OKS: RxPT/MR-FT 17.8 and RxFT 18.9 (p=0.48)). Such individuals are not in the treatment gap as they can be offered UKA with reliable outcomes. This is the first study to demonstrate the value of MR in establishing full thickness disease in patients who may otherwise not have been offered UKA with a positive predictive value of 98.1% for the femur and 97.9% in the tibia.

Several studies have reported negative outcomes for subjects who demonstrate partial thickness in the medial compartment prior to UKA. Pandit et al retrospectively matched a partial thickness group (n=29) to two groups demonstrating full thickness cartilage loss [8]. These groups were identified based on intra-operative descriptions of the femur and tibia and subjects with partial thickness cartilage loss experienced significantly poorer clinical outcomes [8]. Whilst undoubtedly important this study does not aid with pre-operative decision-making as the description of the cartilage damage to the tibia or femur is undertaken at the time of surgery once the decision to proceed with UKA has been made. More recently, the same study group has retrospectively identified 34 patients with partial thickness OA, confirmed pre-operatively, in whom a pre-operative MR was deemed to be unhelpful in identifying full-thickness disease [182]. However, it is not clear what the indications for the MR were for these individuals or at what point the MR was performed relative to the decision to proceed with UKA. In this study the MR was not used as part of the clinical decision making process.

Niinimaki et al looked at the ratio of the medial to lateral joint space width and found that the re-operation rate was 8 times higher in patients who had a medial joint space ≥40% of the lateral joint space [7]. Interestingly, the majority of the subjects with a preserved medial joint space (≥40% of the lateral joint space) had severe medial cartilage damage confirmed at arthroscopy. This would suggest that the pre-operative appearance of an AP radiograph is more important in terms of predicting a successful outcome than the state of the articular cartilage itself. This is not supported by our study, however, patient-reported outcomes are not reported in their study and we do not have long-term follow up data to determine long-term survival and re-operation rates for our group. The hospitals involved in this study performed on average four UKA procedures per year; a volume which alone is associated with poor outcomes [262, 263].

A study from Finland identified 294 patients who underwent UKA for symptomatic OA, 45.6% of whom had radiologically mild OA (KL 0–2) [264]. They determined that in addition to female gender, radiologically mild OA in preoperative weight-bearing AP radiographs increased the risk of revision (OR = 1.89) [264]. This group which includes patients with no radiologically identifiable OA, likely represents a milder OA group than our RxPT/MR-FT and may not be directly comparable.

More recently a retrospective study identified subjects with partial and full thickness OA using 4 radiographic views (weight-bearing AP, lateral, varus stress and full leg standing views) all of whom had undergone UKA (n=33) [261]. The partial thickness group showed similar clinical scores to the full thickness group although they had a trend towards poorer survival at 5yrs (p=0.09) It is possible that by defining the groups based on radiographic findings alone that the extent of cartilage injury was under-estimated in some cases. This may mean that some of the partial thickness group had undiagnosed full thickness lesions and may account for the similar clinical

outcomes recorded. The authors do not comment on the intra-operative assessment of the medial tibio-femoral cartilage.

The radiographs used to define our partial thickness group were limited to AP and lateral weight-bearing views. These views identified full thickness cartilage loss of the medial compartment in 80% of the subjects in our cohort (263 out of 325 subjects). It is not clear how many of the remaining 62 subjects with RxPT would have had full thickness disease on stress views as we do not routinely use these views in our practice. MR offers a consistent and comprehensive assessment of the knee joint offering a valuable description of the state of medial tibio-femoral compartment as well as enabling information to be gained regarding the state of remaining compartments of the knee, the integrity of the ligaments and the presence of any other pathology.

Due to the retrospective nature of the study design it is not possible to determine how accurately the MRI was interpreted prior to surgery. It has been assumed that the operating surgeon was confident that there was exposed bone on the femur and or tibia prior to surgery.

This study is also limited by the short-term nature of the included outcomes. Following arthroplasty surgery, most of the improvement in OKS occurs in the first six months and it is unclear if further clinically important changes arise from 6 months to a year post-operatively [265]. Whilst large-scale studies have used 6 month PROMS to distinguish outcomes in arthroplasty surgery [172, 266] a long-term assessment of patient-reported outcome would still be beneficial. It will be important to follow this group up in the medium and long-term to see if patient reported outcomes deteriorate in line with revision and whether or not this deterioration is significantly different between the two groups.

The prior studies mentioned above [8, 7, 261] all share a common thread which is to try and identify thresholds by which subjects should be excluded from undergoing

UKA for having insufficient cartilage loss in the medial compartment. In combination they confirm that poorer outcomes for patients with partial thickness cartilage loss who are undergoing UKA. The logical corollary to this is to deny patients UKA if their radiographs do not confirm full thickness cartilage loss. However, our subjects only appear to have partial thickness disease and in actuality have full thickness loss confirmed on MR. In so doing we have used MR to broaden the inclusion criteria by which we may deem patients suitable for UKA.

Currently, inclusion criteria for UKA are centred on radiographic findings including the use of valgus and varus stress radiographs when full thickness cartilage loss is not confirmed on weight-bearing AP and lateral radiographs [267]. The role of MRI in selecting patients suitable for UKA has received little attention. Its usefulness in identifying patients with contraindications to the procedure has been questioned with one study suggesting that MR exaggerated abnormalities, including lateral compartment cartilage loss and ACL injury and may lead to incorrectly excluding subjects who would benefit from the procedure [268]. A better understanding of the patterns of osteoarthritis seen on MR and the affects they have on outcome following UKA is needed before such an investigation can be used in isolation. However, our study is focussed on using MR to identify patients that are eligible for UKA based on the presence of full thickness cartilage loss that has not been seen on plain radiographs. To this end its usefulness has been confirmed.

Many surgeons will be comfortable using MR to assess the severity of medial compartment OA and are likely to be using it already to help identify patients who are suitable for UKA. This study supports them proceeding to UKA on the strength of MR findings of full thickness disease in the medial compartment. In so doing it enhances the decision making power of surgeons faced with a symptomatic patient with partial thickness disease on plain radiographs.

8.7. Conclusions.

This is the first study to demonstrate the value of using medial UKA to treat patients who have a partially preserved joint space on plain film radiographs, but full thickness disease confirmed on MR (RxPT/MR-FT). The study highlights the usefulness of MR in the pre-operative work up of patients with osteoarthritis of the knee.

8.8. Future work.

Future studies should focus on the long-term outcomes for this group and other similar groups. Prospective studies that use MR to distinguish patterns and severity of knee OA would enable risk factors associated with a poor or good outcome to be better understood. In particular, determining the significance of specific MR features including the presence of lateral compartment changes, bone marrow oedema and ACL signal abnormality and considering their respective thresholds for surgical intervention would facilitate the use of MR as a decision-making tool.

9. Assimilated thesis discussion.

This thesis has investigated the benefits and harms of surgical intervention for the management of early knee osteoarthritis. It has described the natural history of painful early knee osteoarthritis and identified proximal tibia vara as a risk factor that pre-disposes to more structural progression. It has established the current evidence for surgical intervention in this patient group and reported on outcomes for patients who have undergone surgery for this condition.

Conflict and inconsistencies in the literature regarding risk factors for the progression of osteoarthritis led to the development of the longitudinal cohort study described in Chapters 3 & 4. These chapters focus on subjects with symptomatic EKOA who are not currently considered suitable for arthroplasty surgery. Reassuringly, the majority of these individuals (62.2%) will experience no significant structural progression or symptom worsening over 24 months. Predictors for symptom worsening included being less symptomatic and being overweight at baseline. Predictors for structural progression included more severe structural OA at baseline (reduced baseline JSW) and being more symptomatic at the start of the study. In addition, having a low BMI was protective (i.e. predicted non-progression) over 24 months. The inclusion of lower limb alignment had a significant effect on the predictive models for progression. Malalignment was confirmed as a potent risk factor for OA progression with a more varus knee at greater risk of JSN progression and at lower risk of non-progression.

Chapter 4 details the first study to look at the individual geometric variables that

constitute varus deformity and investigate how they influence progression of disease in symptomatic EKOA. Several factors contributed to both valgus and varus alignment (mLDFA, MPTA and mLDTA), however, only the MPTA had a significant effect on structural progression. The odds of JSN progression occurring at 24 months decreased by 21% for every 1 degree increase (more valgus) in MPTA *(*$p<0.001$). Similarly, a more valgus proximal tibia was associated with a reduced risk of being in both the symptom and structural progression group and the structural progression group.

Chapter 5 used a novel method to capture the large amounts of data generated by the MOAK scoring system and illustrate structural progression in EKOA. It identified a unique pattern of structural progression in subjects with EKOA who demonstrate medial joint space narrowing over 24 months; subjects with proximal tibia vara experienced more focal full thickness cartilage progression in the central medial tibia and those without experienced more diffuse surface area damage.

Chapters 6, 7 and 8 investigate the benefits and harms of surgical intervention for the management of early structural knee osteoarthritis. The systematic review reported in Chapter 6 took a novel disease-based approach to its trials search. It identified moderate to very low quality evidence from trials investigating subjects with symptomatic EKOA. Surgical intervention led to short-term (6-12 months) improvements in pain and function that were non-superior to physical therapy or injectable therapy. There was insufficient evidence provided in this systematic review to define the risk of a serious adverse event associated with surgical intervention for this condition and no trials reported the effects of surgical intervention in this patient group beyond 12 months.

Chapter 7 reports short and mid-term outcomes for a novel neutralising HTO for people with longstanding symptomatic EKOA. Patients with early medial compartment OA and varus deformity can expect, on average, an improvement in Oxford

Knee Score of 15 points at one year following a neutralising HTO. An improvement which is maintained at 3-5 years. Low complication rates were recorded with one patient treated for a non-union and another treated for a superficial infection with oral antibiotics.

The final study described in Chapter 8 demonstrates that, in patients with radiographic partial thickness medial compartment OA of the knee and MR confirmed full thickness cartilage loss (RxPT/MR-FT), Oxford medial UKA can reliably achieve excellent 6-month patient-reported outcomes equivalent to those of subjects that demonstrate radiographic full thickness disease (RxFT). This study has used MRI to reliably identify subjects who are not in the treatment gap with a positive predictive value for assessing exposed bone of 98.1% for the femur and 97.9% in the tibia.

In summary, this thesis has reported the natural history of symptomatic EKOA and identified proximal tibia vara as a potent risk factor for structural progression. The paucity of trials investigating subjects with this disease has been highlighted and surgical interventions which are safe and clinically effective have been identified.

9.1. Clinical relevance

The work described in this thesis has focussed on clinical problems with a view to applying this knowledge directly to a clinical context.

The epidemiological studies described in Chapters 3 and 4 were designed to answer questions that specifically related to a group of patients who represent a unique clinical problem i.e. those patients who find themselves in the 'treatment gap'. Reassuringly, over 24 months the majority of symptomatic patients with EKOA will experience no symptom worsening or structural progression and very few will progress to end-stage osteoarthritis (<1% of KL 1/2 subjects). Delaying surgery for the majority of these individuals is both reasonable and safe as their disease is likely to

remain stable.

There is currently no agreed definition for EKOA and all definitions have arbritrary thresholds inherent to them. A defintion was created de novo for the epidemiological studies (Chapters 3 and 4). A subject needed to have both knee pain and a KL grade 1, 2 or 3 at baseline. Analogous with patients who are in the 'treatment gap'. Small changes to this definition would have yielded differences in the cohorts obtained. It is likely that a purely symptomatic definition would have yielded a greater number of subjects, however, it is not commonplace to see patients with purely osteoarthritic symptoms and no radiological signs in an orthopaedic clinic unless they have had further imaging (e.g. MR) to identify structural pathology. Whilst MRs were available for all subjects only a small subset (n=500) had semi-quantitive or quantitive scoring performed. Extending such scoring systems to all subjects in the cohort may have provided a more detailed description of subjects with EKOA and a higher yield of subjects, however, these scoring systems currently have no validated thresholds which are used to define EKOA and the development of such a defintion was beyond the scope and time constraints of this thesis.

The inclusion of KL grade 1 patients with a 'possible osteophyte' was in an effort to capture those with the earliest radiological signs that are seen in an orthopaedic setting. A definition of KL grade 2 has been widely reported, however, this captures moderate changes and would not have included many subjects with early disease.

The potent effect alignment has on structural progression has been confirmed. Epidemiological studies that do not include assessments of alignment should be interpreted with caution. The observation that proximal tibia vara leads to an increased risk of structural progression over 24 months is a novel and important one. As outlined in the systematic review (Chapter 6) there is limited evidence to support the role of surgery in patients with EKOA. In order to maximise the impact of any inter-

ventions offered it is critical that patients at high risk of progression are identified. Proximal tibia vara is a surgical target that can be corrected with an osteotomy. Its identification as a risk factor for structural progression enables clinicians to offer targeted treatment specifically aimed at slowing progression. High tibial osteotomy for symptomatic EKOA is not widely practiced in the U.K., the results of this thesis lend support to the basic principles of this procedure; 'correct the underlying deformity' [269]. However, clinicians and patients must be clear on the benefits that this research proposes. A clear relationship between proximal tibia vara and symptom worsening has not been identified. A patient complaining of pain wants to be out of pain. Delaying or slowing structural progression may be a logical surgical goal but is likely to come second to the relief of pain.

Structural progression measured by joint space narrowing is still a widely reported outcome for therapeutic intervention in knee osteoarthritis. This study highlights the importance of incorporating alignment in the sample analysis to ensure results of interventions are not unfairly biased by the presence of proximal tibia vara that has not been controlled for.

Excellent outcomes for high tibial osteotomy have been reported in the literature already. The neutralising HTO described in Chapter 7 signals a step away from the traditional valgising osteotomy. It has been hypothesised that a more modest correction will negate the difficulties associated with arthroplasty in this group of patients should the need arise in the future. The study reported excellent results for this procedure in the short and mid-term with high satisfaction and low complication rate. This data is useful to knee surgeons who might be considering HTO surgery but are concerned about the high revision rates for total knee arthroplasty associated with a valgising osteotomy.

The final study outlined in Chapter 8 highlights the usefulness of MR in the pre-

operative work up of patients with osteoarthritis of the knee. In this context, MR, has been able to broaden the inclusion criteria by which we may deem patients suitable for UKA and prevent some patients from languishing in the 'treatment gap'. Many surgeons will be comfortable using MR to assess the severity of medial compartment OA and are likely to be using it already as part of their clinical work-up. This study is the first study to support them proceeding to UKA on the strength of MR findings of full thickness disease in the medial compartment. In so doing it enhances the decision making power of surgeons faced with a symptomatic patient with partial thickness disease on plain radiographs.

In combination these studies have provided support for an evidence-based surgical pathway for patients with symptomatic early osteoarthritis of the knee (see figure 1.1.1) and provided answers to key questions that have been proposed by clinicians, patients and their carers.

9.2. Recommendations for future research

Osteoarthritis represents a significant socio-economic burden to the health of communities around the world. Huge amounts of funding and resources have been dedicated to better understanding this disease process. Consequently, the field of osteoarthritis has become more and more complex. Despite all these efforts it is clear from the work carried out in this thesis that the role of surgical intervention in symptomatic early osteoarthritis of the knee remains poorly defined and lacking in evidence.

The potent effect of alignment on structural progression has implications for future research. Future epidemiological studies investigating progression in EKOA must include an assessment of alignment. Given the effects of proximal tibia vara on structural progression, interventional trials investigating this condition should con-

sider the site of the underlying deformity particularly if structural progression is an outcome of interest. That said, the effects of proximal tibia vara have only been assessed in the static coronal plane. Investigating the effects of proximal tibia vara on gait and pressure distribution within the knee would provide a dynamic context through which this phenotype of alignment could be better understood.

There is growing interest in the factors that lead to the development of proximal tibia vara. Higher levels of sporting activity in youth are associated with the 'constitutional varus' phenotype [32] and in particular high levels of sporting activity in youth are associated with a more varus proxima tibia [36]. A recent study identfied an association between between proximal tibia vara and CAM deformity at the hip and identified physeal disruption of the growth plate in youth as a common causal pathway [270]. Prospective studies investigating the factors that lead to the development of proximal tibia vara are of interest. If a preciptating factor could be identified and the prevalence of proximal tibia vara reduced it is conceivable that this could have a significant impact on the burden of knee osteoarthritis.

The excellent outcomes for a neutralising high tibial osteotomy are encouraging. Intuitively there is likely to be a trade-off between these two procedures. A neutralising osteotomy may increase the likelihood of future arthroplasty surgery compared to a valgising approach. However, the results of subesquent revision surgery may be better with more surgical options retained (i.e. UKA or TKA). Ultimately, it is the patients who should drive the decision-making process as to which surgical pathway is more acceptable. A prospective trial comparing a neutralising osteotomy procedure to a more traditional valgising osteotomy would provide evidence to support which procedure is superior.

The usefulness of MR in the pre-operative work up of patients undergoing UKA has been established. However, only one MR feature in one compartment was considered.

The significance of other MR features and their respective thresholds for surgical intervention is required if MR is going to be an effective decision-making tool in UKA surgery.

A central tenet to surgical practice is to perform the right operation, on the right patient at the right time. In the context of early knee osteoarthritis this represents a significant challenge. The "right operation" remains open to interpretation and in the U.K. the surgery offered to patients varies depending on the skill set and experience of the attending clinician. Re-alignment surgery in the form of a high tibial osteotomy is arguably the most well-described and evidence-based surgical procedure for EKOA. Recent developments have brought osteotomy surgery into the modern era and innovation in this area is continuing at a pace. Finite element modelling enables patient-specific models that can be predict the stresses and strains within the knee joint during motion and can be used to simulate a planned osteotomy and identify the 'safe-correction zone'. In combination with personalised cutting blocks that incorporate 3-dimensional planning with a patient-specific cutting jig the prospect of an individually tailored and accurate HTO procedure will soon become reality. However, it remains to be seen whether such tweaks to surgical technique will have a significant effect on outcome particularly if the outcome of interest is relief from pain.

Most surgeons would consider the patient who is in pain to be the "right patient". However, beyond this, our definitions of the symptomatic patient become very weak. The chronic pain associated with EKOA is a hugely complex and nuanced phenomenon. Nociceptive pain originating from the knee becomes intertwined with psychological coping mechanisms, perceptions of self, social responsibilities and neurophysiological sensitisation syndromes. The acknowledgement that they are in pain may not be sufficient. Surgical trainees are often told that knowing who not to operate on is as important as knowing who to operate on and yet surgeons are

left to rely on their intuition and gut instinct to separate out the individuals who will do well from those who will not. A greater understanding of how the various mechanisms associated with chronic pain impact on surgical outcomes is needed.

Operating on subjects at the "right time" is critical. Clinical pathways from general practice to hospital care are becoming more convoluted and often patients have failed all non-operative management by the time they are seen in an orthopaedic clinic. These types of patients are not always well represented in the literature where participants are often at the start of their clinical journey and may not have exhausted the non-operative management options available to them.

There has been a great deal of progress in the field of osteoarthritis but more needs to be done before we can say we are always performing the right operation, on the right patient at the right time.

Appendices

A. Further analysis for chapter 4

Table A.1.: Multivariate regression analysis to determine the influence of all baseline variables on structural progression over 24 months (JSN >0.7mm)

Baseline joint space narrowing has been exchanged for KL grade in this multivariate model:

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC	1.00	0.99 - 1.02	0.26
Baseline KL grade = 2	1.40	0.75 - 2.61	0.29 .
Baseline KL grade = 3	2.34	1.20 - 4.59	0.01
Age	1.00	0.97 - 1.03	0.96
Gender	1.13	0.69 - 1.86	0.63
BMI	1.01	0.97 - 1.06	0.56
Co-morbidities	0.88	0.67 - 1.16	0.37
Race	1.13	0.67 - 1.91	0.64
Employment	1.21	0.71 - 2.07	0.49
Smoker	1.29	0.82 - 2.02	0.27
Previous knee surgery	0.77	0.44 - 1.34	0.35
mLPFA	1.02	0.98 - 1.06	0.42
mLDFA	1.04	0.94 - 1.15	0.443
MPTA*	0.82	0.74 - 0.90	<0.001
mLDTA	1.02	0.96 - 1.08	0.58

*p=<0.05

Table A.2.: Multivariate regression analysis to determine the influence of all baseline variables on symptom worsening over 24 months (JSN >0.7mm)

Individual alignment variables have been exchanged for overall alignment (HKA) in this multivariate model:

Variable of interest	Odds Ratio	95% CI	p-value
Baseline WOMAC*	0.97	.95 - 0.98	<0.001
Baseline JSN	0.92	0.77 - 1.11	0.41
Age	0.99	0.97 - 1.02	0.63
Gender	1.51	0.94 - 2.44	0.09
BMI*	1.06	1.01 - 1.11	0.01
Co-morbidities	1.11	0.88 - 1.41	0.37
Race	0.74	0.46 - 1.20	0.22
Employment	0.66	0.40 - 1.10	0.11
Smoker	1.24	0.81 - 1.89	0.32 .
Previous knee surgery	1.13	0.67 - 1.90	0.65
HKA	1.05	0.99 - 1.12	0.13

*p=<0.05

B. Search strategies for systematic review: chapter 6

B.1. CENTRAL

Database: Central <1974 to Present>

1. MeSH descriptor: [Osteoarthritis] explode all trees (4136)
2. osteoarthr* (8524)
3. (degenerative near/2 arthritis) (90)
4. arthrosis (379)
5. #1 or #2 or #3 or #4 (8692)
6. MeSH descriptor: [Surgical Procedures, Operative] explode all trees
7. MeSH descriptor: [General Surgery] explode all trees (339)
8. Any MeSH descriptor with qualifier(s): [Surgery - SU] (52644)
9. (surgery* or surgeries or surgical or operat*) (175868)
10. (arthroplast* or hemiarthroplast* or (joint* and replace*)) (8234)

11. Debridement (1722)
12. debride* (1800)
13. repair* (9247)
14. (surface* and replace*) (1326) (110830)
15. resurfac* (491)
16. arthroscop* (3164)
17. (needle* near/4 debridement)
18. (needle* near/4 irrigation)
19. (needle* near/4 lavage)
20. (needle* near/4 washout)
21. Joint near/4 lavage (37)
22. Meniscectomy (259)
23. Chondroplast* (27)
24. gonarthrosis* (212)
25. osteotom* (1157)
26. (device near/4 knee) (66)
27. MeSH descriptor: [Knee Prosthesis] explode all trees
28. knee* and (arthroplast* or implant* or replace* or prosthe* or endoprosthe*)

29. #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 (217264)

30. #5 and #29 (3467)

B.2. MEDLINE

Database: Ovid MEDLINE <1974 to Present>

1. exp osteoarthritis/ (50871)

2. osteoarthr$.tw. (51145)

3. (degenerative adj2 arthritis).tw. (1307)

4. arthrosis.tw. (4887)

5. or/1-4 (73757)

6. exp Surgical Procedures, Operative/ (2681768)

7. exp surgery/ (36205)

8. su.fs. (1721218)

9. (surgery$ or surgeries or surgical or operat$).tw. (1959366)

10. (arthroplast$ or hemiarthroplast$ or (joint$ adj2 replace$)).tw. (51843)

11. Debridement/ (13584)

12. debride$.tw. (20517)

13. repair$.tw. (261141)

14. (surface$ adj replace$).tw. (462)
15. resurfac$.tw. (5929)
16. arthroscop$.tw. (22769)
17. (needle$ adj4 debridement).tw. (9)
18. (needle$ adj4 irrigation).tw. (174)
19. (needle$ adj4 lavage).tw. (117)
20. (needle$ adj4 washout).tw. (50)
21. (Joint adj4 lavage).tw. (225)
22. Meniscectomy.tw. (2337)
23. Chondroplast$.tw. (227)
24. gonarthrosis$.tw. (942)
25. osteotom$.tw. (26377)
26. (device adj4 knee).tw. (258)
27. knee prosthesis.mp. [mesh] (10801)
28. (knee* and (arthroplast* or implant* or replace* or prosthe* or endoprosthe*)).tw. (31471)
29. or/6-28 (4230937)
30. randomized controlled trial.pt. (420176)
31. controlled clinical trial.pt. (90970)

32. randomized.ab. (350194)
33. placebo.ab. (171145)
34. drug therapy.fs. (1870160)
35. randomly.ab. (251242)
36. trial.ab. (362131)
37. groups.ab. (1566486)
38. or/30-37 (3769947)
39. (animals not (humans and animals)).sh. (4226277)
40. 38 not 39 (3244889)
41. 5 and 29 and 40 (6532)

B.3. EMBASE

Database: Embase <1974 to 2016 June 07>

1. exp osteoarthritis/ (97696)
2. osteoarthr$.tw. (69826)
3. (degenerative adj2 arthritis).tw. (1532)
4. arthrosis.tw. (6603)
5. or/1-4 (116009)
6. exp surgery/ (3924247)
7. su.fs. (1866555)

8. (surgery$ or surgeries or surgical or operat$).tw. (2545392)
9. (arthroplast$ or hemiarthroplast$ or (joint$ adj2 replace$)).tw. (58890)
10. Debridement/ (29240)
11. debride$.tw. (23826)
12. repair$.tw. (324456)
13. (surface$ adj replace$).tw. (516)
14. resurfac$.tw. (6983)
15. arthroscop$.tw. (27175)
16. (needle$ adj4 debridement).tw. (9)
17. (needle$ adj4 irrigation).tw. (140)
18. (needle$ adj4 lavage).tw. (168)
19. (needle$ adj4 washout).tw. (73)
20. (Joint adj4 lavage).tw. (275)
21. Meniscectomy.tw. (2677
22. Chondroplast$.tw. (269)
23. gonarthrosis$.tw. (1371)
24. osteotom$.tw. (29460)
25. (device adj4 knee).tw. (331)
26. knee prosthesis/ (6570)

27. (knee* and (arthroplast* or implant* or replace* or prosthe* or endoprosthe*)).tw. (38053)
28. or/6-27 (5366371)
29. random$.tw. (1088136)
30. factorial$.tw. (27740)
31. crossover$.tw. (57580)
32. cross over.tw. (25477)
33. cross-over.tw. (25477)
34. placebo$.tw. (238527)
35. (doubl$ adj blind$).tw. (168718)
36. (singl$ adj blind$).tw. (17677)
37. assign$.tw. (287811)
38. allocat$.tw. (104387)
39. volunteer$.tw. (207215)
40. crossover procedure/ (47215)
41. double blind procedure/ (131219)
42. randomized controlled trial/ (407385)
43. single blind procedure/ (22213)
44. or/29-43 (1710503)
45. 5 and 28 and 44 (4593)

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D. Characteristics of ongoing studies: chapter 6

Title: A Randomized Trial Comparing High Tibial Osteotomy Plus Non-Surgical Treatment and Non-Surgical Treatment Alone

Methods

Study design: Parallel group randomized controlled trial

Participants

Inclusion Criteria:

- Is the subject either:25-55 years old?Older than 55 but still active (ex. physical labour, regular recreational activities)?Does this subject present with varus alignment? (Based on hip to ankle x-rays).
- Does this subject have clinical Knee OA? (MAA <-2° on full limb standing AP) according to the Altman classification primarily involving the medial compartment of the knee?Patient is a good candidate for high tibial osteotomy and will be receiving a PEEK plate, or if receiving an alternate plate, agrees to have the plate removed prior to 1 year postoperative.

Exclusion Criteria:

- Has this subject had a previous HTO or joint replacement in either limb?Is this subject likely to undergo bilateral HTO within the 2 year follow up period?Does this subject have an unstable knee or ligament?
- Does this subject have inflammatory or infectious arthritis of the knee?
- Radiographic disease too advanced for HTO (i.e.. diffuse lateral compartment, patellofemoral joint OA and/or severe enough disease to suggest that joint replacement is the better surgical option) and/or Kellgren and Lawrence grade 4.
- The subject's disease is not advanced enough (symptomatically or radiographically) to warrant HTO.
- Does this subject have a major medical illness with life expectancy <2 years or with an unacceptably high operative risk
- Does this subject have a major neurological deficit that would affect gait?
- Is this subject possibly pregnant or planning pregnancy?
- Is this subject unable to read English?
- Does this subject have a psychiatric illness that limits informed consent?
- Is the subject unlikely to comply with study protocol?

Interventions

- Medial Opening Wedge High Tibial Osteotomy (HTO)
- Non-Surgical Treatment Program

Outcomes

Primary Outcome Measures MRI articular cartilage morphology [Time Frame: Change from baseline to 24 months post operative] 3 Tesla MRI measure of medial tibiofemoral articular cartilage thickness

Secondary Outcome Measures

- Knee Injury and Osteoarthritis Outcome Score (KOOS) [Time Frame: Change from baseline to 24 months post operative]5 subdomains: pain, symptoms, activities of daily living, sport and recreation, quality of lifeWestern Ontario Meniscal Evaluation Tool (WOMET) [Time Frame: Change from baseline to 24 months post operative]
- Biological Markers of Disease Progression [Time Frame: Baseline, 12 and 24 months post operative]Synovial fluid, serum and urine biological markers
- Numeric Rating Scale for Pain [Time Frame: Baseline, 12 and 24 months post operative]0 (no pain) - 10 (worst possible pain)Gait Biomechanics [Time Frame: Baseline, 12 and 24 months post operative]
- Knee frontal, sagittal and transverse plane kinematics and kinetics tested during level walking in a motion analysis laboratory. The measure of most interest is the peak external knee adduction moment during stance phase of walking, expressed in %BW*Ht.
- Isometric Strength Testing [Time Frame: Baseline, 12 and 24 months post operative]Isometric quadriceps and hamstrings strength tested using an isokinetic dynamometer.
- Intermittent and Constant Osteoarthritis Pain Index (ICOAP) [Time Frame:

Change from baseline to 24 months post operative]Short-Form 12 (SF12) [Time Frame: Change from baseline to 24 months post operative]

- Western Ontario and McMaster Universities Arthritis Index (WOMAC) [Time Frame: Change from baseline to 24 months post operative]3 sub domains: pain, symptoms, function

Timeline

- Starting date: September 2014
- Estimated Study Completion Date: July 2019

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Notes

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