The Risk of Knee Pain and Knee Osteoarthritis in Professional Footballers

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Abstract

Introduction:

Knee osteoarthritis (KOA) is a common complex disorder. Although previously believed to be degenerative, KOA is in fact a regenerative condition, compensating against insults sustained at the joint. However, a failure of this compensatory repair process, especially in the presence of constitutional and local joint factors, increases the risk of KOA and inevitably leads to joint-failure (Dieppe and Lohmander, 2005, Arden and Nevitt, 2006, Sandell, 2012).

Diagnosis of KOA may be made via clinical presentation, imaging, or using clinical algorithms, which may be a combination both in addition to biochemical diagnostic tests (Brandt et al., 2003). Knee pain (KP) is the most common symptom, and in the general population its prevalence is 25% (Peat et al., 2001a). Patients may also experience early morning stiffness of the joint and reduced function. Physician-observed signs include crepitus, restricted movement, and bony and soft tissue swellings (Abhishek and Doherty, 2013).

Although considered the gold standard to diagnose KOA, plain film radiography is not without its limitations (Wick et al., 2012). Clinicians, however, favour radiography because it can easily discern two key features of the condition: joint space narrowing (JSN), a surrogate of cartilage loss, and the formation of osteophytes on the joint margin (Roemer et al., 2014). Assessment of radiographs is most commonly undertaken using Kellgren-Lawrence (KL) grade verbal descriptors (Altman et al., 1986a). The prevalence of radiographic KOA (RKOA) may be higher than KP, but there is a discordance between people

reporting symptoms and those with structural change (RKOA) (Peat et al., 2001a, Bedson and Croft, 2008).

A plethora of constitutional risk factors and joint-specific biomechanical factors increase the risk of KOA, including joint injury and occupation (Suri et al., 2012, Silverwood et al., 2015). One such occupation, which has a greater risk of injury are professional footballers (Drawer and Fuller, 2002) and knee injuries account for 17% of all footballing injuries (Ekstrand et al., 2011). Football is one of the most common team sports worldwide, with over 265 million people worldwide play the game (FIFA, 2007a), and of these, 110,000 are male professional footballers (FIFA, 2007b). Although perceived that that footballers are at great risk of long-term consequences such as KOA, due to their high risk of injury, the current evidence supporting this is limited (Kuijt et al., 2012, Tran et al., 2016).

The previous studies observing KOA in footballers are difficult to generalise to the wider football population. This is for a number of reasons, including recruitment of inadequate sample, absence of inappropriate control groups, and differing case definitions, all resulting in a large variation in prevalence of KOA. Thus, there exists a need for a comprehensive study to determine the true prevalence and risk of KOA in retired professional footballers compared to the general population.

Aims:

(1) To determine the prevalence and risk of KOA (measured as KP, RKOA and requirement for total knee replacement (TKR)) in retired professional footballers compared to the general population;

(2) To determine the specific factors (constitutional, biomechanical and football-specific) that are associated with an increased risk of each of these outcomes (KP, RKOA and TKR) within footballers.

Methods:

The Nottingham University Hospitals NHS Trust and the Nottingham Research Ethics Committee (Refs 14/EM/0045; 14/EM/0015) approved this study, which was registered on the clinicaltrials.gov portal (NCT02098044; NCT02098070).

This study design involved carrying out two cross-sectional studies. The Football Study involved distributing 4775 postal questionnaire surveys to retired professional footballers via multiple sources, including football clubs, their former players' associations and the Professional Footballers Association (PFA). The Knee Pain and Related Health in the Community Study (KPIC) involved distributing 40,500 postal questionnaires, via 12 general practice surgeries, to both men and women in the East Midlands general population. However, only men formed the control group for this study. The inclusion criteria for both the footballers and control participants was the same: men aged 40 and older.

The questionnaires, developed based on previously literature, were similar to capture detailed information about KP, undergoing a TKR and putative risk factors for KOA, including knee injuries, surgery and alignment. The questionnaires also gathered information regarding demographics, medical and occupational history, general health and current medication.

Following this, footballers and controls who consented had radiographic assessments of both their knees, including weight-bearing semi-flexed posterior-anterior (PA) view using the Rosen template (Rosenberg et al., 1988) and a seated 30° flexion skyline view. A single observer (GSF) scored all the radiographs as a single mixed batch using HIPAX Dicom software. In addition to the KL grades, the Nottingham Line Drawing Atlas (NLDA) was used (Nagaosa et al., 2000) (Wilkinson et al., 2005), which scored composite joint space narrowing (JSN), composite osteophyte, and a combined global score for each knee.

Primary outcomes observed were current KP, RKOA (measured using the NLDA) and TKR. Secondary outcomes observed were ever having KP (chronic), physician-diagnosed KOA, RKOA (measured using KL grades) and radiographic CC. Power calculations determined the sample size for the questionnaire survey and the radiographic survey. Categorical variables presented as frequency and percent and compared using a chi-squared test. Continuous variables presented as mean and standard deviation and compared using a t-test.

The risk of KOA (measured for each outcome independently) in footballers compared to the controls was determined using a generalised linear model (GLM) with a Poisson distribution, and adjusted for known risk factors (including age, body mass index (BMI) and previous knee injury). The specific risk factors within footballers associated with outcomes of KOA (namely KP, RKOA and TKR) were determined using multivariate logistic regression.

Results:

1207 footballers (response rate of 25.3%) and 4085 control men responded to the Football and KPIC studies respectively, which was far lower than studies previously conducted in both populations. Following this, 470 footballers and 500 men consented to undergoing radiographic assessment of their knees. For participants who returned the questionnaire (footballers and controls), characteristics were compared between those who underwent a knee radiograph and those who did not. Age and sustaining a knee injury were the main factors significantly difference in both.

Footballers were significantly older (3.9 years) than the controls, but were gender-matched (males-only) and had a similar BMI. Footballers had a significantly greater number of injuries (64.5% v. 23.3%) compared to the controls. They also had significantly more body pain (74.7% v. 69.8%) and therefore took more pain-relief medication (61.9% v. 28.5%). However, footballers suffered from far fewer comorbidities compared to the controls (29.4% v. 45.7%).

Footballers had a far greater prevalence of both primary and secondary outcomes. The prevalence of KP was almost twice as great in footballers (52.2%) compared to the controls (26.9%) and this increased prevalence was regardless of age. The peak prevalence of KP also occurred at least ten years earlier in footballers compared to the controls. Although the prevalence of physician-diagnosed KOA was much lower than the prevalence of KP in footballers (28.3%), it was more than double that of the controls (12.2%). Additionally, footballers (11.1%) had almost three times greater prevalence of TKR compared to the controls.

In terms of radiographic measures, the prevalence of NLDA-defined RKOA was much greater in footballers (64.0%) compared to the controls (35.2%) and this remained the case for KL grade-defined RKOA (28.5% v. 14.1%). A stricter KL grade (KL≥3) accounts for the lower prevalence compared to NLDA-defined RKOA. Radiographic CC was also just less than three times more prevalent in footballers (24.3%) compared to the controls (8.8%). Within footballers, RKOA (NLDA) was greater in the right (52.6%) compared to the left (45.3%) knee.

The greater prevalence conferred an increased risk of KOA for all outcomes. Footballers were almost twice as likely to report KP [aRR 1.92, 95% CI 1.78-2.07], more than twice as likely to report RKOA (NLDA-defined) [aRR 2.14, 95% CI 1.87-2.45] and almost three times more likely to report TKR [aRR 2.79, 95% CI 2.42-3.23] compared to the controls (following adjustment for age and BMI). The risk of having a physician diagnosis of KOA was 2.6 times greater [aRR 2.62, 95% CI 2.32-2.96] and the risk of radiographic CC was 3.4 times greater [aRR 3.36, 95% CI 2.41-4.69] in footballers compared to the controls. RKOA measured using KL grades was also slightly greater compared with the NLDA definition [aRR 2.44, 95% CI 1.88-3.15].

The risk factors for KP, RKOA (NLDA-defined) and TKR within footballers were also analysed. Following adjustment for age and BMI, a number of factors were associated with increased risk of each outcome.

The following factors were associated with increased risk of footballers having KP: being overweight [OR 1.55, 95% CI 1.16-2.06] or obese [OR 2.22, 95% CI 1.52-3.24]; having a pattern three digit ratio [OR 1.30, 95% CI 1.02-1.66]; a family history of OA (knee, hip or hand OA); and suffering from gout [OR 2.15,

95% CI 1.48-3.13]. Sustaining a knee injury [OR 4.21, 95% CI 3.27-5.42] and its consequences, surgical intervention [OR 4.37, 95% CI 3.39-5.64] and receiving an intra-articular injection [OR 2.76, 95% CI 2.18-3.50] were most the factors most significantly associated with KP.

Age [OR 1.08, 95% CI 1.05-1.10] and familial KOA or knee replacement were significantly associated with RKOA in footballers. Crystal deposition, typically in patients suffering from gout [OR 3.24, 95% CI 1.41-7.45] or with evidence of CC [OR 4.62, 95% CI 2.61-8.05] were also strongly associated with RKOA. As with KP, injury [OR 2.17, 95% CI 1.43-3.30] and its consequences, namely surgical intervention [OR 4.25, 95% CI 2.78-6.50] and receiving intra-articular injections [OR 1.60, 95% CI 1.10-2.35] were strongly associated with RKOA in footballers. A longer duration of playing football [OR 1.04, 95% CI 1.00-1.08] was also strongly associated with RKOA in footballers. For every 1000 hours trained [OR 1.13, 95% CI 1.07-1.19] and 100 matches played [OR 2.41, 95% CI 1.08-5.36], footballers had an increased risk of RKOA.

Risk factors significantly associated with footballers who had undergone a TKR, included age [OR 1.09, 95% CI 1.07-1.11], being obese [OR 1.77, 95% CI 1.00-3.12] and having gout [OR 3.11, 95% CI 1.96-4.70]. Sustaining a significant knee injury [OR 3.11, 95% CI 1.94-4.99] and receiving an intra-articular knee injection [OR 2.56, 95% CI 1.76-3.73] were also significant risk factors for footballers who underwent a TKR. However, those footballers with a longer duration of playing the game [OR 0.95, 95% CI 0.92-0.98] had a reduced risk of TKR.

Conclusion:

These findings show footballers have a greater risk of KOA compared to the general population, reporting up to three times higher prevalence of various outcomes (KP, RKOA, physician-diagnosed KOA and TKR). The age-prevalence of all outcomes of KOA, are greater in footballers compared to the controls. The high prevalence of injuries significantly account the risk of KOA in footballers compared to the controls (even following adjustment of other risk factors).

Within footballers, knee injuries, together with subsequent investigations (specifically exploratory and interventional arthroscopy) and management (specifically intra-articular knee injections), were strongly associated with risk of KOA (KP, RKOA and TKR independently).

Football's governing bodies need to set out and implement strategies to reduce or even prevent the risk of serious injury (thus reducing the risk of subsequent investigation). This will reduce the risk of long-term consequences, such as KOA. However, whether the Industrial Injuries Advisory Council considers the risk of KOA in footballers an industrial compensable disease remains a question.

Declaration

I declare that the work submitted as part of this thesis is the result of original research. I have conducted it with input as outlined below. It has not already been accepted for any degree and all authors and works to which reference have been made are fully acknowledged.

Professors Michael Doherty, Weiya Zhang, Brigitte Scammell, and Dr Colin Fuller conceptualised the study. Professors Michael Doherty and Weiya Zhang designed the study. Professor Mark Batt and Dr Colin Fuller provided broad support and guidance in terms of executing the study.

Dr Gwen Fernandes (GSF) and I were jointly responsible for recruitment of footballers: I contacted all the football clubs and former players associations; GSF and I together prepared the questionnaire survey packs for distribution to footballers.

I was responsible for organising the radiographic survey: inviting footballers to participate and subsequently arranging radiography appointments. I was also responsible for ensuring individual Spire Healthcare Hospitals across the country received the x-ray jigs to conduct the footballers' radiographs and the footballers' outpatient details prior to their appointments.

I was responsible for the data analysis presented and for writing of this thesis. Professor Michael Doherty, Professor Weiya Zhang and Dr Gwen Fernandes provided support and input. Professor Michael Doherty (principal supervisor),

Professor Weiya Zhang and Dr Gwen Fernandes undertook supervision of this thesis.

GSF was responsible for analysing all the radiographs for both the footballers and the controls (from the Knee Pain and Related Health in the Community Study). GSF also conducted inter-observer reliability with Dr Aliya Sarmanova. Mrs Sally Doherty trained GSF for the radiographic scoring.

Dr Jonathan Moses was responsible for verifying footballers' responses.

Miss Laura Schimpf provided assistance in arranging radiography appointments for all control participants at Nottingham City Hospital Radiology Department.

Miss Emily Cooper (EC) and Dr Chijioke Nwankwor (CN) were responsible for analysing and categorising occupations that were high risk. EC categorised all the footballers' responses and CN categorised all the controls' responses.

EC also assisted arranging footballers' radiography appointments.

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Glossary of Abbreviations

ACL	Anterior cruciate ligament
ACR	American College of Rheumatology
aOR	Adjusted odds ratio
aRR	Adjusted risk ratio
ARUK	Arthritis Research UK
BMI	Body mass index
BML	Bone marrow lesions
BPM	Body pain mannequin
Ca	Cancer
CC	Chondrocalcinosis
CI	Confidence interval *(95% unless otherwise stated)*
DALY	Disability-adjusted life years
DOB	Date of birth
EULAR	European League Against Rheumatism
FA	The Football Association
FIFA	Fédération Internationale de Football Association
FPA(s)	Former Players Association(s)
GBD	Global burden of disease
GLM	Generalised-linear model
GP	General Practitioner
GWAS	Genome-wide Association Studies
HRQoL	Health-related quality of life
HTN	Hypertension
IA	Intra-articular
IGF	Insulin-like growth factor
JSN	Joint space narrowing
KL	Kellgren-Lawrence
KOA	Knee Osteoarthritis
KP	Knee pain
LLI	Limb-length inequality

LMA	the League Managers Association
MI	Myocardial infarction
MMP	Matrix metalloproteinases
MRI	Magnetic resonance imaging
NICE	the National Institute for Health and Care Excellence
NLDA	Nottingham (logically derived) Line Drawing Atlas
NSAID	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OR	Odds-ratio
OTC	Over-the-counter (medication)
PF	Patello-femoral compartment of the knee
PFA	the Professional Footballers Association
PPI	Patient and public involvement
p-y	person-years
QALY	Quality-adjusted life years
QoL	Quality of life
RKOA	Radiographic KOA
RR	Relative risk
TF	Tibio-femoral compartment of the knee
TGF	Transforming growth factor
TIMP	Tissue inhibitors of metalloproteinases
TKR	Total knee replacement
UK	United Kingdom
US	Ultrasound
USA	United States of America
WHO	World Health Organisation
YDL	Years lived with disability
YLL	Years of potential live lost

Football Organisations

FIFA Fédération Internationale de Football Association

FIFA is the international governing body of association football, futsal and beach soccer. It comprises of 209 national associations (including the FA – see below) and is responsible for the organisation of major international football tournaments, most notably the World Cup.

FA The Football Association

The FA is the governing body of football in England. It is the oldest football association in the world and is responsible for overseeing both the amateur and professional game.

PFA The Professional Footballers Association

The PFA is the world's oldest professional sportspersons union, representing professional footballers in England and Wales.

Perform Part of Spire Healthcare

Perform is the Sport and Exercise Medicine (SEM) branch of Spire Healthcare, a leading provider of private healthcare throughout the United Kingdom.

1 INTRODUCTION

1.1 Osteoarthritis

Osteoarthritis (OA) is a debilitating condition, affecting synovial joints as a whole, rather than its individual structures. It is by far the most common form of arthritis (Hunter and Felson, 2006) and poses a large burden to the health service in terms of both direct and indirect costs (Cross et al., 2014).

The term *'osteoarthritis'* is derived from the Greek word, *'osteo-'* meaning bone, and combined with the term, 'arthritis'; from *'arthros-'* meaning joint, and *'-itis'* meaning inflammation. However, OA is not primarily an inflammatory process and the term 'osteoarthrosis' has been used to indicate this dissociation.

The manner of defining OA has evolved, from a single entity joint disease, to a condition with many complex aetiologies. The American College of Rheumatology (ACR) Diagnostic and Therapeutic Criteria Committee appointed a 'Subcommittee on OA' to provide a definition encapsulating OA (Altman et al., 1986b, Schiphof et al., 2014). The Subcommittee 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*".

However, OA may be more succinctly defined as "*a condition of synovial joints, characterised by focal loss of articular cartilage and subchondral bone response*" (Watt I. and Doherty M. in (Brandt et al., 2003); (Dieppe and Lohmander, 2005).

OA, inherent to synovial joints, is a metabolically active process, which has been conserved throughout evolution (Rogers et al., 1981, Hutton, 1987, Jurmain and Kilgore, 1995). Palaeontologists have found archaeological evidence of the condition in diarthrodial joints of mammals (Sokoloff, 1956) and even dinosaurs (Rothschild, 1990),. This suggests OA may not be detrimental, but an adaptive response to joint insults.

Although previously thought of as a degenerative wear and tear disease, OA is a regenerative and often successful repair process (Arden and Nevitt, 2006). A variety of insults may trigger the condition, but OA is typically asymptomatic moreover, compensates against insults. Sometimes, the repair process inadequately compensates against insults. This results in focal cartilage loss occurring primarily in the maximum load-bearing region of the joint, typically in response to local biomechanical stressors. Additionally, the presence of constitutional and systemic factors may increase the risk of the condition (Bland and Cooper, 1984, Brandt et al., 2003, Busija et al., 2010, Hunter and Felson, 2006).

The recurrent failure of the repair process (compensating successfully against joint insults) ultimately leads to 'joint failure' (see Figure 1.1) (Brandt et al., 2003). This 'joint failure' is similar to the failure of other organs in the body, such as the heart (congestive heart failure) or kidneys (renal failure), where a variety of specific initiating diseases lead eventually to a single more homogenous end-stage phenotype (Arden and Nevitt, 2006). It is such patients, who present with symptoms of clinical OA, including pain, disability, and participation restrictions (Abhishek and Doherty, 2013).

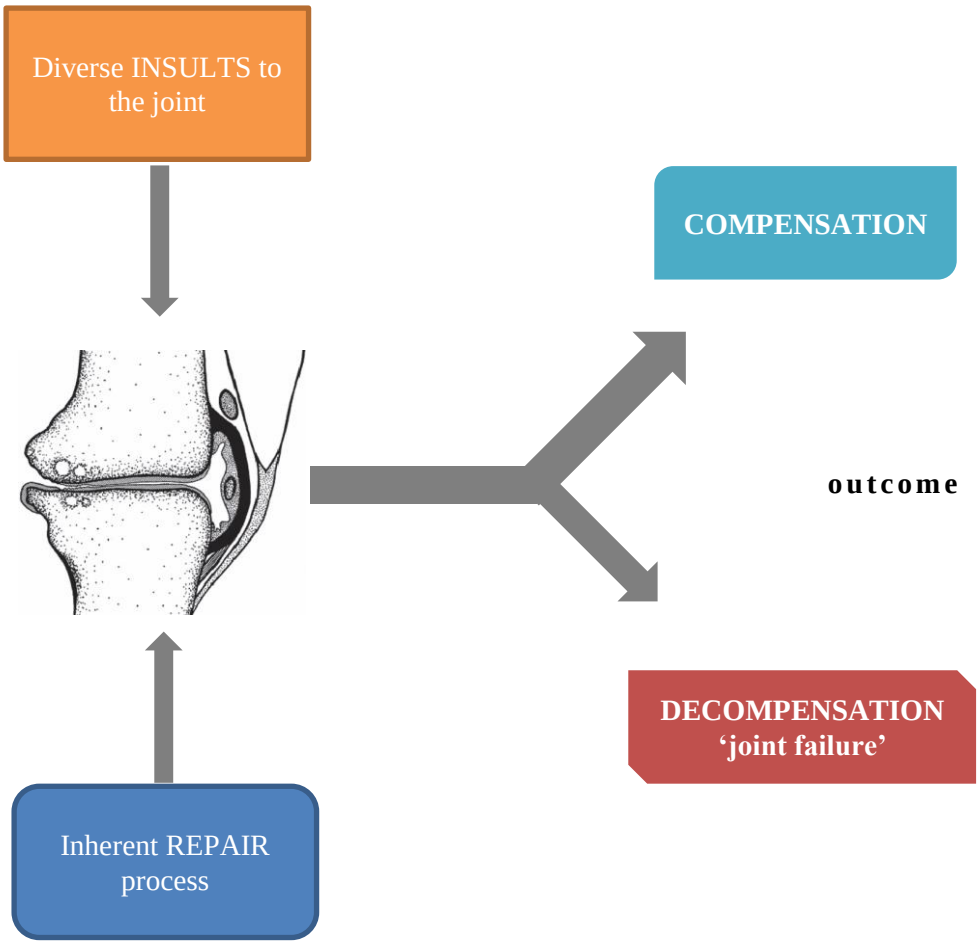


Figure 1.1 – A schematic representing the repair process of OA

This schematic shows the repair process of OA in response to a variety of insults to the joint, involving a response by all joint tissues. Insults include trauma, biomechanical or constitutional factors. The two outcomes are successful repair or compensation against the insult or unsuccessful repair, which ultimately results in joint failure (symptoms and disability)

Image adapted from (Brandt et al., 2003); line drawing of knee provided courtesy of Professor Michael Doherty

1.2 Knee Osteoarthritis

The knee joint is a complex synovial hinge joint, allowing flexion and extension, as well as limited internal and external rotation. It is comprised of two articulations: the tibiofemoral (TF) joint, between the femur and tibia, and the patellofemoral (PF) joint, between the femur and patella. Referred to as a compound joint, the knee joint has two TF (medial and lateral) compartments and one PF compartment (Drake et al., 2010). Due to its complexity, it is vulnerable to injury and the development of OA. This section specifically focuses on knee OA (KOA), including its pathogenesis, clinical presentation, diagnosis and management.

1.2.1 Pathogenesis

The nature of KOA has continued to change, based on improved understanding of the underlying pathological processes. OA was previously seen as degenerative, typically a consequence of wear and tear and ageing of the joint. However, the converse is now believed to hold true: OA is a regenerative process, which presents as symptomatic when the inherent repair process fails, independent of the natural ageing process (Brandt et al., 2003, Arden and Nevitt, 2006, Kumar P., 2009).

OA is a metabolically active process involving a dynamic repair process in response to damage (whether mechanical, inflammatory or metabolic in nature). Understanding the pathology of KOA previously focused on the focal narrowing of the hyaline cartilage and bone remodelling (including the formation of new bony spurs (osteophytes) at the joint margins). However, in addition to the

hyaline cartilage and bone, all tissues within the joint including the fibrocartilage, synovium, the capsule and the muscles are involved in OA (Bland and Cooper, 1984, Brandt et al., 2003).

Following insult to the joint, key pathological changes that occur within the joint include a focal breakdown and loss of the hyaline cartilage in the greatest load-bearing regions of the joint. There is also bone remodelling and new bone formation, as well as synovial fluid hyperplasia and capsular thickening. However, such changes are typically slow responding (Hamerman, 1989, Bland and Cooper, 1984, Kumar P., 2009).

Articular chondrocytes are first to respond, increasing rapidly in activity and number. They also become more hypertrophic in nature. This leads to an increased formation of matrix components, the most abundant of which are collagen proteins. The breakdown of these proteins (the main constituent of collagen) results in cartilage degradation (Bland and Cooper, 1984).

Matrix metalloproteinases (MMP), activated extracellularly, drive the breakdown of the extracellular matrix of collagen. Collagenase (MMP-1 and MMP-13), which cleaves collagen, and stromelysin (MMP-3), which is active against fibronectin and laminin (part of the extracellular matrix) are primary components driving this breakdown, ultimately resulting in OA (Bland and Cooper, 1984, Brandt et al., 2003, Kumar P., 2009, Tang et al., 2009).

Another mechanism disrupting MMP regulation is via tissue inhibitors of metalloproteinases (TIMPs), which also results in a degradation of cartilage and subsequently OA. Deficiencies of growth factors, such as insulin-like growth factor (IGF) and transforming growth factor (TGF), involved in collagen

synthesis may play an active role in impairing matrix repair, inhibiting cartilage formation and leading to OA (Bland and Cooper, 1984, Brandt et al., 2003, Kumar P., 2009, Tang et al., 2009).

Cells within the synovium, synoviocytes, also respond to the repair process and undergo chondroid metaplasia, resulting in the formation of fibrocartilage. Within the synovium, fibrocartilage ossifies slowly forming large osteochondral bodies (as opposed to osteophytes, which occur at the joint margins). The formation of osteophytes initially occurs as a formation of fibrocartilage at the margins of the joint. Following endochondral ossification, this fibrocartilage becomes hardened and results in the formation of spurs, known as osteophytes (Brandt et al., 2003).

These processes defining OA differ from the biochemical processes underlying ageing. The increased turnover of matrix components, and the expression of chondroitin, usually seen in cartilage during early growth, are opposite to that of ageing. In addition, the changes within the cartilage also occur in other tissues of the joint (bone and synovium) to 'repair' the joint following injury. Ageing on the other hand, is not reparative but degenerative, and does not results in new tissue formation (Kempson, 1991, Brandt and Fife, 1986, Loeser et al., 2016).

In addition to these changes in the joint, there is also an interplay involving crystal formation and deposition. There are multiple explanations regarding this and determining the type of crystal formation is necessary. It is evident with increasing age and development of KOA, crystal mineralisation is an integral part especially within the articular and hyaline cartilages (Fuerst et al., 2009a, Fuerst et al., 2009b).

Chondrocalcinosis (CC) is the deposition of calcium pyrophosphate dehydrate (and basic calcium phosphate) crystals within the connective tissue of the joint. EULAR appointed a subcommittee, which concluded calcium pyrophosphate deposition (CPPD) is an umbrella term encapsulating various clinical presentations (of calcium crystal deposition). More specifically, CC is the radiographic evidence of calcification of the hyaline and fibrocartilage and is most likely to co-associate with KOA. Radiographic CC is more likely to occur with prior trauma to the joint (Zhang et al., 2011a)

In addition calcium crystal deposition, KOA is also associated with urate crystal deposition, which is a typical feature of gout (Roddy and Doherty, 2012). The interplay between such crystal formation and KOA has many possible explanations, including both KOA and gout occurring in parallel, or one condition preceding the other. However, a more likely explanation is crystal deposition causing mechanical and inflammatory damage to the joint, which results in an amplification loop relationship (Brandt et al., 2003). Gout is becoming an increasingly prevalent condition and this association with KOA is important to note.

1.2.2 Clinical Presentation

Symptoms

People with KOA typically present to their general practitioner (GP) with pain (in or around the knee joint), which is exacerbated on use and relieved by rest. This ‘mechanical’ pain distinguishes KOA from other inflammatory conditions.

Pain caused by inactivity and early-morning stiffness (usually brief and lasting less than 30 minutes) is usually transient (Abhishek and Doherty, 2013).

KOA is one of multiple sources of chronic pain in the knee joint. Although KP may be attributable to other outcomes (Bedson and Croft, 2008), persistent worsening KP is characteristic of KOA. Such progression of KP leads to disability and, ultimately, the need for a partial or total knee replacement (TKR) (Peat et al., 2001a). In addition to pain, Table 1.1 also describes other symptoms of KOA including functional impairment, anxiety and depression (Kumar P., 2009, Brandt et al., 2003).

Table 1.1 – Symptoms and signs of KOA

Symptoms	**Signs**
Pain	Crepitus
Stiffness	Restricted movement
Functional impairment	Tenderness
	Bony swelling
± anxiety / depression	Deformity (malalignment)
	Muscle wasting / weakness
	± instability
	Effusion soft tissue swelling

Functional impairment is an important consequence, which results in participation restriction and a reduced quality of life (QoL), most likely due to disability. This may include poor mobility, difficulty with daily living activities, isolation from society and financial difficulties due to limited work prospects. However, an explanation for disability and functional impairment is not clear (McAlindon et al., 1993, Badley, 1995).

Patients may also experience anxiety and depression, which correlate with pain reporting. However, the cause and consequence of such psychological factors are difficult to determine. They ma1y be the result of suffering from a chronic condition but also may influence the severity of the pain and disability experience itself (Davis et al., 1992, O'Reilly et al., 1998).

Signs

Physical signs of KOA, observable upon clinical examination, vary greatly (Table 1.1). These include crepitus, a limited range of movements (which results in a loss of function) and bony enlargement of the joint (Brandt et al., 2003, Abhishek and Doherty, 2013).

Crepitus is the coarse crunching sensation (palpable and sometimes audible), caused by roughening of the cartilage surface in severe OA, and even grinding of bone-on-bone on movement of the joint (Brandt et al., 2003). It is more indicative of KOA in the PF rather than TF compartment (Schiphof et al., 2014).

Reduced movement is exacerbated by a modest degree of effusion or soft tissue swelling. Tenderness, along the joint line or peri-articular, may occur in symptomatic joints. Eventually, in patients with advanced KOA, muscle weakness and wasting occurs. Joint deformity, due to a varus or valgus instability, may also occur (Brandt et al., 2003, Kumar P., 2009).

However, patients with KOA do not report all the symptoms or present with all the signs, reflecting the heterogeneity of phenotypic expression of OA.

1.2.3 KOA Diagnosis

Radiography is widely accepted as the gold standard to diagnose KOA, despite its limited use (Roemer et al., 2014, Wick et al., 2012). A systematic review determined twenty-five alternative definitions (based on different criteria) to identify cases of KOA, which highlights the complexity of diagnosing the condition (Schiphof et al., 2008). KOA is most commonly diagnosed following either presentation of clinical symptoms (Section 1.2.2) or using imaging.

Clinical

Pain and associated disability (functional impairment) are characteristic symptoms used to diagnose KOA. Although KP is sufficient to diagnose KOA (Hadler, 1992), clinicians prefer the use of imaging (most commonly radiographs) to confirm underlying structural change.

Epidemiology studies tend to define cases as 'symptomatic KOA', which requires participants to report pain in addition to underlying structural change (Arden and Nevitt, 2006). Additionally, clinical algorithms set out by Rheumatology bodies, including ACR and the European League Against Rheumatism (EULAR), may be used.

American College of Rheumatology (ACR)

The ACR Diagnostic Criteria requires the fulfilment of set criteria to diagnose KOA. Table 1.2 describes two approaches: clinical or clinical and radiological (Altman et al., 1986a) (Lequesne et al., 1987). Up to four (of six) criteria, of varying combinations, are required to be met for diagnosis of KOA.

Table 1.2 – The ACR diagnostic criteria for KOA

	Clinical (A)
1	Knee pain for most days of the prior month
2	Crepitus on active joint motion
3	Morning stiffness lasting less than 30 minutes
4	Age > 38 years
5	Bony enlargement of the knee on examination

OA is diagnosed if items (1, 2, 3, 4) or (1, 2, 5) or (1, 4, 5) are present

	Clinical and Radiological (B)
1	Knee pain for most days of the prior month
2	Osteophytes at joint margin (X-ray)
3	Synovial fluid typical of OA (laboratory-diagnosis)
4	Age > 40 years
5	Morning stiffness lasting less than 30 minutes
6	Crepitus on active joint motion

OA is diagnosed if items (1, 2) or (1, 3, 5, 6) or (1, 4, 5, 6) are present

The ACR Criteria to diagnose KOA used by clinicians, bases a diagnosis of KOA on either clinical (A) or clinical and radiographic (B) presentation of the condition.

European League Against Rheumatism (EULAR)

EULAR-based recommendations to diagnose KOA included the risk factors, subsets of the clinical outcome, signs and symptoms, clinical imaging and diagnostic tests of the condition (Zhang et al., 2010).

Three symptoms and three signs were responsible for diagnosing the majority of cases of KOA. The symptoms were persistent KP, limited morning stiffness and reduced function and the signs were crepitus, restricted movement and bony enlargement. The authors found that when all six symptoms and signs were present, the risk of having RKOA increased to 99% (Zhang et al., 2010).

Radiography

Radiography, specifically, the use of x-rays, is the most favoured approach to determining structural changes of KOA. The two characteristics features of RKOA (Figure 1.2) are the presence of bony osteophytes or spurs at the joint margin, and focal loss of cartilage, seen as a loss of interosseous distance or joint space (joint space narrowing, JSN) on a radiograph.

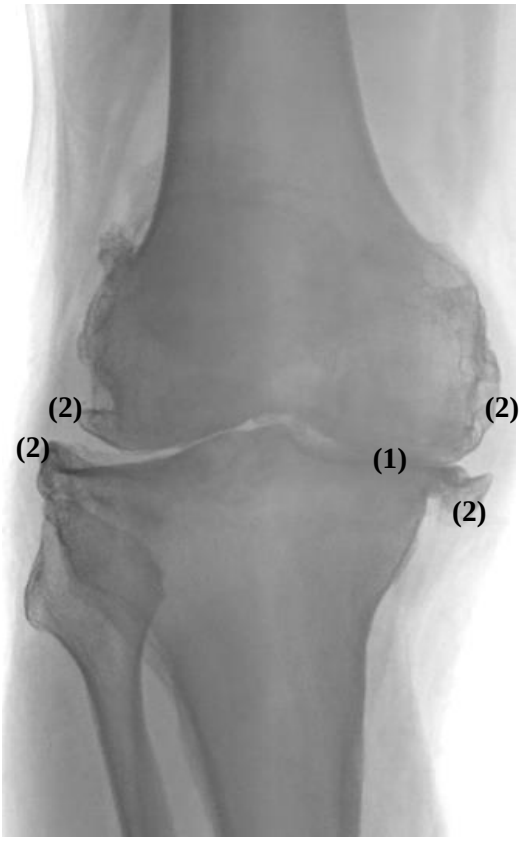


Figure 1.2 – Defining characteristic features of RKOA

The two characteristic features of RKOA, JSN (1) and formation of osteophytes (2) are clearly observable on this radiographic image.

This image was provided courtesy of Professor Michael Doherty

Both features (JSN and osteophytes) are easily discernible on radiographs and the severity of the change reflects the progression of the condition (Lequesne et al., 1987, Brandt et al., 2003). Other features, such as sclerosis, cyst formation or bone remodelling may also be apparent on radiographs (Table 1.3).

The use of radiographs to determine structural change are favoured because they are relatively inexpensive and logistically simple to carry out. It is also relatively straightforward and thus large-scale epidemiological studies favour their use compared to other imaging techniques (Hinman and Crossley, 2007, Kumar P., 2009). Such studies tend to report a high internal validity, which confers strong reproducibility for this imaging technique (Busija et al., 2010).

Table 1.3 – Observable signs of RKOA

Sign	Description
Joint space narrowing (JSN)	JSN is a marker for focal cartilage loss, and/or meniscal attrition or extrusion
Osteophytes	These are bony protrusions (spurs), around the margin of the joint
Subchondral sclerosis	Sclerosis is the thickening or compression of the subchondral trabeculae of the bone
Cysts	Cysts usually appear adjacent to focal cartilage loss (JSN)
Bone remodelling	Increased compensatory osteoblast activity results in altered shape, often enlargement, of the bone

In addition to JSN and osteophyte formation (shown in Figure 1.1), other features of RKOA observable on radiographs include sclerosis, cysts and bone remodelling.

The Kellgren-Lawrence (KL) assessment tool, used for several decades, assesses structural change of KOA observed on radiographs. Originally, clinicians used the KL Atlas to grade the severity of KOA but now favour the use of its verbal descriptors. Although much simpler, the verbal descriptors lack robustness. To

improve upon this, Nagaosa and colleagues (2000) from the University of Nottingham developed logically derived line drawings, referred to as the Nottingham Line Drawing Atlas (NLDA), to improve assessment for KOA.

Kellgren-Lawrence (Grading)

In the 1950's, Dr's J. H. Kellgren and L. S. Lawrence conducted the first large-scale epidemiological study into OA, obtaining x-ray images of the general population from various regions across England (through hospital cohorts). Using these radiographs, they derived a grading system for OA, which adopted their names (Kellgren-Lawrence, KL) (Kellgren and Lawrence, 1957, Kellgren and Lawrence, 1958).

The original KL grading system was an Atlas. In 1961, The World Health Organisation accepted the use of the KL Atlas into medical practice. The Atlas was subsequently published in Atlas of Standard Radiographs, 1963 (Kellgren, 1963). It depicted the progression of KOA in the TF compartment of the knee, irrespective of gender.

However, due to its time-consuming nature, clinicians now favour the verbal descriptors (Table 1.4) over the original Atlas to determine structural change. Although not without its flaws, the verbal descriptors remain the favoured approach to grade KOA structural change. Patients are diagnosed with KOA if they present with structural change equivalent to a KL Grade of 2 or greater ($KL \geq 2$)) (Altman et al., 1986a, Brandt et al., 1991, Arden and Nevitt, 2006).

Table 1.4 – Verbal descriptors for KL Grades (RKOA)

Grade	Description
Grade 0	No narrowing; no osteophyte formation
Grade 1	Doubtful narrowing of joint space and possible osteophyte formation
Grade 2	Definite osteophytes and possible narrowing of joint space
Grade 3	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone ends
Grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

However, the use of this case definition (KL$\geq$2) is limited. It does not account for definitive JSN, a distinct marker of RKOA, but rather focuses on osteophyte formation. Although this may be reflective of early KOA, a more robust case definition would be a KL grade of three or greater (which is indicative for both definitive JSN and definitive osteophyte formation.

A further limitation of the KL assessment tool is its inability to diagnose OA in the PF compartment of the knee. As understanding of KOA evolved, it has become apparent that the condition also affects the PF compartment. However, the KL verbal descriptors are specific only for the TF compartment. Thus, diagnosing structural change in the PF compartment is an extrapolation of the current verbal descriptors (Crossley, 2014, Hinman and Crossley, 2007).

Nottingham Line Drawing Atlas (Scoring)

The NLDA are logically derived line drawings developed by Nagaosa and colleagues. It scores JSN and osteophyte in the three knee compartments independently (Nagaosa et al., 2000), making it a robust adjunct to the verbal descriptors of the KL assessment tool.

The NLDA Scoring determines JSN and osteophyte formation in both men and women independently. JSN was determined from the normal joint space width (JSW) on a three-point interval scale, where zero indicated no reduction of JSW and a score of three indicated bone-on-bone contact. Scores of one and two indicated a reduction of JSW by two-thirds and a third respectively (Nagaosa et al., 2000).

In terms of osteophytes, the largest osteophytes were determined in each region of all compartments. From this, the scores were determined using three-point scale (as with JSN), where zero indicating no osteophyte formation and three indicating the largest osteophyte. The interval scale for both JSN and osteophyte formation is an improvement of the ordinal KL grade, thus structural change analysis in terms of JSN and osteophytes is both independent and more robust (Nagaosa et al., 2000).

Despite the inherent strengths, the NLDA was further refined 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. Additionally, negative scoring for JSN indicated an increase in JSW, which occurs in the contralateral TF compartment to that affected by OA. The use of a five-point scale improves accuracy of the NLDA to discern smaller interval changes for JSN and osteophyte formation (Wilkinson et al., 2005).

The NLDA scoring tool confers several advantages over the KL grading tool when measuring KOA structural change. Separate atlases for men and women (to reflect a larger JSW in men) for each compartment of the knee (TF and PF compartments) were developed. Measuring JSN and osteophyte formation is

independent of each other and measured using mathematically derived interval scales. This interval scale (of equal incremental changes) improves measuring of structural change, resulting in a more robust diagnosis of RKOA (Nagaosa et al., 2000, Wilkinson et al., 2005).

Other Imaging Approaches

Although radiographs are most frequently favoured to determine structural change, other imaging techniques including magnetic resonance imaging (MRI) and ultrasound (US) scans may be used.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) observes the soft tissue structures rather than bony structures observed upon x-ray.

Gudbergsen (2013) noted that bone marrow lesions (BML) occur in the subchondral bone (observable on MRI) following degeneration of the knee joint (Gudbergsen et al., 2013). This occurs simultaneously with subchondral bone expansion and meniscal tears, eventually leading to cartilage loss (Gudbergsen et al., 2013, Roemer et al., 2009, Fanelli et al., 2014).

Schiphof and colleagues (2014) reported that crepitus and a history of patellar pain are indicative of PF compartment lesions (observable on MRI) and support a diagnosis of KOA (Schiphof et al., 2014). Other discernible features of KOA seen on MRI include bone marrow oedema and cartilage lesions, often associated with clinical symptoms.

Although not commonly, due to its high cost and invasive nature, MRI provides an alternate means to diagnose KOA. MRI provides a detailed perspective of

structural abnormalities, in particular, related to the soft tissue in both compartments of the knee (Conaghan, 2006, Conaghan et al., 2006).

Ultrasound Scans

US scans are used to detecting KOA changes including synovial effusion, hypertrophy, and measure of Doppler. Such markers more discernible on US scans than osteophyte formation or JSN (Sarmanova et al., 2016).

However, there is a large discrepancy (5-90%) to diagnose KOA through US scan synovial changes. One study determined the prevalence of KOA, observed as osteophyte formation, as 30% in the population (Abraham et al., 2014). This was similar to the prevalence of KOA reported in The Johnston County OA Project (Jordan et al., 2007) and the Framingham Study (Felson et al., 1987). However, this US scan prevalence of KOA varied significantly to another study observing RKOA (prevalence of 11%) in Nottingham (UK) (Neame et al., 2004).

Despite this, further studies are required to determine definitively whether US, compared to radiography, is an appropriate diagnostic tool for KOA.

Summary of KOA Diagnosis

Clinicians diagnose KOA using many different approaches. Section 1.2.2 provided details of such approaches. Typically, a clinical history and examination may be sufficient; however, the use of established diagnostic criteria or the use of imaging may be additionally used.

Figure 1.3 summarises the various methods of diagnosing KOA. The shaded box indicate the broad approaches and the white box below it list examples of each approach.

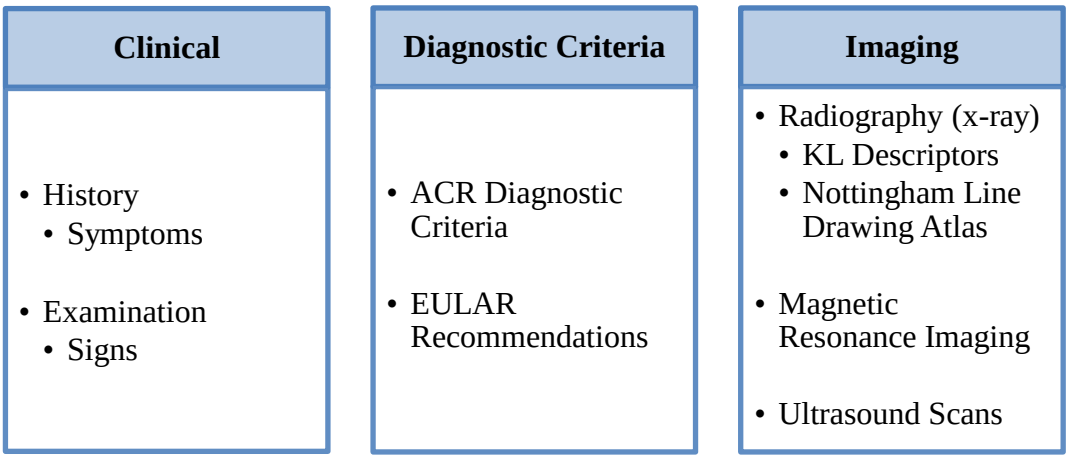


Figure 1.3 – Summary of approaches to diagnosing KOA

1.2.4 KOA Management

OA is a chronic condition with no specific cure. However, good clinical management delays the onset and progression of its debilitating symptoms, helping patients maintain a reasonable quality of life (QoL).

In the UK, the National Institute for Health and Care Excellence (NICE) governs the provision of health and social care through recommended guidelines and protocols. Management of OA requires GPs and clinicians to follows the NICE guidelines for patients presenting with the condition. These guidelines have been derived from the EULAR recommendations, especially for the non-pharmacological management of OA ((NICE), 2008b, (NICE), 2008a, Zhang et al., 2010, Fernandes et al., 2013).

Management of KOA should take into account KP severity, QoL reported by the patient, including any comorbidities, and other lifestyle factors such as

occupation, relationships and leisure activities. GPs should discuss management plans, tailored to individual patients, prior to implementation.

NICE guidelines for the core management approach for patients with KOA are educational advice and information distribution. Following this, physical activity should strongly be encouraged and assistive devices considered for those with daily living difficulties. Pharmacological interventions should be the last resort, before surgical intervention is considered ((NICE), 2008a, (NICE), 2008b).

Non-Pharmacological

Following educational advice to manage KOA, prescribing physical activity, whether aerobic or strengthening exercises, improves joint strength and integrity. For overweight or obese patients, physical activity becomes paramount; to reduce the stress inflicted on the joint and reduce the systemic risk a high BMI confers. Furthermore, physical activity slows the progression of KOA, maintaining or even improving patients QoL (Fernandes et al., 2013). For patients with difficulties with daily living, walking aids and physiotherapy are additional interventions ((NICE), 2008a, (NICE), 2008b).

Weight loss (as a physical therapy) is the ideal management strategy for patients with KOA. A recent study found that weight loss reduces pain in OA-affected joints, although it was unclear whether this was due to an altered biochemical composition in the joint or a reduction of the mechanical stress inflicted upon the joint (Weiss, 2014). It is usually the decline or cessation of physical activity itself, which leads to an increase in BMI and results an increased risk of pain and underlying structural change (of OA) (Lee et al., 2013a).

Pharmacological

Pharmacological interventions are considered as adjunctive interventions for pain relief ((NICE), 2008a, (NICE), 2008b). Paracetamol, followed by non-steroidal anti-inflammatory drugs (NSAIDs) are systemic oral analgesics to consider. However, topical NSAIDs are the favoured first line analgesic to try for KOA due to their equal efficacy as oral NSAID yet far superior safety.

More severe pain resistant to these approaches may require the use of opioids, though poor tolerability due to side effects restricts their usefulness. Intra-articular injection of long-lasting corticosteroids are recommendations to be considered for intermittent treatment of troublesome pain ((NICE), 2008a, (NICE), 2008b).

Surgery

KOA patients who have exhausted all non-pharmacological and pharmacological treatment options may be eligible for surgery. Such patients usually suffer a reduced QoL and surgical intervention, typically TKR, aim to improve this.

For people with severe OA that have not responded to conservative measures, joint replacement is the best option to consider (Dieppe et al., 2011). However, this is not always feasible based on the person's QoL or willingness to undergo surgery (Cross et al., 2000). This approach may also not provide any additional benefit compared to optimised physical or medical therapy approaches (Kirkley et al., 2008) or even other arthroscopic procedures (Leung et al., 2014).

However, undergoing a TKR is usually considered the last resort and only offered to patients with severe KOA, typically reflective of end-stage joint

failure ((NICE), 2008a, (NICE), 2008b). Although TKR surgery is recommended on a ten year cycle, patients with severe disability due to KOA have reported significant improvements in QoL outcomes following undergoing a TKR (Malviya A, 2006).

Summary of KOA Management

Although KOA is a non-curable chronic condition, improvement of patient's lifestyle improves the QoL experienced. NICE recommends a various approaches to managing KOA, including improved self-management (better diet, physical activity) to non-pharmacological and pharmacological (pain-relief medication) approaches. Undergoing joint replacement is usually the last resort for patients with end-stage joint failure (severe KOA). Figure 1.4 summarises these management approaches ((NICE), 2008a, (NICE), 2008b).

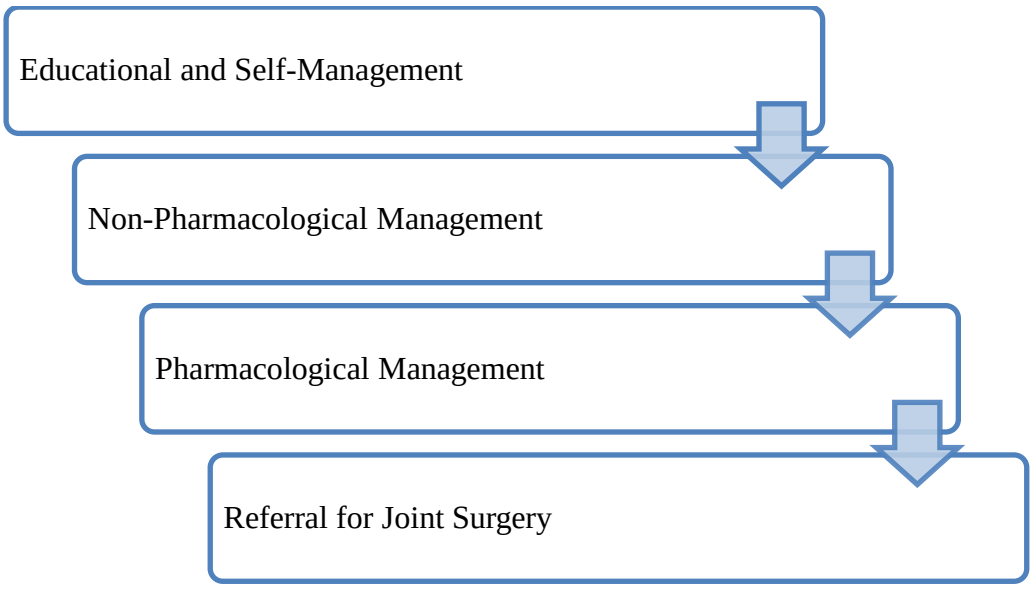


Figure 1.4 – Summary of management options for KOA

1.3 Aetiology of Knee Osteoarthritis

KOA is a common complex disorder with a number of associated risk factors, both systemic and local biomechanical (Suri et al., 2012, Silverwood et al., 2015). Individuals become at risk of the condition when local factors combine in the presence of systemic susceptibility, although local factors themselves, such as joint injury, may be independent determinants for the condition, (Brandt et al., 2003, Sandell, 2012).

One study explored predictive risk factors for 'symptomatic KOA' and RKOA. These were: increasing age, gender, increasing BMI, occupational risk (based on lifting / kneeling), a family history of KOA, having had a knee injury, and participation in sport (Zhang et al., 2011b).

Most studies typically observe risk factors for KOA in the TF compartment of the knee. However, the PF compartment is equally affected (Schiphof et al., 2014), albeit risk factors may vary (Cicuttini et al., 1997).

1.3.1 Constitutional Susceptibility

Figure 1.5 outlines the main systemic (also referred to as constitutional) risk factors for KOA. These factors are generally immutable, but independently not responsible for KOA.

However, the interplay of local factors in the presence of systemic risks increases the risk of KOA. Increasing age and female gender are the greatest systemic risks. Getting older does not directly cause KOA, yet the dramatic rise in the

incidence and prevalence with increasing age is the result of vulnerability to multiple local factors.

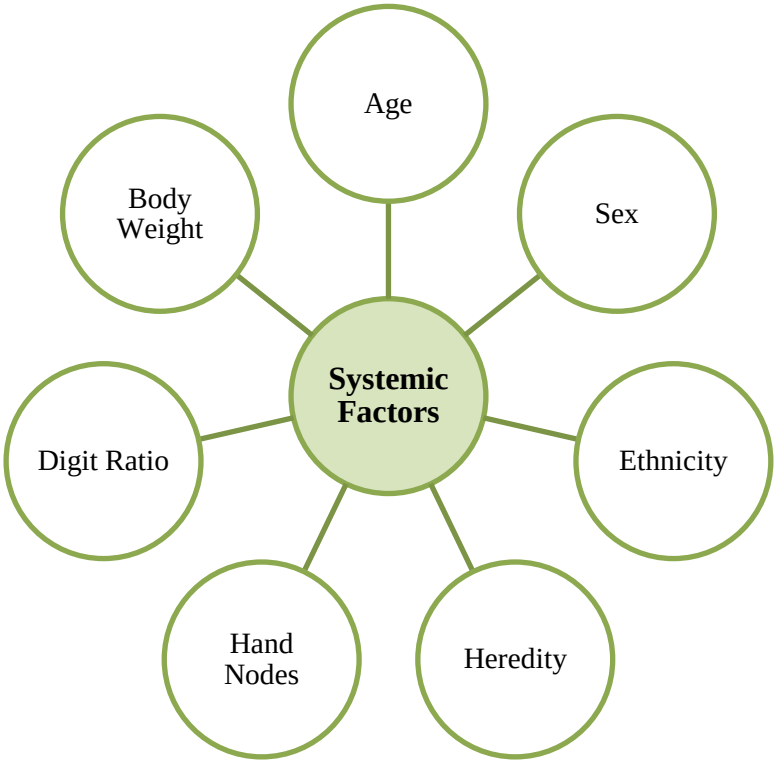


Figure 1.5 – Systemic Risk Factors for KOA

This schematic describes some of the important systemic (constitutional) risk factors for KOA. The systemic, immutable factors listed are age, sex, ethnicity and heredity (including hand nodes and digit ratio), whereas body weight (BMI) is a potentially modifiable systemic factor. Other systemic risk factors may include, bone mineral density, oestrogen-deficiency in women and nutritional factors

Age

Age is the main risk factor of KOA (Sandell, 2012, Suri et al., 2012, Prieto-Alhambra et al., 2013, Silverwood et al., 2015). If we observe the population under the age of 55, the primary causes of KP are injury, trauma or overuse of the joint. However, in those over the age of 55, underlying structural change results in KP, and thus is more likely to be KOA (Peat et al., 2001b).

The risks of KP or RKOA and with age are extensively studied. The ageing process inherently increases the risk for developing KOA. However, the determining the risk effect of age is difficult because various studies have used different age ranges and categories for the populations studied (Felson et al., 1988, Cheng et al., 2000, Lachance et al., 2002, Hootman et al., 2003, Szoeke et al., 2006, Jinks et al., 2008, Zhang et al., 2011b).

The incidence and prevalence of KOA increase with age and more than 60% of people aged 75 and over are diagnosed with the condition, yet this is rare in patients under the age of 45 (Felson and Zhang, 1998). There is a non-linear relationship showing an increased incidence of KOA in those over the age of 50 (Jarvholm et al., 2005). Another study found this effect and further suggested a levelling off and even decline in the incidence of the condition in the population aged over 80 (Oliveria et al., 1995). This is a well-known epidemiological phenomenon, which occurs due to the declining population above this age for alternate reasons.

Sex

Various cohort studies have observed the effect of gender as a risk factor for KOA, showing women to be at greater risk (Manninen et al., 1996, Felson et al., 1997, Seavey et al., 2003, Hochberg et al., 2004, D'Souza et al., 2008, Toivanen et al., 2010, Ingham et al., 2011, Nishimura et al., 2011, Muraki et al., 2012). In the population aged below 45, KOA is more common in men (Roos et al., 1998a).

However, in those over the age of 55, there is a greater incidence and prevalence of KOA in females compared to their age-matched male counterparts.

Silverwood and colleagues reported the odds ratio for developing KOA of 1.68 (95% CI 1.37-2.07) for females (Silverwood et al., 2015). Another study showed the prevalence of radiographic KOA was greater among women (42.1%) compared to men (31.2%) but symptomatic KOA (KP + radiographic KOA) prevalence does not differ (Lethbridge-Cejku et al., 1995).

One of the most likely reasons for this is the decline in the levels of circulating oestrogen in post-menopausal women. The loss of this protective effect results in the increased risk of KOA in women over the age of 50 compared to males (Felson and Zhang, 1998, Hunter and Felson, 2006, Busija et al., 2010). Hart and colleagues have shown oestrogen conferring a protective effect against women developing KOA (Hart et al., 1999) and other bone and joint diseases.

Body Weight

Body mass index (BMI) is simple clinical tool that uses height and weight to determine whether a person is under- or over- weight. The World Health Organisation (WHO) classifies a person's health status based on their BMI as shown in Table 1.5. BMI is calculated by dividing weight (in kilograms) by the square of height (in metres):

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)} / \text{Height (m)}^2$$

Being overweight or obese (BMI >25kg/m^2) increases one's risk for developing KOA. Obesity is classified as both a systemic and a local risk factor due to the metabolic aspect of obesity as well as the increased weight-bearing in the joint (Busija et al., 2010).

Table 1.5 – WHO BMI Classification

BMI (kg/m^2)	Classification
>18.5	Underweight
18.5 – 24.9	Normal Range
25.0 – 29.9	Overweight (Pre-Obese)
30.0 – 39.9	Obese
40.0 +	Morbidly Obese

The World Health Organisation (WHO) body mass index (BMI) classifications to determine obesity. BMI is weight (in kg) divided by the square of height (in metres).

Studies that focused on people that were overweight all strongly reported an increased risk for developing KOA (Felson et al., 1997, Jinks et al., 2006, Reijman et al., 2007, Grotle et al., 2008, Niu et al., 2009, Mork et al., 2012) and this risk appeared much greater in sports persons compared to their general population counterparts (Kujala et al., 1995). Obese patients are also predisposed to a risk of KOA, and this risk is shown to be greater than in those individuals that are overweight (Ettinger et al., 1994, Seavey et al., 2003, Hochberg et al., 2004, Szoeke et al., 2006, D'Souza et al., 2008). This shows that an increase in BMI is strongly associated with an increased risk of developing KOA.

The knee joint is a full weight-bearing joint and being overweight or obese greatly increases the risk for developing KOA compared to the hip or hand OA (Gelber et al., 1999, Busija et al., 2010). Increased body weight, which results in an increased load on the knee joint also leads to joint morphology alteration, which may result in a reduction in joint space and also triggers the onset of KOA (Hunter and Felson, 2006, Lee et al., 2013a).

Body weight, however, is one of the key modifiable factors, which has the greatest impact on reducing the effects of KOA (Lee et al., 2013a). One study in

particular showed obesity being a risk factor for KOA and then highlighted the reduced risk of the condition by modifying weight. Participants that lost weight had a reduced risk for the condition and this was more common, especially in population where KOA is more prevalent (Muthuri et al., 2011a).

However, an increase in weight may not result in additional risk to develop KOA (Felson et al., 1997). Apold and colleagues studied the association between weight gain and TKR, a surrogate marker for severe KOA. The authors observed weight gain across different ages in a large prospective cohort (225,000 individuals) and reported a dose-response relationship between weight gain and the risk of TKR, but this dose-response was reported only in those younger than 40, and was stronger in females than males. Thus preventing significant weight gain before the age of 40 will reduce the risk for developing KOA and the likelihood of having a TKR (Apold et al., 2014). This further suggests that BMI exacerbates the underlying structural change of OA-affected joints, but increases in weight over the age of 40 do not dramatically influence progression of the condition to its end-stage (TKR).

The converse relationship has been shown, whereby weight loss reduces the symptoms of the condition. Two studies have shown that reversing the effects of obesity through weight loss reduced the symptoms (namely KP) of KOA. However, it did not have an effect on the underlying structural changes of KOA (JSN caused by cartilage loss and increased osteophyte formation) (Teichtahl et al., 2014, Weiss, 2014).

Tackling the rising obesity epidemic, especially in the Western population will result in reduced burden of KOA. However, this has proved to be challenging to

date and with the increasing incidence of obesity, KOA poses a serious long-term health problem (Muthuri et al., 2011a, McPherson, 2014).

Ethnicity

Studies of ethnic groups tend to focus on populations in the USA, Europe and China. KOA is more prevalent in African-Americans as well as Asians than European Caucasians. However, hip OA is more prevalent in European Caucasians than any other ethnic group (Hunter and Felson, 2006, Busija et al., 2010). This suggests a possible genetic component to OA.

Both the Johnston County study and Framingham study looked at a sub-cohort of the population aged 45 years and over. African Americans (Johnston County Study) have a slightly higher prevalence of KP and moderate RKOA (Jordan et al., 2007) compared to Caucasians (Framingham Study) (Felson et al., 1987) for those over the age of 45. However, this is significantly greater in those with severe RKOA (Felson et al., 1987, Jordan et al., 2007, Collins et al., 2014).

The prevalence of RKOA is 42.8% and 21.5% in Chinese women and men respectively. Compared to age-matched women in the Framingham cohort, Chinese women had a higher prevalence of RKOA (OR 1.45, 95% CI 1.31-1.60). However, there was no significant increased risk in Chinese men compared to their Caucasian counterparts (Felson et al., 1987, Felson et al., 1997, Woo et al., 1994).

The prevalence of KOA in Japanese men and women over the age of 40 is 42.6% and 62.4% respectively (Neame et al., 2004), further confirming a higher prevalence of the condition in Asian populations compared to Caucasian populations.

Genetics

The risk of genetic influence for developing OA is less well understood than some of the more common risk factors. Heredity of the condition is observable, with first-degree relatives (parents or sibling) more likely to have OA and/or joint replacement (in the joints affected by the condition) (Valdes and Spector, 2011).

The heritability of KOA was previously reported to vary between 39-65% (Cicuttini and Spector, 1997). A more recent classic twin study, reported KOA heritability of 39%, but 60% for hip OA (Dai et al., 2014). These associations were determined taking into account the effect of constitutional risk factors including age, sex and BMI.

Various longitudinal studies report the heritability of KOA as 33% and 73% for the formation of lateral knee osteophytes and the change in medial cartilage volume respectively (Dai et al., 2014). These associations are also stronger if patients have several defective alleles as opposed to a single allele defect, supporting the notion that OA is a multifactorial disease (Cicuttini and Spector, 1996, Spector et al., 1996).

Specific genetic factors play an important role in the development or increased risk of KOA and genome studies seek to understand better these roles. These studies have focused on molecular mechanisms of the disease, such as joint damage, nociception, and chronic pain due to OA. However, this has proved difficult because OA is a common complex disorder, with a multiple of risk factors (Valdes and Spector, 2011, Dai et al., 2014). Table 1.6 outlines some of

the reasons why determining the genetic associations of OA has been difficult to establish.

Table 1.6 – Reasons why determining genetic associations of OA are difficult

Disease Heterogeneity Some patients with OA only present with a localised condition (affecting one joint), whereas other present with generalised OA, which affects many different joints. This varied presentation of the condition makes it difficult to assess the genetic distinctions of the condition within the various joints
Ethnicity Patients with OA from different ethnic groups show significant heterogeneity and this makes it difficult to determine whether genetic associations are due to the condition or the patient's ethnicity
Multiple Genes Susceptibility to developing OA is influenced by multiple genes in small proportions. Determining the effect of these genetic influences requires large sample size studies, which are generally difficult to conduct

Genetic associations of OA are difficult to establish. This table outlines three of the main reasons and possible explanations of each (Chapman and Valdes, 2012, Valdes and Spector, 2011)

Genetic influences may offer some explanation as to why some factors predispose risk to certain populations (Chapman and Valdes, 2012). Asian populations, typically Chinese, have a higher rate of KOA than their European Caucasian counterparts do. One study reported Chinese female patients having a prevalence of KOA of 15.4% (symptomatic – knee pain with underlying structural change) and 42.8% (radiographic – underlying structural change only) respectively (Zhang et al., 2004). This makes such subsets of the populations ideal to detect polymorphism associations for KOA.

Genome-wide association studies (GWAS) are now becoming more commonplace to understand the aetiology and genetic susceptibility for KOA (Dai et al., 2014). Since the human genome was sequenced (Collins et al., 2003), polymorphisms relating to a number of structures in the joint have been identified as susceptible to KOA through GWAS (SC Warner, 2016). One of the most susceptible genes identified is GDF5 (rs143383). Deficiency of this is associated with joint damage and changes in gait and subchondral bone structure, which are joint-specific (Daans et al., 2011).

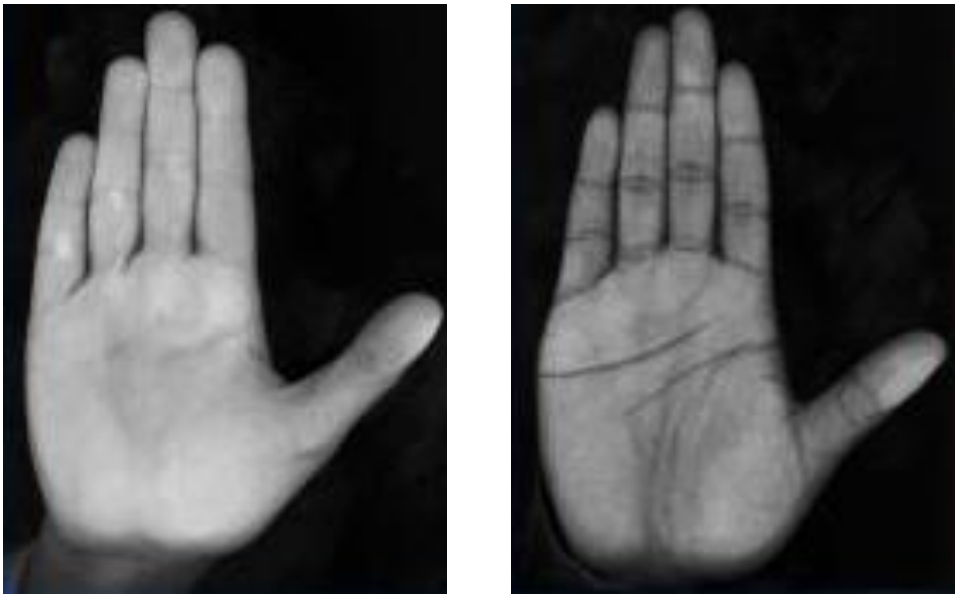
Genetic associations may also help to explain why females may be at greater risk (Valdes and Spector, 2011). A recent study by Dai and colleagues shows that presence of Oestrogen Receptor Alpha 1 (ESR1) single nucleotide polymorphism (namely rs2234693 and rs9340799) is associated with an increased susceptibility with OA. This was greater in females than males (as the gene polymorphism is more common in females) and more so in mild cases of OA (Dai et al., 2014). Such polymorphisms may provide therapeutic target to reduce incidence of the disease, however, further work is required to substantiate this evidence.

Digit Ratio

Digit ratio, more commonly known as 2D:4D ratio refers to the length ratio between the second digit, the index finger (2D) and the fourth digit, the ring finger (4D). There are three possible patterns, namely pattern one (a longer index finger to ring finger), pattern two (equal index and ring finger lengths) and pattern three (a longer ring finger to index finger) (Robertson et al., 2008), as shown in Figure 1.6.

Having a pattern 3 digit ratio highly increases the risk for developing KOA [OR 1.94, 95% CI 1.54-2.44] compared to those that have a digit ratios of pattern 1 or pattern 2. Women with a pattern 3 digit ratio [OR 3.05, 95% CI 2.08-4.47] also have a significantly greater risk of KOA compared with men [OR 1.45, 95% CI 1.08-1.95] (Zhang et al., 2008, Orchard, 2004).

However, data from the Framingham cohort showed that there was no significant risk of KOA for those with a pattern 3 digit ratio compared to those without, for both men [adjusted-OR (aOR) 0.79, 95% CI 0.47-1.33] and women [aOR 1.01, 95% CI 0.44-1.25]. However, the authors suggested that a pattern 3 digit ratio in women with hand OA might be a consequence rather than a cause (Haugen et al., 2011).



A **B**

Figure 1.6 – Possible digit (2D:4D) ratio phenotypes

Digit ratio is the ratio between the index (2D) and ring (4D) digits on the hand. A longer index finger, more typical amongst females, is Pattern 1 (A). A longer ring finger, more common amongst men, is Pattern 3 (B). Equal finger lengths are Pattern 2 (not shown in figure). A Pattern 3 ratio has been associated with an increased risk of developing KOA. *Figure from Columbus State University webpage (University, 2009)*

Generalised Nodal OA

Hand nodes, which are body swellings, may occur in the distal or proximal interphalangeal joints. Nodes in the distal interphalangeal (DIP) joints are Heberden's nodes and those in the proximal interphalangeal (PIP) joints are Bouchard's nodes. Formation of nodes may result in hand OA (known as nodal OA). The ACR criteria for nodal OA is the formation of at least two nodes on two digits in each hand. Nodal OA has been shown to be a risk factor for KOA [pooled OR 1.49, 95% CI 1.05-2.10] (Blagojevic et al., 2010b).

1.3.2 Local and Biomechanical Factors

Local and biomechanical risk factors may be intrinsic or extrinsic in nature. Local factors affect the loading and biomechanics of the joint, influencing whether KOA is likely to develop (Doherty, 2001, Silverwood et al., 2015). Obesity and physical activity are two such extrinsic factors, which in the presence of systemic or local intrinsic factors increase predisposition to KOA. Figure 1.7 identifies the major local-joint and biomechanical factors.



Figure 1.7 – The Local Biomechanical Risk Factors of Knee Osteoarthritis

The schematic above lists some of the local biomechanical risk factors for KOA. Local extrinsic factors include obesity, joint injury, physical activity and occupational demands. The local intrinsic factors are alignment, muscle strength and limb-length inequality. Other local risk factors may include ligament laxity and joint proprioception.

Knee Alignment

Mal-alignment is defined as varus (bow-legged) or valgus (knocked-knee) or normal (which is straight). The gold standard of determining the alignment of the knee joint is observation on full leg-length weight-bearing radiographs. Figure 1.8 presents the three variations of alignment, clearly depicting the femoral-mechanical axis and tibia-mechanical axis, which should be in line for those with a normal alignment.

Ingham et al (2010), however, found this to be very time-consuming and expensive method when conducting epidemiological studies. The authors

proposed a series of line drawings of the leg and foot for such studies so alignment could be self-reported by participants (Ingham et al., 2010).

Sharma et al (2001) have extensively studied alignment as a risk factor for the development and progression of KOA. They have found varus alignment narrows the medial TF compartment and valgus alignment narrows the lateral TF compartment. Both varus [aOR 4.09, 95% CI 2.20-7.62] and valgus [aOR 4.89, 95% CI 2.13-11.20] mal-alignment increased the risk of KOA having adjusted for age, sex, BMI and knee pain (Sharma et al., 2001).

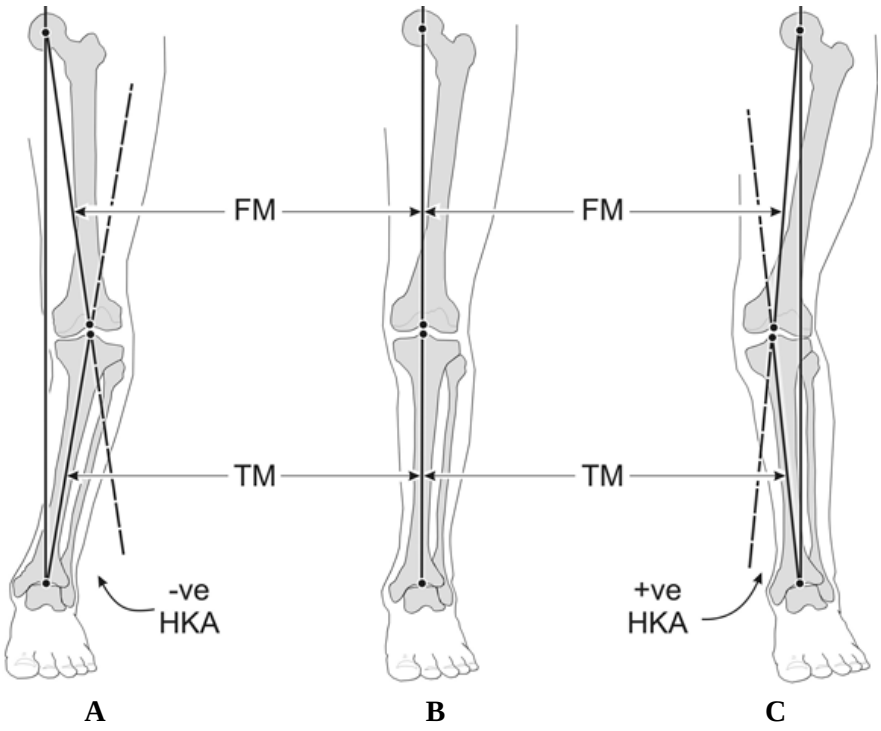


Figure 1.8 – Variations of leg alignment

Leg alignment refers to the shape of the leg. A neutral (B) alignment is straight, whereby the femoral mechanical axis (FM) aligns with the tibia mechanical axis (TM). The hip-knee-ankle (HKA) angle becomes negative with a Varus (A) alignment and positive with a Valgus (C) alignment. Both Varus (describing bow-legged) and Valgus (describing knocked-knees) are malalignments of the leg, which increase the risk of developing KOA.

Image adapted from (Derek et al., 2007)

Occupation

Generally, occupations that involve a high degree of kneeling, squatting, climbing stairs, prolonged standing or lifting are likely to increase the risk of developing OA later in life (Blagojevic et al., 2010a).

The Framingham study cohort showed that men partaking in occupations that involved a high degree of bending and/or kneeling were twice as likely to suffer from OA compared to men whose occupation did not (Felson et al., 1991). A review by Hunter (2002) echoed this, concluding that occupations involving bending, kneeling are associated with OA in later life (Hunter et al., 2002).

Coal mining has been shows to have a very strong association with developing KOA (McMillan and Nichols, 2005). This occupation is now classified as an industrial risk for KOA and is compensable for those developing KOA ((IIAC), 2008). Other occupations with an increased risk of KOA include floor laying (Thun et al., 1987) and dock working (Partridge and Duthie, 1968). Farming has a strong association with the development of hip OA but not KOA (Bishay et al., 1992, Croft et al., 1992, Holmberg et al., 2004).

McWilliams et al (2011) reviewed the occupational risks for KOA, based on occupational activities. These included heavy or manual work, elite sport, squatting, kneeling, lifting and carrying, standing work and knee bending and straining. Sixty-six studies were observed based on the following outcomes of KOA (51 studies), persistent knee pain (12 studies) and KOA progression (3 studies) and found KOA has an increased OR of 1.61 (95% CI = 1.37 – 1.81) across all the studies. However, due to differing study designs, there was a significant heterogeneity reported in the study (McWilliams et al., 2011).

Physical Activity and Injury

The evidence linking physical activity to OA is limited, yet moderate activity may be protective for KOA. However, excessive bending, especially at the knee, due to physical activity or occupation appears to predispose one to OA (Doherty 2001). McAlindon et al (1999) have shown that an increasing duration of heavy physical activity (hours) leads to an increased risk of RKOA [OR 1.30, 95% CI 1.10-1.60]. This was similar for symptomatic KOA but the number of cases was less. However, moderate and light physical activity has no effect on both symptomatic and radiographic KOA (McAlindon et al., 1999)

Sport increases the risk of joint injuries. Buckwalter (2003) suggests high intensity sport leads to post-traumatic OA, a clinical syndrome whereby joint degradation occurs following trauma. This often leads to subsequent joint pain and dysfunction of the joint. Sport-induced OA may therefore be a sub-classification of the condition and differ from OA that occurs due to ageing and obesity (Buckwalter, 2003).

Patello-femoral pain (PFP) is one of the most common problems encountered by sports medicine physicians. PFP is characterised by anterior knee pain and triggered by repetitive activities, including running and squatting, yet subsides when these activities are ceased. The long-term effects of PFP and its relation to KOA require further work to determine whether there is an association or not (Crossley, 2014).

The risk of developing KOA following knee injuries is also very significant. A systematic review, including a meta-analysis reported a high risk of KOA following injury [pooled OR 4.20, 95% CI 3.11-5.66]. The authors concluded

that irrespective of the definition of knee injury, it is key factor that is modifiable to reduce the risk of KOA (Muthuri et al., 2011b). A more detailed, football-specific focus regarding the risk of injury is described in Section 1.5.2.

Muscle Strength and Limb Length

Muscle weakness is an inevitable consequence of symptomatic OA, but the converse also holds in that muscles weakness is a risk factor for developing OA. Keays et al (2010) showed that quadriceps muscle weakness was one of five key factors that increased the risk of OA in the tibio-femoral compartment of the knee. However, it was not a significant factor for OA in the patello-femoral compartment (Keays et al., 2010).

Numerous randomised controlled trials of exercise have shown improvement in symptoms from KOA but a systematic review involving a meta-analysis to assess whether muscle weakness and sensory dysfunction are risk factors for KOA has not been conducted.

Limb-length inequality (LLI) is also another risk factor, albeit less important. LLI occur due to congenital defects or injury in the lower limbs leading to a shift in gait and weight-bearing patterns. This increases a patient's risk of developing OA due to JSN and mal-alignment at the joint. Patients with LLI report symptomatic changes and along with radiographic changes, yet the risk of LLI may be eliminated through surgical intervention (Hunter and Felson, 2006, Golightly et al., 2007).

1.4 Epidemiology of Knee Osteoarthritis

The knee is one of the most commonly affected joints with OA. According to Arthritis Research UK, 6 million people presented with KP to their GP ((ARUK), 2013). However, the population with evidence of structural change of the knee joint, regardless of KP, is far greater (Peat et al., 2001a).

Prevalence (and incidence) of KOA will vary depending on the definition of the condition used. Reporting of symptoms, for example, 'pain in or around the knee joint' is one such clinical definition. Alternatively, the presence of structural change, apparent on imaging (typically radiography) defines RKOA. Epidemiological studies assessing KOA in the population use distinct definitions of the condition (KP or RKOA or the combination of the two), making cross-comparisons difficult (Schiphof et al., 2008).

The discordance between KP and KOA is well established (Lawrence et al., 1966). Peat and colleagues collated data from various studies to present a prevalence staircase of KP and RKOA (Figure 1.9 – adapted from (Peat et al., 2001b)). It shows a discordance between KP and underlying structural change of KOA defined by radiographs.

The overwhelming majority of people with KP that have severe disability will have underlying structural change and account for 1.5% of the adult population over the age of 55. People with KP but less severe disability are likely to have less underlying structural change and account for up to 10% of the population (aged 55 or over). The proportion of people who have reported pain for a one-month period and have some structural change is less than those with some disability (Peat et al., 2001b).



Figure 1.9 – The prevalence of KP and RKOA

This figure reports the number of people with KP (with or without disability) per 10,000 population over the age of 55 in the UK. The shaded region of each bar is the proportion of the population with KP that have RKOA, clearly indicating patients with mild KP are less likely to have RKOA compared with those with severe KP.

Image adapted from (Peat et al., 2001a)

1.4.1 Incidence

Incidence defines the number of new cases of an outcome (condition or disease) in a population over a given period. Discordance between KP and RKOA make incidence of the condition difficult to ascertain (Peat et al., 2001a) (Bedson and Croft, 2008). Incidence of both these outcomes increases with age. Consequently, an ageing population is likely to lead to an increase in incidence of KOA.

Ingham and colleagues conducted a 12-year retrospective study of KP in the general population over the age of 40. The authors found an average incidence of KP of 32 cases per 1000 person-years (p-y), and this was greater in women (34 cases / 1000 p-y) than in men (31 cases / 1000 p-y). Being female increased the risk for KP [Hazard Ratio (HR) 1.27, 95% CI 1.08-1.49]. An increased risk was also apparent in those who were obese [HR 1.80, 95% CI 1.37-2.38] or had previously suffered from a significant knee injury [HR 2.37, 95% CI 1.98-2.38]. KP is a characteristic feature of symptomatic KOA and progression of KP is indicative of the increasing severity of the disease (Lee et al., 2013b).

1.4.2 Prevalence

Knee Pain

When reporting the prevalence of KOA, epidemiological studies have tended to favour the case-definition of 'symptomatic KOA'. This measure includes some form of symptom reporting associated with underlying structural change, defined as a KL grade of at least two.

Based on this case definition, the global prevalence for KOA in those ages 60 and above is approximately 10 percent (Shin, 2014, Heidari, 2011). However, a more robust approach to studying KOA is avoiding the use of the case definition 'symptomatic KOA'. Rather, independently studying the prevalence for KP and RKOA is desirable. The following two points support this notion. Firstly, 50% of the population with structural changes (RKOA) are asymptomatic, and therefore should not be included in the clinical burden of disease. Secondly, 50% of the population over the age of 55 that have KP show no definitive evidence of structural change (Spector TD, 1991, Spector et al., 1991, Peat et al., 2001a).

In the UK, the prevalence for KP ranges from 6.5-28.0%, measured from several studies; namely Chingford (Spector TD, 1991), Calderdale (Badley and Tennant, 1992), Bristol (McAlindon et al., 1992b), Nottingham (O'Reilly et al., 1996), and Tameside (Urwin et al., 1998). Differing case definitions are the primary reason for this wide prevalence range, rather than the geographical region (for each study). Table 1.7 describes the case definitions used by each study and the prevalence for each.

Table 1.7 – Prevalence of KP based on case defintion

Study	Knee Pain Screening Question	Prevalence
Chingford	1. Have you had knee pain at any time in the past month?	13.0%
	2. Have you had knee pain for most days of the past month?	6.5%
Calderdale	Have you had current knee joint problems?	19.0%
Bristol	Have you ever had knee pain for most days of at least one month AND has this knee pain been within the past year?	25.0%
Nottingham	Have you ever have knee pain for most days of at least one month?	25.0%
Tameside	Have you had knee pain for more than one week in the past month?	28.0%

The prevalence of KP reported from various studies ranges from 6.5% to 28.0% based on the different case definitions used (Spector TD, 1991, Badley and Tennant, 1992, McAlindon et al., 1992b, O'Reilly et al., 1996, Urwin et al., 1998)

A further caveat for such epidemiological studies observing the prevalence of KP is the use of questionnaires. KP is always a self-reported measure, but questionnaires may appear crude and not capture truly, the characteristics and prevalence for the outcome. A thorough history and clinical examination are absence when using a questionnaire, however, would be the ideal approach to determining KP. The aforementioned studies, however, all determine the prevalence for KP using questionnaires and thus such bias may not be so apparent.

A subsequently review, which accounts for the studies reported in Table 1.5, reports that one in four people over the age of 55 are likely to suffer from KP (attributable to KOA) (Peat et al., 2001a). In people younger than 55, the source of KP is more likely to be injury-, trauma- or physical activity- related. However,

these untoward factors may results in more persistent, troublesome KP later in life (McAlindon et al., 1992b, Felson et al., 1997).

The prevalence for KP varies globally too. Three studies from the USA reporting KP prevalence have a range between 15% (KP) to 44% (RKOA) (Felson et al., 1987, Anderson and Felson, 1988, Lethbridge-Cejku et al., 1995). In the Netherlands, the prevalence for KP is between 13% (KP) and 29% (RKOA) (Claessens et al., 1990, Odding et al., 1998). A recent study from China reported varying prevalence (5-14%) depending on which regions the condition was observed (Tang et al., 2016). Further population studies in China (Woo et al., 1994) and in Europe (Bergstrom et al., 1986) observed pain (as a clinical outcome for KOA) in elderly (over the age of 70) and reported the knee being the most commonly affected (prevalence ranged from 19-41%).

A recent study conducted on 1700 participants with KP and RKOA, were recruited from the Osteoarthritis Initiative Study. Participants were followed up for a six-year period and the authors found patients were insensitive to increasing pain severity, suggesting pain resulting from KOA is persistent in nature (Collins et al., 2014).

As mentioned with the UK studies, the differences in all these population exist for numerous reasons. Differing case definitions are the most common and likely explanation, but composition of the study group (including age, gender and ethnicity) and the method of data collection (whether postal questionnaire survey or face-to-face interview) are also likely to result in variation of KP prevalence (McCarney R, 1999).

Radiographic Knee Osteoarthritis

The prevalence of RKOA (19-50%) is much greater than 'symptomatic KOA' (7-33%) with increasing age (Felson et al., 1987, Lethbridge-Cejku et al., 1995, Collins et al., 2014). There is, however, a decline in prevalence for those over the age of 80 due to increased mortality associated with other comorbidities (Jordan et al., 2007).

RKOA is based on observable underlying structural change and typically defined as KL≥2 (Kellgren and Lawrence, 1957, Altman et al., 1986a). Two studies from England report the radiographic KOA prevalence as 53% (McAlindon et al., 1992b) and between 41-43% (based on KP criteria) (O'Reilly et al., 1996). For those without KP, the prevalence was 17% (McAlindon et al., 1992b) and 18% (O'Reilly et al., 1996) respectively.

Despite the fact that epidemiology studies prefer the use of radiography to determine KOA, from the prevalence of the two studies reported (McAlindon et al., 1992b, O'Reilly et al., 1996), immediate discordance between structural change and KP can be seen (Bedson and Croft, 2008).

1.4.3 Burden of Disease

OA poses a significant burden on a person's QoL, especially over the age of 65 (Hunter and Felson, 2006, Busija et al., 2010). There is no current cure for the condition and management aims to reduce pain and improve function (Konstari et al., 2014).

People presenting with symptoms, most typically KP, may not necessarily have RKOA. Similarly, those with radiographic changes do not always have symptoms (Arden and Nevitt, 2006). When estimating the burden of OA, people without symptoms (those with the presence of radiographic changes only) should be excluded (Cross et al., 2014).

The Global Burden of Disease (GBD) 2010, a World Health Organisation (WHO) study, ranked OA (hip and knee combined) 11th in terms of years lived with disability (YLD) and 38th in terms of disability-adjusted life years (DALY) (Cross et al., 2014). As the global population ages and the prevalence of obesity rises, it is inevitable that the burden of OA will significantly increase, posing major health, social and financial consequences to society (Cross et al., 2014, Hoy et al., 2014a, Hoy et al., 2014b).

1.5 Professional Footballers Risk of Knee Osteoarthritis

Football is the world's most popular sport. The international governing body, Fédération Internationale de Football Association, estimate over 265 million people actively playing the game, and of these 110,000 are male professional footballers (FIFA, 2007a, FIFA, 2007b). The professional career of footballers lasts, on average, for over 10 years, and footballers are physically very fit to sustain such a career. Despite this, they are subject to adverse consequences of the game, such as injuries (Kuijt et al 2012).

Playing professional football is associated with a high risk of injury, similar to other high contact sports, (Kujala et al., 1995) and direct injuries to the knee account for 17% of all injuries (Hawkins et al., 2001, Ekstrand et al., 2011). In addition to this, knee injuries may occur due to microtrauma and overloading sustained at the joint. This may be the cumulative effect of repetitive, high-intensity activity to meet the demands of match play and training over a footballer's career. One study in particular highlights the fact football has a very high occupational risk of injuries compared to other industrial occupations (Drawer and Fuller, 2002).

Understanding the causes of injuries are key. In addition to seeking measures to prevent or reduce injury, minimising their consequences, both in the short-term (during a footballer's career) and longer-term (suffering from chronic conditions because of the injuries) are important.

1.5.1 The Current Evidence

Several studies have reported that KOA is very prevalent in retired professional footballers (Turner et al., 2000, Drawer and Fuller, 2001, Elleuch et al., 2008, Krajnc et al., 2010, Arliani et al., 2014). However, there is a need to address whether professional footballers are at a significantly increased risk of KOA, and whether it is an occupational risk.

In addition to the constitutional risks (age, gender and BMI) and local-biomechanical risks (including occupational risks due to excessive bending and squatting (Felson et al., 1991)) (Suri et al., 2012, Silverwood et al., 2015), football-specific factors may increase the risk of KOA. Such factors include the risk of joint injury and subsequent arthroscopic or other surgical interventions (which themselves may pose a risk of future KOA) (Buckwalter, 2003, Thelin et al., 2006). Other studies have suggested a causal effect linking lower limb injuries to the development of KOA (Roos, 2005, Toivanen et al., 2010). However, professional footballer remains an unproved occupation hazard for KOA, despite the high incidence of injuries (Hagglund et al., 2009a, Ekstrand et al., 2011) and its subsequent consequences.

A systematic review (Kuijt et al., 2012) identified four studies that observed the prevalence of the condition in professional footballers (Turner et al., 2000, Drawer and Fuller, 2001, Elleuch et al., 2008, Krajnc et al., 2010), conducted over a ten-year period (2000 – 2010). A more recent systematic review (Tran et al., 2016) includes a subsequently published study (Arliani et al., 2014), and all five studies have been summarised in Table 1.8.

Table 1.8 – Previous studies observing KOA in professional footballers

Lead Author	Arliani	Drawer	Elleuch	Krajnc	Turner
Year	2014	2001	2008	2010	2000
Country	Brazil	UK	Tunisia	Slovenia	UK
Study Design	Comparison study	Cross–sectional	Comparison study	Cross–sectional	Cross–sectional
Methodology	Radiograph assessment & questionnaire	Postal questionnaire	Radiograph assessment & questionnaire	Radiograph assessment	Postal questionnaire
Source Population	Former professional soccer players	English Professional Footballers Association	Former players from a local first division club	Former players NK Maribor football club	Former Players Associations
Outcome Measure	RKOA	Self-reported KOA	RKOA	RKOA	Self-reported OA (KOA)
Sample Size	27	185	50	40	284
Non-responders	5	313	-	12	231
Age (years) †	45.7 (5.9)	47.6 (13.2)	49.2 (3.8)	49.2 (9.7)	56.1 (11.8)
Career Duration (years) †	14.9	14.3	10.7 (4.6)	11.3 (4.2)	13.5 (5.3)
Prevalence of KOA (%)	67	40	80	60	46

† Reported as mean (SD)

There have been five previous significant studies of the risks of KOA in professional footballers. A systematic review (Kuijt et al., 2012) consisted of four of these studies (Drawer and Fuller, 2001, Elleuch et al., 2008, Krajnc et al., 2010, Turner et al., 2000), and a more recent review (Tran et al., 2016) accounted for the other study (Arliani et al., 2014).

Only two of the studies (Drawer and Fuller, 2001, Turner et al., 2000) were conducted in the UK. Although demographic factors (age, career duration) were comparable, the prevalence of KOA (40-80%) varied greatly. There are a number of reasons for this, including differing study designs, sample population size and differing case definitions used for KOA.

Other studies that have observed KOA in male football players, but were not excluded. Reasons include: the changing nature of the game (specifically, the intensity, behaviour and speed) (Brouwer et al., 1981, Kujala et al., 1994, Kujala et al., 1995); the population included non-professional players (Roos et al., 1994); and it could not be determined whether the participants were former professional players (von Porat et al., 2004).

The five studies reporting the prevalence of KOA in footballers (Table 1.8) vary significantly (40-80%). Two studies, conducted in the UK, focused on self-reported KOA (40-46%) (Turner et al., 2000, Drawer and Fuller, 2001). The other three studies used radiography and reported a much higher prevalence (60-80%) of the condition (Elleuch et al., 2008, Krajnc et al., 2010, Arliani et al., 2014). The prevalence of structural change (RKOA) is generally higher because not all persons with such change report symptoms, thus resulting in a discordance between the two classifications (Bedson and Croft, 2008).

The methodologies also meant sample sizes varied greatly. The self-reported studies employed questionnaires to collect their data and had a much larger sample size (185-284) compared with studies that used radiography (27-50). The three primary reasons for the large discrepancy for the prevalence of KOA may be due to study design used, sample size recruited and the case definition used.

Study Design

To determine the prevalence of a clinical outcome, a well-designed study should incorporate the use of a control population to compare to the study population. Two of the studies had recruited control groups (Arliani et al., 2014, Elleuch et al., 2008). Although the controls were non-footballers, the selection of

individuals in the control groups were not representative of the general population and thus their findings are not generalizable. The other studies did not have a control group for comparison, which greatly questions the significance of the findings. The use of a suitable control group would have allowed interpretation of the findings of these studies (Record Owner).

Two studies were case-control study designs (Arliani et al., 2014, Elleuch et al., 2008) whereas the other three were cross-sectional study designs (Drawer and Fuller, 2001, Krajnc et al., 2010, Turner et al., 2000). Although cross-sectional studies are easier to conduct, and provide a quick point prevalence of both exposures and outcomes, temporality is difficult to establish. Case-control studies on the other hand, focus on one outcome measure at a time. Although causality may be established, it may not be definitive and the best study design for this are prospective cohort studies (Kleinbaum et al., 1982).

Sample Size

The use of large sample sizes in epidemiological studies (Felson et al., 1987) improves the quality of the study and validity of the results. In some instances, albeit rare, the whole population may be studied (Kuo et al., 2015).

The studies from the systematic review (Kuijt et al., 2012) and subsequent study (Arliani et al., 2014) have relatively small sample sizes compared to other occupational setting studies (Croft et al., 1992, (IIAC), 2008). The small sample sizes (27-50 footballers) of the three radiograph studies (Arliani et al., 2014, Elleuch et al., 2008, Krajnc et al., 2010) were most likely due to logistic and resource constraints. Although the two questionnaire survey studies had larger

sample sizes (184-284 footballers), a lower response rate (56% (Turner et al., 2000) and 37% (Drawer and Fuller, 2001) may mean the results were biased.

Two forms of bias that may influence the results of a questionnaire survey are recall bias and misclassification bias. Recalls bias exists where questionnaire responders did not accurately remember details of exposures and outcomes, and misclassification bias occurs when outcomes were incorrectly identified (either during reporting or analysis), resulting in either an inaccurate reporting of the prevalence. However, a more influential bias is responder bias. This is the fact that people with knee symptoms are more likely respond to the questionnaire survey compared to those without knee symptoms. However, recruiting large sample sizes representative of the source population may overcome these biases.

Outcome Measures

The large variation in prevalence between the studies may also be due to different case definitions used. The two questionnaire studies identified cases as self-reported KOA (based on a physician-diagnosis of the condition) (Turner et al., 2000, Drawer and Fuller, 2001) whereas the other studies identified cases based on radiographic KOA (KL$\geq$2) (Elleuch et al., 2008, Krajnc et al., 2010, Arliani et al., 2014).

There are caveats inherent to both methods, including recall bias for the questionnaire surveys. The radiographic surveys use the definition of KL$\geq$two for KOA, which means not all cases have JSN (a key marker for the condition). Furthermore, it does not take into account symptoms, which are equally, if not more important (Hadler, 1992). However, there is a discordance between KP and

structural change (Bedson et al. 2008), which suggests studying both case definitions.

1.5.2 Potential Risk Factors

Footballers are exposed to certain risk factors (previous injury, occupational risk, physical activity) at a higher rate compared to the general population. However, there is no evidence of a causal link between these factors and KOA in professional footballers.

Knee Injuries

Injuries are an integral part of playing football and repercussions may result in long-term consequences on the quality of life of players. Professional footballers are subject to such high risk of injury through regular engagement in high intensity activity over prolonged periods of time, both during practice and match play (Hagglund et al., 2009a, Kuijt et al., 2012).

According to FIFA, 90% of injuries sustained by professional footballers are joint-specific. Lower limb injuries account for over 61% of the total injuries sustained, and specifically the knee accounts for almost 20% of injuries (FIFA). Consequences of knee injuries may lead to severe consequences later in life (KOA) (Drawer and Fuller, 2001, Turner et al., 2002). However, a better understanding of the causal relationship is required. Furthermore, mitigation of the risk of high impact injuries may have short- and long- term benefits (Hawkins et al., 2001).

Table 1.9 outlines the reasons why epidemiological studies on football injuries are limited. However, despite the heterogeneity in the methods and case definitions, broad comparisons ought to be made to help direct the future of research in this area (Dvorak and Junge, 2000).

Table 1.9 – Reasons why epidemiology studies of sport injuries are limited

Heterogeneity Heterogeneous methods have been employed across different studies
Case Definition The case definition for injuries and the effect of measuring its impact varies between different studies
Study Populations Teams assessed in the different studies have strikingly different characteristics, for example, ages, gender, level competed at

Conducting epidemiological studies into sport injuries are difficult and a few of the reasons for this are outlined in Table 1.9. Focusing on football, reporting of injuries are not always be disclosed to reduce time-lost from playing the game

A review of injury incidence in professional footballers reports the incidence rate between 10-35 injuries per 1000 hours (Dvorak and Junge, 2000). However, injury incidence from a sample of studies ranged from 13.0-28.1 per 1000 hours of match play but was only 1.5-5.9 injuries per 1000 hours for practice (Arnason et al., 1996, Ekstrand et al., 2011, Engstrom et al., 1990, Hagglund et al., 2009c, Hawkins and Fuller, 1999a, Luthje et al., 1996) – reported in Table 1.10.

Table 1.10 – Injury incidence rates in professional footballers

Author (Year)	**Country**	Source Population	**Match Play**	**Practice**
Engstrom (1990)	Sweden	3 elite teams	13.0	3.0
Arnason (1996)	Iceland	10 elite teams	34.8	5.9
Luthje (1996)	Finland	12 teams – highest level	16.6	1.5
Hawkins (1999)	England	4 professional clubs	25.9	3.4
Hagglund (2009)	Sweden	11 clubs – highest league	28.1	4.7
Ekstrand (2011)	Europe	Top 50 UEFA clubs	27.5	4.1

The injury incidence rates (per 1000 hours) in professional footballers is far greater during match play than during practice. This hold true for all professional teams across Europe; one study reported injury incidence of 27.5 (match play) and 4.1 (practice) across the top 50 teams in Europe (Engstrom et al., 1990, Arnason et al., 1996, Luthje et al., 1996, Hawkins and Fuller, 1999b, Hagglund et al., 2009a, Ekstrand et al., 2011).

Knee injuries account for between 14 – 32% of acute injuries in professional football, making it the most commonly injured joint (Engebretsen et al., 2011). They also resulted in the most time lost per season (31%) from playing football. The most serious of these are knee ligament injuries, which resulted in the greatest time lost from the game (Hagglund et al., 2009b).

One study highlighted the fact that anterior cruciate ligament (ACL) injuries were the most common form of injury in professional footballers. However, they were unlikely to occur in isolation because of the complexity of the closely associated structures in the knee joint (Lohmander et al., 2007). Injuries to the medial collateral ligament and lateral meniscus are most commonly associated with ACL injuries and are more likely to result in KOA, with an increased prevalence of between 21-48% in those affected (Lohmander et al., 2007, Oiestad et al., 2009). Additional consequences of ACL injuries and associated structures may be KOA (von Porat et al 2004, Roos et al 2006). Such injuries may even be career ending (Walden et al., 2011).

Knee Surgery

On average, professional footballers have a relatively short career duration (approximately ten years), and the hope is to remain injury-free for the majority of this time (Kuijt et al., 2012). Significant injuries pose a risk to footballers' health and careers prospects, thus require immediate attention to restore normal physiology of the injured joint with minimal time lost from the game (Hagglund et al., 2009a).

Surgical intervention is commonly used to treat knee injuries, but this may not be without consequence. One study reported that footballers who had previously suffered ACL injuries had a higher prevalence of KOA later in life, regardless of whether they had surgical intervention (von Porat et al., 2004). This suggests injury itself, rather surgical intervention, increases the risk of OA. However, a randomised controlled trial reported that arthroscopic surgery conferred no additional benefits to patient-optimised non-pharmacological (for example physical therapy) and pharmacological approaches (Kirkley et al., 2008). Unfortunately, footballers cannot afford such lengthy recovery durations over the course of their career.

Surgical intervention for meniscal injuries presents a contrasting picture. Surgical removal of the meniscus following knee injury leads to increased risk of RKOA in the TF compartment [RR 14.0, 95% CI 3.5-121.2] compared to age- and sex- matched controls (Roos et al., 1998b). However, it is difficult to separate the effects of injury and surgery, which are linked inextricably.

Further investigation, however is required to determine whether surgery itself increases the risk for developing KOA. The need for this is two-fold; firstly,

whether surgical intervention is an independent risk factor for KOA and secondly, whether the type of surgical intervention influences confers different risk.

Intra-articular Knee Injection

The consequences of intra-articular knee injections as a risk factor for KOA are unknown. Within footballers, use of injections in professional football aims to reduce the impact of painful injury and the amount of time lost from the game. Corticosteroid and anaesthetic injections are the most common forms of intra-articular injections and although evidence in the literature is limited, their use is perceived to be widespread (Orchard, 2002).

One study strongly advised against the use of intra-articular anaesthesia injections following meniscal, articular cartilage, or ligament damage. Although they would provide a means to continue playing the game (limiting time loss), full time activity on a compromised injured knee could lead to more severe damage and subsequent longer term problems (increased subsequent time loss from the game, potential career-ending injuries or even chronic disease later in life) (Orchard, 2004).

As with surgery, the evidence in the literature of the effects of injections in professional football (including type, dose and duration of use) is limited. Although their perceived use is negative, the consequences of intra-articular injections to treat or delay the onset of symptoms is speculative and unconfirmed.

1.5.3 Study Rationale

There is a strong need to address the gaps in the literature of whether KOA is an inevitable or likely consequence of playing football professionally. Determining the true prevalence of both KP and RKOA independently (due to discordance) and identifying the particular risk factors that predispose to each is necessary.

Given the limited quality of the existing evidence, a high quality study is required to address this. Conducting a case-control study with a large sample size and appropriate control groups is necessary and separately examining the various aspects that relate to KOA (for example, KP, RKOA, requirement for TKR) would have advantages over using just one case definition. Furthermore, imposing strict inclusion criteria will ensure exposures are attributable to KOA (outcome).

Although perceived that footballers are at increased risk of osteoarthritis, professional football is not an occupational risk ((IIAC), 2005). The current literature is limited. Reported prevalence of the condition varies greatly and studies do not recruit a suitable control group. Furthermore, sample populations are very small and this makes it difficult to generalise current findings. Thus, there remains a need for a robust study to determine whether footballers are at increased risk of KOA.

The current study seeks to address this gap in the literature by determining the risk of KOA (measured using various outcomes: KP, RKOA and TKR) in retired professional footballers compared to the general population; and subsequently, identifying the specific factors that exacerbates such risk for each outcome.

1.6 Chapter Summary

This chapter first presents a general outline of OA (Section 1.1) but focus then shifts to Knee OA (Section 1.2), exploring in detail its aetiology (Section 1.3) and epidemiology (Section 1.4), including its concordance with KP.

The chapter concludes with an account of current literature of KOA in footballers (Section 1.5), exploring the reasons why professional football currently is not considered an occupational hazard for developing KOA. The lack of evidence associating playing professional football with KOA has led to the study rationale (Section 1.6), and its aims and objectives (Chapter 2).

2 STUDY AIMS AND OBJECTIVES

The ***aims*** of this study are:

- to determine the prevalence and risk of KOA in retired professional footballers compared to the general population
- to determine the specific factors that increase this risk of KOA in retired professional footballers

The ***objectives*** are:

1. to determine the prevalence of KOA (as reflected by the prevalence of KP, the presence of structural change (RKOA) and Chondrocalcinosis (CC) and the requirements for knee replacement surgery) in a sample of retired male professional footballers in the UK
2. to determine the attributable risk of each of these outcomes (KP, RKOA, CC and TKR) in professional footballers compared to a sample of men in the general population of the UK (whether footballers are at increased risk of KOA)
3. to identify the specific risk factors (having accounted for confounding) for the various outcome measures (KP, RKOA and TKR) of KOA independently in professional footballers

3 METHODS

This chapter describes in detail the methodology of this study, including study design (Section 3.2), study participants (Section 3.4), methods used for data collection (Sections 3.5 and 3.6) and data management (Section 3.8) and analysis (Section 3.9).

For the remainder of thesis, the term *'footballers'* will refer to study population: retired professional footballers. The term *'controls'* will refer to men (from the East Midlands general population) recruited for the Knee Pain and Related Health in the Community (KPIC) Study, irrespective of occupation. These men formed the control group.

The methods focus on the Football Study (recruitment of footballers). The KPIC Study has a much wider remit than the provision of controls for the Football Study; however, relevant details describing the recruitment of controls are included.

3.1 Research Ethical Approval

The Arthritis and Football Study (referred to as the 'Football Study') and the Knee Pain and Related-Health in the Community Study (referred to as 'KPIC Study') both required independent research approval prior to commencing.

All aspects of the Football Study were approved by the Nottingham University Hospitals NHS Trust and the Nottingham Research Ethics Committee (Reference: 14/EM/0045) and registered on the clinicaltrials.gov portal (NCT02098044).

All aspects of the KPIC Study were approved by the Nottingham University Hospitals NHS Trust and the Nottingham Research Ethics Committee (Reference: 14/EM/0015) and registered on the clinicaltrials.gov portal (NCT02098070).

3.2 Study Design

Independent cross-sectional studies (collect data from one population at a specific point in time), for footballers and the controls, were conducted in two phases.

The first phase was a questionnaire survey (separate questionnaires for footballers and controls) to determine the prevalence of self-reported outcome measures and the associated risk factors associated with KOA. The second phase was a radiographic survey conducted for a subset of each group (footballers and controls) that responded to the questionnaire survey, to determine the prevalence for RKOA and CC.

Finally, nested case-control studies determined the risk factors associated with various outcomes of KOA.

3.3 Source Population

The source population for cases were footballers, who: (1) had previously had played football professionally (held a contract and played for a professional football club); and (2) are presently retired from playing professional football (although they may still play during their leisure time).

The source population for the controls were men from the general population in the East Midlands region of the UK.

3.3.1 Sources of Recruitment

In the UK, no organisation holds a complete record of every retired professional footballer. Therefore, to maximise recruitment, we approached multiple avenues, including professional football clubs and their former players associations (FPA), the Professional Footballers Association (PFA) and the League Managers Association (LMA) (Figure 3.1).

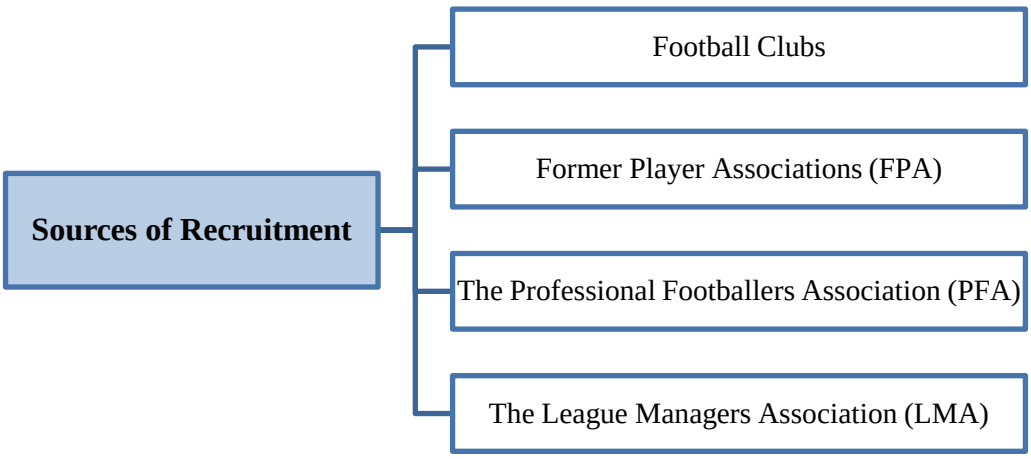


Figure 3.1 – Sources of recruitment for professional footballers

Football Clubs and Former Players Associations

All 92 professional football clubs and/or their FPAs in the top four tiers of the English Football League (namely the Premier League, the Championship, League One and League Two) in the 2014/15 season (August 2014 – June 2015) were invited to participate in our study. Just over 40% responded to our invitation and 21 Football Clubs and FPAs agreed to participate in the Study (Figure 3.2) and distribute questionnaire surveys to their former players.

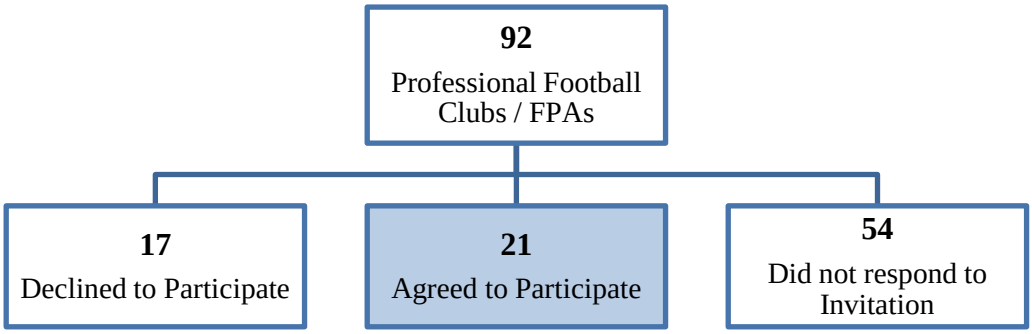


Figure 3.2 – Responses from professional Football Clubs / FPA

The Professional Footballers Association

The PFA held a database of approximately 3000 retired professional footballers and agreed to distribute 2779 questionnaires to all its members. Some footballers had incomplete records (no contact details) and other footballers lived abroad (outside Great Britain) and therefore not included).

An invitation from the Chief Executive Officer for the PFA, Gordon Taylor (Appendix A.3), was sent to all English Football League Clubs in advance of questionnaires being distributed, informing them of the study and encouraging their participation.

It was noted that some footballers may have received multiple questionnaire surveys because they were on the PFA records in addition to their former football clubs. This was unavoidable (due to data protection) and thus, an additional covering note (included with the questionnaires from the PFA) informed footballers of this possibility.

The League Managers Association

The LMA agreed to participate in the study, but requested their members indicate an interest prior to receiving a questionnaire. Only 26 LMA members indicated an interest (by providing their contact details) and those subsequently received questionnaire survey via the post.

3.3.2 Research Collaborators

The study was conducted within the Department of Academic Rheumatology at the University of Nottingham. Arthritis Research UK, via the Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, funded the staff for this study.

The external partners that supported the study and provided part funding for the running costs were Fédération Internationale de Football Association (FIFA) Medical Assessment and Research Centre (F-MARC), The Football Association (FA), the Professional Footballers Association (PFA) and Perform, which is part of the Spire Healthcare group. The support of these organisations was likely to enhance the prestige of the study within the football community and so increase the response rate for the questionnaire survey.

3.4 Participants and Eligibility Criteria

The inclusion criteria for the questionnaire survey were the same for footballers and controls:

- Males over the age of 40
- No known medical conditions that restrict participants responding to the questionnaire (for example, those who are terminally ill, have marked cognitive impairment (including psychiatric disturbance), or are unable to give informed consent will be excluded)

The men's game has been professional for a much longer period than the women's game. A greater source population results in a larger sample size and thus recruitment was restricted to men only. Further to this, the differing demands of the men and women's game makes it difficult to assess the true risk of KOA if both sexes were included. Hence, the focus of this study and hence inclusion criteria were male professional footballers.

The minimum age for participants (both footballers and controls) was 40. Although this is much earlier than the onset of KP in the general population (Peat et al., 2001a), a lower age was set to ensure footballers with early KP or structural change are included within this study remit.

The exclusion criteria set for the radiographic survey was the same for footballers and controls (apart from the fact that footballers had to live within a 40-mile radius of their nearest Spire Hospital).

These exclusion criteria were that participants had:

- Previously not undergone bilateral TKR
- No contra-indications to receiving radiographs of their knees

A TKR is indicative predominantly of clinically severe KOA. Having had a knee replacement, there would be no evidence of structural change observable on the radiographs and thus such participants excluded.

3.5 Questionnaire Survey

Footballers received a questionnaire as part of The Football Study (see Appendix A.1) and controls received a questionnaire as part of The KPIC Study (see Appendix B.1). During the design phase of each, questions pertaining to risk factors and outcome measures were the same. This was important for the analysis so comparisons were valid and robust. The postal questionnaires for both studies were developed from previously published studies (O'Reilly et al., 1996) (Ingham et al., 2011).

3.5.1 Pilot (Patient and Public Involvement)

Patient and public involvement (PPI) is an important procedure throughout any research study. PPI is the active partnership between patients and/or members of the public with researchers. PPI typically involves the contribution or feedback from patients (the end-user) throughout the study, as opposed to at the end of the study. The PPI involvement for this study was key to making the questionnaire more user-friendly and accessible, increasing the likelihood for footballers responding to the questionnaire.

The development for The Football Study and the KPIC Study questionnaires both involved a strong contribution from PPI members. This facilitated the development from the initial to the final questionnaires. Feedback and contributions included wordiness of the questionnaires, the inclusion of the types of questions, the overall focus of the questionnaire and the perceptions of those completing the questionnaire.

The initial draft football questionnaire was a 50-page questionnaire covering aspects of hip, knee and ankle OA. The PPI group included lay personnel from Arthritis Research UK, PFA executive members and other retired professional footballers. The primary feedback was to shorten the length of the questionnaire and focus on one joint in particular, namely the knee joint. The final questionnaire thus focused on the knee OA and its associated risk factors, limited to 20-pages. Included in the questionnaire was a Body Pain Mannequin (BPM), which indicated other regions of the body suffering from pain, which provides an avenue for future research.

A separate PPI group (including patients with KP rather than professional footballers) was set up for the KPIC Study. The development of the questionnaire followed a similar process to ensure the final version was appropriate for its audience. Both questionnaires were finalised in conjunction with each other, so questions pertaining to demographics, knee pain history and KOA-associated risk factors were the same. This meant the responses from the footballers and controls were comparable.

3.5.2 Implementation

Footballers

The Football Study questionnaire was a cross-sectional survey on the population of professional footballers to determine the risk factors for outcome measures of KOA. The aim was to recruit a representative sample of footballers to determine their risk for KP and RKOA.

This study initially set out with the plan of action to work with the football charity, XPRO (Solihull, England). The charity had agreed to support our study and distribute the questionnaires to all its members (approximately 50,000), in turn for their endorsement of the study. Power calculations (Section 3.9.1) used this population estimate provided by XPRO.

However, following a yearlong negotiation with the charity regarding logistics and implementation of the questionnaire phase of the study, their support never materialised. As this approach was unviable, we had to develop a new approach to conducting the study.

This involved approaching official football organisations to determine whether the project was still feasible. The Professional Footballers' Association (PFA) and The League Managers Association (LMA) both offered their support to the study by agreeing to distribute questionnaires to their members. To ensure sufficient numbers for the study each of the 92 professional football clubs and their former players associations (FPAs) were also invited to participate in the study (see Section 3.3.1).

Footballers received their questionnaire surveys (Appendix A.1.) via these sources (Section 3.3.1). A covering explanatory letter from a prominent footballer, Sir Trevor Brooking accompanied the questionnaire (see Appendix A.2). Such a profiled covering letter was included to endorsing the research; enhanced the credibility of the study; and encourage a good response rate from footballers.

Controls

The KPIC Study provided the controls for this study. Recruitment of the participants took place via twelve General Practice surgeries across the Nottinghamshire region. Control participants received their questionnaire (Appendix B.1.) alongside a cover letter (Appendix B.2.) from their General Practitioner (GP) and completed responses directly sent to Academic Rheumatology in the franked self-addressed envelope provided.

3.5.3 Football Questionnaire Content

The Football Study questionnaire was specific to the purpose of this study, but utilised pre-existing instruments to measure some risk factors. Each section for the questionnaire is detailed and any pre-existing tools utilised discussed.

The questionnaire contained several distinct sections, including demographics, career history and occupations, current health and medications, knee pain, knee injuries and surgeries, hand and familial OA and quality of life.

Section 1: Demographics

Age, height, weight (current and in 20s), and ethnicity were the main questions in section 1. Body height and weight are required to determine body mass index (BMI) and the change in BMI from playing career (in 20s) to currently established.

Section 2: Career History and Occupations

This section gained a strong understanding of the career history of footballers. Footballers reported the period over which they played football (both

competitive and professional), the level (tier) they played at, and the intensity of training they underwent. Other key variables included the number of matches played, which position they played in and which foot they preferred playing with. The six longest occupations footballers held once retiring from the sport were reported to account for any subsequent high-risk occupations.

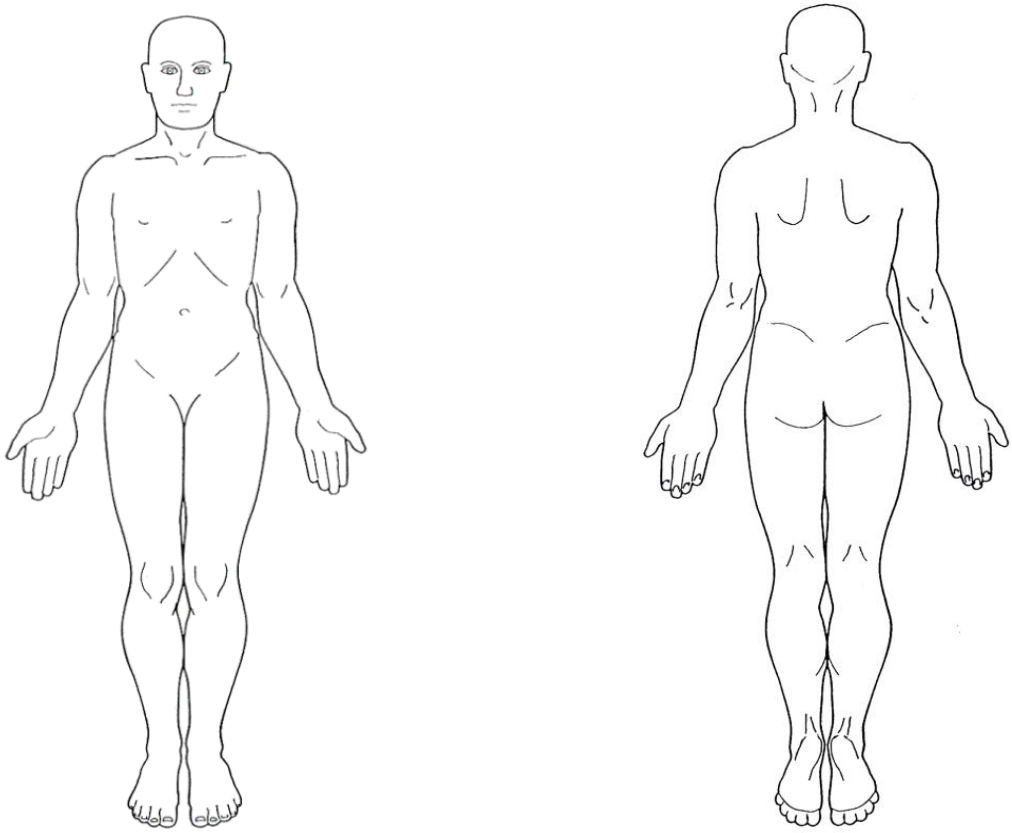
Section 3: Current Health and Medications

Current KP, a primary outcome measure (Section 3.7.1), was identified using the Body Pain Mannequin (BPM). The BPM is a validated instrument, developed at the University of Manchester, to capture pain in any region of the body (MacFarlane et al., 1996) (Hunt et al., 1999). A subsequent study established the reliability of the BPM. The authors reported the line drawing tool was highly consistent for scoring pain, based on classification of cases (Lacey et al., 2005).

Within the Football Study questionnaire, the following question preceded the BPM template (Figure 3.3):

"…indicate where you have suffered any pain for most days in the previous month. By pain we also mean aching, discomfort and/or stiffness. Please do not include pain due to feverish illness such as the flu."

Body pain reported was current (within the past month) and did not include temporary pain (for example, due to the flu). The BPM was delineated by anatomical regions (Appendix F.2) to identify prevalence of pain within these regions. If shaded, Regions 5 (anterior right knee), Region 6 (anterior left knee), Regions 26 (posterior left knee) and Region 27 (posterior right knee) indicated pain in the anterior or posterior region of the knee. Thus, footballers who reported pain in any of the aforementioned regions had current KP.



A **B**

Figure 3.3 – The body pain mannequin tool

The BPM line drawing tool (MacFarlane et al., 1996) reports current body pain (within the past four weeks) in the anterior (A) and posterior (B) regions of the body

This section of the questionnaire (Section 3) also included details on whether footballers suffered from medical comorbidities (current or previous), including cardiovascular condition and cancer. This section also included medication use by footballers, including over the counter (OTC) medications and supplements.

Section 4: Knee Pain

This section reported two further measures of KP. The first was ever having KP:

"Have you ever had significant pain in or around your knees for most days of a one month period?"

The second was having physician-diagnosis of KOA (despite being less robust):

Have you ever been diagnosed with Osteoarthritis in your knees by a physician (for example, your GP)?"

This section also obtained information on knee alignment. This was self-reported using a line drawing instrument (see Figure 3.4), produced and validated in Academic Rheumatology, University of Nottingham (Ingham et al., 2010). Both varus and valgus malalignment were reported currently and during their 20s (to represent constitutional rather than acquired malalignment).

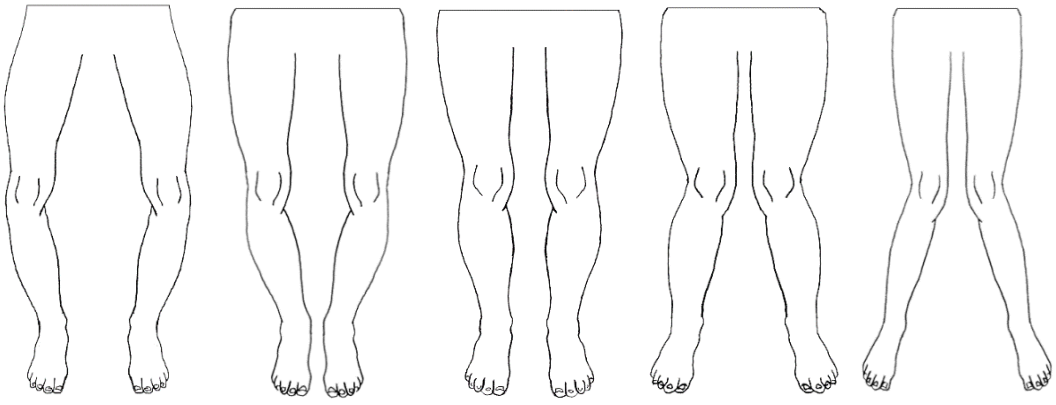


Figure 3.4 – The line drawing tool to determine leg alignment

The line drawing tool shows variations of leg alignment (Ingham et al., 2010). Participants were asked to indicate whether the shape of their legs was best represented by a straight (C), a Varus (A and B) or a Valgus (D or E) alignment.

Section 5: Knee Injuries and Surgery

Following section 2, this section focused predominantly on knee injuries, knee surgeries and intra-articular knee injections (subsequently referred to as knee injections) suffered by footballers during their careers. The question pertaining to significant knee injury, which were football-related, was as follows:

"...one which caused you pain for most days for at least a three month period and resulted in an absence from all training and matches during this time."

A separate question recorded knee injuries, which were non-football related. Both questions included details on the type of injury, knee(s) affected and age at which the injury occurred.

This question differed from the KPIC Study, whereby the following question identified whether participants had suffered a knee injury (regardless of whether it was sport-related):

"*Have you ever suffered a significant knee injury to either of your knees?*"

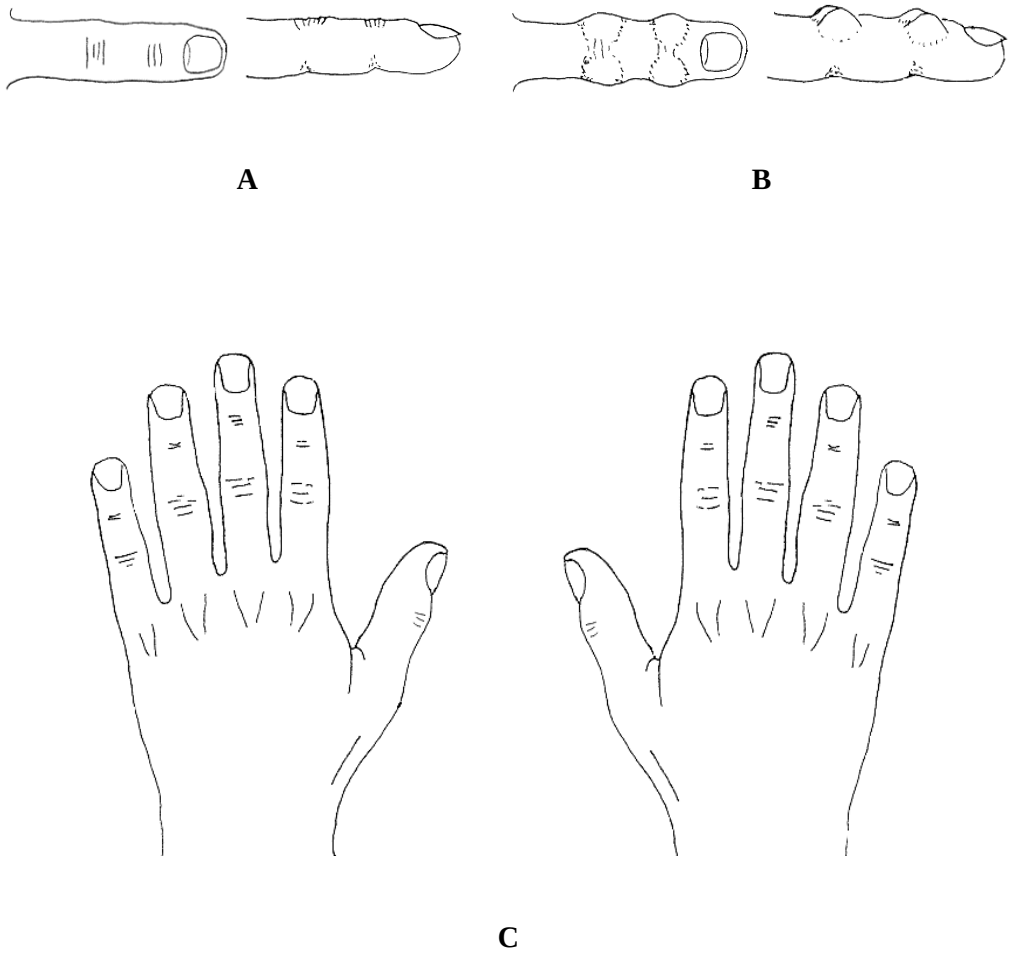
A follow-up question identified the type of injury, but not the age sustained nor the knee affected.

The focus of surgery was the type (investigative, corrective or replacement surgery), which knee and the age when the surgery took place. Intra-articular knee injections during a footballer's career ascertained information about the number and type of injections received over the course of a player's career.

Section 6: Hand and Familial OA

Nodal OA was self-reported using a line drawing tool, developed in the Academic Rheumatology, University of Nottingham (see Figure 3.5) (Rees et

al., 2012). Analysis for nodal OA required determining the number of nodes highlighted per hand using an in-house derived method (see Appendix F.3). Nodal OA was defined as those who reported nodes on at least two rays of both hands (Zhang et al., 2009).



A **B**

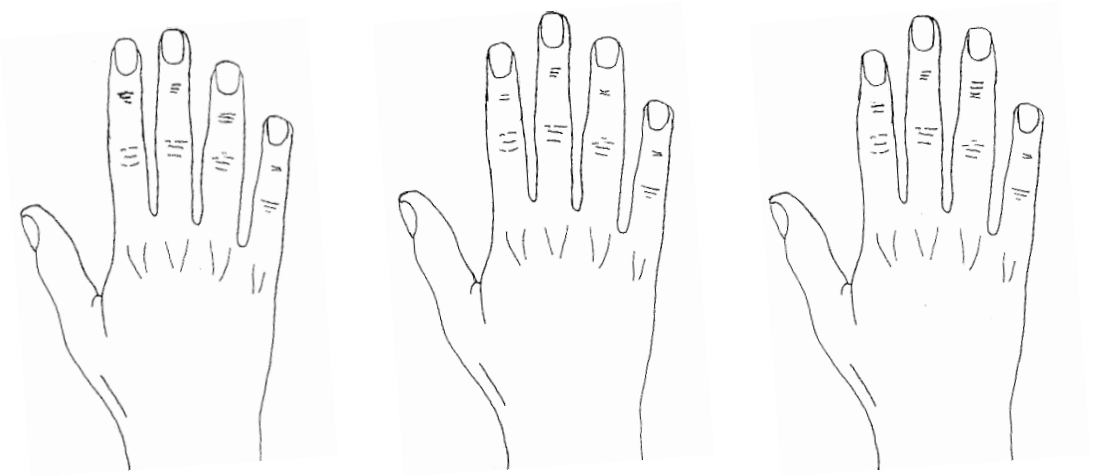
C

Figure 3.5 – The line drawing tool to determine nodal OA

This line drawing tool depicts a normal (A) and node-affected (B) digit. Participants indicated whether the proximal or distal interphalangeal joints of both hands (C) had the presence of nodes. Nodal OA was determined using the ACR Criteria for the condition.

Digit ratio was self-reported using a line drawing tool (see Figure 3.6) produced and validated within Academic Rheumatology, University of Nottingham. This instrument depicts various options for digit length ratio and footballers selected the most appropriate one (Zhang et al., 2008). However, radiographic assessment would have been a more robust measure (Robertson et al., 2008).

There were also questions about any first-degree relatives (parents or siblings) who were known to have hand, knee or hip OA. Footballers were also asked whether any first-degree relatives have undergone joint replacements (knee or hip), which is a surrogate marker for OA.



A **B** **C**

Figure 3.6 – The line drawing tool to determine digit (2D:4D) ratio

Digit ratio is the ratio between the length of the index finger and ring finger. Three variations exist; a longer index finger, known as Pattern 1 (A), a longer ring finger, known as Pattern 3 (C), and both fingers of equal length, known as Pattern 2 (B).

Section 7: Health-related Quality of Life

It was also important to study the effects of chronic conditions in footballers. The Short Form-36 (SF-36) questionnaire is a validated questionnaire, which measures the health-related quality of life (QoL) of responders. The questionnaire is a validated, pre-existing instrument, used regardless of chronic condition suffered. It contains a series of questionnaires to assess the physical and mental (including emotional) components of a responders wellbeing and how they cope with chronic conditions.

Personal Details

The final page included two forms of consent. The first related to the footballer's interest in the radiographic survey that followed the questionnaire. If they indicated an interest, contact details to send formal invitation of participation were required. The second related to willingness to receive information concerning future related studies undertaken by the University of Nottingham.

3.6 Radiographic Assessment

3.6.1 Implementation

Footballers

Following the questionnaire survey, the next phase of the study was a radiographic survey. A signed agreement between Spire Healthcare (UK) and Academic Rheumatology (Appendix D.1) was in place for footballers to attend their nearest Spire Hospital across the country to have radiographs of their knees

Only footballers that indicated interest to participate (via the questionnaire) were included in this phase of the study. The hospital locator tool on the Spire Healthcare website determined the nearest hospitals to a footballer's home address. Only footballers who lived within 40 miles of a hospital received an invitation to have their x-rays due to logistical reasons and to limit expenses to reimburse of their travel.

The invitation to partake in the radiographic survey included a letter from Professor Michael Doherty (see Appendix D.2) along with the patient information sheet (see Appendix D.3) and a consent form (see Appendix D.4). Footballers interested in participating were asked to return their consent form back to Academic Rheumatology in the self-addressed envelope provided.

Footballers who received an invitation letter subsequently received two telephone calls (or an email if unavailable). The first was a follow-up to the invitation letter sent, clarifying any queries with regards to participation. The second, at least one week later, was a reminder regarding their participation. If

footballers were unavailable, they received third (and final) telephone attempt before they were excluded from the survey.

Spire Healthcare

Footballers attended a Spire Healthcare (UK) hospital to have their knee radiographs. These were standardised using a Rosen jig (see Appendix C.1), which were provided to the hospitals from Academic Rheumatology. Given the limited number of jigs, the radiographic survey was implemented in a staggered approach across different Spire Hospitals. Hospitals allocated less than five footballers (living within 40 miles of the hospital) were not included in the survey and those footballers allocated to another Spire Hospital due to cost-effectiveness.

A fortnight prior to the radiographic survey commencing at each hospital, the radiology manager received an email invitation explaining the process for the radiograph survey and the number of footballers allocated to the hospital. Footballers who returned their consent form received a telephone call to: 1) confirm they were eligible for the survey (ensure they have not had a bilateral TKR), 2) arrange an appointment at a time convenient for the footballer, 3) obtain or confirm patient information required by the hospital and 4) discuss receipt of reimbursement for travel expenses.

Outpatient forms (Appendix D.5.) for each patient were completed with patient information (name, date of birth, home address, telephone number, name and address of GP practice and a name of a next of kin) provided by the footballer. This was sent to the Hospital prior to the footballer's appointment. Following

confirmation of the appointment (by the hospital), footballers received an email with the appointment details.

Spire Cambridge Hospital was the first to commence the radiograph survey, and following its success, implementation of the survey then took place at multiple hospitals simultaneously. Footballers had a posterior-anterior (PA) view and skyline view radiograph taken for both their knees.

Following completion of the study at a hospital (all allocated footballers receiving radiographs), the Rosen jigs were sent to the next hospital (randomly selected). The hospital sent the radiographs back to Academic Rheumatology (via a password-encrypted CD) for analysis. Footballers subsequently received a written report regarding their radiographs.

Controls

Only males who responded to the KPIC Study questionnaire were controls for the Football Study (gender-matched). Participants sent their KPIC Study questionnaire back to Academic Rheumatology and Wyman Dillion (Bristol, England) conducted data-entry.

Participants that indicated an interest to participate in further research received an invitation to become a control in the Football Study and have radiograph of their knees. The invitation consisted of a letter from Professor Michael Doherty (Appendix E.1.) together with a patient information sheet (Appendix E.2.) and a consent form (Appendix E.3.). Interested participants returned their consent form to Academic Rheumatology in the self-addressed envelope provided. Participants who had already had a radiograph of their knees (as part of the KPIC

Study) were sent a separate letter requesting consent to use their radiographs as part of the Football Study.

Control participants were invited to City Hospital, Nottingham NHS Trust (where Academic Rheumatology is based) to have a radiograph of their knees. The same protocol to conduct the radiographs applied to footballers and controls (Section 3.6.2).

3.6.2 Protocol

Each participant (footballers and controls) received two standardised x-rays from different views. The first was a standing semi-flexed PA view of the TF compartments of both knees using a Rosen template. The second a 30-degree flexion skyline view of each PF joint with the participant lying on a couch with cushioned support under the knee (see Appendix C.1 for the protocol description (Rosenberg et al., 1988) sent to hospitals).

The University of Nottingham Physics Department produced nine Rosen templates (jigs) for this study. Spire Hospitals received a Rosen template prior to conducting the radiographs, which ensured radiographs were standardised across all footballers and all hospitals. Once all imaging at a hospital was complete, the next hospital received the jigs and the process started over. Nottingham City Hospital also used the jigs to conduct radiographs of all control participants.

3.6.3 Assessment

Scoring of all the footballer and control participant radiographs was by a single observer (GSF) at Academic Rheumatology, ensuring standardisation across both cohorts. Radiographs were scored as a single mixed batch using HIPAX Dicom software.

All radiographs were scoring using both the KL and NLDA assessment instruments for all compartments (two TF and one PF compartment) of both knees. The NLDA instrument provides a more detailed assessment for the extent of structural change and is the primary measure used for this study. The purpose for the KL instrument was to provide comparison of the results to the pre-existing literature.

Intra-rater (GSF) and inter-rater (GSF with AS) reliability was assessed at the start, during and at the end of the study to ensure reproducibility of the results (see Table 3.1). At each assessment, 10 pre-selected (blind of identity) radiographs were scored on two occasions at least two days apart. Scorers were blind to both their previous score and that of the second observer. A kappa (κ) statistic tested agreement between the two scorers.

Landis and Koch proposed a κ-statistic <0 as indicating no agreement, 0.0-0.20 as slight agreement, 0.21-0.40 as fair agreement, 0.41-0.6 as moderate agreement, 0.61-0.80 as substantial agreement and 0.8-1.0 as near-perfect agreement (Landis and Koch, 1977). However, these classifications are not universally accepted. Another researcher, Fleiss proposed an alternate, yet equally arbitrary classification: >0.75 as excellent-, 0.40-0.75 as fair to good- and <0.40 as poor- agreement (J.L.Fleiss, 1981).

Based on Landis and Koch's classification, it can be seen that there was a 'substantial agreement' between the two observers (GSF and AS) for assessing the whole knee at the end of the study (indicated in bold text in Table 3.1). If the classification by Fleiss was used, this also suggests a 'good' agreement. The κ-statistic for the whole knee improved between observations, from before the study to the end of the study, suggesting improved reproducibility of the results.

Table 3.1 – Inter-rater reliability agreement for radiographic assessment

	Pre-Study		**Mid-Study**		**End-Study**	
	κ-statistic	**95% CI**	**κ-statistic**	**95% CI**	**κ-statistic**	**95% CI**
NLDA Score (Osteophytes)						
TF Joint	0.65	0.56-0.75	0.71	0.63-0.79	0.58	0.42-0.72
PF Joint	0.65	0.57-0.73	0.64	0.56-0.71	0.68	0.59-0.76
Whole Knee	0.66	0.60-0.72	0.68	0.63-0.73	**0.65**	0.58-0.72
NLDA Score (JSN)						
TF Joint	0.71	0.58-0.81	0.66	0.52-0.77	0.72	0.57-0.85
PF Joint	0.38	0.20-0.57	0.72	0.61-0.82	0.60	0.26-0.81
Whole Knee	0.59	0.48-0.69	0.69	0.60-0.76	**0.70**	0.57-0.81
KL Grading						
TF Joint	0.68	0.53-0.80	0.77	0.60-0.89	0.57	0.38-0.74
PF Joint	0.58	0.43-0.77	0.74	0.57-0.86	0.66	0.49-0.83
Whole Knee	0.64	0.53-0.75	0.76	0.65-0.84	**0.63**	0.51-0.75

Inter-rater reliability was determined between GSF and AS at the start, during and at the end of the radiographic assessment. Reliability for scoring using both the NLDA and KL tools were assessed, with a moderate to strong overall reliability.

3.7 Outcome Measures

As described (Section 1.3), KOA is a common complex disorder than may be diagnosed in multiple ways. The two most common approaches to determining KOA are if patients have KP or radiographic evidence of severe structural change. The present study assessed KOA by using multiple outcomes that relate to the condition, separated into primary (Section 3.7.1) and secondary (Section 3.7.2) outcome measures.

3.7.1 Primary Outcome Measures

The primary outcome measures (to determine KOA) selected for this study are current KP, RKOA and TKR. Table 3.2 describes each outcome measure and its source. The questionnaire provided the self-reported outcome measures, current KP and TKR. Current KP was determined through the BPM whereas TKR was reported in the questions regarding previous injury and surgery (in cases where TKR was unilateral, it was validated from the radiographic survey wherever possible). Structural change was analysed using the NLDA instrument to determine RKOA. The NLDA instrument was preferred to KL scoring because it provides a more comprehensive analysis of structural change.

Table 3.2 – Primary outcome measures to determine KOA

Outcome Measure	Source
Current Knee Pain	Questionnaire Survey **Question 20** *"Indicate where you have suffered any pain for most days in the previous month"* *(Present if any one of Regions 5, 6, 26 or 27 were shaded on the BPM – see Appendix F.2)*
Radiographic KOA	Radiograph Survey
Nottingham Line Drawing Atlas (NLDA)	**NLDA Score** Dichotomous cut-off (inclusive for both TF and PF compartments) defined as: *"Osteophyte in any compartment of the knee AND JSN in at least one of the TF or PF compartments of the knee."*
Total Knee Replacement	Questionnaire Survey **Question 30** *"If you have suffered a significant football related injury, please could you state the type of injury, which knee was affected and approximately how old you were when the injury occurred?"* **Question 36** *"If you have had any surgery, please state what type of procedure you had, which knee was affected and how old you were when the surgery occurred."*

3.7.2 Secondary Outcome Measures

Two self-reported measures and two structural change measures were analysed as secondary case-definitions (described in table 3.3), the most important of which was measuring RKOA using the KL instrument.

In terms of structural change measures, RKOA assessed using the KL instrument was important for two reasons: firstly, it provided a comparison to the pre-existing literature; and secondly, it provides a comparison to the NLDA instrument. CC was an additional outcome measure analysed for RKOA.

The self-reported measures were ever having KP for at least one month and receiving a physician-diagnosis for KOA, obtained from the questionnaire. Ever having KP is less accurate as footballers may report such pain at an earlier point in their lifetime, which makes the pain less attributable to KOA. A self-reported Physician-diagnosis for KOA is less reliable than a focused clinical assessment (history and examination) or formal medical record.

Table 3.3 – Secondary outcome measures to determine KOA

Outcome Measure	Source
Radiographic KOA	Radiograph Survey
Kellgren Lawrence (KL) Grades Verbal Descriptors	**KL Score (Grade 3 or more)** A dichotomous cut-off defined as KL≥3 (independent for TF and PF compartments): *"Multiple osteophytes (definite) and definite JSN" (ACR criteria)*
Chondrocalcinosis	Radiograph Survey *"Presence of Chondrocalcinosis (cartilage calcification) in hyaline or fibrocartilage of any compartment"*
Knee Pain Ever (1 month)	Questionnaire Survey **Question 21** *"Have you ever had significant pain in or around your knees for most days of a one-month period?"*
Physician-Diagnosed KOA	Questionnaire Survey **Question 25** *"Have you ever been diagnosed with Osteoarthritis in your knees by a physician (e.g. your GP)?"*

3.8 Data Management

3.8.1 Data Collation and Entry

Robust record keeping was essential to manage the large-scale of this study. Each questionnaire was numbered (questionnaire number) prior to being distributed to footballers.

Footballers posted completed questionnaires back to the Department (Academic Rheumatology) via the self-addressed envelope provided. Returned questionnaires were numbered chronologically upon receipt (footballer ID), distinct from the questionnaire number and ensure good record keeping of the responses received.

A questionnaire cover sheet (see Appendix F.1) was completed for each questionnaire received. Contact details were detached from the questionnaire and stored (with the cover sheet) separately to the questionnaire responses. This was essential for the purposes of data protection to maintain anonymity of the footballers.

Entry of the questionnaire responses and contact details were necessary, but carried out and stored independently of each other to maintain data protection.

This author (SMP) developed a database on Microsoft Access 2010 (Windows 7 operating system). GSF and SMP entered the questionnaire cover sheet and contact details. The database was password-encrypted and only two researchers (GSF and SMP) had access to it, again maintaining data confidentiality.

Wyman Dillion (Bristol, England), an external organisation that provided data-entry services, carried out data entry for the questionnaires (void of personal

details). The decision to use an external organisation for this purpose was two-fold: firstly, the time taken to enter the data was far quicker than if it were carried out in-house; and secondly, the company provided a double-entry service, whereby all data was entered twice (which served as a verification process). Wyman Dillon recorded the data in a spreadsheet package (Microsoft Excel). The file was password-encrypted prior to sending it back to Academic Rheumatology for analysis. Wyman Dillion used the spreadsheet package, Excel 2010 (Microsoft Office) to input the data. This was rechecked for entry-errors and formatted as appropriate before any statistical analysis

3.8.2 Data Verification

Verifying the questionnaire responses from the footballers was important to ensure the responses were from professional footballers only. The two aims for this assessment were firstly, to verify the responses received, and secondly, to identify any duplicate responses (because questionnaires were distributed via multiple sources).

To assist with this process, two research assistants were recruited (JPM and EMC). Verification for each questionnaire response to previously published football records confirmed whether the responder played football professionally. 'The PFA Premier and Football League Players' Records 1946 – 2005 (edited by Barry J. Hugman)' (Hugman, 2005) is a book containing the records of footballers that have represented professional football clubs in the UK. At the time of verification, JM and EC made use of the latest edition. However, there has been a subsequent edition dated 1946-2015.

Verification of the questionnaire responses was by comparison to the above named book. Footballer name and date of birth were used to identify players in the book and then verification was through comparison of the following variables; career start date, career end date (only applicable if retired prior to 2005) and number of matches played.

3.8.3 Data Categorisation

The raw data (entered by Wyman Dillion) required data cleaning and categorisation prior to analysis. This was to, firstly, to determine whether data entered appear correct (for example, an age value greater than 100 is highly unlikely), and secondly, to remove such anomalous or blank values by appropriately replacing the entry as a missing value.

Some variables, not collected directly from the questionnaire responses itself, were generated using multiple questions as described in Table 3.4. Other variables were categorised for analysis, namely which tier footballers played in, type of high-risk occupations, type of injuries, surgery and injections.

Table 3.4 – Variables generated from the questionnaire data

Variable	Protocol
Age (years)	**=1 /12/2015 – Date of Birth** *Date of birth was subtracted from 1st December 2015 (the cut-off date for recruitment for the questionnaire survey) and reported in years*
BMI (current) / BMI in 20s	**= Weight / (Height)^2** *Current BMI used **'Current Weight'** and BMI in 20s used **'Weight in 20s'***
Competitive Football Duration (years)	**= Age Started Professional Football – Age Started Competitive Football** *Competitive football duration is the difference in age between commencing professional and competitive football*
Professional Career Duration (years)	**= Year Retired – Year Commenced (Professional Football)** *Professional career duration is the difference in years between commencing and retiring from professional football*
Total Football Duration (years)	**= *Competitive Football Duration* + *Professional Career Duration***
Training Dose per Week (hours)	**= Hours per Day x Days per Week (Training Duration)** *Training dose per week is the number of hours per day spent football training multiplied by the number of days per week spent football training*
Career Training Dose (hours)	**= Training Dose per Week x 40 x Professional Career Duration** *Career training dose is the number of hours per week spent training multiplied by the number of weeks per season (average of 40 weeks) multiplied by the professional career duration*
Comorbidities	*Footballers who reported at least one of: diabetes, myocardial infarction (MI), hypertension (HTN), cancer (Ca) or fibromyalgia*
Current Knee Pain	*Footballers who indicated KP (on any part of their knee) from the BPM*
Current Malalignment	*Footballers who reported a current Varus or valgus malalignment*
Constitutional Malalignment	*Footballers who reported a Varus or valgus malalignment in their 20s*
Familial OA	*Footballers with a first-degree relative (mother, father of siblings) who have hip, knee or hand OA*
Familial Joint Replacement	*Footballers with a first-degree relative who has had a hip or knee replacement*

Football Tiers

The English Football League classifies the top four tiers as professional. At present, these are The Premier League, The Championship, League One and League Two. However, since its inauguration in 1888 the names of these top four tiers have changed on several occasions.

The leagues reported by footballers were categorised into the four tiers based on the period of their career (dates provided) and are outlined in Table 3.5. Footballers are classified separately if they played below tier 4 (Lower Leagues) or abroad (Other Countries).

Table 3.5 – The tiers of the English Football League system

Tier	Leagues included
Tier 1	Premier League (1992 – present) 1st Division (1888 – 1991)
Tier 2	Championship (2005 – present) Division One (1992 – 2004) 2nd Division (1892 – 1991)
Tier 3	Football League One (2005 – present) Division Two (1992 – 2004) 3rd Division (1958 – 1992) 3rd Division North/South (1921 – 1958)
Tier 4	Football League Two (2005 – present) Division Three (1992 – 2004) 4th Division (1958 – 1992)
Reserve League	Football Combination League Football Central League 'Reserves'
Lower Leagues	Any other league(s) lower than Tier 4 (including Conference Leagues)
Other Countries	Any country NOT England (this includes Scotland, Wales, Northern Ireland)

Post-Football Occupations

Footballers reported up to six occupations that they held following retirement from professional football. However, there is no single source of literature to classify whether the listed jobs were high risk for KOA.

Occupations were therefore categorised as high-risk occupations (Palmer, 2012) on a pragmatic basis using the Department of Heath report and as well as other literature (Coggon et al., 2000, (IIAC), 2008, Bishay et al., 1992, McMillan and Nichols, 2005, Partridge and Duthie, 1968, Thun et al., 1987). EC and CN were responsible for categorising the occupational data for the footballers and controls respectively. Table 3.6 shows the high-risk occupation categories identified (by EC and CN) and the types of jobs that fall under each category.

High-risk occupations categories, identified through job titles only, were deemed to involve some extent of physical activity or labour that far exceeds low-demand sedentary work, such as office workers (Felson et al., 1991).

Table 3.6 – Categorisation of high-risk occupations

Occupation Fields	High Risk Category
Auto-Industry Mechanic	Mechanic
Bricklayer Builder Joiner / Carpenter Window Fitter	Construction (Tradesman)
Electrician Carpet Fitters / Floor Layer House Painter Plumber	Tradesman – other
Emergency Services	Emergency Services
Factory Worker Warehouse Worker	Factory / Warehouse Worker
Farmer Gardener Forestry	Land Management / Cultivation
Manual Workers Engineering Gas Engineer	Manual Workers Engineering
Health Services	Health Services
Coal Miner	Coal Miner
Metal Worker	Metal Worker
Porters / Cleaners / Maintenance	PCM (Porter, Cleaner, Maintenance)
PE Teacher	PE Teacher
Postman	Postman
Labourer	Labourer
Road Worker	Road Worker
Shipyard Worker	Shipyard Worker
Sports – Other	Other Professional Sports
Semi-Professional Footballer	Semi-Professional Football
(Football) Coach / Manager	Football Coach / Manager

Knee Injuries

Footballers provided information on the type of significant knee injuries they sustained, both when playing professional football, and non-football related injuries. The range of injuries reported classified into several categories identified in Table 3.7 for analysis. Self-reporting of these injuries meant sub-categorisation (for example, soft tissue injuries) was difficult to establish.

Table 3.7 – Classification of knee injuries

Injury Type	Responses include:
Bone	Injuries related to bone, for example: o Broken bone (tibia or fibula) o Fracture o Dislocation
Soft Tissue	Injuries related to the following soft tissue structures of the knee, including: o Cartilage o Ligament / ACL o Patella Tendon o Meniscus Soft-tissue related conditions resulting in injury, for example: o Osgood Schlatters
Other	Other conditions, for example: o Osteochondritis Dissecans Procedures and/or Operation Consequences of injury, for example: o Lump o Bursae o Cyst o Knee collapse o (Bone) Bruising o Loose (foreign, floating) bodies o Twisting o Jarring o Locking o Strains
KOA	Signs of KOA o Wear & tear o Bony spur o Osteoarthritis

Knee Surgery

Similar to knee injuries, footballers reported knee surgery they had undergone, categorised as either Arthroscopy or TKR – see Table 3.8. Arthroscopy was not sub-categorised because responses were self-reported and such surgery may involve investigation or repair of multiple structures simultaneously. This was the primary source question to determine whether footballers had undergone unilateral or bilateral TKR.

Table 3.8 – Classification of knee surgeries

Surgery Type	**Responses include:**
Arthroscopy	Any explorative, investigative or corrective arthroscopy-related procedures, including: o Keyhole o Flush out o Clean out o Wash out o Exploratory o Scope o Debridement Surgery related to any ligament structures, including: o ACL o MCL o PCL o Cruciates Surgery related to any cartilage / meniscus structures
TKR	Knee replacement

Injections

The question relating to intra-articular knee injections that footballers received had three pre-defined categories, namely Steroid, Anaesthetic and Other. Any responses in the other category were re-categorised if they stated steroid or anaesthetic injections, as detailed in Table 3.9.

Table 3.9 – Classification of intra-articular knee injections

Injections Type	**Responses include:**
Steroid	Steroid Cortisone Corticosteroid
Anaesthetic	Anaesthetic Lignocaine Lidocaine
Other	Any other responses

3.9 Statistical Analysis

The questionnaire survey was quantitatively analysed using the statistical package STATA SE Version 14 (StataCorp) run on Windows 7 operating system. Standard STATA commands were used unless otherwise stated.

3.9.1 Power Calculations

Two power analyses were conducted for this study, one for the prevalence of KOA and the other for the risk (RR) of KOA between footballers and control.

For the prevalence of KOA, the power calculation was based on the potential size of the source population (50,000 quoted by XPRO, Solihull England) and the response rate (37%) from a previous study of a similar design (Drawer and Fuller, 2001): **50,000 x 37% = 18,500.**

Based on this population estimate, using previous research on the prevalence of KOA in footballers (~30%) (Elleuch et al., 2008) and an acceptable deviation (3%), the sample size required varied based on power and significant level:

Power = 80%; Significant Level = 0.05; **Sample Size = 376**

Power = 95%; Significant Level = 0.05; **Sample Size = 855**

For the comparison study (footballers versus controls), the sample size was calculated based on the prevalence of KOA in footballers (~30%) (Elleuch et al., 2008) and the in the controls (15%) (Lawrence et al., 1966):

Probability of KOA in Footballers = **0.30**; Probability of KOA in Controls = **0.15**

Controls per case subject = **1**; Alpha = **0.05**; Power = **0.80**

Estimated sample size = **120 per group** (see graph below)

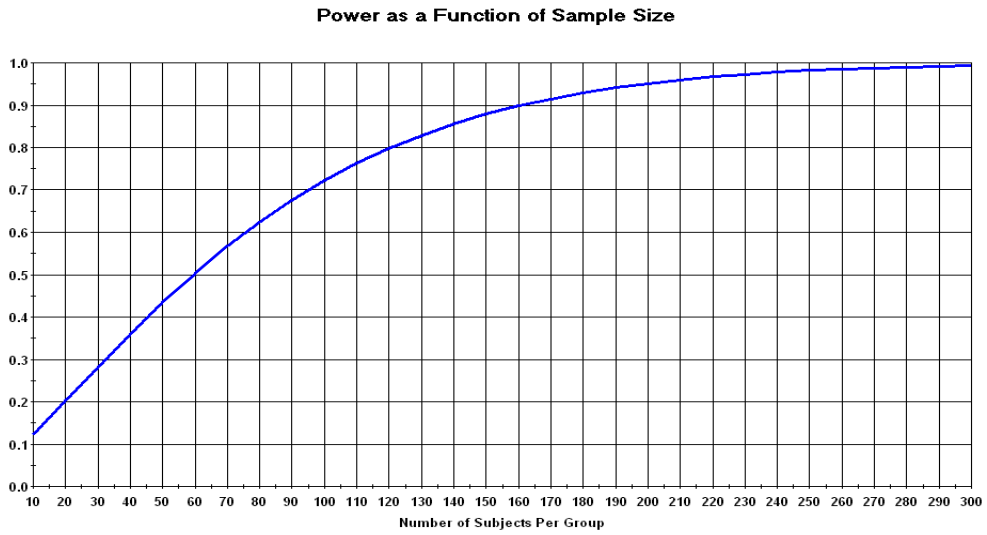


Figure 3.7 – Power as a function of Sample Size

However, after adjusting for potential confounding factors, including age, BMI, nodal OA, the RR is reduced by up to 25% (Elleuch et al., 2008; Kujala et al., 1994; 1995). To maintain a power of 0.80 and significant level of 0.05, the sample size was increased:

Unadjusted RR = **2.0;** Adjusted RR = **1.5**

Sample Size = 480 per group

3.9.2 Generic Statistical Methods

Conducting quantitative analysis follows a three-stage process: firstly, data should be described (known as descriptive statistics); followed by conducting basic statistical tests (known as inferential statistics). Finally, relationships between different data variables, including taking into confounding variables (typically, modelling statistics) are established. It is important to understand the nature of the data, typically its distribution, skewness and variability, as well as the amount of missing data. This avoids incorrect assumptions during the statistical analysis. Statistical analysis carried out for the comparison study was the same for both populations (footballers and controls). Through the statistical analysis, significance was established at when p is less than 0.05 ($p<0.05$).

Descriptive Statistical Methods

Descriptive statistics describes the data using numbers based on the type of variable (categorical or continuous). Identifying the distribution of the data was key to reporting appropriate statistics. Most of the continuous variables (for example, age and BMI) had a Gaussian distribution so are reported as mean and standard deviation (SD). Frequency and percentage were used to present categorical variables (including data that are binary (yes or no) and multiple categories). Descriptive statistics for footballers and controls demographic data precede determining the risk of footballers in footballers compared to the controls (Section 4.2) and the nested case-control studies within footballers (Section 4.3).

Football-specific data (Section 4.3.1) provided a means to plot graphs. Scatter plots compared continuous variables (namely, career duration, matches played,

career-training dose). Box plots compared continuous variables (for example career duration and training dose) by discrete (categorical) variables (for example, tier played in). Prevalence data, reported as percentage, describes the proportion of people with the outcome measure of interest in a given population (either footballers or controls).

Analytical Statistical Methods

Following the descriptive statistics, the risk between populations (footballers and controls) or within populations (footballers only) was determined. The t-test (independent) is the statistical test used to measure continuous data. The test reports two key findings; firstly, the differences in the mean between the two cohorts, and secondly, whether this difference is statistically significant.

Statistical differences between categorical data is determined using the chi-squared test, based on the assumption that each category is greater than n>five (for all categories across both populations). This test measured whether the strength of association between the two categorical variables is statistically significant.

The subsequent two sections describe the different regression approaches adopted based on the study design. The multivariate (multiple variables) regression analysis modelled the data to assess whether change in certain variables (risk factors) predicted changes in other variables (outcome measures).

3.9.3 Comparison Study Analysis Approach

Relative risk (RR) is the ratio of the probability of having the outcome in an exposed group (footballers) to the probability of having the outcome in the unexposed group (controls). This was selected rather than odds ratio (OR) for reporting of risk when accounting for footballers and controls for three reasons: (1) RR is more intuitive to understand; (2) the outcome measures are common in the populations studied (prevalence greater than 10%), and (3) this is a comparison of two cross-sectional studies rather than a case-control study (Viera, 2008).

The generalised linear model (GLM) is a large class of models, in which the response variable is assumed to follow an exponential distribution, which is often non-linear. This class of modelling is different to the general linear model, which is a conventional linear regression model for a continuous response variable. Table 3.10 presents three subset models for GLM analysis in addition to logistic regression, describing the advantages and disadvantages of each. The subset classes for the GLM model are identified in parentheses (Cummings, 2009).

GLM has three components: a random component, referring to the probability distribution for the response variable; a systematic component, which specifies the explanatory variables; and finally, a link function, which combines the random and systematic components. The subset model selected for the GLM depends on the distribution for the random component, and the link and systematic components follow suite (Cummings, 2009).

Comparing the three models (GLM) reporting RR (Table 3.10), a Poisson Distribution was most appropriate to account for the lack of convergence when analysing some covariates (Binomial Distribution was chosen initially but convergence issues were encountered) (Greenland, 2004) (Cummings, 2009). The Huber Sandwich estimate equation was used to determine the CI to ensure they were not exaggerated (Huber, 1967).

Table 3.10 – Regression methods to determine risk of outcome measures

Regression Method	Advantage	Disadvantage(s)
Logistic Regression -reports OR	Quick and simple to calculate	-Should not be used for common outcome (prevalence >10%) -Not intuitive to understand
GLM **(Binomial Distribution)** -reports RR	Most straight forward / commonly used for GLM models	-Convergence issues, especially if model contains continuous variables -Fitted probabilities may include negative values, therefore difficult to determine maximum likelihood estimation
GLM **(Poisson Distribution)** -reports RR	Provides solution to failed convergence issues	Fitted probabilities may be greater than one – care should be taken when reporting results
GLM **(Cox Distribution)** -reports RR	Time period set as constant so Poisson distribution adopted	-Coefficients may be overestimated; however, this may be overcome through adjustment approach -Complex to generate because time-element and censorship are required

Regression modelling reporting the RR was conducted for all primary and secondary outcome measures. Further models adjusting for multiple covariates were generated to report risk (RR) when such variables were taken into account. These included the classic risk factors for KOA, namely age, BMI, knee injury and high-risk occupation amongst others.

3.9.4 Nested Case-Control Study Analysis Approach

Determining the risk factors for the primary outcome measures within footballers followed a nested case-control study. Based on the study design, logistic regression was used for the statistical analysis and risk is reported as OR. This is, the odds of the outcome occurring in the exposed group compared to the odds of the outcome occurring in the unexposed group.

The use of multivariate logistic regression reports the OR having accounted for multiple factors simultaneously. To determine the risk factors for each primary outcome measure (namely, current KP, RKOA or TKR); a back-step model approach was used.

The first step (crude analysis) was to assess independently multiple risk factors (including constitutional, local biomechanical and football-specific) for the outcome measure. The OR, confidence interval (CI) and significance (p-value) were determined. The second step was to include all the significant variables from the crude analysis into one model (for each outcome measure independently), and determine whether each remained significant.

Non-significant variables were excluded, one at a time (starting with the least significant), and the model were calculated until all variables within the model remained statistically significant. The remaining variables in the model were the risk factors for the outcome measure studied when accounting for all other variables.

4 RESULTS

This chapter describes the study results to achieve the study objectives (outlined in Chapter 2), in the following sections:

- **Recruitment** (Section 4.1) – this section describes the recruitment for questionnaire and radiographic surveys for both the footballers (Arthritis and Football Study) and controls (KPIC Study)

- **Comparison Study** (Section 4.2) – this section describes the comparison between footballers and controls in terms of characteristics, prevalence and relative risk for the outcome measures

- **Nested Case-Control Study** (Section 4.3) – this section describes the characteristics of the football population in detail and then the nested case-control studies. These were carried out for independently for each primary outcome to determine the risk factors within footballers

- **Discordance Analysis between KP and KOA within Footballers** (Section 4.4) **–** the discordance between KP and RKOA is explored in this section, highlighting the fact that footballers with KP and RKOA are not mutually inclusive

4.1 Recruitment

Professional footballers were recruited from the Arthritis and Football Study and controls were recruited from the KPIC Study.

Figures 4.1 and 4.2 describe the recruitment of footballers and controls respectively. The number of questionnaires distributed and the numbers invited back for the radiograph phase of the study are detailed. The shaded boxes indicate the final number of questionnaire responses received and number of footballers and controls that had radiographs of their knees.

4.1.1 Footballers

Almost 5000 questionnaires (n=4775) were distributed to retired professional footballers via multiple channels (Section 4.1).

The response rate for questionnaires received from footballers (excluding any duplicates and those under the age of 40) was 25.3%. Although this response rate is lower than that of previous studies conducted, 37% (Drawer and Fuller, 2001) and 55% (Turner et al., 2000), the final number of footballers recruited (1207) is more than four times greater than previously studied. Furthermore, the sample size was sufficient based on the previous calculations (see Section 3.9.1).

71.3% of the footballers who returned their questionnaire consented to participating in the radiograph phase of the study, but only 470 footballers (54.7%) had radiographs of their knees. Although this was slightly lower than anticipated (expected: 480), a 1:1 ratio of footballers and controls was achieved.

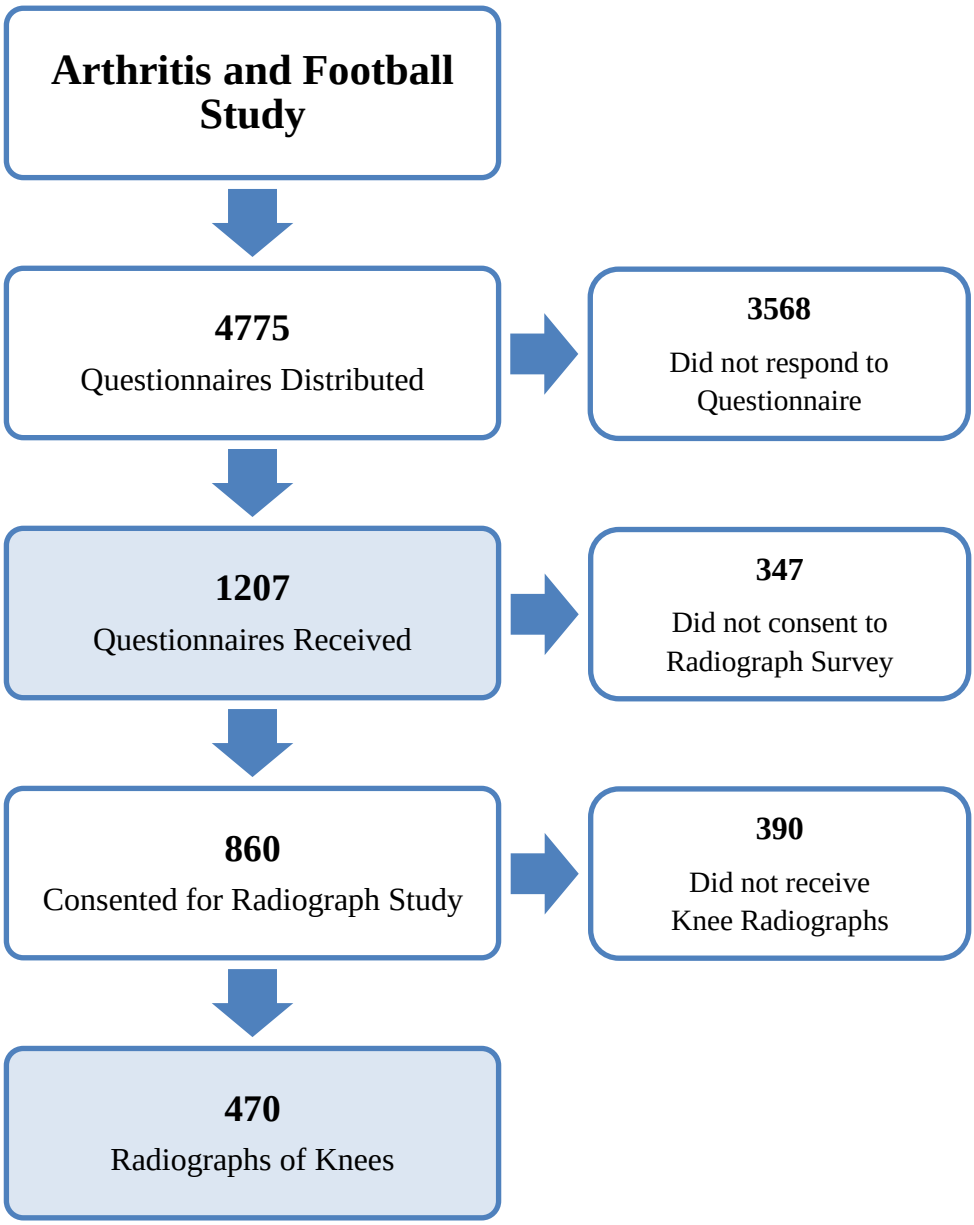


Figure 4.1 – Recruitment for the Arthritis and Football Study

The flowchart shows the recruitment figures for each phase of the Arthritis and Football Study. The shaded boxes show the final numbers of footballers that partook in the questionnaire (n=1207) and radiograph (n=470) phases of the study respectively.

4.1.2 Controls

The KPIC Study has 9513 questionnaires returned from men and women, but a lower response rate (23.5%) compared to the Football Study. However, this was far lower than previous studies conducted within the same region: 70% (Ingham et al., 2011) and 81.9% (O'Reilly et al., 1996). 4085 men responded to the questionnaire survey was just less than half (42.9%) of the total number of responders.

For the controls, 54.1% of men (2210) expressed consent to undergo radiographic assessment. However, only 500 men (22.6%) had radiographs of their knees, attending their appointment at Nottingham City Hospital (Nottingham University Hospital NHS Trust). However, the number recruited was more than required (expected: 480 – see Section 3.9.1) and achieving a 1:1 ratio of footballers and controls meant this was sufficient.

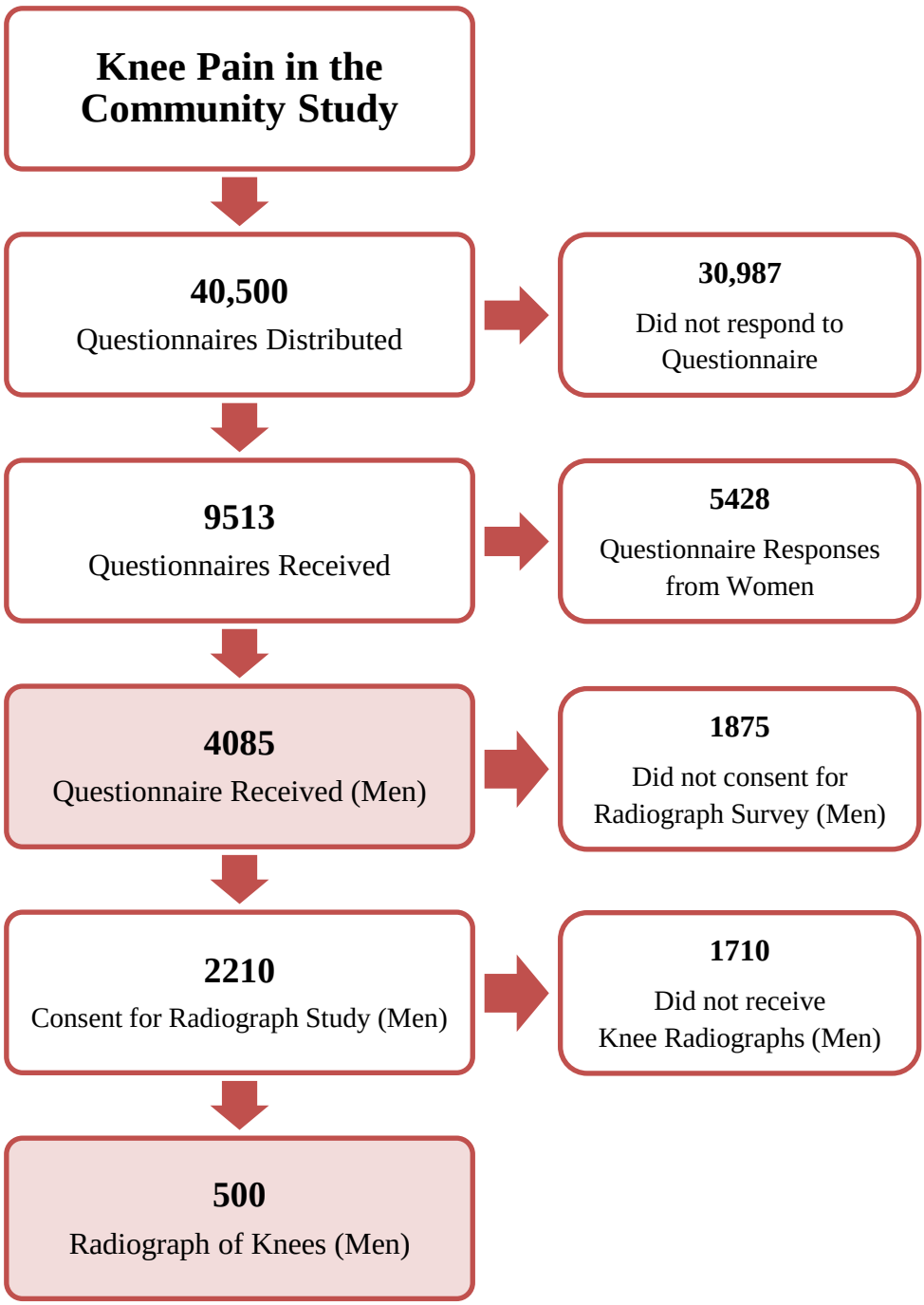


Figure 4.2 – Recruitment for the Knee Pain in the Community (KPIC) Study

The flowchart shows the recruitment figures for each phase of the Knee Pain in the Community (KPIC) Study. The shaded boxes show the final number of men (which were the controls) that partook in the questionnaire (n=4085) and radiograph (n=500) phases of the study respectively.

4.1.3 Sources of Recruitment for Footballers

Twenty-one football clubs and FPAs (22.8%) agreed to participate in the study of the 92 football clubs in the English Football League's top four tiers (2014/15 season).

Table 4.1 provides the breakdown of the number of clubs / FPA within each region of England that distributed questionnaires and the percentage of the total number of clubs within that region. No clubs / FPAs from the North East (4) or South West (7) regions took part in the study.

Table 4.1 – Regional distribution of football clubs / FPAs

Regions of Great Britain	**Clubs Invited**	**Clubs / FPA in Study**	
		n	%
East Anglia	9	3	(33.3)
East Midlands	7	3	(42.9)
London	13	3	(23.1)
North East	4	0	(0.0)
North West	19	5	(26.3)
South East	9	2	(22.2)
South West	7	0	(0.0)
West Midlands	10	4	(0.4)
Yorkshire and Humber	11	1	(0.1)
Wales	3	1	(33.3)
	92	**21**	**(22.8)**

Table 4.2 provides a detailed breakdown of each club / FPA that participated in the study (in addition to the PFA and LMA), the number of questionnaires each distributed and the corresponding number for the map showing their geographical distribution (Figure 4.3).

Table 4.2 – Questionnaire distribution to football clubs / FPAs / PFA / LMA

Source	Number on Map (Figure 4.3)	Questionnaires Distributed
Arsenal FC	1	75
Bolton Wanderers FC	2	20
Chelsea FC	3	75
Coventry City FPA	4	215
Derby County FC	5	220
Ipswich Town FC	6	152
Liverpool FC	7	10
Luton Town FC	8	110
Manchester City FPA	9	60
Manchester United FC	10	10
Newport County FPA	11	70
Northampton Town FC	12	90
Norwich City FC	13	100
Notts County FC	14	233
Portsmouth FC / FPA	15	210
Reading FPA	16	150
Sheffield Wednesday FC	17	20
Stoke City FPA	18	30
Walsall FPA	19	20
West Bromwich Albion FPA	20	50
West Ham United FC	21	50
The PFA		2779
The LMA		26
		4775

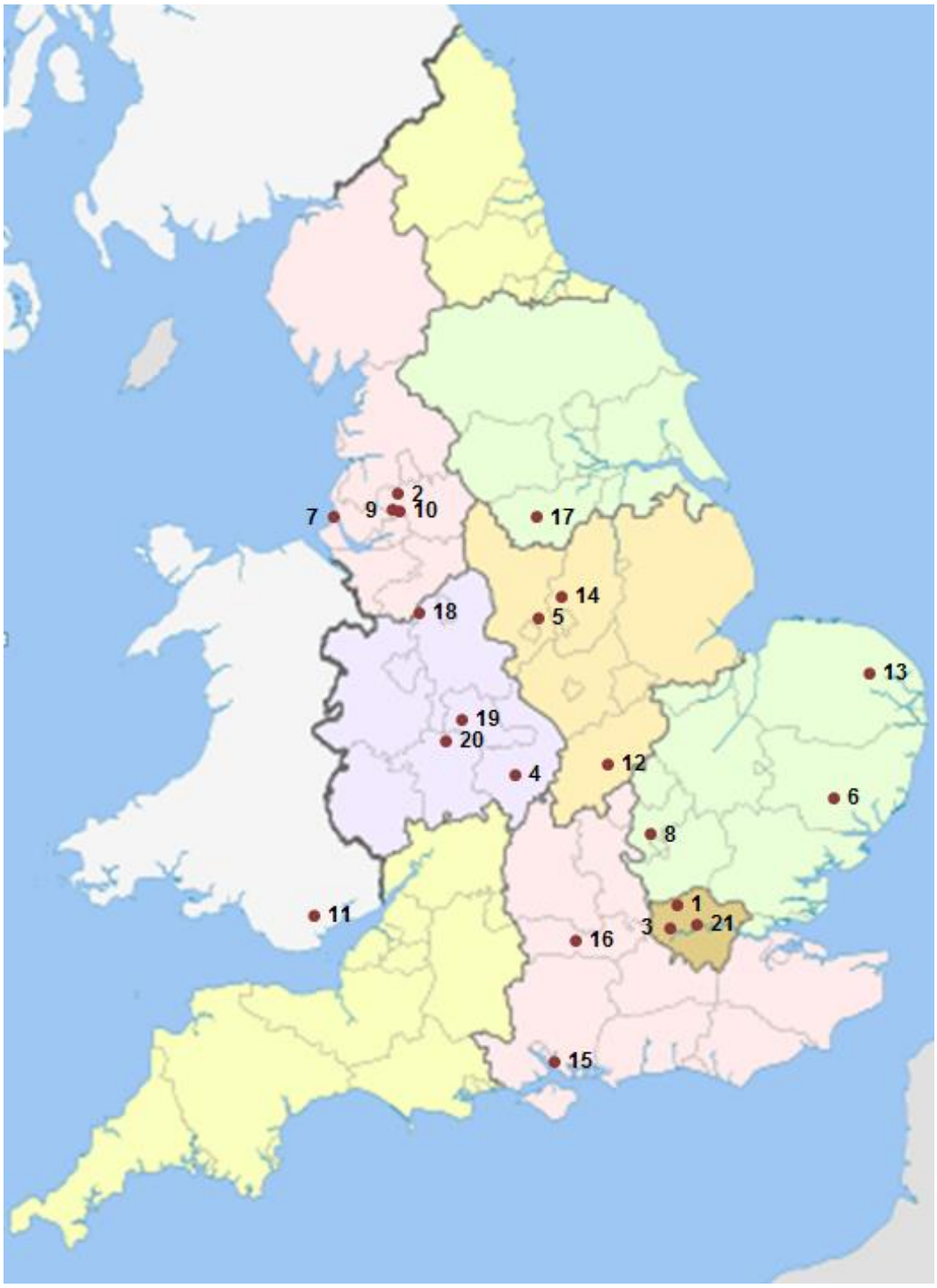


Figure 4.3 – Geographical distribution of football clubs / FPAs

This map shows the geographical distribution of football clubs and FPAs (across England and Wales) that agreed to participate in the study. The numbers correspond to the different participating clubs and FPAs shown in Table 4.2.

Table 4.3 shows the shows the number of eligible footballers for each Spire Hospital site, the number that attended their appointment and the final uptake rate at each site. Thirty-one Spire Hospitals participated in the study.

Of the 860 footballers that indicated interest during the questionnaire phase of the study, 470 had radiographs of their knees. The main reason for the lack of participation was either ineligibility due to having had a bilateral TKR or unavailability during the study period.

Sixty footballers did not receive an invitation for the radiography phase of the study, despite indicating their interest. The reasons for this were two-fold. The overwhelming majority (97%) lived more than 40 miles away from their nearest Spire Hospital (including living abroad) and hence did not meet the inclusion criteria. The remainder did not provide adequate contact details and were unobtainable.

Table 4.3 – Allocation of footballers to Spire Hospitals

Spire Hospital	Footballers within 40 miles	Attended X-ray Appointment	Uptake Rate (%)
Alexandra (Chatham)	19	8	42.1
Bristol	20	11	55.0
Bushey	13	6	46.2
Cambridge	15	13	86.7
Cardiff	40	24	60.0
Cheshire (Warrington)	15	8	53.3
Dunedin (Reading)	21	7	33.3
Edinburgh	20	9	45.0
Elland (Leeds)	38	22	57.9
Fylde Coast (Blackpool)	22	7	31.8
Gatwick Park (Horley)	20	14	70.0
Harpenden	28	19	67.9
Hartswood (Brentwood)	18	9	50.0
Hull & East Riding	19	11	57.9
Leeds	13	7	53.8
Leicester *	82	46	56.1
Little Aston (Sutton Coldfield)	42	25	59.5
Liverpool	16	8	50.0
Manchester	39	35	89.7
Methley Park (Methley)	29	12	41.4
Norwich	29	26	89.7
Parkway (Solihull)	36	23	63.9
Portsmouth	13	9	69.2
Regency (Macclesfield)	36	17	47.2
Roding (Redbridge)	28	11	39.3
South Bank (Worcester)	8	5	62.5
Southampton	31	24	77.4
Thames Valley (Slough)	11	11	100.0
Washington	41	23	56.1
Wellesley (Southend-on-Sea)	25	11	44.0
Yale (Wrexham)	13	9	69.2
	800	**470**	**58.8**

This table shows the number of footballers allocated to each of the 31 Spire Hospitals. The numbers (and the uptake rate) of footballers that had radiographs of their knees at each Hospital is described.

*15 footballers had their radiographs at Nottingham City Hospital (Nottingham University Hospitals NHS Trust) instead of Spire Leicester Hospital due to feasibility

4.2 Comparison Footballer-Control Study

The use of a suitable control population alongside the study population validates the results obtained, so they may be generalised to the wider population of interest. This section addresses the first aim and first two objectives of this study. It describes the characteristics (Section 4.2.1) and prevalence (Section 4.2.2) of the outcome measures (described in Section 3.7) for both the study population (footballers) and the control population (men from the general population). The section concludes with reporting of the relative risks for each outcome (Section 4.2.3).

4.2.1 Population Characteristics

The characteristics for the two study populations, footballers (n=1207) and controls (n=4085) are summarised in Table 4.4. The summary statistics reported were statistically different ($p<0.001$) for the majority of the characteristics between footballers and controls. Having body pain and a pattern three digit ratio were also significantly different ($p<0.01$), however BMI and handedness were not statistically different.

Footballers were significantly younger (3.9 years) than the controls (59.0 years v. 62.9 years), but both populations reported a similar BMI (27.3kg/m^2 v. 27.5 kg/m^2). This is despite the strict inclusion criteria (males over the age of 40) for both populations.

Both populations reported a similar number of participants that were right handed (89.0% in footballers and 88.3% in controls). Just under two-thirds of footballers (60.7%) had a pattern 3 digit ratio, which was almost six percent

greater than the controls (54.8%). In addition, footballers reported significantly more nodal OA compared to the controls (7.1% v. 5.6%).

Almost two-thirds of footballers worked in at least one high-risk occupations (61.5%), following retirement from playing the sport professionally. This was significantly greater than the controls, of whom 53.5% had reported ever working in at least one high-risk occupation.

Footballers were also at greater risk of knee injuries and other consequences of playing the sport professionally. The number of footballers that reported having had a significant knee injury was significantly greater than the controls (64.5% v. 23.3%), and this resulted in a more than two-fold increased risk [RR 2.14, 95% CI 2.03-2.26].

Footballers also had a significantly greater rate (more than double the prevalence) of knee malalignment, both constitutional and current. Current malalignment was reported more often than constitutional malalignment in both groups, but the increase from constitutional to current malalignment was greater in footballers.

Footballers suffered with significantly more body pain compared with controls (74.7% v. 69.8%). Such body pain may be more severe in footballers as significantly more footballers (61.9%) took pain-relief medication compared to the controls (28.5%). However, despite having more body pain, significantly fewer footballers suffered from co-morbidities (determined as those suffering at least one of diabetes, HTN, MI, Ca, fibromyalgia) compared with controls (29.4% v 45.7%), suggesting a long-term positive health benefit from having played professional football.

Table 4.4 – The characteristics of Footballers and Controls

	Footballers	Controls	p-value
N	**1207**	**4085**	
Age (years), mean (SD)	59.0 (11.7)	62.9 (10.4)	<0.001
BMI (kg/m^2), mean (SD)	27.3 (3.2)	27.5 (4.7)	0.139
Right Handed, n (%)	1057 (89.0)	3474 (88.3)	0.529
Pattern 3 Digit Ratio, n (%)	733 (60.7)	2237 (54.8)	0.003
Nodal OA, n (%)	86 (7.1)	218 (5.6)	<0.001
Knee Injury, n (%)	778 (64.5)	953 (23.3)	<0.001
High Risk Occupation, n (%)	742 (61.5)	2185 (53.5)	<0.001
Malalignment, n (%) †			
Constitutional	193 (16.0)	278 (6.8)	<0.001
Current	289 (24.6)	434 (11.2)	<0.001
Body Pain, n (%) ‡	901 (74.7)	2574 (69.8)	0.001
Taking Pain-Relief Medication, n (%)	747 (61.9)	1166 (28.5)	<0.001
Comorbidities, n (%) #	355 (29.4)	1868 (45.7)	<0.001

This table reports on the characteristics for both the footballers and the controls. The statistical differences for each factor are determined by the reported p-value ($p<0.05$).

† Malalignment was measured in the right knee (symmetry assumed) and includes those who are Varus or Valgus

‡ Body pain is pain reported in at least one region of the body (see Appendix F.2) for most days in the previous month, including aching, discomfort and/or stiffness

Co-morbidities adjusted for are diabetes / hypertension / myocardial infarction / cancer / fibromyalgia

Participants who returned the questionnaire and had an x-ray were compared to participants who returned the questionnaire but did not have an x-ray for footballer (Table 4.5) and controls (Table 4.6). The shaded boxes in Figure 4.1 and 4.2 indicate the groups compared for footballers and controls respectively.

This analysis was to determine whether there were systematic differences in the groups that agreed to take part in the radiographic survey. The characteristics compared between the two groups for each population were those reported in Table 4.4.

Footballers that had x-rays (Table 4.5) were 2.3 year younger than those who did not and significantly, more had a pattern 3 digit ratio (6.6%), knee injury (10.9%) and current malalignment (5.6%).

For controls that had x-rays (Table 4.6), they were in fact 1.5 years older than their counterparts who did not have an x-ray. However, a pattern 3 digit ratio and knee injury were also more common (both 7.7%). However, fewer controls that had x-rays reported body pain or worked in high-risk occupations.

Table 4.5 – Comparison between Footballers (x-ray v. no x-ray)

	X-Ray	No X-Ray	p-value
N	**470**	**737**	
Age (years), mean (SD)	57.6 (10.7)	59.9 (12.2)	0.001
BMI (kg/m^2), mean (SD)	27.4 (3.0)	27.1 (3.0)	0.1149
Right Handed, n (%)	304 (64.8)	409 (55.8)	0.002
Pattern 3 Digit Ratio, n (%)	307 (67.6)	426 (61.0)	0.023
Nodal OA, n (%)	61 (6.6)	55 (7.5)	0.568
Knee Injury, n (%)	334 (71.1)	444 (60.2)	<0.001
High Risk Occupation, n (%)	285 (60.6)	457 (62.0)	0.633
Malalignment, n (%) †			
Constitutional	75 (16.3)	118 (16.4)	0.940
Current	129 (28.0)	160 (22.4)	0.031
Body Pain, n (%) ‡	345 (73.4)	556 (75.4)	0.428
Taking Pain-Relief Medication, n (%)	294 (62.7)	453 (61.5)	0.670
Comorbidities, n (%) #	126 (26.8)	229 (31.1)	0.113

Table 4.6 – Comparison between Controls (x-ray v. no x-ray)

	X-Ray	No X-Ray	p-value
N	**491**	**3594**	
Age (years), mean (SD)	64.2 (9.4)	62.7 (10.5)	0.002
BMI (kg/m^2), mean (SD)	27.3 (4.5)	27.5 (4.7)	0.299
Right Handed, n (%)	431 (89.4)	3043 (88.2)	0.417
Pattern 3 Digit Ratio, n (%)	302 (61.5)	1935 (53.8)	0.001
Nodal OA, n (%)	38 (8.0)	180 (5.2)	0.013
Knee Injury, n (%)	148 (30.1)	805 (22.4)	<0.001
High Risk Occupation, n (%)	228 (46.4)	1957 (54.5)	0.001
Malalignment, n (%) †			
Constitutional	37 (7.7)	241 (7.2)	0.662
Current	58 (12.0)	376 (11.1)	0.535
Body Pain, n (%) ‡	138 (28.1)	1338 (37.2)	<0.001
Taking Pain-Relief Medication, n (%)	150 (30.6)	1016 (28.3)	0.294
Comorbidities, n (%) #	235 (47.9)	1663 (45.4)	0.312

† Malalignment includes Varus or Valgus; ‡ Body pain reported in at least one region of the body; # Co-morbidities include diabetes / HTN / MI / Ca / fibromyalgia

4.2.2 Prevalence

Prevalence is the number of cases in a defined population at a given point in time. This section reports the prevalence for all outcome measures for footballers and controls.

Prevalence of Primary Outcomes

Table 4.7 reports the prevalence of the three primary outcomes (Section 3.7.1). All three outcomes are significantly higher ($p<0.001$) in footballers compared to the controls.

Table 4.7 – The prevalence of the primary outcomes for footballers and controls

Outcome	**Prevalence**, n (%)		**p-value**
	Footballers	Controls	
Current KP	630 (**52.2**)	1100 (**26.9**)	<0.001
RKOA (NLDA)	301 (**64.0**)	173 (**35.2**)	<0.001
TKR	134 (**11.1**)	157 (**3.8**)	<0.001

More than half of the footballers reported having current KP (52.2%), which was almost twice as high as the prevalence in the controls (26.9%). The prevalence of RKOA, assessed using the NLDA, was also higher in footballers (64.0%) compared to the controls (35.2%). For both footballers and controls, the prevalence of RKOA was higher than the prevalence of KP.

TKR is indicative of 'joint failure' due to severe KOA. The prevalence of TKR in footballers (11.1%) is almost three times higher than in the controls (3.8%).

This follows suit of having more symptoms (current KP) and structural change (RKOA) beforehand.

Prevalence by Age

Figures 4.4, 4.5, and 4.6 present the prevalence by age of KP, RKOA, and TKR respectively.

The prevalence of KP is greater in footballers compared to controls for all age groups (Figure 4.4). This is in line with the overall greater prevalence of KP in footballers (52.2%) compared to the controls (26.9%). The prevalence of KP in footballers, however, does increase between the ages of 40-50, before declining slightly, albeit remaining greater than the prevalence of KP in the controls. The controls, however, do not exhibit the same trend and the prevalence of KP remains approximately the same for all age groups. Furthermore, the prevalence of KP was at least 50% of footballers between the age 40-45 and for those over aged 80 it remained greater than 40%. However, for the controls, the prevalence of KP only slightly increased above 30% for those between the ages of 40-49, but remained less than this for all other age groups.

Interaction analysis between age and being a professional footballer (yes or no) determined whether they have an additive effect on KP. Measuring age as a continuous [OR 1.50, 95% CI 0.29-7.75 ($p=0.629$)] variable with football status was insignificant, which confirms no additive effect on whether a participant presented with KP. However, when measuring interaction using age as a categorical variable [OR 2.19, 95% CI 1.42-3.37] ($p<0.001$)] it is significant, which means participants with KP are more likely to be footballers, especially across age groups.

Figure 4.5 shows the prevalence of RKOA (assessed using the NLDA) for footballers and controls. Footballers have a greater prevalence of RKOA compared to controls for all age groups. Footballers (26.2%) and controls (21.1%) have a similar prevalence of RKOA between the ages of 40-44. However, there is a marked difference in RKOA prevalence between the ages of 45-54. Footballers report a far greater prevalence of RKOA at ages 45-49 (47.5%) and 50-54 (65.8%) compared to the controls (8.7% and 9.1% respectively). Over the age of 55, this marked difference in prevalence of RKOA remains far greater in footballers (67.3%-85.7%) compared to the controls (35.3%-55.0%).

Finally, Figure 4.6 reports the prevalence of TKR by age. The prevalence of TKR does not differ between footballers and controls under the age of 50. Interestingly, between the age of 50-54, the prevalence of those that had undergone a TKR was slightly greater in the controls (2.2%) compared to the footballers (1.8%). Above the age of 55, the prevalence of undergoing a TKR increases gradually for the controls from 3.3% to 9.5%. However, the increase in prevalence of TKR in footballers (above the age of 55) was much greater, from 8.7% to 33.3%. A third of footballers over the age of 80 had undergone a TKR, which was more than three times greater than for the controls.

Interaction analysis for TKR, when measuring age as a continuous [OR 6.00, 95% CI 0.39-92.28 (p=0.199)] or categorical [OR 1.51, 95% CI 0.09-24.34 (p=0.771)] variable with football status, were both insignificant, which confirms no additive effect on whether a participant presented with TKR.

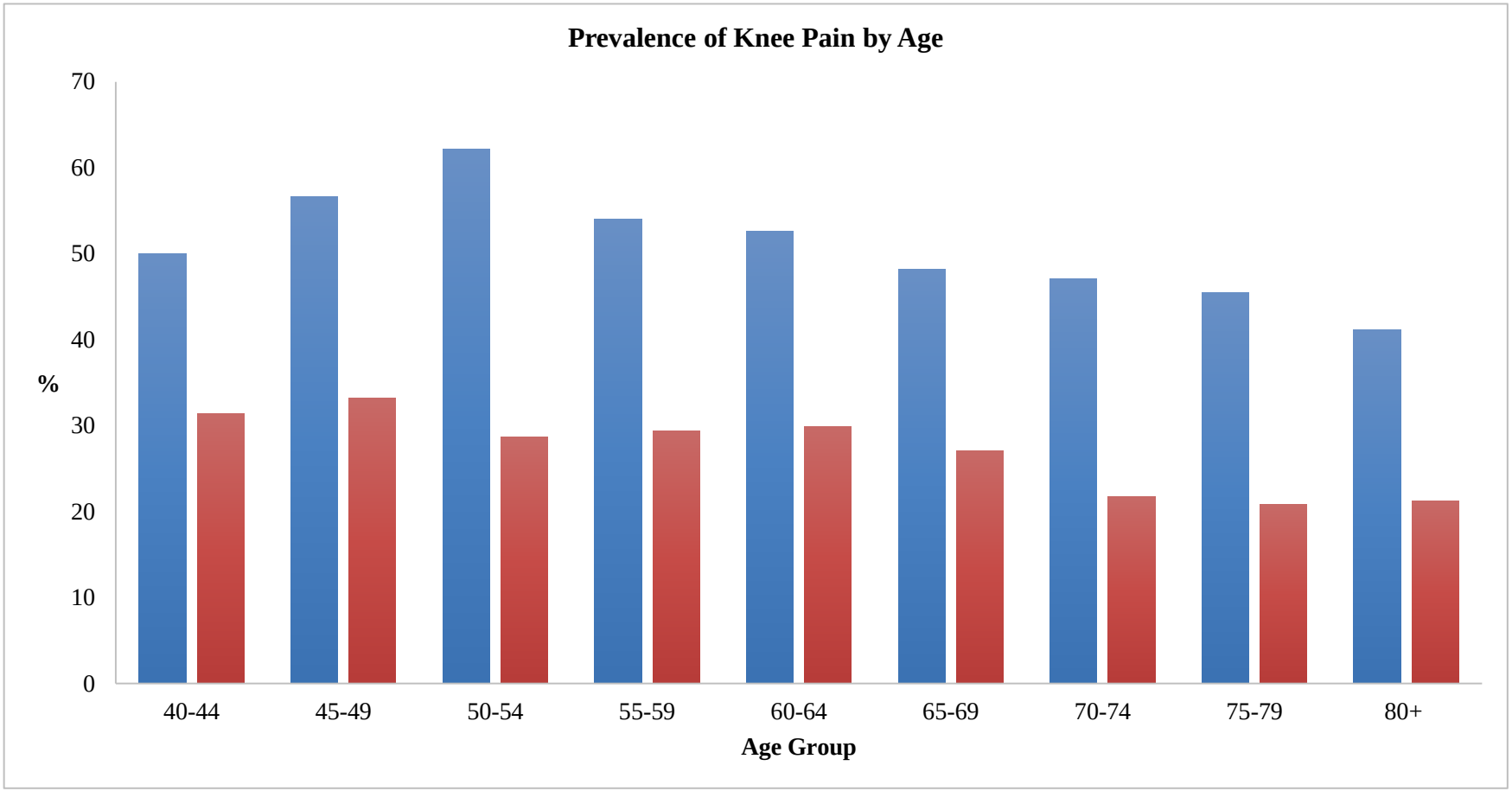


Figure 4.4 – The prevalence of current KP in Footballers (blue) and Controls (red) by age

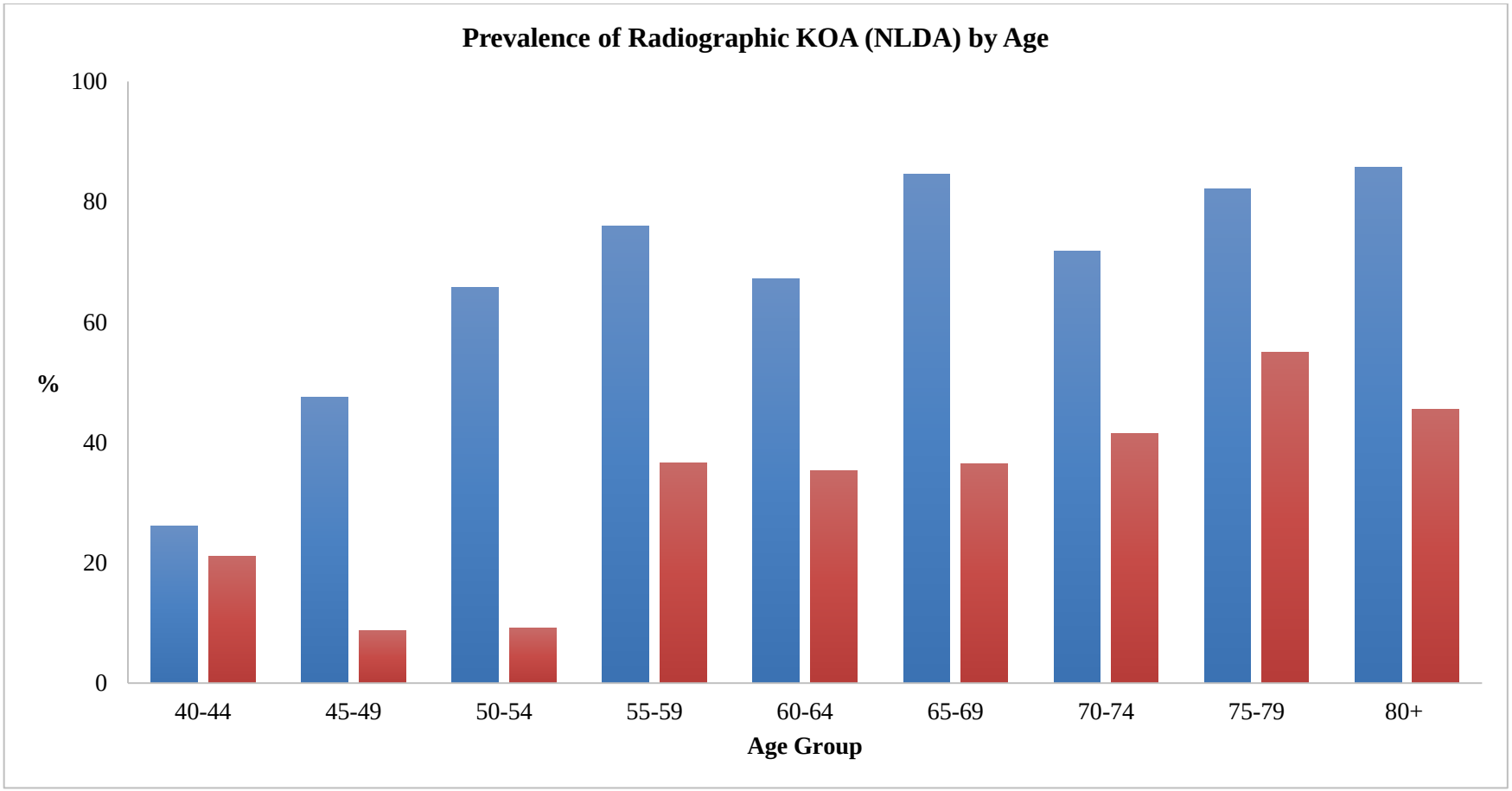


Figure 4.5 – The prevalence of RKOA (assessed using NLDA) in Footballers (blue) and Controls (red) by age

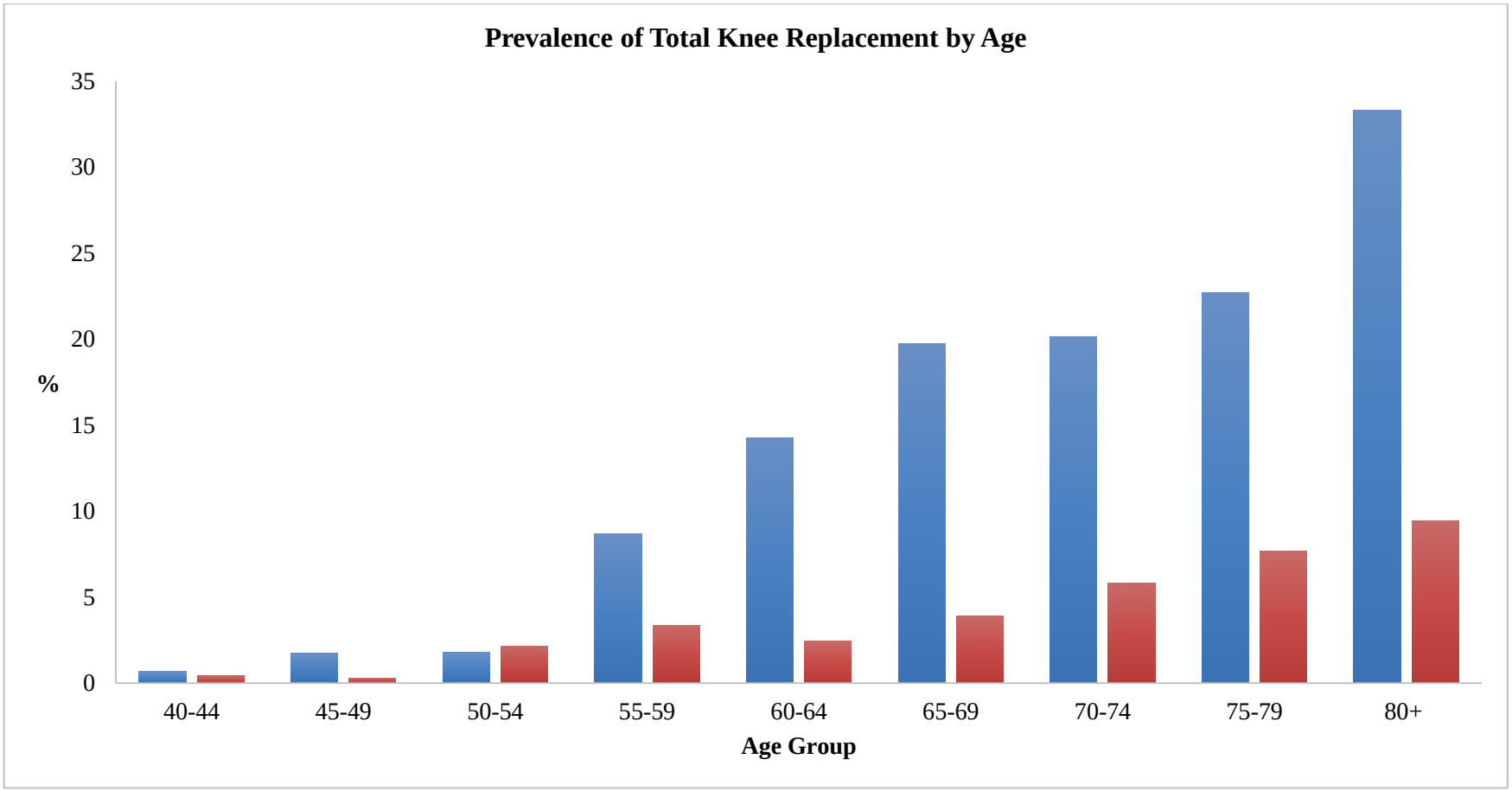


Figure 4.6 – The prevalence of TKR in Footballers (blue) and Controls (red) by age

Prevalence of RKOA using the NLDA

Unlike the KL verbal descriptor grades, the NLDA is a continuous scale, which does not have categorical cut-offs. As reported (Section 3.7.1), the definition used to dichotomise RKOA presence based on the NLDA was *"Osteophyte in any compartment of the knee AND JSN in at least one of the TF or PF compartments of the knee."*

As reported, the prevalence of RKOA using the NLDA is greater in footballers compared to the controls (64.0% v. 35.2%). This section further explores the prevalence of the individual components (JSN and osteophyte) of the NLDA for the right and left knees in footballers and controls.

The global score of the NLDA is the based on the individual JSN and osteophyte component scores. In terms of the global score, footballers had a greater prevalence of RKOA compared to controls (Table 4.8), in both the right (52.6% v. 28.7%) and left (45.3% v. 24.6%) knee respectively.

Table 4.8 – The prevalence of RKOA using the NLDA global score

RKOA (NLDA)	**Prevalence**, n (%)	
	Footballers	Controls
Right Knee Global Score	247 (**52.6**)	141 (**28.7**)
Left Knee Global Score	213 (**45.3**)	121 (**24.6**)

Table 4.9 reports the prevalence, by tertiles, for NLDA components in the right and left knees of footballers and controls. In terms of the global score, the prevalence of footballers in tertile three was greater compared to the controls for both the right (40.6% v. 19.4%) and left (42.8% v. 23.6%). The prevalence of

controls in tertile one, however, was greater compared to the footballers. This trend (a higher prevalence of tertile three scores for footballers and a higher prevalence of tertile one scores for the controls) also held true for both the osteophyte and JSN component scores for both knees.

Table 4.9 – Prevalence of RKOA measured using NLDA

RKOA (NLDA)	**Prevalence**, n (%)	
	Footballers	Controls
Global Score		
Right Knee		
Tertile 1	121 (**25.7**)	212 (**43.2**)
Tertile 2	158 (**33.6**)	185 (**37.7**)
Tertile 3	191 (**40.6**)	94 (**19.4**)
Left Knee		
Tertile 1	128 (**27.3**)	231 (**47.1**)
Tertile 2	141 (**30.0**)	144 (**29.3**)
Tertile 3	201 (**42.8**)	116 (**23.6**)
Osteophyte Score		
Right Knee		
Tertile 1	146 (**31.1**)	253 (**51.5**)
Tertile 2	132 (**28.1**)	144 (**29.3**)
Tertile 3	192 (**40.9**)	94 (**19.1**)
Left Knee		
Tertile 1	123 (**26.2**)	218 (**44.5**)
Tertile 2	147 (**31.3**)	161 (**32.9**)
Tertile 3	200 (**42.6**)	111 (**22.7**)
JSN Score		
Right Knee		
Tertile 1	139 (**29.6**)	243 (**49.6**)
Tertile 2	164 (**34.9**)	153 (**31.2**)
Tertile 3	167 (**35.5**)	94 (**19.2**)
Left Knee		
Tertile 1	161 (**34.3**)	255 (**52.0**)
Tertile 2	118 (**25.1**)	126 (**25.7**)
Tertile 3	191 (**40.6**)	109 (**22.2**)

Prevalence of Secondary Outcomes

Footballers had a significantly ($p<0.001$) higher prevalence for each of the secondary outcomes compared to the controls, presented in Table 4.10.

Table 4.10 – Prevalence of the secondary outcomes in footballers and controls

Secondary Outcomes	**Prevalence**, n (%)		**p-value**
	Footballers	Controls	
1. KP Ever (1 Month)	745 (**61.7**)	1807 (**44.2**)	<0.001
2. GP-Diagnosed KOA	341 (**28.3**)	500 (**12.2**)	<0.001
3. RKOA (KL)	135 (**28.5**)	38 (**14.1**)	<0.001
4. CC	114 (**24.3**)	43 (**8.8**)	<0.001

The prevalence of footballers (61.5%) ever having KP for a period of at least one month was almost 20% greater compared to the controls (44.2%). However, the prevalence was more than twice as great in footballers compared to controls for: GP diagnosis of KOA (28.3% v. 12.2%) and having RKOA (KL grades verbal descriptors) (28.5% v. 14.1%).

In terms of CC, which is closely associated with structural change, the prevalence in footballers (24.3%) was almost a three times greater than in the controls (8.8%). This is in-line with the fact footballers have more an increased prevalence of RKOA (assessed using both the NLDA and KL grade descriptors).

Prevalence of RKOA using the KL grades

Table 4.11 reports the prevalence of RKOA using the dichotomous KL cut-off (KL≥grade 3) in footballers and controls, independently for the TF and PF joints.

Footballers had more RKOA (KL) in the TF compartment of the right knee (15.7%) compared to the controls (4.6%). In the TF compartment of left knee, prevalence of RKOA was more than twice as great in footballers compared with controls (11.6% v. 5.0%). The prevalence of RKOA in the PF compartment was also greater in footballers compared to the controls for both the right (8.9% v. 5.9%) and left (8.1% v. 5.6%) knees, although less pronounced.

Table 4.11 – The prevalence of RKOA using the dichotomous KL cut-off

RKOA (KL)	**Prevalence**, n (%)	
	Footballers	Controls
TF Compartment		
Right Knee	69 (**15.7**)	22 (**4.6**)
Left Knee	51 (**11.6**)	24 (**5.0**)
PF Compartment		
Right Knee	39 (**8.9**)	28 (**5.9**)
Left Knee	36 (**8.1**)	27 (**5.6**)

4.2.3 Risk

This section presents the relative risk the for outcome measures (primary and secondary). Footballers had a higher prevalence of the outcomes compared to the controls (Section 4.2.2) and relative risk establishes whether this increased prevalence confers a statistically significant increased risk.

There were three adjusted models, in addition to the crude risk. Model 1, adjusted for age and BMI, was selected as the main model for risk, to prevent over-adjustment. Models 2 and 3 accounted for additional significant factors (established from the univariate analysis).

Primary Outcome Measures

Table 4.12 reports the crude (RR) and adjusted risks (aRR) for the primary outcomes in footballers compared to the controls. Footballers had almost twice the risk, which was significant, of having current KP compared to the controls [RR 1.94, 95% CI 1.80-2.09].

Table 4.12 – The crude and adjusted risk (RR) of the primary outcome measures in footballers compared to the controls

Outcome Measure	**Relative Risk**, RR (95% Confidence Interval)			
	Crude	Model 1	Model 2	Model 3
Current KP	1.94 (1.80-2.09)**	**1.92** (1.78-2.07)**	1.49 (1.37-1.61)**	1.45 (1.33-1.57)**
RKOA (NLDA)	1.81 (1.58-2.08)**	**2.14** (1.87-2.45)**	1.85 (1.60-2.13)**	1.85 (1.60-2.14)**
TKR	2.14 (1.87-2.45)**	**2.79** (2.42-3.23)**	1.74 (1.52-2.00)**	1.70 (1.47-1.97)**

RR for the outcomes were determined using GLM (with a Poisson distribution), adjusted as follows:

Crude – RR not adjusted

Model 1 – RR adjusted for age, BMI

Model 2 – RR adjusted for age, BMI, knee injury, nodal OA

Model 3 – RR adjusted for age, BMI, knee injury, nodal OA, knee alignment (constitutional), high-risk occupation, pattern 3 digit ratio

* $p<0.05$; ** $p<0.001$

When adjusting for the effects of age and BMI, this risk did not change much. However, when accounting for the effects of having had a knee injury and nodal OA in addition to age and BMI, the risk of footballers having KP was lower, but still almost 50% significantly greater compared to the controls [aRR 1.49, 95% CI 1.37-1.61]. When adjusting further for other factors (constitutional malalignment of the knee, having had a high-risk occupation and having a pattern three digit ratio), footballers still had a 45% increased risk of KP [aRR 1.45, 95% CI 1.33-1.57].

Footballers also had a greater risk of RKOA (NLDA) compared to the controls, and this was much greater than that of KP, following adjustment of the same factors. The risk of RKOA in footballers was more than two-fold compared to controls [aRR 2.14, 95% CI 1.87-2.45] having adjusted for age and BMI. When accounting for injury and nodal OA, the risk of footballer having RKOA was still 85% greater compared to the controls [aRR 1.85, 95% CI 1.60-2.13], which remained the same following further adjustment.

In terms of TKR, footballers had a two-fold increased risk compared to the controls [RR 2.14, 95% CI 1.87-2.45] and following adjustment of age and BMI, this risk increase to almost a three-fold [aRR 2.79, 95% CI 2.42-3.23]. However, the risk of footballers having a TKR following adjustment of injury and other factors (including age and BMI) was almost 70% [aRR 1.70, 95% CI 1.47-1.97]. However, this was less than the risk of footballers having RKOA (85%) but greater than the risk of footballers having KP (45%) compared to the controls.

Exploring the risk of RKOA using NLDA in more detail, the right and left knee were compared (Table 4.13). Footballers had a greater risk of RKOA (NLDA) compared to controls, regardless of the knee affected.

However, when adjusting for age and BMI, the risk of RKOA in footballers compared to the controls was greater in the left knee [aRR 2.25, 95% CI 1.87-2.70] compared to the right knee [aRR 2.11, 95% CI 1.53-2.18]. This remained the case when adjusting for all further factors (described previously) for both the right [aRR 1.83, 95% CI 1.53-2.18] and left [aRR 1.92, 95% CI 1.58-2.33] knees, although this was less than two-fold increased risk.

Table 4.13 – The crude and adjusted risk (RR) of RKOA (NLDA) in footballers compared to the controls for both the right and left knees

RKOA Outcomes	**Relative Risk**, RR (95% Confidence Interval)			
	Crude	Model 1	Model 2	Model 3
NLDA Global Score				
Right Knee	1.83 (1.55 – 2.15)	**2.11** (1.53 – 2.18)	1.83 (1.53 – 2.18)	1.83 (1.54 – 2.19)
Left Knee	1.83 (1.53 – 2.21)	**2.25** (1.87 – 2.70)	1.92 (1.58 – 2.32)	1.92 (1.58 – 2.33)

RR for the outcomes were determined using GLM (with a Poisson distribution), adjusted as follows:

Crude – RR not adjusted

Model 1 – RR adjusted for age, BMI

Model 2 – RR adjusted for age, BMI, knee injury, nodal OA

Model 3 – RR adjusted for age, BMI, knee injury, nodal OA, knee alignment (constitutional), high-risk occupation, pattern 3 digit ratio

* $p<0.05$; ** $p<0.001$

Secondary Outcome Measures

Table 4.14 reports the crude (RR) and adjusted risks (aRR) for the secondary outcomes in footballers compared to the controls. Footballers had a 40% increased risk compared to controls of ever having knee pain for a duration of one month, [RR 1.40, 95% CI 1.32-1.48], which was significant. However, following adjustment for all factors (described at the beginning of Section 4.2.3), this risk became insignificant [aRR 1.04, 95% CI 0.98-1.10].

All the other secondary outcomes were more than two-fold greater risk in footballers compared to the controls: physician-diagnosis of KOA [RR 2.31, 95% CI 2.04-2.61], RKOA (KL) [RR 2.02, 95% CI 1.56-2.63] and CC [RR 2.76, 95% CI 1.99-3.84].

When accounting for age and BMI, the risk of physician-diagnosed KOA in footballers increased more than 2.5 times compared to the controls [aRR 2.62, 95% CI 2.32-2.96], but slightly less for RKOA (KL) [aRR 2.44, 95% CI 1.88-3.15]. However, the risk of CC was almost 3.5 greater in footballers compared to the controls when adjusted for age and BMI [aRR 3.36, 95% CI 2.41-4.69].

As observed for the risk of the primary outcomes, adjusting for injury and nodal OA in addition to age and BMI result in a lower risk compared to adjusting for age and BMI alone. When adjusting for all other factors, footballers still had a significantly greater risk of the following outcomes compared to the controls: 77% increased risk of physician-diagnosed KOA [aRR 1.77, 95% CI 1.55-2.02]; two-fold increase of RKOA (KL) [aRR 2.05, 95% CI 1.56-2.71]; and two-and-a-half fold increase of having CC [aRR 2.53, 95% CI 1.78-3.60].

Table 4.14 – The risk (RR) of the secondary outcome measures in footballers compared to the controls

Outcome Measures	**Relative Risk**, RR (95% Confidence Interval)			
	Crude	Model 1	Model 2	Model 3
KP Ever (1 Month)	1.40 (1.32-1.48)**	**1.41** (1.33-1.49)**	1.06 (1.00-1.12)	1.04 (0.98-1.10)
Physician-Diagnosed KOA	2.31 (2.04-2.61)**	**2.62** (2.32-2.96)**	1.83 (1.61-2.09)**	1.77 (1.55-2.02)**
RKOA (KL)	2.02 (1.56-2.63)**	**2.44** (1.88-3.15)**	2.08 (1.58-2.74)**	2.05 (1.56-2.71)**
CC	2.76 (1.99-3.84)**	**3.36** (2.41-4.69)**	2.59 (1.82-3.69)**	2.53 (1.78-3.60)**

RR for the outcomes were determined using GLM (with a Poisson distribution), adjusted as follows:

Crude – RR not adjusted

Model 1 – RR adjusted for age, BMI

Model 2 – RR adjusted for age, BMI, knee injury, nodal OA

Model 3 – RR adjusted for age, BMI, knee injury, nodal OA, knee alignment (constitutional), high-risk occupation, pattern 3 digit ratio

* $p<0.05$; ** $p<0.001$

Table 4.15 presents the risk of RKOA for both the TF and PF compartments of the right and left knees. Footballers were at greater risk compared to the controls for RKOA (KL) in the right TF compartment [RR 3.42, 95% CI 2.15-5.43] compared with RKOA (KL) the left TF compartment [RR 2.31, 95% CI 1.45-3.70]. The risk, following adjustment of known factors, footballers had almost 3.5 times greater in of RKOA (KL) in their right TF compartment [aRR 3.42, 95% CI 2.06-5.66] but two-fold increased risk in their left TF compartment [aRR 2.21, 95% CI 1.34-3.64].

In terms of the PF compartment, footballers had a greater risk of RKOA (KL) but this was not significant in either the right [aRR 1.49, 95% 0.90-2.44] or left [aRR 1.60, 95% CI 0.96-2.70] knees (following adjustment for all factors). However, when adjusting for age and BMI only, footballers had a greater risk of RKOA (KL) compared to the controls in the PF compartment of their left knee [aRR 2.04, 95% CI 1.26-3.28] compared with their right knee [aRR 1.85, 95% CI 1.15-2.97], which was significant.

Table 4.15 - The crude and adjusted risk (RR) of RKOA (KL) in footballers compared to the controls for both the right and left knees

RKOA Outcomes	**Relative Risk**, RR (95% Confidence Interval)			
	Crude	Model 1	Model 2	Model 3
KL Scoring				
TF Compartment				
Right Knee	3.42 (2.15 – 5.43)	**4.11** (1.56 – 2.06)	3.52 (2.14 – 5.81)	3.42 (2.06 – 5.66)
Left Knee	2.31 (1.45 – 3.70)	**2.78** (1.75 – 4.42)	2.28 (1.39 – 3.75)	2.21 (1.34 – 3.64)
PF Compartment				
Right Knee	1.51 (0.95 – 2.41)	**1.85** (1.15 – 2.97)	1.55 (0.96 – 2.51)	1.49 (0.90 – 2.44)
Left Knee	1.44 (0.89 – 2.33)	**2.04** (1.26 – 3.28)	1.76 (1.09 – 2.85)	1.60 (0.96 – 2.70)

RR for the outcomes were determined using GLM (with a Poisson distribution), adjusted as follows:

Crude – RR not adjusted

Model 1 – RR adjusted for age, BMI

Model 2 – RR adjusted for age, BMI, knee injury, nodal OA

Model 3 – RR adjusted for age, BMI, knee injury, nodal OA, knee alignment (constitutional), high-risk occupation, pattern 3 digit ratio

* $p<0.05$; ** $p<0.001$

4.3 Nested Case-Control Study: Footballers Only

A nested case-control study is a variation of the case-control study design, whereby selection of the controls differs. The incident cases in this section are footballers with the primary outcomes (current KP, RKOA (NLDA) and TKR) and controls are footballers without the outcome. The risk factors associated with different KOA measures, current KP (Section 4.4.1), RKOA (Section 4.4.2) and TKR (Section 4.4.3); within footballers were determined using logistic regression modelling.

4.3.1 Footballer Characteristics

This section describes in further detail, all footballers characteristics subsequently measured as exposures for each of the primary outcomes (Sections 4.3.3, 4.3.4 and 4.3.5).

Age

The average age of footballer that responded to the survey was just under 60 years old (59.0 years). Although the majority of footballers were between the ages of 50-59 (27.5%), just over a fifth (21.4%) were aged 70 or older. Table 4.16 shows a full distribution of this data.

Table 4.16 – The age distribution of footballers

Age Group[1]	n	(%)
40-49	319	(26.6)
50-59	330	(27.5)
60-69	295	(24.5)
70-79	207	(17.2)
80+	51	(4.2)

[1] Ages grouped by deciles

BMI

Table 4.17 shows the distribution of footballers current BMI and BMI in their 20s. During their playing career (in their 20s), almost 80% of footballers reported a normal BMI. Less than 0.5% of footballers were reportedly obese. However, following retirement from the sport, a majority of footballers (61.5%) are overweight. The distribution of current BMI for footballers is normal compared to a positive skew for BMI during their 20's.

Table 4.17 – The BMI distribution of footballers

BMI Category [1]	n (%)			
	Current		**During Career** [2]	
Normal	255	(21.6)	936	(78.3)
Overweight	726	(61.5)	256	(21.4)
Obese	200	(16.9)	4	(0.3)

[1] BMI categories are defined according to the WHO criteria (Section 1.3.1): Normal (18.0-24.9kg/m^2); Overweight (25.0-29.9kg/m^2); Obese ($\geq$30.0kg/m^2)

[2] footballers BMI during their career was measured as 'BMI in 20s'

Familial OA

Just over half of all footballers had at least one first-degree relative (parent or sibling) with knee (24.0%), hip (16.4%) or hand (18.0%) OA. Maternal OA was more prevalent than OA in other relations. In terms of joints, maternal hand OA was most frequently reported (12.7%). OA (either the knee, hip or hand) was more prevalent in footballers' parents compared to their siblings (Table 4.18).

Table 4.18 – The proportion of footballers with familial OA

Relation	OA, n (%)		
	Knee	**Hip**	**Hand**
Mother	117 (9.7)	85 (7.0)	153 (12.7)
Father	100 (8.3)	69 (5.7)	36 (3.0)
Sibling(s) [1]	73 (6.0)	45 (3.7)	28 (2.3)

[1] includes all (up to three) siblings

Joint replacement is a surrogate marker for severe OA. Hip replacements (16.4%) were more common than knee replacements (15.7%). Hip replacements were most common in mothers of footballers (6.7%) but knee replacements were most common in fathers (5.6%), as reported in Table 4.19.

Table 4.19 – The proportion of footballers with familial joint replacements

Relation	Joint Replaced, n (%)	
	Knee	**Hip**
Mother	61 (5.1)	81 (6.7)
Father	68 (5.6)	65 (5.4)
Sibling(s) [1]	60 (5.0)	52 (4.3)

[1] includes all (up to three) siblings

Knee Alignment

Table 4.20 reports the prevalence of constitutional and current knee malalignment in footballers. Knee malalignment currently (24.6%) is far more common than constitutional malalignment (16.4%). Both currently and constitutionally, a varus malalignment was more common than a valgus malalignment.

Table 4.20 – The proportion of footballers with knee mal-alignment

Knee Alignment	n (%)			
	Current		Constitutional [1]	
Straight	885	(75.4)	986	(83.6)
Varus	248	(21.1)	181	(15.4)
Valgus	41	(3.5)	12	(1.0)

[1] self-reported as alignment during 20s

High-Risk Occupation

Following retirement from professional football, working as a football coach or manager was the most common high-risk occupation identified (55.5%), reported in Table 4.21. The next most common high-risk occupation were construction tradesman (9.5%), including bricklayers, builders, carpenters and window fitters.

Only three percent of footballers went on to work in jobs that were occupational hazards for developing OA, including coal miners (0.8%) and farmers (Land Management / Cultivation category) (2.2%).

Footballers reported up to six occupations following retirement from professional football. Thus, high-risk category may account for a footballer more than once (hence, 'Total' row on Table 4.21 is more than sample size of footballers recruited).

Table 4.21 – The proportion of footballers working in high-risk occupations following retirement

High-Risk Occupation Category [1]	n	(%) [2]
Coal Miner	10	(0.8)
Construction (Tradesman)	115	(9.5)
Emergency Services	62	(5.1)
Factory / Warehouse Worker	54	(4.5)
Football Coach / Manager	670	(55.5)
Health Services	15	(1.2)
Labourer	20	(1.7)
Land Management / Cultivation	26	(2.2)
Manual Workers Engineering	23	(1.9)
Mechanic	15	(1.2)
Metal Worker	24	(2.0)
Other Professional Sports	39	(3.2)
Porters, Cleaners, Maintenance	38	(3.1)
PE Teacher	42	(3.5)
Postman	46	(3.8)
Semi-Professional Football	46	(3.8)
Road Worker	6	(0.5)
Shipyard Worker	1	(0.1)
Tradesman – other	77	(6.4)
Total:	1329	

[1] footballers may have worked in more than one high-risk occupation following retirement and thus accounted for in multiple categories

[2] percent (%) reported per population (1207 footballers)

Medication

Pain relief is the most common management approach for KOA following educational advice and lifestyle changes (including physical activity). The majority of footballer (61.9%) took pain medications, including analgesics, opioids and OTC medication. This suggests chronic pain is a severe problem in

footballers, which may be the results of insults and injuries sustained throughout their careers.

Comorbidities

Footballers reported other health conditions or disease they suffered from and fewer than half (46.4%) reported not suffering from any comorbidities. Table 4.4 described 29.4% of who suffered at least one of the following comorbidities: diabetes, hypertension, myocardial infarction, cancer, or fibromyalgia.

Hypertension was the most common comorbidity (21.5%) reported amongst footballers. Other cardiovascular-related comorbidities, namely diabetes (4.5%) and myocardial infarction (3.4%) were less prevalent. Cancer was reported in 7.2% of footballers and 8.0% suffered from depression.

Other rheumatic conditions (not OA) reported include, gout (11.8%), rheumatoid arthritis (11.5%) and fibromyalgia (0.3%). The prevalence of fibromyalgia in footballers was on par with that for widespread pain (1.0%) defined by the ACR criteria (pain in both sides of the body, above and below the waist, in addition to axial skeletal pain: cervical spine, anterior chest, thoracic spine or lower back).

21.5% of footballers reported suffering from other comorbidities, including OA of any joint (3.4%).

Body Pain

Body pain, determined from the BPM, was pain reported during the past four weeks (current). Almost three-quarters of footballers (74.6%) reported pain in at least one region of the body as presented in Table 4.22.

Pain in and around the knee joint (52.2%) was most common (Regions 5, 6, 26, 27 – Appendix F.2) and half of the footballers reported pain in at least one lower limb joint (knee, hip or ankle). Lower back pain (28.7%) was present in just less than a third of footballers, which was more than twice as prevalent as pain in the upper back, neck and spine (12.1%).

Table 4.22 – The distribution of body pain for footballers

Anatomical Region	Region(s) on BPM [1]	Body Pain	
		n	(%) [2]
Neck and Spine	19, 43, 44	109	(9.0)
Upper Back	33, 34	38	(3.1)
Lower Back	32	347	(28.7)
Hip	7, 8, 30, 31	405	(33.6)
Knee	5, 6, 26, 27	630	(52.2)
Foot and Ankle	1, 2, 22, 23	293	(24.3)
Body Pain (any)	1-45 (any)	901	(74.6)

[1] see Appendix F.2 for full breakdown of anatomical regions on BPM

[2] percent (%) reported per population (1207 footballers)

Football-Specific Factors

Section 2 of the football questionnaire (see Appendix A.1) surveyed footballers regarding their professional careers. This section presents the characteristics of these factors, in addition to local risk factors (namely injury and subsequent surgery) inextricably linked to footballers' careers.

Knee Injury

A majority of footballers (64.5%) suffered at least one significant knee injury during the course of their career. The number of footballers that suffered right

knee injuries (52.9%) were slightly more than those suffering left knee injuries (43.5%). However, right knee injuries appear to be more repetitive (Table 4.23). The majority of footballers, however, only suffered one or two injuries per knee throughout the course of their career. Less than five percent of footballers suffered more than five injuries to either their right (4.2%) or left (3.5%) knees.

Table 4.23 – The distribution of footballers by number of knee injuries sustained

Injury Count	Knee, n (%) [1]			
	Right		**Left**	
1	197	(16.3)	202	(16.7)
2	139	(11.5)	126	(10.4)
3-4	118	(9.8)	81	(6.7)
5+	51	(4.2)	42	(3.5)

Footballers sustained an average of 1.4 significant knee injuries over the course of their career, with 1686 injuries reported. Footballers may have sustained more than one significant knee injury, regardless of type (Table 4.24), and thus accounted for more than once.

Soft tissue injuries (83.0%) were by far the most common, regardless of the knee affected. However, identifying specific soft-tissue structures was difficult due to the self-reported nature of the data.

Bone injuries (related to the three long bones in the lower limb), which was the second most common injury only accounted for 6.1% of all injuries reported by footballers. However, almost two percent of footballers reported injuries as signs and symptoms for KOA (identified as KOA and TKR on Table 4.22).

Table 4.24 – The distribution of footballers by type of knee injury sustained

Injury Type [1]	Knee, n			Total, n (%) [2]	
	Right	Left	Unknown		
Bone	42	44	17	**103**	(8.5)
Soft Tissue	768	620	12	**1400**	(116.0)
Other	52	43	0	**95**	(7.8)
Unknown	21	16	29	**66**	(5.5)
KOA	3	6	1	**10**	(0.8)
TKR	6	5	1	**12**	(9.9)

[1] reporting of KOA and TKR 'injuries' correlated to reporting of outcomes from other sources; categories kept broad to prevent misclassification

[2] percent (%) reported per population (1207 footballers); footballers may have reported more than one type of injury and thus accounted for on each occasion

Knee Injection

44.5% of footballers reported having at least one intra-articular injection, of which cortisone injections (70.9%) were the most common, followed by anaesthetic injections (17.3%), reported in Table 4.25. Although the average number of injections over the course of a footballer's career was 7.5 (± SD 11.2) injections, footballers reported between 1 and 100 injections. The median (inter-quartile range), however, was four (2-8).

Table 4.25 – The distribution of footballers by type of intra-articular injection

Injection Type [1]	Knee, n			Total, n (%) [2]	
	Right	Left	Both		
Cortisone	179	118	170	**467**	(38.7)
Anaesthetic	43	33	38	**114**	(9.4)
Don't Know	23	14	14	**51**	(4.2)
Other	13	7	7	**27**	(2.2)

[1] injection categories obtained from questionnaire

[2] percent (%) reported per population (1207 footballers)

Total Football Duration

Footballers first start playing football competitively just before their eleventh birthday (10.7 years), but the youngest footballer was four years old. Following playing competitive football for just over seven years, footballers then turned professional just prior to their eighteenth birthday.

The average career duration for professional footballers was almost fourteen years and therefore the total duration of having played football far exceeds two decades (21.1 years). Two scatter graphs were generates to show the correlation between professional career duration and training dose (Figure 4.7) number of matches (Figure 4.8).

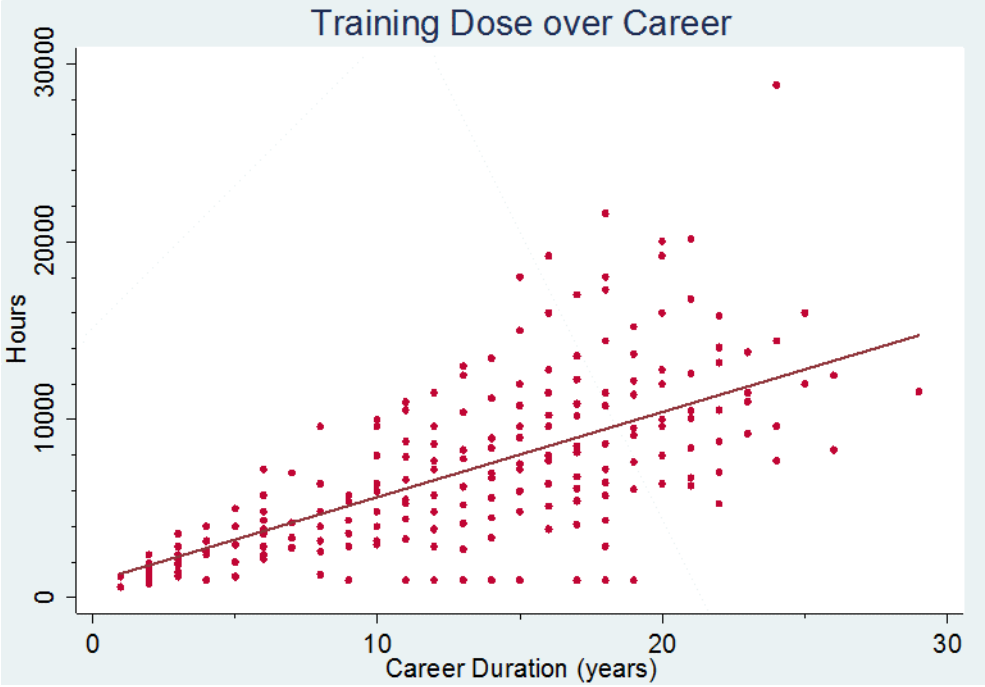


Figure 4.7 – A scatter plot showing training dose (hours) over the career duration

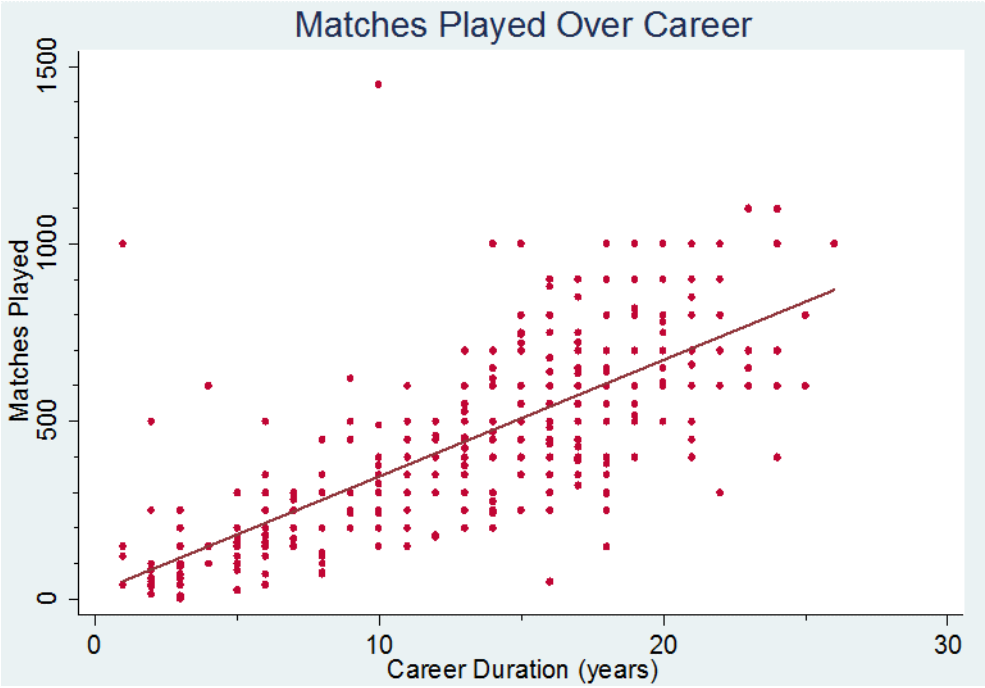


Figure 4.8 – A scatter plot showing matches played over career duration

Training Dose

Career training dose was determined by the number of hours training per day (hours trained per day x days trained per week) multiplied by 40 weeks per season multiplied by career duration.

On average, footballers trained for three hours per day for five days of the week (Table 4.26). This equates to almost 15 hours per week (14.3 hours per week) and almost 8000 training hours over the course of a career. The majority of footballer (56.4%) trained between 4000-8000 hours throughout their professional career. However, 1.2% of footballers had a training dose for less than 1000 career-hours, but 27.0% had more than 10,000 career-hours (Table 4.27).

Table 4.26 – The average training duration of footballers

Training Duration	n	(%)
Hours per Day		
<3	431	(35.7)
3-	471	(39.0)
4-	211	(17.5)
≥5	69	(5.7)
Days per Week		
<4	37	(3.1)
4-	326	(27.0)
5-	685	(56.8)
≥6	123	(10.2)
Hours per Week [1]		
<10	155	(12.8)
10-	390	(32.3)
15-	389	(32.2)
≥20	221	(18.3)

[1] hours per week calculated by multiplying hours per day and days per week

Table 4.27 – The cumulative training dose for footballers over their career

Career Training Dose (hours) [1]	n	(%)
<1000	14	1.2
1000-	171	15.1
4000-	334	29.5
7000-	307	27.1
≥10,000	306	27.0

[1] career training dose calculated by multiplying hours per week trained and number of weeks per season (40) and career duration

Matches Played

Throughout their career, footballers played almost 500 matches (465), with the overwhelming majority playing between 200 to 800 matches. 13.3% of footballers played fewer than 200 matches whilst 10.6% played more than 800 matches.

Tier

The majority of footballers (30.6%) played in tier 1 for the majority of their career. A further 21.9% played in Tier 2 and 19.3% played in Tier 3 for the majority of their careers. Just over ten percent of footballers played in tier 4 (10.3%) or in lower, reserve or international leagues (12.4%) for the majority of their career.

In addition to the tier played in for the majority of their careers, footballers indicated additional leagues they played in. Table 4.28 describes the proportion of footballers playing in other tiers, with the majority playing in Tiers 2 and 3. Player or club migration across tiers may be the main reasons for this.

Table 4.28 – The distribution of footballers by additional tiers

Additional Tiers [1]	n	(%) [2]
Tier 1	1	(0.1)
Tier 2	61	(5.1)
Tier 3	249	(20.6)
Tier 4	245	(20.3)
Reserve Leagues	198	(16.4)
Lower Leagues	33	(2.7)
Other Countries	149	(12.3)

[1] the leagues in which footballers played, in addition to the league they played for the majority of their career

[2] percent (%) reported per population (1207 footballers)

Figure 4.9 presents a box-plot for the average career duration for footballers across the tiers played in for the majority of their career. Footballers in tier one had the longest average career duration (16.3 ± 4.3 years) compared with footballers in tiers two (14.1 ± 5.3 years), three (13.2 ± 5.0 years) and four (11.7 ± 5.1 years). The career duration for footballers below tier 4 was almost half (8.8 ± 6.9 years) compared to those in tier one. A one-way ANOVA determined the career durations across different tiers was statistically significant ($p<0.001$).

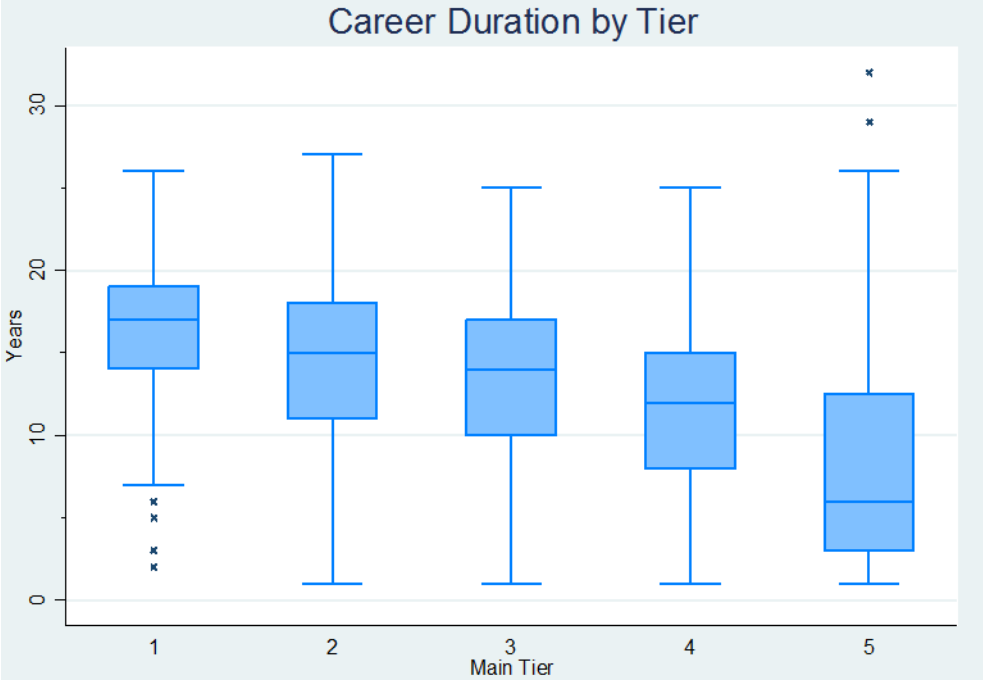


Figure 4.9 – A boxplot showing footballers' career duration by main tier

Footballers in tier 1 had a career training dose (9350 hours) that was almost twice the duration of the footballers that played below tier four (4191 hours). Figure 4.10 presents a box plot, which indicates footballers' career-training dose decreases for the lower tiers. A one-way ANOVA determined these differences in career training dose to be statistical significant ($p<0.05$).

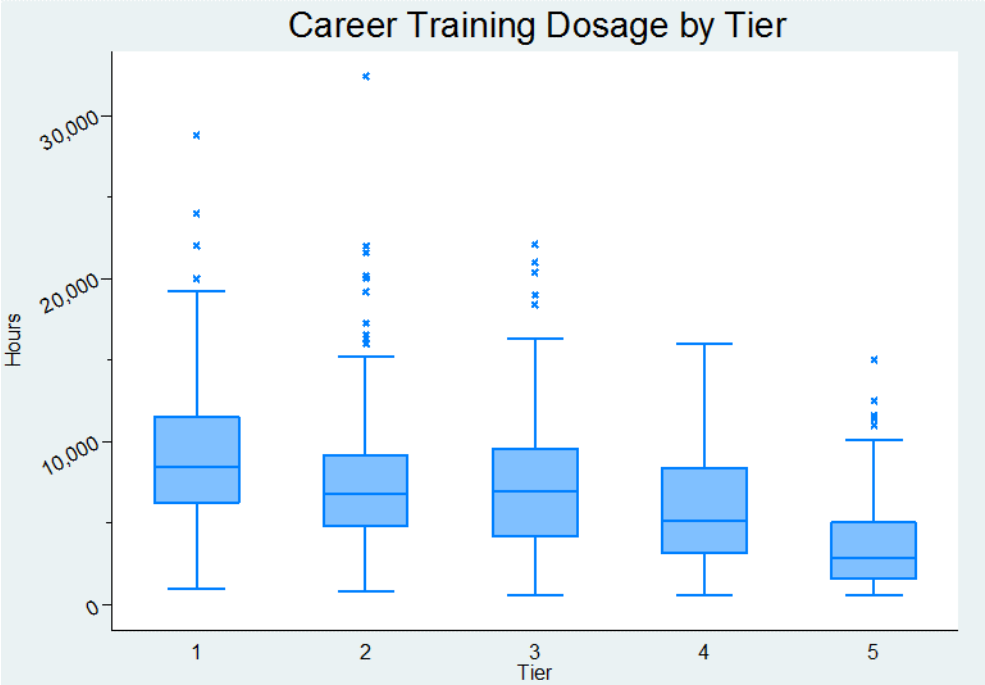


Figure 4.10 – A boxplot showing footballers' career training dose by main tier

Position

The most common player formation in football is 1-4-4-2 (goalkeeper-defenders-midfielders-forwards) and the proportion of responders were expected to follow suit (9.0% goalkeepers; 36.4% defenders and midfielders; 18.2% forwards).

Conducting a one-sample binomial test for each position reported whether the proportion of responders was different from that expected. 9.4% of responders were goalkeepers, which was not statistically different. However, the proportion of defenders (33.6%, $p<0.036$), midfielders (27.8%, $p<0.001$) and forwards (29.1%, $p<0.001$) were statistically different to that expected. However, this may be due to fluidity between playing position classifications.

Almost a quarter of footballers (23.9%) were two-footed, comfortable using both their right and left foot, but the majority (59.3%) preferred playing with their right foot.

4.3.2 Prevalence within Footballers

Chapter 4.2 reports the prevalence of current KP and ever having KP for at least one month in footballers. The football question also ascertained a further measure of ever having KP for at least three months, not determined in the controls. This section reports the age of onset of ever having KP, either for a one or three month duration and the proportion of footballers within each age decade to have KP (either ever or currently).

The prevalence of footballers with current KP is 52.2%. For footballers who reported ever having KP, the prevalence of those with KP for one month and three months was 61.7% and 56.4% respectively. The vast majority of footballers (91.4%) that reported ever having KP for one month subsequently had KP for three months.

Age of Onset for Chronic Knee Pain

Figure 4.11 shows the distribution for the age of onset of chronic KP (ever having KP lasting at least one or three months). Age of onset is a measure of incidence and was the first recorded age for such pain.

The peak incidence of chronic KP (one month and three-month durations) were between the ages of 30-34, which is toward the end of footballers' careers. Less than 1% of footballers report such pain before the age of 15, most likely due to

injuries (football or non-football related) sustained early in life. Despite increasing age, footballers were still reporting the onset of KP for the first time after the age of 70, most likely due to ageing, although this was only one percent of the population.

The proportion of footballers reporting chronic KP for a 1-month duration was greater than 3-month duration until the age 50 (age group 50-54). The shift in duration for chronic KP suggests those reporting KP for a 1-month period at a younger age were likely to report KP for a 3-month period as they got older.

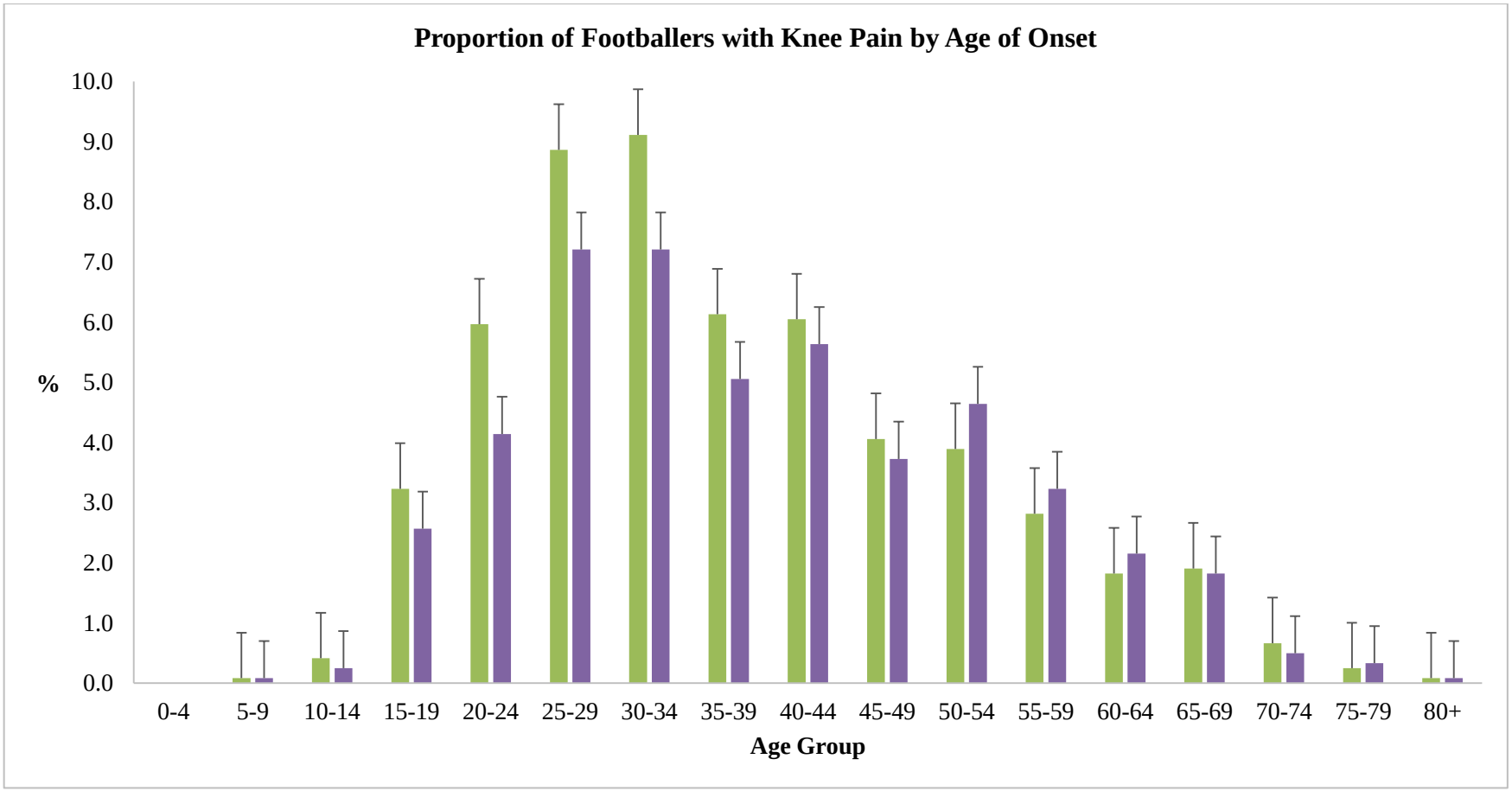


Figure 4.11 – The age of onset of KP lasting for either 1-month (green) or 3-months (purple) in footballers

4.3.3 Risk Factors for Current Knee Pain

Population Characteristics (Knee Pain)

Just over half of footballers (52.2%) presented with current knee pain compared to footballers without knee pain. Table 4.29 compares the characteristics of these two population subsets.

There were statistical differences ($p<0.001$ level) for BMI (defined as underweight or normal, overweight and obese), familial KOA, joint injury, surgery, having injections and suffering from gout. Other significantly different variables ($p<0.01$ level) were age, familial hip OA and familial hand OA.

Footballers with KP were more likely to report being obese (20.1%) compared with footballers that did not have KP (13.5%), whereas more footballers without KP reported having a BMI within the normal range. Footballers with KP reported a higher prevalence (at least 23%) of first-degree relatives with OA, whether hip, hand and knee and the prevalence of footballers suffering from gout was almost twice as common if they reported KP.

The majority of footballers with KP reported having a knee injury or surgery (79.5%), which far exceed the proportion of footballers without KP (48.0%). Surgery, which refers to exploratory, investigative or corrective surgery (usually arthroscopic intervention), followed suite with similar proportions as injury. This suggests surgical intervention itself usually followed suffering an injury. Almost 25% more footballers with KP reported receiving intra-articular knee injections compared with footballers that did not report KP.

A pattern 3 digit ratio and constitutional malalignment were also significantly different ($p<0.05$). Footballers with KP reported a higher prevalence (almost 10%) of having a pattern 3 digit ratio and 4.3% more malalignment in their knees (constitutionally) compared with footballers without KP. Despite being a known risk factor, there was no statistical difference in the prevalence of high-risk occupation, for footballers with and without KP.

There was no significant differences for the football-specific factors (duration, intensity, level and position) between footballers with KP and footballers without KP. However, the risk of these factors are included in the risk factor analysis (see Section 4.4.1.2).

Table 4.29 – Characteristics of footballers with and without current Knee Pain

	Knee Pain	No Knee Pain	p-value
N (%)	630 (52.2)	577 (47.8)	-
Age (years), mean (SD)	58.07 (0.45)	59.94 (0.51)	0.005
BMI (kg/m2), n (%)			<0.001
<25	108 (17.5)	147 (26.1)	
25 –	386 (62.5)	340 (60.4)	
≥30	124 (20.1)	76 (13.5)	
Pattern 3 Digit Ratio, n (%)	400 (54.6)	333 (45.4)	0.031
Nodal OA, n (%)	48 (7.6)	38 (6.6)	0.486
Familial: n (%)			
Knee OA	152 (64.1)	85 (35.9)	<0.001
Hip OA	104 (61.5)	65 (38.5)	0.009
Hand OA	119 (62.0)	73 (38.0)	0.003
Knee Replacement	96 (15.2)	72 (12.5)	0.166
Hip Replacement	106 (16.8)	77 (13.3)	0.092
Constitutional Malalignment, n (%)	114 (18.4)	79 (14.1)	0.049
High Risk Occupation, n (%)	402 (63.8)	340 (58.9)	0.082
Use of Statins, n (%)	87 (13.8)	81 (14.1)	0.899
Suffers from Gout, n (%)	97 (15.4)	45 (7.8)	<0.001
Injury, n (%)	501 (79.5)	277 (48.0)	<0.001
Surgery, n (%) †	500 (79.9)	274 (47.6)	<0.001
Injection, n (%)	354 (56.2)	183 (31.7)	<0.001
Total Football Duration, (years), mean (SD)	20.8 (6.1)	21.4 (5.9)	0.093
Career Training Dose, (hours), mean (SD)	7854 (4219)	7822 (4133)	0.899
Matches Played, mean (SD)	454 (241)	477 (240)	0.089
Main Tier, n (%) ‡			
One	181 (28.7)	173 (30.0)	0.633
Two	135 (21.4)	118 (20.5)	0.677
Three	122 (19.4)	101 (17.5)	0.405
Four	58 (9.2)	61 (10.6)	0.427
Position, n (%)			
Goalkeeper	68 (10.8)	45 (7.8)	0.074
Defender	204 (32.4)	200 (34.7)	0.402
Midfielder	175 (27.8)	161 (27.9)	0.961
Forward	181 (28.7)	170 (29.5)	0.780

† refers to exploratory / investigative / corrective surgery; ‡ the tier footballers played in for the majority of their career (assessed independently)

Risk Factors (Knee Pain)

Multivariate logistic regression identified the exposures that increased the risk of KP in footballers. Table 4.30 presents the significant exposures that increased the risk of KP, determined using three models. These were a univariate analysis, whereby exposures were unadjusted (Crude model), an age- and BMI-adjusted model (Adjusted 1 model), and a multivariate adjusted model (Adjusted 2 model). All exposures observed were binary data, except for age, which was continuous, and BMI, which was categorical (namely normal, overweight and obese BMI). The risk of each exposure was presented as OR and risk factors identified with a single or double asterisk were statistically significant ($p<0.05$ or $p<0.01$ respectively).

Crude Model

The risk of each exposure was determined independently in this model (Table 4.30 – Crude OR). Footballers that reported knee injuries [OR 4.21, 95% CI 3.27-5.42] and had knee surgeries [OR 4.37, 95% CI 3.39-5.64] were more than four times more likely to have KP. Other exposures, which conferred more than twice the risk for footballers having KP, were being obese (2.22 times), suffering from gout (2.15 times) and receiving intra-articular injections (2.76 times).

Increasing age, being overweight, having a pattern three digit ratio, having a first-degree relative (mother, father or sibling) with OA (hip, hand or knee) and knee malalignment (constitutionally) were other exposures that increased the risk for KP in footballers. Exposures related specifically to playing professionally (duration, intensity, level and position) were not significant risk factors for KP in footballers.

Table 4.30 – Risk factor analysis for current Knee Pain in footballers

Exposure	**Odds Ratio, OR** (95% CI)		
	Crude	Adjusted 1 [#]	Adjusted 2 [##]
Age	0.99 (0.98-1.00)**	0.99 (0.98-1.00)**	0.99 (0.98-1.00)
BMI (kg/m2)			
<25	1.00	1.00	1.00
25 –	1.55 (1.16-2.06)**	1.50 (1.13-2.01)**	1.42 (1.03-1.97) *
≥30	2.22 (1.52-3.24)**	2.28 (1.55-3.33)**	2.16 (1.40-3.34)**
Pattern 3 Digit Ratio	1.30 (1.02-1.66) *	1.34 (1.05-1.72) *	1.32 (1.00-1.73) *
Nodal OA	1.17 (0.75-1.82)	1.21 (0.77-1.92)	1.14 (0.68-1.92)
Familial:			
Knee OA	1.81 (1.37-2.47)**	1.85 (1.37-2.51)**	1.62 (1.12-2.35)**
Hip OA	1.56 (1.12-2.17)**	1.50 (1.06-2.11) *	1.16 (0.77-1.75)
Hand OA	1.61 (1.17-2.21)**	1.63 (1.18-2.25)**	1.10 (0.75-1.62)
Knee Replacement	1.26 (0.91-1.75)	1.21 (0.87-1.71)	0.87 (0.57-1.33)
Constitutional Malalignment	1.37 (1.00-1.87) *	1.28 (0.93-1.76)	1.18 (0.83-1.68)
High Risk Occupation	1.23 (0.97-1.55)	1.19 (1.94-1.51)	1.27 (0.97-1.67)
Use of Statins	0.98 (0.71-1.36)	0.96 (0.68-1.37)	0.89 (0.59-1.34)
Suffers from Gout	2.15 (1.48-3.13)**	2.16 (1.46-3.20)**	1.64 (1.04-2.57) *
Injury	4.21 (3.27-5.42)**	4.22 (3.26-5.48)**	2.40 (1.73-3.35)**
Surgery †	4.37 (3.39-5.64)**	4.19 (3.23-5.43)**	2.32 (1.66-3.24)**
Injection	2.76 (2.18-3.50)**	2.55 (2.01-3.25)**	1.46 (1.10-1.92)**
Total Football Duration	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.97 (0.94-0.99)**
Career Training Dose (per 1000 hours)	1.00 (0.97-1.03)	1.00 (0.97-1.03)	0.98 (0.95-1.02)
Matches Played (per 100 matches)	0.66 (0.41-1.07)	0.64 (0.39-1.04)	0.55 (0.32-0.95) *
Main Tier ‡			
One	0.94 (0.73-1.21)	0.97 (0.75-1.25)	0.86 (0.64-1.15)
Two	1.06 (0.80-1.40)	1.07 (0.80-1.42)	0.98 (0.71-1.36)
Three	1.13 (0.85-1.52)	1.09 (0.81-1.47)	1.28 (0.91-1.80)
Four	0.86 (0.59-1.25)	0.88 (0.60-1.30)	0.95 (0.62-1.47)
Position			
Goalkeeper	1.43 (0.96-2.12)	1.33 (0.89-1.98)	1.29 (0.81-2.05)
Defender	0.90 (0.71-1.15)	0.86 (0.68-1.11)	0.74 (0.57-0.99)
Midfielder	0.99 (0.77-1.28)	1.00 (0.77-1.29)	1.14 (0.85-1.54)
Forward	0.97 (0.75-1.24)	1.05 (0.81-1.35)	1.09 (0.81-1.46)

[#] OR adjusted for age and BMI (adjusted 1); [##] OR adjusted all factors significant from crude analysis (adjusted 2); * $p<0.05$; ** $p<0.01$; † refers to exploratory / investigative / corrective surgery; ‡ the tier footballers played in for the majority of their career (assessed independently)

Age- and BMI-adjusted Model

Table 4.30 also presented the age- and BMI- adjusted OR for each exposure (Adjusted 1 OR). This is the risk of KP given the exposure, having accounted for the effects of age and BMI.

As per the Crude model, knee injuries and knee surgeries conferred the greatest risk (footballers were more than four times likely to have KP). All other significant risk factors from the Crude model, except for constitutional malalignment, remained significant when accounting for age and BMI.

Multivariate Model

This model presented the risk of KP for each exposure, having accounted for multiple factors (Table 4.30 – Adjusted 2 OR). The factors adjusted for in this multivariate model were: age, BMI, pattern three digit ratio, familial OA (hip, hand and knee), constitutional malalignment, suffering from gout, knee injuries, knee surgeries and intra-articular injections. These factors were selected basis they were statistically significant in the crude analysis.

Footballers who had had at least one knee injury [OR 2.40, 95% CI 1.73-3.35] had 2.4 times increased risk of KP, having accounted for known other significant factors. Footballers also had a high risk of KP (more than two times) if they were obese [OR 2.16, 95% CI 1.40-3.34] or had had surgery [OR 2.32, 95% CI 1.66-3.24].

Other exposures, which conferred an increased risk of KP in footballers, having accounted for other known significant risk factors, were having gout, being overweight, a pattern three digit ratio, a family history of KOA, or an intra-articular injection. An interesting finding, however, showed that footballers who

played football for a longer period (total football duration) [OR 0.97, 95% CI 0.94-0.99] had a three percent lower risk of having KP. This suggests that once accounting for significant factors; a longer duration of playing football (both competitive and professional) reduces the risk of KP, based on the 'survival-of-the-fittest' phenomenon.

These significant factors in the Adjusted 2 model all reported an OR that was statistically significant, indicating an increased risk for KP within footballers. However, a back-step approach to model (rather than simple adjustment) the true risk factors was favoured.

A logistic regression model, with significant variables (indicated by a single or double asterisk in Adjusted 2 column of Table 4.30), was generated. To determine the risk factors for KP in footballers, non-significant variables ($p>0.05$) were removed from this model, starting with the least significant (largest p-value), until the model only contained significant variables ($p<0.05$).

This modelling approach reported the significant risk factors for KP in footballers. These risk factors, described in Table 4.31, are; being overweight [OR 1.49, 95% CI 1.09-2.04] or obese [OR 2.19, 95% CI 1.44-3.31], having a family history of KOA [OR 1.77, 95% CI 1.28-2.45], having had a knee injury [OR 2.34, 95% CI 1.71-3.21], knee surgery [OR 2.30, 95% CI 1.68-3.17] or receiving an intra-articular injection [OR 1.58, 95% CI 1.21-2.06]. Each risk factor was statistically significant (at least $p=0.01$) and footballers that reported any of these factors would have an increased risk of KP between 49 – 134%.

Table 4.31 – Risk factors for current Knee Pain in footballers (back-step model)

	Coefficient	SE	p-value	OR (95% CI)
BMI (kg/m2)				
<25	-	-	-	1.00
25 –	0.401	0.1600	0.012	1.49 (1.09-2.04)
≥30	0.782	0.2114	<0.001	2.19 (1.44-3.31)
Family KOA	0.573	0.1646	0.001	1.77 (1.28-2.45)
Injury	0.852	0.1611	<0.001	2.34 (1.71-3.21)
Surgery †	0.835	0.1620	<0.001	2.30 (1.68-3.17)
Injection	0.457	0.1355	0.001	1.58 (1.21-2.06)

† refers to exploratory / investigative / corrective surgery

4.3.4 Risk Factors for Radiographic Knee Osteoarthritis

Population Characteristics (RKOA)

Almost two-thirds (64.0%) of footballers had structural change indicative of RKOA (assessed using NLDA tool). Table 4.32 summarises characteristics of footballers with RKOA compared to footballers without RKOA.

The following characteristics were significantly different: ($p<0.001$): age, the presence of CC, and having had a knee injury, or knee surgery. Footballers with RKOA were 7.5 years older and three times more footballers had evidence of CC. More than 15% of footballers who had RKOA also had knee injuries (78.0% v. 62.1%) and almost 30% more had undergone knee surgery (82.7% v 53.0%).

More footballers with RKOA (compared to those without RKOA) had a family history of KOA ($p=0.025$), knee replacement ($p=0.040$), suffered from gout (0.004), and received an intra-articular knee injection ($p=0.015$). Footballers who had RKOA also played football (21.8 years v. 21.2 years) and trained for a longer period, as well as playing more matches (485 matches v. 434 matches).

There was no significant differences in BMI status, digit ratio, nodal OA, malalignment, high risk occupation (post-football), use of statins, tier played in and positioned played for footballers with and without RKOA.

For comparison, Appendix G.2 (Characteristics of Footballers with RKOA (KL)) presents the characteristics of footballers with RKOA measured using the KL verbal descriptors. Using this outcome measure, only 28.7% of footballers had RKOA.

Table 4.32 – Characteristics of footballers with and without RKOA (NLDA)

	RKOA	No RKOA	p-value
N (%)	301 (64.0)	169 (36.0)	
Age (years), mean (SD)	60.3 (10.1)	52.8 (10.2)	<0.001**
BMI (kg/m2), n (%)			0.307
<25	59 (20.1)	33 (19.6)	
25 –	181 (61.6)	113 (67.3)	
≥30	54 (18.4)	22 (13.1)	
Pattern 3 Digit Ratio, n (%)	196 (67.1)	111 (68.5)	0.761
Nodal OA, n (%)	21 (27.3)	10 (28.6)	0.887
Familial: n (%)			
Knee OA	81 (26.9)	30 (17.8)	0.025 *
Hip OA	51 (16.9)	24 (14.2)	0.436
Hand OA	55 (18.3)	31 (18.3)	0.985
Knee Replacement	64 (21.3)	23 (13.6)	0.040 *
Constitutional Malalignment, n (%)	47 (15.8)	28 (17.2)	0.696
High Risk Occupation, n (%)	180 (59.8)	105 (62.1)	0.620
Use of Statins, n (%)	45 (15.0)	18 (10.7)	0.185
Suffers from Gout, n (%)	37 (12.3)	7 (4.1)	0.004 **
Presence of CC, n (%)	98 (32.6)	16 (9.5)	<0.001 **
Injury, n (%)	231 (78.0)	103 (62.1)	<0.001 **
Surgery, n (%)	249 (82.7)	89 (53.0)	<0.001 **
Injection, n (%)	160 (53.2)	70 (41.4)	0.015 *
Total Football Duration, (years), mean (SD)	21.8 (6.0)	20.2 (6.2)	0.008 **
Career Training Dose, (hours), mean (SD)	8283 (4220)	6553 (3395)	<0.001 **
Matches Played, mean (SD)	485 (240)	434 (250)	0.03 *
Main Tier, n (%) ‡			
One	91 (30.2)	51 (30.2)	0.990
Two	67 (22.3)	35 (20.7)	0.696
Three	59 (19.6)	31 (18.3)	0.739
Four	30 (10.0)	23 (13.6)	0.231
Position, n (%)			
Goalkeeper	33 (11.0)	16 (9.5)	0.611
Defender	106 (35.2)	57 (33.7)	0.745
Midfielder	86 (28.6)	44 (26.0)	0.555
Forward	75 (24.9)	51 (30.2)	0.217

† refers to exploratory / investigative / corrective surgery; ‡ the tier footballers played in for the majority of their career (assessed independently)

Risk Factors (RKOA)

To determine the risk factors for RKOA (measured using NLDA) within footballers, multivariate logistic regression was used. Table 4.33 presents the three models generated, indicating risk for each exposure. These models were a Crude model (unadjusted), an age- and BMI-adjusted model (Adjusted 1) and a multiple variable adjusted model (Adjusted 2).

Crude Model

Having had surgery [OR 4.25, 95% CI 2.78-6.50] or the presence of CC [OR 4.62, 95% CI 2.61-8.05], footballers were more than four times likely to have RKOA. Other risk factors that increased the risk of RKOA by more than two-fold included: suffering from gout [OR 3.24, 95% CI 1.41-7.45] and sustaining a knee injury [OR 2.17, 95% CI 1.43-3.30]. Footballers also had a 2.4 times increased risk of RKOA for every 100 matches they played.

Other factors that also increased the risk of RKOA included age (8%), having a family history of KOA or knee replacement (both 71%), receiving intra-articular injections (60%) and the total football duration (4%). For every 1000 hours trained, footballers also had a 13% increased risk of RKOA.

Age- and BMI- Adjusted Model

When adjusted for age and BMI, factors from the crude analysis that were statistically significant remained so. However, this was not the case for matches played, and there was no significant association for footballers with RKOA for every 100 matches they played. Footballers that played in the forward position had a 12% reduced risk of RKOA (when adjusted for age and BMI), but this should be treated with caution because its initial association was not significant.

Table 4.33 – Risk factor analysis for RKOA (NLDA) in footballers

Exposure	Odds Ratio, OR (95% CI)		
	Crude	Adjusted 1 #	Adjusted 2 ##
Age	1.08 (1.05-1.10)**	1.08 (1.05-1.10)**	1.07 (1.05-1.10)**
BMI (kg/m2)			
<25	1.00	1.00	1.00
25 –	0.90 (0.55-1.46)	0.92 (0.55-1.54)	0.80 (0.44-1.44)
≥30	1.37 (0.71-2.64)	1.18 (0.59-2.36)	1.10 (0.48-2.49)
Pattern 3 Digit Ratio	0.94 (0.62-1.42)	0.92 (0.59-1.44)	0.95 (0.57-1.58)
Nodal OA	0.94 (0.39-2.28)	0.81 (0.29-2.30)	0.46 (0.11-1.90)
Familial:			
Knee OA	1.71 (1.07-2.73)*	1.87 (1.14-3.07)*	1.47 (0.76-2.85)
Hip OA	1.23 (0.73-2.09)	1.41 (0.81-2.46)	1.10 (0.55-2.21)
Hand OA	1.00 (0.61-1.62)	0.98 (0.59-1.65)	0.56 (0.30-1.06)
Knee Replacement	1.71 (1.02-2.88)*	1.99 (1.15-3.44)*	1.75 (0.86-3.58)
Constitutional Malalignment	0.90 (0.54-1.51)	1.15 (0.66-1.99)	0.91 (0.48-1.70)
High Risk Occupation	0.91 (0.62-1.34)	1.00 (0.66-1.51)	0.94 (0.58-1.53)
Use of Statins	1.48 (0.83-2.65)	0.70 (0.36-1.35)	0.85 (0.40-1.79)
Suffers from Gout	3.24 (1.41-7.45)**	2.71 (1.13-6.49)*	1.40 (0.53-3.74)
Presence of CC	4.62 (2.61-8.05)**	3.69 (2.02-6.75)**	2.63 (1.35-5.14) **
Injury	2.17 (1.43-3.30)**	2.88 (1.81-4.59)**	1.15 (0.62-2.13)
Surgery †	4.25 (2.78-6.50)**	5.43 (3.34-8.83)**	4.29 (2.26-8.15) **
Injection	1.60 (1.10-2.35)*	1.66 (1.11-2.50)*	0.79 (0.48-1.31)
Total Football Duration	1.04 (1.01-1.08)**	1.04 (1.00-1.08)*	1.00 (0.94-1.05)
Career Training Dose (per 1000 hours)	1.13 (1.07-1.19) *	1.10 (1.04-1.17) *	1.07 (0.99-1.16)
Matches Played (per 100 matches)	2.41 (1.08-5.36) *	1.77 (0.77-4.07)	1.10 (0.32-3.84)
Main Tier ‡			
One	1.00 (0.67-1.51)	0.81 (0.52-1.27)	0.52 (0.30-0.91) *
Two	1.05 (0.83-1.32)	1.10 (0.86-1.40)	1.07 (0.81-1.41)
Three	1.03 (0.88-1.21)	1.05 (0.89-1.25)	1.09 (0.89-1.32)
Four	0.92 (0.79-1.06)	0.96 (0.82-1.12)	0.98 (0.82-1.16)
Position			
Goalkeeper	1.18 (0.63-2.21)	1.14 (0.58-2.24)	1.13 (0.52-2.48)
Defender	1.03 (0.85-1.26)	1.12 (0.90-1.39)	1.22 (0.95-1.56)
Midfielder	1.04 (0.91-1.20)	1.07 (0.91-1.24)	1.04 (0.87-1.24)
Forward	0.94 (0.84-1.04)	0.88 (0.78-0.98)*	0.85 (0.74-0.97) *

OR adjusted for age and BMI (adjusted 1); ## OR adjusted all factors significant from crude analysis (adjusted 2); * p<0.05; ** p<0.01; † refers to exploratory / investigative / corrective surgery; ‡ the tier footballers played in for the majority of their career (assessed independently)

Multivariate Model

When conducting multivariate analysis, each factor was adjusted for all the significant factors identified from the crude analysis. These were: age, having a family history of KOA (or knee replacement), suffering from gout, having a presence of CC, sustained a knee injury, undergone knee surgery, received a knee injection, duration of having played professional football, career training dose and number of matches played.

When adjusting each exposure for the aforementioned risk factors, most of these risk factors were no longer significant. However, footballers had a 7% increased risk of RKOA with age [OR 1.07, 95% CI 1.05-1.10]. Footballers were also more than 2.5-fold likely to have RKOA if they had evidence of CC [OR 2.63, 95% CI 1.35-5.14]. For footballers who had undergone surgery [OR 4.29, 95% CI 2.26-8.15], they were more than four-fold likely to have RKOA.

Two results which were, however, unexpected were footballers whose main tier was tier 1 [OR 0.52, 95% CI 0.30-0.91] and footballers who played in a forward position [OR 0.85, 95% CI 0.74-0.97]. Footballers had a reduced risk of RKOA of 48% and 15%, if they played in tier one or a forward position respectively, having adjusted for all factors significant in the crude analysis. A small sample size may have resulted in such footballers having a reduced risk of RKOA.

4.3.5 Risk factors for Total Knee Replacement

Population Characteristics (TKR)

TKR is another primary outcome measured in this study. In terms of KOA, it is as a surrogate marker for end-stage of the condition. Patients suffering from severe structural change, which caused severe pain, and was beyond physiological repair, would have received a TKR. 11.1% of footballers reported having a TKR. Although the prevalence was far lower than the prevalence of KP or RKOA, these are less severe outcome measures more common in the population.

Footballers who had a TKR were more than ten years older than footballers who did not receive a TKR and a greater proportion were obese. However, these differences were not significant.

Some characteristics were significantly different between footballers who had undergone a TKR and those who had not. Nodal OA was almost three times as more common in footballers who had a TKR (17.2% v. 5.9%); and a greater proportion used statins; and more than twice as many footballers with TKR reported suffering from gout (25.4% v. 10.1%). Footballers who underwent a TKR also suffered more injury, surgery and more received IA injections, but also played fewer matches (424 v. 470).

These differences between footballers with and without TKR are described in Table 4.34. There were no statistically significant differences for all other variables reported.

Table 4.34 – Characteristics of footballers with and without TKR

	TKR	No TKR	p-value
N (%)	134 (11.1)	1073 (88.9)	
Age (years), mean (SD)	68.6 (9.0)	57.8 (11.4)	0.053
BMI (kg/m2), n (%)			0.084
<25	24 (18.3)	231 (22)	
25 –	76 (58.0)	650 (61.9)	
≥30	31 (23.7)	169 (16.1)	
Pattern 3 Digit Ratio, n (%)	85 (69.7)	648 (62.9)	0.142
Nodal OA, n (%)	23 (17.2)	63 (5.9)	<0.001
Familial: n (%)			
Knee OA	23 (17.2)	214 (19.9)	0.445
Hip OA	15 (11.2)	154 (14.4)	0.321
Hand OA	24 (17.9)	168 (15.7)	0.501
Knee Replacement	17 (12.7)	151 (14.1)	0.662
Hip Replacement	13 (9.7)	170 (15.8)	0.062
Constitutional Malalignment, n (%)	28 (22.1)	165 (15.7)	0.067
High Risk Occupation, n (%)	79 (59.0)	66. (61.8)	0.525
Use of Statins, n (%)	31 (23.1)	137 (12.8)	0.001
Suffers from Gout, n (%)	34 (25.4)	108 (10.1)	<0.001
Injury, n (%)	112 (83.6)	666 (62.1)	<0.001
Surgery, n (%)	134 (100)	640 (59.9)	<0.001
Injection, n (%)	87 (64.9)	450 (41.9)	<0.001
Total Football Duration, (years), mean (SD)	13.2 (5.2)	14.0 (5.6)	0.099
Career Training Dose, (hours), mean (SD)	8203 (4575)	7796 (4216)	0.311
Matches Played, mean (SD)	424 (246)	470 (240)	0.037
Main Tier, n (%) ‡			
One	46 (34.3)	308 (28.7)	0.178
Two	26 (19.4)	227 (21.2)	0.638
Three	23 (17.2)	200 (18.6)	0.678
Four	7 (5.2)	112 (10.4)	0.056
Position, n (%)			
Goalkeeper	12 (9.0)	101 (9.4)	0.864
Defender	44 (32.8)	360 (33.6)	0.869
Midfielder	30 (22.4)	306 (28.5)	0.135
Forward	48 (35.8)	303 (28.2)	0.068

† refers to exploratory / investigative / corrective surgery; ‡ the tier footballers played in for the majority of their career (assessed independently)

Risk Factors (TKR)

As with KP and RKOA, risk factors for TKR in footballers were determined using multivariate logistic regression. Table 4.35 presents the crude, age- and BMI- adjusted and multivariate-adjusted models for risk factors associated with having undergone a TKR.

Crude Model

From the crude analysis, factors that were associated with undergoing a TKR were: increasing age [OR 1.09, 95% CI 1.07-1.11], being overweight [OR 1.77, 95% CI 1.00-3.12], and having nodal OA [OR 3.32, 95% CI 1.98-5.57]. Footballers who took statins [OR 2.05, 95% CI 1.32-3.19], or suffered from gout [OR 3.04, 95% CI 1.96-4.70] had a two- and three-fold increased risk respectively of undergoing a TKR. Sustaining a knee injury [OR 3.11, 95% CI 1.94-4.99] and receiving intra-articular knee injections [OR 2.56, 95% CI 1.76-3.73] also resulted in an increased TKR risk.

However, footballers who had a longer total football duration (competitive and professional durations combined) were 5% less likely to have undergone a TKR [OR 0.95, 95% CI 0.92-0.98]. The association between surgery and KOA was not applicable due to collinearity because all footballers who underwent a TKR had indicated having surgery.

Age- and BMI- adjusted Model

For the age- and BMI- adjusted model, most factors that were statistically significant in the crude analysis, remained significant when adjusted for age and BMI. However, were more than two-fold more likely to undergo a TKR if they had constitutional malalignment [OR 2.04, 95% CI 1.25-3.33], having adjusted

for age and BMI. The significant association of statins (crude analysis), however was removed when accounting for the effects of age and BMI.

Multivariate Model

Finally, multivariate analysis was conducted by adjusting all variables by those factors identified as significant during the crude analysis. Footballers were 11% more likely to undergo a TKR with increasing age [OR 1.11, 95% CI 1.08-1.13]. Having nodal OA [OR 2.28, 95% CI 1.26-4.14], constitutional malalignment [OR 1.98, 95% CI 1.17-3.36], and intra-articular injections [OR 2.24, 95% CI 1.42-3.53] increased the risk of undergoing a TKR by at least two-fold. Having sustained a knee injury [OR 3.73, 95% CI 2.12-6.58] increased the risk of TKR by almost four-fold.

Footballers who had played football for a longer duration, had a 6% reduced risk of undergoing a TKR [OR 0.94, 95% CI 0.91-0.97], following adjustment of significant risk factors.

The risk factors for having undergone at TKR are in line with the findings of risk factors for KP and RKOA, supporting the notion that TKR is a marker for end-stage OA. The findings also further support the conclusions formerly made, that knee injury is the greatest driver of KOA and subsequent intervention (surgery) and management (intra-articular injections) further increase the risk of KOA.

Table 4.35 – Risk factor analysis for TKR in footballers

Exposure	Odds Ratio, OR (95% CI)		
	Crude	Adjusted 1 #	Adjusted 2 ##
Age	1.09 (1.07-1.11)**	1.09 (1.07-1.11)**	1.11 (1.08-1.13)**
BMI (kg/m2)			
<25	1.00	1.00	1.00
25 –	1.13 (0.69-1.82)	1.50 (0.90-2.50)	1.40 (0.81-2.44)
≥30	1.77 (1.00-3.12)*	2.03 (1.11-3.73)*	1.69 (0.87-3.27)
Pattern 3 Digit Ratio	1.35 (0.90-2.03)	1.33 (0.86-2.05)	1.40 (0.88-2.23)
Nodal OA	3.32 (1.98-5.57)**	2.24 (1.28-3.90)**	2.28 (1.26-4.14)**
Familial:			
Knee OA	0.83 (0.52-1.34)	1.00 (0.61-1.66)	0.86 (0.50-1.48)
Hip OA	0.75 (0.43-1.32)	0.90-(0.50-1.64)	0.92 (0.49-1.74)
Hand OA	1.18 (0.73-1.88)	1.24 (0.75-2.04)	0.92 (0.53-1.60)
Knee Replacement	0.89 (0.52-1.52)	1.29 (0.73-2.29)	1.56 (0.84-2.87)
Constitutional Malalignment	1.52 (0.97-2.39)	2.04 (1.25-3.33)**	1.98 (1.17-3.36)*
High Risk Occupation	0.89 (0.62-1.28)	0.90 (0.61-1.33)	0.95 (0.62-1.45)
Use of Statins	2.05 (1.32-3.19)**	1.00 (0.62-1.61)	0.84 (0.50-1.40)
Suffers from Gout	3.04 (1.96-4.70)**	1.76 (1.09-2.86)*	1.37 (0.82-2.28)
Injury	3.11 (1.94-4.99)**	4.83 (2.87-8.13)**	3.73 (2.12-6.58)**
Surgery †	N/A	N/A	N/A
Injection	2.56 (1.76-3.73)**	3.23 (2.13-4.88)**	2.24 (1.42-3.53)**
Total Football Duration	0.95 (0.92-0.98)**	0.95 (0.92-0.98)**	0.94 (0.91-0.97)**
Career Training Dose (per 1000 hours)	1.02 (0.98-1.07)	1.00 (0.95-1.05)	1.05 (0.99-1.12)
Matches Played (per 100 matches)	0.44 (0.21-0.95) *	0.37 (0.15-0.88) *	0.66 (0.21-2.03)
Main Tier ‡			
One	1.30 (0.89-1.90)	1.11 (0.74-1.67)	1.08 (0.69-1.70)
Two	0.90 (0.57-1.41)	1.03 (0.64-1.67)	0.93 (0.55-1.56)
Three	0.90 (0.56-1.45)	0.91 (0.55-1.53)	1.03 (0.60-1.78)
Four	0.47 (0.22-1.04)	0.72 (0.32-1.63)	0.67 (0.29-1.57)
Position			
Goalkeeper	0.95 (0.51-1.77)	0.87 (0.45-1.68)	0.91 (0.44-1.87)
Defender	0.97 (0.66-1.42)	1.27 (0.84-1.92)	1.22 (0.78-1.91)
Midfielder	0.72 (0.47-1.11)	0.78 (0.49-1.23)	0.85 (0.52-1.40)
Forward	1.42 (0.92-2.07)	1.03 (0.69-1.56)	0.98 (0.63-1.52)

OR adjusted for age and BMI (adjusted 1); ## OR adjusted all factors significant from crude analysis (adjusted 2); * $p<0.05$; ** $p<0.01$; † refers to exploratory / investigative / corrective surgery; ‡ the tier footballers played in for the majority of their career (assessed independently)

4.4 Discordance Analysis within Footballers

Chapter 1.4 alludes to a discordance between KP and RKOA in the general population. Not all patients with KP have severe structural change and not all patients with RKOA (severe structural change) report KP.

The section explores the discordance between KP and RKOA, suggesting the extent to which this occurs in footballers. RKOA was assessed using the NLDA and KL and its discordance is presented for both assessment approaches.

4.4.1 Radiographic KOA (NLDA) vs. Knee Pain

Almost half (47%) of all footballers who underwent radiographic analysis had KP. The Venn diagram (Figure 4.12) clearly shows this overlap of footballers with both RKOA and KP (220 footballers).

Almost three times as many footballers with RKOA (NLDA) had KP (73.1%) compared with those who did not have KP (26.9%). However, for those footballers without RKOA, the proportion who had KP (46.2%) was similar to the proportion did not have KP (53.9%). Thus, footballers had more than a three-fold risk of RKOA if they had KP [OR 3.17, 95% CI 2.13-4.71].

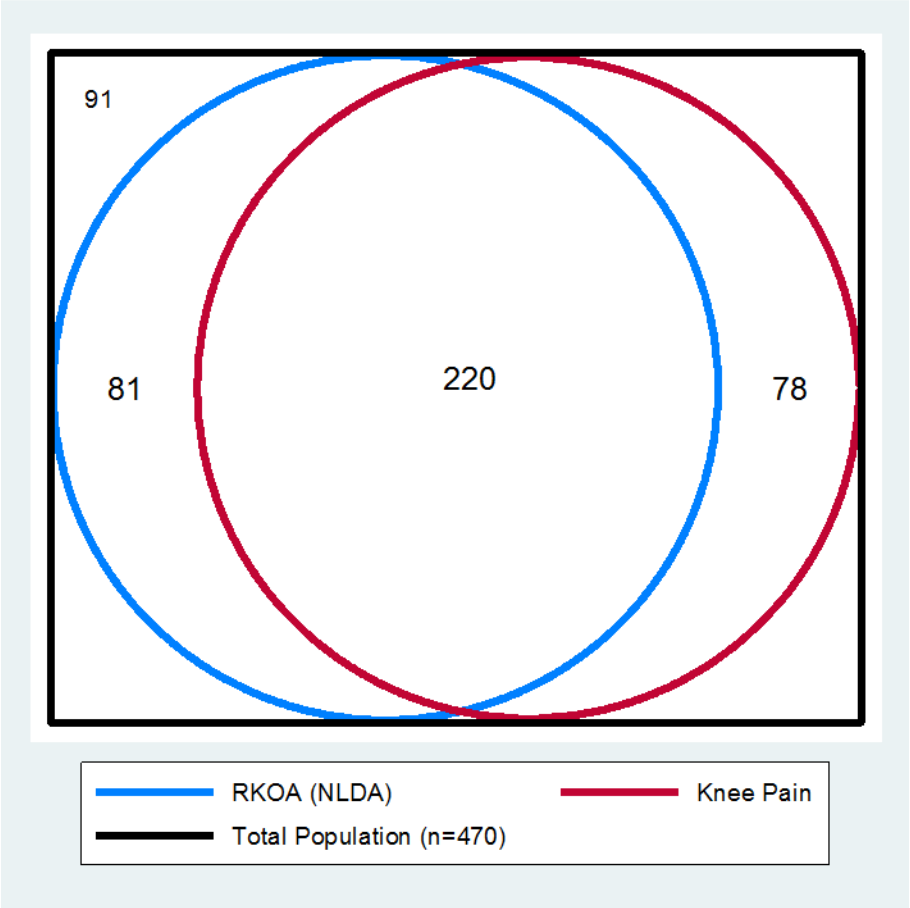


Figure 4.12 – A Venn showing the discordance between RKOA (NLDA) and KP

4.4.2 Radiographic KOA (KL) vs. Knee Pain

When KL (KL≥3) was used to determine RKOA, only 19% of footballers who took part in the radiographic survey presented with both RKOA and KP. The more stringent KL cut-off resulted in fewer footballers having RKOA compared to using the NLDA. This is reported in the Venn diagram on Figure 4.13.

However, the overwhelming majority of footballers who had RKOA (KL) had KP (85.6%) compared to those that did not have KP (14.3%). As previously, a similar proportion of footballers who did not have RKOA (KL) reported having KP (57.0%) and not having KP (43.0%). However, the risk of having RKOA

(KL) if footballers had KP was more than four-fold [OR 4.53, 95% CI 2.48-8.29).

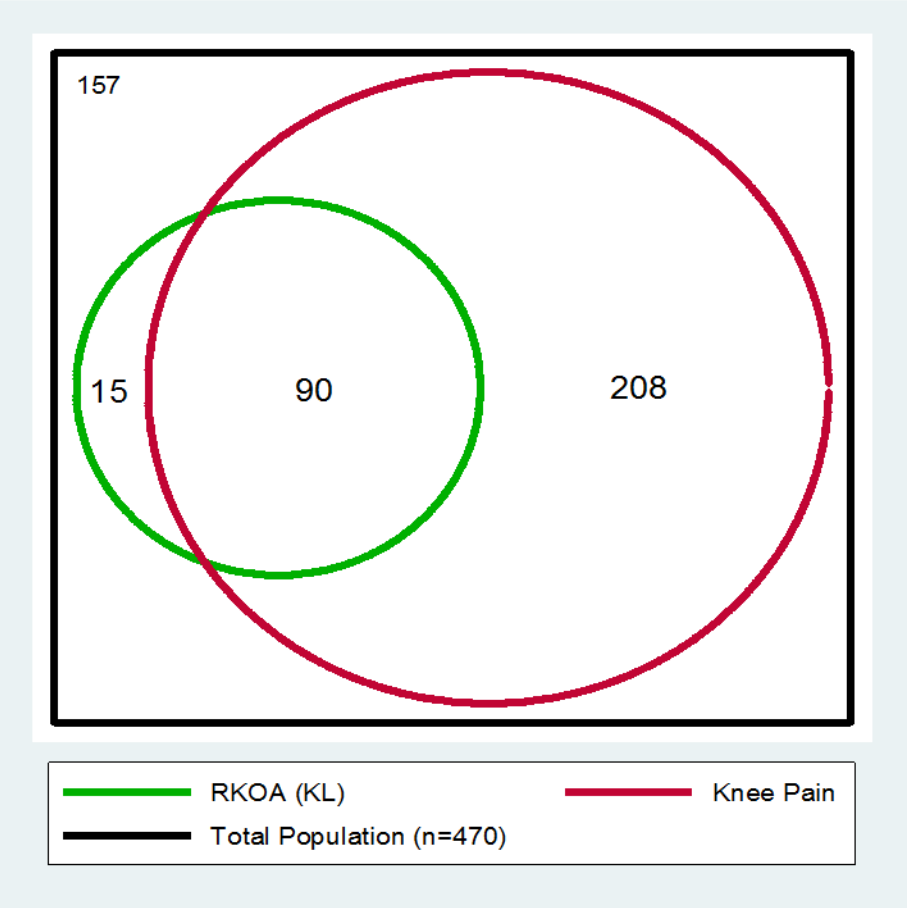


Figure 4.13 - A Venn showing the discordance between RKOA (KL) and KP

These discordance results show two findings: firstly, the prevalence of KP and RKOA are significantly different and studying both outcome measures are necessary when reporting KOA. Secondly, the NLDA scoring tool has a better sensitivity for current KP, given RKOA, whereas KL scoring tool has a better specificity for current KP.

5 DISCUSSION

This is the first large-scale study of its kind to: (1) determine the prevalence and risk of KOA (assessed by various measures) in retired professional footballers, compared to the general population; and (2) and investigate the factors associated with an increased risk of KOA (measured as KP, RKOA and TKR) within footballers.

5.1 Main Findings

This study, which recruited 1207 footballers, was the largest observational study of KOA in retired professional footballers. Almost four times as many male controls (n=4085) were recruited from the parallel KPIC Study.

Recruitment of footballers (Figure 4.1) and controls (Figure 4.2) account for each participant contacted. Consenting participants who partook in the questionnaire survey subsequently attended radiographic assessment. There was a low response rate (approximately 25%) for both the footballers and the controls recruited, and thus systematic differences between those participants who did and did not respond may be apparent.

Differences between the populations who partook in the questionnaire survey, and had an x-ray and those who did not have an x-ray were compared (Table 4.5 – Footballers; Table 4.6 – Controls). Both footballers and controls who underwent an x-ray were significantly more likely to have sustained a knee injury. Injury is a strong risk factor for KOA (Muthuri et al., 2011b, Silverwood

et al., 2015) and this is suggestive that such participants may suffer from more KP or RKOA.

Participants who had an x-ray may have been interested to enquire as to whether sustaining an injury resulted in long-term damage to their knee. The opportunity to receive an x-ray with no personal expense, may have also appealed to some participants. However, such participants may have undergone radiographic assessment purely from an altruistic point of view, volunteering their time as a means of giving back to their former profession.

In terms of participants who responded to the questionnaire and underwent an x-ray, significance of other risk factor (age and digit ratio, and malalignment (footballers-only) and nodal OA (controls-only)) are unlikely to have influenced their decision to partake in the radiographic analysis. Chapter 5.2 discusses whether this results in a caveat of this study.

The first objective of the study was to determine the prevalence of KOA. Footballers had a higher prevalence of KOA compared with the general population controls: measured as current KP (52.2% v. 26.9%), RKOA (NLDA) (64.0% v. 35.2%), and TKR (11.1% v. 3.8%).

In terms of the second objective, footballers had a greater risk of KOA, when adjusted for age and BMI, measured using the aforementioned outcomes (KP, RKOA, and TKR). The risk of current KP in footballers compared to the controls was almost two-fold greater [aRR 1.92, 95% CI 1.78-2.07], following adjustment for age and BMI. Footballers also had more than two-fold increased risk of RKOA (NLDA) [aRR 2.14, 95% CI 1.87-2.45] and almost a three-fold increased risk of TKR [aRR 2.79, 95% CI 2.42-3.23] compared to the controls.

The third objective identified risk factors associated with each primary outcome within footballers. Following adjustment for age and BMI, the factors significantly associated with increased odds of KP were age, BMI, digit ratio (pattern 3), a family history of OA (knee, hip, hand), having gout, sustaining a knee injury, knee surgery, and receiving intra-articular injections.

For RKOA, these factors were age, family history of KOA, having gout or CC, sustaining a knee injury, knee surgery, and intra-articular injection. Additionally, football-specific factors were associated with an increased risk of RKOA, when adjusting for age and BMI. These were football duration (cumulative years playing competitive and professional football) and career training dose.

Finally, factors associated with an increased TKR risk, following age and BMI adjustment were: age, being obese, having nodal OA, a constitutional malalignment, having gout, sustaining a knee injury, and receiving an intra-articular knee injection.

These findings suggest that, in addition to demographical factors (namely age, BMI) or suffering an inter-related comorbidity (gout), sustaining a significant knee injury, having had knee surgery, or receiving intra-articular knee injection are the key risk factors for KOA within footballers.

Objective 1: The Prevalence of KOA

KOA is a common complex disorder (Sandell, 2012), diagnosed using various outcome measures (as presented in Section 1.2.3). However, patients are more likely to report with the condition if they experience symptoms and thus KP

should be the malady (Hadler, 1992), not RKOA. Considering this, this study observes two outcomes of KP: the first was current KP; and the second was ever having KP (for at least a one-month period).

The prevalence of current KP in the controls (26.9%) was similar to previous observational studies from the UK: 20.1% (in males) (McAlindon et al., 1992a), 25.0% (O'Reilly et al., 1996) and 28.0% (Urwin et al., 1998) (for both genders), as well as a review, which reported the prevalence as 25.0% (Peat et al., 2001a). This suggests the control population is representative of the UK general population and may be an adequate control group to which to compare footballers. The increased prevalence (almost two-fold) of KP in footballers is therefore comparable to the general population. However, generalising this finding to the wider population of retired footballers is difficult to ascertain because the demographics of the non-responders (footballers who received the questionnaire but did not respond) is unknown. Further to this, the size and demographics of the source population itself (all retired professional footballers in the UK) is also unknown. Thus, despite the higher prevalence of KP in footballers compared to the controls, caution is necessary when generalising these findings.

Exploring this in further detail, footballers report a greater prevalence of current KP across all age groups and the prevalence is much greater in those under the age of 55, compared to the controls (see Figure 4.4). The prevalence of KP does not equate to that of the general population after the age of 55, typically the onset of pain attributable to KOA in the general population (Peat et al., 2001a). This suggests that KP in footballers over the age of 40 is a long-term consequence

(that is, KOA) with serious repercussions (Kuijt et al., 2012), rather than a short-term consequence (knee trauma or injury).

One such example may be following retirement from playing professionally, footballers may be limited or unable to work due to such musculoskeletal pain and disability. Despite being under the national retirement age (advised as 65 years old (Gov.uk)), not holding a full-time occupation for up to 25 years leads to a significant burden, both on the health services (Cross et al., 2014)as well as the economy of the country. A further explanation for the much greater prevalence of KP, especially in footballers under the age of 55 (compared to the controls), may be due to overuse of the joint (through repetitive running and training) in footballers compared to the controls.

The prevalence of KP in footballers and controls declines after the age of 70 (figure 4.4), but this is more likely due to both population suffering from other more severe comorbidities, or even mortality, rather than KP (or KOA) becoming less prevalent. The decline in the controls is synonymous with previously reported literature, whereby KP peaks at the age of 70 (Peat et al., 2001a). The fact that KP remains more prevalent in footballers, regardless of age strongly suggests that the early onset of pain is more likely to be due to joint overuse and hence longer-term consequences, rather than short-term effects.

Footballers (61.7%) also had a greater prevalence of ever having KP (for at least one month) compared to the controls (44.2%). Comparison of this finding to the existing literature is limited because previous studies further quantify this KP by limiting it to the past year (rather than ever) (McAlindon et al., 1992a, McAlindon et al., 1993, O'Reilly et al., 1996). The prevalence of ever having

KP in footballers may be greater, however, due to footballers being more likely to sustain knee injuries and joint overuse (due to playing professionally) compared to the controls.

In terms of physician-diagnosed KOA, footballers (28.3%) had twice the prevalence compared to the controls (12.0%). Despite having more than two-fold greater prevalence of physician-diagnosed KOA, the prevalence within footballers is in line with previous studies where footballers self-reported KOA (32.0% and 28.8%) (Drawer and Fuller, 2001, Turner et al., 2000).

This increased prevalence in footballers accords with the increased prevalence of KP reported by footballers, however, such diagnosis may be based on additional measures (for example, imaging) rather than KP alone. Although this emphasises the increased prevalence of KOA in footballers, the measure itself is not as robust due to the influence of multiple biases (recall bias and misclassification bias) and the variability of diagnoses offered by different physicians. This finding also suggests that only half the population (whether footballers or controls) consult their physician and are diagnosed with KOA, despite a much greater proportion experiencing KP symptoms.

Footballers had a greater prevalence of RKOA compared to the controls, whether assessed using NLDA (64.0% v. 35.2%) or KL (28.5% v. 14.1%). The differences between the two measures, however, are due to the case definitions and different scoring methods utilised by each approach (Arden and Nevitt, 2006, Schiphof et al., 2008).

Since its conception (Nagaosa et al., 2000) and improvement (Wilkinson et al., 2005), use of the NLDA has been limited. For this study, its use was preferred

because it scores osteophytes and JSN independently, on a continuous scale (0-60), with independent atlases for the TF and PF compartments (Nagaosa et al., 2000). This provides a more robust assessment of RKOA, and additionally, the following definition dichotomised whether participants had RKOA: *"osteophyte in any compartment of the knee AND JSN in at least one of the TF or PF compartments of the knee"*.

RKOA was also scored using the KL grade verbal descriptors. Although these do not provide such an exhaustive assessment (Duncan et al., 2006), they remain the gold-standard approach for in imaging diagnosis (Kellgren and Lawrence, 1952, Kellgren and Lawrence, 1957) (Schiphof et al., 2008). Furthermore, their use means findings are comparable to existing literature, both within footballers (Arliani et al., 2014, Elleuch et al., 2008, Krajnc et al., 2010), and the general population (McAlindon et al., 1992a, McAlindon et al., 1992b) (O'Reilly et al., 1998).

The prevalence of RKOA assessed using the NLDA was more than two-fold greater compared to using the KL grade for both footballers and controls. The primary reason for this is the case definition for the NLDA is more lenient and forgiving, accounting for a larger prevalence of the population.

The prevalence of RKOA (KL) in footballers (28.5%) was more than two-fold greater compared to the controls (14.1%). However, this was lower than that previously reported: 67%, 80% and 60% (Arliani et al., 2014, Elleuch et al., 2008, Krajnc et al., 2010) respectively. The prevalence of RKOA (KL) in the controls was also lower than previously reported in literature (McAlindon et al., 1992b, O'Reilly et al., 1996, Zhang et al., 2011b). The primary reason for this is

the fact different case definitions are used. This study defines RKOA as a KL grade of three or greater, whereas the existing literature defines RKOA as KL grade of two or greater. Despite capturing a greater proportion of the population that may have change indicative of RKOA, the existing literature's definition is not definitive for JSN (only osteophyte formation). This suggests that the prevalence of RKOA from previous studies may include cases that may not be cases of RKOA (resulting in an over-estimating of prevalence) or detection of potential early cases of RKOA (rather than definitive cases).

The prevalence of RKOA using the NLDA from this study (64.0%) are similar to previous studies: 60% (Krajnc et al., 2010) and 67% (Arliani et al., 2014), but the differing methods of assessment (NLDA v KL) mean these findings cannot be generalised.

Previous studies observing RKOA in footballers have only focused reporting in the TF compartment (Arliani et al., 2014, Elleuch et al., 2008, Krajnc et al., 2010). However, this study presents a novel finding for the prevalence of RKOA in the PF compartment of the knee. Whilst the prevalence of TF RKOA is greater in the dominant (right) leg of footballers compared to the controls, the converse holds true for PF RKOA. This is likely to be due to greater joint overloading and rotation of non-weight bearing contralateral (non-dominant) leg in footballers when striking the ball with their dominant leg. A previous study suggests a similar greater prevalence of RKOA in the non-dominant leg (Krajnc et al., 2010).

Evidence of CC on radiograph is associated with RKOA. Footballers had almost a three times greater prevalence of CC (24.3%) compared to controls (8.8%). In

the general population, the prevalence of CC (for those aged 60 and over) ranges between 7.0-10.0% (Richette and Bardin, 2010), which is similar to that reported in the controls. CC is closely associated with RKOA and there is an interplay between joint injury, the formation of calcium crystals, and structural change (RKOA). Injury is a known risk factor for KOA (Muthuri et al., 2011b) and injury has shown to be closely associated with CC formation (Zhang et al., 2011a). Thus, an increased risk of injury (more than two-fold) in footballers compared to the general population is more likely to result in CC formation, thus footballers having a higher prevalence that the controls. Further to this, given the close association of CC with RKOA, and footballers will also have a far greater prevalence of RKOA compared to the controls, especially if they have previously sustained a significant knee injury.

The prevalence of TKR in footballers (11.1%) was almost three times more than the controls (3.8%). TKR is a surrogate measure of severe KOA and undergoing a TKR is consequence of suffering from severe symptoms (KP) as well as having advanced structural damage (RKOA). The fact footballers have a much greater prevalence of the outcome further highlights the fact that all measures of KOA (whether defined by symptoms, imaging or even surgery (TKR)) are more evident in footballers.

Previous literature within footballers has not explored multiple outcomes of KOA simultaneously, with studies focusing on either, self-reported physician-diagnosed KOA (Drawer and Fuller, 2001, Turner et al., 2000) or RKOA only (Arliani et al., 2014, Elleuch et al., 2008, Krajnc et al., 2010). By exploring KP, the malady (Hadler, 1992), as well as other measures (RKOA, TKR, and CC), the prevalence of the condition in footballers can more definitely concluded.

Comparing these results to a suitable control group (which is reflective of the general population), the increased prevalence can confidently be generalised to the wider football population as a whole.

Objective 2: The Risk of KOA

Footballers have almost a two-fold greater risk of KP [RR 1.94, 95% CI 1.80-2.09] compared to the controls and this remains similar when adjusting for age and BMI [aRR 1.92, 95% CI 1.78-2.07]. There is no significant difference between the crude and adjusted (age and BMI) risks, which suggests that these factors are not responsible for the increased risk of KP within footballers. However, when adjusting for injury and nodal OA, in addition to age and BMI, the risk of KP in footballers reduces to just less than 50%.

Injury is the most significant risk factor independently, conferring more than two-fold increased risk in footballers compared to the controls. Injury is a major factor contributing to the increased risk of KP and KOA (Silverwood et al., 2015), and the findings from this study are consistent with the literature.

Although footballers had a higher prevalence of knee injuries compared to the controls, this may be due for two reasons: firstly, the nature of footballers' careers, and secondly, the difference in phrasing of the questions. Footballers are exposed to increased risk of injury due to the nature of the sport (Drawer and Fuller, 2002) and previously shown to have a high risk of injury (Dvorak, 2011, Dvorak and Junge, 2000, Ekstrand et al., 2011). However, the differences may also be due to the differences in the phrasing of the questions pertaining to injury in the footballers and controls questionnaires respectively. Despite injury

conferring an increased risk for KOA, the two aforementioned points may be a caveat in interpretation of the results.

Injury is defined as having had a significant knee injury (at least once), and although this explains, to some extent, the increased risk of KP, it does not account for the entire explanation. This increased risk of KP (45%) is still present when accounting for other known risk factors (constitutional malalignment, having a high-risk occupation and a pattern 3 digit ratio). This suggests that playing professional football itself is a risk factor for current KP. This may be due to football being a potential high-risk occupation, which involves footballers undergoing repetitive twisting, turning and squatting movements (during either training or match play), which have previously been identified as occupational hazards.

Repetitive use, leading to overuse, of the knee joints through training and match play may result in the joint sustaining micro-trauma. Although in itself not significant, the cumulative affects over the course of a footballer's career (professional career duration reported in this study of 13.9 years, which is similar to the literature (Kuijt et al., 2012)) exposes footballers to a risk not sustained by non-professional footballers. Other consequences of significant knee injuries, including having knee surgery (typically arthroscopy), receiving intra-articular knee injections, or even becoming varus-mal-aligned may increase footballers' predisposed risk to developing KP at a higher rate compared to the controls.

The crude risk of footballers having a physician-diagnosis of KOA is more than two times greater than the controls [RR 2.31, 95% CI 2.04-2.61] and when accounting for injury in addition to age, BMI and nodal OA, this risk is reduced,

to 83%, yet still remains significant [aRR 1.83, 95% CI 1.55-2.02]. As with KP, injury explains a large proportion, but not all of the risk of footballers' receiving a diagnosis of KOA.

Although physicians may base such a diagnosis on symptoms (KP), it may be more likely that such diagnosis was confirmed using radiography in addition, as typically favoured by clinicians (Arden and Nevitt, 2006). The fact that footballers were more likely to be in contact with medical personnel, or receiving imagining of their joints, compared to the general population, determining RKOA would be more likely, resulting in footballers receiving such a diagnosis. This is apparent due to the increased risk of sustaining significant injuries, of which footballers are likely to suffer more than one in the same knee (footballers that sustained more than one injury in the right knee (25.5%) or left knee (20.6%) far exceed that of the controls).

In terms of RKOA, when measured using NLDA, footballers had almost two-fold increased risk compared to the controls [RR 2.14, 95% CI 1.87-2.45], which was similar to RKOA measured using KL [RR 2.02, 95% CI 1.56-2.63]. When adjusting for pre-defined risk factors, the risk of RKOA in footballers, when measured using NLDA was 85% [aRR 1.85, 95% CI 1.60-2.14] but greater than two-fold when measured using KL [aRR 2.05, 95% CI 1.56-2.71].

The risk for both NLDA- and KL- assessed RKOA were greater than KP in footballers compared to the controls. These findings are consistent with the literature, which reports that structural change (as seen on radiography), regardless of symptoms, is prevalent at a much higher rate in the general population.

Footballers may be predisposed to more of structural change, due to a number of reasons. Footballers have a two-fold increased risk of significant knee injuries compared to the controls, and these result in additional consequences. The most common consequence following a significant knee injury is receiving surgical intervention (most commonly some form of explorative or corrective arthroscopy). Regardless of its manner, surgical intervention increases the risk of RKOA (structural change) in the joint due to its structures being manipulated.

Intra-articular injections into the knee joint may also be a negative consequence following a knee injury that increases the risk of structural change in the joint. The prevalence of footballers that received intra-articular injections were much greater than the controls, and this may have untoward consequences concerning the structures within a joint, resulting in RKOA. Typically, steroidal injections would be the most frequently administered injection to footballers, to either relieve pain and/or ensure footballers immediately return to playing (Orchard, 2002, Orchard, 2004). Constant loading (through running, twisting and turning) on a damaged joint leads to further structural damage. Having received injections in the joint to anaesthetise the pain, such consequences would be more severe as the body's internal mechanisms to indicate damage would be suppressed.

Current medical practice indicates patients should receive no more than four steroidal injections into the same joint in a given 12-month period. However, from the results of this study, footballers were reporting far greater numbers of injections per season (less than 12-month period), which highlights a significant concern in terms of mismanagement of footballers. Long-term joint damage is thus almost inevitable and the far greater prevalence and risk of objective

measures (RKOA, TKR and CC) in footballers compared to the controls is indicative of this.

A further reason for RKOA is due to the altered alignment of the knee joint, which may be due to a number of reasons (including injury and over use). An altered alignment, results in changes in joint loading. The regions that are most-weight bearing part of the joint may change and sustain increased risk of JSN due to cartilage degradation. This is a cardinal feature of RKOA as seen on radiography, which increases footballers' risk of having such an outcome.

Objective 3: The specific factors associated with an increased risk of KOA (within footballers)

This objective determined whether the factors that are associated with an increased risk of the outcomes of KOA (KP, RKOA, and TKR) are in line with the existing literature (Suri et al., 2012, Silverwood et al., 2015) or differ within footballers.

Some of the risk factors associated with current KP within footballers (crude analysis) were the same as known risk factors: increasing age, being overweight or obese, having a family history of OA, constitutional malalignment and having had a knee injury. However, additional factors that predisposed a significant risk were suffering from gout, having had knee surgery or intra-articular knee injections. These additional factors may be consequences of known risk factors, such as knee injury, as opposed to newly identified risk factors.

Constitutional risk factors include increasing age and BMI, which are established risk factors for the outcome. Previous studies have also linked a pattern 3 digit ratio and a family history of OA with a significant increased risk of KOA, as seen in this study. The risks predisposed by these factors are inherent, and although not inevitable, they do increase the likelihood of the outcome. In terms of local biomechanical factors, joint injury and constitutional malalignment are shown to increase the risk of KP.

Knee injuries resulted in more than four-fold increased odds of footballers having KP [OR 4.21, 95% CI 3.27-5.42] compared to not having KP for the known risk factors. The increased odds of surgery was greater [OR 4.37, 95% CI 3.39-5.64], but this may be due to having knee injury rather because footballers would not receive surgical intervention in their joint without reason.

As with KP, knee injury and its consequences were significant risk factors for developing RKOA. However, the association of surgery [OR 3.40, 95% CI 2.18-5.29] was greater than that of injury [OR 2.36, 95% CI 1.54-3.63]. Surgery in the majority of cases (>90%) were some form of arthroscopic exploration or manipulation, which would have inevitably affected other close-lying structures in the complex knee joint. This manipulation, rather than the cause (injury) is more likely to increase the odds of long-term consequences such as structural changes (RKOA) within the joint. The increased odds of RKOA if footballers suffered from gout [OR 2.33, 95% CI 1.22-4.48] suggests that crystal deposition within the joint further affects the structure. This increased the risk of cartilage degradation that results in RKOA, further supporting the amplification loop theory (Roddy and Doherty, 2012).

Structural change, however, is an inevitable consequence of ageing. In the general population, the overwhelming majority of people will have some extent of structural change (Brandt et al., 2003), whether in the presence or absence of symptoms. It is only when these changes become very severe (KL grade of three or greater) or present with symptoms (KP) that it is recognised as a clinical outcome of KOA (Abhishek and Doherty, 2013). Its prevalence is greater than KP, and the fact that KOA is an inherently conserved repair process (Brandt et al., 2003) other constitutional factors (apart from ageing) are unlikely to be associated. It is the joint-specific factors, such as knee injury, and its consequences, that are likely to determine whether RKOA is clinically occult or prevalent.

Further to this, evidence of CC was assessed in footballers who underwent knee radiographs. CC was more frequency in footballers with RKOA, resulting in an increased risk of more than three and half times (even when adjusting for age and BMI), which strongly suggests both CC and RKOA are likely to occur simultaneously. This close association is almost suggestive of the amplification loop theory purported with the close association of gout (urate crystals) and RKOA.

Furthermore, RKOA is associated strongly with both injury and CC (Neame et al., 2003). Previous literature has shown injury to be a risk factor for CC (Ledingham et al., 1993), and so concordance between the two outcomes (RKOA and CC) are highly likely, especially following footballers sustaining a significant knee injury. Furthermore, inadequate compensatory repair of the joint following injury results in structural alterations of the joint, which may also

facilitate the deposition of calcium crystals and thus result in CC, and in the longer term, RKOA.

TKR is the result of end-stage KOA when the joint repair process cannot compensate against insult (Brandt et al., 2003) and structural change and symptoms are concurrently experienced. Thus, risk factors established for footballers who had undergone TKR had much greater odds, indicative of the seriousness of KOA.

Increasing age (9% increased risk, even when adjusted for age and BMI) was a risk factor for footballers undergoing a TKR. This may be due to age being a previously known risk factor but also the fact the population studied are footballers. Nodal OA conferred more than three-fold increased risk for footballers undergoing a TKR, and this remained more than two-fold increased risk when adjusting for age and BMI. This strongly suggests a close association with nodal OA and KOA, which is in line with that previously meta-analysis (Blagojevic et al., 2010b). However, this risk is much greater, compounded by the fact the population studied were professional footballers.

An interesting finding was that constitutional malalignment was not significantly associated with footballers undergoing a TKR. However, this risk became significant when adjusting for age and BMI. This suggests that the maligned joint had adapted, especially during the footballers' careers when sustaining repetitive microtrauma and external insults. However, with age (and increasing BMI), footballers with mal-aligned joints were more likely to require a knee replacement, due to the irreversible damage sustained during their professional career.

Footballers who had sustained a knee injury were more than three-fold likely to undergo a TKR. This association is in line with that reported for KP and RKOA, highlighting the fact significant knee injury is likely to be the greatest driver of all outcomes of KOA in later life. Following adjustment for age and BMI, the risk of TKR, for footballers who had sustained a knee injury, was almost five-fold, suggesting that an ageing joint and increasing weight bearing at the joint (due to increased BMI) further increases the risk of serious consequences (TKR) of an already damaged joint.

All footballers who underwent a TKR had undergone surgical intervention resulting in complete concordance. Receiving an intra-articular injection, however, also resulted in an increased risk of TKR, most likely due to footballers playing through the pain-barrier (having received corticosteroid injections), which inevitably inflicts longer-term damage on the joint, not immediately apparent.

Despite footballers having a greater risk of TKR (surrogate for end-stage KOA), there was a converse association for total football duration. For every additional year footballers had played the sport (competitively and professionally), they had a five percent reduced risk of undergoing a TKR. This reduced risk of TKR is paradoxical because footballers thus have increased exposure to playing the sport (which increases their risk of repetitive microtrauma or major injury). The reduced risk, however, may be explained by the 'survival of the fittest' phenomenon (Kuijt et al., 2012), whereby footballers who played for a longer time are more resilient to longer-term consequences, despite increased exposure to the game, due to better adaptation to the insults sustained.

Having identified the risk factors, sustaining a knee injury, undergoing knee surgery and receiving an intra-articular injection were factors strongly associated with an increased risk of all measures of KOA (KP, RKOA and TKR). However, despite their association, surgery and intra-articular injections may not be risk factors for KOA. Footballers underwent knee surgery or received an intra-articular injection most likely after having suffered a knee injury (although this was not true in all cases), depending on the extent of the injury. Thus, these are treatment measures in response to knee injuries sustained and are therefore likely to be associated with KOA. Knee injections (typically steroidal) may have meant footballers playing with a damaged joint, which may have resulted in chronic pain or the need for joint replacement due to the microtrauma sustained following an injury. Knee surgery, typically following injury, involves manipulation of the joint may have resulted in structural changes (RKOA). Although it may be necessary in the majority of cases, some footballers may have equally benefitted from rest and recuperation. However, previous management of knee injuries in professional aimed for return to play for footballers, without considering the longer-term consequences suffered.

Thus, knee injury itself (in the presence of other factors) may be a sufficient cause for the onset of KOA, regardless of intra-articular injections and knee surgery. Although associated with an increased risk of KOA, intra-articular knee injections and/or knee surgery are not necessary factors on the causal pathway for KOA. Their association, however, may be due to the close relationship with knee injury, based on these factors being treatment approaches, rather than causal factors for KOA.

Further analysis conducted measured the discordance between the subjective (KP) and objective (RKOA) measures of KOA. As previously reported in the literature, accurately encapsulating the extent of KOA in the population is difficult because there is a discordance between patients who have KP, those who have structural change (evident as RKOA), and those who have both KP and evidence of RKOA (Peat et al., 2001a, Bedson and Croft, 2008). RKOA in this study was measured using two different assessment tools, the NLDA and the KL verbal descriptors and discordance of each with KP was measured (Figures 4.12 and 4.13 respectively). As previously described in the literature, there remains a discordance between footballers who have KP and those with structural change (RKOA).

Discordance for KOA occurs because not all participants who report KP have structural change sufficient to diagnose as RKOA. This could be due to the fact KP was determined as pain within the 'past month' only and underlying structural changes may not be evident. However, KP reported may be due to other reasons, including other pathologies, for example tendonitis, referred pain due to systemic disease, or even non-physical pain, for example due to depression (Bedson and Croft, 2008). Thus, structural changes within the joint may not be apparent in such cases.

Conversely, footballers that did not report pain may have had structural changes within the joint. The definition(s) used to classify footballers with RKOA have: (i) not been used before (NLDA), and (ii) are more stringent (KL grade 3 rather than KL grade 2) than widely reported in the literature (Arden and Nevitt, 2006). Thus, discordance between footballers with RKOA and KP differs when structural change is assessed using the NLDA compared to the KL descriptors.

The ageing process is typical factor associated with structural change (Arden and Nevitt, 2006), but such changes may not elicit pain in or around the joint. As presented in the introduction, KOA is a regenerative condition, adaptive to insults sustained to the joint. However, an unsuccessful repair process may result in structural changes within the joint, in the absence of pain (Brandt et al., 2003, Arden and Nevitt, 2006).

A further reason, for structural change within the joint may be due to footballers having sustained long-term repetitive over-use of the joint, including suffering micro- and macro-trauma, due to playing football professionally for a long period. However, this notion may also be the reason, there is less discordance between KP and RKOA (whether NLDA or KL) in footballers, compared to that previously reported in the general population (Peat et al., 2001a).

In light of these findings, it is evident that injury is a significant risk burden for footballers developing KOA following conclusion of their playing career. Compared to all other factors studied, injury is by far the most influential risk factor and conferred significant risk of footballers developing KOA.

Knee injuries and its football-specific consequences (multiple surgical interventions and multiple intra-articular injections) are the strongest risk factors most significantly associated with outcomes of KOA (KP, RKOA and TKR). Reducing the risk and prevalence of knee injuries in football, with improved management (if suitable, physical therapy and rest instead of surgical intervention and intra-articular injections), would greatly reduce the prevalence and risk of KOA in footballers. This provides a key avenue for football governing bodies to approach and minimise the risk of footballers sustaining and

suffering from significant knee injuries. It is understood that prevention is not possible due to the demands inevitable nature of the vocation, but measures put into place to reduce the rate and risk of injury would dramatically decrease the risk of long-term consequences, such as KOA in retired professional footballers.

5.2 Strengths and Limitations

There are several caveats of this study. The use of a self-reported postal questionnaire survey, which is inherent with recall and misclassification bias.

Recall bias pertains to individuals responding inaccurately to the questionnaires due to not being able to remember events or occurrences from the past. Although it is a significant caveat, it is generally unavoidable in cross-sectional surveys of a self-reported nature. This may lead to an over- or under- estimation of the prevalence of different exposures or outcomes. However, the prevalence of the primary self-reported outcomes in the controls is in line with other population-based studies, and this suggests that the estimates are unlikely to be biased.

Data from footballer questionnaire responses (name, DOB, career duration and matches played) were compared to pre-existing literature, which listed all professional football players in the English Football League System (JM). A Bland-Altman plot reported there was no differences in agreement between the questionnaire responses and published data, suggesting recall bias for footballers was limited, especially concerning football-specific exposures.

The prevalence of RKOA varied from that previously reported. However, the KL definition used in this study ($KL \geq 3$) differs from that previously used ($KL \geq 2$). Although this may have resulted in an under-estimation of the prevalence of RKOA, this study's definition is more robust as cases identified have definite osteophyte formation and definite (as opposed to possible) JSN.

No previous studies (in footballers) have used the NLDA to define RKOA. However, the findings (prevalence and risk factors within footballers) is comparable to RKOA defined using KL, which makes suggests that the scoring

tool is equally sufficient. Furthermore, radiographic assessment (by GSF) had strong Kappa-coefficient values compared with an independent assessor (AS), which indicated strong agreement and thus robustness of the results.

There was also an element of attrition bias within both the studies, whereby not all participants who indicated an interest in the radiographic survey received had their knees imaged. Despite the loss to follow-up, the sample sizes were on par with the sample size calculations for the radiographic survey and were sufficient to elicit a valid finding.

Misclassification bias may have occurred when determining the case-definitions for each outcome. The favourable approach for the self-reported outcomes would be to conduct a full clinical assessment of every participant (both footballers and controls), but this was not possible due to logistics (the football survey was UK-wide) and limited resources. However, validated instruments designed for questionnaire use, with input from footballers, patients and general public volunteers, helped improve the design of the questionnaires for clarity and usability.

Not all Football Clubs eligible agreed to participate in the study and not all footballers would have been on former player databases (limiting the size of the source population). However, recruitment of participants was through multiple routes: footballers via two professional organisations (the PFA and LMA) as well as Football Clubs and FPAs; and controls via twelve GP surgeries across the East Midlands region, which maximised the sample sizes recruited.

Furthermore, the response rates to the questionnaire surveys in both footballers and controls were relatively low. We are unable to ascertain whether the

responders differ to the non-responders (in terms of demographics) because such information was not available for the non-responders. This was due to data protection and confidentiality because the samples were recruited from databases held by external organisations. Further to this, recruitment of large sample sizes (for both footballers and controls), this was not sufficient to overcome sampling bias that may have resulted.

Following the analysis comparing participants (footballers and controls) who responded to the questionnaire, and had an x-ray or did not have an x-ray, knee injury frequency was significantly different between the populations. Participants who had sustained at least one knee injury were more likely to consent to undergoing an x-ray compared to those who had not.

Extrapolating this finding, we can predicted that participants who did not respond were less likely to have a knee injury (or consequences, for example KOA) and thus an inherent caveat to this study may be the overestimation of the prevalence and risk findings. To determine whether this held true, however, analysis of non-responder demographics is required. Both the footballer and control cohorts, however, had large attrition rates, as the majority of questionnaire responders did not undergo radiographic assessment. This suggests, although there were systematic differences in terms of certain risk factors, the attrition rate from the questionnaire survey to the radiographic assessment may account for this.

Controls were from a region of the UK (East Midlands) that was formerly a major region for coal mining, which is an established risk factor for KOA in men. However, such regional biases would be expected result in a higher

prevalence of KOA (rather than lower), which demonstrates the increased risk in footballers even more profoundly.

The use of plain film radiographs to determine structural change of RKOA is the widely accepted gold standard in clinical practice. However, they are insensitive to soft tissue and other changes indicative of early KOA, better assessed by other techniques such as MRI. Although this may underestimate the prevalence of structural KOA, the logistics and resources required were beyond the remit for this study.

This study included male footballers only. The female professional game is more limited, resulting in a smaller source population, and the demands of the sport vary between genders. Thus, these results are more accurate (internal validity) and generalizable (external validity) to wider retired male professional footballer population.

5.3 Future Work

To build on the efforts of this study, identifying future work is important. Firstly, carrying out a longitudinal observational study, either in the form of a cohort study or multiple subsequent cross-sectional studies (over a period). The advantages of a longitudinal study compared with the current case-control study, is that exposures are followed up over time and incidence as well as prevalence for the outcome of interest are determined. Conducting multiple cross-sectional studies is more cost effective and easier to implement logistically. Furthermore, there is likely to be less minimise attrition bias (loss to follow-up).

However, the advantage of a cohort longitudinal study is that surveillance of particular exposures, for example, injuries, may be set up. The advantages of this are two fold; firstly provide a baseline from which outcomes may be followed up over time, and secondly, aim to minimise or even prevent the negative consequences of the exposure itself. For example, within footballers, monitoring injury rates through surveillance would help to capture the frequency, type and duration of the injuries sustained and protocols implemented to reduce the effect of these.

An ideal scenario, given infinite resources, would be to conduct thoroughly a clinical enquiry for all the self-reported risk factors assessed in this study, namely KP, physician-diagnosed KOA and TKR. Implementation of this would require an independent observer to determine or confirm the reporting of such outcomes, further validating the response received participants. However, this is almost impossible in large-scale epidemiological studies, especially those conducted over a wide geographical area. Differences in training of such

observers and the regional variability that result are just two immediate drawbacks (aside from resources and logistics) that would make this unfeasible.

Using multiple approach to ascertain structural change would be more accurate. In addition to plain-film radiography used for this study, the use of MRI would help to detect both soft tissue structures and early changes of KOA. Although a previous study has used MRI, the sample size (27) is very small to determine any drawn any definitive conclusions.

Finally, taking this study design and implementing it across different countries where football is equally popular (for example, Germany, Italy and Spain) would provide comparisons across different nations. This would confirm whether the increased risk of KOA in footballers is generalizable, or specific to a UK population. Furthermore, conducting multi-regional studies will also help to ascertain specific regional risk factors.

Although this study has been conducted in footballers from the UK, the accuracy and reliability of the results (good internal validity) mean findings may be applicable to the wider football population (good external validity). This is despite the fact that both the source population and non-responders population demographics remain unknown, offset by a large sample size.

5.4 Overall Conclusions

This study is the first of its kind to combine a cross-sectional study with a nested case-control study to: (1) examine the prevalence of KP and KOA in professional footballers and (2) identify the risk factors that increase the predisposition to developing these outcomes.

The major findings of this study are:

1) Footballers report a prevalence of current knee pain (52.2%) almost twice as great as controls (26.9%) derived from the general population, which confers almost a two-times greater risk.

2) The prevalence of KP, RKOA and TKR is greater in footballers compared to controls across all age groups.

3) Footballers have a greater prevalence (64.0% v. 35.2%) and risk of RKOA (NLDA-defined). Although the definition for KL grade RKOA was more stringent than previous studies (KL$\geq$3), almost a third of footballers were still affected (28.7%). The risk of having RKOA varied between 2.14 times (NLDA) to 2.44 times (KL grade) greater in footballers compared to the controls.

4) Footballers also reported almost three times greater prevalence of having a TKR (11.1% v. 3.8%) and radiographic CC (24.3% v 8.8%) compared to controls, which is reflective of an increased risk of RKOA.

5) Knee injuries account for the majority, but not all of the risk of KOA (all outcome measures: KP, RKOA and TKR) in footballers compared to the controls, suggesting playing the sport itself is a risk.

6) Within footballers, significant knee injury and its consequences (surgical intervention and intra-articular injections) were all (independently) significantly associated all KOA outcomes (KP, RKOA and TKR).

7) Other risk factors significantly associated with KOA outcomes, within footballers only, were identified.

    a. Risk factors associated with KP: increasing weight, having a family history of OA (knee, hip or hand) and having gout

    b. Risk factors associated with RKOA: increasing age, family KOA, having gout and CC. Footballers also had an increased risk of RKOA for every 1000 hours they trained, 100 matches they played and every additional year they played the sport.

    c. Risk factors associated with TKR: increasing age, obesity, nodal OA and having gout. A longer football duration resulted in a reduced risk of having a TKR, possibly due to survival of the fittest phenomenon.

8) Football governing bodies should strongly note these findings and implement approaches to minimise the risk of injury in footballers, thereby reducing possible long-term consequences (for example, KOA) following retirement.

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Appendices

A. The Football Study Questionnaire Survey

A.1 Questionnaire

Osteoarthritis Risk in Retired Professional Footballers

The risk of joint injury in football players is increased due to several risk factors. We want to find out about these risk factors for knee osteoarthritis in retired professional football players.

We would be very grateful if you could take the time to complete this questionnaire. **Your responses are valued and are vitally important to this project.** It takes approximately 25 minutes to complete.

Please ensure that **you** complete this questionnaire and do not pass it on for someone else to complete. **All answers are strictly confidential**. Please return this questionnaire in the pre-paid envelope provided.

Please ring Dr Gwen Fernandes on (0115) 823-1679 if you have any questions.

Thank you for your assistance with this important area of research.

SECTION 1 – About Yourself

1. Date of Birth:

D	D		M	M		Y	Y	Y	Y
Day			*Month*			*Year*			

2. Height: *Please complete one box only*

☐ feet ☐☐ inches **OR** ☐☐☐ centimetres

3. Weight: *Please complete one box only*

☐☐ stones ☐☐ pounds **OR** ☐☐☐ kilograms

4. How much did you approximately weigh **in your 20's**?

☐☐ stones ☐☐ pounds **OR** ☐☐☐ kilograms

5. Nationality: _____

6. Which ethnic group best describes you?

☐ White-Caucasian ☐ White-Hispanic

☐ Black-African ☐ Black-Caribbean

☐ Chinese ☐ Indian

☐ Other, *please specify*: _____

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SECTION 2 – About Your Career

7. At what **age** did you start playing **competitive** team football?

   _____ Years old

8. At what **age** did you start playing football **professionally** (i.e. signed a contract)?

   _____ Years old

9. Please state the time that you played professional football *(e.g. 1986 – 1999):*

   From _____ to _____

10. Which league did you play in for the **majority** (most matches) of your professional **career**?

    _____

11. Please could you indicate any **other leagues** you have played in during your professional career.

    ☐ Premier League
    ☐ Championship
    ☐ League One
    ☐ League Two
    ☐ Old Division 1 (pre-1992)
    ☐ First Division (1992-2004)
    ☐ Old Division 2 (pre-1992)
    ☐ Other, *please specify*:

    _____

12. Approximately how many matches (playing for <u>at least half the match</u>) did you take part in during your professional career (please include first team, reserve and international games) *(e.g. 100 matches)*

    _____ matches

13. What position did you **mainly** play during your professional career?
    Please tick one box only.

    ☐ Goalkeeper ☐ Defender ☐ Midfielder ☐ Forward

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14. When playing football, are you generally:

☐ Right-footed ☐ Left-footed ☐ Equally proficient

15. On average, how many **hours per day** and how many **days per week** did you spend **training** (during your professional career)?

_____ Hours per day **AND** _____ Days per week

16. Please indicate your reason(s) for retiring from professional football?
Please tick all that apply.

☐ Football-related Injury, *please specify*: _____

☐ Age

☐ Chronic Knee Pain

☐ Contract Not Renewed

☐ Other, *please specify*: _____

17. In addition to playing football professionally, please list six other main (longest duration) occupations you have had. State whether the occupation was full time (F) or part time (P)* and the number of years spent in each occupation.

List of Occupations	**Full time** (F) or **Part time** (P)	**Time Period** *(e.g. 3 years)*
1)		
2)		
3)		
4)		
5)		
6)		

***Full time:** More than 20 hours per week; **Part time:** 20 hours or less per week*

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SECTION 3 – About Your Current Health

We would now like to ask you some questions about your current health.

18. Have you **ever** been diagnosed by your doctor as having had any of the following? *Please tick all that apply. If none, please tick Not Applicable.*

☐ Diabetes ☐ High Blood Pressure ☐ Heart Attack ☐ Cancer

☐ Depression ☐ Rheumatoid Arthritis ☐ Gout ☐ Fibromyalgia

☐ Other, *please specify:* ☐ Not Applicable

_____

19. Please list **all your current medication** including those prescribed by your doctor and those bought yourself over the counter (e.g. paracetamol, vitamin supplements, glucosamine, etc.). State the date you started taking each medication.

Name of Medicine ……Date Started _____

Name of Medicine ……Date Started _____

Name of Medicine ……Date Started _____

Name of Medicine ……Date Started _____

Name of Medicine ……Date Started _____

Name of Medicine ……Date Started _____

Name of Medicine ……Date Started _____

Name of Medicine ……Date Started _____

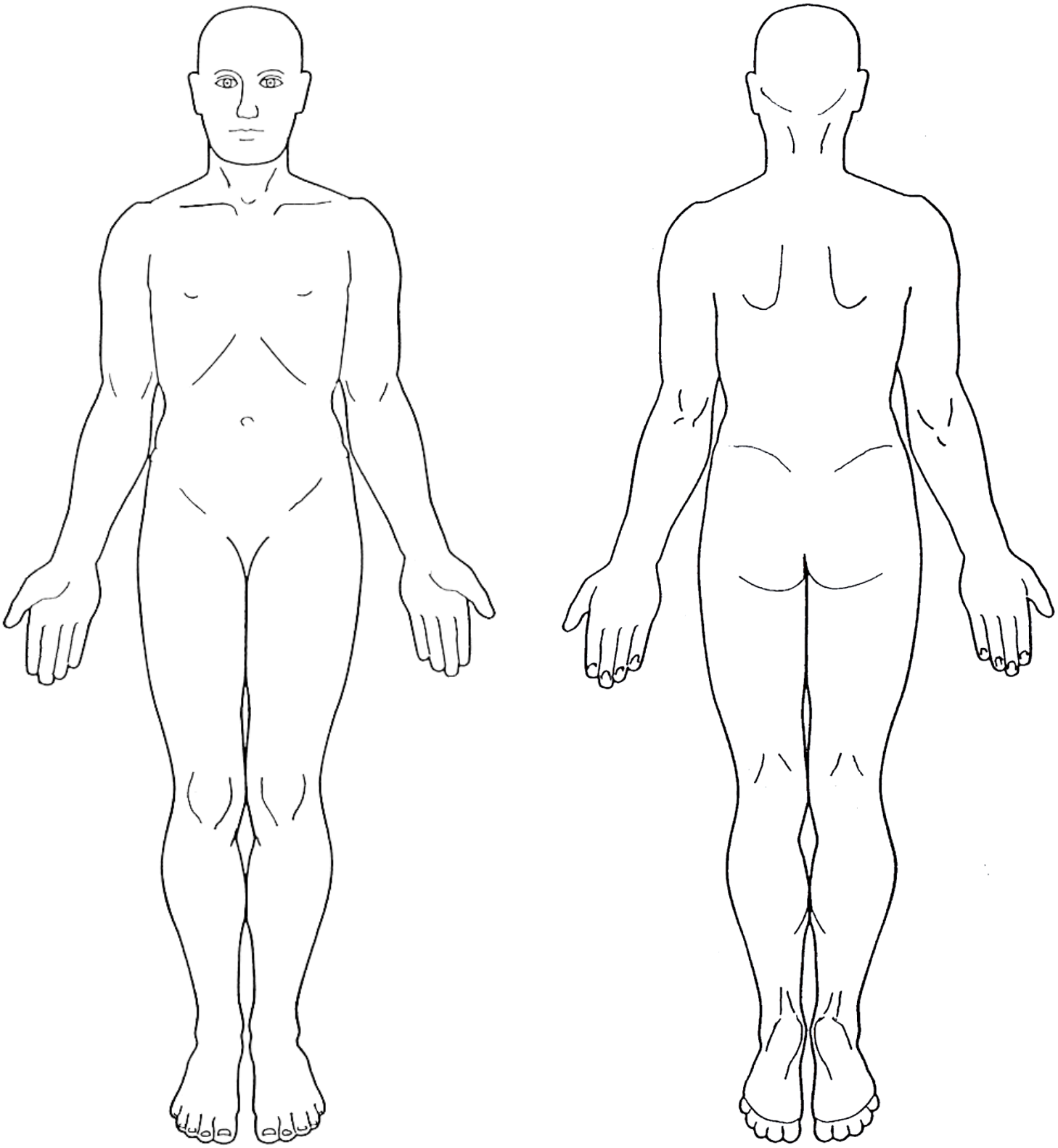
Name of Medicine ……Date Started _____

Name of Medicine ……Date Started _____

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20. Please *shade* in the diagram below to indicate where you have suffered **any pain for most days in the <u>previous month</u>.** By pain we also mean aching, discomfort and/or stiffness. Please <u>do not</u> include pain due to feverish illness such as the flu.

If you **have not** had any body pain that has lasted for most days in the previous month*, please <u>tick</u> this box***.**	☐



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SECTION 4 – About Your Knees

21. Have you **ever** had significant pain in or around your knees for **most days of a one month period**?

☐ Yes

☐ No *(Please go to **Question 23**)*

22. At what age did you first notice this type of knee pain?

_____ years old

23. Have you **ever** had significant pain in or around your knees for **most days over a three month period?**

☐ Yes

☐ No *(Please go to **Question 27**, page 8)*

24. At what age did you first notice this type of knee pain?

_____ years old

25. Have you ever been diagnosed with **Osteoarthritis** in your knees by a physician *(for example, your GP)?* If yes, please state how old you were when diagnosed.

☐ Yes, _____ years old

☐ No

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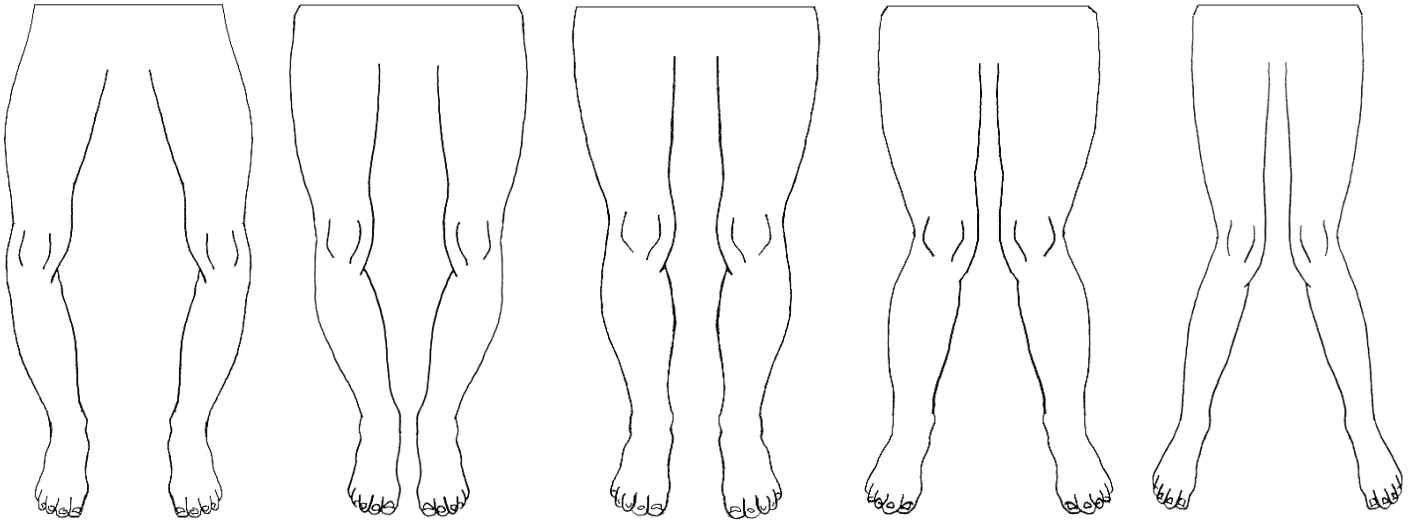
26. Please could you indicate the knee(s) in which you experienced **significant pain** and at what age(s) it affected you? *By significant pain, we mean pain you have had for most days for **at least a three month period.** Please tick all that apply.*

Age (years)	Right Knee Pain	Left Knee Pain
10 – 15	☐	☐
16 – 20	☐	☐
21 – 30	☐	☐
31 – 40	☐	☐
41 – 50	☐	☐
51 – 60	☐	☐
61 – 70	☐	☐
71 – 80	☐	☐
81 – 90	☐	☐

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27. We are interested in the angle of your legs (that is, straight legs, bow-legged or knock knees) as this may have relevance to the development of osteoarthritis.

Please look at your legs **whilst standing** (preferably in front of a mirror) and then indicate the angle of your legs based on the diagrams below.



A Very Bow Legged	**B** Bow Legged	**C** Straight	**D** Knocked-Knee	**E** Very Knocked-Knee

a) Which diagram best shows the **current** angle of **each** of your legs?

Right Leg	☐	**A**	☐	**B**	☐	**C**	☐	**D**	☐ **E**
Left Leg	☐	**A**	☐	**B**	☐	**C**	☐	**D**	☐ **E**

b) Which diagram do **you think** best shows the angle of **each** of your legs **<u>in your 20s</u>?**

Right Leg	☐	**A**	☐	**B**	☐	**C**	☐	**D**	☐ **E**
Left Leg	☐	**A**	☐	**B**	☐	**C**	☐	**D**	☐ **E**

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SECTION 5 – Injuries and Surgeries to your Knees

28. Have you ever had a **significant** football-related **injury** to your knees? *We describe a significant injury as one which caused you pain for **most days for at least a three month period** and resulted in an absence from all training and matches during this time*.

☐ Yes

☐ No *(Please go to **Question 31,** page 10)*

29. Please state the **total** number of significant football related **injuries** you have had through your professional football career in both your right and left knees.

Right Knee: _____ injuries **Left Knee:** _____ injuries

30. If you **have** suffered a significant football related injury *(e.g. anterior cruciate ligament (ACL) rupture, cartilage injury, fracture)*, please could you state the type of injury, which knee was affected and approximately how old you were when the injury occurred.

Type of Football Injury	Right Knee	Left Knee	Age when Occurred
1)	☐	☐	
2)	☐	☐	
3)	☐	☐	
4)	☐	☐	
5)	☐	☐	
6)	☐	☐	

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31. Similarly, if you **have** suffered a significant **NON-football** related injury, please could you state the type of injury, which knee was affected and approximately how old you were when the injury occurred.

Type of Non-Football Injury	Right Knee	Left Knee	Age when Occurred
1)	☐	☐	
2)	☐	☐	
3)	☐	☐	
4)	☐	☐	

32. Have you **ever** had any injections into your knees?

☐ Yes ☐ No *(Please go to **Question 35,** page 11)*

33. If you **have had injections** into your knees, please indicate which injection(s) you have had into each knee. *Please tick <u>all</u> that apply*.

Type of Injection	Right Knee	Left Knee
Cortisone (Steroid)	☐	☐
Anaesthetic (Lignocaine)	☐	☐
Don't Know	☐	☐
Other, *please specify* _____	☐	☐

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34. We would now like to know the greatest number of injections you have had into each of your knees.

a) What is the greatest number of injections you had into each knee in any **season.**

Right Knee: _____ injections **Left Knee:** _____ injections

b) What is the total number of injections you have had into each knee over the course of your **professional career.**

Right Knee: _____ injections **Left Knee:** _____ injections

35. Have you ever had surgery to your knees?

☐ Yes ☐ No *(Please go to **Question 37**, page 12)*

36. If you **have had any surgery** *(e.g. knee joint replacement, cartilage removed or key-hole surgery)*, please state what type of procedure you had, which knee was affected and how old you were when the surgery occurred.

Type of Surgery	Right Knee	Left Knee	Age when Occurred
1)	☐	☐	
2)	☐	☐	
3)	☐	☐	
4)	☐	☐	
5)	☐	☐	
6)	☐	☐	

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SECTION 6 – About Your Hands

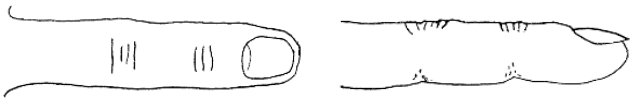
We can sometimes estimate the risk of knee osteoarthritis from your hands. Therefore, we would like to know more about your hands.

37. Are you generally:

☐ Right-handed ☐ Left-handed ☐ Equally proficient

A finger **node** is a firm, bobbly swelling on the back of the finger joint. Finger nodes sometimes relate to arthritis at the hand and other joints. They look like the examples below.

A finger **without** nodes:



A finger **with** nodes:



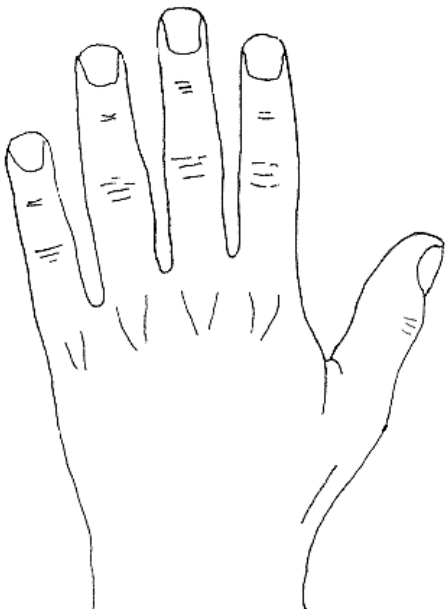
Please could you look at your hands and then answer the following questions.

38. Do you think you have any **nodes/swellings** on your hands?

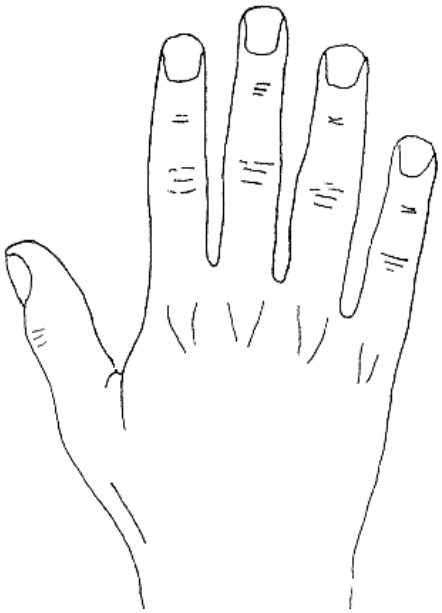
☐ Yes ☐ No *(Please go to **Question 40,** page 13)*

39. If yes, for each hand please circle the finger joint(s) where you have these nodes. *Please circle ALL the joints that are affected.*

LEFT



RIGHT

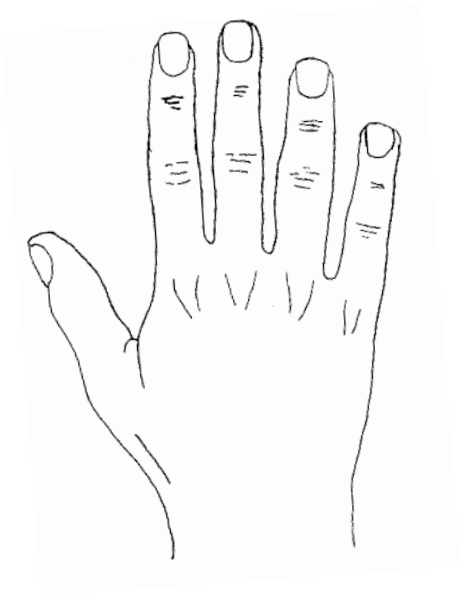
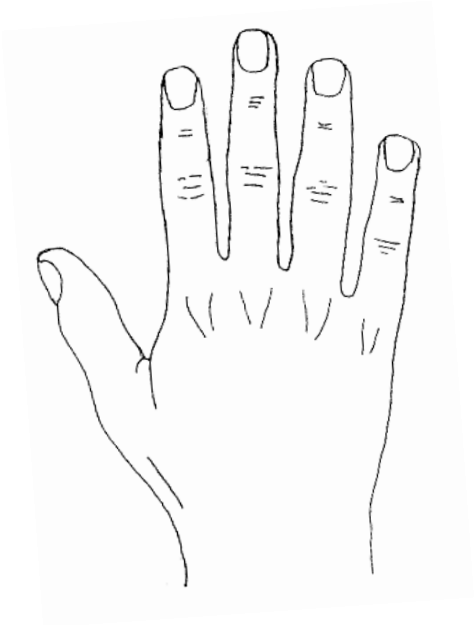
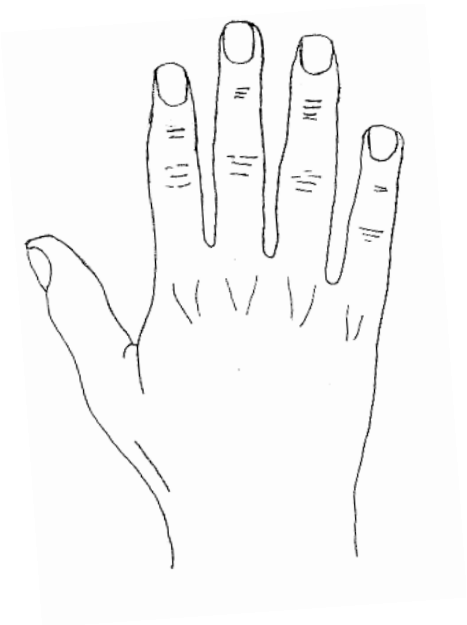


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40. The 2D:4D ratio is the ratio between the index and ring finger. The length of these two fingers has been associated with competitiveness, athleticism and more recently knee osteoarthritis.

Please look at your **right hand** with your fingers straight in line with your forearm. Ignore your middle finger and focus only on your right index and ring fingers.

a) Indicate by ticking one of the three diagrams below which one **best** shows the length of your right index finger in comparison to your right ring finger.
Please tick the appropriate box.

Index finger is longer than ring finger	**Both fingers are of equal length**	**Ring finger is longer than index finger**
		
☐	☐	☐

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41. Please could you indicate whether any member of your immediate family (parents and/or siblings) has been diagnosed with **osteoarthritis** by a medical professional? *Please tick all that apply*.

Family Member	Hands (Finger Nodes)	Knee	Hip
Mother	☐	☐	☐
Father	☐	☐	☐
Sibling	☐	☐	☐
Sibling	☐	☐	☐
Sibling	☐	☐	☐

42. Please could you also indicate whether any member of your immediate family (parents and/or siblings) has had knee or hip replacement surgery? *Please tick all that apply.*

Family Member	Knee Joint Replacement	Hip Joint Replacement
Mother	☐	☐
Father	☐	☐
Sibling	☐	☐
Sibling	☐	☐
Sibling	☐	☐

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SECTION 7 – About Your Quality of Life

The following questions are regarding your health-related quality of life. We are able to assess the impact any long-term conditions may have on your day-to-day life.

The questions below have been adapted from a standardised and validated questionnaire. ***Please tick one box for every question***

43. In general, would you say your health currently is:

☐ *Excellent* ☐ *Very Good* ☐ *Good* ☐ *Fair* ☐ *Poor*

44. **Compared to one year ago**, how would you rate your general health **now**?

Much better now than one year go	*Somewhat better now than one year ago*	*About the same as one year ago*	*Somewhat worse now than one year ago*	*Much worse now than one year ago*
☐	☐	☐	☐	☐

45. The following questions are about activities you may do during a typical day. **Does your health limit you** in these activities? If so, how much?

	Yes, Limited <u>a lot</u>	*Yes, Limited <u>a little</u>*	*Not limited at all*
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
Lifting or carrying groceries	☐	☐	☐
Climbing **several** flights of stairs	☐	☐	☐
Climbing **one** flight of stairs	☐	☐	☐
Bending, kneeling, or stooping	☐	☐	☐
Walking **more than a mile**	☐	☐	☐

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	Yes, Limited <u>a lot</u>	*Yes, Limited <u>a little</u>*	*Not, limited at all*
Walking **half a mile**	☐	☐	☐
Walking **100 yards** *(approximately 100 metres)*	☐	☐	☐
Bathing and dressing yourself	☐	☐	☐

46. During the **past month,** have you had any of the following problems with work or other regular daily activities **as a result of your physical health?**

	Yes	*No*
Cut down on the **amount of time** you spent on work or other activities	☐	☐
Accomplished less than you would like	☐	☐
Were **limited** in the **kind** of work or other activities	☐	☐
Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐	☐

47. During the **past month,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (e.g. feeling depressed or anxious)?

	Yes	*No*
Cut down on the **amount of time** you spent on work or other activities	☐	☐
Accomplished less than you would like	☐	☐
Didn't do work or other activities as **carefully** as usual	☐	☐

48. During the **past month,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	*Slightly*	*Moderately*	*Quite a bit*	*Extremely*
☐	☐	☐	☐	☐

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49. How much **physical** pain have you had during the **past month?**

None	*Very Mild*	*Mild*	*Moderate*	*Severe*	*Very Severe*
☐	☐	☐	☐	☐	☐

50. During the **past month** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	*Slightly*	*Moderately*	*Quite a bit*	*Extremely*
☐	☐	☐	☐	☐

51. These next questions are about how you feel and how things have been with you **during the past month.** Please give the **one** answer that is closest to the way you have been feeling for **each** item.

How much time **during the last month…**

	All of the time	*Most of the time*	*A good bit of the time*	*Some of the time*	*A little of the time*	*None of the time*
Did you feel full of life?	☐	☐	☐	☐	☐	☐
Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
Did you feel worn out?	☐	☐	☐	☐	☐	☐
Have you been a happy person?	☐	☐	☐	☐	☐	☐
Did you feel tired?	☐	☐	☐	☐	☐	☐

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52. During the **past month**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives etc.)

All of the time	*Most of the time*	*Some of the time*	*A little of the time*	*None of the time*
☐	☐	☐	☐	☐

53. How **TRUE** or **FALSE** is **each** of the following statements for you?

	Definitely True	*Mostly True*	*Don't know*	*Mostly False*	*Definitely False*
I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
I am as healthy as anybody I know	☐	☐	☐	☐	☐
I expect my health to get worse	☐	☐	☐	☐	☐
My health is excellent	☐	☐	☐	☐	☐

(Please turn over for the final page)

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Thank you very much for taking the time to complete this questionnaire.

Please ensure you have **fully** completed it before returning it.

We would like to emphasise that your contact details and responses will be kept **completely confidential** and will only be seen by the direct study team (Academic Rheumatology, University Of Nottingham).

You will be **anonymised** in all further analysis.

We would like to invite a sample of respondents to participate in the second stage of this study. This stage will take place at a medical centre not far from you and will involve x-rays of your knees so that we can study any structural changes of osteoarthritis.

Please tick this box if you are interested ☐

If you are suitable for the study, you will receive an information sheet about this stage of the study. You will then be able to decide whether you would like to participate.

Academic Rheumatology may also wish to contact you regarding future studies related to professional football, osteoarthritis and general health.

Please tick this box if you are interested ☐

Please complete your details below, in order for us to be able to contact you:

Full Name: _____

Address: _____

_____

_____

Best Daytime Phone Number: _____

If you are happy for us to email you, please provide your email address below:

Email address: _____ @ _____

Thank you for your time

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A.2 Cover Letter – Sir Trevor Brooking (The FA)

Osteoarthritis Risk in Professional Footballers Study

6th February 2014

Osteoarthritis (OA) is by far the most common form of arthritis. The knee joint is commonly affected and knee OA is a leading cause of pain and disability worldwide. Symptoms range from disturbed sleep to not being able to walk far or get into and out of a car without wincing. This can have a major effect on a person's quality of life. There is no cure and although medical treatments may improve symptoms many people eventually require knee replacement surgery.

Professional footballers undergo long periods of intense physical training to earn a living. Their knees are placed under repetitive strain and are prone to injury and these stresses may lead to the development of knee OA. As a former professional footballer, I know first-hand of this. A few years ago I had a knee replacement procedure for my left knee, and have benefited immensely from that successful operation in my daily work commitments since. Unfortunately, there is very little research on this important topic. It is still unclear as to how much of an increased risk footballers may be at of developing knee OA because of their profession.

This nation-wide research project is the first study of its kind. It is funded by Arthritis Research UK and FIFA and is supported by The FA, The PFA and XPro. The research team need your help to find out how common OA is among professional footballers compared to the general population. We know some of the risk factors for developing knee OA such as direct knee injury, being slightly bow-legged or being overweight. However, we need to do more to comprehensively document all risk factors and you can directly help by taking part in this research. The attached questionnaire is quick, easy to follow and will impact upon the way footballers train, practice and play.

I fully support this nation-wide study and urge you to do the same. Even if you do not have knee pain or knee OA, your response is just as important and vital to the research. It will be of immense benefit to the current football community and would help direct the game for future generations of footballers. Thank you for your time and effort.

My Best Wishes,



Sir Trevor Brooking CBE



A.3 Cover Letter – Gordon Taylor (The PFA)

20 Oxford Court,
Bishopsgate,
Manchester
M2 3WQ

Telephone: 0161 236 0575
Facsimile: 0161 228 7229
Email: info@thepfa.co.uk
Website: www.thepfa.com

PROFESSIONAL FOOTBALLERS' ASSOCIATION

Chief Executive: Gordon Taylor OBE, BSc (Econ), Hon DArt, Hon MA, FRSA

Ref: GT/ZH/2058

11th March, 2015

Dear Club Secretary,

Re: Study - Risk Of Osteoarthritis In Professional Footballers

I am writing regarding a study on the Risk of Osteoarthritis in Professional Footballers which is being funded by Arthritis Research UK with additional support and funding from FIFA, the FA, the PFA and Spire Healthcare.

Although there are many benefits from participating in the world's most popular sport of football such as improving levels of fitness, health, strength and endurance, one of the downsides of playing football, particularly at professional level, is the susceptibility to suffer from Osteoarthritis.

Osteoarthritis is the most common form of arthritis and can cause serious pain, functional limitations and affect a person's quality of life. Professional footballers undergo long periods of intense physical training to earn a living. Their knees are placed under repetitive strain and are prone to injury.

Often, these stresses can lead to the development of knee osteoarthritis. The Study Team researching the 'Risk of Osteoarthritis in Professional Footballers' is based at the Department of Academic Rheumatology and the Arthritis Research UK Centre for Sports, Exercise and Osteoarthritis (University of Nottingham). The Team have been actively working with football clubs and Football Associations across the country to determine the risk of knee osteoarthritis in later life that results from playing professional football as a young man. They are undertaking a questionnaire study of all retired professional footballers in the United Kingdom and subsequently undertaking knee x-rays on a sample of questionnaire responders.

Hopefully, the Study will offer a better understanding of the effects of osteoarthritis in former professional footballers and will lead to the implementation of a number of preventative measures for the benefit of players in the future.

The Study Team would like to send the questionnaire to as many retired professional male footballers as possible, who are now over the age of 40, and who have previously held a full-time contract with a professional football club. The Study Team can arrange to deliver questionnaires that are pre-packed and ready to be posted to the ex-players. All printing and postage costs including a pre-paid return envelope will be fully paid for by the project. If you have a list or database of ex-players who would qualify for this Study and would be keen and willing to share their experiences, we at the PFA, would be very grateful for your support and assistance in sending the questionnaires to your former players.

We look forward to hearing from you and working together to make this project a success. If you would like any further information or to participate, please contact the Study Team (arthritisfootball@nottingham.ac.uk) or direct telephone for Dr Gwen Fernandes and/or Mr Sanjay Parekh on 0115 823 1679 / 823 1759.

Kind regards.

Yours faithfully,



GORDON TAYLOR OBE
Chief Executive

B. The KPIC Study Questionnaire Survey

B.1 Questionnaire

Nottingham University Hospitals NHS
NHS Trust

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Knee Pain and Related Health

Knee pain, often due to osteoarthritis, is a very common problem affecting 1 in 4 people over the age of 40. We want to understand why some people are more affected than others and the risk factors and health problems associated with knee pain. We would therefore be very grateful if you would take the time to complete this questionnaire, **regardless of whether or not you have knee pain**. We hope you find it interesting. It takes approximately 30 minutes to complete. Most of the questions just require a tick in a box, but for others, clear instructions are given.

We would also be grateful if you could confirm, on the last page of the questionnaire, whether you would be willing to complete a follow-up questionnaire in approximately one year's time and also whether you would like to receive information about further research which will involve a single visit to the Nottingham City Hospital, clinical assessments and an x-ray.

Please return this questionnaire, in the pre-paid envelope **(no stamp required)** to Academic Rheumatology at the Nottingham City Hospital as soon as possible.

Your answers are strictly confidential

If you have any questions or require any assistance completing the questionnaire please telephone: Nadia Frowd on 0115-8231676

Thank you for your assistance with this important area of research.

Chief Investigator – Professor Michael Doherty

Approved by: Nottingham 2 Research Ethics Committee

Funded by: Arthritis Research UK
Providing answers today and tomorrow

Office use only SURGERY ID

SECTION 1 – About Yourself

1. What is your Date of Birth?

D D Day M M Month Y Y Y Y Year

2. What Sex are you?

☐ Male ☐ Female

3. What is your Height? *Please complete one box only*

☐ Feet ☐☐ inches **OR** ☐☐☐ centimetres

4. What is your Weight? *Please complete one box only*

☐☐ stones ☐☐ pounds **OR** ☐☐☐ kilograms

5. Please can you list all **main occupations** you have had, state whether the occupation was full time (F) or part time (P)* and the number of years spent in each occupation.

List of Occupations	**Full time** (F) or **Part time** (P)	**Time Period** *(e.g. 3 years)*
1)		
2)		
3)		
4)		
5)		
6)		
7)		

***Full time:** *More than 20 hours per week*
***Part time:** *20 hours or less per week*

SECTION 2: About Your Medical History and Medication

6. Have you **ever** been diagnosed by your doctor as having any of the following?

- ☐ High Cholesterol
- ☐ Diabetes
- ☐ Heart Attack / Angina
- ☐ Stroke
- ☐ Hypertension / High Blood Pressure
- ☐ Irritable Bowel Syndrome
- ☐ Osteoarthritis of the Hip
- ☐ Fibromyalgia
- ☐ Osteoarthritis of the Knee
- ☐ Chronic Fatigue Syndrome
- ☐ Cancer *Type:* _____

Other medical conditions not listed above: _____

_____

7. Have you broken either of your legs **in the last 10 years**?

☐ Yes ☐ No

If yes, at what age did this break occur? _____ *years old*

If yes, which bone did you break? _____

8. Have you **ever** suffered significant injury to either of your knees?

☐ Yes, *please specify:* _____ ☐ No

If yes, at what age did you suffer the knee injury? _____ *years old*

Did this knee injury require that you see a doctor or go to a hospital for treatment?

☐ Yes ☐ No

9. Please list **all** your **current medication** including those **prescribed by your doctor** and those you **bought yourself** over the counter (*please **include any hormonal medication** such as oestrogen supplements, **vitamin supplements and alternative medicines**). Please indicate the approximate number of months or years you have taken each of these.*

Name of Medication	Duration	
	Years	Months
1)		
2)		
3)		
4)		
5)		
6)		
7)		
8)		
9)		
10)		

10. Have you ever taken any **"statins"** medications for lowering your cholesterol and lipids? Examples of statins are Atorvastatin (also known as Lipitor), Simvastatin (also known as Zocor), and Rosuvastatin (also known as Crestor)

☐ Yes ☐ No

Are you still taking a statin?

☐ Yes ☐ No

For approximately how many years have you taken a statin? _____*years*

SECTION 3: About Your Knee Pain

11. Have you **ever** had pain in or around a knee on most days for **at least a month**?

☐ Yes ☐ No ***(if No, please go to Section 4)***

If yes, at what age did you first notice this type of knee pain? _____ *years old*

12. Have you had knee pain on most days of **this past month**?

☐ Yes ☐ No

13. Has your current knee pain lasted **more than 3 months**?

☐ Yes ☐ No

14. Since it has started, do you think the severity of your knee pain has overall…

☐ Greatly Improved ☐ Slightly Improved ☐ Remained the Same ☐ Worsened

15. Which knee(s) do you / did you experience the pain in?

☐ Right ☐ Left ☐ Both

If both, which overall is the worst knee?

☐ Right ☐ Left ☐ Equal

16. Have you ever had any injections into your knee?

☐ Yes ☐ No

17. If you answered "**yes**", was it:

☐ Steroid Injection ☐ Hyaluronic Acid Injection ☐ Don't Know

18. Have you **ever** had an operation on either of your knees?

☐ Yes ☐ No

If yes, what type of operation did you undergo? *(If you did not undergo one of the specific operations then please leave the related boxes blank)*

Type of Operation	**Which Knee?** (Right, Left, Both?)	**Age at Time of Operation** *(years)*
Arthroscopy / Telescope / Keyhole		
Ligament Repair		
Meniscus or Cartilage Removal		
Joint Replacement		
Other, *please specify* _____		

19. Have you **ever** consulted a healthcare professional (eg your GP, a hospital specialist, a physiotherapist etc) about your knee pain?

☐ Yes ☐ No

20. Approximately how many different things have you tried for your knee pain (including things like drugs, exercise, changes to diet, footwear modifications etc)? Please include <u>everything</u> you have tried, regardless of whether or not it was recommended by a healthcare professional.

☐

21. Which of the various things you have tried has helped your knee pain the most?

_____

22. **The following questions are to be answered by people who have knee pain.**

We want you to tell us about the knee **where you have the greatest pain**. To get a better sense of the different types of knee pain you may experience, we would like to ask you about any "constant pain" (pain you have all the time) separately from any pain that you may experience less often, that is ''intermittent'' (pain that comes and goes).

We appreciate that some of these questions may seem a bit repetitive but they have been shown to provide important information about knee pain. **Please answer ALL the questions**.

For each of the following questions please select the answer that best describes **on average your <u>constant knee pain</u> in the PAST WEEK.**

	Not at all	**Mildly**	**Moderately**	**Severely**	**Extremely**
a. In the past week, how intense has your CONSTANT KNEE PAIN been?	☐	☐	☐	☐	☐
b. In the past week, how much has your CONSTANT KNEE PAIN affected your sleep?	☐	☐	☐	☐	☐
c. In the past week, how much has your CONSTANT KNEE PAIN affected your overall quality of life?	☐	☐	☐	☐	☐
d. In the past week, how frustrated or annoyed have you been by your CONSTANT KNEE PAIN?	☐	☐	☐	☐	☐
e. In the past week, how upset or worried have you been by your CONSTANT KNEE PAIN?	☐	☐	☐	☐	☐

23. Now please select the response that best describes **on average your knee pain that comes and goes in the PAST WEEK**

	Not at all	Mildly	Moderately	Severely	Extremely
a. In the past week, how intense has your **knee pain that comes and goes** been?	☐	☐	☐	☐	☐
b. In the past week, how much has your **knee pain that comes and goes** affected your sleep?	☐	☐	☐	☐	☐
c. In the past week, how much has your **knee pain that comes and goes** affected your overall quality of life?	☐	☐	☐	☐	☐
d. In the past week, how frustrated or annoyed have you been by your **knee pain that comes and goes**?	☐	☐	☐	☐	☐
e. In the past week, how upset or worried have you been by your **knee pain that comes and goes**?	☐	☐	☐	☐	☐
f. In the past week, how frequently has this **knee pain that comes and goes** occurred?	☐	☐	☐	☐	☐

We now want to ask you about **any kind of knee pain** that you may be currently experiencing

24. **Over the past month**, in your most painful knee, does pain **run up or down** your leg?

☐ Yes ☐ No

Please tell us about the **intensity of discomfort** you experience in or around your **most painful knee.**

25. How would you rate your most painful knee pain on a 0-10 scale at the present time, that is **right now**, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (Please circle only ONE number)

No Pain **Pain as bad as it could be**

0	1	2	3	4	5	6	7	8	9	10

26. In the **past month**, how intense was your **'worst knee pain'** rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (Circle only ONE number)

No Pain **Pain as bad as it could be**

0	1	2	3	4	5	6	7	8	9	10

27. In the **past month**, on **average**, how **intense** was the pain in your **most painful knee** rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (That is, your usual pain at times you were experiencing pain.) (Circle only ONE number)

No Pain **Pain as bad as it could be**

0	1	2	3	4	5	6	7	8	9	10

28. This next question is on the pattern of your pain in your **most painful knee.** Which of the 4 different options below is the one that best describes the pattern of your worst knee pain over the past month? (Tick <u>one</u> box)

☐  Persistent pain with slight fluctuations

☐  Persistent pain with pain attacks

☐  Pain attacks without pain between them

☐  Pain attacks with pain between them

29. Please select the response that best describes the **<u>type of pain</u> in your most painful** knee over the **past month**. Please do not leave any questions blank and tick one box.

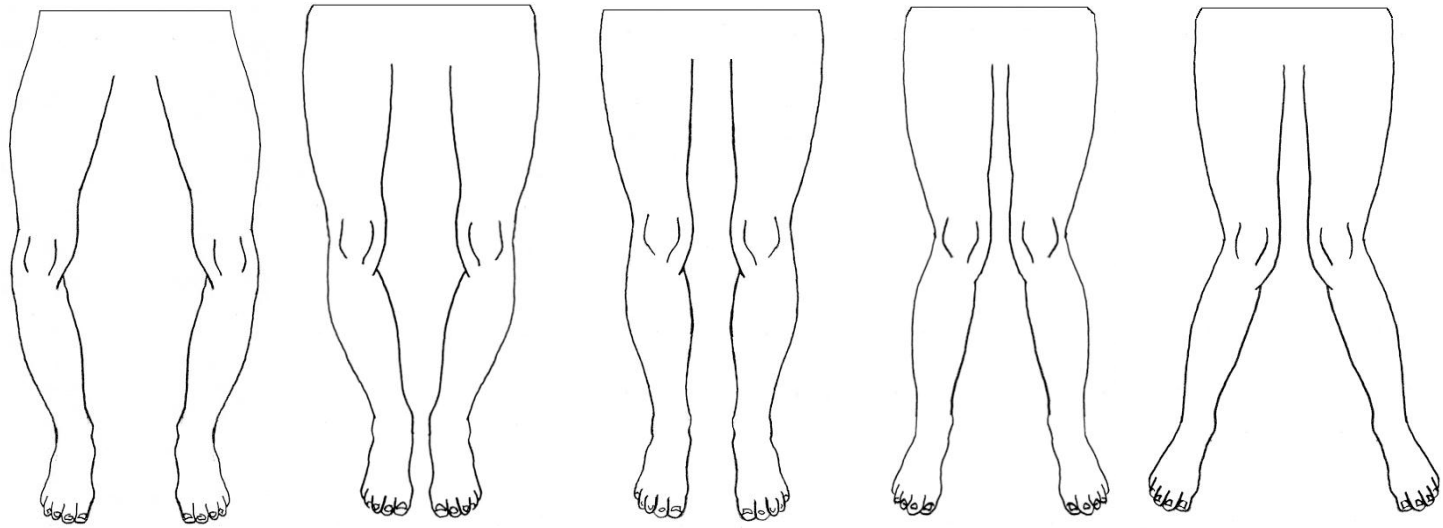
	Never	**Hardly Noticed**	**Slightly**	**Moderate**	**Strongly**	**Very Strongly**
a. Do you suffer from a <u>burning</u> sensation (eg stinging nettles) in or around your most painful knee?	☐	☐	☐	☐	☐	☐
b. Do you have a <u>tingling or prickling</u> sensation in the area of your most painful knee 'pain' (eg like crawling ants or electrical tingling?)	☐	☐	☐	☐	☐	☐
c. Is <u>light touching</u> (clothing, a blanket) in this area painful?	☐	☐	☐	☐	☐	☐
d. Do you have <u>sudden</u> pain attacks in the area of your most painful knee 'pain', like electrical shocks?	☐	☐	☐	☐	☐	☐
e. Is <u>cold or heat</u> (bath water) in this area occasionally painful?	☐	☐	☐	☐	☐	☐
f. Do you suffer from a sensation of <u>numbness</u> in or around your most painful knee?	☐	☐	☐	☐	☐	☐
g. Does slight <u>pressure</u> in this area, (e.g. with a finger), trigger pain?	☐	☐	☐	☐	☐	☐

SECTION 4: About the Angle of your Legs

30. We are interested in the angle of your legs (that is, straight legs, bow-legged or knock knees) as this may have relevance to the development of osteoarthritis.

Please look at your legs **whilst standing** (preferably in front of a mirror) and then indicate the angle of your legs based on the diagrams below.

Most people will have similar angulations in their left and right knees, but in a few people these angulations may differ. We therefore would like you to score your knees separately.



A Very bow legged	**B** Bow legged	**C** Straight	**D** Knocked-knee	**E** Very knocked-knee

a) Which diagram best shows the **current** angle of **each** of your legs?

Right Leg	☐	**A**	☐	**B**	☐	**C**	☐	**D**	☐ **E**
Left Leg	☐	**A**	☐	**B**	☐	**C**	☐	**D**	☐ **E**

b) Which diagram do **you think** best shows the angle of **each** of your legs **in your 20s?**

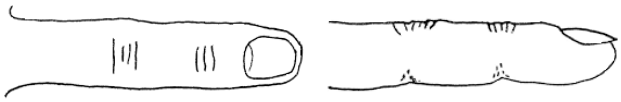
Right Leg	☐	**A**	☐	**B**	☐	**C**	☐	**D**	☐ **E**
Left Leg	☐	**A**	☐	**B**	☐	**C**	☐	**D**	☐ **E**

SECTION 5: About Your Hands

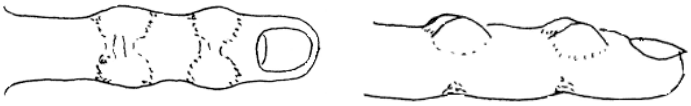
We are interested in knowing whether you have any finger nodes. These sometimes relate to arthritis in the hand and other joints.

A finger **node** is a firm, bobbly swelling on the back of the finger joint. They look like the examples below:

A finger **without** nodes:



A finger **with** nodes:



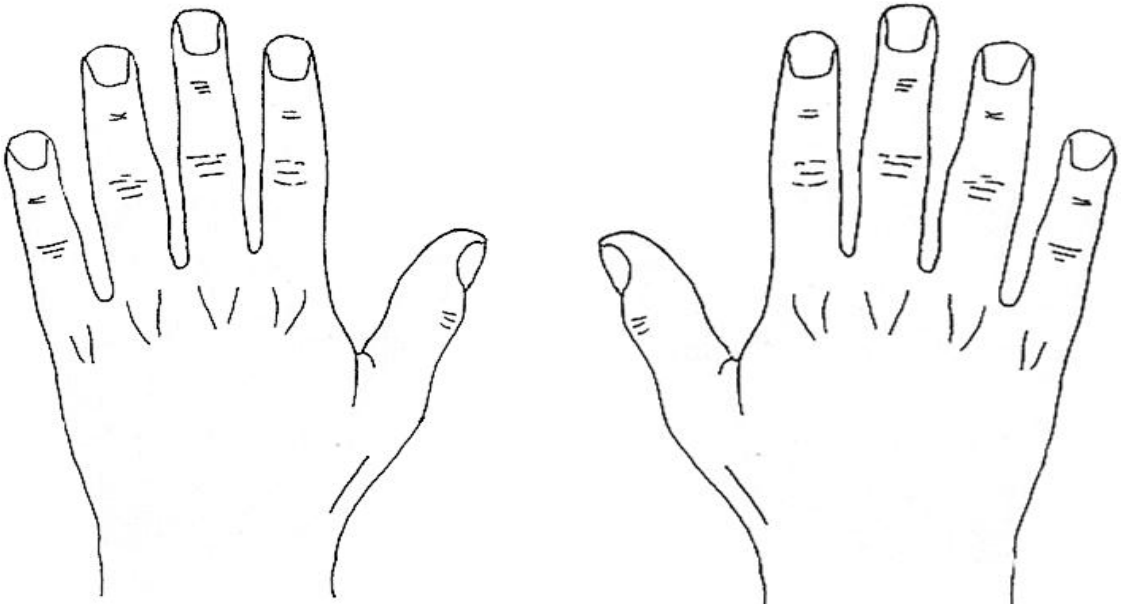
Please look at your hands and then answer the following questions

31. Do you think you have any **nodes/swellings** on your hands?

☐ Yes ☐ No ***(if No, please go to Question 32)***

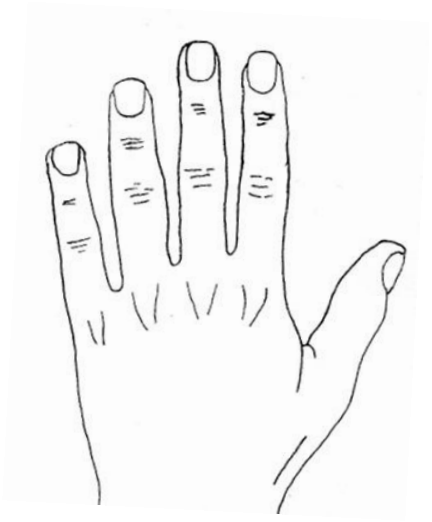
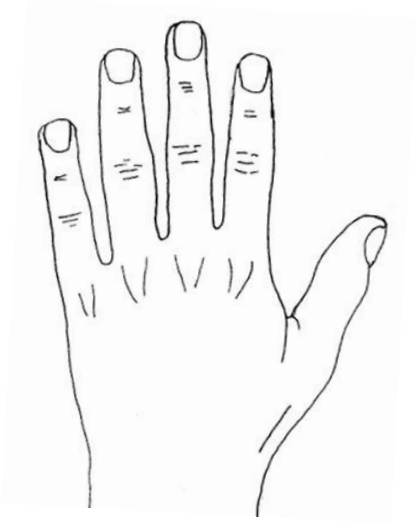
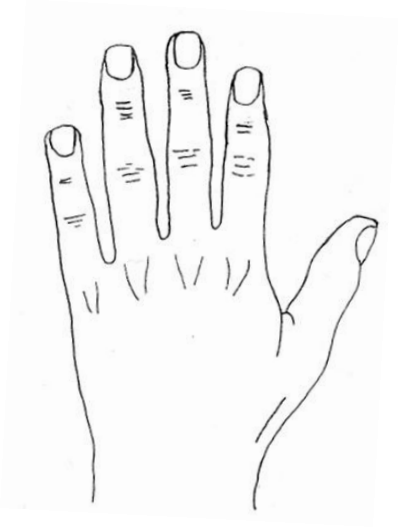
If yes, for each hand please circle the finger joint(s) where you have these nodes. *Please circle ALL the joints that are affected*

LEFT **RIGHT**



32. We are now interested in which of your **index** and **ring** fingers is longer. **First,** please look at one of your hands with your **fingers straight in line with your forearm.** If you have arthritis in the hands please look at the hand with less arthritis.

Ignore your middle finger and try to **<u>focus only on your index and ring fingers.</u>** Select from the pictures below the one that best shows the length of your **index finger** in comparison to your **ring finger** and tick the appropriate box.

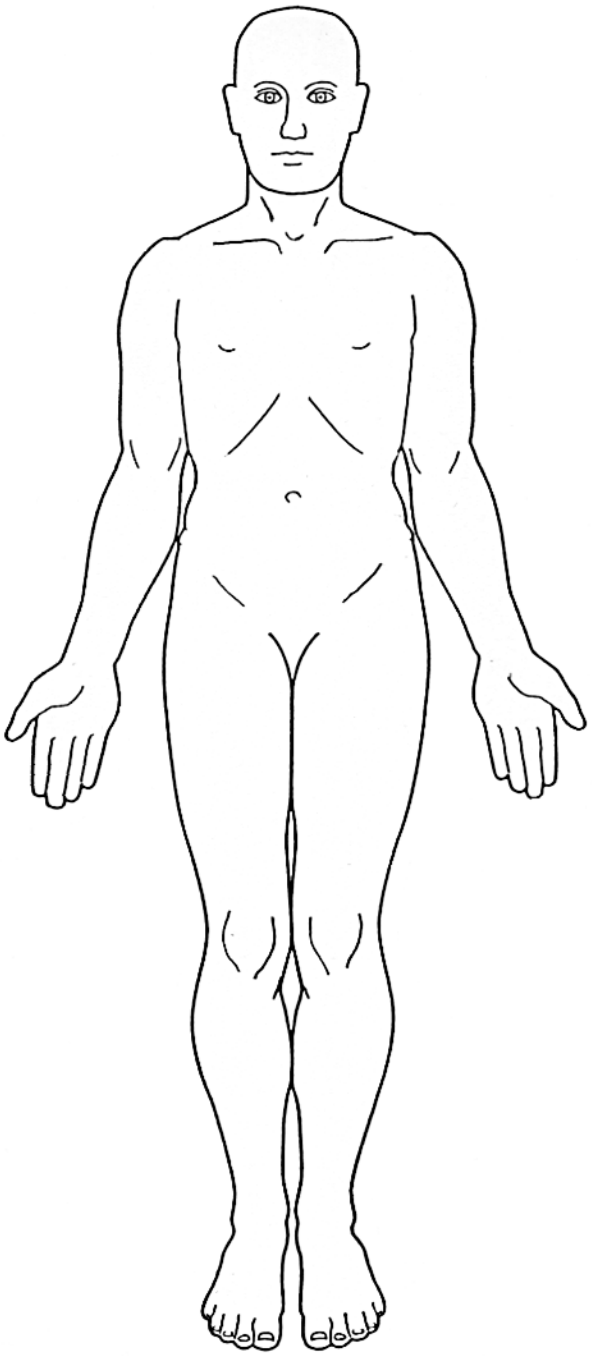
<u>Index finger longer</u> than ring finger	**Both fingers are of <u>equal length</u>**	**<u>Ring finger is longer</u> than index finger**
		
☐	☐	☐

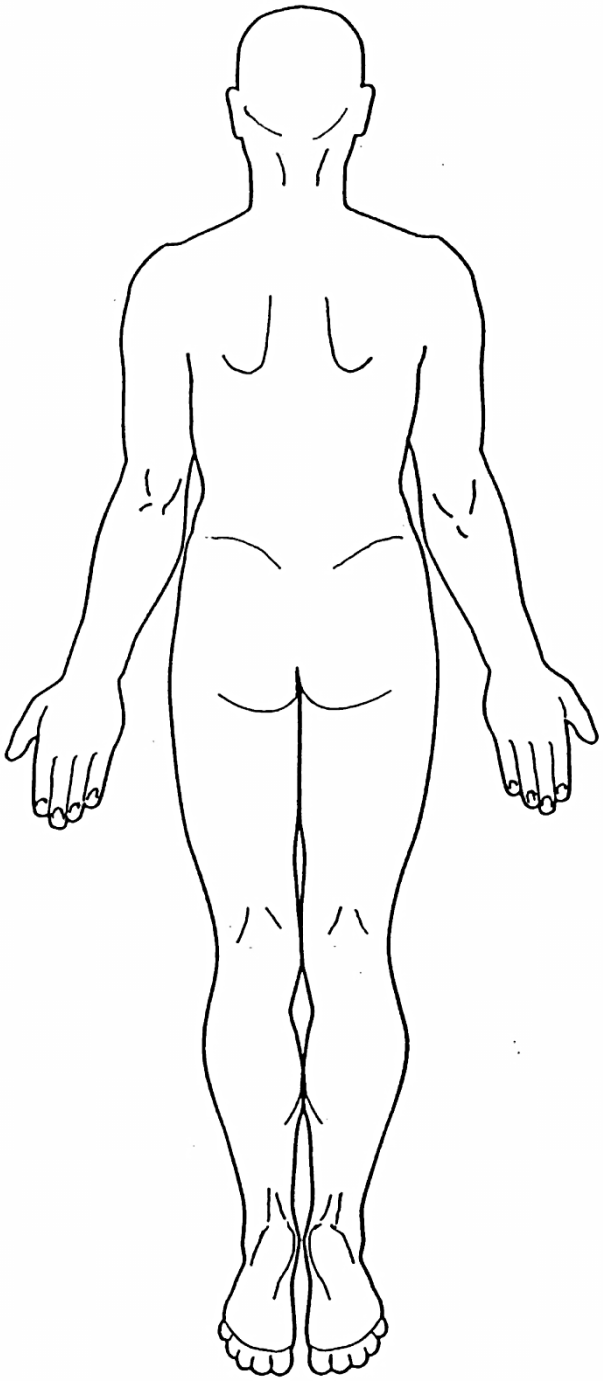
33. Which **hand do you use more often** for writing and brushing your teeth?

☐ Right-Handed ☐ Left-Handed ☐ Equally Proficient

SECTION 6: About Pain Anywhere in your Body

34. This question is about **recent pain** you may have had in **any part of your body**. Please shade in the diagram below to indicate where you have suffered **any pain for most days in the previous month.** By pain we also mean aching, discomfort and/or stiffness. Please **do not include** pain due to feverish illness such as flu. If you **do not have any body pain** that has lasted one day or longer in the last 4 weeks, please tick this box ☐ and move to **SECTION 7.**





35. How much physical pain have you had during the **past 4 weeks**? *(please tick one)*

None	Very mild	Mild	Moderate	Severe	Very Severe
☐	☐	☐	☐	☐	☐

36. If you answered “moderate” or “severe” or “very severe”, has this pain lasted **more than 3 months?**

☐ Yes ☐ No

37. Of the areas highlighted on the previous page, where do you have the strongest pain or the one that disturbs you the most?

_____

38. Have you **ever** consulted a doctor (GP or hospital) about this pain in your body?

☐ Yes ☐ No

SECTION 7: The Way You Feel

39. The following questions are designed to help us to know how you feel. Read each item below and place tick ✓ the box next to the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies. Your immediate reaction to each item will probably be more accurate than a long, thought-out response.

a. I feel tense or 'wound up'
☐ most of the time
☐ a lot of the time
☐ from time to time, occasionally
☐ not at all

b. I still enjoy the things I used to enjoy
☐ definitely as much
☐ not quite so much
☐ only a little
☐ hardly at all

c. I get a sort of frightened feeling as if something awful is about to happen
☐ very definitely and quite badly
☐ yes, but not too badly
☐ a little, but it doesn't worry me
☐ not at all

d. I can laugh and see the funny side of things
☐ as much as I always could
☐ not quite so much now
☐ definitely not so much now
☐ not at all

e. Worrying thoughts go through my mind
☐ a great deal of the time
☐ a lot of the time
☐ not too often
☐ very little

f. I feel cheerful
☐ never
☐ not often
☐ sometimes
☐ most of the time

g. I can sit at ease and feel relaxed
☐ definitely
☐ usually
☐ not often
☐ not at all

h. I feel as if I am slowed down
☐ nearly all the time
☐ very often
☐ sometimes
☐ not at all

i. I get a sort of frightened feeling like 'butterflies' in the stomach
☐ not at all
☐ occasionally
☐ quite often
☐ very often

j. I have lost interest in my appearance
☐ definitely
☐ I don't take as much care as I should
☐ I may not take quite as much care
☐ I take just as much care as ever

k. I feel restless as if I have to be on the move
☐ very much indeed
☐ quite a lot
☐ not very much
☐ not at all

l. I look forward with enjoyment to things
☐ as much as I ever did
☐ rather less than I used to
☐ definitely less than I used to
☐ hardly at all

m. I get sudden feelings of panic
☐ very often indeed
☐ quite often
☐ not very often
☐ not at all

n. I can enjoy a good book or radio or television programme
☐ often
☐ sometimes
☐ not often
☐ very seldom

SECTION 8: About your Quality of Life

We want to know how you react to illness or pain. Please answer all questions below. Tick one answer even if you cannot answer accurately. Answer the other few questions with a few words or sentences.

40. How often do you see a doctor?

☐ Almost never ☐ Only very rarely ☐ About 4 times a year ☐ About once a month ☐ About once a week

41. How many different doctors, chiropractors or other health specialists have you seen in the past year?

☐ None ☐ 1 ☐ 2 or 3 ☐ 4 or 5 ☐ 6 or more

42. How many times have you had treatment during the past year? (For example, drugs, change of drugs, surgery, etc.)

☐ None ☐ 1 ☐ 2 or 3 ☐ 4 or 5 ☐ 6 or more

If yes, what were the treatments?

_____

_____

The next three questions concern your bodily symptoms (for example, pain, aches, pressure in your body, breathing difficulties, tiredness, etc.).

43. Does your pain or other bodily symptoms stop you from working (including both work outside the home and your housework)?

☐ No ☐ Rarely ☐ Sometimes ☐ Often ☐ Most of the time

44. Does your pain or other bodily symptoms stop you from concentrating on what you are doing?

☐ No ☐ Rarely ☐ Sometimes ☐ Often ☐ Most of the time

45. Does your pain or other bodily symptoms stop you from enjoying yourself?

☐ No ☐ Rarely ☐ Sometimes ☐ Often ☐ Most of the time

46. In general, would you say your health currently is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

47. The following questions are about activities you may do during a typical day. **Would your health limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	Not, limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
Climbing **several** flights of stairs	☐	☐	☐

48. During the **past month,** have you had any of the following problems with work or other regular daily activities **as a result of your physical health?**

	Yes	No
Accomplished less than you would like	☐	☐
Were **limited** in the **kind** of work or other activities	☐	☐

49. During the **past month,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (e.g. feeling depressed or anxious)?

	Yes	No
Accomplished less than you would like	☐	☐
Didn't do work or other activities as **carefully** as usual	☐	☐

50. During the **past month** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

51. These next questions are about how you feel and how things have been with you **during the past month.** Please give the **one** answer that is closest to the way you have been feeling for **each** item.

How much time **during the last month…**

	None of the time	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

52. During the **past month**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives etc).

None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
☐	☐	☐	☐	☐	☐

53. Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, knee pain, hip pain, back pain or muscle pain. We are interested in the types of thoughts and feeling that you have **when you are in pain**. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. **Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.**

	Not At All	Slight Degree	Moderate Degree	Great Degree	All the time
a. I worry all the time about whether the pain will end	☐	☐	☐	☐	☐
b. I feel I can't go on	☐	☐	☐	☐	☐
c. It's terrible and I think it's never going to get any better	☐	☐	☐	☐	☐
d. It's awful and I feel that it overwhelms me	☐	☐	☐	☐	☐
e. I feel I can't stand it anymore	☐	☐	☐	☐	☐
f. I become afraid that the pain will get worse	☐	☐	☐	☐	☐
g. I keep thinking of other painful events	☐	☐	☐	☐	☐
h. I anxiously want the pain to go away	☐	☐	☐	☐	☐
i. I can't seem to keep it out of my mind	☐	☐	☐	☐	☐
j. I keep thinking about how much it hurts	☐	☐	☐	☐	☐
k. I keep thinking about how badly I want the pain to stop	☐	☐	☐	☐	☐
l. There's nothing I can do to reduce the intensity of the pain	☐	☐	☐	☐	☐
m. I wonder whether something serious may happen	☐	☐	☐	☐	☐

54. How often during the **past 4 weeks** did you:

	All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a. get enough sleep to feel rested in the morning?	☐	☐	☐	☐	☐	☐
b. awaken short of breath or with a headache?	☐	☐	☐	☐	☐	☐
c. have trouble falling asleep?	☐	☐	☐	☐	☐	☐
d. have trouble staying awake during the day	☐	☐	☐	☐	☐	☐

55. **In the past month**, did you feel tired on most days?

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

Thank you very much for taking the time to complete this questionnaire.
We would like to emphasise that your contact details and responses will be kept **completely confidential**

We would be grateful if you could now answer the following questions regarding your willingness to participate further in our research.

1] To enable us to evaluate the development and progression of knee pain, we would like to send you a follow-up questionnaire in approximately one years' time. We would therefore be grateful if you could confirm below whether you are happy to receive a follow up questionnaire and also whether you give your permission for us to contact your GP, the Health and Social Care Information service or other central UK NHS body to confirm your contact details, at the time of mailing the follow up questionnaire:

No, I do not want to receive a follow up questionnaire ☐

Yes, I would be willing to receive a follow up questionnaire and give my permission for the research team to contact my GP, the Health Social Care Information Service or other central UK NHS body to confirm my contact details ☐

If you have answered '*Yes*' above, please sign and date:

_____ _____
Signature Date

2] Depending on your responses in this questionnaire, you may be eligible to participate in a more detailed assessment which involves a clinical assessment and knee x-rays at Nottingham City Hospital. If you are eligible, would you be interested in receiving information that explains this part of the study in detail? Receiving information would not commit you to being in this study.

Yes, I would like to receive written information ☐

No, I would not like to receive written information ☐

3] Finally, your responses to this questionnaire may make you eligible to participate in future research studies on osteoarthritis at the University of Nottingham. If you are interested, please could you indicate this by ticking the relevant box below? Again, receiving further information would not commit you to being in further studies.

Yes, I would like to receive written information ☐

No, I would not like to receive written information ☐

If you have answered yes to the questions on page 21, please confirm your contact details below:

Full Name: _____

Address: _____

_____

_____

Best Daytime Phone Number: _____

If you are happy for us to email you, please provide your email address below:

Email address: _____ @ _____

Thank you for your time.

Please return this questionnaire in the pre-paid envelope provided.

B.2 Cover Letter – Letter from GP Practice

Headed paper please

Dear ,

Knee Pain and General Health in the Community

We are currently helping the Arthritis Research UK Pain Centre, based in the Academic Rheumatology Unit of the University of Nottingham to undertake a study on the natural history of knee health in the community. They are looking for people both with and without knee pain. We are writing to you because we think you may be interested and suitable to be considered for this study.

I enclose a questionnaire from Professor Doherty, Head of Academic Rheumatology who is directing the research. The research team in Academic Rheumatology would be grateful if you could complete and return the questionnaire, in the enclosed freepost envelope, **even if you have never experienced knee pain**. It should take you approximately 30 minutes to complete. Completion of this questionnaire is entirely voluntary and whatever your decision concerning the questionnaire, your medical care at your surgery or at the hospital will not be affected in any way.

Please be assured that none of your personal details have or will be passed from this surgery to the Academic Rheumatology.

If you have any questions about the research, please do not hesitate to contact a member of the study team in Academic Rheumatology who will be pleased to assist you. You will find their contact details on the front of the questionnaire.

Kind Regards

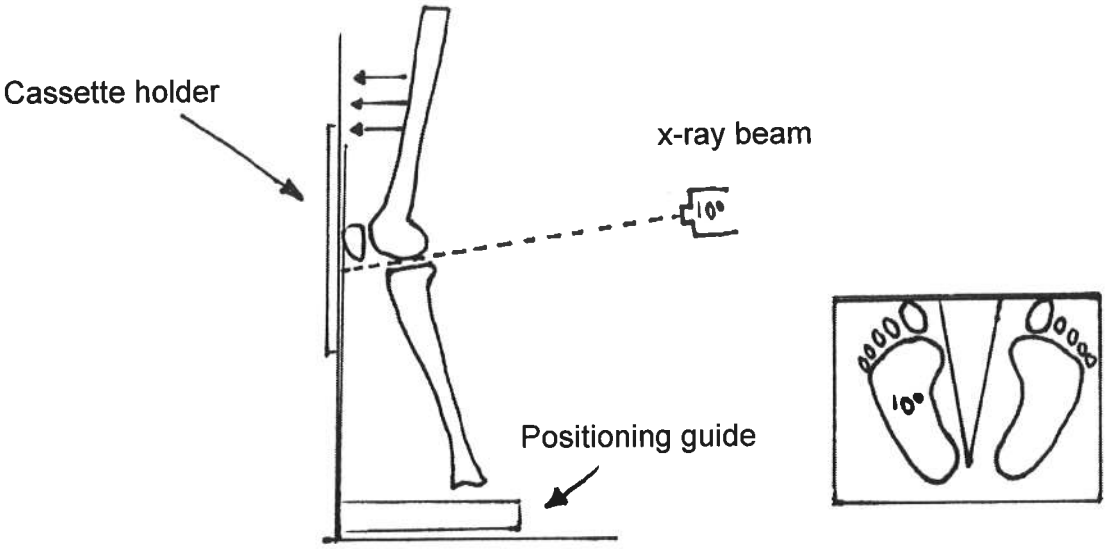
Yours sincerely

C. The Radiographic Protocol

C.1 Rosen Template Protocol

X-Ray procedures PA Knees

A single PA view of each knee is obtained with the participant standing and facing the cassette holder. The anterior wall of the positioning guide is in contact with the cassette holder. The participant stands on the position guide with the index foot aligned with the support. The big toes of both feet are in contact with the front edge of the position guide. The index foot is fixed in 10° external rotation against the V-shaped support on the base of the jig
The knee of interest is centred on the film. The body weight is evenly distributed between both legs. The knees are flexed until the knees and anterior thigh contact the jig. The source image distance (FFD) must be 40 inches /100cm. the x-ray beam is centred on the joint line of the knee of interest posteriorly and is angulated caudally 10°.

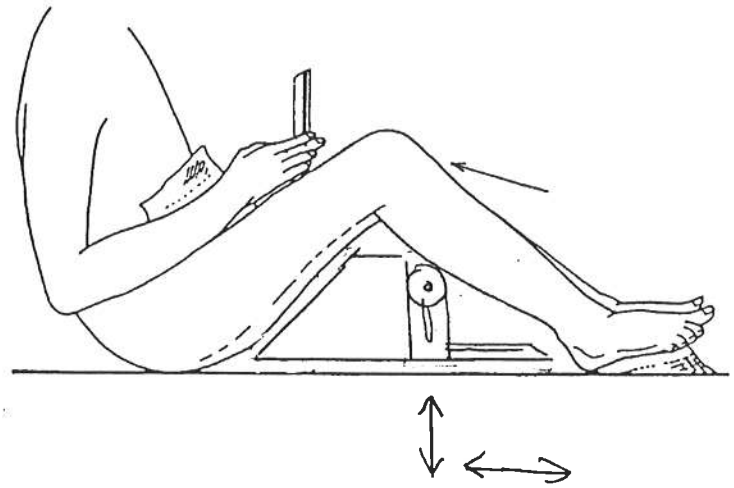


Criteria for image evaluation: Knee

1. Each knee is radiographed separately on a film
2. The joint spaces of the knee must be radiographically open
3. The long axis of the tibia is vertical
4. There is no rotation of the knee
5. All the joints, including osteophytes, are on the film
6. Left/right markers are on each film
7. Film is not under or over exposed
8. The metallic beads in the centre of the positioning guide must be visualised on the radiograph

Protocol for Skyline Patella

- The patient is seated on the x-ray couch, with both legs outstretched. The patient's back is supported if necessary. (The patient can also lie flat on the couch but will still need to hold the cassette).
- The jig is positioned under the knee to be examined with the thigh supported on the angled portion.
- The adjustable roller is then positioned to allow the heel to come down towards the couch so that the toes do not obscure the patello-femoral joint.
- The patient holds the x-ray cassette with both hands. The film is held vertically and placed approximately 6 inches proximal to the femoral condyles. Use lead mat to protect gonads.
- The x-ray beam is directed perpendicular to the film at a distance of 100-cm focus film distance.
- The x-ray beam is collimated (reduced/ limited) to include the patello-femeral joint.
- Recommended a 10Kvp increase in exposure from the antero-posterior projection.
- A Right/ Left anatomical marker is placed on the film to indicate the Right or Left knee.



x-ray procedure: skyline view

the participant is seated on the x-ray table, using the skyline jig to create a 45º. The cassette is placed on the anterior surface of the thigh centred over the knee. The x-ray beam is directed perpendicular to the cassette to pass between the femoral condyles and the patella articular surfaces. The exact angle of the beam will depend upon the the degree of flextion of the knee and the participant's individual body habitus.

Criteria for image evaluation: skyline knees

1. Both patellas should be in seen in profile
2. Both patello femoral articulations should be radiographically open
3. Neither knee should be rotated

ID ☐☐☐☐ INT ☐☐ date right ☐☐/☐☐/☐☐☐☐ date left ☐☐/☐☐/☐☐☐☐

Comments Rt Knee

Tibio-Femeral Rt Knee ☐ PAWtB ☐ NonWtB ☐ Unread ☐ N/A ☐ **Lt Knee** ☐ PAWtB ☐ NonWtB ☐ Unread ☐ N/A

Lateral	Medial	Lateral	Medial
Osteophytes 0 1 2 3 4 5 Fem ☐☐☐☐☐☐ Tib ☐☐☐☐☐☐	0 1 2 3 4 5 ☐☐☐☐☐☐ ☐☐☐☐☐☐	0 1 2 3 4 5 Fem ☐☐☐☐☐☐ Tib ☐☐☐☐☐☐	0 1 2 3 4 5 Fem ☐☐☐☐☐☐ Tib ☐☐☐☐☐☐
Joint Space Narrowing -1 0 1 2 3 4 5 ☐☐☐☐☐☐☐	-1 0 1 2 3 4 5 ☐☐☐☐☐☐☐	**Joint Space Narrowing** -1 0 1 2 3 4 5 ☐☐☐☐☐☐☐	-1 0 1 2 3 4 5 ☐☐☐☐☐☐☐
Minimal Joint Space ☐☐.☐☐ mm 0 ☐ **Valgus** ☐☐ **Varus** ☐☐	☐☐.☐☐ mm	**Minimal Joint Space** ☐☐.☐☐ mm 0 ☐ **Valgus** ☐☐ **Varus** ☐☐	☐☐.☐☐ mm
Chondrocalcinosis ☐ Yes ☐ No Fibrocartilage ☐ Yes ☐ No Hyaline cartilage ☐ Yes ☐ No	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No
Subluxation ☐ No ☐ Yes If yes, then: ☐ Lat ☐ Med	**Attrition** ☐ No ☐ Yes	**Subluxation** ☐ No ☐ Yes if yes, then: ☐ Lat ☐ Med	**Attrition** ☐ No ☐ Yes
Kellgren – Lawrence Grade ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4		**Kellgren – Lawrence Grade** ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4	

Comments Lt Knee

☐ **Skyline** ☐ **Flexed Lat** ☐ **Straight lat** ☐ **Not available** ☐ **Skyline** ☐ **Flexed Lat** ☐ **Straight lat** ☐ **Not available**

Lateral	Medial	Lateral	Medial
Osteophytes 0 1 2 3 4 5 Pat ☐☐☐☐☐☐ Fem ☐☐☐☐☐☐	0 1 2 3 4 5 ☐☐☐☐☐☐ ☐☐☐☐☐☐	0 1 2 3 4 5 Pat ☐☐☐☐☐☐ Fem ☐☐☐☐☐☐	0 1 2 3 4 5 ☐☐☐☐☐☐ ☐☐☐☐☐☐
Joint Space narrowing -1 0 1 2 3 4 5 ☐☐☐☐☐☐☐	-1 0 1 2 3 4 5 ☐☐☐☐☐☐☐	-1 0 1 2 3 4 5 ☐☐☐☐☐☐☐	-1 0 1 2 3 4 5 ☐☐☐☐☐☐☐
Minimal Joint Space ☐☐.☐☐ mm	☐☐.☐☐ mm	**Minimal joint Space** ☐☐.☐☐ mm	☐☐.☐☐ mm
Subluxation ☐ No ☐ Yes If yes, then: ☐ Lat ☐ Med	**Attrition** ☐ No ☐ Yes	**Subluxation** ☐ No ☐ Yes if yes, then: ☐ Lat ☐ Med	**Attrition** ☐ No ☐ Yes
K-L Grade ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4		**K-L Grade** ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4	
Other calcifications ☐ No ☐ Yes		**other calcifications** ☐ No ☐ Yes	

D. The Football Radiographic Survey

D.1 Spire Healthcare Contract



SERVICES RENDERED AGREEMENT

BETWEEN

UNIVERSITY OF NOTTINGHAM

AND

SPIRE HEALTHCARE LIMITED

AND

CLASSIC HOSPITALS LIMITED

RGS 114063

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THIS AGREEMENT is dated 01 October 2014

PARTIES

(1) **Spire Healthcare Limited** incorporated and registered in England with company number 01522532 whose registered office is at 3 Dorset Rise,London, EC4Y 8EN (**SHL**);

(2) **Classic Hospitals Limited** incorporated and registered in England with company number 05384616 whose registered office is at 3 Dorset Rise,London, EC4Y 8EN (**CHL**),

SHL and CHL, together, referred to as "**the Provider**"; and

(3) **The University of Nottingham** of University Park, Nottingham NG7 2RD, United Kingdom (**Sponsor**),

each a "**Party**" and together "**the Parties**".

BACKGROUND

Sponsor wishes to engage the services of the Provider. The Provider has agreed to provide such services, as described more fully in Schedule 1, in accordance with the terms and conditions set out below. In consideration of the services and obligations pursuant to this agreement, the Sponsor has paid £1 to the Provider; receipt of which is hereby acknowledged.

AGREED TERMS

1. DEFINITIONS AND INTERPRETATION

1.1 Clause, schedule and paragraph headings shall not affect the interpretation of this agreement.

1.2 A **person** includes a natural person, corporate or unincorporated body (whether or not having separate legal personality).

1.3 The Schedules shall form part of this agreement and shall have effect as if set out in full in the body of this agreement. Any reference to this agreement includes the Schedule.

1.4 Unless the context otherwise requires, words in the singular shall include the plural and in the plural include the singular.

1.5 A reference to a statute or statutory provision is a reference to it as it is in force for the time being, taking account of any amendment, extension, or re-enactment, and includes any subordinate legislation for the time being in force made under it.

1.6 Any obligation in this agreement on a person not to do something includes an obligation not to agree or allow that thing to be done.

1.7 References to clauses and schedules are to the clauses and schedules of this agreement.

1.8 **"Patient"** means a person who receives treatment or care as part of the provision of the Services.

1.9 **"Minimum Dataset"** means the patient information to be provided by the Sponsor to the Provider as set out in Schedule 1.

2. OBLIGATIONS OF THE PARTIES

2.1 Provider shall carry out at its premises the services, as described at Schedule 1 (the "**Services**"). The work will take place in one of the hospitals listed in Schedule 2. The Services will be carried out in compliance with all necessary statutory and legal requirements including the Care Quality Commission and any other relevant health and safety regulation.

2.2 The Provider shall be entitled to refuse to treat or continue to treat a Patient:

(a) who is unsuitable for treatment on clinical grounds;

(b) who is temporarily unsuitable for treatment on clinical grounds for as long as such unsuitability remains;

(c) who has not validly consented to the treatment provided under the Services; and

(d) for any unreasonable behaviour of the Patient which is unacceptable to the Provider, its staff or the consultant or other named professional clinically responsible for the management of the care of such Patient.

2.3 The Provider's complaints and incident reporting procedures, as amended from time to time, will apply to this Agreement. Upon request, the Provider will make a copy of each available to the Sponsor.

2.4 At the time of sending the referral to the Provider, the Sponsor will also send the Minimum Dataset for the referred Patient.

3. FINANCE

No fees will be paid by the Provider in respect of the Services except that all bookings that are cancelled within 24 hours of the appointed time, or for which Patients do not attend, shall be charged at £25 each.

4. INTELLECTUAL PROPERTY

4.1 Nothing in this agreement shall affect the ownership of any intellectual property in existence prior to commencement of, or developed during, the provision of Services by the Provider ("**Background IPR**"). Such intellectual property shall remain the property of the Party introducing the same and shall be made available to the other Party as reasonably required, solely for the purpose and duration of the provision of the Services. Background IPR will be maintained as confidential by both Parties in accordance with Clause 5 below.

4.2 Any results generated in the course of the Services, excluding any Background IPR (**Results**), shall be the property of the Sponsor.

5. CONFIDENTIAL INFORMATION AND PUBLICATION

5.1 Confidential Information shall mean all confidential information (however recorded or preserved) disclosed or made available, directly or indirectly, to a party (the "**Recipient**") by the other party (the "**Disclosing Party**") or its employees, officers, representatives or advisers and marked or identified as confidential at the time of disclosure, but not including any information that:

(a) is or becomes generally available to the public (other than as a result of its disclosure by the Recipient or its representatives in breach of this agreement), (except that any compilation of otherwise public information in a form not publicly known shall nevertheless be treated as Confidential Information); or

(b) was available to the Recipient on a non-confidential basis prior to disclosure by the Disclosing Party; or

(c) was, is or becomes available to the Recipient on a non-confidential basis from a person who, to the Recipient's knowledge, is not bound by a confidentiality agreement with the Disclosing Party or otherwise prohibited from disclosing the information to the Recipient; or

(d) was lawfully in the possession of the Recipient before the information was disclosed to it by the Disclosing Party as evidenced by written records; or

(e) the parties agree in writing is not confidential or may be disclosed; or

(f) is required to be disclosed by virtue of law, regulation or order of a court of competent authority, provided always that reasonable endeavours are made to notify and consult with the Disclosing Party prior to disclosure; or

(g) is developed by or for the Recipient independently of the information disclosed by the Disclosing Party.

5.2 The Parties agree to maintain the confidential nature of any Confidential Information received under this Agreement.

6. WARRANTY AND INDEMNITY

6.1 Neither party shall be liable to the other for any death or injury, unless it is caused by the negligence of that party or its representatives, nor shall it be liable to the other for any loss or damage whatsoever unless it is caused by its wilful default or that of its representatives.

7. TERM AND TERMINATION

7.1 The work will be deemed to have commenced on 1st September 2014 and is expected to be completed by 31st December 2015.

7.2 Either party may terminate this agreement upon giving 2 months' notice to the other.

7.3 Either party may terminate this agreement upon giving 1 months' notice to the other in the event that the other party is in breach of this agreement and such breach has not been rectified or the party in question has not taken reasonable steps to rectify within 30 days' of notification.

8. ENTIRE AGREEMENT AND VARIATION

8.1 This agreement constitutes the entire agreement between the parties and supersedes and extinguishes all previous drafts, agreements, arrangements and understandings between them, whether written or oral, relating to its subject matter.

8.2 Each party agrees that it shall have no remedies in respect of any representation or warranty (whether made innocently or negligently) that is not set out in this agreement. Each party agrees that its only liability in respect of those representations and warranties that are set out in this agreement (whether made innocently or negligently) shall be for breach of contract.

8.3 No variation of this agreement shall be effective unless it is in writing and signed by each of the parties (or their authorised representatives).

9. NO WAIVER

9.1 Failure to exercise, or any delay in exercising, any right or remedy provided under this agreement or by law shall not constitute a waiver of that or any other right or remedy, nor shall it preclude or restrict any further exercise of that or any other right or remedy.

9.2 No single or partial exercise of any right or remedy provided under this agreement or by law shall preclude or restrict the further exercise of that or any other right or remedy.

10. ASSIGNMENT

Except as otherwise provided in this agreement, no party may assign, sub-contract or deal in any way with, any of its rights or obligations under this agreement or any document referred to in it, save that the Disclosing Party may assign its rights under this agreement to any entity in its Group on prior written notice to the Recipient.

11. NOTICES

11.1 Any notice required to be given under this agreement, shall be in writing and shall be delivered personally, or sent by pre-paid first class post or recorded delivery or by commercial courier, to each party required to receive the notice at its address as set out below:

(a) University of Nottingham: Research & Graduate Services, University of Nottingham, Kings Meadow Campus, Lenton Lane, Nottingham NG7 2NR

For the attention of: Head of Research Grants and Contracts

(b) Spire Healthcare: Registered Office

For the attention of: The Company Secretary

(c) Classic Hospitals: Registered Office

For the Attention of: the Company Secretary

or as otherwise specified by the relevant party by notice in writing to each other party.

11.2 Any notice shall be deemed to have been duly received:

(a) if delivered personally, when left at the address and for the contact referred to in this clause; or S

(b) if sent by pre-paid first class post or recorded delivery, at 9.00 am on the second Business Day after posting; or

(c) if delivered by commercial courier, on the date and at the time that the courier's delivery receipt is signed.

11.3 A notice required to be given under this agreement shall not be validly given if sent by e-mail.

12. NO PARTNERSHIP

Nothing in this agreement is intended to, or shall be deemed to, establish any partnership or joint venture between any of the parties, constitute any party the agent of another party, nor authorise any party to make or enter into any commitments for or on behalf of any other party.

13. THIRD PARTY RIGHTS

13.1 A person who is not a party to this agreement shall not have any rights under or in connection with it.

14. GOVERNING LAW AND JURISDICTION

14.1 This agreement and any dispute or claim arising out of or in connection with it or its subject matter or formation (including non-contractual disputes or claims) shall be governed by and construed in accordance with the laws of England.

14.2 The parties irrevocably agree that the courts of England shall have exclusive jurisdiction to settle any dispute or claim that arises out of or in connection with this agreement or its subject matter or formation (including non-contractual disputes or claims).

Schedule 1 : Services

1. The Provider will provide un-reported baseline imaging using tibiofemoral and patellafemoral radiographs on the individuals referred to it by the Sponsor. The required images are not standard clinical views but views produced using rigs that have been designed to extract optimal views of the tibiofemoral compartment and patella (see Fig 1).

2. The x-rays performed by the Provider will be provided on an un-reported. X Ray scoring and clinical evaluation (including any reporting of abnormality to the patient and/or their healthcare provider) will be done by the Sponsor.

3. The parties shall comply with the following referral protocol:

    a. Dr Gwen Fernandes will, on behalf of the Sponsor, personally contact the hospitals to check availability for the provision of Services before recruiting Patients in order to ensure that the Provider has capacity and agrees to likely timescales in advance;
    b. Dr Gwen Fernandes will, on behalf of the Sponsor, contact the relevant hospital to agree local appointment availability;
    c. The Sponsor will obtain consent in relation to the provision of Services from each Patient;
    d. The Sponsor will confirm the appointment date and time with the relevant Spire hospital and the Patient and will provide the Minimum Dataset to the hospital;
    e. Dr Fernandes will, on behalf of the Sponsor, send an email confirmation to the Patient and the relevant hospital with a scanned copy of the Patient's Minimum Dataset.
    f. The Sponsor will call each Patient the day before their appointment to remind them of this.

4. The Minimum Dataset is, in relation to each Patient:

    a. patient information sheet; and

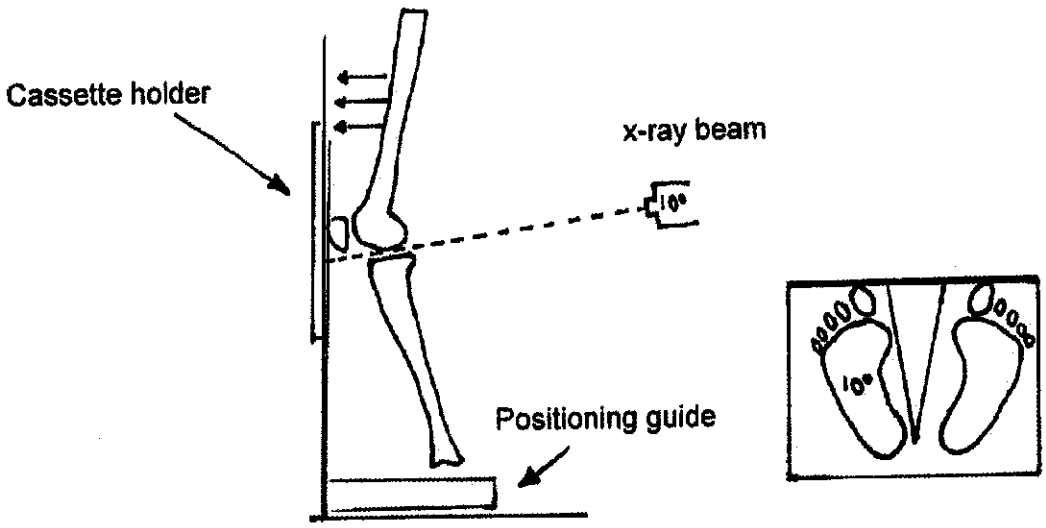
    b. consent form.

Figure 1

X-Ray procedures PA Knees

A single PA view of each knee is obtained with the participant standing and facing the cassette holder. The anterior wall of the positioning guide is in contact with the cassette holder. The participant stands on the position guide with the index foot aligned with the support. The big toes of both feet are in contact with the front edge of the position guide. The index foot is fixed in 10° external rotation against the V-shaped support on the base of the jig
The knee of interest is centred on the film. The body weight is evenly distributed between both legs. The knees are flexed until the knees and anterior thigh contact

the jig. The source image distance (FFD) must be 40 inches /100cm. the x-ray beam is centred on the joint line of the knee of interest posteriorly and is angulated caudally 10°.



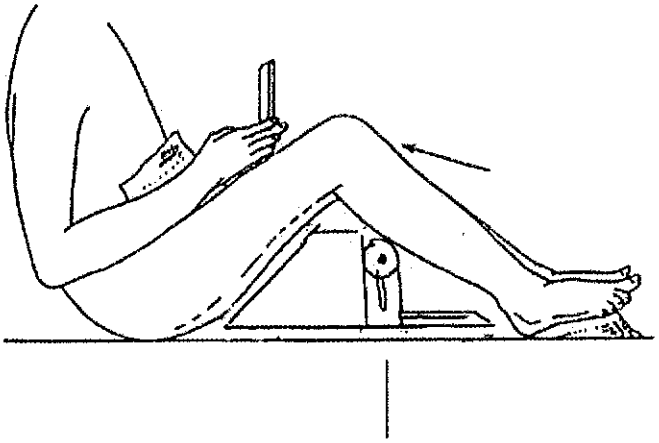
Criteria for image evaluation: Knee

1. Each knee is radiographed separately on a film
2. The joint spaces of the knee must be radiographically open
3. The long axis of the tibia is vertical
4. There is no rotation of the knee
5. All the joints, including osteophytes, are on the film
6. Left/right markers are on each film
7. Film is not under or over exposed
8. The metallic beads in the centre of the positioning guide must be visualised on the radiograph

Protocol for Skyline Patella

- The patient is seated on the x-ray couch, with both legs outstretched. The patient's back is supported if necessary. (The patient can also lie flat on the couch but will still need to hold the cassette).
- The jig is positioned under the knee to be examined with the thigh supported on the angled portion.

- The adjustable roller is then positioned to allow the heel to come down towards the couch so that the toes do not obscure the patello-femoral joint.
- The patient holds the x-ray cassette with both hands. The film is held vertically and placed approximately 6 inches proximal to the femoral condyles. Use lead mat to protect gonads.
- The x-ray beam is directed perpendicular to the film at a distance of 100-cm focus film distance.
- The x-ray beam is collimated (reduced/ limited) to include the patello-femeral joint.
- Recommended a 10Kvp increase in exposure from the antero-posterior projection.
- A Right/ Left anatomical marker is placed on the film to indicate the Right or Left knee.



x-ray procedure: skyline view

the participant is seated on the x-ray table, using the skyline jig to create a 45°. The cassette is placed on the anterior surface of the thigh centred over the knee. The x-ray beam is directed perpendicular to the cassette to pass between the femoral condyles and the patella articular surfaces. The exact angle of the beam will depend upon the the degree of flextion of the knee and the participant's individual body habitus.

Criteria for image evaluation: skyline knees

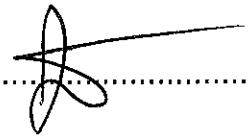
1. Both patellas should be in seen in profile
2. Both patello femoral articulations should be radiographically open
3. Neither knee should be rotated

SCHEDULE 2 - Hospitals

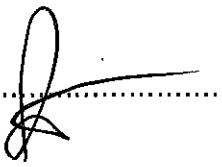
Spire Healthcare Limited	Classic Hospitals Limited
Spire Alexandra Hospital Spire Bristol Hospital Spire Bushey Hospital Spire Cambridge Lea Hospital Spire Cardiff Hospital Spire Cheshire Hospital Spire Murrayfield Hospital and Spire Shawfair Hospital (Edinburgh) Spire Murrayfield Hospital (Wirral) Spire Gatwick Park Hospital Spire Harpenden Hospital Spire Hartswood Hospital Spire Leeds Hospital Spire Leicester Hospital Spire Little Aston Hospital Spire Manchester Hospital Spire Norwich Hospital Spire Parkway Hospital Spire Portsmouth Hospital Spire Roding Hospital Spire South Bank Hospital Spire Southampton Hospital Spire Sussex Hospital Spire Thames Valley Hospital Spire Tunbridge Wells Hospital Spire Washington Hospital Spire Wellesley Hospital The Montefiore Hospital, Brighton	Spire Clare Park Hospital Spire Dunedin Hospital Spire Elland Hospital Spire Fylde Coast Hospital Spire Hull and East Riding Hospital Spire Liverpool Hospital Spire Methley Park Hospital Spire Regency Hospital Spire St Saviours Hospital Spire Yale Hospital

Signed by
for and on behalf of the University
of Nottingham .....

Signed by
for and on behalf of SPIRE
Healthcare Ltd .....



Signed by
for and on behalf of Classic
Hospitals Ltd .....



D.2 Invitation Letter from Professor Michael Doherty

Arthritis Research UK | centre for sport, exercise & osteoarthritis

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Mr «Forename» «Surname»
«Address_Line_1»
«Address_Line_2»
«Town__City»
«Postcode»

Academic Rheumatology
Clinical Sciences Building
City Hospital
Nottingham
NG5 1PB, UK

Tel: +44 (0) 115 8231679
Fax: +44 (0) 115 8231757
gwen.fernandes@nottingham.ac.uk

4th January 2016

Dear Mr «Surname»,

Osteoarthritis and Football Study

Many thanks indeed for returning the questionnaire on knee pain and osteoarthritis in retired professional footballers. We very much appreciate you taking the time to complete the form and to contribute to this study.

As you will remember, you indicated you would be willing to receive information about a further stage of the study which will involve an x-ray assessment of your knees at your local SPIRE hospital. I am pleased to enclose further information with this letter. Please take time to read the information thoroughly and discuss it with friends and family should you wish to.

A member of the research team will contact you shortly to discuss with you whether you would like to participate in this part of the study. They will be able to answer any questions you may have at this time. If you are willing to volunteer, they will also ask you some questions to ensure that you are eligible to take part in this phase of the study and will then arrange the appointment for you to attend your local Spire hospital. .

Once again, many thanks for contributing already to this research and for expressing an interest in participating further by having an x-ray of your knees.

Yours sincerely,

Professor Michael Doherty

Professor of Rheumatology/Chief Investigator

D.3 Patient Information Sheet

OSTEOARTHRITIS RISK IN PROFESSIONAL FOOTBALLERS

Phase II: INFORMATION SHEET (Principal Investigator: Professor Michael Doherty)

Chief Investigator: Michael Doherty, Professor of Rheumatology

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like further information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Knee osteoarthritis (KOA) is a leading cause of pain and impaired mobility. Professional footballers are thought to be at increased risk of KOA because of both the physically demanding training they have to undertake and the knee injuries they often sustain during matches. The current study will determine whether footballers are at increased risk of KOA compared to the general population, after adjustment for other known causes of KOA.

The first stage of the study was a postal and on-line questionnaire sent to a large number of footballers registered with the UK Professional Footballers Association (PFA) (or XPRO) to determine the frequency of knee symptoms, knee injuries and need for knee surgery and to enquire concerning other known risk factors for KOA. A sample of the responders are now being invited to a SPIRE hospital for knee x-rays to confirm whether they have KOA. The prevalence of knee pain and OA in the footballers will then be compared to that in age-matched male controls derived from the Nottinghamshire community. Controls will be identified from a questionnaire survey on knee pain that is being undertaken for a separate study in Nottingham. Again, a sample of responders will be invited to undergo x-rays of their knees at the City Hospital Nottingham.

Why have I been invited?

You have already very kindly completed and returned a postal questionnaire about your general health and specifically your knee health. In this you indicated that you would be willing to receive further information about Phase II of the study which involves radiographic evaluations of your knees By indicating that you wished to receive more information, you did not agree to participate in the study. You should read this information sheet in detail before deciding whether you wish to take part or not. We need to recruit 855 individuals for this part of the study.

Do I have to take part?
No. You should only take part in this study if you want to. It is entirely up to you whether or not you wish to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form for and knee x-rays.

You are free to withdraw at any time, without having to give a reason. This in no way will influence the medical care you receive from your GP or local hospital, or in any way affect your legal rights.

What will happen to me if I take part?
If you inform us that you are happy to take part in this study, you will be contacted by telephone by the research team to arrange an appointment at your local SPIRE hospital facility to see a radiographer. This initial appointment will take around 1 hour. You will be given the opportunity to ask any questions you have about the study prior to signing a consent form. A brief review of your medical history will also be undertaken.

Following this, radiographs of both of your knees will be taken using a standardized mechanism called a jig (a custom-made Perspex stand) so as to obtain the best possible views of your knees. Your radiographs will be taken in two positions, once when you are standing and another when you are seated on an x-ray couch.

What are the possible disadvantages and risks of participating in this study?
In general, there are very few disadvantages or risks of participating in this study.
If eligible, you will be invited for knee x-rays as the radiation dose from the procedure is very small. The effective dose for this study has been estimated to be roughly equivalent to half a day of average background radiation in the UK. There are no other side-effects associated with this study.

What are the possible benefits of taking part in this study?
We will be able to give you feedback on the research findings and will also be happy to describe the findings from your x-rays. The research team will facilitate this.
By taking part in this research study, you will be helping us to understand the risk factors for knee OA in retired professional footballers and allow us to estimate the risks and eventually mitigate these through appropriate therapeutic and rehabilitation strategies. It may also have an impact on the way players currently train, practice and play football.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to Dr Gwen Fernandes who will do her best to answer your questions (telephone number: 0115-823-1679).

If you remain unhappy, and wish to complain formally, the Patient Advice and Liaison Service provide a confidential service and can also advise you regarding the NHS complaints procedure. This service at Nottingham City Hospital can be contacted on 0115 969 1169 (extension 59671) or on pals@nuh.nhs.uk.

Will my taking part in the study be kept confidential?
If you join the study, some parts of your medical records and data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential,** stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.
The results of the study may be published in medical literature, but your identity will not be revealed.

We will ask for your permission to store your personal details on a secure database within Academic Rheumatology to enable us to invite you to take part in future research studies. If this happens, you will be given the opportunity to decide whether you would like to take part or not. If you state that you do not wish to be contacted regarding future studies your personal details will be destroyed when the results from the study have been analysed.

All research data will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?
Your participation in the study is voluntary and you are free to withdraw at any time, without giving reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Will I be paid for participation in this study?
Participation in this study is entirely voluntary. You will receive no payment for your participation however your travel costs to and from the SPIRE facility will be reimbursed.

What will happen to the results of the research study?
We hope that the results of this study will lead to a better understanding of the risk factors of KOA and help guide future management of this common type of arthritis. Results from the study will be submitted for publication in scientific and medical journals and presented at medical scientific meetings. We will also provide you with a summary of the results if you wish.

Who is organising and funding the research?
This study is organised by members of staff in Academic Rheumatology, a department of the University of Nottingham based at the City Hospital. The study is being funded by the Arthritis Research UK (ARUK), an arthritis medical research charity and Federation Internacionale de Football (FIFA), the international governing body of association football.

Who has reviewed the study?
This study has been reviewed by the Nottingham1 Research Ethics Committee.

Further information and contact details:

Study Contact:

Dr Gwen Fernandes, Clinical Researcher, Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB
Tel: 0115 823 1679

Chief Investigator:

Professor Michael Doherty, Professor of Rheumatology, Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB

Thank you for taking the time to read this information sheet.

D.4 Consent Form

OSTEOARTHRITIS RISK IN PROFESSIONAL FOOTBALLERS: Phase II CONSENT FORM

REC ref: 14/EM/0045 (Principal Investigator: Professor Michael Doherty)

	Please initial below
1. I confirm that I have read and understand the information sheet dated the 5 June 2014 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.	
3. I understand that relevant sections of my study notes may be looked at by responsible individuals from the University of Nottingham or the City Hospital (Nottingham University Hospitals NHS Trust) or from regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.	
4. I understand that participating in this study will involve me attending my nearest SPIRE hospital facility where a radiographer will take an x-ray of my knees.	
5. I agree to participate in the above study	

_____	_____	_____
Name of Participant	Signature of Participant	Date
_____	_____	_____
Name of Researcher	Signature of Researcher	Date

D.5 Spire Outpatient Form

Spire

OUTPATIENT INFORMATION SHEET

NAME: Mr _____

DATE OF BIRTH: _____

ADDRESS: _____

_____

_____

TELEPHONE _____

GP & ADDRESS: _____

_____

INSURANCE DETAILS:

(POLICY) Payment Plan #**285037**

(AUTHORISATION CODE) N / A

NEXT OF KIN: _____

APPT DATE & TIME: _____

REFERRER: Dr Gwen Fernandes/ Mr Sanjay Parekh (University of Nottingham, Arthritis and Football Study)

EXAMINATION: Bi-lateral knee x-rays (research X-rays as per provided protocol)

E. The Controls Radiographic Survey

E.1 Invitation Letter from Professor Michael Doherty

Arthritis Research UK | centre for sport, exercise & osteoarthritis

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Academic Rheumatology
Clinical Sciences Building
City Hospital
Nottingham
NG5 1PB, UK

Tel: +44 (0) 115 8231679
Fax: +44 (0) 115 8231757
gwen.fernandes@nottingham.ac.uk

Mr «Forename» «Surname»
«Address»
«Town»
«City»
«Postcode»

24th September 2015

Dear Mr «Surname»,

Osteoarthritis and Football Control Group Study

Many thanks indeed for returning the questionnaire on knee pain in the community. We very much appreciate you taking the time to complete the form and to contribute to this study.

As you will remember, you indicated you would be willing to receive information on future research studies on osteoarthritis at the University of Nottingham. We are currently conducting a study on knee pain and arthritis in retired professional footballers. In order to understand the risk factors involved, professional footballers will be compared to age-matched men in the general population. I am pleased to enclose further information with this letter. Please take time to read the information thoroughly and discuss it with friends and family should you wish to.

Please could you complete the reply sheet enclosed if you are interested and return it in the pre-paid envelope provided. A member of the research team will then contact you and will be happy to answer any questions you may have. If you are willing to volunteer, they will also ask you some questions to ensure that you are eligible to take part in this phase of the study and will then arrange the appointment for you to attend Nottingham City Hospital for a blood sample and an x-ray of your knees.

Once again, many thanks for returning the questionnaire and your interest in this important area of research.

Yours sincerely,



Professor Michael Doherty

Professor of Rheumatology/Chief Investigator

E.2 Patient Information Sheet

KNEE PAIN AND RELATED HEALTH IN THE COMMUNITY STUDY
PARTICIPANT INFORMATION SHEET

Chief Investigator: Michael Doherty, Professor of Rheumatology

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like further information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
Knee pain due to osteoarthritis (OA) is a leading cause of pain and reduced mobility in adults over the age of 50. Although certain risk factors for the development of osteoarthritis (eg getting older, genetic makeup) are known, it is still unclear why some people with OA develop progressively severe pain, while others with a similar amount of OA change have mild, or even no pain.

The purpose of this study is to try and determine the natural history of knee pain and knee osteoarthritis and the reasons why some individuals with knee OA develop severe pain and others do not. To do this, a range of assessments will be undertaken at an initial hospital appointment and will then be repeated approximately one year later. The assessments include an x-ray of your knees, tests to measure muscle strength, quantitative sensory testing (QST), collection of a blood and urine sample to measure chemical changes which associate with pain and OA and, if you are agreeable, a genetic analysis of your blood sample.

Individuals with mild knee pain, severe knee pain and individuals with no knee pain are being invited to participate in the study to enable comparisons to be made between the different categories of knee pain and to identify features that may help explain the differences in pain severity between individuals.

Why have I been invited?
You have already very kindly completed and returned a postal questionnaire about your general health and specifically your knee health. In this you indicated that you would be willing to receive further information about the second phase of the study which involves having x-rays of your knees and providing a blood and urine sample. By indicating that you wished to receive more information, you did not agree to participate in this study. You should read this information sheet in detail before deciding whether you wish to take part or not. We need to recruit 400 individuals for this part of the study.

Do I have to take part?
No. You should only take part in this study if you want to. It is entirely up to you whether or not you wish to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form when you attend for the blood tests and knee x-rays. You are free to withdraw at any time, without having to give

a reason. This in no way will influence the medical care you receive from your GP or local hospital, or in any way affect your legal rights.

What will happen to me if I take part?
If you inform us that you are happy to take part in this study, you will be contacted by the research team to arrange a single morning appointment to attend the Nottingham City Hospital to see a research nurse. This initial appointment will take around 2 hours. You will be given the opportunity to ask any questions you have about the study before being asked to sign a consent form. You will then be given a one minute self-reported questionnaire on physical activity. The following assessments will then be undertaken:

- **Fasting blood and urine sample collection**

You will be asked to have nothing to eat or drink after 10 pm from the night before your appointment so that you can provide fasting blood and urine samples when you attend for your appointment. Further details concerning the collection of the urine sample will be confirmed when you are contacted by the research team and a summary of the information will be sent to you with the confirmation of your appointment. The research nurse will take a sample of 10 mls of blood (2 teaspoons) from a vein in your arm. We will then provide you with a light refreshing breakfast and a hot drink.

- **Muscle Strength/Balance Tests**

Measurement of muscle strength of your hands, knees (thigh muscles) and hips using a hand held machine. Measurements will be done three times in succession. Your balance will be assessed by asking you to stand on a force plate (with pressure sensors built in) for approximately 1 minute and this will allow balance of pressure between the left and right foot to be measured.

- **Gait Analysis and Functional Tests**

You will be asked to walk at your natural pace on a gait mat for 5 minutes while real-time recordings of your foot patterns, stride length, walking speed and angles of your feet are recorded. We will use standardized functional measures to assess your physical functioning.

- **Ultrasound:**

An ultrasound machine will be used to image both your knee joints for any underlying inflammation or swelling. This is a non-invasive procedure; it does not involve any exposure to ionizing radiation and has no detrimental side effects.

- **Quantitative Sensory Testing (QST)**

QST will be used to measure how sensitive your nerves are to changes in mechanical pressure or sharpness. Pressure sensitivity is tested by using a probe to apply pressure to specific sites including your knee, shin and to the front of your chest. To test for sensitivity to sharpness a "pinprick" stimulator will be applied to your skin and you will be asked to rate the pain or sharpness you experience on a given scale. The stimulator will be applied on your knee for less than a second each time. The "pinprick" stimulators are designed to not puncture your skin and the devices are always disinfected before application. So that you know what to expect, the researcher will demonstrate the tests one of your hands or your other knee. Any sensation of pain or pressure will be mild and temporary in nature.

- **X-rays of your knees**

You will also be asked to visit the X-ray Department at the Nottingham City Hospital to have x-rays of both your knees.

What are the possible disadvantages and risks of participating in this study?
X-raying your knees involves exposure to a very small amount of additional radiation. As part of everyday living everyone is exposed to naturally occurring background radiation. The x-rays from this trial have been estimated to be roughly equivalent to half a day of background radiation in the UK. At this dose level no harmful effects of radiation have been demonstrated and the risk is believed to be minimal.
During the QST you may feel slight discomfort in the area the probe was placed but this is only temporary feeling.
The blood tests may cause you some mild discomfort and occasionally a small bruise.

What are the possible benefits of taking part in this study?
You will not benefit directly from participation in this study but the results from the study may allow us to better understand the factors that cause different degrees of pain severity in people with knee pain. This may subsequently lead to better assessment and possibly better management of people with painful knees and OA.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to (to be confirmed) who will do their best to answer your questions.

If you remain unhappy, and wish to complain formally, the Patient Advice and Liaison Service provide a confidential service and can also advise you regarding the NHS complaints procedure – details can be obtained from your hospital.

What will happen to any samples I give?
The blood and urine samples will be stored securely with a code unique to you at the University of Nottingham under the University's Human Tissue Research Licence (no 12265). These samples will only be used for arthritis related research and will only be used by Professor Doherty's team in Nottingham, by close collaborating scientific research partners, or by laboratories who have been contracted to perform some of the sample processing work. Such third parties will not have access to your personal details and all samples will be identified only by a unique study number.

Will any genetic tests be done?
Yes. The genetic research will involve the identification of genes that associate with pain and with the development of OA. These genetic tests are not an essential part of the main study and are not a requirement for you to take part in the study.

Will my taking part in the study be kept confidential?
If you join the study, some parts of your medical records and data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential,** stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.
The results of the study will be published in medical literature, but your identity will not be revealed.

We will ask for your permission to store your personal details on a secure database within Academic Rheumatology to enable us to invite you to take part in future research studies. If this happens, you will be given the opportunity to decide whether you would like to take part or not. If you state that you do not wish to be contacted regarding future studies your personal details will be destroyed when the results from the study have been analysed.

X-rays will be stored electronically on the Nottingham University Hospital system (PACS). The images would be available for review if required for clinical purposes by other doctors and clinicians based at the Nottingham City Hospital and QMC campus.

All research data will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?
Your participation in the study is entirely voluntary and you are free to withdraw at any time, without giving reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of your General Practitioner/Family doctor (GP)
All the procedures outlined above are being carried out for research purposes only and your GP will not routinely be informed of your participation in the study. However, if it is felt that it would benefit your medical care if we inform your GP of your examination and, if relevant, x-ray findings, this will be discussed with you at the appointment. Professor Doherty will only write to your GP to inform him of the examination and x-rays findings if you confirm that you are happy for him to do so.

Will I be paid for participation in this study?
The study is entirely voluntary. You will receive no payment for your participation however all your travel costs to and from the City Hospital will be reimbursed.

What will happen to the results of the research study?
We hope that the results of this study will lead to a better understanding of the risk factors for knee pain severity and OA and help guide future management of this common type of arthritis. Results from the study will be submitted for publication in scientific and medical journals and presented at medical scientific meetings. We will also provide you with a summary of the results if you wish.

Who is organising and funding the research?
This study is organised by members of staff in Academic Rheumatology, a department of the University of Nottingham based at the City Hospital. The study is being funded by the Arthritis Research UK (ARUK) Pain Centre here at the University of Nottingham.

Who has reviewed the study?
This study has been reviewed by the Nottingham2 Research Ethics Committee.

Further information and contact details:

Study Contacts: Laura Marshall, Research Metrologist or Nadia Frowd, Clinical Coordinator, Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB
Tel: 01158231676

Chief Investigator: Professor Michael Doherty, Professor of Rheumatology, Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB

Research Contacts:
Helen Richardson, Research Coordinator: Tel: 0115 8231754

Thank you for taking the time to read this information sheet.

E.3 Consent Form

Nottingham University Hospitals NHS
NHS Trust

Arthritis Research UK | pain centre

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

KNEE PAIN AND RELATED HEALTH IN THE COMMUNITY STUDY
CONSENT FORM
(Principal Investigator: Professor Michael Doherty)

REC ref: **14/EM/0115**

Name of Researcher:

Name of Participant: **ID** | | | | | |

		Please initial below
1.	I confirm that I have read and understand the information sheet version 5 dated 7th July 2015 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.	
3.	I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I understand that my personal details will be kept confidential.	
4.	I understand that participating in this study involves having an x-ray of my knees.	
5.	I understand that the study involves providing a blood sample (10ml) and a urine sample.	
6.	I understand that the blood sample may be used for genetic testing. I understand the cells in my blood and urine will also be tested for biomarkers (blood components such as enzymes, hormones, proteins, lipids) that might identify risk or severity of osteoarthritis and changes associated with pain. I understand that samples taken for this study will be stored in the Clinical Sciences Building, Nottingham City Hospital. I understand that I will not receive the results of the genetic or biomarker tests.	
7.	I agree to take part in Quantitative Sensory Testing (QST).	
8.	I agree that the samples I have given and the information gathered about me can be stored by Professor Doherty in the Clinical Sciences Building for possible use in future studies relating to pain and/or osteoarthritis. I understand that some of these studies may be carried out by researchers other than the current team led by Professor Doherty who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and I will not be identified in anyway. (Optional)	

KNEE PAIN AND RELATED HEALTH IN THE COMMUNITY STUDY
CONSENT FORM
(Principal Investigator: Professor Michael Doherty)

Name of Participant: **ID** | | | | | |

9. I understand that my data will be stored safely and securely on a database in a password encrypted format. ☐

10. I understand that my GP will not routinely be informed of my participation in the study but agree to my GP being informed of findings which will benefit my future medical care (Optional). ☐

11. I agree to participate in the above study. ☐

Name of participant	Signature of participant	Date

Name of researcher	Signature of researcher	Date

F. Methods

F.1 Questionnaire Cover Sheet

OA and Football Study Log

Date Questionnaire Received	
Footballer ID	
Questionnaire ID	
Date Checked	
Checked By	
Information Requested:	X-rays ☐ Further Information ☐
Date PIS and Cover Letter Sent	
Details Entered on Database (Date)	
Details entered on the Database by	
Comments:	

SPIRE Appointment Phone Log

Date Phoned	Phoned By:	Outcome of Phone Call

Appointment Booking Log

1) Appointment Date and Time:
2) If re-booking, appointment date and time:

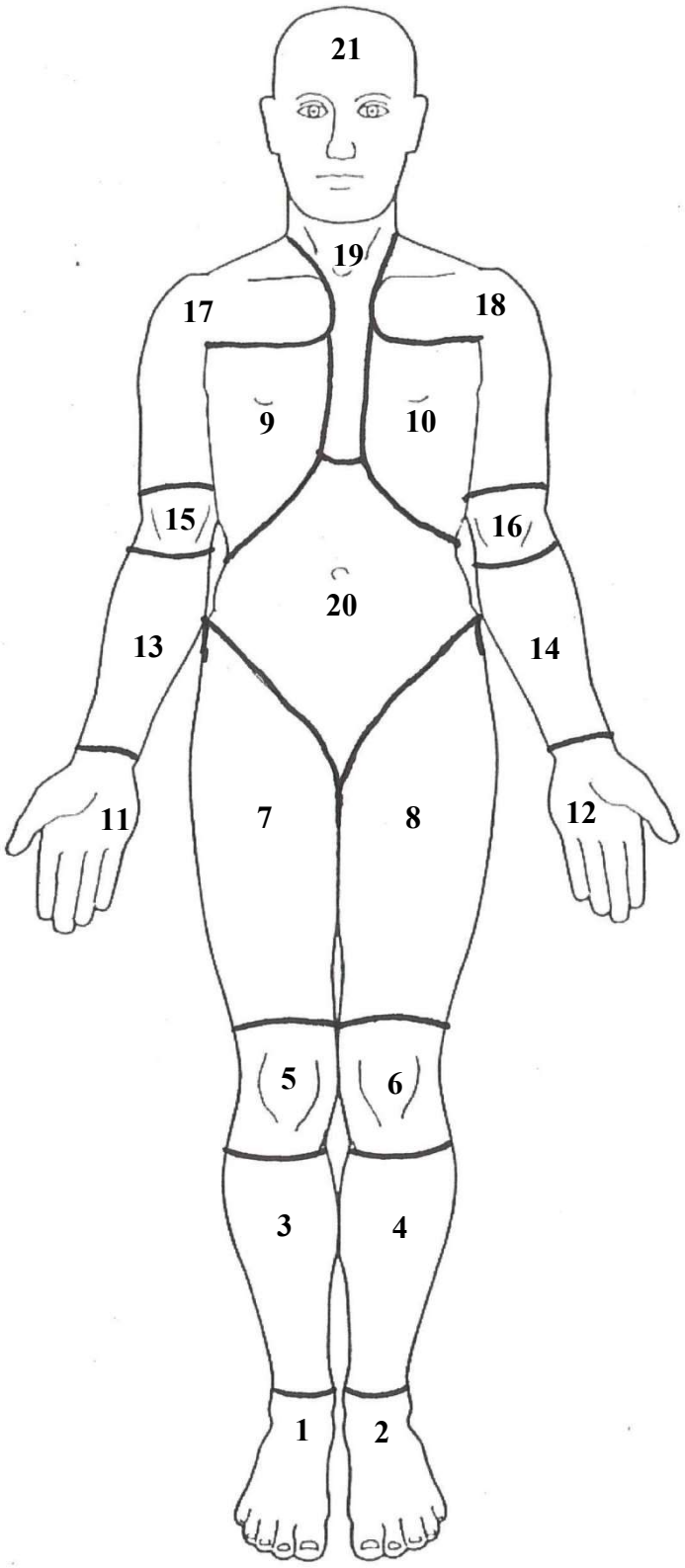
Attended: YES ☐ NO ☐ If no, why

_____

Date Consent Form Received:
Date X Ray Received:

F.2 Body Pain Mannequin (BPM) Classification

Anterior BPM



1 Right foot and ankle

2 Left foot and ankle

3 Right lower leg

4 Left lower leg

5 Right knee

6 Left knee

7 Right upper leg / hip

8 Left upper leg / hip

9 Right upper chest

10 Left upper chest

11 Right hand

12 Left hand

13 Right lower arm

14 Left lower arm

15 Right elbow

16 Left elbow

17 Right upper arm / shoulder

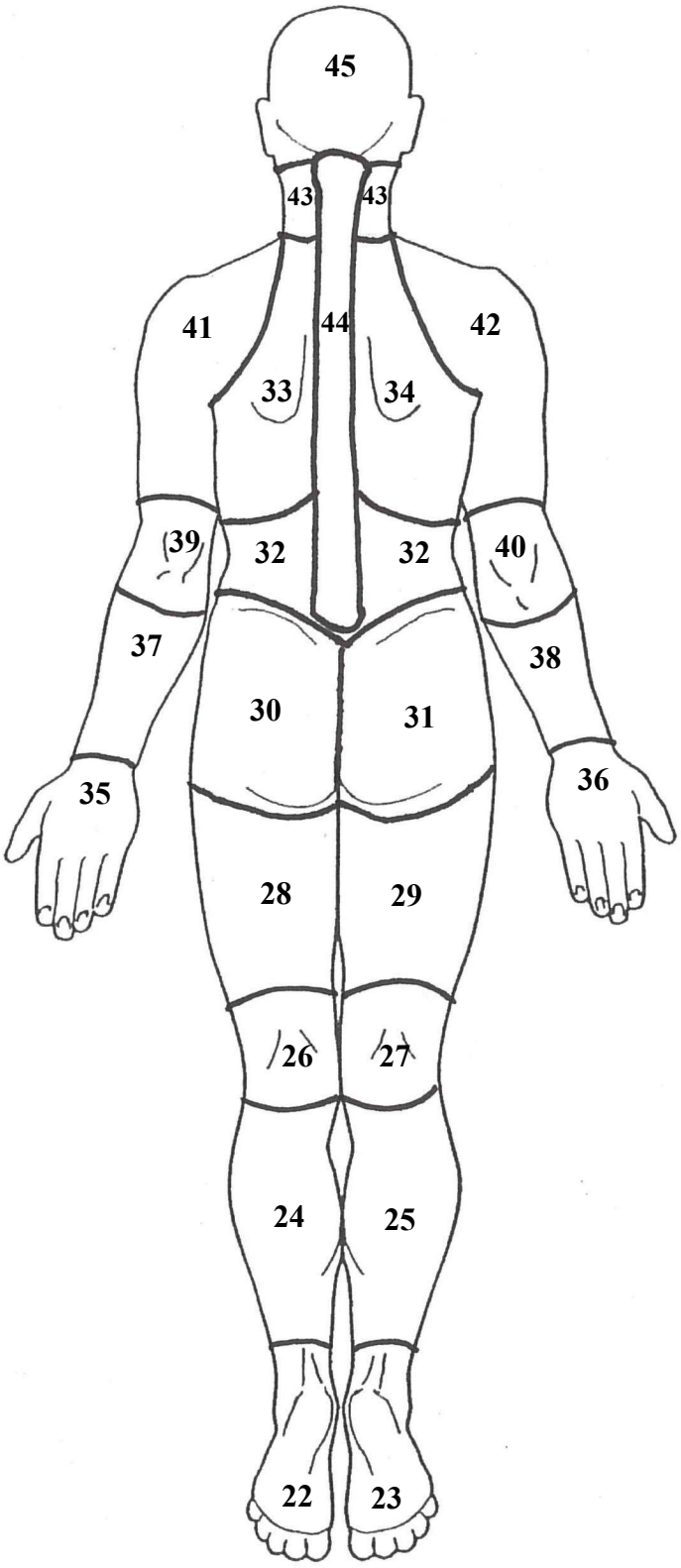
18 Left upper arm / shoulder

19 Neck

20 Abdomen

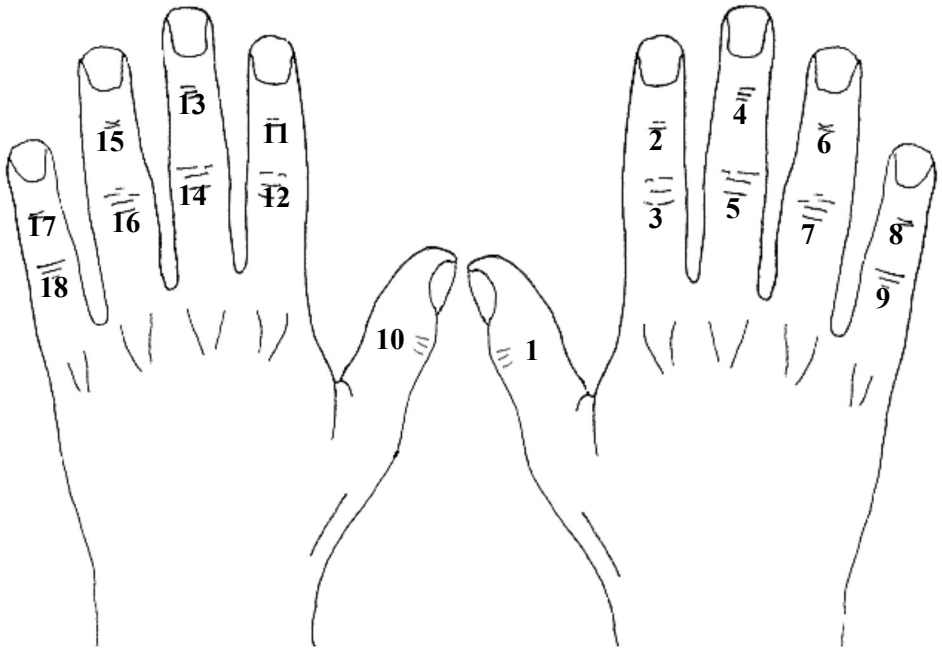
21 Head

Posterior BMP



22 Left foot and ankle
23 Right foot and ankle
24 Left lower leg
25 Right lower leg
26 Left knee
27 Right knee
28 Left upper leg
29 Right lower leg
30 Left hip
31 Right hip
32 Lower back
33 Left upper back
34 Right upper back
35 Left hand
36 Right hand
37 Left arm
38 Right arm
39 Left elbow
40 Right elbow
41 Left shoulder
42 Right shoulder
43 Neck
44 Spine
45 Head

F.3 Hand Node Classification



Left Hand **Right Hand**

1	Right thumb DIP	**10**	Left thumb DIP
2	Right index finger DIP	**11**	Left index finger DIP
3	Right index finger PIP	**12**	Left index finger PIP
4	Right middle finger DIP	**13**	Left middle finger DIP
5	Right middle finger PIP	**14**	Left middle finger PIP
6	Right ring finger DIP	**15**	Left ring finger DIP
7	Right ring finger PIP	**16**	Left ring finger PIP
8	Right little finger DIP	**17**	Left little finger DIP
9	Right little finger PIP	**18**	Left little finger PIP

G. Statistical Analysis

G.1 GLM (Poisson distribution) Univariate Analysis

(Univariate Analysis – RR)	**Current KP**	**TKR**
Footballer (crude)	1.94 (1.80-2.09) p<0.001	2.89 (2.31-3.60) p<0.001
Age (years)	0.99 (0.98-0.99) p<0.001	1.07 (1.06-1.08) p<0.001
BMI (kg/m^2)	1.04 (1.03-1.05) p<0.001	1.06 (1.04-1.07) p<0.001
Right Handed	1.07 (0.96-1.18) p=0.222	0.92 (0.67-1.28) p=0.633
Pattern 3 Digit Ratio	1.07 (0.99-1.15) p=0.111	1.07 (0.85-1.34) p=0.569
Nodal OA	1.54 (1.36-1.74) p<0.001	2.91 (2.16-3.93) p<0.001
Knee Injury	2.30 (2.13-2.48) p<0.001	3.70 (2.93-4.67) p<0.001
High Risk Occupation	1.40 (1.29-1.52) p<0.001	1.35 (1.07-1.70) p=0.011
Malalignment		
Constitutional	1.42 (1.28-1.58) p<0.001	2.71 (2.08-3.54) p<0.001
Current	1.73 (1.59-1.88) p<0.001	2.62 (2.05-3.35) p<0.001
Body Pain	N/A	0.71 (0.55-0.92) p=0.010
Taking Pain Medication	1.82 (1.69-1.97) p<0.001	3.53 (2.79-4.48) p<0.001
Comorbidities	1.02 (0.94-1.10) p=0.709	1.71 (1.37-2.14) p<0.001

G.2 RKOA (KL Assessment)

Characteristics of Footballer with RKOA (KL)

	RKOA	No RKOA	p-value
n, (%)	134 (28.5)	336 (71.5)	
Age (years), mean (SD)	60.7 (9.8)	56.3 (10.8)	<0.001 **
BMI (kg/m^2), n (%)			0.708
<25	23 (17.6)	69 (20.9)	
25 –	85 (64.8)	209 (63.1)	
≥30	23 (17.6)	53 (16.0)	
Pattern 3 Digit Ratio, n (%)	89 (69.5)	218 (66.9)	0.586
Nodal OA, n (%)	10 (31.3)	21 (23.3)	0.593
Familial: n (%)			
Knee OA	29 (21.6)	82 (24.4)	0.524
Hip OA	22 (16.4)	53 (15.8)	0.863
Hand OA	24 (17.9)	62 (18.5)	0.891
Knee Replacement	28 (20.9)	59 (17.6)	0.401
Constitutional Malalignment, n (%)	17 (12.8)	58 (17.7)	0.196
High Risk Occupation, n (%)	80 (59.7)	205 (61.0)	0.793
Use of Statins, n (%)	23 (17.3)	40 (11.9)	0.123
Suffers from Gout, n (%)	19 (14.2)	25 (7.4)	0.024 *
Presence of CC, n (%)	63 (47.0)	51 (15.2)	<0.001 **
Joint Injury, n (%)	104 (79.4)	230 (69.5)	0.032 *
Surgery, n (%) †	117 (81.3)	221 (66.0)	<0.001 **
Injections, n (%)	78 (58.2)	152 (45.2)	0.011 *
Total Football Duration, (years), mean (SD)	21.7 (5.9)	21.0 (6.2)	0.275
Career Training Dose, (hours), mean (SD)	8305 (3889)	7377 (4046)	0.027 *
Matches Played, n (%)	474 (239)	464 (247)	0.6933
Main Tier, n (%) ‡			
One	42 (31.3)	100 (29.8)	0.736
Two	35 (26.1)	67 (19.9)	0.142
Three	27 (20.2)	63 (18.8)	0.728
Four	13 (9.7)	40 (11.9)	0.495
Position, n (%)			
Goalkeeper	18 (13.4)	31 (9.2)	0.178
Defender	43 (32.1)	120 (35.7)	0.456
Midfielder	39 (29.1)	91 (27.1)	0.658
Forward	34 (25.4)	92 (27.4)	0.657

† refers to exploratory / investigative / corrective surgery; ‡ the tier footballers played in for the majority of their career (assessed independently); * p<0.05, ** p<0.01

Risk Factor Analysis for RKOA (KL)

Exposure	**Odds Ratio, OR (95% Confidence Interval, CI)**		
	Crude	Adjusted 1 [#]	Adjusted 2 [##]
Age	1.04 (1.02-1.06)**	1.04 (1.02-1.06)**	1.03 (1.00-1.05) *
BMI (kg/m^2)			
<25	1.00	1.00	1.00
25 –	1.22 (0.72-2.08)	1.25 (0.73-2.15)	1.08 (0.60-1.94)
≥30	1.30 (0.66-2.57)	1.20 (0.60-2.40)	1.11 (0.51-2.42)
Pattern 3 Digit Ratio	1.13 (0.73-1.76)	1.14 (0.72-1.80)	1.02 (0.62-1.68)
Nodal OA	1.28 (0.52-3.14)	1.28 (0.51-3.23)	1.71 (0.57-5.15)
Familial:			
Knee OA	0.86 (0.53-1.38)	0.88 (0.54-1.45)	0.94 (0.54-1.64)
Hip OA	1.05 (0.61-1.81)	1.12 (0.65-1.96)	1.26 (0.68-2.36)
Hand OA	0.96 (0.57-1.62)	0.96 (0.56-1.63)	0.78 (0.42-1.44)
Knee Replacement	1.24 (0.75-2.05)	1.42 (0.85-2.39)	1.44 (0.81-2.58)
Constitutional Malalignment	0.68 (0.38-1.22)	0.76 (0.41-1.39)	0.63 (0.32-1.23)
High Risk Occupation	0.95 (0.63-1.42)	1.03 (0.67-1.57)	0.80 (0.50-1.29)
Use of Statins	1.55 (0.89-2.70)	1.14 (0.62-2.06)	1.40 (0.72-2.73)
Suffers from Gout	2.06 (1.09-3.87) *	1.67 (0.85-3.26)	1.50 (0.69-3.22)
Presence of CC	4.96 (3.16-7.79)**	4.41 (2.76-7.05)**	4.04 (2.45-6.66)**
Joint Injury	1.69 (1.04-2.74) *	1.81 (1.10-2.99) *	0.83 (0.44-1.56)
Surgery †	3.55 (2.03-6.19)**	3.69 (2.09-6.53)**	3.12 (1.50-6.46)**
Injections	1.69 (1.12-2.53) *	1.71 (1.13-2.60) *	0.96 (0.59-1.57)
Total Football Duration	1.02 (0.98-1.05)	1.04 (0.98-1.05)	0.98 (0.93-1.03)
Career Training Dose	1.06 (1.01-1.11) *	1.04 (0.99-1.10)	1.01 (0.95-1.07)
Matches Played	1.18 (0.52-2.70)	1.04 (0.44-2.44)	0.47 (0.15-1.43)
Main Tier ‡			
One	1.08 (0.70-1.66)	0.97 (0.62-1.52)	0.78 (0.46-1.31)
Two	1.19 (0.94-1.51)	1.24 (0.97-1.57)	1.27 (0.97-1.69)
Three	1.03 (0.87-1.22)	1.04 (0.87-1.24)	0.97 (0.80-1.18)
Four	0.94 (0.80-1.11)	0.99 (0.84-1.17)	1.06 (0.89-1.28)
Position			
Goalkeeper	1.53 (0.82-2.83)	1.49 (0.79-2.81)	1.68 (0.82-3.45)
Defender	0.92 (0.75-1.14)	0.97 (0.78-1.21)	0.96 (0.75-1.22)
Midfielder	1.03 (0.89-1.20)	1.02 (0.88-1.19)	1.05 (0.88-1.24)
Forward	0.97 (0.87-1.09)	0.95 (0.84-1.06)	0.93 (0.81-1.06)

[#] OR adjusted for age and BMI (adjusted 1); [##] OR adjusted all factors significant from crude analysis (adjusted 2); * p<0.05; ** p<0.01; † refers to exploratory / investigative / corrective surgery; ‡ the tier footballers played in for the majority of their career (assessed independently)