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MORPHOLOGICAL RISK FACTORS FOR KNEE OSTEOARTHRITIS

Dr. Anand R Nair, MBBS, MD

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Abstract

Background

The knee, particularly the medial tibiofemoral joint (TFJ) and patellofemoral joint (PFJ) compartments, is a common joint affected by osteoarthritis (OA) and results in significant healthcare burden. Knee OA shows familial clustering, although the mechanism for inherited predisposition remains unclear. Morphological variations of the femur, tibia and patella can biomechanically affect the loading of the knee joint and predispose to knee OA, which may in part explain the heritability of the condition. Although several morphological features of the hip joint are recognised to predispose to hip osteoarthritis (OA), only a few shape variants at the knee are known to associate with knee OA. This study aimed to validate existing morphological features, and identify novel morphological features associated with knee OA. In addition, the clinical relevance of these morphological variations was examined by evaluating their association with knee pain severity, and severity of structural changes.

Method

Study design: case control study using data from the Genetics of Osteoarthritis and lifestyle (GOAL) study.

Sample size: Control group n=408 (816 knees assessed), case group n= 315 (315 knees assessed)

Control definition: GOAL participants without knee pain or radiographic OA changes in both knees, defined as osteophyte score ≤1 and joint space narrowing score (JSN) 0 according to the Nottingham logically devised line drawing atlas (NLDLDA).

Case definition: Structurally unaffected knees of individuals with OA in the contralateral knee as defined above.

Radiographic measurements: After a literature review, 12 radiographic morphological features, six of them novel were assessed. They were measured on skyline and posterior-anterior (PA) radiographic images using HIPAX software. Additionally, data for varus-valgus alignment at the knee was available from a previous PhD project at the University of Nottingham (Abhishek et al, 2012), and were included in this study. A single observer performed all radiographic measurements in the current study. Reproducibility of measurements was determined at the study start, middle and end.

Unaffected knees of unilateral knee OA cases were compared to the normal knees of controls, after confirming the assumption that the morphology of the right and left knee of people without knee OA is symmetrical. This indicates that similar morphological changes would be present in the unaffected knee as in the affected knee before the latter developed structural changes of OA.

Statistical analysis: Symmetry of these morphological measures between right and left knee was examined using paired t test and minimal detectable change (MDC). Reproducibility was assessed using intra-class correlation coefficient (ICC). Univariate and multivariate association of morphological measures and risk factors for OA such as age, gender, height and weight were determined using linear regression using data from the control group. Association of morphological features and unilateral knee OA (defined as OA in either PFJ or TFJ), PFJ OA (defined as OA in PFJ) and TFJ OA (defined as OA in TFJ) were determined using binary logistic regression and odds ratio (OR) and 95% confidence interval (CI) calculated.

Diagnostic ability of the morphological features as a composite function in the prediction of unilateral knee OA, PFJOA and TFJOA was determined using receiver operating characteristic (ROC) curves. Data analysis was conducted using STATA version 15, and $p<0.05$ was considered as statistically significant. Bonferroni corrections were applied for multiple testing where appropriate.

Finally, further analyses were performed to examine whether morphological features that were significantly associated with the presence of knee OA, PFJOA or TFJOA were also associated with increasing severity of WOMAC pain score, summated osteophyte scores and summated JSN scores of the NLDLDA, and KL grade. For the analyses examining association with structural changes, morphological measurements in the unaffected knee of the case group were the independent (exploratory) variable and the structural changes in the contralateral affected knee were the dependent variable. The univariate and multivariate analyses were carried out using linear regression, and β-coefficient (β-coef), p values and 95%CI were calculated.

Results The mean and standard deviation (SD) for age, height and weight of cases and controls were 64 (8.6) and 62 (8.5) years, 166.7 (14.2) and 167.5 (11.1) cm, and 78.3 (14.4) and 77.1 (15.7) kg respectively. Mean difference between left and right sides in controls was less than the MDC for all measurements suggesting right-left symmetry. Results of linear regression, showed patellar width had positive association with height [βcoef=0.4; 95%CI 0.3, 0.42] and weight [βcoef=0.05; 95%CI 0.01, 0.1]. Age of the participants had a positive association with patellar thickness [βcoef= 0.01; 95%CI 0.04, 0.3]. Female gender associated negatively with patellar

width [βcoef=-2.5; 95%CI-4,-0.93] and condylar width [βcoef=-3.33; 95%CI -4.5,-2.15].

Narrow sulcus and condylar angles, increasing distal femoral, proximal tibial tilt and increasing varus alignment associated with knee OA. ROC curves including all significant morphological features and age, gender, height and weight predicted knee, PFJ, and TFJ OA with area under the curve (AUC) of 0.91, 0.89, and 0.90 respectively. On the contrary, a model only containing age, gender, height and weight predicted knee, PFJ, and TFJ OA with AUC of 0.59, 0.67, and 0.59 respectively. As distal femoral and proximal tibial tilt were correlated (r=0.54), only distal femoral tilt was included in the prediction model. Sensitivity analysis replacing distal femoral tilt with proximal tibial tilt did not change the results.

Sulcus angle, condylar angle, distal femoral tilt, proximal tibial tilt and varus alignment were examined for association with WOMAC pain score, summated osteophyte score and summated JSN score of the NLDLDA, and the KL score. A narrow condylar angle associated with increasing severity of WOMAC pain score [β-coef=-0.16; 95%CI -0.29,-0.02)] and also associated with increasing summated osteophyte scores of the NLDLDA [β coef=-0.15; 95%CI -0.31, -0.001]. Varus alignment showed a positive association with summated NLDLDA osteophyte scores [βcoef=2.19; 95%CI 1.18, 3.20] and increasing KL grades [βcoef=0.54; 95%CI 0.32, 0.76].

Conclusion This study has identified several morphological features that associate with knee OA. These features together with age, gender, height and weight predicted OA status to a high degree of accuracy. While there are some variations between morphological features associated with TFJ OA and PFJ OA, sulcus angle and

condylar angle associated with both PFJ and TFJ OA suggesting potential shared mechanisms for these variants of knee OA. Narrow condylar angle was associated with both structural and symptomatic features of knee OA, while varus alignment associated with structural features alone. The results of our study should be validated in independent datasets.

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Abbreviations

ACL	Anterior cruciate ligament
ACR	American college of Rheumatology
AUC	Area under the curve
BO	Bisect offset
BMD	Bone mineral density
BMI	Body mass index
BML	Bone marrow lesion
CEA	Centre edge angle
ECM	Extracellular matrix
ESR	Erythrocyte sedimentation rate
FAI	Femoral acetabular impingement
GOAL	Genetics of Osteoarthritis and Lifestyle
HOX	Homeobox genes
HRT	Hormone replacement therapy
ICC	Intra-class correlation coefficient
JSN	Joint space narrowing
JSW	Joint space width
K/L	Kellgren and Lawrence
IVU	Intravenous urography
LDA	Line drawing atlas
MDC	Minimum detectable change
MRI	Magnetic resonance imaging
MOST	Multicentre OA study
NLDLDA	Nottingham logically devised line drawing atlas
NHANES	National Health and Nutrition Examination Survey
OA	Osteoarthritis

OR	Odds ratio
OARSI	Osteoarthritis Research Society International
QTF	Quadriceps tendon strain force
RA	Rheumatoid arthritis
RF	Rheumatoid factor
ROC	Receiver operating characteristics
RR	Risk ratio
ROAD	Research on osteoarthritis and osteoporosis against disability study
SA	Sulcus angle
SD	Standard deviation
SEM	Standard error of mean
SNPs	Single nucleotide polymorphism
TFJ	Tibio femoral joint
TKR	Total knee replacement
THR	Total hip replacement
TA	Trochlear angle
VAS	Visual analogue scale
WHO	World Health Organization

Chapter 1: INTRODUCTION

1.1 Definitions of osteoarthritis

Osteoarthritis (OA) is by far the commonest form of arthritis worldwide (Breedveld, 2004). Although our knowledge of OA is advancing, its aetiology and pathogenesis are still not fully understood (Breedveld, 2004).

There have been several attempts to define OA. The American College of Rheumatology (ACR) in 1986 defined OA as "A heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins" (Altman et al., 1986a). In 1994, the World Health Organization (WHO) brought out a new definition of OA which states that: "OA is a result of both mechanical and biological events that uncouple the normal balance between degradation and synthesis by articular cartilage chondrocyte, extracellular matrix, and subchondral bone" (Mollenhauer and Erdmann, 2002).

Dieppe and Lohmander (2005a) emphasised that OA is a disease of the whole joint and is not limited just to cartilage, but also involves bone, synovium/capsule, muscles and ligaments. Bauer and colleagues defined OA as a degenerative disease (Matthews, 1953). Similarly, Felson et al (2000b) defined OA as a chronic degenerative disorder of diarthrodial (synovial) joints characterized by focal loss of hyaline cartilage and increased bone growth at the joint margins.

According to the current definition by the Osteoarthritis Research Society International (OARSI), “Osteoarthritis is a disorder that can affect any moveable joint of the body, for example knees, hips, and hands. It can show itself as a breakdown of tissues and abnormal changes to cell structures of joints, which can be initiated by injury” (Lane et al., 2011). Recent studies are based on the fact that OA is not a single disease but a group of conditions which may share similar risk factors, biological and morphological features but different clinical phenotypes (Glyn-Jones et al., 2015).

1.2 The nature of Osteoarthritis

OA is a common complex disorder with multiple genetic, constitutional and environmental risk factors (Valdes et al., 2013). Structural changes akin to OA are also seen in other animals in diarthrodial joints (Kuyinu et al., 2016)

Archaeological insights into the evolutionary antiquity of the condition in many species, including dinosaurs, upholds the theory that not all instances of structural changes of OA can be considered harmful, and it may reflect a potentially beneficial and adaptive response to joint insult (Doherty et al., 2016)

OA is therefore best viewed as a metabolically active, dynamic process with a slow inherent reparative phase. It can affect any synovial joint but is most prevalent in knees, finger-interphalangeal joints, thumb bases, first metatarsophalangeal joints, spinal facet joints and the hips (Bland and Cooper, 1984).

A variety of joint insults might trigger the need to repair (Doherty et al., 2016). As part of the adaptive response, the cartilage enhances its metabolic activities, and osteocytes also increase their activity with new bone formation and remodelling of the joint in an attempt to compensate for tissue loss, and with an effort to redistribute mechanical forces across the affected joint (Doherty et al., 2016). For instance, the formation of marginal osteophytes with capsular thickening may help to maintain joint stability. The outcome of a joint with OA depends on the balance between the severity and chronicity of the insult and the effectiveness of the repair response (Radin and Rose, 1986). The concept of OA as a repair process is shown in Figure 1.

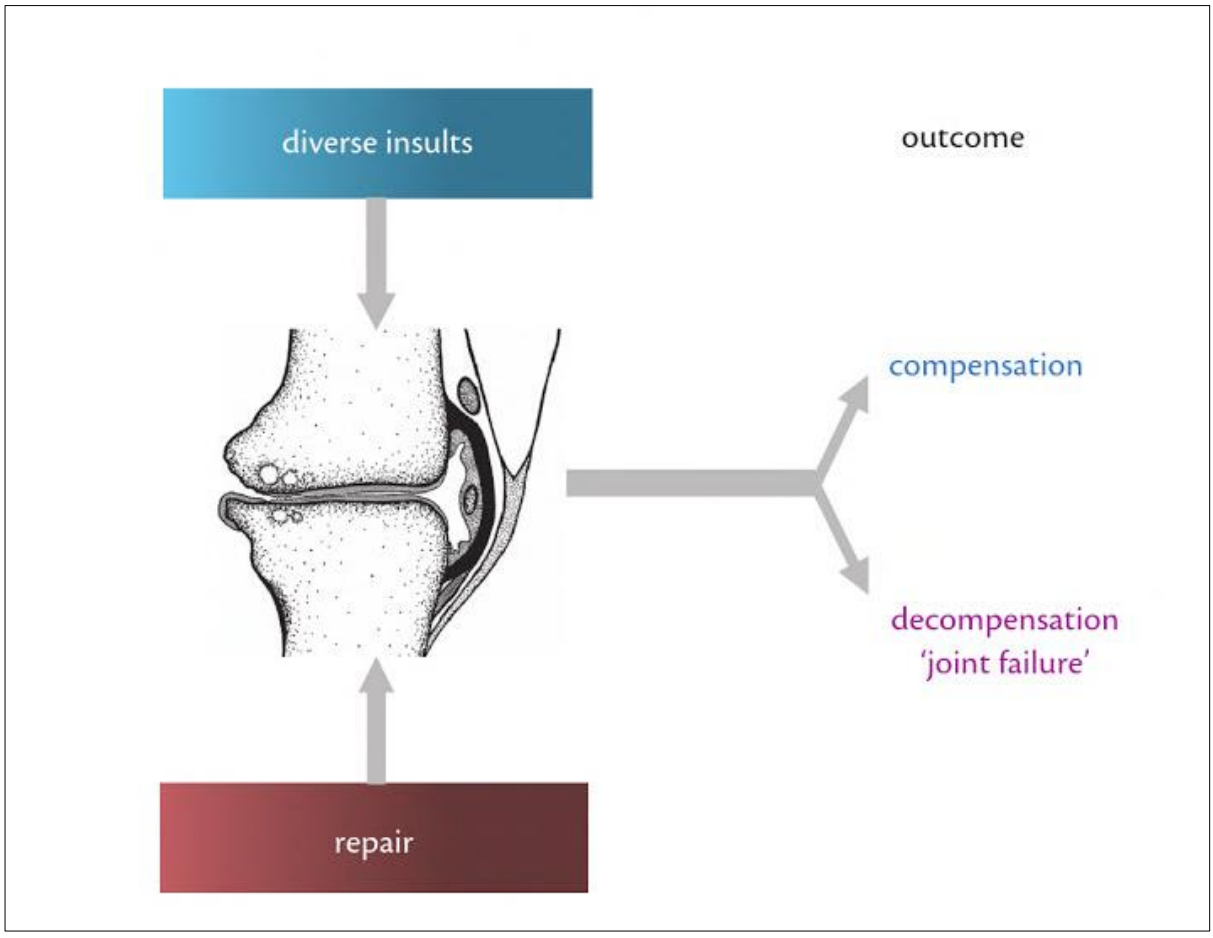

Figure 1. A schematic representation of OA repair process
Source: (Doherty et al., 2016)

In most cases, the repair and remodelling successfully counteract and address the adverse effects with no symptoms, while in others there is a degree of failure to repair with appreciable functional restriction. However, in some cases the severity of insults with poor tissue response lead to decompensated OA with associated continuity of attempted repair and remodelling resulting in an increased risk of associated symptoms, disability and progression of structural damage (Radin and Rose, 1986). This signifies “joint failure” with marked heterogeneity at target sites (Radin and Rose, 1986) (Doherty et al., 2016).

OA is different from changes in the joint that occur with ageing as the biochemical aberrations include expression of chondroitin epitopes, angiogenesis, matrix turnover and increased vascularity such as that seen in young cartilage (Hamerman, 1989). OA is asymptomatic for the majority of people and its clinical presentation can be different at each joint (Lane et al., 2011). For instance asymptomatic OA is very common in lower cervical and lumbar apophyseal joints but less so at hips (Lane et al., 2011) (Doherty et al., 2016). One feature of OA which remains unanswered is its selectivity for involvement of target sites (Doherty *et al.,*2016).

Even though the final outcome of OA could be severe e.g. joint failure resulting in total joint replacement, it is not always progressive. There may be a favourable outcome even in many cases of symptomatic OA (Atkinson, 1996) (Doherty *et al.,*2016).

1.3 Pathogenesis

Studies show that OA affects the whole joint and has regenerative, reparative and degenerative pathological processes (Dieppe, 2011) (Glyn-Jones et al., 2015). Cartilage, subchondral bone, synovium and capsule all have an important role in the pathogenesis of OA (Dieppe, 2011) (Glyn-Jones et al., 2015). The cartilage consists of extracellular matrix (ECM) which contains collagen and aggrecan (Pearle et al., 2005). Type II collagen forms the main structural protein component of the cartilage. The triple helical strands of collagen have very high tensile strength and are inter-linked by sulphide bonds to form a lattice. Aggrecan is the main proteoglycan present in cartilage and is retained within the collagen fibril lattice, it is hydrophilic in nature and plays an important role in maintaining osmotic pressure (Vincent, 2004). It never expands itself to its full volume and remains under saturated, but as it absorbs water and expands its volume, it is kept in check by the strong collagen lattice (Goldring and Marcu, 2009). When cartilage undergoes loading, water is squeezed sideways, allowing cartilage depression and a subsequent shock absorber effect, and when the load is removed water is rapidly drawn back again restoring the cartilage to its original shape (Goldring and Marcu, 2009) (Doherty et al., 2016).

A diverse range of insults to the joint can trigger the onset of OA. In the early phase of OA there is increased production of Type II collagen and aggrecans (Poole et al., 2002). This is followed by the proteolytic degradation of the matrix by enzymes such as aggrecanases, collagenases, and matrix metalloproteinases (MMP) (Poole et al., 2002) (Felson, 2004). Collagenase (MMP-1 and MMP-13) and stromelysin (MMP-3),

are the primary components driving this breakdown, which ultimately leads to loss of cartilage volume. MMP-13 is the main enzyme responsible for the degeneration of the cartilage ECM (Maldonado and Nam, 2013). The major collagenase-producing cells are mesenchymal cells such as fibroblasts and chondrocytes, which synthesize and secrete these enzymes. These cytokines act primarily through cell surface receptors, and their signalling is mediated by complexes of nuclear onco-proteins, leading to the activation of pro-collagenase gene transcription. Increased MMP-13 activity plays an important role in the induction and pathogenesis of OA. In addition, MMP-13 also causes articular cartilage degradation and pathological changes in joints which are manifested as synovial hyperplasia and synovitis with diffuse mononuclear cell infiltration in the synovium (Maldonado and Nam, 2013).

Eventual depletion of the proteoglycans affects the water binding capacity. As a result, the ECM becomes hyper-hydrated (Vincent, 2004) (Maldonado and Nam, 2013). In order to maintain homeostasis, the chondrocytes produce excess extracellular matrix components, which allows the cartilage to absorb more water, and undergo hypertrophy. The action of physical forces on this softened cartilage can lead to matrix fibrillation and matrix fragment delamination, the two features which are considered typical pathological features of OA (Glyn-Jones et al., 2015, Vincent, 2004). Contrary to chondrocyte necrosis, apoptosis takes place as a result of chemical signals derived from the matrix degradation products (Vincent, 2004).

The pathological process in articular cartilage can be divided into three stages. Firstly, there is matrix degradation with increased water content and reduced aggrecan concentration (Lorenz and Richter, 2006). The second stage involves chondrocyte

repair, where chondrocytes increase their number and metabolic activity assuming a hypertrophic phenotype in clones or nests of chondrocytes. This state may exist for years. In the final stage, the chondrocyte is unable to compensate for the matrix breakdown resulting in marked loss of cartilage and bone on bone contact in maximum weight-bearing parts of the joint (Lorenz and Richter, 2006).

In the subchondral bone, the osteoblast-osteoclast system results in bone resorption and bone formation in the subchondral plate (Glyn-Jones et al., 2015). This can be seen as thickening and sclerosis on plain radiographs. This bone remodelling is an important pathological feature of OA (Felson, 2004). The overall increase in the bone volume makes the articular plate more stiff compared to normal. In addition to this, in later stages of OA progression, trabecular micro-fractures lead to further stiffening of the bone (Felson, 2004). The remodelling of the bone is intuitive, beneficial and compensates for altered mechanical forces, but if it is insufficient and fails, then micro-fractures and bony necrosis may result. (Vincent, 2004, Glyn-Jones et al., 2015).

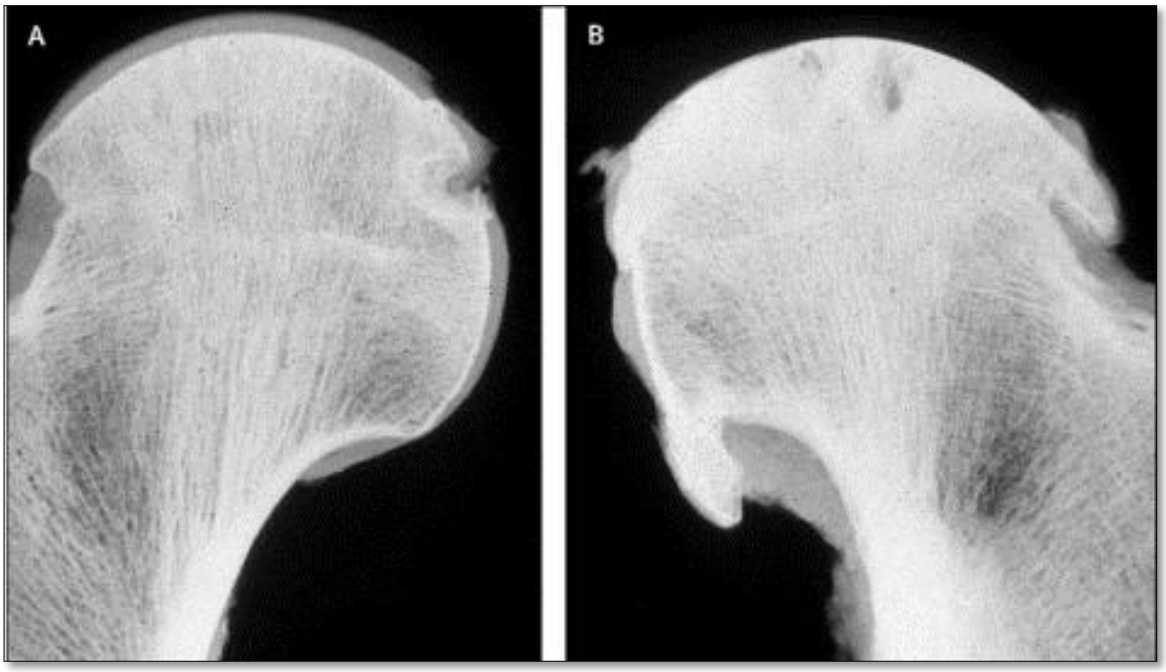

Figure 2. Radiographs of Normal (A) & (B) Osteoarthritic femoral head

Loss of articular cartilage, subchondral sclerosis, loss of sphericity of the head, large marginal osteophytes can be seen in figure 2(B)

Source : (Dieppe and Lohmander, 2005).

Synovial hypertrophy and inflammation are also features of OA. However, it is focal in OA i.e. localised to a part of the joint, or in a few joints, than the generalised inflammation and synovitis seen in RA (Goldenberg et al., 1982). The cartilage breakdown products catalyze synovial inflammation, stimulating inflamed synovium to produce catabolic and inflammatory chemicals that lead to increased production of proteolytic enzymes which may enhance cartilage breakdown, thereby creating a positive feedback loop (Houard et al., 2013).

The histological features seen are synovial tissue inflammation, hyperplasia with an increased number of lining cells, and a mixed cellular infiltrate (Glyn-Jones et al., 2015, Vincent, 2004). Macrophages and T cells are commonly seen in synovial tissue of OA (Glyn-Jones et al., 2015). However, unlike the primary synovitis in RA marginal cortical bone erosion does not occur. Pathological features in knee OA compared to a normal knee joint are shown in Figure 2.

The capsule and intra-articular ligaments which help in stabilizing the joint are also affected by OA. The pathological changes that can been seen in them are thickening, laceration and scarring. Enthesophytes, considered as a marker of bone forming phenotype, can also be observed at the insertion of the capsule, ligaments and tendons in OA (Hardcastle et al., 2014).

1.4 Clinical features

OA is commonly occult and benign. OA may be localized to one joint, a few joints or be more generalized, and the onset of symptoms is usually insidious (Hunter et al., 2008). It presents with joint pain, movement restriction and functional impairment. Factors such as age of onset, joints involved and rate of progression differ from site to site and between individuals (Arnoldi et al., 1975). Clinical features may also depend upon the degree of joint damage and other associated co-morbidities (Arnoldi et al., 1975). Often, there is poor correlation between the clinical symptoms and the structural changes observed on radiographs (Lawrence et al., 1966) (Hunter et al., 2008) (Allen et al., 2009a).

Pain is the usual first and major complaint of OA, and the usual reason for people to seek help from health care providers (Brandt, 1989). Pain occurs with joint use and is relieved by rest (Hunter et al., 2008). It may progress slowly over months to years with changing intensity throughout the day (Allen et al., 2009a, Hunter et al., 2008).

There are various theories regarding the pain mechanisms but the pathogenesis of pain in OA is incompletely understood. Studies suggest both peripheral and central mechanisms are involved (Hunter et al., 2008).

Pain may arise from synovium, subchondral bone, periosteum, capsule, tendons or ligaments but the hyaline cartilage is aneural, and by definition cannot be a source of pain (Hunter et al., 2008) (Weisman, 2013).

Another common symptom of OA is stiffness (Bellamy and Buchanan, 1986, Bellamy et al., 2002). Stiffness is a subjective feeling of inability to freely move a joint (Weisman, 2013). It may occur in the morning on first arising or later in the day after periods of rest but is usually brief (less than 30 minutes) (Weisman, 2013, Bellamy and Buchanan, 1986) and “wears off” as the joint again starts to move. Symptoms including movement restriction and functional impairment may lead to poor mobility and affect the daily activity of the individual (Bijlsma, 2012).

The signs that may be detected on clinical examination include reduced range of movement, weakness and even wasting of the muscles that act over the affected joint, joint-line and peri-articular tenderness, bony swelling, malalignment and course crepitus (Abhishek and Doherty, 2013), (Doherty et al., 2016). Crepitus is the grating sensation and sound produced by the friction between the damaged articular cartilage or bone rubbing on bone (Bijlsma, 2012)

Clinical features of knee OA

Usage-related knee pain, short-lived morning and inactivity stiffness and reduced function are the three main symptoms that are recommended for the diagnosis of knee OA (Altman et al., 1986a) (Zhang et al., 2010). The medial compartment of the TFJ and the PFJ are most commonly affected. Pain is usually well localised and anteromedial in medial compartment TFJ OA and immediately behind the patella in PFJ OA (Heidari, 2011, Weisman, 2013).

Signs of knee OA include joint-line tenderness on palpation, only small-to-modest joint effusions, crepitus on active and passive joint movements, restricted flexion and/or extension and in advance cases malalignment such as varus or valgus deformities, and fixed flexion (Weisman, 2013, Heidari, 2011).

1.5. Diagnosis of osteoarthritis

1.5.1 Clinical

The American College of Rheumatology (ACR) criteria is a widely used method of classifying knee OA for epidemiological and clinical trial purposes (Altman et al., 1986b). The ACR diagnostic criteria for Knee OA is shown in Table 1

Table 1. ACR diagnostic criteria for Knee OA

Clinical and laboratory	Clinical and radiographic	Clinical
Knee pain plus at least 5 of the following;	Knee pain plus at least 1 of the following	Knee pain plus at least 3 of the following
Age>50 years	Age >50years	Age>50years
Stiffness<30mins	Stiffness<30 minutes	Stiffness<30mins
Crepitus	+	Crepitus
Bony tenderness	Crepitus	Bony tenderness
Bony enlargement	osteophytes	Bony enlargement
No palpable warmth		No palpable warmth
ESR<40mm/h		
RF<1:40		
Synovial fluid consistent with OA		
Sensitivity,92%	Sensitivity,91%	Sensitivity,95%
Specificity,75%	Specificity86%	Specificity69%

ACR: American college of Rheumatology; ESR: Erythrocyte sedimentation rate, RF Rheumatoid factor; OA Osteoarthritis

The European League against Rheumatism (EULAR) has also developed an evidence based recommendation for the diagnosis of knee OA considering risk factors, signs and symptoms, subsets of clinical outcome, clinical imaging and diagnostic tests (Zhang et al., 2010). It was recommended that a confident clinical diagnosis of knee OA can be made according to three symptoms (persistent knee pain, limited morning stiffness, reduced function) and three signs (crepitus, movement restriction and bony enlargements). This was because when these three symptoms and three signs are present, the chance of having radiographic knee OA rose to 99% (Zhang et al., 2010).

1.5.2 Radiographic evaluation

Radiography is the most commonly used imaging technique in the evaluation of OA, despite the advent of newer imaging techniques such as MRI, and ultrasonography (Braun and Gold, 2012). It is inexpensive, readily interpreted and widely available. The three most common views used for a knee radiograph are a posterior-anterior view for the TFJ compartments and flexed lateral or skyline views for the PFJ.

A weight-bearing PA view is preferred for demonstrating knee OA changes. The weight-bearing radiographs better demonstrate narrowing of the affected medial or lateral TF compartments and varus or valgus deformity than non-weight bearing radiographs (Leach et al., 1970). A semi-flexed weight-bearing PA view has better sensitivity for detecting JSN than an extended PA weight-bearing view (Duncan et al., 2007) and hence is recommended by OARSI for evaluating TFJ OA (Hunter et al., 2015).

A skyline view of the PFJ is usually preferred over a lateral PF view for demonstrating changes of OA (Cicuttini et al., 1996) (Hunter et al., 2015). It provides a clearer view of joint space width and also allows the determination of medial and lateral narrowing in the PFJ (Cicuttini et al., 1996) (Hunter et al., 2015). Although various angles of flexion are used in skyline, 20^0-30^0 degrees are most commonly used (Luo et al., 1997), (McNally, 2001), since this is the minimum angle of flexion needed to obtain the view. In addition to this, at this angle the lateral retinaculum attains maximum tension and also there is high chance of patellar subluxation being apparent (Luo et

al., 1997), (McNally, 2001). The most widely used radiographic methods of assessing OA severity are semi-quantitative. Plain films are used to detect osteophyte formation, JSN, cysts and subchondral sclerosis. The most commonly used of these is the global Kellgren and Lawrence (K/L) grading system (Table 2)

Table 2.Kellgren Lawrence grading of OA

Grade	OA signs
0	No radiographic features of OA are present.
1	Doubtful JSN and possible osteophyte.
2	Definite osteophytes and possible JSN
3	Multiple osteophytes, definite JSN, some sclerosis, possible bony deformity.
4	Large osteophytes, marked JSN, severe sclerosis and definite bony deformity.

JSN-Joint space narrowing

Source: (Kellgren and Lawrence, 1957)

The advantage of this scoring method is that it can easily provide a 0-4 grade of overall OA presence and severity. However, it has been criticized for using an ordinal not interval scale, for weighting osteophyte more than JSN, focusing just on the TFJ and providing a single combined score for both compartments (not allowing separate assessment of medial and lateral TFJs and ignoring the PFJ) and for combining osteophyte and JSN measurements, thus preventing study of individual OA characteristics (Roemer et al., 2011).

Another scoring system was developed by Altman *et al* which focused on individual radiographic features in the TFJ compartments and was more sensitive in detecting TFOA progression than the K/L system(Altman et al., 1987). Similarly, Spector *et al*

developed a scoring system which included both lateral flexion view and skyline view for the assessment of individual features of the knee (Spector et al.,1992). The Osteoarthritis Research Society (OARS) atlas developed (Altman et al., 1995) by Altman *et al* is accepted by many as the current standard radiographic atlas for OA (Lanyon et al., 1998). This atlas has the advantage of having the skyline view of the PF compartment and also allowed scoring of individual features. However, this atlas has been criticised for the following reasons.

- photographic reproduction of the atlas was expensive and was not readily available,
- there was difficulty in comparing between photographs due to differences in intensity and magnification,
- having uncommon osteophyte shapes, inclusion of too many features that may distract the observer, and
- also proposing an ordinal scale (Nagaosa et al., 2000)

A series of line drawing atlases was developed by Nagaosa et al (Nagaosa et al., 2000) and later by Wilkinson et al in Nottingham, UK (Wilkinson et al., 2005).

JSN and osteophyte were the only two features selected in this atlas, since they were the accepted cardinal feature of pathological and radiographic OA.

This system separately grades osteophyte and JSN in the three compartments of the knee. JSN was determined initially from the normal joint space width on weight bearing semi-flexed PA and skyline views. This was then divided using a three-point interval scale, in which zero indicated no reduction of JSW and a score of three

indicated bone-on-bone contact. This was determined by examination of community-derived people with no knee pain and no RKOA. Since joint space width differs by gender but not age, different images are used for men and women for this measure. Scores of one and two indicated a reduction of JSW by two-thirds and one third respectively (Nagaosa et al., 2000).

For osteophytes a three point scale (as with JSN) was used initially to determine the grades. A Community-based sample of 715 sets of bilateral knee radiographs were used to select grade 3 describing maximum osteophyte size and hand tracing of this was made. This was determined in each region of all compartments. Grade 1 and grade 2 osteophyte were determined as one third and two thirds of the size (length and width) respectively of the maximum grade 3 osteophyte at each site (Nagaosa et al., 2000).

Despite the strengths of this atlas the NLDLDA was further modified to improve its use as a clinical assessment tool. The three-point scale was upgraded to a five-point scale for scoring both JSN and osteophyte formation (Figure 3 and Figure 4). Additionally, negative scoring for JSN indicated an increase in JSW, which commonly occurs in OA particularly in the contralateral TF compartment or contralateral side of the PF compartment to that affected by OA.

The use of a five-point scale improves sensitivity of the NLDLDA to discern smaller interval changes for JSN and osteophyte formation (Wilkinson et al., 2005).

JSN grading in the NLDLDA

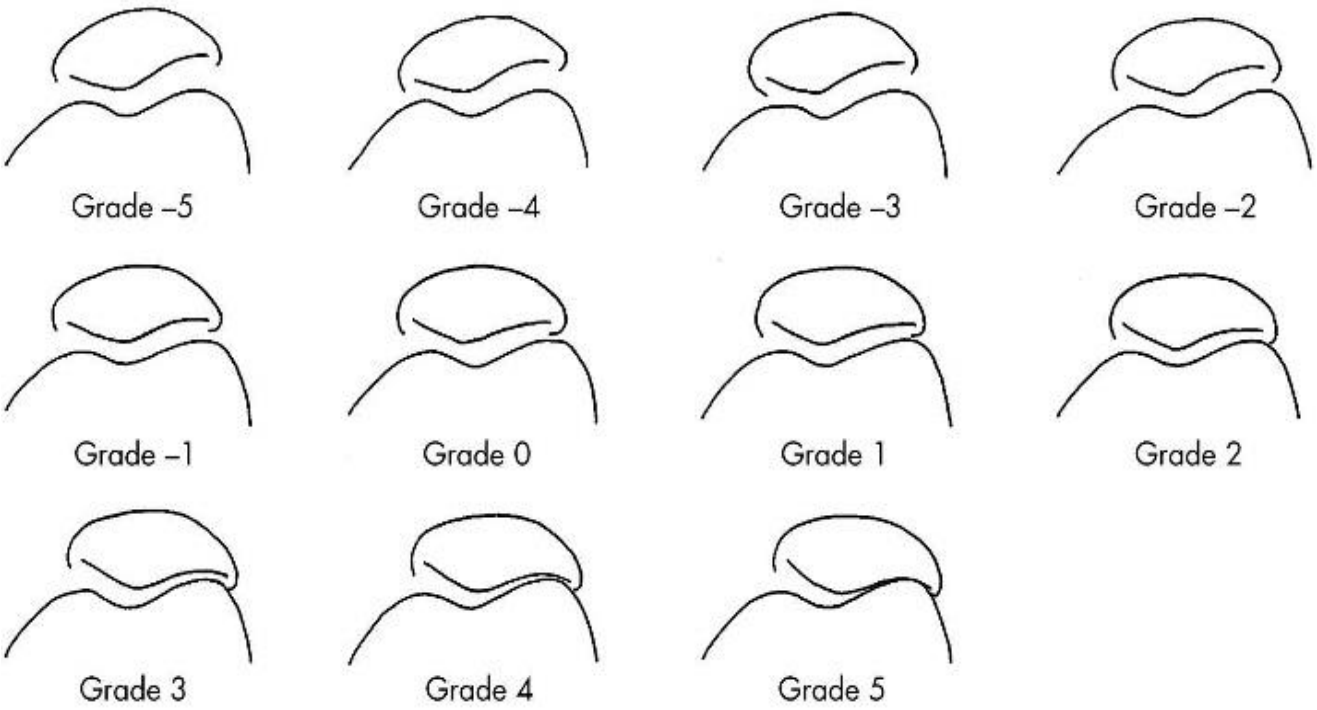

Figure 3. −5 to +5 NLDLDA

NLDLDA: Nottingham logically devised line drawing atlas; lateral patello-femoral joint space width for women. Grades −5 to +5 (reduced size).

Source: (Wilkinson et al., 2005)

Osteophyte grading in NLDLDA

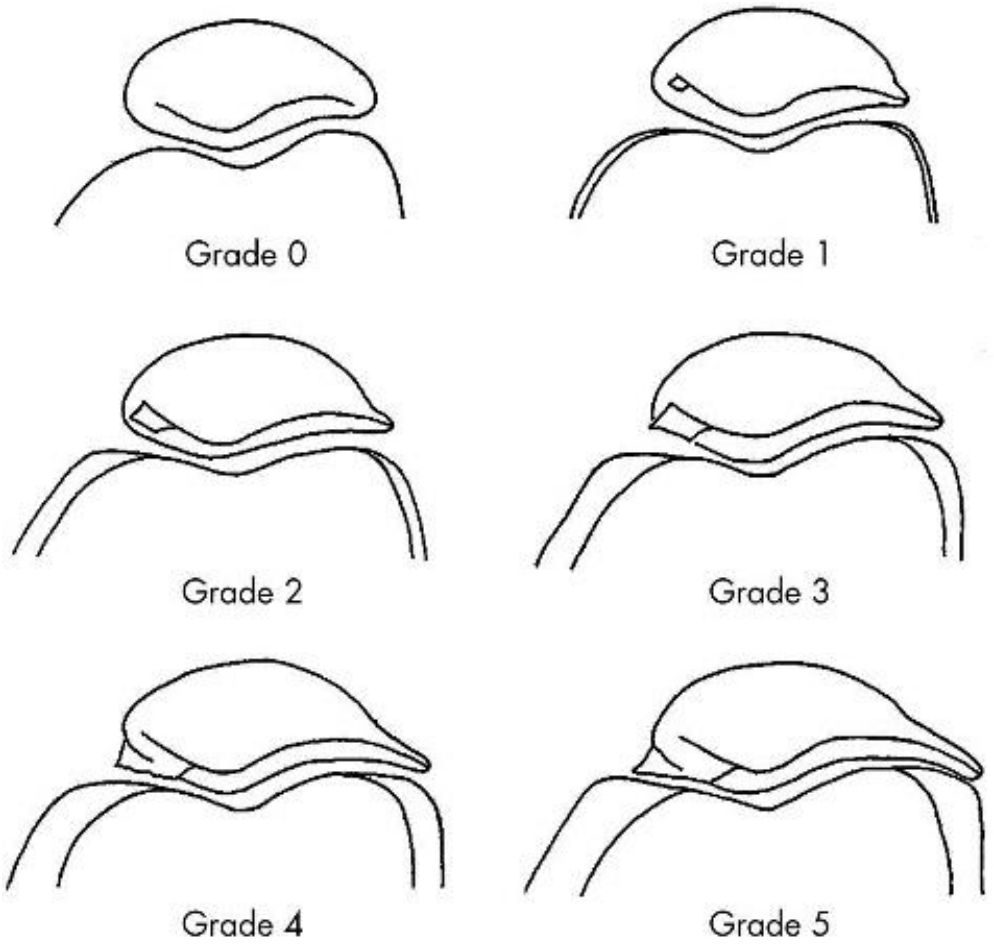

Figure 4: –5 to +5 NLDLDA:

NLDLDA: Nottingham logically devised line drawing atlas; Osteophyte in the patello-femoral sites Grades 0 to 5 (reduced size),

Source: (Wilkinson et al., 2005)

Advantages of this system are as follows

1. Good reproducibility.
2. Greater range of score from 0-5 grades.
3. Separates JSN grading for men and women, as men have more cartilage depth than women.
4. Separately illustrates the 2 key radiographic features, hence has less distraction from other features – a problem with photographic atlas systems of scoring.
5. Grading with interval rather than ordinal scales.
6. Individual and separate assessment of the three compartments

Other imaging techniques are magnetic resonance imaging (MRI) and ultrasound.

1.6 Management of OA

Currently there is no disease-modifying OA treatment, so the main aim of management is to improve patient-centred outcomes such as pain, function, participation and Quality of Life. Management of OA includes various approaches ranging from education and self-management to non-pharmacological and pharmacological approaches. Joint replacement is usually kept as a last resort for patients with end-stage joint failure that is resistant to other treatments (NICE 2008a, NICE 2008b). Principles of OA management are shown in Figure.5

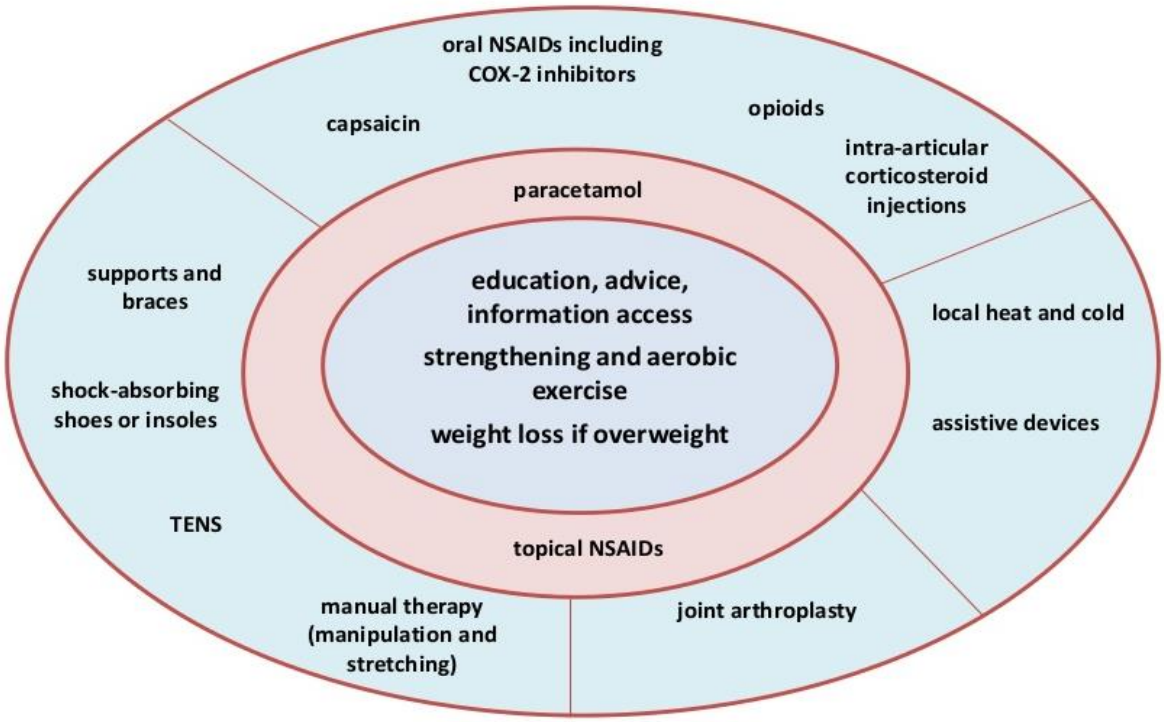

Figure 5. NICE guidelines for management of OA.

Core treatments are shown in the centre TENS- Transcutaneous electric nerve stimulation therapy; Source (NICE 2008)

1.7 Anatomy of the knee joint

The knee (Figure 6) is the largest synovial joint in the body (Standring and Borley, 2008). It is a modified hinge joint which permits flexion and extension and also very slight internal and external rotation (Moore et al., 2014).

Articulating Surfaces

The knee is one of the more complex joints in the body. The complexity is due to the interaction between three articulating surfaces (Moore et al., 2014, Standring and Borley, 2008). These are

- two TF articulations (lateral and medial)
- one patellofemoral articulation

The patella is the largest sesamoid bone in the body and is embedded within the quadriceps tendon proximally and laterally and the patellar tendon distally. There are two condylar articulations between the medial and lateral condyles of the femur and the patella and one saddle joint between the femur and the patella

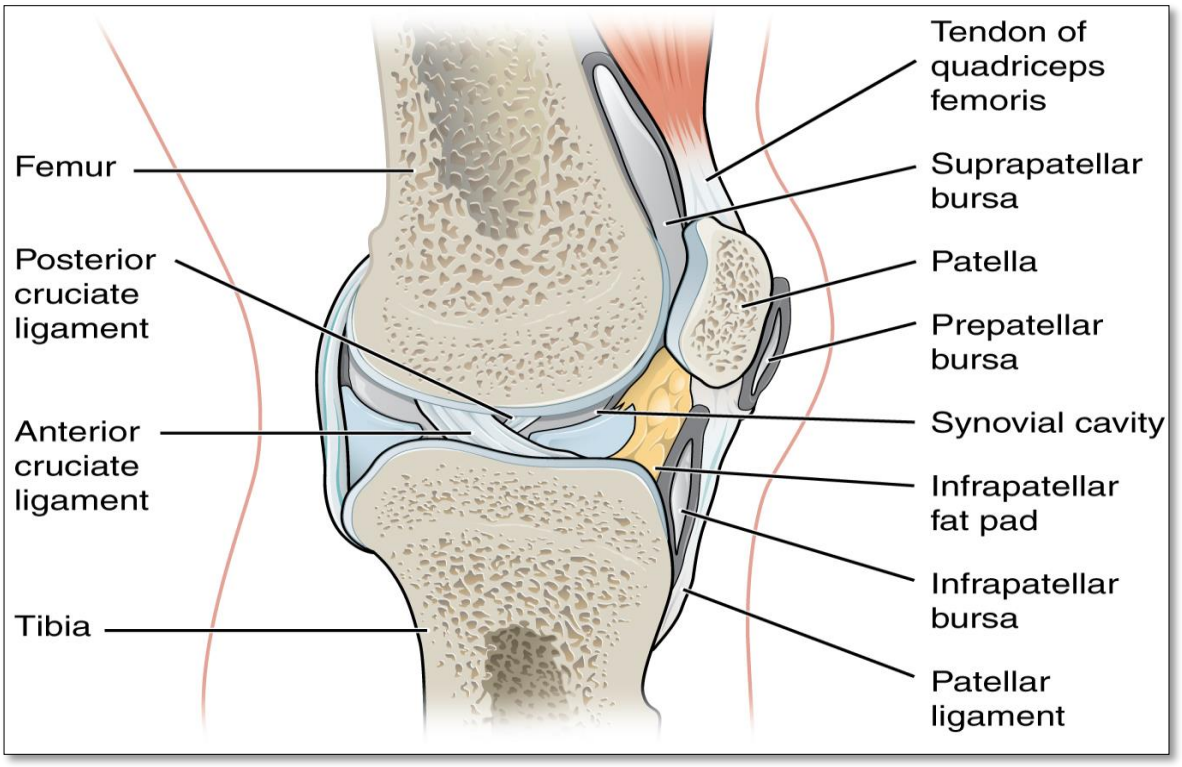

Figure 6. Knee joint
Source: (Project: Anatomy & Physiology Chapter 9. Authored by: OpenStax College. Provided by: Rice University Project: Anatomy & Physiology)

The knee joint is supported and stabilized by the action of the following (Moore et al., 2014)

- ligaments connecting the femur and tibia
- actions of surrounding muscles and their tendons

Ligaments

The knee joint has the following ligaments (Table 3)

Table 3: Ligaments of the knee joint

1.	Ligamentum patellae
2.	Medial collateral ligament
3.	Lateral collateral ligament
4.	Oblique popliteal ligament
5.	Arcuate popliteal ligament
6.	Anterior cruciate ligament
7.	Posterior cruciate ligament
8.	Transverse ligament

Movements of the knee

The movements at the knee are flexion, extension, medial rotation and lateral rotation. Several muscles help to produce movements at the knee joint.

1.8 Biomechanics of the knee

1.8.1 Tibiofemoral joint

Knee motion is normally defined to be starting from 0^0 (the neutral position) when the tibia and femur are in the same line in the sagittal plane. During knee extension, as in standing, this neutral position of the knees helps the legs to support the body weight. Active flexion of the knee leads to around 130^0 of flexion, whereas passive flexion may reach 160^0. Passive flexion often involves tibial internal rotation and the passing of the femoral condyles over the horns of the lateral meniscus (Standring & Borley, 2008)

During walking, the knee flexes to around 67^0 when the leg is swinging past the supporting leg. This prevents dragging of toes on the ground and when the swinging leg reaches the first contact with the ground, extension of the knee occurs, moving the foot forwards for heel strike.

The mid-stance phase involves knee flexion of 15^0, so that the centre of gravity of the body can move forward at almost constant height and the impact energy can be absorbed by quadriceps stretching (Standring & Borley, 2008).

Tibial internal-external rotation also takes place while walking. In the last phase of extension, external rotation of the tibia occurs, a process known as "screw home". It is thought that this rotation enables “locking” of the framework and the soft tissues, thereby stabilizing the knee position. During stance phase, the femur is internally rotated against the locked knee and the tibial external rotation leads to inversion of the foot at the subtalar joint, locking the structure of the foot. The knee flexion that takes place after the contact on ground during heel strike enables the tibia to rotate internally. This again helps in eversion of the foot thereby relaxing its structure and absorbing energy. In the toe-off position the tibia rotates externally with knee extension (Standring & Borley, 2008).

1.8.2 Patello-Femoral Joint

The PFJ further improves the quality of knee flexion and extension. Forces acting on the PFJ are formed by the action of the quadriceps muscle and the angle of flexion of the knee. It is determined by the distance between the PFJ and the centre of gravity. The maximum load on the PFJ is during weight-bearing activities with flexion of the knee (Schindler and Scott, 2011, Standring and Borley, 2008).

In the PFJ, the patella plays an important role in knee joint kinematics. It assists knee extension, by spacing the quadriceps and patellar tendons away from the femur and thus improving the efficiency of the quadriceps muscle (Standring and Borley, 2008). It also helps in increasing the force of extension along with range of motion. During flexion it also helps in equal distribution of the PF compressive force on the femur, enhancing the contact area. Moreover, it guides the extensor mechanism by centralising the divergent pull from the quadriceps and transferring the forces to the patella tendon and also protects the extensor framework from dislocating (Schindler and Scott, 2011).

The quadriceps muscles and patellar tendons combine to produce a lateralizing force vector, which is the Q- angle effect. The Q angle can be defined as the angle between the line of pull of the quadriceps and the patella tendon Q angle and is affected by hip rotation, tibial rotation and quadriceps tension. It is around $12\text{-}15^0$ in males and $15\text{-}18^0$ in females (Figure 7)

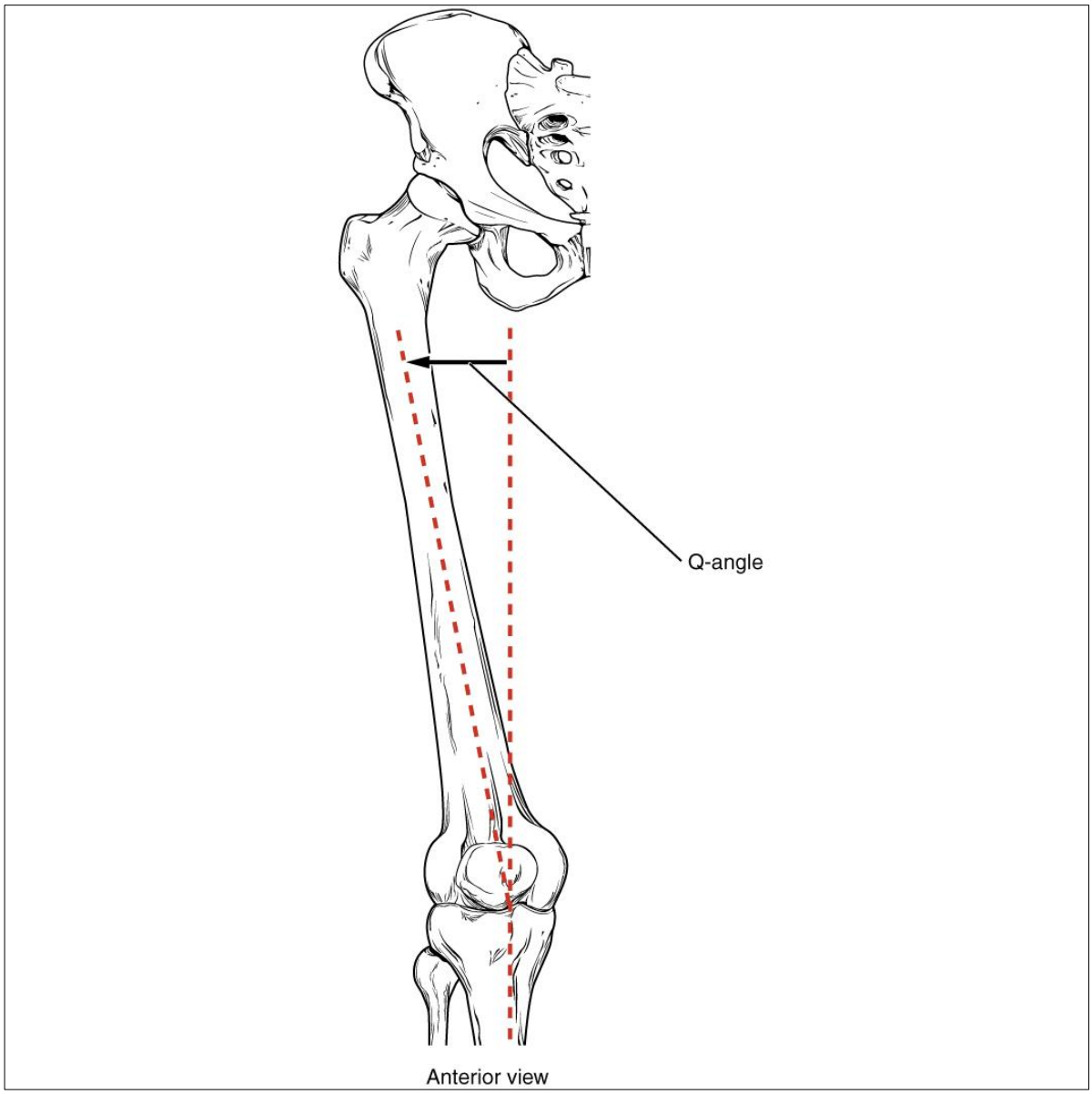

Figure 7. Q angle
Source : (OpenStax College, Radiopaedia.org, rID: 44015)

The PF contact area ranges from the medial margin of the medial facet to the lateral margin of the lateral facet. The patella maintains a lateral shift and a small degree of rotation around a longitudinal axis during flexion. At around 30^0 to 60^0 knee flexion

the contact is at the centre, and towards the superior pole at 90^0, and above 90^0 of flexion the patella moves centrally across the medial and lateral condyles. During full flexion the lateral femoral condyle is fully covered by the lateral patella, whereas the medial condyle remains uncovered. The patella also undergoes $12\text{-}15^0$ rotation, mostly beyond 50^0 of flexion (Figure 8)

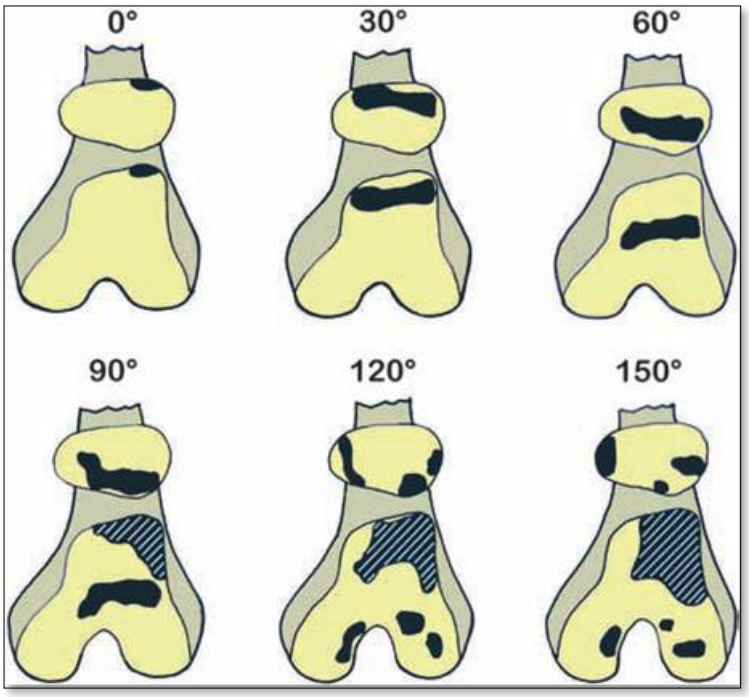

Figure 8. Patellar contact areas
Source: (Schindler and Scott, 2011)

There are several forces acting on the patella (Figure 9). The patello-femoral compressive force (PCF) is the load acting only on the patella.

The patella-femoral reaction force (PRF) is the resultant vector of the quadriceps tendon strain force (QTF) and the patella tendon strain force. The tendon femoral

reaction force (TRF) is the force between the quadriceps tendon and the trochlea (Schindler and Scott, 2011)

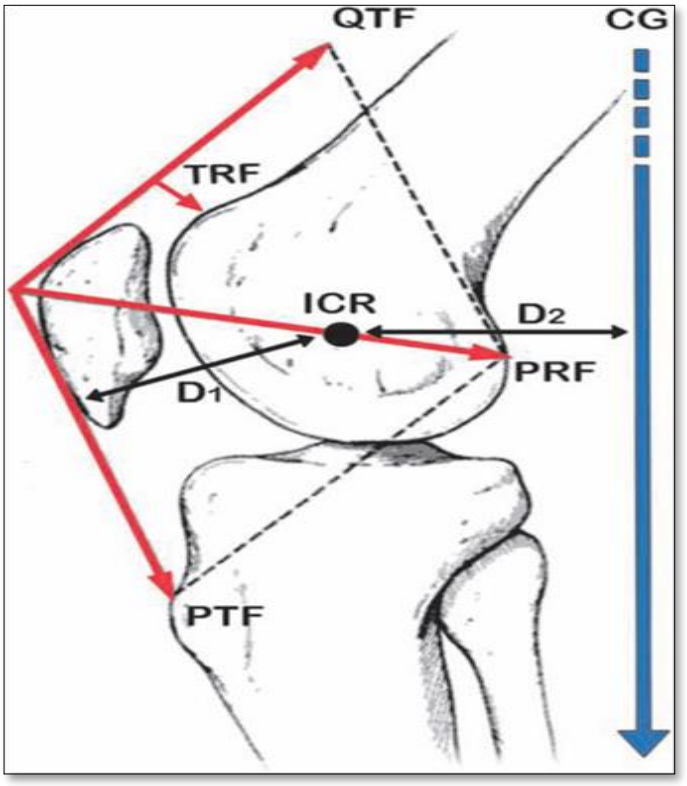

Figure 9. Patellar forces
Source: (Schindler and Scott, 2011)

According to the “parallelogram of forces” the PRF acts perpendicular to the articulating surface of the patella. The PRF also acts in the opposite direction to the resultant force vector of the patellar tendons and quadriceps force. PRF rises with

increasing flexion because on flexion the angle becomes more acute, so the resultant force vector rises. During flexion the quadriceps power also increases further, thus increasing the forces.

Above 60^0 of flexion, the patella force is 1·25 times more than the quadriceps force, however the PRF is only 1/3 of the quadriceps force. When viewed in the coronal plane, the line of pull between the quadriceps and patella tendon is influenced by the Q-angle. In the axial plane the force is directed inwards (Standring and Borley, 2008, Schindler and Scott, 2011).

The static forces can be calculated by measuring the distance between the line of the body weight (centre of gravity) and the PFJ. Any change in the posture such as leaning forward or backward will affect this distance, thereby affecting static force transmission. During full extension of the knee, the line of body weight falls anterior to the knee, so that moment arms (perpendicular distance from the line of force and the joint axis) will be 0 therefore no forces are acting on the PFJ. Conversely, when the line of body weight falls posteriorly to the PFJ, muscle and patellar tendon tension increases thereby increasing the PF compressive forces (Schindler and Scott, 2011).

In normal daily activities such as walking, along with knee flexion, flexion of the hip also occurs. This helps in bringing the line of body weight in front of the knee and reducing the moment arm. Similarly in stair ascend (Figure 10) the line of body acts above the PFJ, so the moment arm is short and the PRF low, whereas in stair descend it is the opposite (Schindler and Scott, 2011)

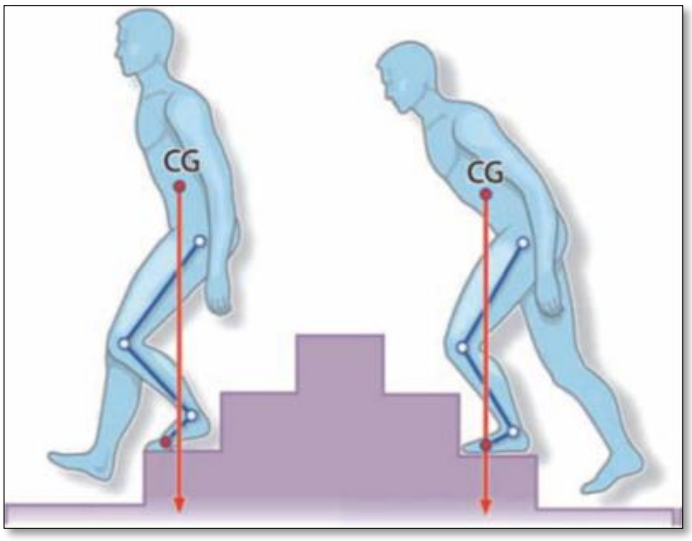

Figure 10. Stair ascend and descend
Source: (Schindler & Scott, 2011)

The predicted force value can be calculated by using the following formulae:

Stair ascend 1.8 to 2.3 times the body weight

Stair descend 2.9 to 6 times the body weight

Jogging 7.7 times the body weight

Jumping 20 times the bodyweight.

The PFR was reported to be maximum at 70^0-75^0 flexion.

1.9 Epidemiology

Prevalence and incidence

The joints most commonly affected by OA are the knees, hips, hands, spine and foot (Stanishewski and Zimmermann, 2015). In comparison, OA of wrists, shoulders, elbows and ankles is less common. The weight-bearing joints like hips and knees have the highest population impact of the disease requiring expensive treatments including surgery (Litwic et al., 2013b).

Prevalence

Pereira et al, conducted a systematic review and meta-analysis of 72 cross-sectional and longitudinal studies worldwide and reported that overall prevalence of hand OA (43.3%) was higher than for knee (23.9%) or hip OA (10.9%) (Pereira et al., 2011).

Another study utilised data in the UK Clinical Practice Research Datalink (CPRD), that includes data on around 17.5 million people, and reported joint specific prevalence rates of symptomatic OA (severe enough to result in general practitioner consultation) to be highest for the knee (2.9%) followed by the hip (1.5%), and the hand (0.5%) (Swain et al., 2020).

Another study in Japan, using data from the 3rd follow-up of the ROAD study reported a high prevalence of knee OA (over 90%). The prevalence of erosive hand OA in the same study was around 5% (Kodama et al., 2016)

The global prevalence of knee OA was examined by a recent study which reported a prevalence of 16% in people aged 15 and above and a prevalence of 22.9% among individuals of age group 40 and over (Cui et al., 2020). This study also reported that radiographic knee OA (28.7% prevalence) was more prevalent than the symptomatic knee OA (12.4% prevalence) (Cui et al., 2020).

The other two main studies which have assessed the prevalence of OA in the general population are the Zoetermeer study (van Saase et al., 1989) and the National Health and Nutrition Examination Survey (NHANES) (Litwic et al., 2013a). The Zoetermeer survey investigated the prevalence of OA across 22 joints in a random sample of 6,585 individuals in the Zoetermeer village of Netherlands and found that 75% of women aged 60–70 years had OA at the distal interphalangeal (DIP) joints (van Saase et al., 1989). It was also reported that by the age of 40 years between 10-20% of individuals had severe radiographic OA in hands and feet (Litwic et al., 2013a), (van Saase et al., 1989). Women of all ages had higher prevalence of OA in the knees, hands and feet than men.

These data were then compared to prevalence of OA data obtained from 10 smaller populations ,which included the UK, native American Indian, Japanese, Bulgarians, South Africans and the US NHANES population which had around 6,913 individuals

(Litwic et al., 2013a). Variations in prevalence rate of OA with respect to individual joints were noted. Bulgarians had a lower prevalence of DIP OA compared to the Zoetermeer population, whereas the American Indians had a higher prevalence of DIP joint OA (Litwic et al., 2013a).

In the Framingham study, the prevalence of radiographic knee OA among individuals aged more than 45 and 80 years were 19.2% and 43.7% respectively (Felson, 1990). However the prevalence of symptomatic knee OA were comparatively lower in NHANES (12.1%) and in the Johnston County Osteoarthritis project (16.3%) (Litwic et al., 2013b).

Incidence

The joint-specific OA incidence is highest for knee (2.3 per 1,000 person years) followed by hip (1.1 per 1,000 person years) wrist and hand (0.65 per 1,000 person years) and ankle and foot (0.2 per 1,000 person years) (Swain et al., 2020). These incidence rates were higher in women than in men (Swain et al., 2020).

Similarly, another study reported highest incidence rate of OA at the knee (3.5 per 1,000 person years), followed by hip (1.4 per 1,000 person years) and hand OA (1.3 per 1,000 person years) (Kodama et al., 2016).

A population-based health care database study which aimed to determine the incidence of OA using consultation events reported that the incidence rate increased significantly between 45 and 64 years of age, reaching the highest at 75–84 years. The joint-specific incidence, expressed per 1,000 persons in the study, was 1.4 (95% CI 1.1, 1.7), 3.5 (95% CI 3.1, 3.9) and 1.3 (95% CI 1.1, 1.6) for hip OA, knee OA and hand OA, respectively (Yu et al., 2015).

Another study reported the global incidence of knee OA in individuals who were aged 20 and above as 203 per 10,000 person-years (Cui et al., 2020). Knee OA incidence in the United Kingdom, was reported as 315 per 10,000 person-years in the same study (Cui et al., 2020).

To summarize, OA is present worldwide. However, there is inconsistent evidence as to whether incidence of OA differs between various ethnic groups. Any variations that occur may be due to differences in genetic factors, lifestyle changes, social habits (e.g. squatting increasing risk of OA in certain joints), occupations, and other biological factors.

1.10 Risk factors for OA

Both systemic and local factors play an important role in development of OA (Litwic et al., 2013a),(Johnson and Hunter, 2014). The systemic factors such as age, gender and genetics can act either directly by damaging the joint tissues or by affecting the repair system making the joints more vulnerable to injury (Litwic et al., 2013a). The local factors (e.g. injury) which are usually biomechanical in nature, can abnormally affect the forces at the joints. The three strongest risk factors of OA are age, obesity and joint injury (Johnson and Hunter, 2014). Risk factors for development of OA are shown in Table 4 and Figure 11.

Table 4. Risk factors for development of OA

Risk factor	Hip OA	Knee OA	Hand OA
Obesity	+	++	+
Age	++	++	++
Female Gender	+	++	++
Ethnicity	**- -**	++	**- -**
Genotype	++	++	++
High BMD	++	++	++
Muscle weakness	NA	**-**	NA

*++: good evidence increases risk, +: weak evidence increases risk, Blank: inconsistent**,-**: weak evidence of protective effect**, - -**: good evidence of protective effect, BMD-Bone mineral density, NA Not applicable*

Source: (Litwic et al., 2013a)

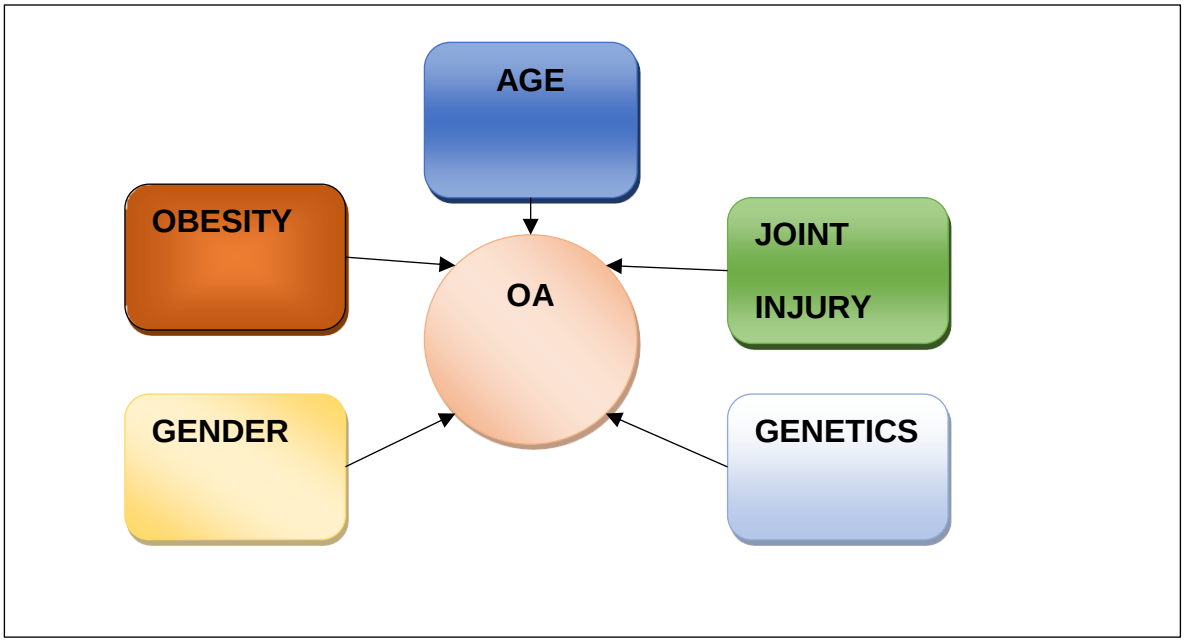

Figure 11. Risk factors for knee OA

1.10.1 Age

Ageing is a major risk factor for OA at any joint site (Neogi and Zhang, 2013b). The rise in both incidence and prevalence of OA with age is possibly due to the combined effect of various risk factors and biological changes that takes place along with ageing (Zhang and Jordan, 2010).

The metabolic changes that take place in the cartilage with ageing may not be able to cope with the biochemical changes in the disease process leading to stress fractures (Felson, 1988). In addition to that, neuromuscular decline that takes place along with ageing reduces the supporting capacity of muscles and tendons making the joints more susceptible to repetitive micro-trauma (Felson, 1988). Oxidative stress also may contribute to the association of OA with age (Litwic et al., 2013b).

Many population-based studies have focused on the association between age and OA. Some of them that show the prevalence of knee OA with age are shown in Table 5 (Lawrence et al., 2008)

Table 5. Prevalence of symptomatic and radiographic knee OA

Age (in years)	Source	Prevalence (%)
≥ 26	Framingham OA study	4.9
≥45	Framingham OA study	6.9
≥45	Johnston County OA project	16.7
≥60	NHANES-III	12.1

[1] *National health and nutrition examination survey III*

1.10.2 Gender

Up to the age of 45 years the prevalence of knee OA is higher in men than in women but after the age of 45 years the opposite is true (Neogi and Zhang, 2013a). Moreover, after the age of 45years the rate of rise of prevalence of knee OA with respect to increasing age is also higher in women than in men (Felson et al., 2000).

Reports from a meta-analysis of population-based studies suggest that men have a lower risk of developing knee OA with a risk ratio of 0.63 (Srikanth et al., 2005). It was also reported that women tend to develop a more severe form of OA with greater structural changes and more pain and disability after the menopause (Srikanth et al., 2005).

A role of oestrogen deficiency in the development of knee OA has been suggested in postmenopausal women (Felson et al., 2000, Nevitt and Felson, 1996, Roman-Blas et al., 2009, Wluka et al., 2001). Oestrogen receptors are found on human articular chondrocytes and osteocytes (Schicht et al., 2014). It has also been found that women using hormone replacement therapy (HRT) have more knee cartilage which suggest a protective effect for oestrogen (Wluka et al., 2001). However, this is not supported by the findings of all studies and an excess of oestrogen could lead to an increase in the bone mineral density and thereby increase OA incidence (Bergink et al., 2005)

1.10.3 Genetics

An in-depth study of the role of genes in development of OA is of paramount importance as it should aid better understanding of the molecular pathogenesis of OA by identifying the genes responsible for disease risk and progression. Secondly, identifying the genes could enable early detection of individuals at high risk of OA and facilitate early management and treatment (Valdes and Spector, 2008). Many studies have focused on the genetic aspects of OA, and reports suggest that at least 40%-60% of the risk of developing OA is genetically determined depending on the affected site (Warner and Valdes, 2016). Candidate polymorphisms associated with hip & knee OA are shown in Table 6

Approaches used to determine the role of genes in OA include twin studies, family aggregation studies, linkage analysis and candidate gene association studies, and Genome-Wide Association studies (GWAS). The classical twin study and the family study have also explored the role of genes associated with cartilage volume, change in lower muscle strength and pain score (Valdes and Spector, 2008, Clement, 2013).

Table 6. Candidate polymorphisms associated with hip & knee OA

SNP Risk Allele	Gene	Odds ratio	Joint	Functional relevance to OA
rs143383-T	*GDF5*	1.16	Knee	Affects chondrogenesis and joint element formation
rs7639618-G	*DVWA*	1.43	Knee	Involvement in metabolism of cartilage
rs7775228-T	*HLA-DQB1*	1.34	Knee	Immunologic mechanisms
rs3815148-C	*COG5*	1.14	Knee	Expression in OA joint environment
rs4730250-G	*DUS4L*	1.17	Knee	Expression in OA joint environment
rs11842874-A	*MCF2L*	1.17	Knee and hip	Affects nociception and skeletal system development
rs12107036-G	*TP63*	1.21	Knee	Unknown; involvement in facial shape development
rs8044769-C	*FTO*	1.11	Knee, Hip	Increased risk of obesity

Source : (Zengini et al., 2016)

Heritability of a disease can be defined as the degree to which inheritance plays a role in the etiology of a disease. The heritability of OA in twins and family studies is given below in Table 7

Table 7. Heritability of Osteoarthritis related traits in twins and family study

Trait	Heritability (%)	Kinship
Generalised OA	42%	Parent child pair, Sibling pairs
Radiographic -hip OA	60%	Twins
Radiographic knee OA	39%	Twins
Radiographic hand OA	59%	Twins

Source : (Warner & Valdes, 2016)

Sibling recurrence (lambda sib) risk can be determined by identifying those individuals who have end-stage knee OA requiring total knee replacement (TKR) and then estimating the prevalence of OA in their siblings, which may be compared with a general population to obtain risk ratio (RR) , (Clement, (2013) ., Neame et al., 2004). Some of them are shown in Table 8.

Table 8. Risk of OA or joint replacement in siblings of people with total joint replacement

Condition	Siblings Recurrence Risk
Total knee replacement for OA	4.81
Knee OA	2.08
Tibio femoral OA	2.13
Patellofemoral OA	1.66
Antero-medial knee OA	3.21

Source : (Valdes & Spector, 2008)

1.10.4 Ethnicity

OA prevalence and joints affected by OA differs according to ethnicity.

For instance, according to results of the NHANES 1 survey, Afro-Caribbean people had a higher prevalence of knee OA than whites, especially in women (OR=2.12, 95% Cl 1.39−3.23) (Anderson & Felson, 1988).

There are many potential explanations for this such as occupational risk factors, walking barefoot, walking along rough paths and comparatively higher bone mass (Anderson and Felson, 1988). Moreover, the African–American population had more severe symptomatic and radiographic OA than Caucasian people and even structural and clinical progression of the knee OA was greater (Allen et al., 2009b). Compared to the western world the prevalence of knee OA among the older population is much higher in Asian countries in both rural and urban regions (Fransen et al., 2011).This is possibly due to various physical activities such as squatting, kneeling, frequent stair climbing or heavy physical work.

In Japan the Research on OA and osteoporosis against disability study (ROAD) study which was a large population based cohort study, reported that people who perform activities such as squatting or kneeling more than 2 hours per day have twice the risk of developing moderate to severe radiographic knee OA. In addition to that, prolonged standing, walking and even climbing many times a day were also associated risk factors (Yoshimura, 2011, Fransen et al., 2011).

Similarly, in a study conducted in Beijing, squatting was an important risk factor for developing TFJ OA. Overall knee OA was more common in elderly Chinese women than men (Zhang et al., 2001).

1.10.5 Obesity

Obesity is another major risk factor for OA, especially knee OA (Muthuri et al., 2011, Anderson and Felson, 1988, Coggon et al., 2001). Reports from a meta-analysis of 47 observational studies with 44,6219 participants suggest that people who were obese had a 2.78 (95%CI 2.45,3.15) times higher risk of knee OA (Muthuri et al., 2011)

The incidence of knee, hip, and hand OA for normal weight individuals was 3.7, 1.7, and 2.6 per 1,000 person-years, but for obese class II individuals was 19.5, 3.8, and 4.0 per 1,000 person-years, respectively (Nelson, 2018) . A British general population based study showed that women in the highest group of body mass index (BMI) had a 6.17 times (95%CI 3.26, 11.7) increased odds of knee OA and 17.99 (95%CI 6.25, 51.73) times more chance of having bilateral knee OA, compared to women in the lowest tertile of BMI (Hart and Spector, 1993). The SWAN study in Michigan, which is a population based longitudinal study, showed an association between higher BMI and increased risk of developing knee OA among both African-American (OR=7,95%CI 2, 24.7) and Caucasian women (OR=3.9,95%CI 1.5,10.4) (Lachance et al., 2001).

There are currently two theories, one mechanical and one metabolic, on how obesity leads to the development of OA. Firstly, increased loading on the joints may lead to cartilage damage (Mundermann et al., 2005, Felson, 1996).

The increased bone mineral density seen in obese individuals will further increase the forces across the joints. Muscle strength is also strongly influenced by body mass, associating negatively with increasing BMI.

A decrease in muscle strength may reduce the shock-absorbing ability of the joint which may lead to cartilage fibrillation, changing the normal cartilage structure and initiating a local immune response (Felson, 1996).

Leptin has now been identified as a possible metabolic factor responsible for the association between OA and obesity. Leptin is a small (16kd) polypeptide encoded by the obese (*ob*) gene. It is produced in the white adipose tissue and its function is to maintain the balance between food intake and energy expenditure at the hypothalamic level. Leptin and its receptor have been found in human chondrocytes, osteophytes, synovium and infrapatellar fat pad and are associated with growth factor synthesis, anabolism and even cartilage destruction (Dumond et al., 2003). It also has a direct pro-inflammatory and a catabolic role in cartilage metabolism (Simopoulou et al., 2007)

1.10.6 Occupation

Overall, jobs that require standing (>2h per day), excessive kneeling, squatting, lifting and climbing steps can lead to the development of knee OA (Blagojevic et al., 2010). According to the results from the Framingham study, men who undertook regular knee bending as a part of their occupation had an increased risk of developing knee OA (OR=2.22, 95%CI 1.38, 3.58). Moreover, these men had higher risk of developing severe radiographic OA and bilateral radiographic knee OA (Felson et al., 1991),(McWilliams et al., 2011)(McWilliams et al., 2011)(McWilliams et al., 2011)(McWilliams et al., 2011)(McWilliams et al., 2011)(McWilliams et al., 2011).

Interestingly, in the same study knee OA was not associated with similar occupational exposure for women (Felson et al., 1991).. Another MRI study which examined the association of occupations involving either frequent squatting, heavy weight lifting, or kneeling with cartilage morphology at the PFJ and TFJ found that these activities had a higher chance of a poor cartilage morphology score at the PFJ (OR=1.8, 95%CI 1.1, 3.2) (Amin et al., 2008). Coal mining (McMillan and Nichols, 2005) and other occupations such as floor-laying (Thun et al., 1987) and dock working (Partridge and Duthie, 1968) are found to have a higher risk of developing knee OA.

In one study farmers (farming for at least 10 years) had higher risk of developing hip OA than the control group (OR=9.3, 95%CI 1.99, 44.5)(Croft et al., 1992). In another case control study based in Japan it was found that people who used to lift heavy

objects (50 Kg or more) as a part of their occupation had an increased risk of developing hip OA (OR=4.0, 95% CI 1.1-14.2) (Yoshimura et al., 2000).

Hand OA was associated with occupations such as the textile industry which involved the use of manual dexterity especially pincer grip of the hand (Hadler et al., 1978).

1.10.7 Physical activity & joint injury

Usually moderate physical activities have a beneficial effect at the joint by stimulating chondrocytes and osteocytes and strengthening the periarticular muscle thereby stabilizing the joint. However, it can be damaging if there is an excessive load on the joints.

A longitudinal MRI study that examined the relation between physical activity and knee structure found that walking at least 10,000 steps/day was associated with 1.52 (95% CI 1.05, 2.20) fold greater chance of having cartilage loss (Dore et al., 2013). Certain sports make joints more prone to injuries. Vingard and colleagues conducted a case control study comparing men up to the age of 49 years who required Total hip replacement (THR) to men in the general population and found that individuals who have had more exposures to any kinds of sports had 4.5 times of developing hip OA than those with low exposure (Vingård et al., 1993).

In one UK study it was found that the prevalence of knee pain, physician-diagnosed knee OA, total knee replacement and radiographic knee OA were all two to three fold higher in ex-professional footballers than men in the general population (aRR= 2.21, 95% CI 1.92 , 2.54). (Fernandes et al., 2018). ACL injuries are reported to be the most common form of knee injury in professional footballers. However, ACL injury is unlikely to occur in isolation because of the complexity of the closely associated structures in the knee joint (Lohmander et al., 2007)

In a meta-analysis, Ajuied et al reported that after ACL injury, the RR of developing OA ranged between 3.89 and 3.84 for minimal (grade I and II) and moderate to severe OA, respectively. They also reported that non-operatively treated ACL-injured knees had significantly higher RR of developing any grade of OA (RR, 4.98; range 2.45-10.15; P < .00001) compared to those treated with reconstructive surgery (RR, 3.62; range, 2.40- 5.47 P < .00001) (Ajuied et al., 2014).

Simon et al reported that, after a period of 5 to 15 years of attaining initial injury, 80% of ACL injured knees demonstrate radiographic evidence of OA (Simon et al., 2015). Additionally, it was reported that individuals who sustained an ACL injury while playing soccer had a 51% higher chance of developing OA (Simon et al., 2015)

Øiestad et al reported that the prevalence of OA in knees after an isolated ACL injury was 0% to 13%. They also reported that this figure rose to 21% to 48% when there were associated meniscal injuries (Øiestad et al., 2009).

Similarly a case-control study that used the OA Initiative (OAI) database, a prospective, longitudinal, multicentre cohort study of knee health in patients at risk for knee OA, found a significant association between development of radiographic OA and meniscus tears, with greater risk for radial tears (OR, 5.92; 95% CI, 1.7,7.5) and also with extrusion (OR, 3.03; 95% C 1.4,6.5) (Badlani et al., 2013).

In a case control study using the CPRD, ACL injury was associated with a seven times greater risk of subsequent TKR (95% CI 4.73, 10.31). Meniscal injury also was associated with a 15 times higher chance of subsequent TKR for OA. (95% CI 13.88 ,16.69) (Khan et al., 2019).

There is not much evidence to conclude whether running is associated with development of knee OA (Lo et al., 2017) (Kumar, 2017). In a retrospective cross-sectional study using data from 2,637 participants from OAI, Lo *et al* reported that there was no evidence for increased risk of symptomatic knee OA among self-selected runners compared with non-runners in a cohort recruited from the same community (Lo et al., 2017).

Long-distance running among healthy older individuals was not shown to be associated with accelerated radiographic OA, but actually improved outcomes in people with knee OA, in one prospective observational study (Kumar, 2017). This may be because of the benefits of exercise in improving musculoskeletal disability, pain and functional capacity. Indeed Kumar et al reported that running reduced the need of knee replacement by around 50% compared with non-runners (Kumar, 2017).

1.10.8 Bone mineral density

The physical properties of bone can influence the risk of developing OA**.** An inverse relationship between OA and osteoporosis has been described in many studies. In the Rotterdam study which examined the relationship between (BMD) and OA in an elderly population of 2,745 (1624 women) it was reported that high BMD associated with radiographic OA (Burger et al., 1996). Nevitt and colleagues examined the relationship between BMD and incident and progressive TFJ OA in a large study of men and women aged 50-79 years and found that high BMD was associated with greater risk of developing OA (2.3-2.9 times greater than with low BMD group) (Nevitt et al., 2010).However, in the same study, high BMD was not associated with progressive knee OA (Nevitt et al., 2010).

High BMD was associated with hip OA in a study conducted by Foss and Byers (1972) in 100 hip OA cases. They also noticed that osteoporosis and OA did not exist at the hip at the same time (Foss and Byers, 1972). Using data from the Chingford study it was reported that women with high BMD had a higher risk of developing knee OA but there was no association between high BMD and hand OA (Spector et al., 1997). However, low BMD was associated with progression of OA in other studies (Zhang et al., 2000).

1.10.9 2D:4D ratio

The index: ring finger ratio, also known as the 2D:4D ratio, is the ratio of the length of the index finger (second digit 2D) to the ring finger (fourth digit 4D). It is generally assessed clinically with hands flat, fingers together, and with the middle finger aligned with the forearm. The three patterns are Type 1 (index finger longer than ring finger), Type 2 (index finger the same length as the ring finger) and Type 3 (index finger shorter than ring finger) (Robertson et al., 2008) as shown in Figure 12. The length of both fingers can also be measured on hand radiographs from the base of the proximal phalanx to the tip of the distal phalanx to give a more precise ratio, and estimation of the 2D:4D metacarpal ratio on radiographs has also been used (Robertson et al., 2008). Usually males have a smaller 2D:4D ratio (Robertson et al., 2008).

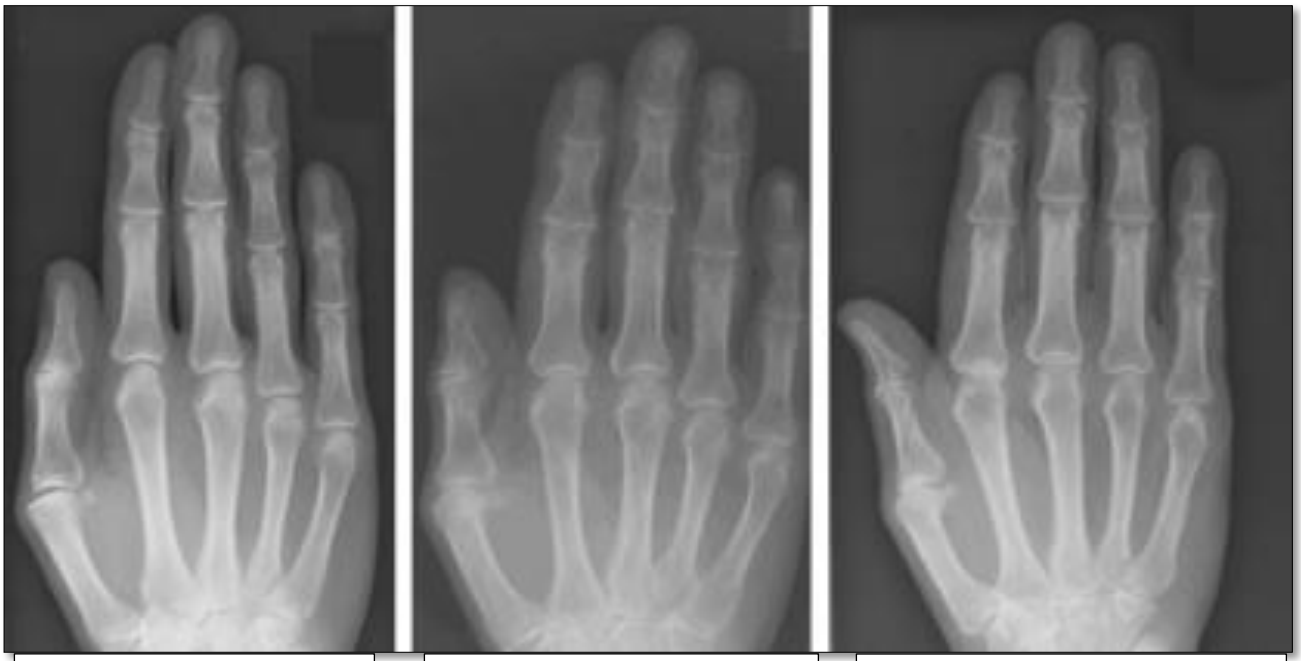

Figure 12. Radiographs showing the three finger patterns
Source: (Robertson et al., 2008)

In one study it was found that pattern 3 associated with knee OA (OR =1.94, 95% CI 1.54, 2.44) compared to the other two patterns (Zhang et al., 2008a). This association was greater in women (OR=3.05, 95% CI 2.08, 4.47) than men (Zhang et al., 2008a). The same association was seen for the 2D:4D metacarpal ratio (Robertson et al., 2008). A subsequent study also found pattern 3 to associate with knee OA (OR 2.59, 95% CI 1.54-4.37) (Ferraro et al., 2010). Exposure to prenatal androgen that influences the skeletal development can explain the association between 2D:4D ratio and OA (Brown et al., 2002).

Moreover, it has been hypothesized that homeobox (HOX) genes, which are linked with embryonic segmentation, are also involved in the development of bones, cartilages and tissues of fingers and toes, which could influence bone and joint morphology. This may explain the association between 2D:4D ratio as a marker of people at risk for developing OA (Zhang et al., 2008).

1.10.10 Joint morphology

The knee joint, in particular the medial TF and PF compartments, is a common site to be affected by OA and results in a significant health care burden (Heidari, 2011, Weisman, 2013). Knee OA shows familial clustering and relatively high heritability (40-60%), though the mechanism for inherited predisposition remain unclear (Warner and Valdes, 2016, Neame et al., 2004). It is known that rare monogenic disorders that result in severe developmental abnormality of joint shape (congenital dysplasias) can result in dramatic early onset OA, and there is growing interest in the possibility that more subtle variation in joint shape may explain some of the heritability seen in common OA (Doherty et al., 2008).

Morphological variation in joint shape has been studied mainly at the hip, where the “pistol grip”(non-spherical head) deformity (Doherty et al., 2008), smaller neck shaft angle (Doherty et al., 2008) and mild acetabular dysplasia (McWilliams et al., 2010) have been identified to predispose to hip OA. Association of bone shape and hip OA from different studies is summarized in Table 9. Some of the bone shapes found to be associated with knee or hip OA are shown in Figure 13.

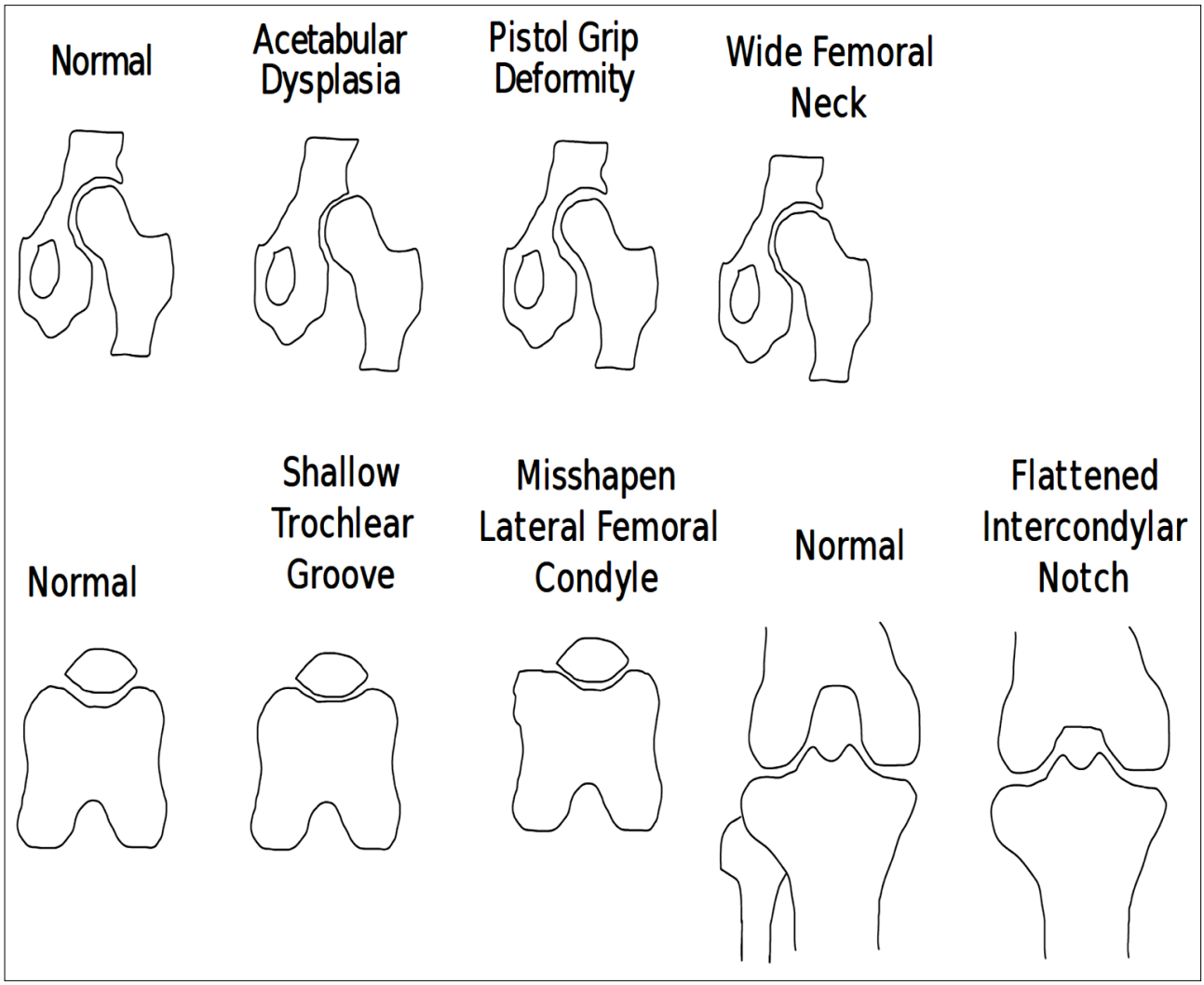

Figure 13. Bone shapes associated with OA
Source: (Baker-LePain and Lane, 2012)

Table 9. Association of bone shape and hip OA

Author	Study design	Measures	N	Age (year)	Gender (%female)	OR/RR (95%CI)[1]
Reijman *et al* 2005	Cohort	CEA	835	≥55	57%	2.4(1.2-4.7)
		ADI				2.3(1.5-3.5)
Chung *et al* 2010	Cross-sectional	CEA	674	60-75	57%	10.2(0.6-56.7)
Mc Williams *et al* 2010	Cross sectional	CEA	1674	≥45	46.3%	10.05(2.89-35.01)
		ADI				2.53(1.28-5.00)
Giori *et al* 2003	Cross sectional	Pincer grip	230	72	65%	Higher prevalence of acetabular retroversion in cases compared to controls
Javed *et al* 2009	Cohort	Wide femoral neck	5,245	72.6		1.7(1.1-2.3) (RR)
Johnsen *et al* 2009	Cross sectional	CEA	315	20-65	52%	0.96(0.09-1.02)

OR: odds ratio; RR: relative risk; CI: confidence interval, n: study population; CEA –lateral central edge angle of Wiberg; ADI-acetabular depth index.[1] OR unless specified

Femoroacetabular impingement

Femoroacetabular impingement (FAI) is a dynamic condition in which extra bone grows along one or both sides of the hip joint, resulting in an irregular shape. During their movement, the bones exert pressure against each other since they don't fit perfectly. There are three types of FAI, specifically: pincer, cam, and combined impingement. In a nested case control study of 1,003 women (age group 44-67) from the Chingford study, Nicholls and colleagues found that the cam deformity is associated with total hip arthroplasty (OR=1.06, 95% CI)(Nicholls et al., 2011).

"Pistol grip" deformity

Aspherical femoral head shape which gives the appearance of a "pistol grip" deformity is a typical radiographic sign of cam-type femoroacetabular impingement. Non-spherical femoral head ("pistol grip" deformity) is a shape variant in which the femoral head-neck junction flattens along its supero-lateral aspect resembling an old-fashioned pistol (Figure 14). One study using data from the Genetics of osteoarthritis and lifestyle (GOAL) study compared the unaffected hip in 965 people with unilateral hip OA to 1,123 controls without radiographic hip OA and found an association between pistol grip deformity and hip OA (OR=6.95;95%CI 4.6,10.4) (Doherty et al., 2008). A separate study with identical design using data from the GOAL study reported a correlation between acetabular shape and hip OA (McWilliams et al., 2010).

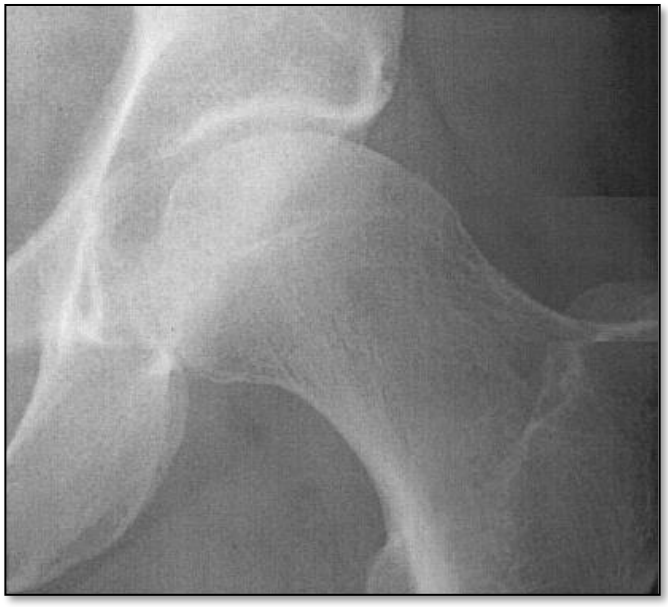

Figure 14. Pistol grip deformity
Source: (Doherty *et al.,* 2008)

Gosvig and colleagues performed a study using the data from Copenhagen OA sub-study cohort, a cross sectional population based radiographic and questionnaire database of 4,151 Danish Caucasian individuals with mean age of 60 years. They found that pistol grip deformity was associated with prevalent radiographic hip OA (OR=2.2, 95%CI 1.71, 2.80). They used the triangular index method (Figure 15) to determine the pistol grip deformity (Gosvig et al., 2010). The triangular index was determined by first measuring the radius (r) of the femoral head. Followed by measuring ½ r along the line B, that passes through the centre of femoral neck and the corresponding perpendicular height (H) as shown in diagram below. The pathologically increased radius (R) is found by applying the Pythagorean law for triangular figures ($a^2 + b^2 = c^2$). Asphericity was defined as $R \geq r + 2$ mm on a radiograph (Gosvig et al., 2010).

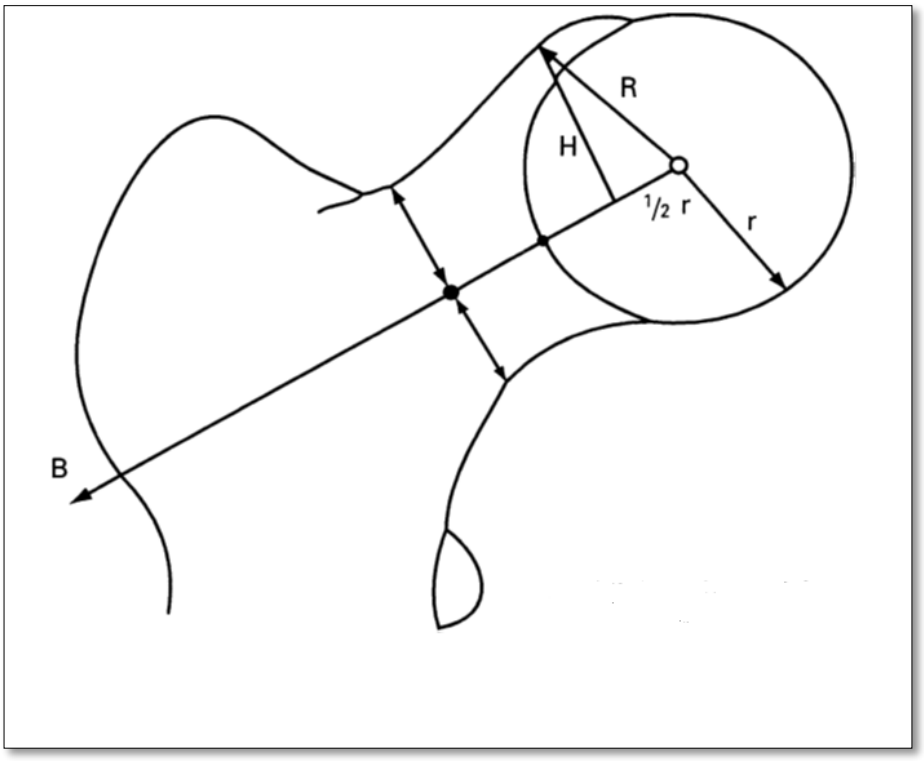

Figure 15. Triangular index for evaluation of pistol grip deformity

R-modified triangular index height

Source: (Gosvig et al., 2010).

Acetabular dysplasia

A longitudinal study performed by Reijman and colleagues in the Rotterdam cohort investigated the association between mild-moderate acetabular dysplasia and incident radiographic hip OA. The study included 835 men and women (age ≥55years) who had radiographs of their hips and were followed up to a mean of 6.6 years. Acetabular dysplasia was assessed using the centre edge angle and acetabular depth as shown in Figure 16 (Reijman et al., 2005). It was found that acetabular dysplasia (centre-edge angle<25^0) had 4.3 times (95%CI 2.2-8.7) more chance of developing incident radiographic hip OA.

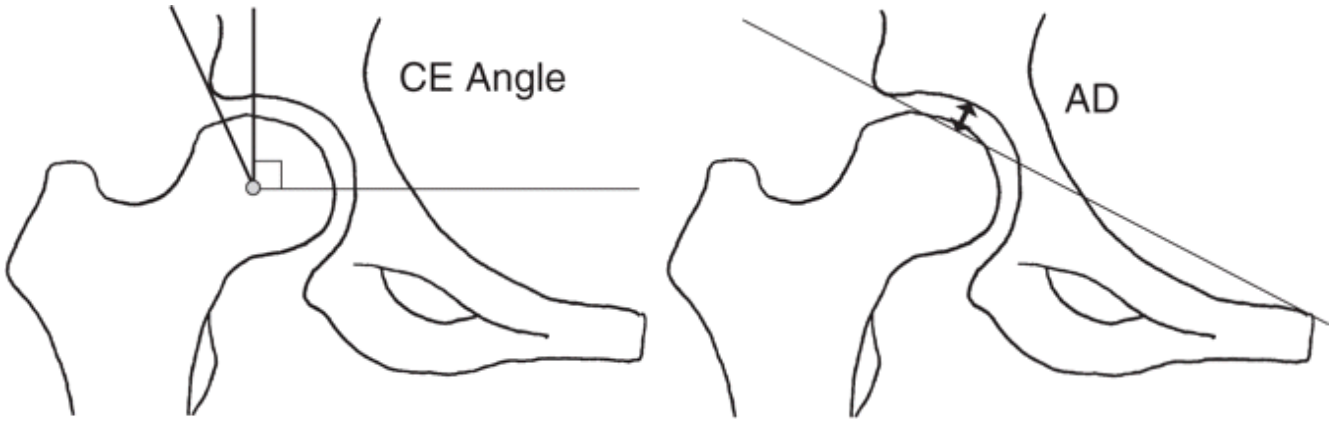

Figure 16. Measures of acetabular depth (AD) and centre edge (CE) angle
Source: (McWilliams et al., 2010).

Similarly, Lane and colleagues reported an association between acetabular dysplasia (OR= 2.8, 95%CI 1.0, 7.9) and abnormal centre edge angle (OR= 3.3, 95%CI 1.1, 10.1) with incident hip OA. In this study, participants were 9,704 white women aged ≥65 years recruited from the US multicentre cohort Study of Osteoporotic Fractures (SOF) (Lane et al., 2000). These two studies mentioned above provide strong evidence that acetabular dysplasia is a risk factor of hip OA and not a consequence of the disease itself. The results of the GOAL study mentioned earlier, also support the hypothesis that acetabular shape changes precede the appearance of hip OA. In that study, the lowest tertile of acetabular dysplasia (mild dysplasia) had a 2.5 (95%CI 4.87, 13.35) times higher association with hip OA (McWilliams et al., 2010).

Wide femoral neck

Javaid and colleagues examined data from the cohort Study for osteoporotic fractures (SOF) of 5245 postmenopausal Caucasian women (mean aged 72.6yrs) and observed that a wider femoral neck had a higher risk of prevalent (RR 1.6, 95%CI 1.0-2.4] and incident hip OA (RR 1.7, 95%CI 1.0, 2.3). Also a longer femoral neck had a decreased risk of incident radiographic hip OA (RR=0.8, 95%CI 0.7-1.7). The measurements used in this study are outlined in Figure 17.

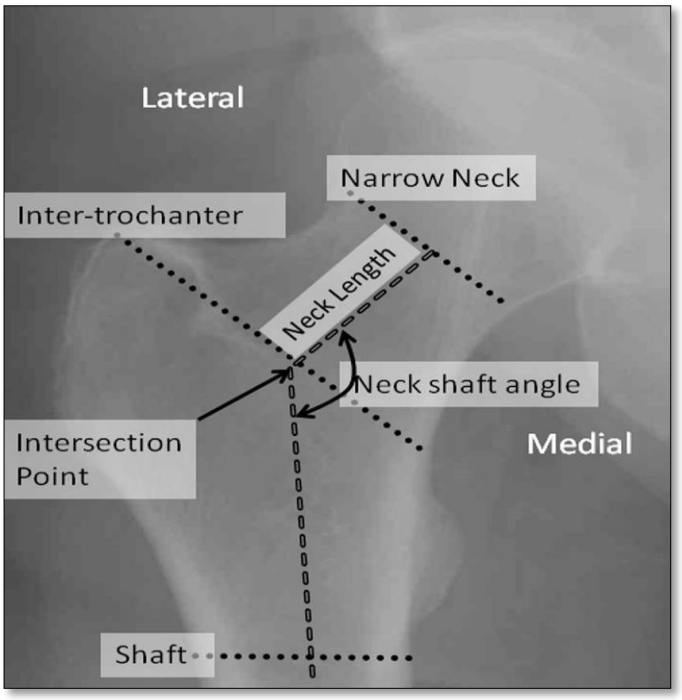

Figure 17. Measurement locations for hip structure analysis
Source: (Javaid et al., 2009)

Knee Morphology

Knee morphology variants are less frequently appreciated as risk factors for knee OA than hip morphology variants as risk factors for hip OA. However, several studies suggest that knee morphology variants are risk factors for knee OA. Abnormal patellar, tibial and femoral morphology, or changes in their alignment could contribute to the incidence and progression of knee OA by altering the joint loading forces beyond the capacity of the tissues (Hinman and Crossley, 2007). There are several possibilities that are viable on theoretical grounds alone. For example, a laterally displaced or a tilted patella is likely to enhance lateral PFJ compartmental loading. A high riding patella would decrease the cartilage contact area, while a narrow trochlear groove could affect the joint stability.

Imaging techniques such as CT, MRI and radiographs are commonly used in studies to determine the association between OA and morphology or alignment. Most of these studies have examined the association of bone morphology and OA progression (Macri et al., 2016). A summary of results of studies which have investigated the association of knee morphology is shown in Table 10.

Table 10. Studies assessing knee morphology and knee OA

Author year	Study design	N	Age/avg age	Gender (female)	Measures	Associated condition	OR/RR (95%CI)
(Stefanik et al., 2012a)	Cohort	3206	59—79	63%	LTI	PFJ BML	2.6(1.9-3.7)
					TA	Cartilage damage	2.0(1.25-3.5)
					SA		1.5(1.1-2.1)
(Davies Tuck et al 2008)	Cross sectional	100	63.3	61%	SA	↑medial patella cartilage volume	9.1(3.2-15.0) P=0.003
(Hunter et al., 2007)	Cohort	3,075	70–79	59.7%	BO	+ JSN Progression	2.2 P<0.0001
					PT	- JSN progression	P<0.0001
(Haverkamp et al., 2011).	Cross sectional	609	45-65		Mode 2		2.0(1.5 2.67)
					Mode 4	Knee OA	1.81(1.38-2.38)
					Mode 15		1.67 (1.31-2.11)
(Sharma et al., 2010a)	Longi -tudinal	1752	61.3	59%	Varus - alignment	Incident knee OA	1.49(1.06-2.10).
						Knee OA progression	3.59 (2.62-4,92)

[1]-Lateral trochlear inclination,[2]-Trochlear angle;[3]-sulcus angle,[4]- Bisect offset;[5]-Patellar tilt;+-risk of;- protective effect, OR-odds ratio, RR risk ratio, avg-average, JSN Joint space narrowing, BML-Bone marrow lesion, PFJ-patello femoral joint N-sample size.

Source: (Baker-LePain and Lane, 2012)

The Multicentre OA (MOST) study, which is a prospective cohort study of 3,206 individuals (age 50-79 years) who either had knee OA or were at high risk, examined the association between trochlear morphology and PFJ cartilage damage and bone marrow lesions. In this MRI study, the trochlear morphology was assessed on the lateral trochlear inclination, medial trochlear inclination, sulcus angle and trochlear angle, as shown in Figure 18. In this study the sulcus angle was defined as the angle between the medial and lateral trochlear facets. Lateral and medial trochlear inclination was defined as the angle between the posterior condylar line and a line along the lateral and medial patellar facets. Stefanik and colleagues defined the lateral trochlear angle (TA) as the angle between the posterior condylar line and a line passing along the most anterior margin of the medial and lateral trochlear facets (Stefanik et al., 2012a)

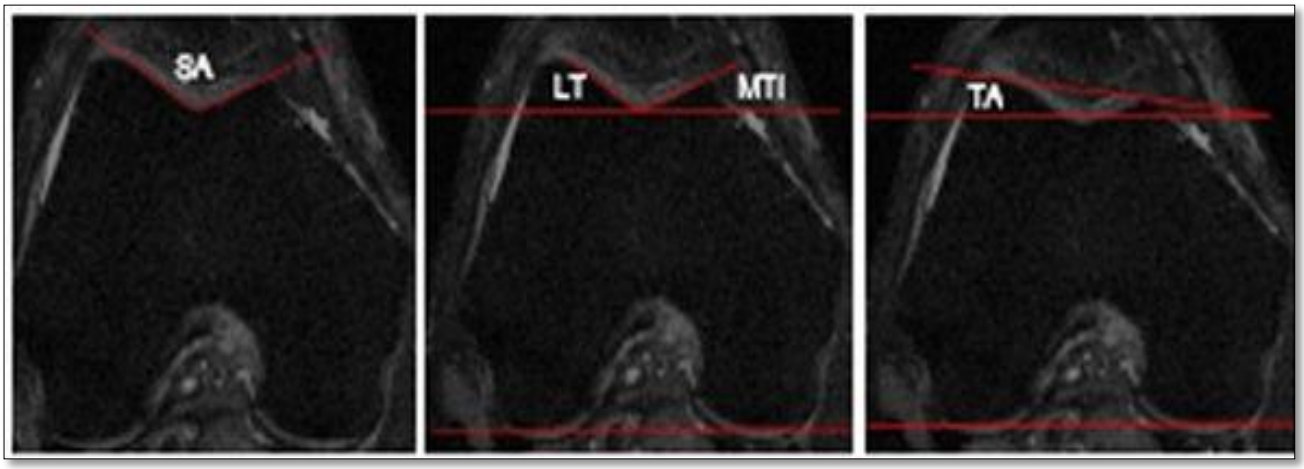

Figure 18. Measurement of trochlear morphology in the MOST study
SA- sulcus angle, LTI –lateral trochlear inclination. MTI-medial trochlear inclination, TA- trochlear angle.

Source: (Stefanik et al., 2012a)

It was reported that in participants with knee OA a low lateral trochlear inclination had the strongest association with cartilage damage (OR=2.6, 95%CI 1.9, 3.7) and BML (OR 2.3, 95%CI 1.5, 3.3) in the lateral PFJ. Similarly, a low trochlear angle associated with cartilage damage in the lateral PFJ compartment with an OR of 2.0 (95%CI 1.2, 3.5). Also, cartilage damage associated with increasing sulcus angle (OR=1.5, 95%CI 1.1, 2.1) (Stefanik et al., 2012a)

Davies–Tuck et al investigated the association of baseline sulcus angle (measured on skyline PFJ radiographs) and patella cartilage volume measured at baseline and also at 2 years follow-up (using MRI) in a community based population with knee OA (mean age 63.3 years, women 61%) (Davies-Tuck et al., 2008a). The sulcus angle was defined as the lines joining the highest points of the medial and lateral condyles and the lowest point of the intercondylar sulcus. Shallow and deep sulcus angles measured in this study are shown in Figure 19 and Figure 20

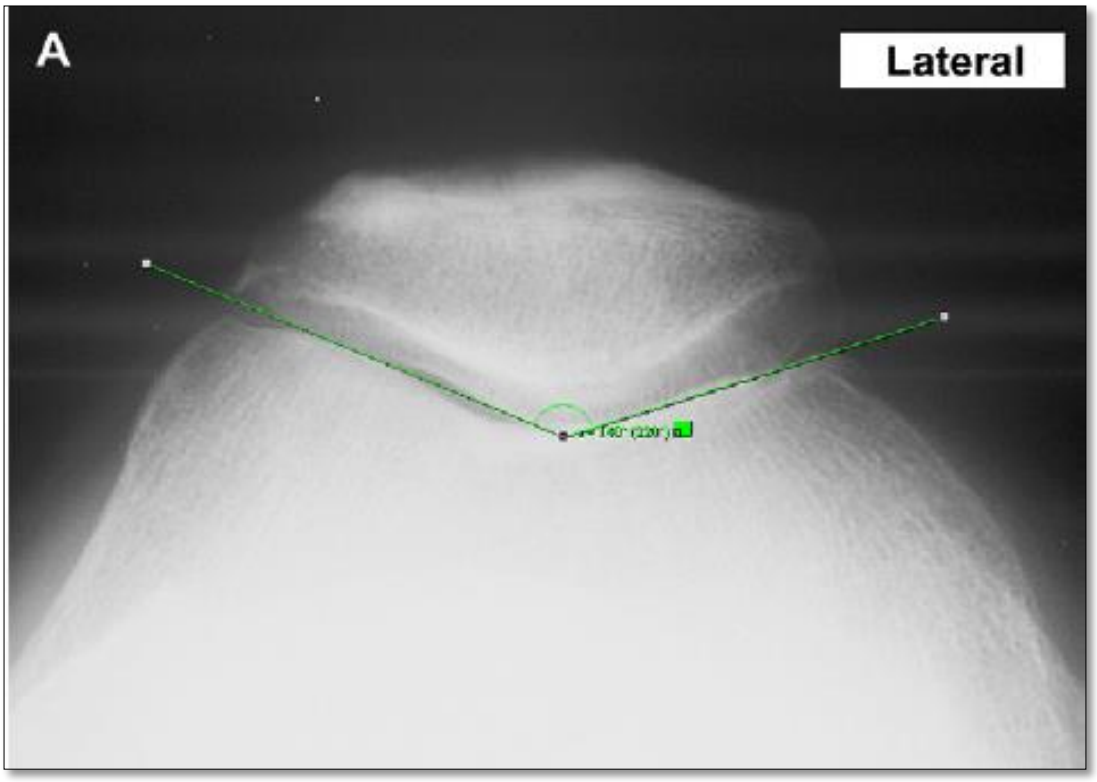

Figure 19. Sulcus angle (shallow)
Source: (Davies-Tuck et al., 2008b)

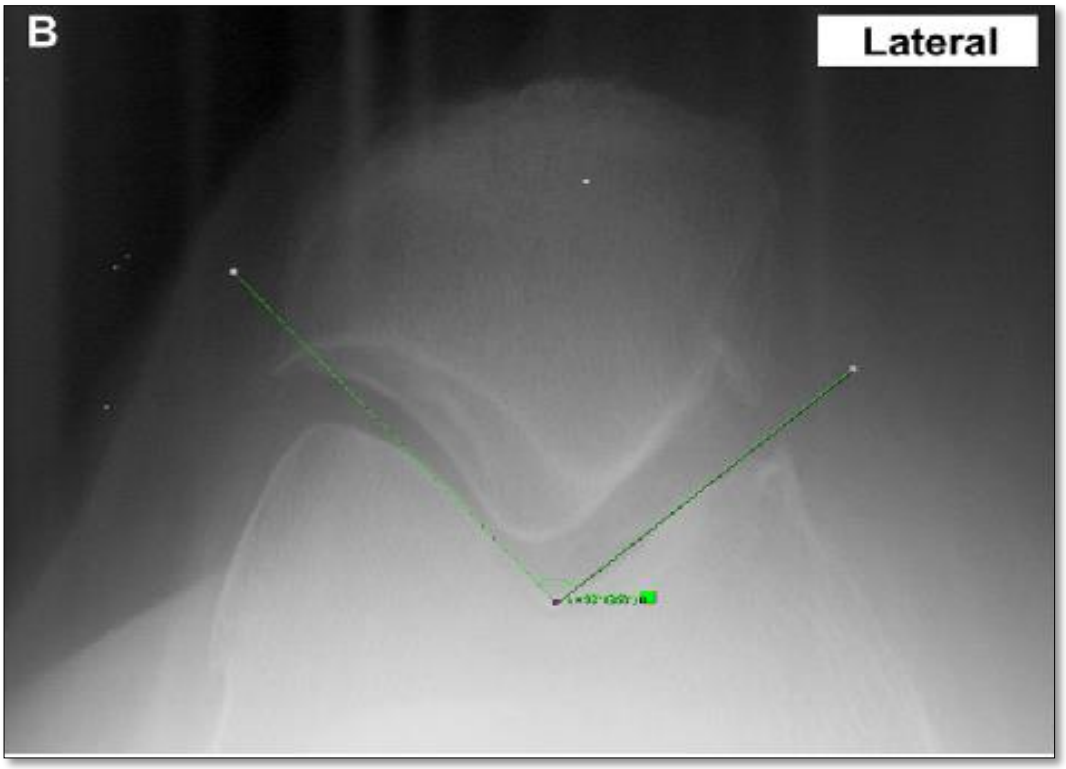

Figure 20. Sulcus angle (deep)
Source: (Davies-Tuck et al., 2008b)

They found that there was a 9.1mm^3 (95% CI 3.2, 15.0) increase in the medial patella cartilage volume for every 1^0 increase in the sulcus angle (i.e. shallower sulcus angle) at baseline (p=0.003), and there was a statistically significant association between sulcus angle and annual cartilage volume change (Davies-Tuck et al., 2008a).

Another study (Hunter et al., 2007c) examined the association between patellar malalignment and PFJ OA progression using radiographic data from the health ABC Knee OA Study, a US multicentre cohort study of 3,075 Caucasian and black men and women (mean age 73.6, 40.3% male). Sulcus angle, patellar tilt angle and bisect offset were used to determine patellar malalignment. The method used to determine the sulcus angle was similar to the two studies mentioned above. The patellar tilt was

defined as the angle formed by a line joining the maximum width of the patella (AB) and the posterior condyles (BC) as shown in Figure 21. Normal tilt range was 0-5 degrees

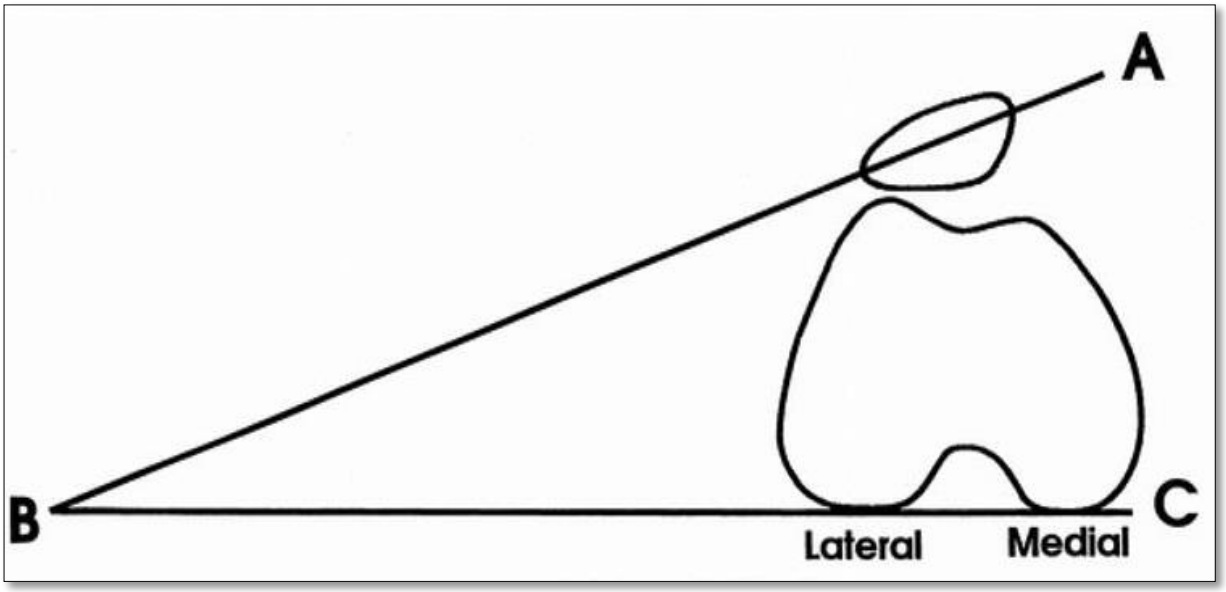

Figure 21. Patellar tilt
Source: (Hunter et al., 2007c)

The bisect offset was measured by drawing a line connecting the posterior femoral condyles (AB) and then projecting a perpendicular line anteriorly through the deepest point (Figure 22).

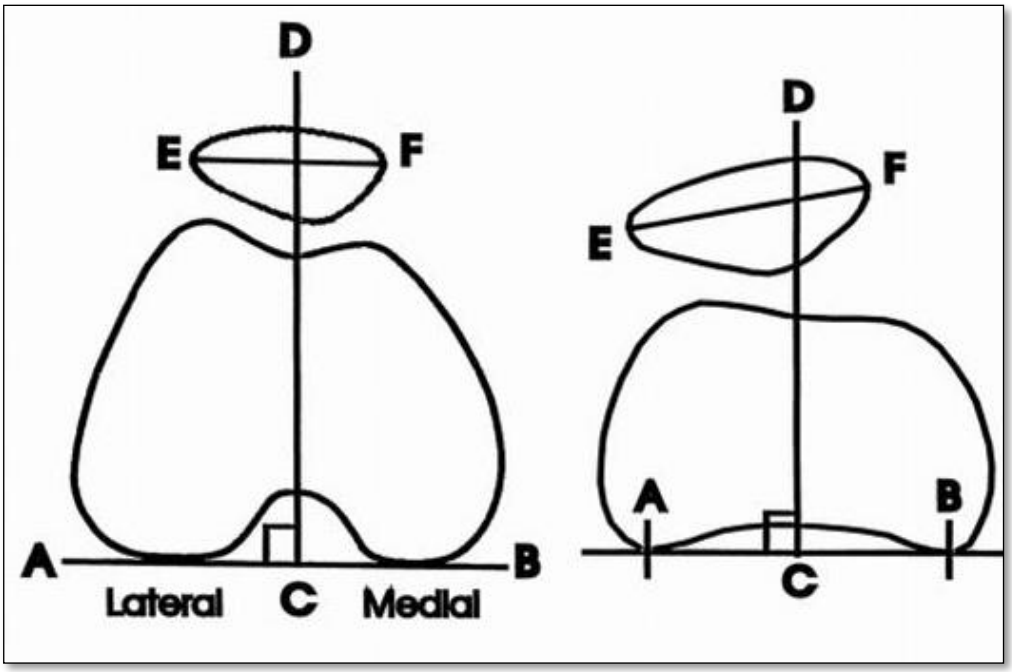

Figure 22. Bisect offset
Source: (Hunter et al., 2007c)

The study found that medial displacement of the patella was a risk factor for medial JSN progression (OR=2.2, 95%CI 1.71, 2.81). However, a more tilted patella had a protective effect $p<0.0001$ (Hunter et al., 2007c).

The Insall-Salvati index used in this study provides a quantitative estimation of the vertical height of the patella. It is the ratio of the patellar tendon length in relation to the diagonal length of the patella (Figure 23) (Ali et al., 2010).

Patella baja and alta are indicated by an index value of <0.8 and >1.2 respectively (Ali et al., 2010)

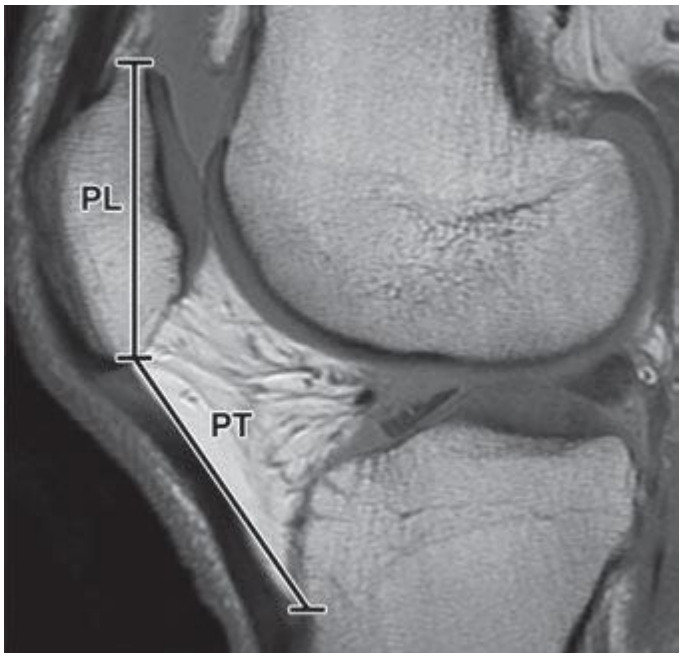

Figure 23. Insall-Salvi index
Patellar length (PL) length of patellar tendon
Source: (Ali et al., 2010)

Higher riding patella or patella alta which was determined by a high ISR ratio was negatively associated with decreased medial patella cartilage volume in one community-based study of adults aged between 25-60 years (Regression coefficient -3187 mm^3, 95% CI -5510, -864 mm^3) (Tanamas et al., 2010b).

In the same study, a wider lateral condyle patella was associated with increased medial patellar cartilage volume (Regression coefficient 51.38 mm^3, 95% CI 1.68, 101.08 mm^3) and a reduction in WOMAC pain score. A decreased WOMAC pain score was associated with increased lateral condyle-patella angle (Regression coefficient -1.57, 95% CI -3.05, -0.09) (Sheehan et al., 2009).

Additionally wider sulcus angle was associated with an increase in medial and lateral patellar cartilage volume (Sheehan et al., 2009).

Similarly, in a cohort study of participants aged between 50-79 years with knee OA or at risk of knee OA, a higher ISR was associated with PFJ cartilage damage (Stefanik et al., 2010)

One cross sectional study examined the association between patellar alignment and PFJOA among 213 individuals with knee OA. They found a wider sulcus angle was associated with increased cartilage loss (OR= 2.0 95%CI 1.2, 3.6) (Kalichman et al., 2007b). They also found a more laterally displaced patella with higher lateral patellar tilt angle LPTA (OR=0.3, 95%CI 0.2, 0.5) was associated with increased cartilage loss and BMLs (Kalichman et al., 2007b).

Global shape of tibiofemoral joint

Using statistical shape modelling, Haverkamp and colleagues (2011) compared the morphology of knee in people with radiographic knee OA (n=609 women (1218 knees)) with a normal control group from the Rotterdam study (aged 45-65). They found that 3 modes of knee shape, i.e. shapes 2, 4, and 15, showed significant association with radiographic OA (Haverkamp et al., 2011). Modes 2, 4, and 15 described the width of femoral and tibial bones (Figure 24), changes in knee flexion, and elevation of lateral tibial plateau respectively, and associated with radiographic knee OA with OR (95%CI) of 2.03 (1.55- 2.66), 1.81 (1.38-2.38) and 1.67 (1.31- 2.11) respectively (Haverkamp et al., 2011).

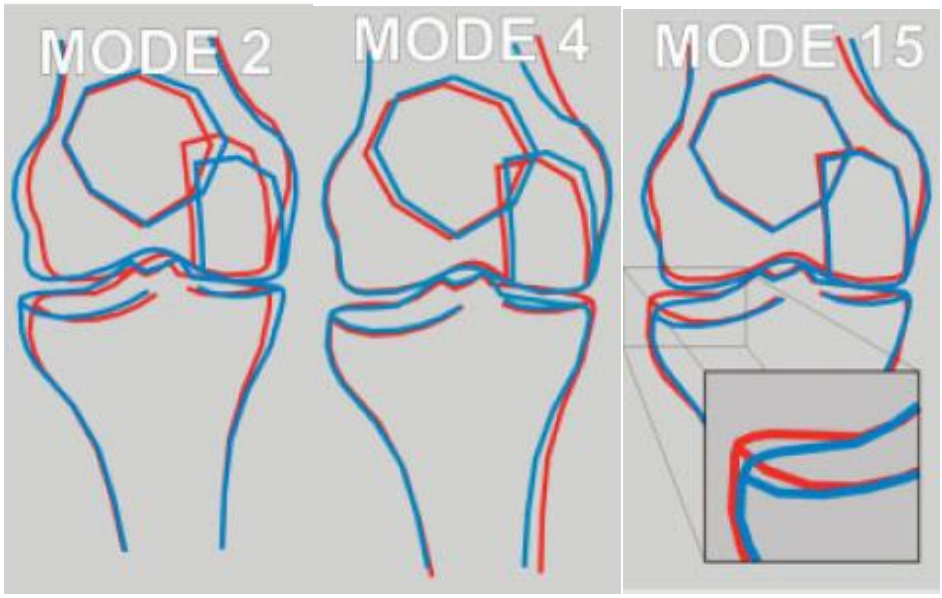

Figure 24. Visual representation of Mode 2, Mode 4, Mode 15

Source: (Haverkamp et al., 2011)

Varus Valgus alignment

Frontal plane mal-alignment at the knee has been associated with incidence and progression of knee OA in many studies. Sharma and colleagues examined the association of knee alignment and the risk of incident and progressive radiographic TFJOA in an observational longitudinal sub-study of the MOST study. They found varus alignment to associate with incident knee OA (aOR=1.49, 95%CI 1.06, 2.10), and also with medial TFJ OA progression (aOR=3.59, 95%CI 2.62, 4.92) (Sharma et al., 2010a).

Another prospective cohort study used 1,501 participants from the Rotterdam cohort to examine the association between varus and valgus alignment and incidence and progression of knee OA (Brouwer et al., 2007). They found obese and overweight participants with varus alignment had a 2-times higher risk (OR 2.06, 95% CI 1.28, 3.32) of knee OA development. Varus alignment associated also with progression of OA also (OR 2.90, 95% CI 1.07, 7.88) (Brouwer et al., 2007).

One study with 292 people with knee OA found varus alignment to associate with increased risk of isolated medial PFJOA progression (aOR =1.85, 95%CI 1.00, 3.14) while valgus association associated with lateral PFJOA progression (aOR=1.64, 95% CI 1.01, 2.66) (Cahue et al., 2004).

Teichtahl and colleagues examined cross-sectional and longitudinal associations between patella cartilage volume and knee alignment in 99 participants with knee OA

and found there was 23.4mm^3 reduction in patellar cartilage volume per-year for every 1^0 increase in valgus angulation (Teichtahl et al., 2008).

1.11 Study rationale and hypothesis

OA can contribute to changes in the shape of bone, but variations in bone morphology may also contribute to the development of OA (Baker-LePain and Lane, 2012). Morphological variations in the hip are now well known to predispose to OA. Currently there are only a few morphological features found to be associated with knee OA such as varus and valgus knee alignment (Sharma et al., 2010a), sulcus angle (Davies-Tuck et al., 2008a), a high ISR (Ali et al., 2010), and a laterally displaced patella (Hunter et al., 2007c). However, there are several limitations in the previous studies examining association between knee morphology and knee OA. These are:

1. Most studies had a small sample size.
2. Only or two measurements only were examined in the majority of studies.
3. Most studies examined association between morphological features and progression of OA rather than development of OA, and risk factors for OA progression differ from those of incident OA
4. Some of the studies that use active shape modelling yield results that are difficult to understand, explain to patients, and use in clinical practice.
5. Influence of age, obesity, gender and height along with the morphological features on knee OA were not examined.

Hence, there is a need to look at this comprehensively in a new dataset using simple imaging techniques.

In this study, we will compare the morphology of the unaffected knee of the unilateral knee OA cases with normal knees of the controls. We hypothesize that the unaffected

knee of people with unilateral knee OA had similar morphology as the affected contralateral knee before the onset of OA. We will attempt to prove this hypothesis in the first part of our study, before proceeding further with the second part of the study. We are confident this hypothesis will hold true, as, we have confirmed this hypothesis at the hip previously (Abdul-Rahim et al, 2013). As variation in the bone morphology can affect the biomechanics of the knee, thereby increasing the risk of OA at the knee.

1.11 Aim and objectives of the thesis

The overall purpose of this PhD is to identify the radiographic morphological features that are associated with knee OA, PFJ OA and TFJ OA respectively using radiographic images. Specific objectives include:

1. To examine whether morphological measurements at the knee are symmetrical between left and right knees of participants without radiographic and clinical knee OA.
2. To determine whether these measurements differ with respect to age, gender, weight and height in people without clinical and radiographic knee OA.
3. To determine whether these morphological features are independent risk factors for knee OA.
4. To determine whether these morphological features predict knee OA, TFJ OA, PFJ OA, on their own or when combined together with age, gender, weight and height.
5. To examine whether morphological risk factors that associate with OA are associated with increasing severity of WOMAC pain scores.
6. To examine whether morphological risk factors that associate with OA are also associated with more osteophyte formation, more severe JSN, and worse KL grade.
7. To examine whether morphological features that associate with OA are associated with greater progression of VAS pain score.

The measurements specifically assessed in this study are:

- **Angular measurements**: Sulcus angle, patellar angle, condylar angle, distal femoral tilt, condylar plateau angle, proximal tibial tilt, varus and valgus alignment
- **Linear measurements**: patellar width, patellar thickness, medial condylar height, lateral condylar height, intercondylar width, condylar width.

CHAPTER 2: METHODS

2.1 Source population - Genetics of osteoarthritis and lifestyle study

The Genetics of Osteoarthritis and Lifestyle (GOAL) study was a case-control study of 45-80 year-old Caucasians that recruited 1042 participants with severe knee OA, 1007 participants with severe hip OA, and 1121 participants without hip or knee OA, living in or around Nottingham. Ethical approval was granted by the Nottingham City Hospital Local Research Ethics Committee (reference EC02/06) in February 2002.The project was funded by AstraZeneca, UK as a collaborative project with the University of Nottingham, UK.

2.2 Participants for GOAL study

Participants were classified following recruitment (Figure 25). Cases were participants with severe symptomatic large joint OA who referred to hospital for consideration of surgery or having already undergone total joint replacement for symptomatic OA at the hip or the knee in the previous 2 years.

Hip OA cases

All the hip OA cases were Nottinghamshire residents who underwent or were awaiting a total hip replacement (THR) for primary hip OA. They were recruited from the

orthopedic waiting lists of the City Hospital Nottingham (CHN), Queens Medical Centre (QMC) or Kings Mill hospital which are all in the Nottinghamshire area.

Knee OA cases

Recruitment of the knee OA cases were in the same manner as that for hip OA, except for a small number of severe symptomatic knee OA cases who were recruited from a secondary care rheumatology knee clinic at the Nottingham University Hospitals NHS Trust. For those who had already undergone a TJR, their pre-operative knee or pelvis radiographs were examined to confirm that the total joint replacement was performed for OA.

Controls

Controls were defined as individuals without symptoms, signs or radiographic evidence of OA at both the knees and hips. The control group were all Nottinghamshire residents recruited from lists of people who had undergone intravenous urography (IVU) at QMC or CHN. This identified patients who had a radiograph of the pelvis which was examined to confirm whether they had radiographic hip OA, inflammatory arthritis or partial or total joint replacement. The exclusion criteria for the GOAL study is shown in Table 11.

2.3 Recruitment of Genetics Osteoarthritis and Lifestyle (GOAL) participants

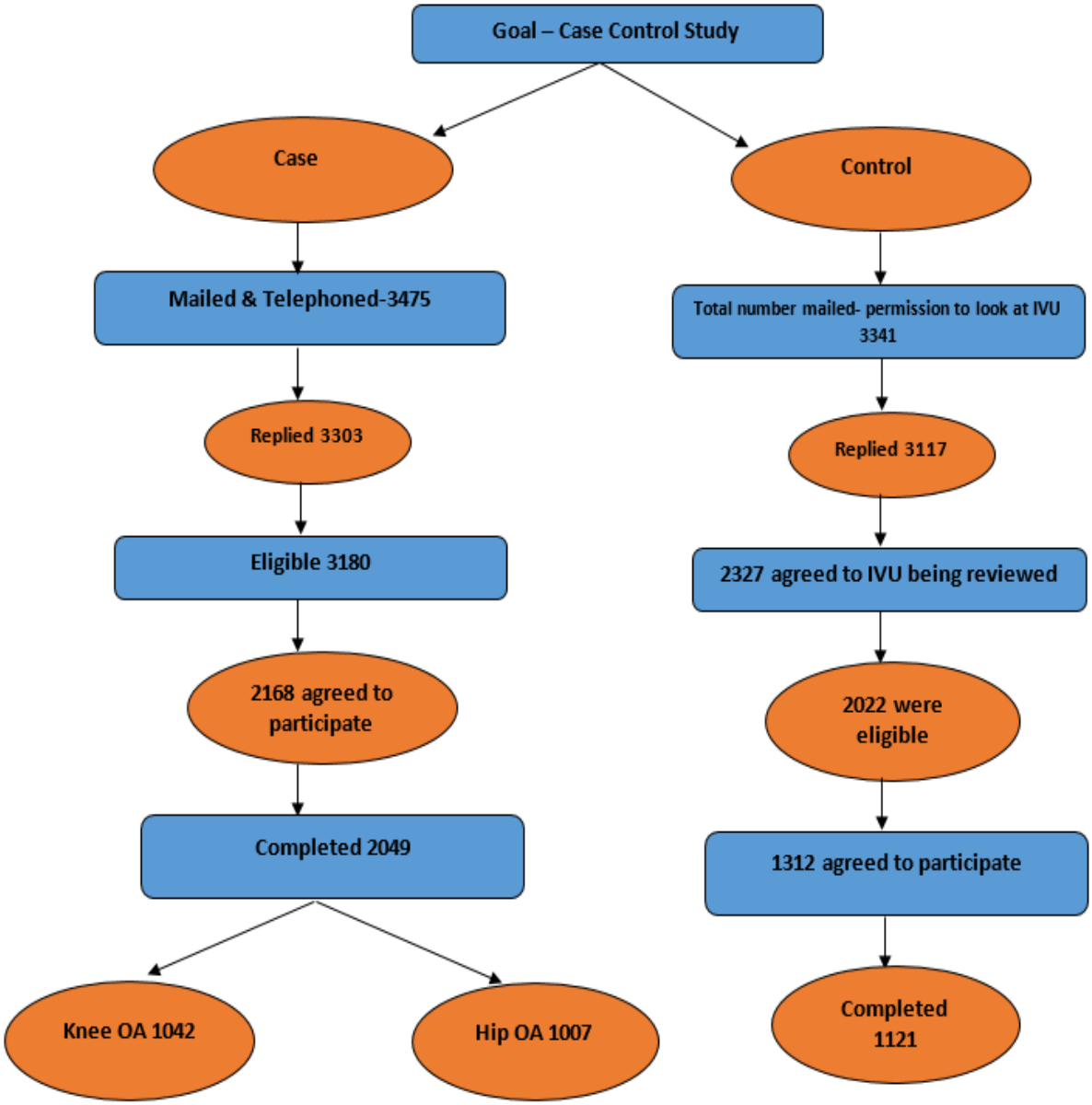

Figure 25. Recruitment of GOAL Participants

Table 11. GOAL study exclusion criteria

Ankylosing spondylitis
Perthe's disease
Hip dysplasia
Polio
Congenital deformities
Avascular necrosis of femur neck or the distal femoral condyle
Inflammatory arthritis
Major trauma prior to a joint replacement
Paget's disease of bone
Any long-term, serious illness e.g. carcinoma, dementia, respiratory problem
Inability to give informed consent

2.4 Research assessments

Participants attended for a single research assessment. At this visit, they completed a standardised questionnaire, and underwent clinical examination and investigations. The participants' height, waist, hip and arm span were measured in centimetres. Their weight was measured in kilograms. BMI was calculated and categorized according to the WHO classification (normal weight 18.5–24.9, overweight: 25.0–29.9, obese: 30.0–34.9 kg/m^2). Information about self-reported knee and hip pain were collected. History of severe knee or hip injury was defined as any self-reported fracture, injury that required immobilization or use of crutches for ≥ 2weeks, or surgery to the joint.

AUSCAN and WOMAC questionnaires were used to assess pain, function and stiffness of the hand and knee respectively. Participation in exercise was self-reported. Regular exercise was defined as any activity performed ≥ 20mins at a time and ≥ 3 times a week that lead to breathlessness, sweating or a rise in pulse rate. Clinical examination of the knees, hips, hands and feet were performed by trained research metrologists.

At the knee, joint line tenderness, crepitus and movement restriction were assessed. At the hip, pain or movement restriction during flexion or internal rotation were assessed. Inspection and palpation of the hand were done to assess any bony swelling, crepitus or restriction and to document presence of any Bouchard's and Heberden's nodes.

Calcaneal BMD was also measured using a Norland Apollo 501A00z densitometer. Blood and urine samples were taken and urine, serum and DNA were stored for future analyses.

2.5 Radiographic assessment

Standardised radiographs of knees and pelvis were undertaken to confirm presence and degree of OA. The pre-surgical radiographs of participants who had total joint replacement (TJR) were copied and scored with HIPAX Digicom digitizing software (Zhang et al., 2008b).

Bilateral posterior-anterior weight-bearing semi-flexed knee radiographs were obtained with the Syna Flexer positioning frame with feet externally rotated at 10^0 and thighs and knees and thighs touching the vertical platform anteriorly. The X-ray beams were projected at 10^0. Individual skyline 30^0 flexion views of both patellofemoral compartments were obtained with the participant lying on a couch (supine) with proforma support under the knees, and the beam angled from feet to knees. A single antero-posterior view of the pelvis was obtained with the participant supine and the feet internally rotated at 10^0 (70 kV exposure, 100cm focus to film distance).

Separate radiographs of left and right hands were obtained. The participants were seated near the X-ray table with hand flat on the table, with fingers spread apart and middle finger aligned with the forearm. Exposure was 48KV, 3.2 mAs.

The 2D:4D length ratio was determined on hand radiographs by using a visual classification and measured radiographic 2D:4D (index: ring finger) length ratio (Zhang et al., 2008b, Doherty et al., 2008)

A single trained research metrologist scored these radiographs. Osteophytes at each of the eight sites of the knee (medial and lateral tibial, femoral, patellar, and trochlear) were graded according to their size (grade 0 - 5) (Nagaosa et al 2002). JSN at TFJ (medial and lateral) and PFJ compartment were scored using an ordinal line diagram atlas (grade -1 to 5) (Wilkinson et al., 2005). Negative scores in this indicated joint space widening (Wilkinson et al., 2005)

2.6. Morphology features of knee OA study

The current study was a case control study, using data from the GOAL study. Participants with unilateral knee OA (cases) and controls without radiographic or clinical knee or hip OA in both knees formed the study population for this project (Figure 26).

2.6.1 Case and control definition

For this study cases comprised the unaffected knees of participants with unilateral knee OA. The unaffected knee of the cases were required to have a score of zero or one for osteophytes and a score of zero for JSN (equate to be a normal KL of 0) on the NLDLDA. (Nagaosa et al., 2000). Controls were participants without knee pain in either knee, and radiographic scores of 0 to 1 for osteophyte and a score of 0 for JSN using the NLDLDA.

2.6.2 Rationale for case control selection:

As has been observed previously at the hip (Abdul-Rahim et al, 2013), if participants without arthritis exhibit symmetry of constitutional morphological measures between the right and left knees, it can be assumed that the unaffected knee of cases represents the morphology of the affected knee before the onset of OA.

Hence in this study, unaffected knees (i.e. case knees) of the participants with the unilateral knee OA were compared with the same side of knees selected from among the control knees.

A similar strategy has been used in other studies at the hip joint (Doherty et al., 2008), (McWilliams et al., 2010). However, to confirm that this assumption holds true at the knee, all the PF and TF morphological measurements were compared between right and left control knees to assess symmetry and to confirm this hypothesis at the knee

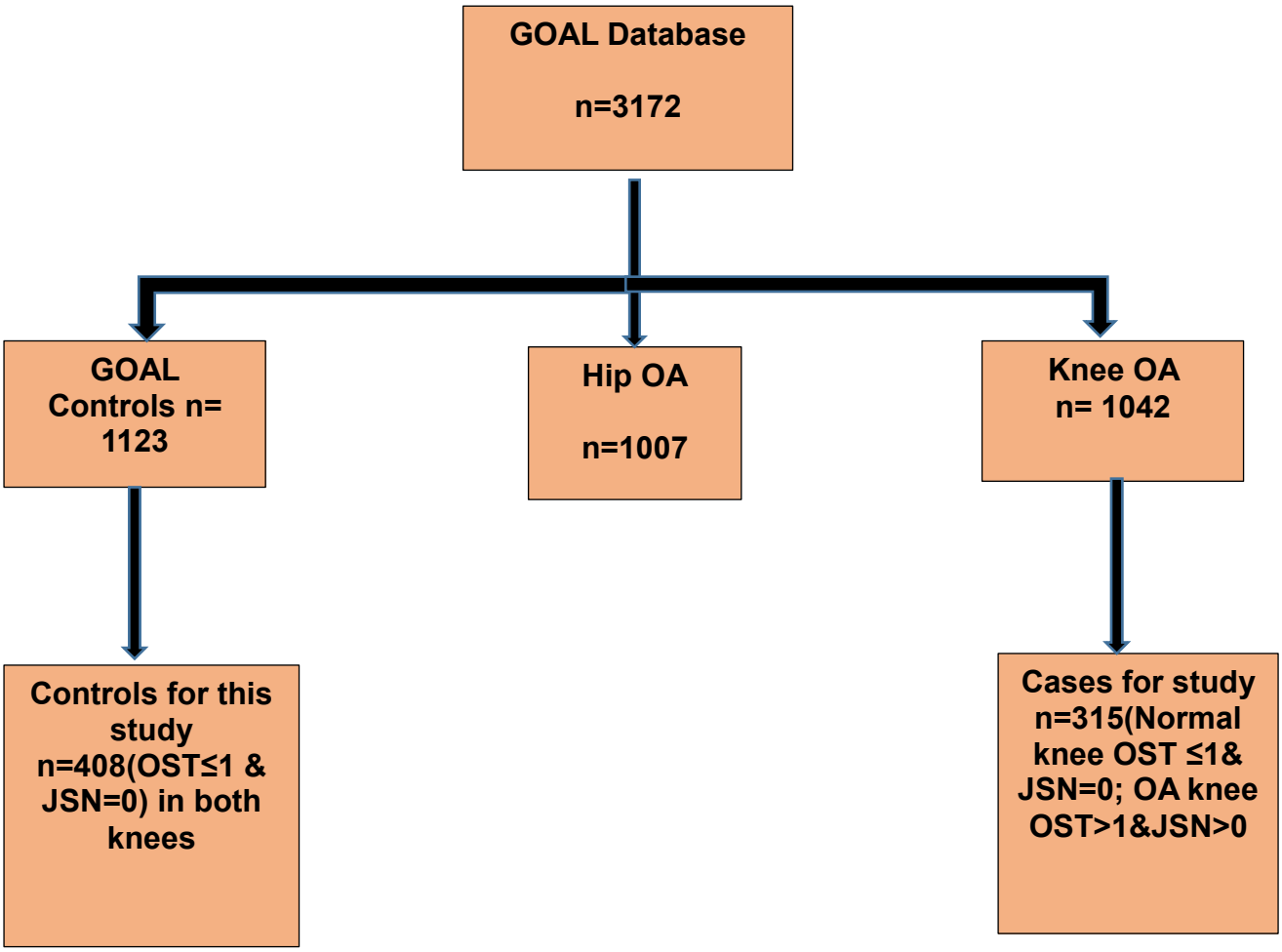

Figure 26. Recruitment of cases and controls for the Knee OA study

OST-osteophyte; JSN-Joint space narrowing

2.6.3 HIPAX software

All radiographs were measured using HIPAX computerised software. This is specifically designed for measuring geometrical parameters on radiographs. It allows the observer to make straight line measurements and measurements of angles between visually determined points (Figure 27). Linear and angle parameters are calculated electronically correct to two decimal places after all the anatomical landmarks have been identified. Also, the accuracy of measurements can be improved by magnifying the image.

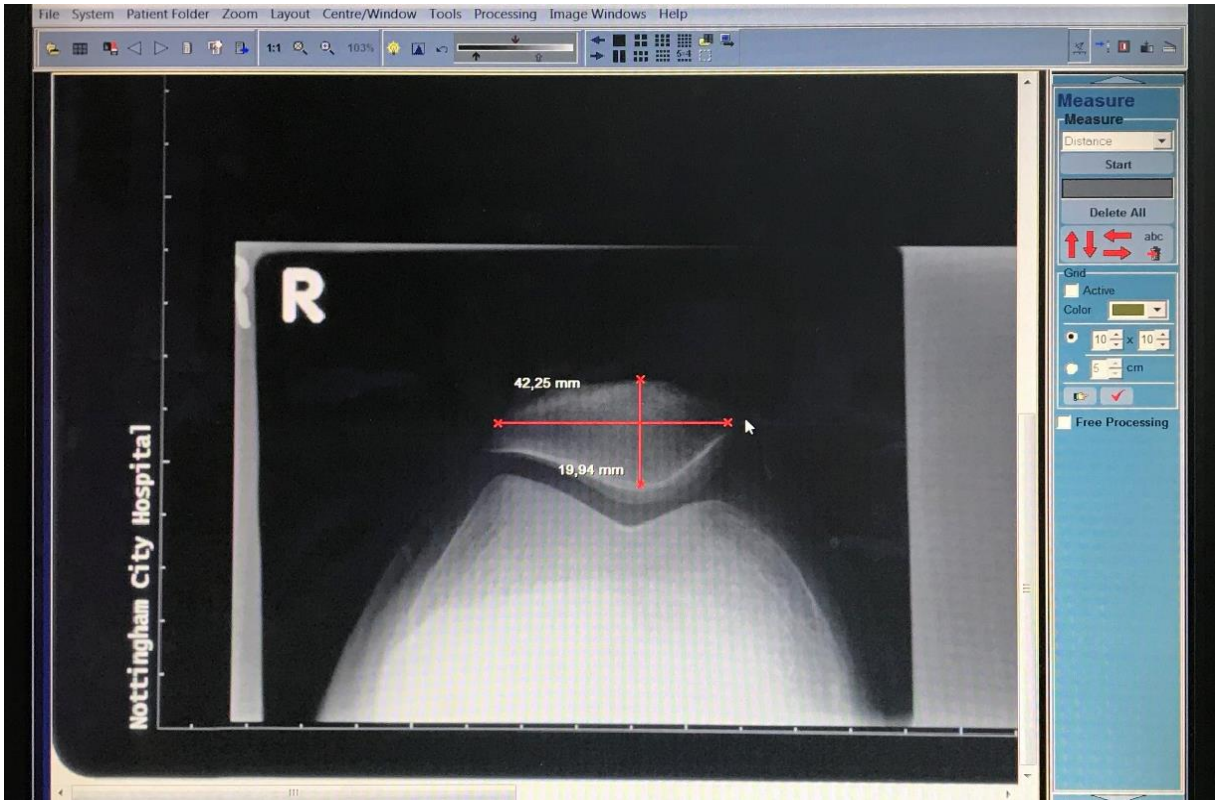

Figure 27. Measurement using HIPAX software *(A skyline view showing how patellar thickness and patellar width measured using HIPAX software)*

2.6.3 Measurements

There were nine morphological features at the PFJ and three morphological features at the TFJ studied in this project, which included angular and linear measurements. These measurements were either identified following a literature search, or conceptualised following discussion with the supervisors. Skyline view radiographs were used for PFJ measurements and posterior-anterior knee radiographs for TFJ measurements. Varus and valgus alignment measured by Abhishek et al (2012) as part of his thesis work (Abhishek et al., 2012) was included as a measurement in this study.

Measurements on the skyline view

1. Patellar angle

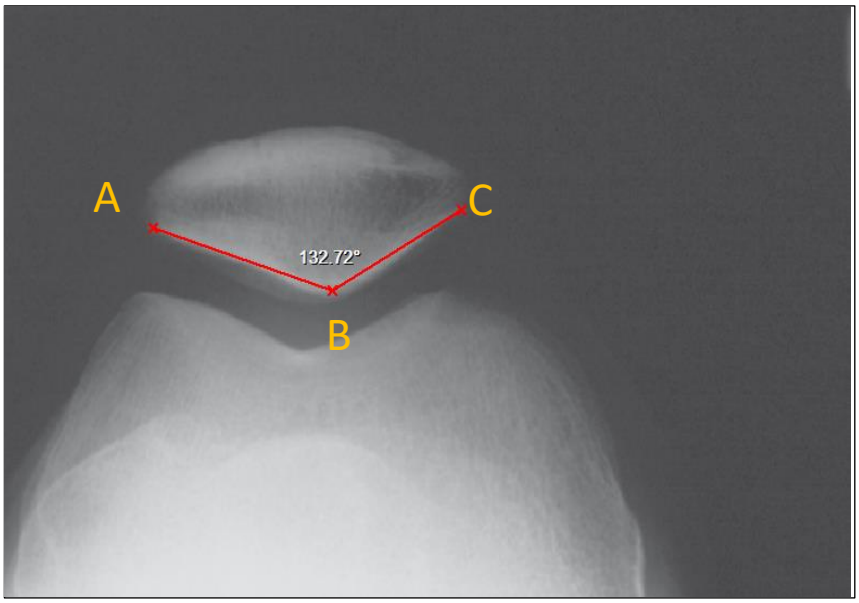

Figure 28. Patellar angle

This is the angle between the medial and lateral facets of the patella with the point of the patellar central ridge as the zenith (angle ABC in Figure 28).

Method - A straight line is drawn joining the most lateral point on the lateral facet of the patella to the patellar central ridge. Another straight line is drawn from the most medial point on the medial facet of the patella to the patellar central ridge. The patellar angle is the angle formed where the two lines meet at the patellar central ridge(Yang et al., 2009).

2. Sulcus angle

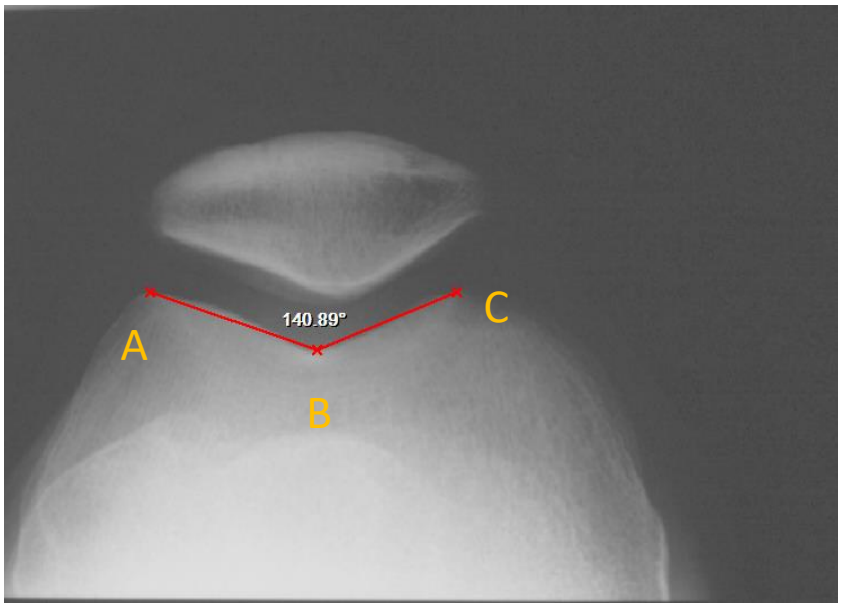

Figure 29. Sulcus angle

This is the angle between the medial and lateral condyles of the femur with the lowest trochlear point as the zenith (angle ABC in Figure 29).

Method - A straight line is drawn along the medial and lateral condyles of the femur, from the highest point to the lowest point on the trochlea. The sulcus angle is the angle between the medial and lateral condyles of the femur with the lowest trochlear point as the zenith (angle ABC in Figure 29) (Yang et al., 2009, Hunter et al., 2007b).

3. Patellar thickness

This is the widest vertical height of the patella (Figure 30).

Method - A transparent ruler placed perpendicular to the horizontal margin of the screen is used to identify the landmarks. As the ruler is moved across from the lateral to the medial part of the patella, perpendicular to the lowest margin of the radiograph, the widest vertical distance gives the maximum patellar thickness (Yang et al., 2009).

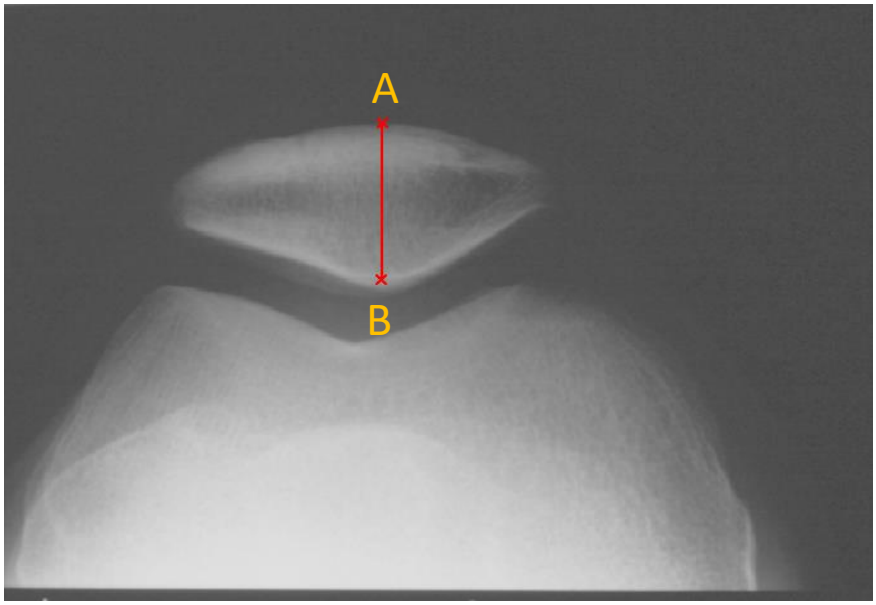

Figure 30. Patellar thickness

4. Patellar width

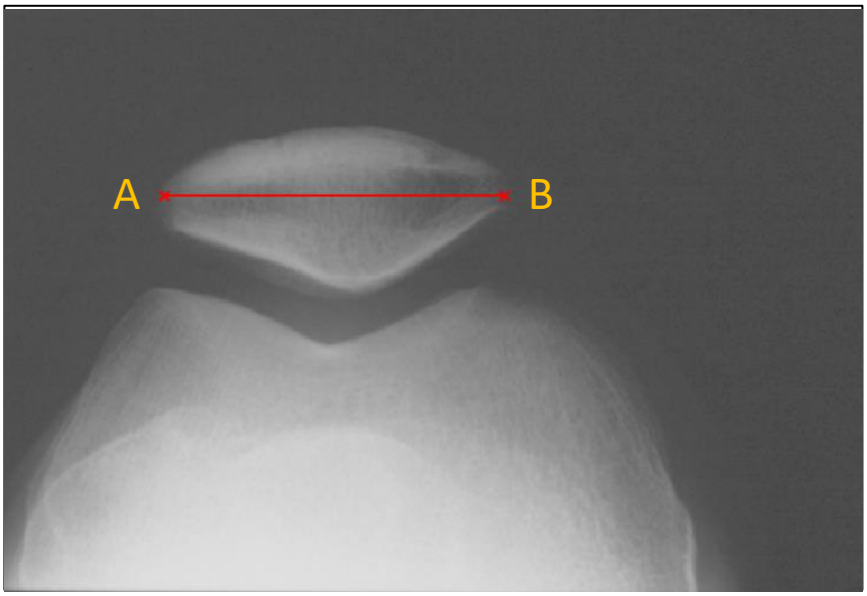

Figure 31. Patellar width

This is the widest horizontal distance between the most medial (A) and lateral (B) points of the patella as shown in Figure 31.

Method - A transparent ruler is placed horizontally, perpendicular to the vertical margin of the screen and moved from the bottom of the patella to its top and parallel to the lower border of the radiograph. The widest horizontal distance is identified and measured (Yang et al., 2009).

5. Condylar width

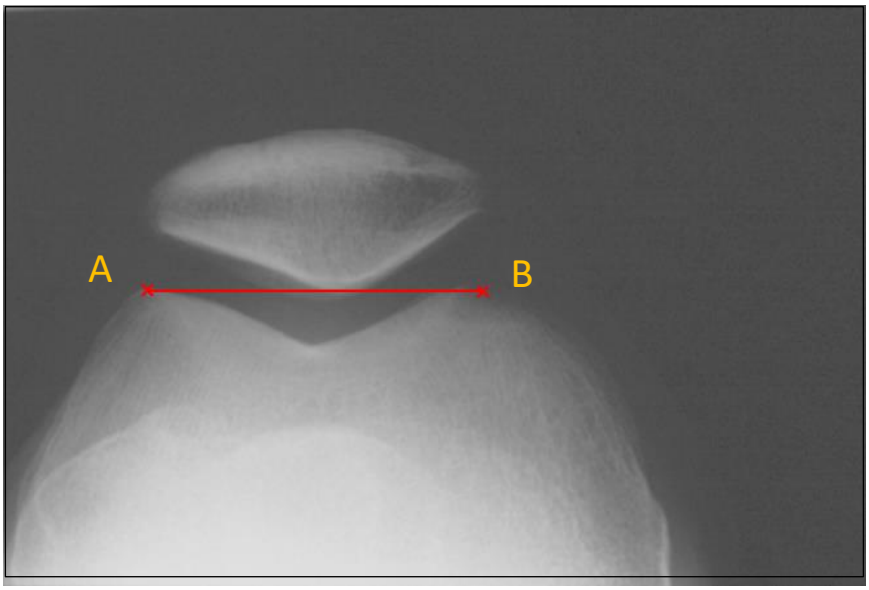

Figure 32. Condylar width

Condylar width is the width between the prominences of the medial and lateral femoral condyles (Figure 32)

Method - The highest points as shown in Figure 35 of the medial (A) and lateral (B) condyles of the femur are selected and a straight line is drawn joining them and parallel to the lowest margin of the radiograph. This length (AB) is the condylar width (Yang et al., 2009).

6. Condylar angle

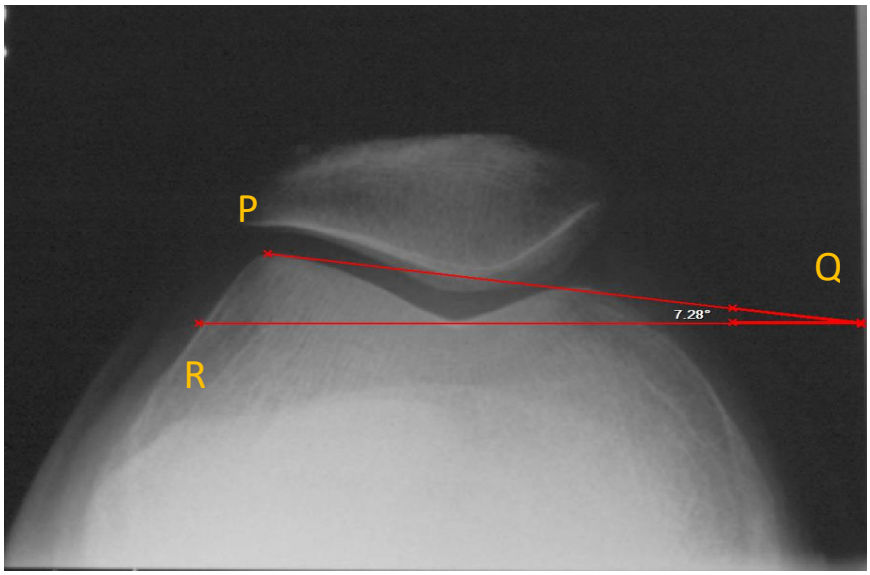

Figure 33. Condylar angle

Condylar angle denotes the slope of the femoral condyles.

Method - A line is drawn along the highest point of the medial and lateral condyles of the femur (Line PQ in Figure 33). A second line (RQ) is drawn horizontally, perpendicular to the vertical margin of the screen, along the condyles passing through the lowest trochlear point and parallel to the lower margin of the radiograph. The angle formed by the intersection of the lines (angle PQR) is the condylar angle.

7. Intercondylar width and medial and lateral condylar height

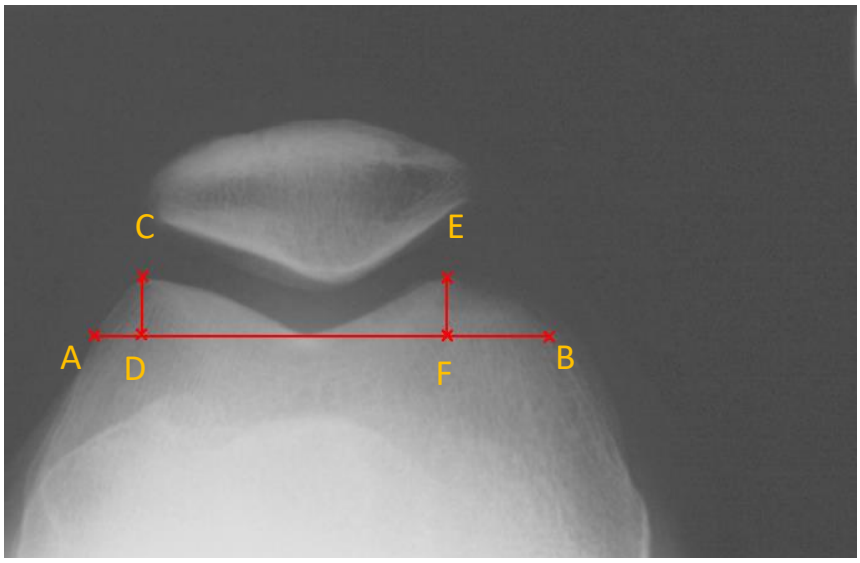

Figure 34. Intercondylar width and Lateral condylar height

Method - A horizontal line is drawn across the medial and lateral femoral condyles passing through the lowest trochlear point and parallel to the lower margin of the radiograph, perpendicular to the horizontal margin of the screen (Line AB in Figure 34). Two vertical lines are drawn from the highest points in the medial and lateral femoral condyles which intersect the horizontal line AB at right angles (D and F). The distance between D and F gives the intercondylar width. The vertical lines CD and EF represent the heights of the medial and lateral femoral condyles.

Measurements on the Postero-anterior view (TFJ)

8. Condylar plateau angle

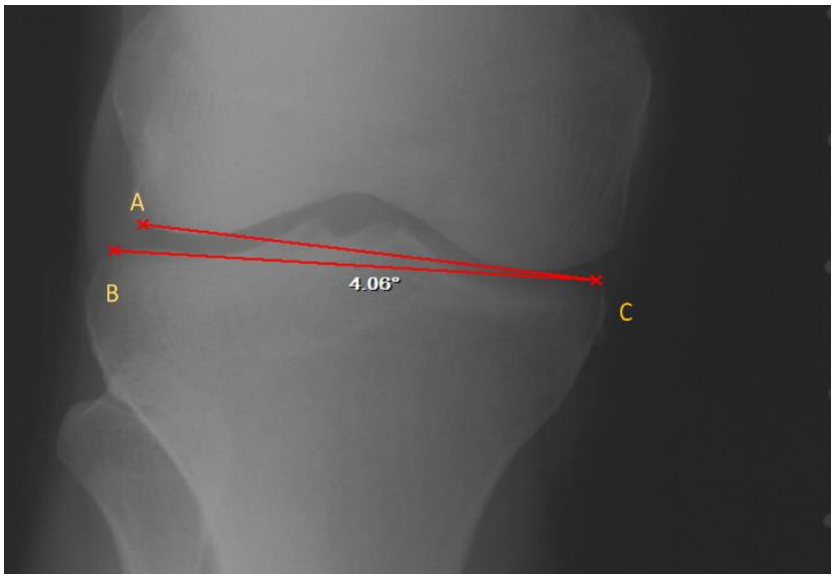

Figure 35. Condylar plateau angle

The CPA (condylar plateau angle) is the angle between the bony outline of the tibia and femur respectively, at the knee joint.

Method - A straight line is drawn along the two lowest points of the medial and lateral distal femoral condyles and along the highest points of the medial and lateral proximal tibial plateaus as shown in Figure 35. The angle formed where these two lines meet (ACB) is the Condylar plateau angle (Cooke et al., 1997).

9. Distal femoral tilt

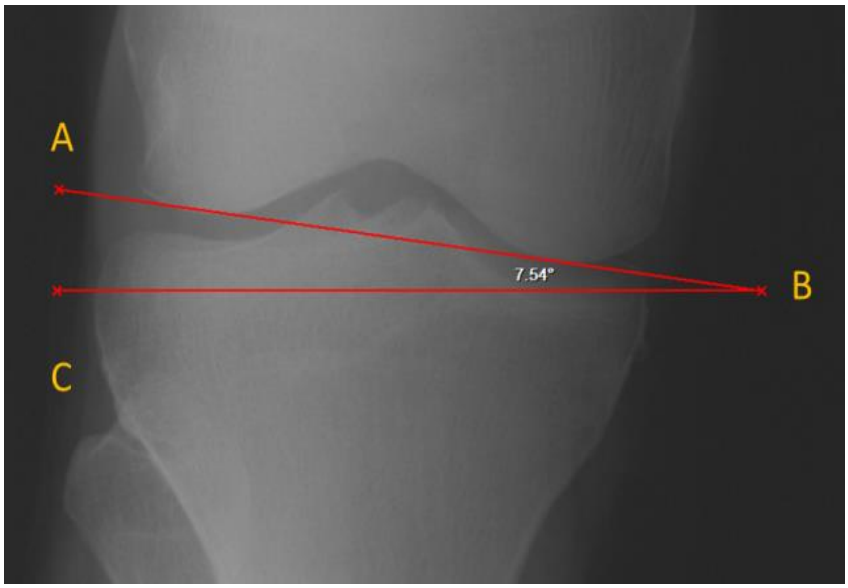

Figure 36. Distal femoral tilt

Distal femoral tilt denotes the tilt of the distal femur.

Method - A straight line (AB in Figure 36) is drawn along the lowest points of the medial and lateral distal femoral condyles. A horizontal line parallel to the lowest margin of the radiograph drawn and brought up from below till it meets point B. The angle formed where these two lines meet is the distal femoral tilt angle (angle ABC in Figure 36).

10. Proximal tibial tilt

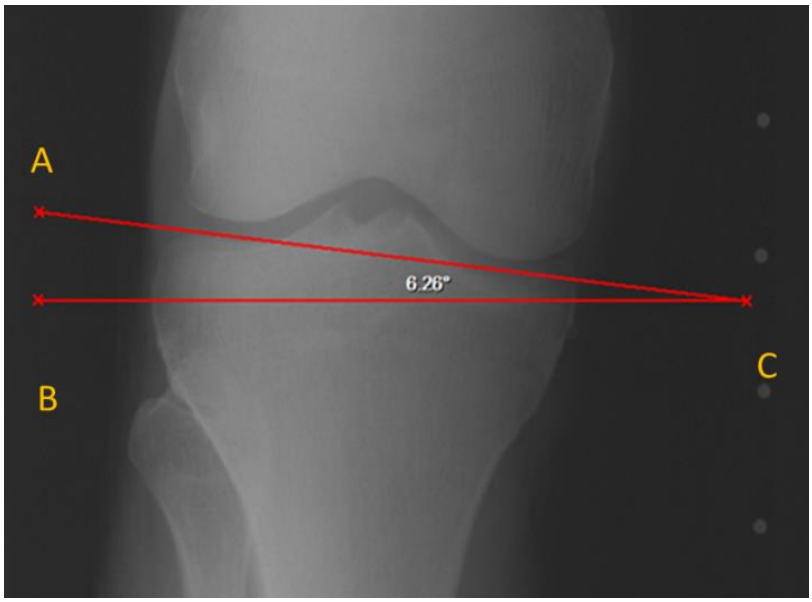

Figure 37. Proximal tibial tilt

Proximal tibial tilt denotes the tilt of the proximal tibia.

Method - A straight line (AC in Figure 37) is drawn along the highest points of the medial and lateral plateaus of the proximal tibia. A horizontal line parallel to the lowest margin of the radiograph is drawn, touching the lower end of the first line. The angle formed where these two lines meet gives the proximal tibial tilt angle (ACB in Figure 37).

If the angle opens laterally it denotes a medial tilt of the tibia and if it opens medially it denotes a lateral tilt.

11.Varus or valgus alignment

Frontal plane knee alignment should ideally be measured by mechanical axis, since it is the gold standard method of knee alignment assessment (Figure 38). Mechanical axis is the formed by a line from the centre of the femoral head to the tibial spine centre and from the centre of tibial spines to the midpoint of the talus at the ankle joint (Moreland et al., 1987).Frontal plane knee malalignment can be assessed using radiographs that include at least 10 cm of the femoral shaft and 10 cm of the tibial shaft. This is called the anatomic axis, and the mechanical axis can be estimated from it as described by Krause et al (Kraus et al., 2005).

Method

A line from the midpoint of the femoral shaft 10 cm from the knee joint was joined with a line from the midpoint of tibial shaft 10cm from the knee joint to the centre of tibial spines (Kraus et al., 2005).

Mechanical axis was calculated from the anatomic axis using the following formulae (Kraus et al., 2005).

AP view: Mechanical axis = (anatomic axis)*0.67 + 55.86

PA view: mechanical axis = (anatomic axis)*0.69 + 53.6.

These formulae show the relationship of the mechanical axis angle and anatomic axis, which was determined using regression analysis (Kraus et al., 2005).

Definition of varus and valgus knee alignment in this study

Varus was defined as knees >2^0 less than neutral using mechanical axis (180^0)

Valgus was defined as knees >2^0 more than neutral using mechanical axis (180^0).

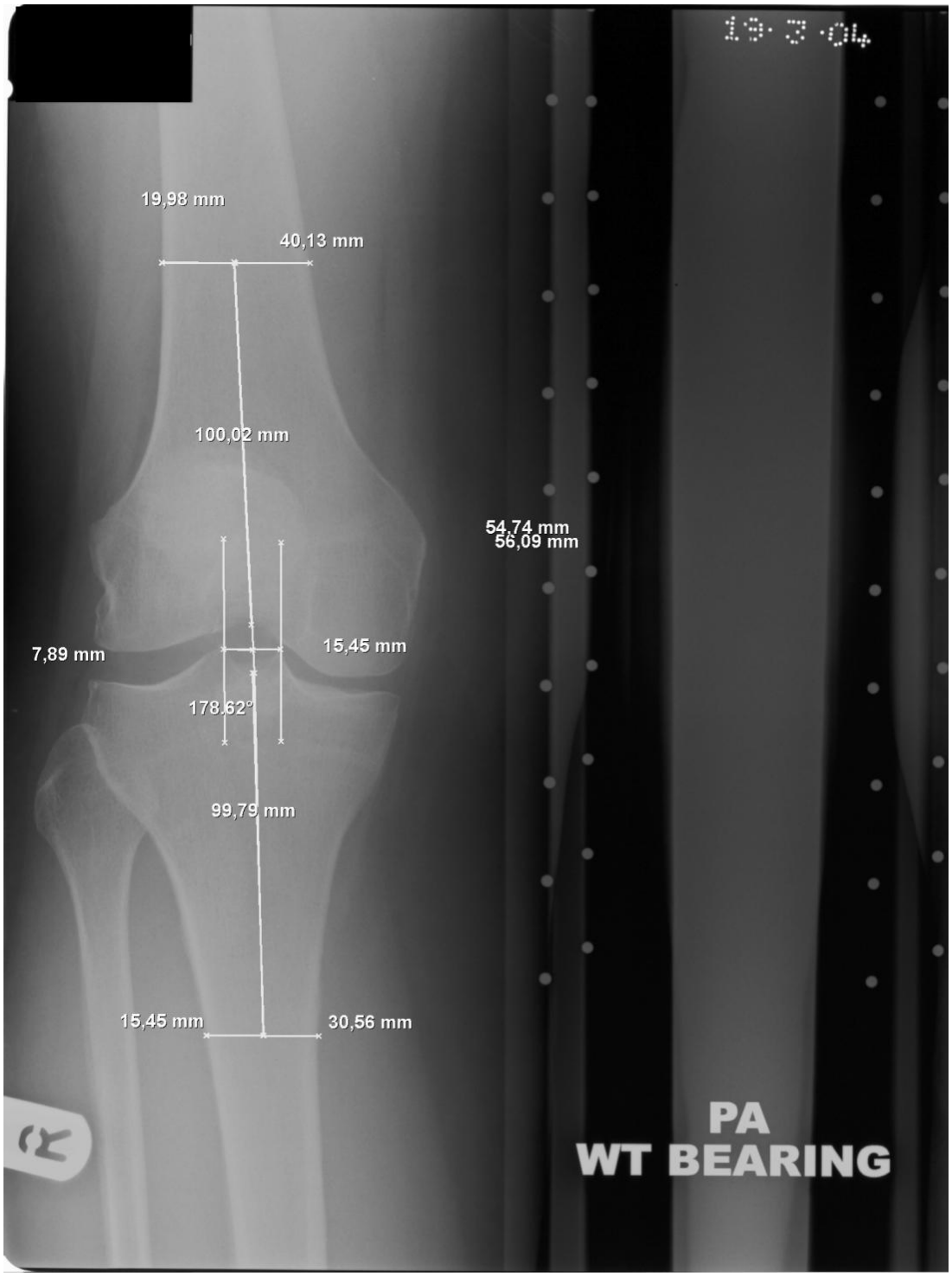

Figure 38. Illustration of method for measuring radiographic frontal plane knee alignment
Source: (Abhishek et al., 2012)

2.6.4 Statistical analysis

1. Descriptive analysis

Mean (SD) and n (%) were used for descriptive purposes. One way ANOVA, and independent sample T-test was used for continuous data and Chi-square test was used for dichotomous and categorical data for descriptive analysis.

2. Measurement of reproducibility

Intra-observer reproducibility of all morphological measurements was determined by re-measuring a random sample of 20 knee radiographs, 10 from the right and left knee respectively. The observer was blinded to the initial scores. As all the 12 measures provided continuous data, the intra-class correlation coefficient (ICC) was used to assess reproducibility. Two way random model with absolute agreement was used to determine reliability. This was used because the same rater is performing the test at two time points and also because this model is suitable for rater-based clinical methods (Koo and Li, 2016). The intra-rater reliability of measurements were undertaken on three different occasions at the beginning, middle and at the end of the measurements.

This was done to assess the overall reproducibility during the entire period of data collection rather than selecting just at the early phase, when the observer had the least experience, or the last phase of study, when despite more experience, assessment may potentially be less precise due to observer tiredness or poorer concentration.

3. Symmetry of the measurements

All the measurements in the normal control group were examined for right-left symmetry. The symmetry of the measurements were examined in two steps. First a paired t test was used to examine whether there was a statistically significant differences between the left and right sides. The mean difference (and 95% confidence interval) between the two sides were also calculated for each measurement.

As a second step, the Minimal Detectable Change (MDC) test was calculated. The MDC is defined as the minimum change that is required to distinguish true change from a change due to variability in performance or error in measurement (Nair et al., 2012).

The MDC was calculated by multiplying the standard error of the measurement (SEM) by the z score associated with either 90% or 95% confidence level and the square root of 2. Thus,

MDC = z-score x SEM x square root of 2.

The SEM measures the amount of error in the measurement. The SEM was calculated using the formula: $SEM=s\sqrt{(1 - r)}$, where, s is the standard deviation (SD) of first and second measurements and r is the intra-class correlation coefficient (ICC) (Wu et al., 2011).

ICC was determined using 2-way random model with an absolute agreement coefficient.

The MDC can be calculated based on 95% confidence interval (CI; z=1.96) or on 90% CI (z=1.65) (Nair et al., 2012). The percentage of CI is selected depending on the precision needed for the score estimate. However, MDC_{90} is commonly used (Wu et al., 2011). The criteria for symmetry in this study was that the mean difference between the left and right sides should be less than the MDC_{90}.

4. Correlation between morphological features

The correlation between 14 morphological measurements was examined with Pearson correlation. Correlation coefficient (r) and p values were calculated.

The cut offs used for interpretation of the correlation results is shown in Table 12

Table 12. Correlation between morphological features

Size of Correlation	Interpretation
0.90 to 1.00 (−0.90 to −1.00)	Very high positive (or negative) correlation
0.70 to 0.90 (−0.70 to −0.90)	High positive (or negative) correlation
0.50 to 0.70 (−0.50 to −0.70)	Moderate positive (or negative) correlation
0.30 to 0.50 (−0.30 to −0.50)	Low positive (or negative) correlation
0.00 to 0.30 (0.00 to −0.30)	negligible correlation

Source: (Koo and Li, 2016)

5. Association between morphological features and patient characteristics

The association between patient characteristics such as age, gender, height and weight and morphological measurements were examined in the normal control group.

Univariate association between risk factors of OA such as age, gender, height, weight and the measurements were determined using linear regression. The β-coefficient, p values and 95% CI were estimated. Linear regression was used since it is the ideal option to determine the association between the dependent and independent variable and also because all variables were continuous. Multivariate analysis adjusted for age, gender, height and weight was performed, β-coefficient, P values and 95% CI were estimated.

6. Association between morphological features and knee OA

Logistic regression was used to determine the association between morphological features and knee OA. The unaffected knees of the cases were compared to the same side of the controls.

For this analysis, the knee OA group was classified into knee OA (defined as OA in either PFJ or TFJ), and PFJ OA (defined as OA in only the PFJ) or TFJOA (defined as OA only in the TFJ) for sub-group analyses. Results were presented as unadjusted odds ratio (OR), adjusted OR and 95% CI.

Following this step, morphological features that had significant association were assessed for their correlation with each other, and significantly correlated measurements were replaced sequentially. A final multivariate analysis was performed for all significant feature to adjust for confounding due to age, gender, height and weight. Adjusted OR and 95%CI were presented for knee OA, PFJ OA and TFJ OA.

Bonferroni corrected statistical significance of $p<0.003$ was set for all the analysis. This was calculated by dividing *p*-value with 13, the number of measurements investigated in this study. Adjusted p values were calculated by the formulae $a'=1-(1-a)^{1/k}$. Where a'=Bonferroni correction, a=critical p value and k=number of test.

7. Cumulative risk analysis

The disease prediction ability of the morphological features as a composite function was determined using receiver operating characteristics (ROC) curves.

The ROC curve is an effective method that measures the performance of a diagnostic test. It uses a plot of test sensitivity as the y coordinate versus its 1-specificity or false postive rate as the X co-ordinate. Area under the curve (AUC) measures the accuracy of the test (Kumar and Indrayan, 2011). The guide for classifying the AUC is shown in Table 13.

Table 13. Guide for interpretation of AUC

AUC	Interpretation
0.90-1	Excellent
0.80-0.90	Good
0.70-0.80	Fair
0.60-0.70	Poor
0.50-0.60	Fail

AUC-area under the curve

Source : (Kumar and Indrayan, 2011)

Three separate ROC curves were determined with knee OA, PFJ OA and TFJ OA as the outcome. The exposure variables used for each of the above outcomes were:(1) morphological features that were significantly associated in the multivariate analysis combined with *a priori* selected patient characteristics (age, gender, height and weight); and (2) a *priori* selected patient characteristics alone. This was done in order to identify the best model of disease prediction. AUC and 95%CI for each group were presented. Data management and statistical analysis was conducted using STATA version 15.

8. Association of significantly associated morphological features with WOMAC pain score

Morphological features that were significantly associated with Knee OA, PFJOA or TFJOA were assessed to determine whether they were associated with increasing severity of WOMAC knee pain score.

WOMAC is a self-administered health status measure that assesses the dimensions of pain, stiffness and function (either separately or as an overall index) in patients with OA of the hip or knee (Woolacott et al., 2012). Under each dimension there are a number of questions designed to assess the clinical severity of the disease (5 questions for pain, 2 questions for stiffness and 17 questions for physical function) (Woolacott et al., 2012). The five pain questions consist of pain experienced during five different activities, specifically walking on a flat surface, going up or down stairs, at night while in bed, sitting or lying, and standing upright. The patient's response to each question produces a score that is then summed to calculate an aggregated score for the pain dimension. This summated pain score was used for the analysis.

Morphological features of the structurally normal case knees were compared to the WOMAC pain score that would be driven predominantly by disease in the contralateral knee. Linear regression was used in this analysis. Multivariate analysis adjusted for age, gender, height and weight and each of the morphological features were performed, and β-coefficient, P values and 95% CI were estimated.

9. Association of significantly associated morphological features with osteophyte and joint space narrowing

Morphological features that were significantly associated with Knee OA, TFJ OA and PFJ OA respectively were selected to examine their association with summated osteophyte and summated JSN scores using the NLDA. For this the morphological features were assessed in the structurally normal knees of the OA group and the osteophyte scores and JSN scores were assessed in the contralateral knee with structural changes of OA. Linear regression was used to examine association. Separate analysis of PF measurements with PFJ structural changes and TF measurements with TFJ structural changes were also carried out. Multivariate analysis adjusted for age, gender, height and weight and each of the morphological features were performed, and β-coefficient, p values and 95% CI were calculated.

10. Association of significantly associated morphological features with Kellgren Lawrence scores.

Morphological features that were significantly associated with Knee OA, TFJ OA and PFJ OA respectively were selected to examine their association with KL score. For this, the morphological features were assessed in the structurally normal knees of the case group and the KL scores were assessed in the contralateral knee with structural changes of OA. Linear regression was used to examine association. Association between PFJ measurements and PFJ KL score, and TF measurement with TFJ KL score were examined. Multivariate analysis adjusted for age, gender, height and weight and each of the morphological features were performed, and β-coefficient, p values and 95% CI were calculated.

11. Association of significant morphological features with progression of pain.

This analysis was restricted to participants in the control group i.e. without radiographic knee OA and without knee pain at the time of the baseline visit. Morphological features that significantly associated with knee OA, TFJ OA or PFJ OA were examined to determine whether they are associated with progression of knee pain over time. For this, the 12 year follow up data of the GOAL study was used (Warner et al., 2017). In this study, participants of the GOAL study were sent a questionnaire survey and 1151 replies were received. They answered the following question about knee pain: (1) "Have you ever had pain in or around the knee on most days for at least a month? If so, have you experienced any pain during the last year?"; (2) "Have you had pain within the last year in or around the knee that occurred on most days for at least a month?"; and (3) "Have you had knee pain on most days of the last month?" The answer to the third question was used to ascertain the presence of pain for the purpose of this study. The severity of pain was rated using a 10 cm visual analogue scale (VAS). A score of 60 or higher was considered high pain The dichotomous variable (high or low pain) was used as the outcome variable. Logistic regression was used to determine the association between morphological features and presence of severe pain at follow-up. Results were presented as unadjusted odds ratio (OR), adjusted OR and 95% CI.

Chapter 3 RESULTS

3.1 Participants, demographic characteristics and reproducibility of measurements

3.1.1 Study participants

An overview of participants in the GOAL study and the present study is presented in Figure 26 (Chapter 2 Methods)

There were 723 participants in this study. In the present study, controls were participants with bilateral normal knees, defined as having no knee pain and no radiographic features of OA as per the NLDLDA (JSN score <1, Osteophyte score =<1). Cases were the normal knees of people with unilateral knee OA.

3.1.2 Demographic characteristics

The demographic characteristics of cases and controls are summarized in Table 14. In the control group, 54% of the population were women, whereas 59% of the case population were women. This was statistically significant (p=0.03). The participants of the case group were statistically significantly older than control group participants, however, this difference was relatively modest (mean difference =2.00; 95%CI 1.90 to 2.95 years). Height and weight were not significantly different in the two groups but participants in the case group had a significantly higher mean BMI than the controls (mean difference=2.30; 95%CI 0.95,0 3.65 kg/m^2).

Table 14. Demographic characteristics of cases and controls

	Controls (n=408)	Cases (n=315)	p value
Age (years) Mean (SD)	62.10 (8.57)	64.0 (8.6)	<0.001
Weigh t(kg) Mean (SD)	76.95(15.72)	78.3 (14.41)	0.41
Height (cm) Mean (SD)	167.57(11.10)	166.7(14.20)	0.31
BMI (kg/m2) Mean (SD)	27.8 (10.65)	30.1(20.08)	0.01
Gender (female n%)	54%	59%	0.03

SD standard deviation

3.1.3 Reproducibility of morphological measurements

Reproducibility of the measurements was assessed at the beginning, in the middle, and at the end of the study. There was excellent agreement between the two readings of the same observer at these three time points with an ICC ranging from 0.82-0.94 for all morphological measurements. The results of the intra-rater reliability are shown in Table 15.

There was excellent intra-rater agreement between knee malalignment measurements which was undertaken by Abhishek et al and ICC results were as the following 1st set 0.98 (95% CI, 0.95, 0.99), 0.96(95%CI 0.89-0.98), 0.99 (95% CI 0.97-1.00) (Abhishek et al., 2012).

Table 15. Reproducibility of measurements performed at three time points during the study

Measurements	ICC first	95%CI		ICC second	95%-	CI	ICC third	95%	CI	Mean ICC
Sulcus angle[1]	0.85	0.39-	0.96	0.92	0.30-	0.98	0.96	0.46-	0.99	0.91
Patellar angle[1]	0.90	0.67-	0.97	0.84	0.62-	0.94	0.77	0.01-	0.94	0.83
Condylar angle[1]	0.74	0.18-	0.93	0.9	0.77-	0.94	0.85	0.30-	0.96	0.83
Patellar thickness[1]	0.96	0.85-	0.99	0.77	0.35-	0.93	0.98	0.92-	0.99	0.91
Patellar width[1]	0.92	0.73-	0.98	0.8	0.40-	0.94	0.96	0.84-	0.99	0.89
Medial condylar height[1]	0.95	0.83-	0.99	0.88	0.61-	0.96	0.76	0.03-	0.94	0.86
Lateral condylar height[1]	0.72	0.22-	0.92	0.92	0.74-	0.98	0.83	0.36-	0.95	0.82
Condylar width[1]	0.98	0.94-	0.99	0.85	0.52-	0.96	0.99	0.97-	0.99	0.94
Intercondylar width[1]	0.98	0.92-	0.99	0.99	0.96-	0.99	0.71	0.41-	0.87	0.89
Condylar plateau angle[1]	0.99	0.97-	0.99	0.74	0.29-	0.92	0.77	0.01-	0.94	0.83
Distal femoral tilt[1]	0.96	0.85-	0.99	0.7	0.19-	0.91	0.98	0.92-	0.99	0.88
Proximal tibial tilt[1]	0.89	0.61-	0.97	0.84	0.48-	0.95	0.94	0.76-	0.98	0.89

ICC-Intra-class correlation; 95%CI-95%confidence interval 1 All angles measured in degrees, and all distances in millimetres

3.2 Morphological measurements in controls

3.2.1 Symmetry of the morphological measurements

The symmetry of the morphological measurements was determined using paired t-test and minimal detectable change test (MDC). The results of the paired t-test in Table 16 show that the mean differences between left and right sides for most of the measurements were not statistically significant. There were significant differences in condylar plateau angle ($p<0.001$), condylar width ($p<0.001$), patellar width ($p<0.001$) and sulcus angle ($p<0.001$) even after Bonferroni correction. However, the magnitude of these differences were small (Table 17), and was less than the minimum detectable change (MDC) on each side (Table 17). Taken together these findings suggest that morphological measurements are symmetrical between the left and right side in individuals without knee OA.

Table 16. Results of paired t-test performed between left and right sides to assess symmetry

Measurements	Right Knee Mean (SD)	Left Knee Mean (SD)	Mean difference	*p value*
Sulcus angle[1]	141.47 (5.32)	142.5 (5.39)	1.07	<0.001
Patella angle[1]	135.27(6.34)	135.3(6.8)	0.03	0.89
Condylar angle[1]	14.01(9.15)	14.88(2.8)	0.87	0.05
Patella thickness[1]	23.19(3.11)	23.36(2.6)	0.16	0.18
Patella width[1]	49.04(6.45)	48.2 (6.07)	-0.76	<0.001
Condylar height lateral[1]	7.11(1.70)	6.8(1.41)	-0.24	0.26
Condylar height medial[1]	8.82(1.95)	9.05(2.2)	0.22	0.31
Condylar width[1]	65.77(6.72)	65.05(7.0)	-0.71	<0.001
Intercondylar width[1]	46.63(5.70)	46.4(5.25)	-0.20	0.18
Condylar Plateau angle[1]	5.42(0.93)	5.63(1.00)	0.21	<0.001
Distal femoral tilt[1]	2.73(1.51)	2.60(1.57)	-0.12	0.08
Proximal tibial tilt[1]	2.35(1.03)	2.51(1.13)	0.16	0.12
Varus valgus alignment[1]	179.83(1.25)	179.89(1.26)	-0.06	0.2

SD-standard deviation [1]All angles measured in degrees, and all distances in millimetres

Table 17. Tests for symmetry using minimal detectable change

Measurements	Mean difference between right and left knee measurements	MDC 90% level Left knee	MDC 90% level Right knee
Sulcus angle[1]	1.07	3.25	3.14
Patella angle[1]	0.03	3.84	3.16
Condylar angle[1]	0.87	3.36	3.84
Patella thickness[1]	0.16	3.70	3.15
Patella width[1]	-0.76	3.80	3.72
Condylar height lateral[1]	-0.24	1.64	2.70
condylar height medial[1]	0.22	2.86	3.05
Condylar width[1]	-0.71	3.35	2.82
Intercondylar width[1]	-0.20	3.01	1.81
Condylar plateau angle[1]	0.21	0.88	1.23
Distal femoral tilt[1]	-0.12	3.39	3.37
Proximal tibial tilt[1]	0.16	2.04	1.81

MDC- Minimal detectable change, [1]All angles measured in degrees, and all distances in millimetres; Symmetrical if mean difference < MDC in left and right knee

3.2.2 Correlation between morphological measurements

Table 18 shows the correlation between the morphological measurements.

Anatomically related morphological features such as condylar width and intercondylar width were highly correlated with each other ($r=0.78$; $p<0.001$). Similarly, as expected, patellar thickness and patellar width correlated with each other ($r=0.55$; $p<0.001$). Condylar width moderately correlated with patellar thickness ($r=0.54$; $p<0.001$) and patellar width ($r=0.59$, $p<0.001$).

Patellar angle and sulcus angle showed low positive correlation, ($r=0.45$, $p<0.001$). Similarly proximal tibial tilt and distal femoral tilt had a moderate correlation ($r= 0.42$; $p<0.001$).

In general, PFJ measurements such as sulcus angle, condylar angle, patellar width, patellar width correlated with each other. Intercondylar width correlated negatively with measurements at TFJ such as condylar plateau angle, distal femoral tilt, and proximal tibial tilt and varus valgus measures.

Table 18. Correlation coefficient between morphological features: data for the right knee

	Sulcus angle	Patellar angle	Condylar angle	Patellar thickness	Patellar Width	Condylar height medial	Condylar height lateral	Condylar width	Inter condylar width	Condylar plateau angle	Distal femoral tilt	Proximal tibial tilt	Varus valgus
Sulcus angle(r)	1.00												
Patellar angle(r)	0.45*	1.00											
Condylar angle(r)	-0.08*	-0.06	1.00										
Patellar thickness (r)	0.003	0.03	0.05	1.00									
Patellar width(r)	0.15*	0.27*	-0.01	0.55[1]	1.0								
Condylar height media(r)	-0.21	0.00	0.04	0.20*	0.15*	1.00							
Condylar height lateral(r)	-0.44*	-0.16*	0.16*	0.17*	0.13	-0.02	1.00						
Condylar width(r)	-0.02	0.13	-0.01	0.54[1]	0.59[1]	0.03	0.26	1.0					
Intercondylar width(r)	0.13*	0.24*	0.04	0.58*[1]	0.69*[1]	0.23*[1]	0.12*	0.78*[1]	1.0				
Condylar plateau angle(r)	-0.05	-0.004	0.09*	-0.05	-0.07	-0.02	-0.01	-0.08*	-0.03	1.00			
Distal femoral tilt(r)	-0.04	-0.06	-0.10*	0.04	-0.01	0.01	-0.01	-0.00	-0.03	0.15*	1		
Proximal tibial tilt(r)	-0.06	0.00	-0.07	-0.01	0.03	-0.00	-0.02	0.04	-0.004	0.06	0.42*[1]	1.0	
Varus valgus(r)	-0.05	-0.03	-0.01	0.01	-0.03	-0.04	-0.05	0.01	-0.01	-0.13*	-0.05	-0.11	1

**-significant p value at p<0.05 1: Measurements which were moderately to highly correlated; r-pearson coefficient*

3.3.3. Association of tibio femoral morphological features and demographic characteristics

Table 20 shows the association of TFJ morphological features with participant characteristics. Of the three angular measurements, condylar plateau angle [βcoef =-0.02; 95%CI -0.03, -0.004)] and distal femoral tilt [βcoef =0.03; (95%CI -0.05,-0.01)] were negatively associated with age after adjusting for other covariates. The distal femoral tilt angle became smaller by 0.03^0 for every year increase in age. Similarly, condylar plateau angle decreased by 0.02^0 with increasing age. However, after Bonferroni correction only distal femoral tilt remained significantly associated with age ($p<0.003$). Valgus malalignment associated with increasing age, however, it was not statistically significant on adjusting for multiple tests.

Varus alignment (11%) was more common in men than in women (5%) $p<0.001$, but there was no statistically significant difference in valgus alignment between men and women. Varus knees showed an initial association with gender [βcoef =-0.05; (95%CI -0.08, -0.01)], however when adjusted for confounders the initial association became non-significant.

Condylar plateau angle was negatively associated with weight [βcoef=-0.004 (95%CI -0.012, -0.003], the angle becoming smaller by 0.004^0 for each kg increase in weight. Similarly, weight associated positively with varus malalignment. However, these associations became non-significant after correcting for multiple testing.

Height was negatively associated with the condylar plateau measurement [βcoef=-0.01(95%CI -0.03,-0.001], the angle decreasing by 0.01^0 for every cm increase in height. However, this was not significant after Bonferroni correction.

In summary, TFJ measurements do not change with age, sex, height or weight with the single notable exception of distal femoral tilt increasing with age.

Table 19. Association of TFJ measurements and participant characteristics

	β-coef (95%CI)	*p* value	β-coef adjusted(95%CI)*	*p* value	*Adjusted p values*
Age					
Condylar plateau angle[1]	-0.01(-0.03,-002)	0.01	-0.02(-0.03,-0.004)	0.03	0.004
Distal femoral tilt[1]	-0.03(-0.05,-0.01)	<0.001[2]	-0.03(-0.05, -0.01)	<0.001[2]	<0.001[2]
Proximal tibial tilt[1]	0.004(-0.01,.01)	1	0.002(-0.01,0.02)	1	1
Varus knees[1]	002(-0.00,0.004)	0.08	0.001(-0.0007, 0.003)	0.22	0.02
Valgus knees[1]	-0.002(-0.003, -0.0001)	0.04	-0.002(-0.004, -0.0005)	0.03	0.004
Gender(Female)					
Condylar plateau angle[1]	0.12(-0.10,0.32)	0.24	-0.24(-0.52, 0.05)	0.10	0.008
Distal femoral tilt[1]	-0.10(-0.40, 0.23)	1	-0.4(-0.8, 0.06)	1	1
Proximal tibial tilt[1]	-0.13(-0.37,0.10)	0.30	-0.2(-0.5,0.12)	0.40	0.04
Varus knees[1]	-0.05(-0.08, -0.01)	<0.001[2]	-0.03(-0.08, 0.01)	0.15	0.01
Valgus knees[1]	-0.01(-0.04,0.02)	0.32	-0.04(-0.08, 0.005)	0.08	0.006
Weight					
Condylar plateau[1]	-0.01(-0.01, -0.0001)	0.04	-0.004(-0.012,0.003)	0.06	0.005
Distal femoral tilt[1]	-0.01(-0.02,0.001)	0.01	-0.01(-0.02,-0.003)	0.20	0.02
Proximal tibial tilt[1]	0.003(-0.003,0.01)	0.31	0.004(-0.01,.01)	0.51	0.06
Varus knees[1]	0.001(0.00,0.02)	<0.001[2]	0.002(0.0002.0.003)	0.023	0.004
Valgus knees[1]	0.0005(-0.0004, 0.002)	0.28	0.0003(-0.0008,0.002)	0.61	0.07
Height					
Condylar plateau[1]	-0.01(-0.02, -0.001)	0.04	-0.01(-0.03,-0.001)	0.03	0.004
Distal femoral tilt[1]	-0.01(-0.03,0.003)	0.12	-0.01(-0.21,0.003)	0.20	0.02
Proximal tibial tilt[1]	0.003(-0.01,0.01)	1	-0.01(-0.03,0.01)	0.45	0.05
Varus knees[1]	0.00(-0.0009,0.002)	0.51	-0.0005(-0.002,0.001	0.59	0.06
Valgus knees[1]	0.0002(-0.001, 0.002)	0.67	-0.001(-0.003, 0.0009)	0.31	0.03

**-adjusted for- age, gender, height, weight; All angles measured in degrees; [2] significant after Bonferroni correction*

3.4.3. Association between patello-femoral joint measurements

Association of PFJ measurements and age is shown in Table 21. Of the angular measurements at the PFJ, only patellar angle showed an association with age [βcoef=0.10 (95%CI 0.01, 0.2); p=0.03]. As the age of the participants increased, patellar angle became wider by $0.10mm^0$ for each year increase in age. However, this was not statistically significant after correcting for multiple testing.

Of the linear measurements, patellar thickness had a positive association with age [βcoef=0.01(95%CI 0.04, 0.31; p<0.001)] which was significant after correcting for multiple tests. The linear measurements such as patellar width, condylar height medial, condylar width and intercondylar height showed an initial association with age on univariate analysis. However, this become non-significant when adjusted for gender, weight and height.

Table 20. Association of PFJ measurements and age

Measurements	β-coef (95%CI)	*p* value	β-coef adjusted (95%CI)*	*p* value	*Adjusted p values*
Sulcus angle[1]	0.04(-0.02,0.10)	0.20	0.03(-0.04,0.12)	0.40	0.04
Patellar angle[1]	0.11(0.04,0.2)	<0.001[2]	0.10(0.01,0.20)	0.03	0.004
Condylar angle[1]	0.004(-0.04,0.031)	1	0.01(-0.04,0.31)	1	1
Patellar width[1]	0.12(0.04,0.21)	<0.001[2]	0.02(-0.04,0.1)	1	1
Patellar thickness[1]	0.1(0.03,0.10)	<0.001[2]	0.01(0.04,0.32)	<0.001[2]	<0.001[2]
Condylar height medial[1]	0.05(0.01,0.11)	0.03	0.1(-0.002,0.10)	0.10	0.01
Condylar height lateral[1]	0.01(-0.02,0.03)	1	-0.01(-0.4,01)	1	1
Condylar width[1]	0.2(0.10,0.23)	<0.001[2]	0.1(-0.01,0.1)	0.11	0.01
Inter Condylar width[1]	0.13(0.11,0.2)	<0.001[2]	0.1(0.003,0.1)	0.12	0.009

**-adjusted for gender, weight, height [1] All angles measured in degrees, and all distances in millimetres; [2] significant after Bonferroni correction*

3.4.4 Association between patello-femoral joint measurements and gender

Table 21 shows the association of PF morphological features with gender in the normal knees.

Patellar angle had a negative association with female gender [βcoef=-1.85 (95%CI -2.65, -1.05); p=0.03] but this association was not significant after Bonferroni correction.

Among the linear measurements, patellar width (95%CI -4, -0.93; p<0.001), condylar width (95%CI -6.74,-3.43; p<0.001) and intercondylar width (95%CI -4.5,-2.15; p<0.001) showed a negative association with female gender. The βcoef of these measurements ranged from -2.5 to -5.1 (p<0.001), which remained statistically significant even after correction for multiple testing.

Table 21. Association between PFJ measurements and gender

Measurements	β-coef (95%CI)	*p* value	β-coef adjusted(95%CI)*	*p* value	Adjusted p values
Sulcus angle[1]	-0.9(-2,0.14)	1	-0.5(-2.0,1.1)	0.5	0.05
Patellar angle[1]	1.6(-2.9,-0.33)	<0.001[2]	1.85(-2.65,-1.05)	0.03	0.004
Condylar angle[1]	0.05(-0.52,0.63)	0.9	1(-1.6,3.6)	1	1
Patellar width[1]	5(-6.21,-3.92)	<0.001[2]	-2.5(-4,-0.93)	<0.001[2]	<0.001[2]
Patellar thickness[1]	-2.43(-2.95,-1.91)	<0.001[2]	-0.52(-1.2,0.2)	0.14	0.01
Condylar height medial[1]	0.84(-1.6, 0.001)	0.05	-0.2(-1.4,1.01)	0.10	0.01
Condylar height medial[1]	0.75(-1.18,-0.3)	<0.001[2]	-0.41(-1.0,0.2)	0.21	0.02
Condylar width[1]	8.3(-9.31,-6.95)	<0.001[2]	-5.1(-6.74,-3.43)	<0.001[2]	<0.001[2]
Inter Condylar width[1]	-6.2(-7.1,-5.4)	<0.001[2]	-3.33(-4.5,-2.15)	<0.001[2]	<0.001[2]

**-adjusted for age, gender, weight, height; [1] All angles measured in degrees, and all distances in millimetres;[2] significant after Bonferroni correction*

3.4.5. Association between patello-femoral measurements and weight

Table 22. Association between patello-femoral measurements and weight

Measurements	β-coef (95%CI)	*p* value	β-coef adjusted (95%CI)*	*p* value	*Adjusted p value*
Sulcus angle[1]	0.02(-0.01,0.05)	0.21	0.02(-0.02,.06)	1	1
Patellar angle[1]	0.05(0.01.0.1)	0.01	0.04(-0.004,0.1)	0.12	0.009
Condylar angle[1]	-0.01(-0.03.0.10)	0.45	-0.01(-0.03,0.01)	0.40	0.04
Patellar width[1]	0.12(0.11,0.15)	<0.001[2]	0.05(0.01,0.0.6)	<0.001[2]	<0.001[2]
Patellar thickness[1]	0.05(0.03,0.0.1)	<0.001[2]	0.003(-0.02,.02)	1	1
Condylar height medial[1]	0.02(-0.003,01)	0.11	0.02(-0.02,0.05)	0.32	0.03
Condylar height lateral[1]	0.01(-0.01,0.2)	0.32	-0.02(-03,.002)	0.11	0.01
Condylar width[1]	0.2(0.14,0.22)	<0.001[2]	0.1(0.01, 0.10)	0.06	0.02
Inter Condylar width[1]	0.14(0.11,0.17)	<0.001[2]	0.12(0.11,14)	<0.001[2]	<0.001[2]

**adjusted for age, gender and height. [1] All angles measured in degrees, and all distances in millimetres [2] significant after Bonferroni correction*

Table 22 shows association of morphological features at the PFJ and weight.

Patellar width and Intercondylar width remained positively associated with weight. As weight increased the intercondylar width (95%CI 0.11, 0.14; p<0.001) increased by 0.12 mm. These associations remained significant after correcting for multiple testing

3.4.6. Association between patello-femoral measurements and height

Table 23 shows the association of morphological features at the PFJ and height.

Patellar thickness (95%CI 0.13, 0.25; p<0.001) and intercondylar width (95%CI 0.10, 0.24; p<0.001) had a positive association with height. These measurements increased by 0.2mm as the height of the participants increased. Similarly, as the height of the participants increased patellar width (95%CI 0.3, 0.42; p<0.001) and condylar width (95%CI 0.14, 0.24); p<0.001) also increased by 0.4 mm and 0.15 mm respectively. These measurements remained statistically significant even after Bonferroni correction.

Table 23. Association between PFJ measurements and height

Measurements	β-coef unadjusted(95%CI)	*p* value	β-coef adjusted(95%CI)*	*p* value	*Adjusted p values*
Sulcus angle[1]	0.04(-0.01,0.1)	0.14	0.05(-0.01,0.1)	0.1	0.007
Patellar angle[1]	0.1(0.01,0.16)	0.03	0.04(-0.03,0.11)	0.23	0.02
Condylar angle[1]	-0.002(-0.04,0.03)	0.90	0.01(-0.04,0.1)	1	1
Patellar width[1]	0.3(0.24,0.36)	<0.001[2]	0.4(0.31,0.42)	<0.001[2]	<0.001[2]
Patellar thickness[1]	0.16(0.13,0.2)	<0.001[2]	0.2(0.13,0.25)	<0.001[2]	<0.001[2]
Condylar height medial[1]	0.4(-0.004,0.1)	0.13	0.01(-0.07,0.1)	0.11	0.008
Condylar height lateral[1]	0.05(0.02,0.1)	12	0.04(0.01,0.1)	0.20	0.02
Condylar width[1]	0.42(0.36,0.48)	<0.001[2]	0.15(0.14, 0.24)	<0.001[2]	<0.001[2]
Inter Condylar width[1]	0.34(0.29,0.39)	<0.001[2]	0.21(0.10,0.23)	<0.001[2]	<0.001[2]

**-adjusted for age, gender and height ; [1] All angles measured in degrees, and all distances in millimetres; [2] significant after Bonferroni correction*

3.4.7. Key findings

After adjusting for multiple testing and other demographic features, most measurements did not vary with age, sex, height or weight. However, there were certain notable exceptions.

Firstly, increasing age was significantly associated with increasing patellar thickness and lower distal femoral tilt. Weight had a significant positive association with patellar width and intercondylar width. Height had a significant positive association with patellar width, condylar width, patellar thickness and intercondylar width

Finally, women had a smaller patellar width, condylar width and intercondylar width compared to men.

It was of interest that none of the angles varied with age, sex, height or weight.

3.5. Morphological features of knee joints in the case group

There were 315 cases with unilateral knee OA (defined as OA in any knee compartment, i.e. JSN score>0 and osteophyte score>1 in one knee, but, no JSN or osteophytes in the other knee). TFJ OA was more common than PFJ OA. The total number of TFJ OA cases (defined as OA in only medial and/or lateral TF compartments, using the same definition of OA as above) were 185 (58%), whereas the total number of PFJ OA cases (defined as OA in only PFJ, using the same definition of OA as above) were 85 (27%). The total number of participants who had OA in both the TFJ and PFJ were 45 (14%).

3.5.1. Comparison of morphological measurements between cases and controls

Comparison of morphological measurements in the unaffected knees of the unilateral knee OA group and normal knees in the control group are shown in Table 24.

The angular measurements at the PFJ, namely the sulcus angle (mean difference= 3.09; 95%CI 0.85, 0.92, P <0.001) and condylar angle (mean difference=4.31; 95%CI 3.81, 4.80; p<0.001) were wider in the control group than in the case group. These differences remained statistically significant after Bonferroni correction.

Similarly, the linear measurements - intercondylar width and condylar width - were smaller in cases than controls by a mean of 1.4 (95%CI 0.14, 2.67; p=0.01) and 1.23

(95%CI 0.29, 2.18; p=0.03) mm respectively, and their mean difference was statistically significant. However, after correction for multiple testing, this become non-significant. The mean differences between the cases and controls were not statistically significant for patellar width, patellar thickness or condylar medial height. Lateral condylar height was the only linear measurement at the PFJ which was significantly greater in cases that controls (mean difference=0.8 mm, 95%CI 1.24,-0.48; p<0.001). This remained significant after correction for multiple testing.

Conversely, all the TFJ morphological measurements were greater in the case group than in controls. However, the mean difference was only statistically significant for proximal tibial tilt. Proximal tibial tilt was greater in cases than controls by a mean of 0.40 (95%CI -0.61,-0.2; p<0.001). In the case group 18% of the participants had varus knees, whereas only 5% of control group participants had varus knees (P<0.001). Although valgus knees were more common in cases than controls this was not statistically significant.

Table 24. Comparison of morphological features between cases and controls

Measurements	Cases Mean (SD)	Controls Mean (SD)	Mean difference (95%CI)	*p value*
Sulcus angle[1]	139.4(5.0)	142.5(5.35)	3.09(0.85, 0.92)	<0.001[2]
Patellar angle[1]	135.0(5.17)	135.3(6.78)	0.30(-0.80, 1.41)	0.51
Condylar angle[1]	10.5(2.75)	14.8(2.87)	4.31(3.81, 4.80)	<0.001[2]
Patellar thickness[1]	23.2(2.7)	23.4(2.83	0.17(-0.31, 0.66)	0.48
Patellar width[1]	47.68(5.94)	48.34(6.14)	0.66(-0.39, 1.73)	0.21
Condylar height medial[1]	6.29(1.39)	6.87(4.18)	0.57(-0.04, 1.20)	0.06
Condylar height lateral[1]	9.94(2.10)	9.08(2.20)	-0.86(-1.24, -0.48)	<0.001[2]
Condylar width[1]	63.69(7.59)	65.10(7.09)	1.41(0.14, 2.67)	0.03
Intercondylar width[1]	45.27(5.61)	46.5(5.30)	1.23(0.29, 2.18)	0.01
Condylar plateau angle[1]	5.39(1.1)	5.42(0.93)	.023(-0.17, 0.22)	0.80
Distal femoral tilt[1]	2.92(1.39)	2.70(1.50)	-0.22(-0.52, 0.07)	0.14
Proximal tibial tilt[1]	2.76(0.98)	2.35(1.03)	-0.40(-0.61, -0.2)	<0.001[2]

SD-standard deviation; [1] All angles measured in degrees, and all distances in millimetres [2] significant after Bonferroni correction

Morphological features and association with knee OA.

The association between PFJ and TFJ measurements and knee OA were examined separately. Associations were adjusted for age gender, height and weight.

3.5.2. Association between PFJ measurements and knee OA

The association between PFJ measurements and knee OA is shown in Table 25

Of the angular measurements, sulcus angle and condylar angle were both associated with knee OA. A narrow sulcus angle was associated with knee OA (aOR=0.93, 95%CI 0.89, 0.96; p<0.001). Similarly, a smaller condylar angle associated with knee OA (aOR=0.59, 95%CI 0.38, 0.51; p<0.001). These two measurements remained statistically significant even after Bonferroni correction.

There was no association between intercondylar width and knee OA on univariate analysis. However, a significant association between intercondylar width and knee OA was observed when this analysis was adjusted for confounders (aOR=0.92; 95%CI 0.88, 0.96; p<0.001).

This remained significant even after correction for multiple testing error. This suggests that, as the intercondylar width decreased the risk of developing knee OA increased.

Table 25. Association between PFJ morphological features and knee OA

Measurements	OR (95%CI)	*p value*	aOR (95%CI)*	*p value*	*Adjusted p value*
Sulcus angle[1]	0.89(0.86,0.92)	<0.001[2]	0.93(0.89,0.96)	<0.001[2]	<0.001[2]
Patellar angle[1]	0.99(0.96,1.02)	0.61	1.01(0.99,1.04)	0.50	0.05
Condylar angle[1]	0.59(0.54,0.65)	<0.001[2]	0.44(0.38,0.51)	<0.001[2]	<0.001[2]
Patellar thickness[1]	0.98(0.92,1.0)	0.05	0.93(0.86,1.0)	0.05	0.004
Patellar width[1]	0.98(0.95,1.01)	0.38	0.97(0.94,1.0)	0.14	0.01
Condylar height medial[1]	0.89(0.79,1.00)	0.05	1.15(0.02,1.3)	0.05	0.004
Condylar height lateral[1]	1.19(1.10,0.89)	<0.001[2]	0.79(0.71,1.8)	0.61	0.07
Condylar width[1]	0.98(0.95,1.0)	0.11	1.02(0.99,1.05)	0.10	0.007
Intercondylar width[1]	0.97(0.93,1.00)	0.05	0.92(0.88,0.96)	<0.001[2]	<0.001[2]

**adjusted for age, gender, weight, height. OR-odds ratio. [1] All angles measured in degrees, and all distances in millimetres. [2] significant after Bonferroni correction at p<0.003*

3.5.3. Association between TFJ measurements and knee OA

The association between TFJ measurements and knee OA is shown in Table 26

At the TFJ, distal femoral tilt and proximal tibial tilt both associated with knee OA. A wider distal femoral tilt angle associated with knee OA (OR=1.3, 95%CI 1.2, 1.5; p<0.001). Similarly, as the proximal tibial tilt became wider the risk of developing knee OA increased (OR=1.5; 95%CI 1.23, 1.78; p<0.001). These two associations remained significant even after Bonferroni correction.

Varus knees showed association with knee OA (OR=3.06, 95%CI 1.95, 4.82; p<0.001) which remained significant after Bonferroni correction at p<0.003.

Table 26. Association between TFJ measurements and knee OA

Measurements	OR (95%CI)	*p value*	aOR*(95%CI)	*p* value	*Adjusted p value*
Condylar plateau angle[1]	0.97 (0.81,1.1)	0.77	0.96 (0.80,1.2)	0.70	0.08
Distal femoral tilt[1]	1.16 (1.02,1.3)	0.01	1.3(1.2,1.5)	<0.001[2]	<0.001[2]
Proximal tibial tilt[1]	1.35 (1.15,1.60)	<0.001[2]	1.5 (1.23,1.78)	<0.001[2]	<0.001[2]
Varus knees[1]	3.20 (2.06,4.96)	<0.001[2]	3.06 (1.95,4.82)	<0.001[2]	<0.001[2]
Valgus knees[1]	1.68 (1.04, 2.69)	0.03	1.90 (1.17,3.08)	0.009	0.02

OR-odds ratio;,-adjusted for age, gender, height, weight. [1] All angles measured in degrees [2] significant after Bonferroni correction at p<0.003*

3.5.4. Association of morphological measurements and PFJ OA

Table 27 shows the association of the morphological features and OA at the PFJ. Angular measurements, namely sulcus angle (aOR=0.86, 95%CI 0.80, 0.92; p<0.001) and condylar angle (aOR=0.31, 95%CI 0.21, 0.46; p<0.001) associated with PFJ OA. A narrow angle associated with higher risk of PFJ OA in both these measurements, and their association remained statistically significant even after Bonferroni correction.

Among the linear measurements at the PFJ, both patellar thickness (aOR=0.74, 95%CI 0.61, 0.89; p<0.001) and patellar width (aOR=0.89, 95%CI 0.83, 0.95; p<0.001) showed statistically significant association with PF OA when these measurements were adjusted for confounders. Smaller patella width and lower patellar thickness both associated with higher risk of PFOA.

Condylar height lateral (p=0.02) and intercondylar width (p=0.01) also showed association with PFJ OA. However, these were not statistically significant after Bonferroni correction for multiple testing.

None of the TFJ measurements showed association with PFJ OA once corrected for multiple testing.

Table 27. Association of measurements and PFJ OA

Measurements	OR	*p value*	a-OR*	*p* value	*Adjusted p value*
Sulcus angle[1]	0.87(0.82,0.92)	<0.001[2]	0.86(0.80,0.92)	<0.001[2]	<0.001[2]
Patellar angle[1]	0.96(0.92,1.01)	0.17	0.96(0.91,1.01)	0.12	0.009
Condylar angle[1]	0.57(0.49,0.66)	<0.001[2]	0.31(0.21,0.46)	<0.001[2]	<0.001[2]
Patellar thickness[1]	0.97(0.87,1.08)	0.65	0.74(0.61,0.89)	<0.001[2]	<0.001[2]
Patellar width[1]	0.96(0.91,1.00)	0.10	0.89(0.83,0.95)	<0.001[2]	<0.001[2]
Condylar height medial[1]	0.95(0.81,1.1)	0.5	0.93(0.80,1.10)	0.43	0.04
Condylar height lateral[1]	1.14(1.00,1.31)	0.04	1.18(0.02,1.36)	0.12	0.009
Condylar width[1]	0.95(0.92,1.0)	0.05	1.00(0.93,1.08)	0.84	0.14
Intercondylar width[1]	0.93(0.88,0.99)	0.03	0.91(0.84,0.98)	0.04	0.004
Condylar plateau angle[1]	0.88(0.64,1.21)	0.45	1.07(0.70,1.62)	0.74	0.10
Distal femoral tilt[1]	1.08(0.89,1.30)	0.43	1.25(0.99,1.58)	0.06	0.01
Proximal tibial tilt[1]	1.18 (0.92,1.52)	0.18	1.15(0.87,1.50)	0.32	0.03
Varus knees[1]	2.54(1.25, 5.16)	0.01	2.67(1.24, 5.72)	0.04	0.004
Valgus knees[1]	1.12(0.46,2.72)	0.78	1.25(0.47, 3.33)	0.64	0.08

OR-odds ratio,-adjusted for age, gender, height, weight. [1] All angles measured in degrees, and all distances in millimetres; [2] significant after Bonferroni correction at p<0.003*

3.5.5. Association between morphological measurements and TFJ OA

Table 28 shows the association of morphological measurements and TFJ OA.

At the PFJ, sulcus angle (aOR=0.88, 95%CI 0.84, 0.92; p<0.001) and condylar angle (aOR=0.60, 95%CI 0.55, 0.66; p<0.001) both showed association with TFJOA. As these angular measurements became smaller the risk of TFJ OA increased. These measurements showed significant association even after Bonferroni correction at p<0.003

Of the linear measurements, condylar height lateral and intercondylar width both showed association with TFOA (p=0.01), but these became non- significant after Bonferroni correction at p<0.003.

At the TFJ, distal femoral tilt (aOR=1.37, 95%CI 1.20, 1.57; p<0.001) and proximal tibial tilt (aOR=1.38, 95%CI 1.20, 1.57; p<0.001) both showed association with TFJ OA. Wider angles in these two measurements associated with higher risk of developing TFJOA. Varus alignment showed an association with TFJ OA (aOR=3.92, 95%CI 2.44, 6.29) which remained significant after Bonferroni correction.

Table 28. Association between measurements and TFJ OA

Measurements	OR(95%CI)	*P value*	a-OR*	*p value*	*Adjusted p value*
Sulcus angle[1]	0.89 (0.85,0.93)	<0.001[2]	0.88(0.84,0.92)	<0.001[2]	<0.001[2]
Patellar angle[1]	0.99 (0.96,1.02)	0.82	0.98(0.95,1.02)	0.5	0.05
Condylar angle[1]	0.60 (0.54,0.66)	<0.001[2]	0.60(0.55,0.66)	<0.001[2]	<0.001[2]
Patellar thickness[1]	1.01 (0.94,1.08)	0.68	0.96(0.87,1.05)	0.41	0.04
Patellar width[1]	0.99 (0.96,1.03)	0.90	0.98(0.95,1.02)	0.57	0.07
Condylar height medial[1]	0.88 (0.77,1.00)	0.05	0.86(0.75,1.98)	0.13	0.01
Condylar height lateral[1]	1.2 (1.11,1.34)	<0.001[2]	1.23(0.01,1.35)	0.06	0.05
Condylar width[1]	0.99 (0.96,1.01)	0.53	0.97(0.93,1.01)	0.10	0.007
Intercondylar width[1]	0.97 (0.93,1.01)	0.13	0.93(0.89,0.98)	0.01	0.02
Condylar plateau angle[1]	0.98 (0.80,1.19)	0.85	1.02(0.83,1.25)	0.85	0.14
Distal femoral tilt[1]	1.17 (1.02,1.34)	0.02	1.37(1.20,1.57)	<0.001[2]	<0.001[2]
Proximal tibial tilt[1]	1.38 (1.20,1.67)	<0.001[2]	1.38(1.15,1.64)	<0.001[2]	<0.001[2]
Varus knees[1]	4.08 (2.60,6.40)	<0.001[2]	3.92(2.44,6.29)	<0.001[2]	<0.001[2]
Valgus knees[1]	1.94(1.18, 3.18)	0.009	2.09(1.24, 3.52)	0.005	0.01

*aOR-odds ratio; *-adjusted for age, gender, height, weight. [1] All angles measured in degrees, and all distances in millimetres. [2] significant after Bonferroni correction at p<0.003*

3.5.6. Summary of the key findings

The key findings are summarised in Figure 39. A narrow sulcus angle, narrow condylar angle, shorter intercondylar width, varus malalignment, increased distal femoral tilt and proximal tibial tilt all associated with knee OA.

With regard to patellofemoral OA, narrow sulcus angle, narrow condylar angle and a smaller patella were all risk factors for PFJ OA.

Similarly, narrow sulcus angle and narrow condylar angle associated with TFJ OA. However, varus malalignment, and an increased distal femoral tilt and proximal tibial tilt showed association with TFJ OA.

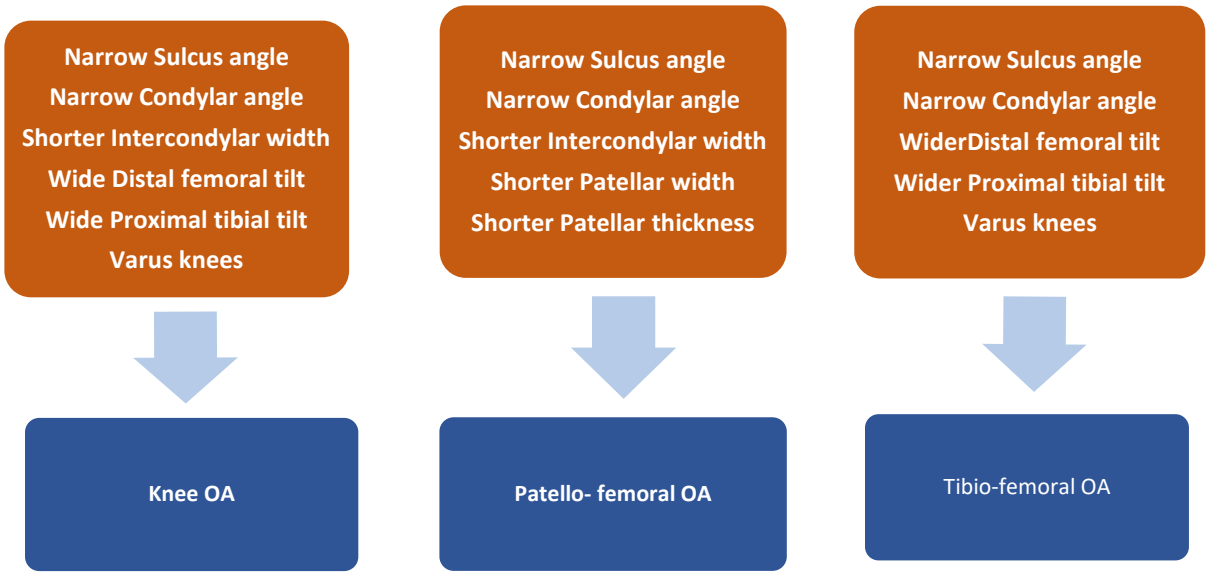

Figure 39. Morphological features which were associated with knee OA, patella-femoral OA and tibio-femoral OA

3.6. Multiple regression analysis of morphological features

3.6.1. Multiple regression analysis between measurements and knee OA

Among the 14 morphological features, six were significantly associated with knee OA, namely sulcus angle, condylar angle, intercondylar width, distal femoral tilt and proximal tibial tilt, and varus alignment. Of these measurements, distal femoral tilt and proximal tibial tilt were correlated with one another ($r=0.42$ $p<0.001$) (Table 18) . There were no other statistically significant correlations between the other measurements that associated with knee OA. Multiple regression test for five of these measurement were performed with the replacement of proximal tibial tilt with distal femoral tilt. Also a separate analysis was performd with the replacement of distal femoral tilt with proximal tibial tilt (Table 29)

Table 29. Results of multiple regression analysis between measurements and knee OA

Measurements	aOR (95% CI)	*p value*
Sulcus angle*	0.83 (0.80,0.87)	<0.001
Condylar angle*	0.52 (0.48,58)	<0.001
Intercondylar width*	0.97 (0.93,1.01)	0.13
Distal femoral tilt[1*]	1.08 (0.96,1.22)	0.20
proximal tibial tilt[2*]	1.21 (1.02,1.44)	0.04
Varus knees*	3.11(1.73,5.58)	<0.001

[1]–excludes proximal tibial tilt, [2]–excludes distal femoral tilt; aOR-adjusted for age, sex, height, weight and any other morphological features in the table, All angles measured in degrees, and all distances in millimetres*

A narrower sulcus angle, narrower condylar angle, and increasing proximal tibila tilt and varus alignment were each independently associated with knee OA. However distal femoral tilt and intercondylar width became non-significant on adjusting for other measurements.

3.6.2. Multiple regression analysis between measurements and PFJ OA

The morphological features which were associated with PFJ OA were sulcus angle, condylar angle, intercondylar width, patellar thickness and patellar width. Of these, patellar thickness and patellar width were correlated ($r=0.55, p<0.001$). Therefore a multiple regression test was perfomed for four measurements with the replacement of patellar width for patellar thickness in one test and replacement of patellar thickness for patellar width in another. The results of the multiple regression analysis are given in Table 30.

Sulcus angle and condylar angle each remained statistically significantly associated with PFJ OA after multivariate adjustment. However, patellar width, patellar thickness and intercondylar width were no longer statistically significantly associated. A narrow sulcus angle and narrow condylar angle associated with PFJ OA.

Table 30. Results of multiple regression analysis between measurements and PFJOA

Measurements	aOR(95%CI)	*p-value*
Sulcus angle*	0.86 (0.81,0.91)	<0.001
Condylar angle*	0.48(0.41,0.56)	<0.001
Intercondylar width*	0.95(0.87,1.05)	0.12
Patellar width[1*]	0.99(0.92,1.07)	0.9
Patellar thickness[2*]	0.98(0.55,0.90)	0.81

[1]-excludes patellar thickness; [2]-excludes patellar width OR-adjusted for age, sex, height , weight and any other morphological features in the table, All angles measured in degrees, and all distances in millimetres*

3.6.3. Multiple regression analysis between measurements and TFJ OA

The morphological features which were associated with TFJOA were sulcus angle, condylar angle, distal femoral tilt, proximal tibial tilt and varus alignment. Of these, distal femoral tilt and proximal tibial tilt were correlated ($r=0.55, p<0.001$). Therefore a multiple regression test was perfomed for four measurements with the replacement of distal femoral tilt for proximal tibial tilt in one test and replacement of proximal tibial tilt for distal femoral tilt in another. The results of the multiple regression analysis are shown in Table 31. Sulcus angle, condylar angle, distal femoral tilt, proximal tibial tilt and varus alignment remained statistically significant after multivariate adjustment.

A narrow sulcus angle and narrow condylar angle, and increasing distal or proximal femoral tilt associated with TFJ OA.

Table 31. Results of multiple regression analysis between measurements and TFJOA

Measurements	aOR(95%CI)	*p value*
Sulcus angle*	0.86(0.82,0.91)	<0.001
Condylar angle*	0.52(0.42,0.57)	<0.001
Distal femoral tilt[1*]	1.14(1.01,1.30)	0.03
Proximal tibial tilt[2]	1.21(1.01,1.46)	0.03
Varus knees*	3.61(1.97,6.61)	<0.001

1-excludes proximal ;2-excludes distal femoral tilt ,OR-adjusted for age, sex, height , weight and any other morphological features in the table; All angles measured in degrees, and all distances in millimetres*

3.6.4. Summary of the key findings

Results of multiple regresson analysis showed a narrow sulcus, narrow condylar angle, wide proximal tibial tilt and varus alignment were associated with knee OA. However, a narrow sulcus angle and a narrow condylar were only associated with PFJOA. With regards to TFJOA, a narrow sulcus angle, narrow condylar angle, wide femoral tilt, wide proximal tibial tilt and varus alignment had a significant association.

3.7. Cumulative risk models using receiver operating characteristic (ROC) curves

3.7.1. ROC curve for knee OA

Three ROC curves plotted for the outcome knee OA (defined as OA in either TFJ or PFJ) is shown in Figure 40. Morphological features such condylar angle, proximal tibial tilt and varus alignment when combined together showed high cumulative risk of knee OA with an AUC of 0.91 (95%CI 0.89, 0.93) There was only a slight increase when patient characteristics were combined with morphological features, age, gender, height and weight with an AUC of 0.92. A ROC curve plotted with patient characteristics age, gender, weight, carried poor cumulative risk of knee OA with an AUC of 0.60 (95%CI 0.54, 0.63).

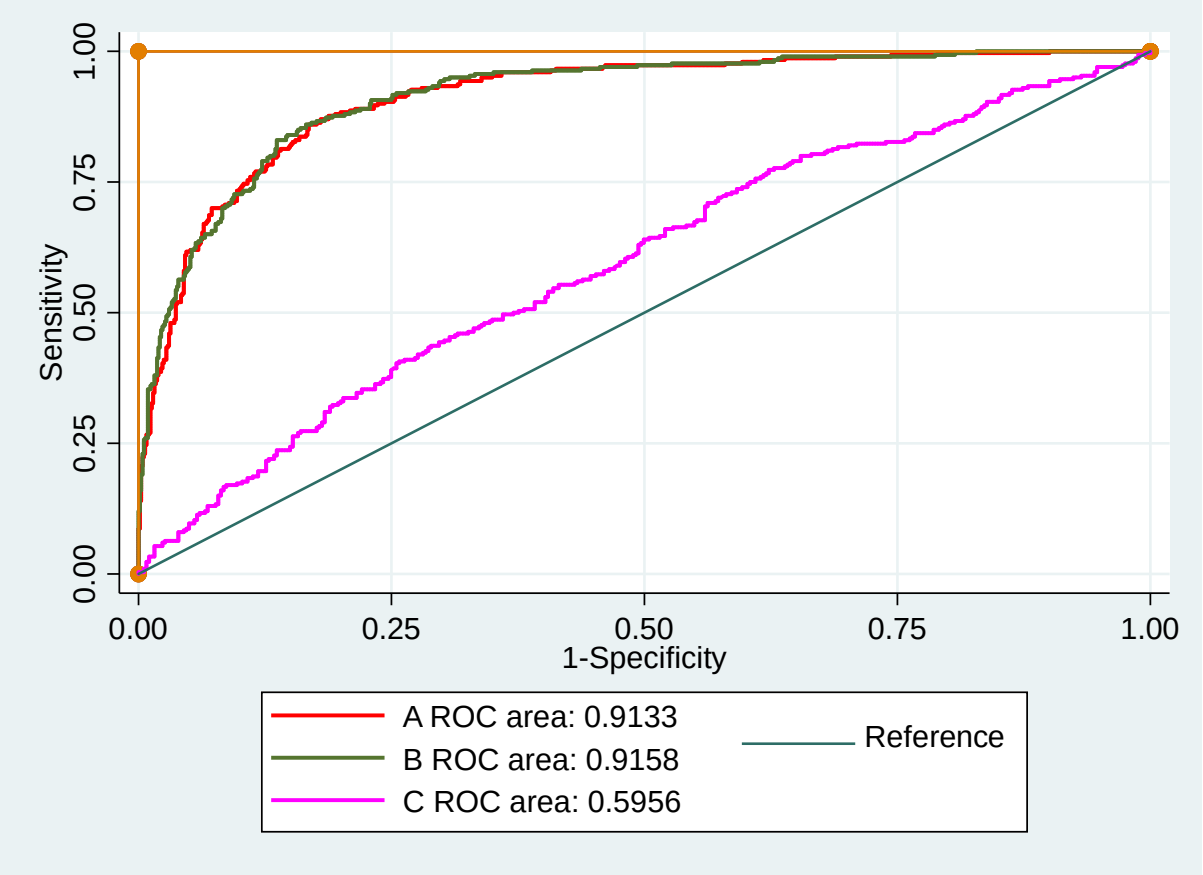

Figure 40. ROC curve for knee OA

Graph A plotted with only morphological features; graph B plotted with morphological features + demographic features, graph C plotted with demographic features only

3.7.2. ROC curve for PFJOA using morphological and demographical features

Three ROC curves plotted for the outcome PFJ OA are shown in Figure 41. Morphological features such as sulcus angle condylar angle when combined together showed a high cumulatiuve risk of PFJOA with an AUC of 0.91 (95%CI 0.86, 0.95). There was only a slight increase when patients characteristics were added to the morphological features age, gender, height and weight (AUC 0.91; 95%CI 0.87 0.95). A ROC curve plotted with patient characteristics age, gender, weight, carried poor cumulative risk of PFJOA with an AUC of 0.68 (95%CI 0.60, 0.74)

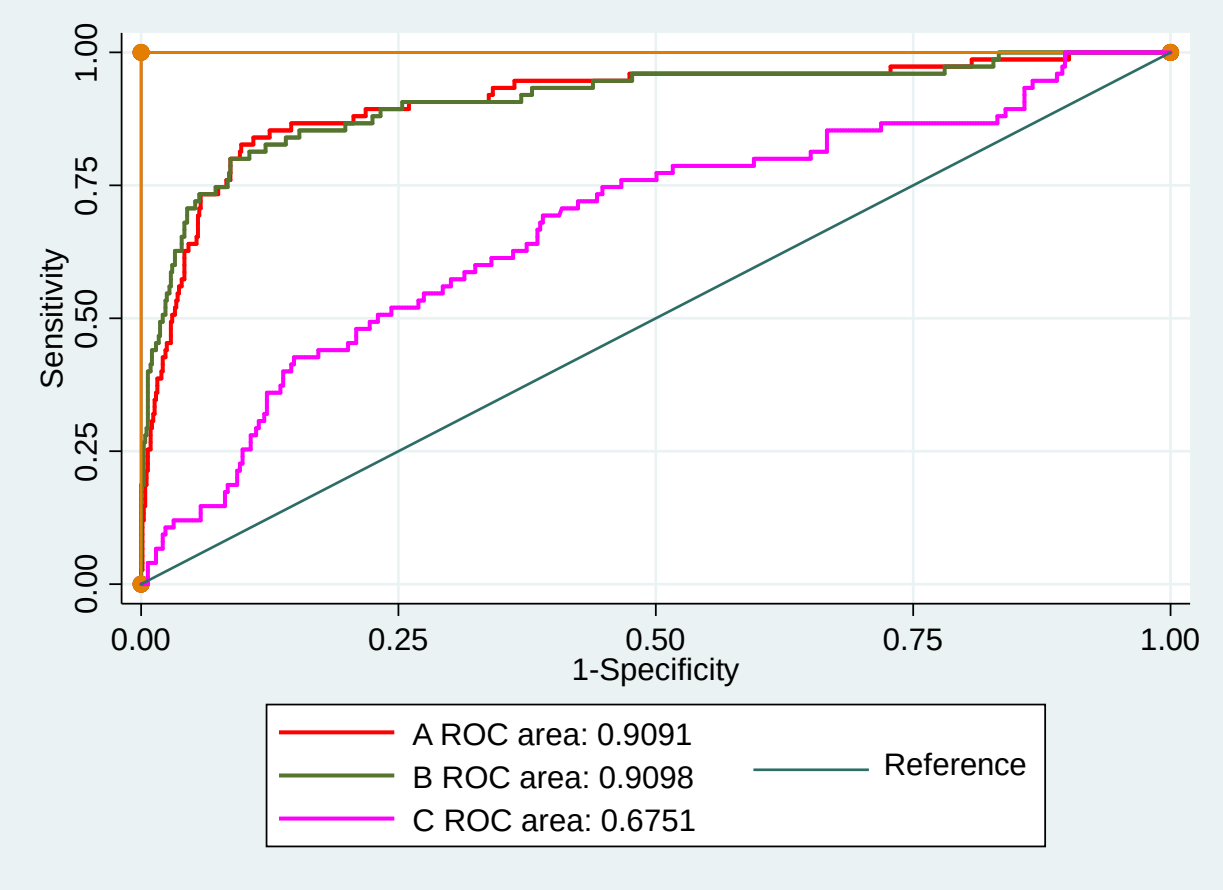

Figure 41. ROC curve for PFJOA

Graph A plotted with only morphological features; graph B plotted with morphological features + demographic features, graph C plotted with demographic features only

3.7.3. ROC curve for TFJOA using morphological and demographical features

Three ROC curves plotted for the outcome TFJ OA are shown in Figure 42 Morphological features sulcus angle, condylar angle, distal femoral tilt, varus knees when combined together carried a high cumulative risk of TFJ OA with an AUC of 0.91 (95%CI 0.89, 0.93).There was only a slight increase when patient characteristics were added to the morphological features age, gender, height and weight (AUC 0.92; 95%CI 0.89, 0.94). A ROC curve plotted with patient characteristics age, gender, weight showed a poor cumulative risk of TFJOA with an AUC of 0.59 (95%CI 0.54, 0.63)

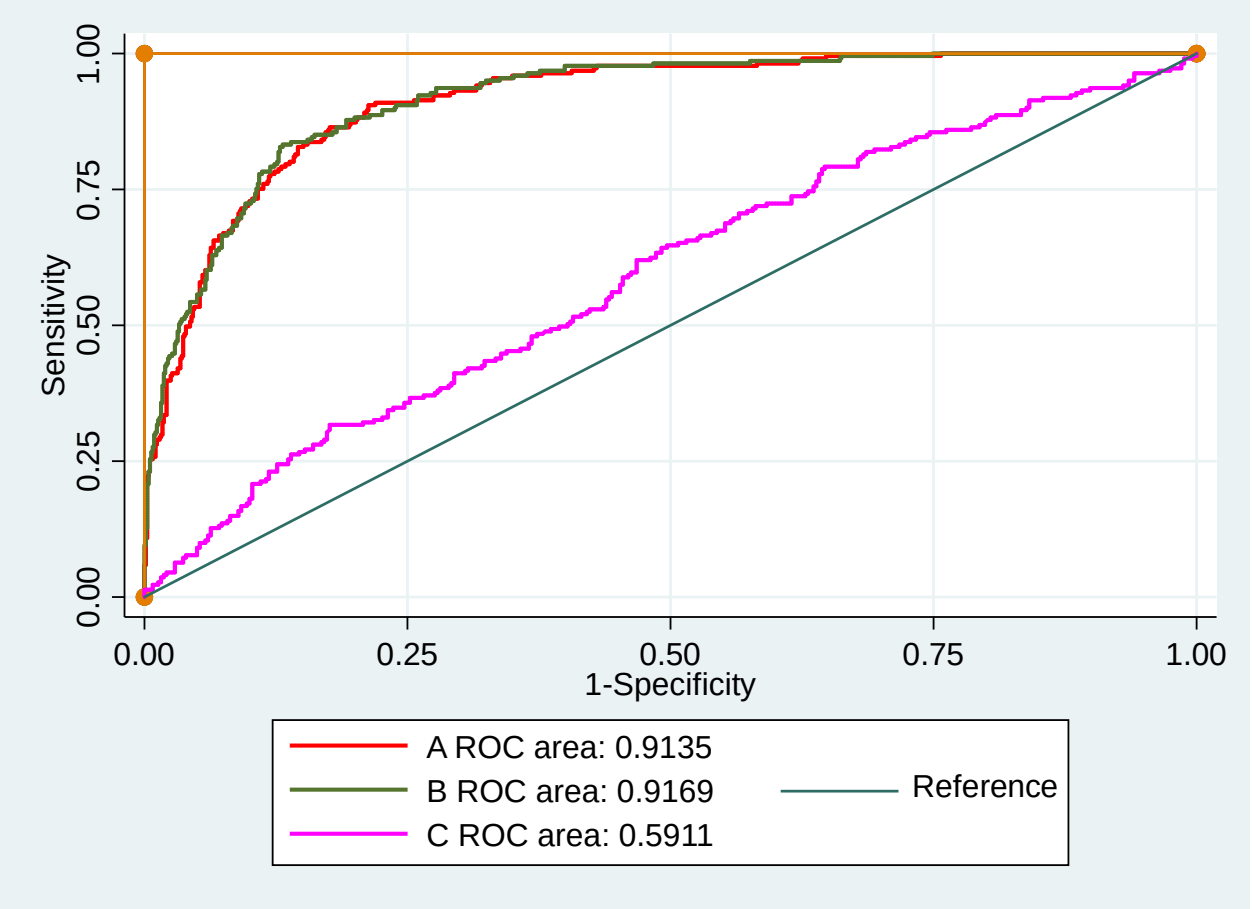

Figure 42. ROC curve for TFJOA

Graph A plotted with only morphological features; graph B plotted with morphological features + demographic features, graph C plotted with demographic features only

3.7.7. Radiographic representation of morphological features that were associated with knee OA

The following radiographic images were selected on the basis of ranking. The tenth and ninetieth percentile of each measurement have been chosen to represent smaller larger measures of each measurements. The fiftieth percentile is also shown in the middle.

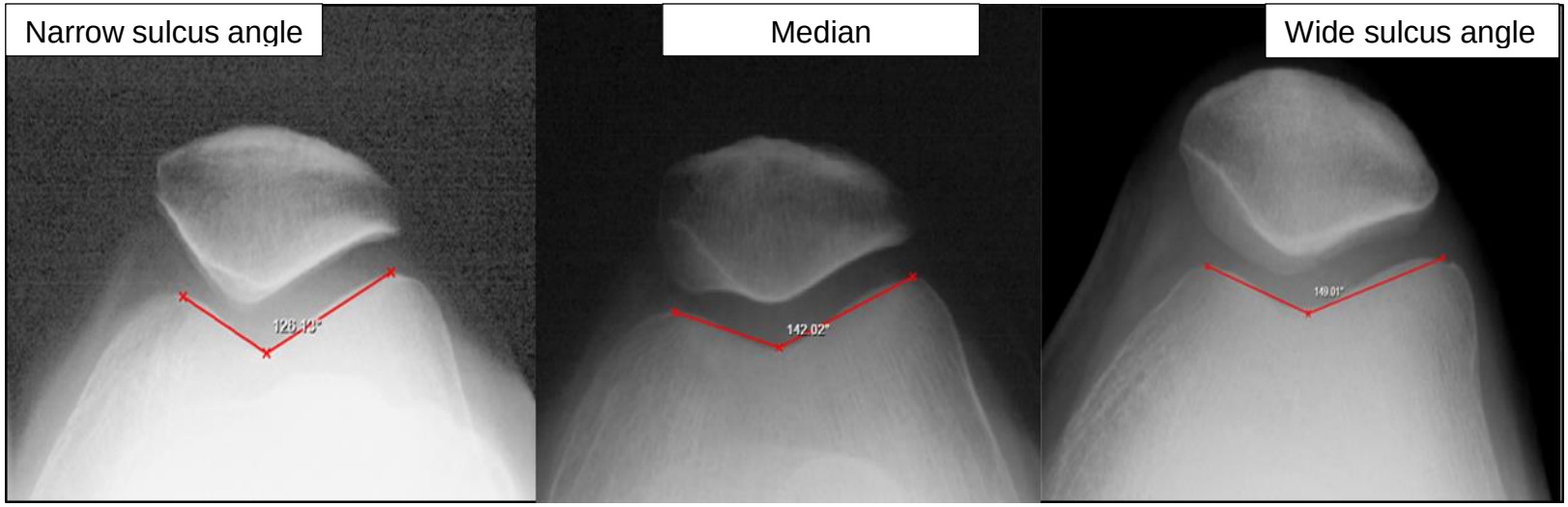

Figure 43. Radiographic view of sulcus angle

A narrow sulcus angle was associated with knee OA, PFJOA and TFJOA.

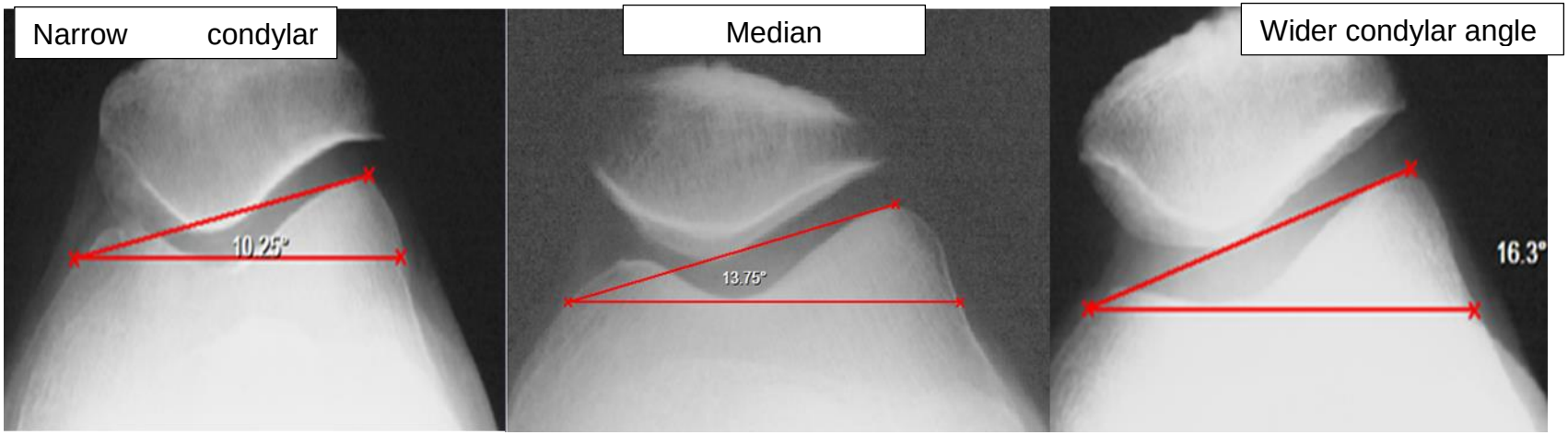

Figure 44. Radiographic view of condylar angle

A narrow condylar angle was associated with knee OA, PFJOA and TFJOA.

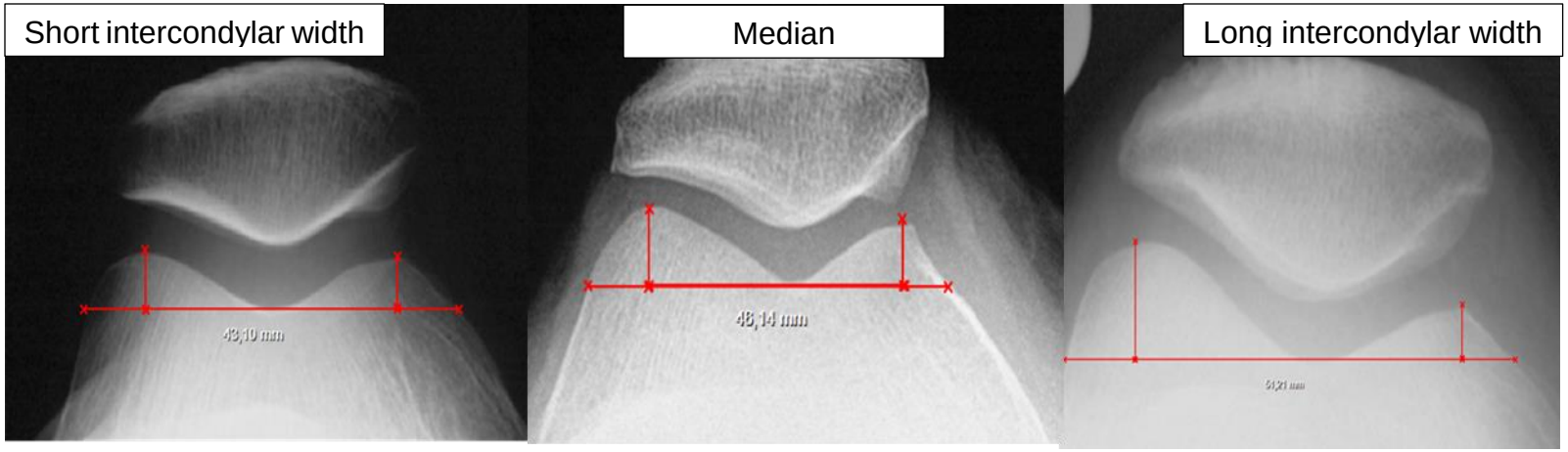

Figure 45. Radiographic view of intercondylar width

A shorter intercondylar width was associated with knee OA.

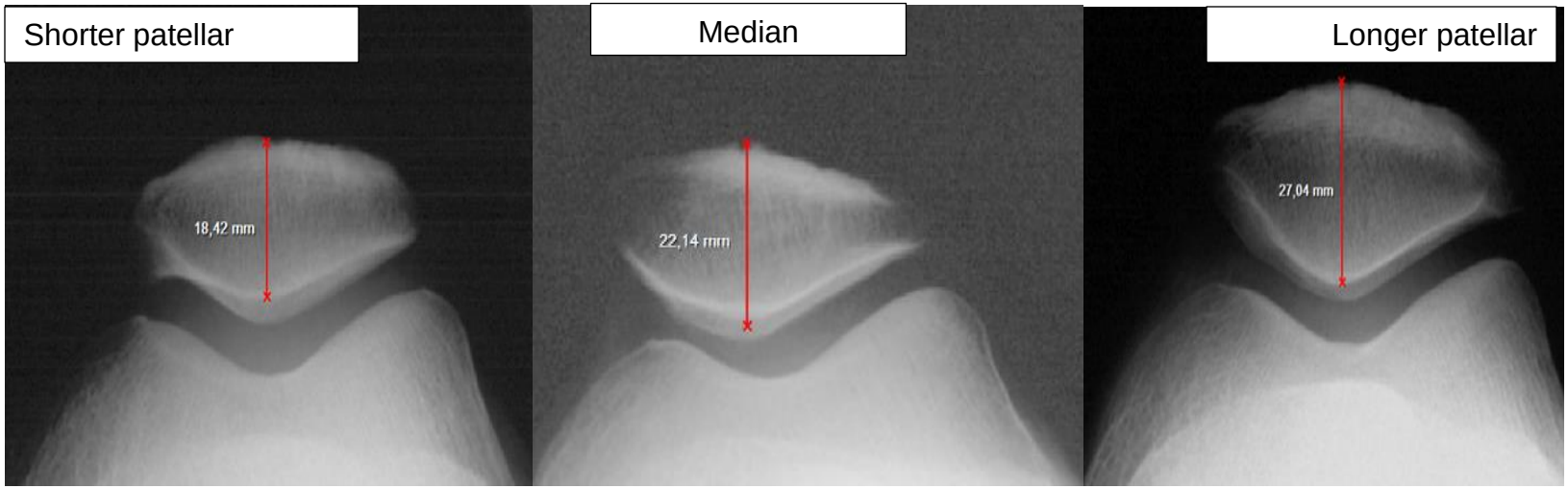

Figure 46. Radiographic view of patellar thickness

A shorter patellar thickness was associated with PFJOA.

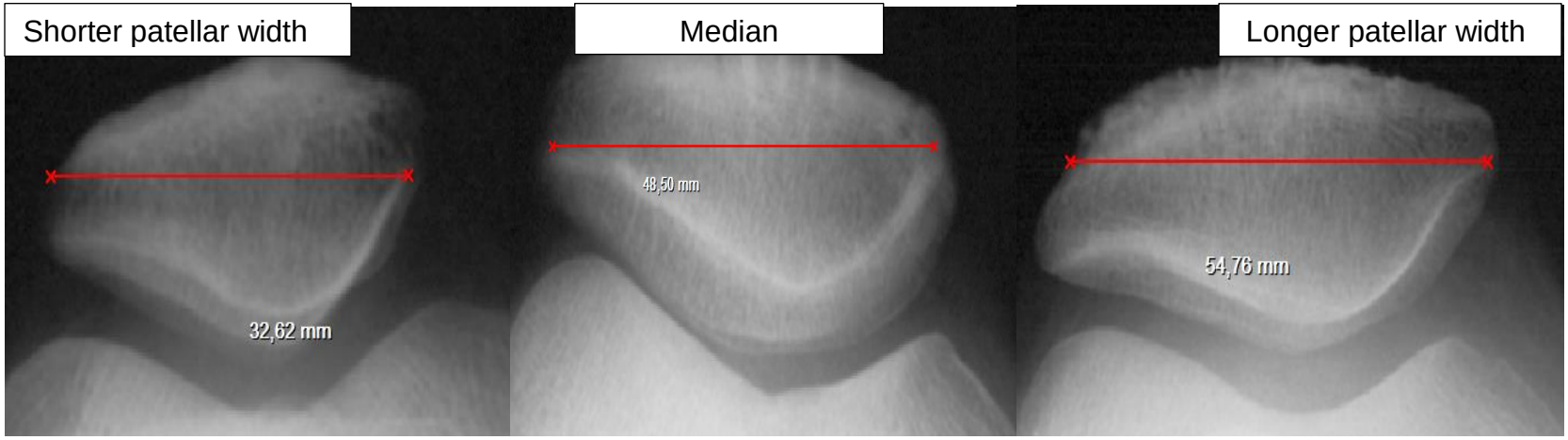

Figure 47. Radiographic view of patellar width

A shorter patellar width was associated with PFJOA.

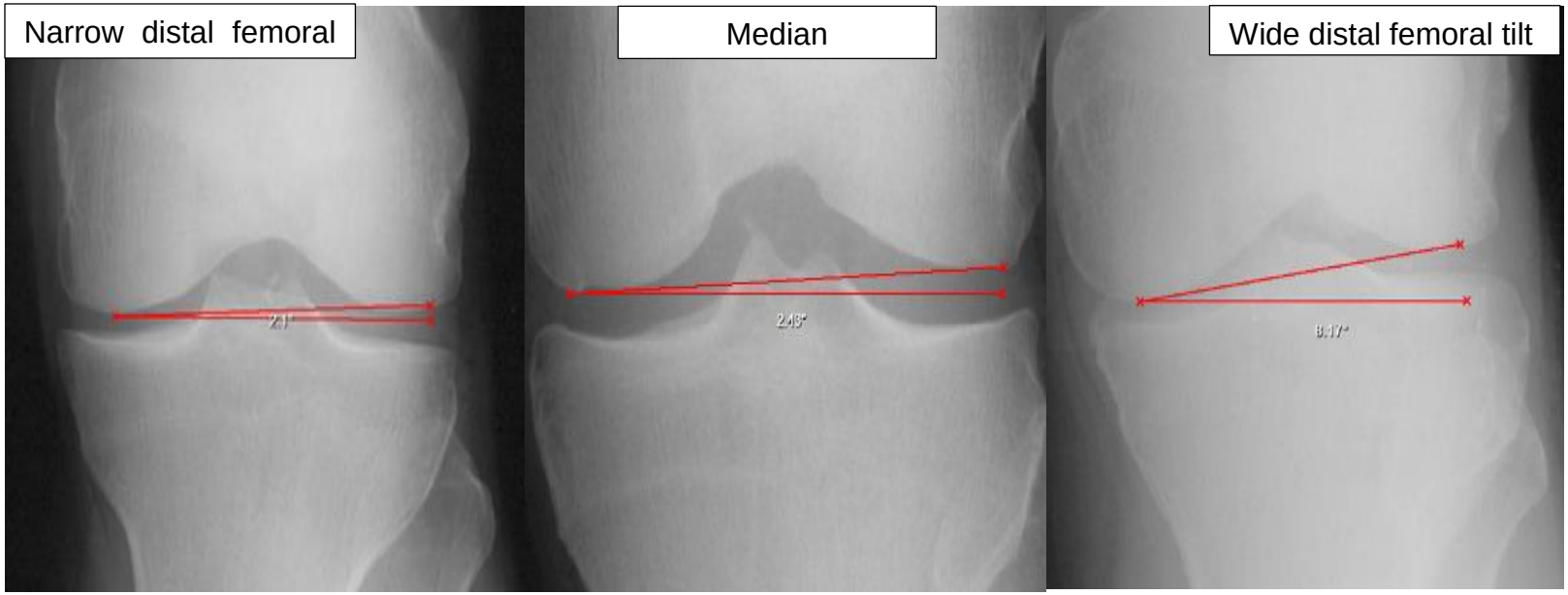

Figure 48. Radiographic view of distal femoral tilt

A wide distal femoral tilt was associated with knee OA and TFJOA.

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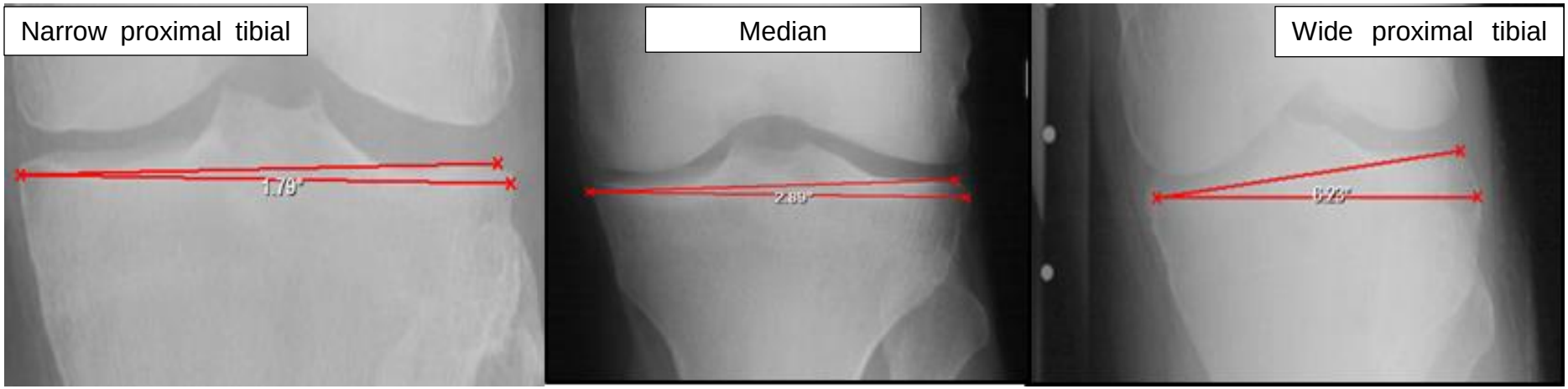

Figure 49. Radiographic view of proximal tibial tilt

A wide proximal tibial tilt was associated with knee OA and TFJOA.

3.8 Clinical significance of morphological features

3.8.1 Association of morphological features and increasing severity of WOMAC pain score

Table 32 shows the association between all morphological features that were significantly associated with knee OA, (knee OA, PFJOA and TFJOA) and increasing severity of the WOMAC summated pain score. Among the five measurements, condylar angle negatively associated with increasing severity of pain score [β-coef =-0.16 (95%CI -0.29,-0.02)]. In other words, as the condylar angle became narrower the WOMAC pain severity increased. None of the other measurements showed any association with WOMAC pain score.

Table 32. Association of morphological features and increasing severity of WOMAC pain score

Measurements	β-coef (95%CI)	*p* values	β-coef adjusted[1] (95%CI)	*p* values
Sulcus angle	-0.02(-0.08,0.04)	0.47	-0.04(-0.11,0.02)	0.25
Condylar angle	-0.12(-0.25,0.001)	0.05	-0.16(-0.29,-0.02)	0.01*
Distal femoral tilt	-0.11(-0.36, 0.13)	0.35	-0.10(-0.35, 0.13)	0.39
Proximal tibial tilt	-0.29(-0.65, 0.06)	0.11	-0.35(-0.72,0.01)	0.06
Varus alignment	0.50(-0.38, 1.38)	0.26	0.68(-0.21,1.58)	0.13

[1]-Adjusted to age, gender, weight, height and any other morphological features in the table. significant p value*

3.8.2 Association of morphological features and summated osteophyte score (Nottingham line drawing atlas)

Table 33 shows the association between all significant morphological features that were significantly associated with knee OA (knee OA, PFJOA and TFJOA) and osteophyte score of the affected OA knee.. Condylar angle negatively associated with osteophyte scores [βcoef=-0.15; 95%CI -0.31, -0.001]. In other words, the narrower the condylar angle the higher the osteophyte score. Varus alignment showed a positive association with osteophyte scores [βcoef=2.19; 95%CI 1.18, 3.20]. No association was seen for the other three morphological features that were assessed.

Table 33. Association of morphological features and summated osteophyte score

Measurements	β-coef(95%CI)	*p* values	β-coef adjusted[1](95%CI)	*p* values
Sulcus angle	-0.01(-0.09, 0.06)	0.68	-0.01(-0.09, 0.07)	0.79
Condylar angle	-0.20(-0.35, -0.06)	0.005	-0.15(-0.31, -0.001)	0.03*
Distal femoral tilt	-0.03(-0.32,0.25)	0.81	-0.05(-0.34,0.22)	0.69
Proximal tibial tilt	-0.19(-0.61,0.23)	0.37	-0.11(-0.54,0.31)	0.59
Varus alignment	2.46(1.48,3.44)	<0.001*	2.19(1.18,3.20)	<0.001*

[1-]Adjusted to age, gender, weight, height and any other morphological features in the table.* significant p value

3.8.3 Association between measurements and compartment specific osteophyte score (Nottingham Line drawing Atlas)

Table 34 shows the association between significant PF and TF measurements with osteophyte scores of the PFJ and TFJ compartment, respectively, of the contralateral OA knee. In this analysis, association of PF measurements with NLDLDA osteophyte scores of the PFJ compartment, and TF measurements with NLDLDA osteophyte scores of the TFJ, were examined. One PF measurement, specifically the condylar angle, negatively associated with osteophyte scores of the PFJ compartment [βcoef=-0.15; 95%CI -0.31, -0.001], whereas varus alignment, which is a TF measurement, showed a positive association with increasing osteophyte scores of the TFJ compartment [βcoef=2.19; 95%CI 1.18, 3.20]. No associations were seen for the other three morphological features that were assessed.

Table 34. Association between morphological features and osteophyte scores.

Measurements	β-coef (95%CI)	*p* values	β-coef adjusted[1](95%CI)	*p* values
Sulcus angle[2]	-0.005(-0.04, 0.03)	0.76	-0.006(-0.04, 0.03)	0.73
Condylar angle[2]	-0.12(-0.19, -0.05)	0.001	-0.86(-0.15, -0.01)	0.01*
Distal femoral tilt[3]	0.002(-0.12,0.13)	0.96	-0.02(-0.15,0.10)	0.73
Proximal tibial tilt[3]	-0.12(-0.31,0.06)	0.19	-0.06(-0.25,0.12)	0.47
Varus alignment[3]	1.03(0.57,1.48)	<0.001*	0.95(0.49,1.41)	<0.001*

[1]-Adjusted to age, gender, weight, height and any other morphological features in the table.-significant p value.[2]-Patellofemoral measurements; [3]-Tibiofemoral measurements*

3.8.4 Association of morphological features and summated joint space narrowing scores (NLDLDA)

Table 35 shows the association between morphological features that were significantly associated with knee OA (knee OA, PFJOA and TFJOA) and JSN score of the contralateral OA knee. None of the measurements showed any association with overall JSN scores of the NLDLDA.

Table 35. Association of morphological features with summated joint space narrowing scores

Measurements	β-coef(95%CI)	*p* values	β-coef adjusted[1] (95%CI)	*p* values
Sulcus angle	0.01(-0.02,0.05)	0.39	0.01(-0.02,0.04)	0.60
Condylar angle	0.02(-0.04,0.08)	0.58	0.01(-0.06,0.08)	0.22
Distal femoral tilt	-0.02(-0.15, 0.11)	0.74	0.01(-0.14, 0.16)	0.14
Proximal tibial tilt	-0.06 (-0.24,0.11)	0.47	-0.08 (-0.26,0.10)	0.38
Varus alignment	-0.28(-0.91,0.34)	0.34	-0.25(-0.91,0.41)	0.44

[1]-Adjusted to age, gender, weight, height and any other morphological features in the table

3.8.5 Association between measurements and compartment specific joint space narrowing scores of the NLDLDA

Table 36 shows the association between significant PF and TF measurements and JSN score of the contralateral OA knee. In this analysis the association of PF measurement with NLDLDA JSN scores of the PFJ compartment, and TF measurements with NLDLDA JSN scores of the TFJ compartment, were examined.

Table 36. Association of morphological features with compartment-specific joint space narrowing scores

Measurements	β-coef(95%CI)	*p* values	β-coef adjusted[1] (95%CI)	*p* values
Sulcus angle[2]	0.01(-0.006,0.03)	0.17	0.01(-0.007,0.03)	0.23
Condylar angle[2]	0.001(-0.03,0.03)	0.93	0.004(-0.03,0.04)	0.82
Distal femoral tilt[3]	0.09(0.001, 0.17)	0.04	0.08(-0.007, 0.17)	0.07
Proximal tibial tilt[3]	0.02 (-0.10,0.15)	0.75	0.04(-0.09,0.18)	0.52
Varus alignment[3]	0.35(0.008,0.70)	0.04	0.33(-0.01,0.69)	0.06

[1]-Adjusted to age, gender, weight, height and any other morphological features in the table.

[2] Patellofemoral measurements; [3]-Tibiofemoral measurements.

3.8.6 Association of morphological features with Kellgren and Lawrence scores

Table 37 shows the association between morphological features significantly associated with any of the outcomes and KL scores. PF measurements were examined for association with PFJ KL scores and TF measurements with TFJ KL scores separately. One PF measurement, specifically the condylar angle, negatively associated with KL scores of the PF compartment [βcoef=-0.03; 95%CI-0.05, -0.01]. In other words, the narrower the condylar angle the higher the KL score in the PF compartment. Varus alignment, which is a TF measurement, associated positively with KL score of the TF compartment [βcoef=0.54(95%CI 0.32, 0.76)].

Table 37. Morphological features and Kellgren and Lawrence scores at PFJ and TFJ

Measurements	β-coef(95%CI)	*p* values	β-coef adjusted (95%CI)[1]	*p* values
Sulcus angle[2]	-0.005(-0.02, 0.01)	0.37	-0.005(-0.02, 0.004)	0.26
Condylar angle[2]	-0.03(-0.05, -0.01)	<0.001*	-0.03(-0.05, -0.01)	0.002*
Distal femoral tilt[3]	0.007(-0.06,0.06)	0.98	-0.0004 (-0.06,0.06)	0.99
Proximal tibial tilt[3]	-0.05(-0.14, 0.03)	0.25	-0.03(-0.12, 0.05)	0.45
Varus alignment[3]	0.61(0.40, 0.82)	<0.001*	0.54(0.32, 0.76)	<0.001*

[1]-Adjusted to age, gender, weight, height and any other morphological features in the table. significant p value. [2]-Patellofemoral measurements; [3]-Tibiofemoral measurements.*

3.8.7 Association of morphological features and progression of visual analogue scale pain scores.

Table 38 shows the association of morphological features and progression of pain from baseline to the follow-up period of 12 years. A total of 140 participants in the GOAL control group had single follow-up VAS pain data. Of these, 22 participants had high VAS score (≥6), while 118 participants had low VAS score (<6). None of the morphological features showed any association with incidence of knee pain. The results remained unchanged after adjusting for age, gender, height and weight.

Table 38. Morphological features and progression of visual analogue scale pain scores.

Measurements	OR (95%CI)	*p* value	aOR (95%CI)[1]	*p* value
Sulcus angle	0.98 (0.89, 1.08)	0.80	0.97(0.87, 1.08)	0.60
Condylar angle	1.01 (0.85, 1.19)	0.90	1.00 (0.83, 1.20)	0.96
Distal femoral tilt	1.12 (0.75, 1.67)	0.57	1.12(0.74, 1.70)	0.58
Proximal tibial tilt	0.62 (0.34, 1.11)	0.11	0.64(0.34, 1.20)	0.16
Varus alignment	0.87 (0.10, 7.64)	0.90	0.76(0.06, 8.55)	0.82

OR-odds ratio; [1]-adjusted for age, gender, height, weight and any other morphological features in the table

Chapter 4 DISCUSSION

4.1 Key findings

This is the largest study to date to investigate the radiographic morphological features that might predispose to knee OA, and the first to separately investigate both the PFJ and the TFJ compartments. We compared morphological features of unaffected knees of unilateral knee OA participants with controls without knee OA on the assumption that in people with unilateral knee OA, the unaffected knee represents the constitutional shape of the affected knee of that individual prior to the onset of OA. This strategy was supported by the findings of right-left symmetry in knees of the non-OA control group for all 14 morphological features.

We found that 5 of the morphological features associated with increased risk of overall knee OA, specifically sulcus angle, condylar angle, distal femoral tilt, proximal tibial tilt and varus malalignment.

Larger measures of distal femoral tilt and proximal tibial tilt and increasing varus malalignment associated with TFJ OA but not with PFJ OA. However, smaller sulcus angle condylar angle associated with both PFJ OA, TFJ OA and knee OA at either compartment as a composite measure.

These associations were independent of age, gender, height and weight.

In addition, a model including all significantly associated morphological features carried a high cumulative risk of knee OA, PFJOA and TFJOA, and this only increased marginally on adding age, gender, height and weight to the model.

We also examined for possible associations between the five morphological features that are associated with knee OA, PFJOA and TFJOA with WOMAC pain score, and summated radiographic scores. Of the five morphological features, only a narrow condylar angle associated with higher WOMAC pain severity. A narrow condylar angle also associated with higher summated and PF osteophyte scores, and higher PF KL scores, but showed no association with JSN scores. The only other feature that showed associations with radiographic scores was increasing varus alignment which associated with higher summated and TF osteophyte scores and with higher TF KL scores. In the 12 year follow-up questionnaires for participants in the non-OA control group within GOAL none of the morphological features associated with development of incident knee pain, although because of the very small sample size this analysis may have had insufficient statistical power to detect such an association.

4.2 Relation with previously published research

Morphological measurements and knee OA

Femoral sulcus angle, which represents the deepest depression of the trochlear groove, has been a focus of great interest in previous studies (Hunter et al., 2007a), (Tanamas et al., 2010a), (Davies-Tuck et al., 2008a).

A wide sulcus angle was found to associate with lower risk of knee OA in our study. This result accords with findings of previous studies which has used various methods for shape analysis. In one prospective study, Davies-Tuck *et al* examined the association of sulcus angle and patellar cartilage volume on MRI and found that as the sulcus angle became wider by 1^0 there was an associated increase in the medial patellar cartilage volume by $9.1mm^3$ (95% CI 3.2, 15.0) on cross-sectional analysis, however, there was no association with longitudinal change over a two year period (Davies-Tuck et al., 2008a). The latter finding may be due to the relatively small sample size (n=100) or relatively brief follow-up of two years. Also, participants already had established knee OA. Similarly, in another cohort study of healthy adults (aged 40-69years) without OA, Teichtahl *et al* found that a wider sulcus angle associated with increased patellar cartilage volume. For every 1^0 increase in the angle there was an increase of patellar cartilage volume by 8.70 mm^3 (95% CI 2.15, 15.26) suggesting a wider sulcus angle has a protective effect against cartilage degeneration and OA (Teichtahl et al., 2007). Tanamas and colleagues also previously reported that a wider sulcus

angle associated with increased lateral patella cartilage volume (Regression coefficient 43.27 mm^3, 95% CI -2.43, 88.98 mm^3) in a cross-sectional study of obese or overweight adults recruited from community advertising and obesity clinics (Tanamas et al., 2010a). However, there was no association between sulcus angle and WOMAC pain. This study was conducted among 240 community-based adults having knee pain and were aged 25-60 years in age.

However, some of our results are discordant with those of previous studies. For example, in a cross-sectional study with 213 participants with knee OA, Kalichman et al (2007) found an increasing sulcus angle to associate with increased lateral and medial cartilage loss (OR= 2.8; 95%CI1.6,4.8) (Kalichman et al., 2007a). Similarly, in a cohort study of 3,075 participants (mean age 73 years) with and without knee pain, Hunter and others found a wider sulcus angle to associate with medial JSN progression (OR=2.99; 95%C 1.30, 6.43) (Hunter et al., 2007a).

Contrary to our findings, in a prospective cohort study of 3,026 individuals, aged 50 to 79 years, who had knee OA or were at a high risk of knee OA at baseline, Stefanik et al, reported a wider sulcus angles had higher chance of cartilage damage (OR=1.5; 95% CI 1.1, 2.1) and BML OR=1.6 (95% CI 1.1, 2.3) (Stefanik et al., 2012b).

In a retrospective MRI study, Tsalvas and colleagues compared participants with normal knees to those with PFJOA and found a correlation between cartilage defects and wider sulcus angle (spearman's rank correlation= 0.443;$p<0.001$) (Tsavalas et al., 2012).

However, despite having a good sample size (n=516), the study was only limited to participants with PFJOA.

A wide sulcus angle was associated with knee OA in some studies. Most of those used MRI images to measure sulcus angle (Kalichman et al., 2007a), (Tsavalas et al., 2012), (Stefanik et al., 2012). The mean values of sulcus angle was also different in these studies. In our study the mean (SD) value of sulcus angle was found to be 142.5 (5.39) which was in line with other radiographic bone morphology studies (Davies-Tuck et al., 2008). (Mulligan and Jones, 1997) which has examined sulcus angle.

For instance, the mean value of sulcus angle was 130.9 (8.9) in (Stefanik et al., 2012) and 132 (7.2) in (Tsavalas et al., 2012). Difference of anatomical location of the femoral condyle at which the measurement of sulcus angle was taken in MRI studies might explain this variation. However one MRI based study had a similar findings as ours of narrow sulcus angle being a risk factor for OA (Tanamas et al., 2010a).

In addition, we have used skyline views to determine sulcus angle, whereas different views were used in MRI - axial MRI view in (Stefanik et al., 2012) and sagittal view in (Kalichman et al., 2007a) which could have resulted in observational variations.

We found a strong association between a narrower condylar angle, which may result in a more laterally placed patella due to the pull of vastus lateralis, and associate with knee OA. These findings accord with most other studies (Hunter et al., 2007a), (Kalichman et al., 2007a). Although using different nomenclature (lateral patellar tilt angle, LPTA), the method of determining this angle in previous studies was similar to that used in our study. Kalichman *et al* (2007) found a narrower condylar angle to be associated with lateral cartilage loss (aOR=0.3; 95%CI 0.2,0.5) and BMLs (aOR=0.4; 95%CI 0.2,.0.8) (Kalichman et al., 2007a). In this above mentioned cross-sectional observational study of 214 participants with symptomatic knee OA, MRI was used to determine the condylar angle and radiographs were used for evaluation of PFJOA.

A narrow condylar angle associated with increasing severity of cartilage lesions in a radiographic study (n=595) conducted by Hunter et al. It was also reported that a wider condylar angle had a protective effect against PFJOA progression (aOR=0.19; 95%CI 0.09, 0.43) (Hunter et al., 2007a).

Similarly in an MRI study of 240 participants with knee pain, Tanamas et al found that as the condylar angle became wider, the medial patellar cartilage volume also increased. They also found a reduction in the WOMAC pain score when the condylar angle became wider, suggesting a protective effect (Regression coefficient 51.38 mm3, 95% CI 1.68, 101.08 mm3) (Tanamas et al., 2010a)

A wider distal femoral tilt and wider proximal tilt was found to be associated with knee OA, and TFJOA in our study. Driban and colleagues reported a similar association between increasing tibial slope and accelerated knee OA in a radiographic case-control study (aOR = 1.15, 95 % CI 1.01, 1.32). Accelerated knee OA was defined as present if the K/L increased from <2 to 3 or 4 within 48 months. However, they did not find any association between increasing tibial slope and more mildly progressive OA defined as a one grade increase in KL score and excluding cases with accelerated OA progression (aOR = 1.04, 95% CI 0.91-1.19). Although using different nomenclature, their method of measurement of tibial slope was similar to our method of measuring proximal tibial tilt (Driban et al., 2016) .

Another nested matched case-control study design study with 354 control knees and 354 case knees investigated whether the morphology of proximal tibiofibular joint (PTFJ) is associated with increased risk of incident radiographic OA over 4 years in the OAI study (Chang et al., 2020). They found that greater contact area [aOR=1.64(95% CI 1.26, 2.16)], higher load-bearing area [aOR= 2.39; (95%CI 1.48, 3.86] and greater posterior stress-bolstering area [aOR=2.79; (95% CI 1.60, 4.87)] of PTFJ were all associated with increased risks of incident radiographic PTFJ OA (Chang et al., 2020). Since the fibula is on the lateral side, greater load is on the medial tibial plateau with increased upward and forward force from the fibula, thereby increasing the force across the medial tibio femoral compartment. Any changes in the normal joint geometry may result in excessive loading forces thereby increasing the risk of development of knee OA (Chang et al., 2020) .

The association between knee malalignment and knee OA has been reported previously [(Cahue et al., 2004);(Elahi et al., 2000);(Sharma et al., 2010b); (Brouwer et al., 2007)] with varus alignment being a strong risk factor associated with knee OA.

Sharma and colleagues (2010) found varus malalignment to be associated with incident TFJ OA (aOR=1.49; 95%CI 1.06.2.10). Their definition of varus alignment was similar to that used in our study (≤178°). Despite having a bigger sample size than our study, their study was limited to participants with TFJ OA.

Brouwer et al (2007) found varus alignment to be associated with both incidence (aOR= 2.06, 95% CI 1.28, 3.32) and progression (aOR= 2.90, 95% CI 1.07, 7.88) of knee OA (Brouwer et al., 2007).

Varus alignment was found to increase the risk of medial PFJOA progression (aOR =1.85, 95% CI1.00, 3.44) in a study conducted by Cahue et al (2004). However, their study had the limitation of not being a population-based study.

Valgus alignment was not associated with knee OA in our study. However, valgus alignment was found to be a risk factor for knee OA in some previous studies [(Teichtahl et al., 2008); (Cahue et al., 2004); (Elahi et al., 2000)].

This may be because the sample size of valgus knees in our study was small and hence might have given insufficient statistical power to determine a significant association.

Two of the novel measurements in our study, specifically patellar thickness and patellar width, were found to associate with PFJOA. Smaller measures of these two (i.e. a smaller patella) associated with PFJOA. Previous studies have not examined these morphological features, and further studies of these findings seem warranted. A smaller patella may lead to patellar displacement and joint instability.

Other novel measurements in our studies such as condylar plateau angle, patellar width, condylar width, medial condylar height and lateral condylar height had no association with knee OA, TFJOA and PFJOA.

To summarize, most of our findings are consistent with the results of previous studies, while some disagreement is evident especially with regard to sulcus angle. A wide sulcus angle was associated with knee OA in some studies. Most of those used MRI images to measure sulcus angle (Kalichman et al., 2007a), (Tsavalas et al., 2012), (Stefanik et al., 2012). The mean values of sulcus angle was also different in these studies. In our study the mean (SD) value of sulcus angle was found to be 142.5 (5.39) which was in line with other radiographic bone morphology studies (Davies-Tuck et al., 2008). (Mulligan and Jones, 1997) which has examined sulcus angle. For instance, the mean value of sulcus angle was 130.9 (8.9) in (Stefanik et al., 2012) and 132 (7.2) in (Tsavalas et al., 2012). Difference of anatomical location of the femoral condyle at which the measurement of sulcus angle was taken in MRI studies might explain this variation. However one MRI based study had a similar findings as ours of narrow sulcus angle being a risk factor for OA (Tanamas et al., 2010a).

In addition, we have used skyline views to determine sulcus angle, whereas different views were used in MRI - axial MRI view in (Stefanik et al., 2012) and sagittal view in (Kalichman et al., 2007a) which could have resulted in observational variations.

Most of the studies which have previously reported a wider sulcus angle as risk factor of progression of OA (Kalichman et al., 2007a), (Tsavalas et al., 2012) and not of OA incidence. Bone remodelling and osteophyte formation might have already occurred in these studies causing variation in the sulcus angle findings.

Hence these finding cannot be generalised to sulcus angle as a risk factor for incident OA.

Severity and definition of OA in studies might have also affected the results. GOAL participants included as cases in this study had severe end-stage knee OA, while participants in other studies has less severe knee OA (Tsavalas et al., 2012).

In conclusion, the findings of this and previous studies suggest that an excessive widening or narrowing of sulcus angle could have detrimental effect on the cartilage and thereby increasing the risk of OA incidence and progression. Further studies are warranted to confirm this.

The finding of an association between narrower condylar angle and a higher WOMAC pain score is in line with one other study (Tanamas et al., 2010b). Tanamas et al, in a community-based study of 240 adults aged between 25- 60 years, examined the association between condylar angle and WOMAC pain score. They reported that for every one degree increase in condylar angle, WOMAC pain was reduced by 3.13 units (95% CI -5.60, -0.67). (Tanamas et al., 2010b).

In our study, a narrow condylar angle also associated with higher summated and PF osteophyte on the NLDLDA scores and higher KL grading. A similar finding was reported in a cross-sectional observational study which examined the association between condylar angle and osteophytosis (Kalichman et al., 2007b) in 126 men and 87 women with TFJOA. They found that as the condylar angle became narrower the risk of developing osteophytes in the lateral PF compartment reduced [OR=.0.35; 95%CI 0.21, 0.60] (Kalichman et al., 2007b). Thus, these findings suggest a narrow condylar angle is a risk factor for both structural and symptomatic knee OA.

We found that increasing varus alignment was associated with increasing summated and TF osteophyte scores of the NLDLDA and higher KL grading. Several studies have examined the relationship between knee joint alignment and the radiographic features of knee OA (Teichtahl et al., 2007), (Felson et al., 2004), (Im et al., 2016), (Laxafoss et al., 2013). Teichtahl and colleagues, in a study of one hundred and twenty one participants with symptomatic knee OA, reported that increasing varus knee alignment was associated with increasing risk of

radiographic osteophyte formation [βcoef =0.90 (95% CI: 0.83,0.97) ; p=0.005]. Felson and colleagues, in a study of 270 subjects , reported that radiographic compartment osteophyte score had a strong association with malalignment to the side of the osteophyte [OR =1.9 (95% CI 1.5, 2.5, P<0.001)] (Felson et al., 2004).

In another study, that examined the association between varus knee alignment and KL grade of 251 people with symptomatic knee OA, varus alignment was found to associate with increased KL grade [βcoef=6.11; 95%CI 4.46, 7.78; p=0.0001] (Im et al., 2016). A Danish cohort study with 3,488 participants also reported a significant linear association between varus alignment and increased KL score in knees [βcoef =0.55; 95 %CI 0.29, 0.81; p<0.05)] (Laxafoss et al., 2013). The findings of our study are consistent with these previous studies.

Variation of morphologic measurements with demographic characteristics.

In our study, measurements such as patellar width, patellar thickness, condylar width, and intercondylar width had positive associations with increasing height of the participants.

Teichtahl and colleagues have attributed to the fact that height related increase in the bone dimension and corresponding increase in the stress on the joint may be responsible for this variation of bone morphology with height (Teichtahl et al., 2012).

Most of the measurements were bigger in men compared to women in our study. Bigger body size in men and difference in the lower extremity loading between men and women may explain this finding. This difference with gender is to due increased androgen levels in men and also the direct role played by androgen in skeletal growth (Clarke and Khosla, 2009). Before puberty in both sexes, the bone dimension increase progressively and similarly. Boys attain puberty about 2 years later than girls, resulting in larger bone dimensions (Nieves et al., 2005), which further increases in size due to the effect of androgens.

Mahfouz et al found that women had smaller knees than men, with a mean 5mm smaller anterior-posterior dimension than women of all ethnic groups (Mahfouz et al., 2012).

Similarly, in a study of 1,000 patients who were awaiting TKR, it was reported that women had smaller bones and narrower distal femoral geometry than men ($p<0.001$) (Bellemans et al., 2010). Additionally, they found women had

comparatively smaller medio-lateral tibial dimension than men (Bellemans et al., 2010). One MRI study reported that men had 4-16% larger knee morphological features than women (Han et al., 2016).

Previous studies using statistical shape modelling have also explored the association between gender and bone shapes [(Wise et al., 2016); (Wise et al., 2018) ; (Ding et al., 2005)]. In a case-control study of 608 individuals with and without knee OA, statistical shape modelling was used to determine the association of distal femur and proximal tibial shape with knee OA and gender. This study reported that tibial mode 2, tibial mode 3, tibial mode 10 and femoral mode 4 were significantly associated with gender ($p<0.05$) (Wise et al., 2018). Similarly, distal femoral modes 1,3,5,6,8,12 and proximal tibial modes 2, 3, 4 were associated with gender ($p<0.01$) in another radiographic study with 340 participants without OA (Wise et al., 2016).

Age was positively associated with patellar thickness and negatively associated with distal femoral tilt in our study. Age related increase in knee bone shape might be the reason for this. In addition, it is hypothesised that, the need to maintain adequate bone mechanical competence in the face of declining bone density may result in age related variation (Ding et al., 2005).

Association of knee morphology and age was examined in a cross-sectional MRI study of 373 participants conducted by Ding et al (Ding et al., 2005). They reported that medial and lateral tibial bone surface area was positively associated with age ($\beta=3$ to $4.7mm^2$/year; $p<0.05$). Additionally, patellar bone volume had a positive association with age ($\beta=34.4$/year; $p<0.05$).

In another MRI cross-sectional study of 535 non-arthritic knees, femoral condylar measurements - specifically femoral width, medial posterior condylar offset, and distance from the distal and posterior cartilage surface to the medial/lateral epicondyle - were negatively associated with age ($p<0.001$)(Han et al., 2016). Similarly, in another MRI study, measurements such as epicondylar width, intercondylar height and width and medial and lateral condylar width were found to be negatively associated with age ($p<0.01$) (Murshed et al., 2005).

To sum up, we found that the linear measurements in our study varied with age, height, weight and gender. However, it was of interest that none of the angular measurements varied with age, sex, height or weight. This suggests that there is a proportional change in size of different bones resulting in maintained relative alignment.

Cumulative risk model.

We examined the cumulative risk contribution from the knee morphological features and demographic features to predict knee OA. We found that 90% of risk can be explained by these morphological features together with age, gender, height and weight.

Risks prediction models for knee OA have been developed in previous studies (Zhang et al., 2011), (Magnusson et al., 2019), (Kerkhof et al., 2014), (Takahashi et al., 2010), (Blanco et al., 2015).

The Nottingham 12 year risk prediction study developed risk prediction models for incidence of radiographic knee OA (model 1), and incidence of symptomatic knee OA (model 2) (Zhang et al., 2011). Participants in this study consisted of 424 people aged over 40 years recruited by knee pain questionnaire. Model 1 and model 2 were developed with age, gender, BMI, occupational exposure, family history and knee injury as the exposures.

Predictability power of these two models were moderate with an AUC of 0.69 and 0.70 in the Nottingham knee OA retrospective cohort study population; AUC of 0.60 and 0.60 in the Osteoarthritis initiative cohort study and an AUC of 0.74 and 0.79 in the GOAL study (Zhang et al., 2011). Although not directly comparable to our study as we did not perform risk prediction modelling, the AUC was smaller than in our study.

Magnusson et al developed a model to predict the 40 year risk of knee OA in (Magnusson et al., 2019) in a cohort study with 40,118 young men aged 18 years. Exposures variables included in the model were age, BMI and knee injury. This model showed a moderate predictability with AUC of 0.60 (Magnusson et al., 2019).

Similarly, another study developed and validated a prediction model for incident radiographic knee OA. Participants of this study consisted of aged 55 years or older individuals recruited from the Rotterdam Study, which was a prospective cohort study of men and women. They reported moderate predictability with an AUC of 0.60. The model included age, BMI, gender genetic scores, questionnaire variable and biochemical marker as the exposure group (Kerkhof et al., 2014).

Another study used genetic factors specifically ASPN, GDFS and DVWA and clinical information such as age, gender, BMI in their models for predicting knee OA (Takahashi et al., 2010). The study consisted of 933 OA and 1,225 controls who were recruited from various Japanese medical institutes. Model 1 was developed with only the number of risk alleles for genes such as ASPN, GDFS and DVWA. Model 2 was a combination of both genetic factors and clinical information of the participants (age, sex, BMI). Model 1 predicted knee OA poorly of AUC 0.554, while Model 2 had a good predictability power of AUC 0.867 (Takahashi et al., 2010).

Similarly a predictive model for knee OA with good accuracy (AUC of 0.82) was reported in a previous study which had 595 knee OA participants (Blanco et al., 2015). The predictive variables included in this study were a combination of genetic and clinical features (Blanco et al., 2015).

We developed cumulative risk model with knee morphological features and demographic features. However this model still requires validation in an external population. Ideally a risk prediction model requires development and validation. For instance the Nottingham 12 year risk prediction model has been validated in one internal and two external population (Zhang et al., 2011). Hence our model can be only considered as a cumulative risk model confined to our study and not as a knee OA risk prediction model in general.

It is worth mentioning that one of the models developed by us which included only demographic features such as age, gender, height and weight as the exposure group, predicted knee OA poorly. However when significant morphological features were added to this model, it enhanced the ability of predictability for knee OA remarkably. Hence this highlights the role of the identified morphological features in prediction of knee OA.

4.3 Possible biomechanical explanations

Stability and optimal distribution of load across the knee is necessary for normal functioning of the joint. This in turn depends upon the geometry and properties of the articulating joint. Any changes in the joint geometry can alter congruity and lead to abnormal loading and subsequent stress and damage to joint tissues (Guccione et al., 1994) .

Distal femoral condyles undergo internal rotation to the patella at 90^0 during knee flexion. A wider distal femoral tilt can cause the patellar tendon to be abnormally twisted and can exert more PF force on the patella (Kawahara et al., 2015).

The shape and slope of the proximal tibia have an important role in biomechanics of the knee by contributing forces across the anterior cruciate ligament (ACL) (Lansdown and Ma, 2018). Proximal tibial slope was found to have a direct relationship with cruciate ligament forces, tibial shear force and anterior tibial translation in both non weight-bearing and weight-bearing conditions (Shelburne et al., 2011).

As the proximal tibial slope increases the anterior tibial translation increases, thereby increasing the stress on the ACL. For 5^0 increase in the proximal tibial tilt, forces across the ACL will be increased by 136 N. It is increased to 460 N when the proximal tibial tilt becomes wider by 10^0 (Marouane et al., 2015).

An increasing proximal tibial tilt can exert more load on the ACL which can result in ACL injury. Hence a wide distal femoral and wide proximal tibial tilt can disturb the normal biomechanics and potentially predispose to knee OA.

A wider sulcus angle and a wider intercondylar width provide a better area for articulation with the patella, thereby reducing PF contact stress and providing an optimal retro-patellar joint load (Davies-Tuck et al., 2008a), (Teichtahl et al., 2007),(Tanamas et al., 2010a). With a narrow sulcus angle and a smaller intercondylar width, the contact area between the patella and sulcus angle is reduced as it tracks along the femur. This may result in instability to the PFJ and lead to an asymmetrical distribution of forces and an abnormal mechanical joint load within the joint. With the shearing forces being constantly increased, such knees remain vulnerable to severe stresses that can lead to pathological changes in the cartilage (Schindler and Scott, 2011).Decrease in contact area is also an important cause of pain due to the increased cartilage stress (Sheehan et al., 2009).

Additionally, a wider sulcus has a direct relationship with patellar cartilage thickness (Davies-Tuck et al., 2008a). Patellar cartilage thickness increases as the angle becomes wider, and hence may exert a protective effect against the degenerative process of OA (Davies-Tuck et al., 2008a) (Teichtahl et al., 2007). Hence a narrow sulcus angle and narrow intercondylar width may predispose to knee OA.

A narrower condylar angle suggests a more laterally placed patella.

During knee movement, a laterally placed patella would be compressed against the lateral femoral condyle instead of distributing load evenly between the lateral and medial PF compartments. Abnormally high forces of compression, mainly

acting on lateral PF compartment could contribute to an abnormal load on the cartilage and resulting its degeneration (Kalichman et al., 2007b), (Tsavalas et al., 2012).

The articular pressure is distributed evenly on the lateral and medial patellar facets at the physiological Q -angle (Huberti and Hayes, 1984) (Elahi et al., 2000). Varus alignment increases the adduction thereby increasing the Q-angle, which exerts more stress to the medial PF compartment. This abnormal loading pressure may have detrimental effects on the cartilage, leading to its degeneration (Sharma et al., 2010b).

Narrow condylar angle was associated with increasing severity of WOMAC pain score and osteophyte scores of the NLDLDA in our study. One plausible explanation is that a medially inclined patella due to a narrower condylar angle offsets the natural tendency of the patella to track laterally. This might cause abnormally high pressure across the affected joint and subsequent pain produced from PF OA. Patellar instability, caused by a narrow condylar angle may lead to excessive traction and compression forces on articulating cartilage of the patella and femur and can accelerate osteophyte formation and also lead to JSN. (Kalichman et al., 2007b)

Varus alignment was associated with structural features of knee OA. In knee joints with pre-existing damage due to OA, the added asymmetrical pressure due to varus alignment may lead to further damage in the joint surface and additional JSN. Osteophyte formation may be the result of bone remodelling in order to maintain the structural stability (Laxafoss et al., 2013) so higher osteophyte

scores would be consistent with the joint response to abnormal biomechanical forces.

4.4 Limitations of the study.

There are several caveats to this study.

1. This was a case-control study and can only identify associations. Ideally, a prospective study is required to determine the temporal association between risk factors and development or progression of OA.
2. This was a radiographic study, involving two two-dimensional views of the knee. Compared to MRI, plain radiographs are relatively insensitive at identifying the early changes of knee OA (Podlipská et al., 2016). It is therefore possible that some knee radiographs included in the study had radiographically undetected early or mild OA.
3. There might have been some variations in positioning which might have affected the accuracy of the radiographic measurements. However, a standard positioning protocol was followed for all radiographs, and a protocol was followed for all measurements undertaken using a ruler to maintain the position throughout.
4. GOAL was a hospital-based study in the UK, which was mainly designed to investigate the association of genetic-environmental interaction in Caucasians with OA. The generalizability of the findings to other populations and ethnic groups remains in question, and further studies in other populations are required.
5. This study was undertaken in a hospital setting and was not a random population sample, so there may have been some selection bias, especially

with respect to the non-OA control group. Selection of advanced knee OA requiring TJR might be another bias since some patients might have had cardiovascular disease or other comorbidities, which are considered relative contraindications for surgery.

6. Inter-rater reproducibility with a different reader was not undertaken in this study although intra-rater reliability was undertaken at three different times and shown to be very good.

7. This study is based on the assumption that the unaffected knees represents the morphology of the affected knees before the onset of OA. However, since knee OA is predominantly bilateral it is possible that the apparently unaffected contralateral knee had undergone early bone remodeling as part of the process of OA which might have occurred before the presence of other OA features, such as osteophyte and narrowing, that are evident on radiographs.

   In addition to this, abnormal gait changes and load-bearing due to knee OA on the other side might have affected the normal biomechanics of the normal contralateral knee. Ideally a prospective study is required to examine early adult constitutional shape and subsequent development of incident knee OA.

8. Patellar height was not examined in our study. A high ISR which suggests patella alta has been found to be associated with knee OA in previous studies [(Tanamas et al., 2010b); (Stefanik et al., 2010)]. However, this measurement requires a lateral view for examination.

9. WOMAC knee pain scores do not differentiate between TF or PF pain, and only relate to pain in the past two-day period. However, the WOMAC score was the main pain score used in GOAL and has been widely utilized in many studies of knee OA. Other studies may use different questions to ascertain presence of pain.

10. We used the anatomic axis to determine the frontal plane knee alignment. The mechanical axis can be estimated from this, as described by Krause et al (Kraus et al., 2005). Mechanical axis is the gold standard measure of knee alignment and is the angle formed by a line from the centre of the head of the femur to the centre of the tibial spines and from the centre of the tibial spines to the midpoint of the talus at the ankle joint (Moreland et al 1987). However, this requires a weight-bearing AP radiograph of both lower extremities from the pelvis to the ankle (Moreland et al 1987; Sharma et al 2001). These full-limb radiographs are expensive, entail radiation exposure to the pelvis, require skilled radiographers and special equipment (Kraus et al 2005). Additionally, the anatomic axis has a good to excellent correlation with the mechanical axis (r=0.54-0.88). In a recent study, the anatomic axis measured using the method described by Krause et al was shown to have the best correlation with the hip-knee angle (r=0.65) (McDaniel et al 2010).

4.5 Implications of the study and future work

Identifying the morphological risk factors for knee OA, and subsequent development of a risk prediction model helps to identify subsets of people at higher risk of developing knee OA. These angular and linear measures of knee morphology can be easily measured on radiographs and could be used in the clinical setting to identify those who are vulnerable to develop knee OA. Early intervention and disease prevention techniques such as weight loss, strengthening exercise, and minimization of specific activities that may cause adverse biomechanical stress could be advised to such people at high risk.

Future studies should address the caveats raised in the previous section. We hypothesize that these abnormal measurements are constitutional risk factors for the development of knee OA, hence for future prospective studies it is important to include and adjust for the variation in these morphological features.

Future prospective studies should include more sensitive imaging techniques, such as MRI or CT, to detect and measure bone changes and provide three dimensional details. Also, the application of statistical shape models in future studies can help in describing the variation in whole knee joint geometry with respect to OA and so may be better at predicting knee OA development with better sensitivity and specificity.

Future studies should also investigate further role of genetics in variation of bone shape that predates OA, using research methods such as Mendelian randomization that can aid in establishing causal effects of exposure on the disease without being affected by confounders.

4.6 Conclusion

This case-control study investigated the association of morphological features with knee OA by comparing the unaffected knees of people with unilateral knee OA to knees of people with no knee OA. The symmetry of measurements between left and right knees in both men and women in the normal control group support the assumption that in unilateral knee OA participants, the morphology of the unaffected knee reflects the morphology of the OA affected knee prior to the onset of OA. We have identified morphological features that can act as independent risk factors of OA or as a group when combined with the other known risk factors of OA such as age, gender, weight and height. Narrow condylar angle associated with both structural and symptomatic features of knee OA, while varus mal-alignment associated with structural features alone. Further prospective studies are required to confirm these findings.

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