Prevalence and risk factors of foot/ankle osteoarthritis and pain in retired male professional footballers compared to general population male controls: a cross-sectional study.

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Declaration

I declare that this thesis is my own work and any assistance I received is listed below. This work has not been submitted for any other degree, diploma or qualification. All the authors and works to which reference has been made are fully acknowledged. Professors Weiya Zhang, Michael Doherty, Mark Batt, Dr Colin Fuller, and Dr Gwen Fernandes conceptualised the study. Dr Shima Espahbodi and I jointly developed the questionnaire and survey packs and applied for research ethics under the supervision of Professors Weiya Zhang and Michael Doherty. I undertook the radiographic assessment across 5 National Health Service (NHS) hospitals in Nottingham, Manchester, Leeds, Southampton and London with the help of another PhD student Miss Monirah Shuaib. Also, Dr Bonnie Millar and her team assisted in arranging radiography appointments and access to the 5 NHS hospital sites. I conducted the data analysis and wrote this thesis under the supervision of my PhD supervisors, Professors Weiya Zhang and Michael Doherty.

Abstract

Background

Osteoarthritis (OA) is the most common form of arthritis that affects synovial joints. The prevalence of foot/ankle OA is less understood than hip, knee and hand OA. Foot and ankle injuries account for approximately one-fifth of all injuries sustained during professional football play. Injury is the major risk factor associated with a four-fold increased risk of knee OA in male professional footballers. However, despite the high incidence of injuries to the foot/ankle in professional footballers, there is a lack of evidence relating this to OA development and the associated risk factors at this site. Whether foot/ankle OA in professional footballers is more common than in the general population remains unknown. This study examined the prevalence of foot/ankle OA and pain in retired male professional footballers compared to general population male controls and risk factors associated with the increased risk in retired male professional footballers.

Objectives

This research aimed to answer three questions: [1] whether retired male professional footballers are more likely to have foot/ankle OA and pain than general population male controls; [2] what specific risk factors are associated with foot/ankle OA within retired male professional footballers; and [3] is there any difference in the quality of life and performance of functional tests between retired male professional footballers and general population male controls?

Methods

A cross-sectional comparative study was conducted in the United Kingdom (UK) between August 2020 and March 2023. Postal questionnaires were sent to 878 retired professional footballers in the UK and to 1060 men in the general population in the East Midlands region of England, all of whom had participated in our previous study that focused on knee OA. Participants who completed and returned their questionnaires, who indicated willingness to attend hospital for foot/ankle radiographs, and who resided reasonably close to one of five collaborating National Health Service (NHS) hospitals (Nottingham, Manchester, Leeds, Southampton and London) were invited to undergo bilateral foot and ankle radiographic assessment, irrespective of any self-reported foot/ankle OA outcomes. During the same visit, the Four-Square Step Test (FSST) and a 10-Metre Walk Test (10-MWT) were performed to measure objective performance-related functional outcomes. Pain was defined as current pain for most days in the past month and as ever pain for ≥ 3 months in the past. General practitioner (GP) diagnosed foot/ankle OA and forefoot/ankle surgery were self-reported. Radiographic OA (ROA) was defined as osteophytes (OP) ≥2 or joint space narrowing (JSN) ≥2 on either dorso-plantar or lateral views using the Menz atlas (scale 0-3). Symptomatic radiographic OA (sROA) was defined as the presence of ROA and pain for most days in the past month at the same joint using foot manikin.

The prevalence of each foot/ankle OA outcome was compared between footballers and controls. Robust Poisson regression model was used to calculate the adjusted relative risks (aRRs) with 95% confidence interval (CI). The aRR was adjusted for the significant potential confounding factors identified from the univariate analysis. A nested case-control study was conducted on 63 cases (footballers with self-reported foot/ankle OA) and 361 controls (footballers without self-reported foot/ankle OA). Logistic regression was used to calculate the adjusted odds ratio (aOR) and 95% CI.

Results

In total, 468 footballers (53%) and 619 controls (58%) completed the questionnaire. Of 362 footballers and 497 controls who consented to radiographic assessment, 113 footballers and 319 controls completed the radiographic assessment and performance functional tests. Compared to controls, footballers were younger (mean age 63.27 versus 68.42 years; $p<0.001$) and had a higher socioeconomic status (median 8.00 versus 6.50; $p<0.001$), and a significantly higher prevalence of current foot/ankle pain (35%, 95% CI 29.7-39.5 versus 26%, 95% CI 21.4-28.9; p=0.003) and GP-diagnosed foot/ankle OA (13%, 95% CI 9.1-15.9 versus 8%, 95% CI 4.3-8.5; p=0.011) than controls. Footballers scored higher on the SF-36 physical component than controls (mean 72.02 versus 69.25; p=0.046), with no significant difference in mental component scores (mean 77.98 versus 77.27; p=0.559).

After adjusting for confounding factors, footballers were more likely to have current foot/ankle pain (aRR 1.33, 95% CI 1.09-1.62), GP-diagnosed foot/ankle OA (aRR 1.77, 95%CI 1.22-2.57), forefoot/ankle

surgery (aRR 2.80, 95% CI 2.04-3.84), foot/ankle ROA (aRR 1.04, 95% CI 1.01-1.07) and sROA (aRR 1.63, 95% CI 1.21-2.19) but not ever foot/ankle pain for ≥ 3 months. According to Menz's definition (either osteophyte or JSN≥2), the prevalence of ROA of the foot/ankle OA was not different between footballers and controls. However, it was significantly different when “definite osteophyte plus definite narrowing” was used to define OA. The joint-specific analysis demonstrated that the ankle was the most common joint to be affected by OA in footballers compared controls. Foot/ankle injury (44.71% versus 18.73%, p<0.001) and injection (53.13% versus 6.25%; p<0.001) were different between the two groups. These were identified as the major risk factors associated with the increased odds of self-reported foot/ankle OA within footballers, the aOR being 4.23 (95% CI 1.88-9.48, p<0.001) for foot/ankle injury and 2.62 (95% CI 1.19-5.78, p=0.017) for foot/ankle injection, respectively.

Conclusion

Retired male professional footballers were more likely to have self-reported and radiographic foot/ankle OA than general population male controls. The ankle appeared to be the joint most affected by OA in footballers compared to general population. Injury and injection were the two major risk factors associated with the increased risk of foot/ankle OA in footballers. Further studies are needed to develop preventive strategies to reduce the risk of foot and ankle OA in current and future professional footballers.

List of publications relating to the PhD work

Research articles:

[1] Espahbodi, S., Fernandes, G., Hogervorst, E., **Thanoon, A**., Batt, M., Fuller, C.W., Fuller, G., Ferguson, E., Bast, T., Doherty, M. and Zhang, W. Foot and ankle Osteoarthritis and Cognitive impairment in retired UK Soccer players (FOCUS): protocol for a cross-sectional comparative study with general population controls. *BMJ Open* 2022;12:e054371

[2] Espahbodi S, Hogervorst E, Macnab TP, **Thanoon A**, Fernandes GS, Millar B, Duncan A, Goodwin M, Batt M, Fuller CW, Fuller G, Ferguson E, Bast T, Doherty M, Zhang W. Heading Frequency and Risk of Cognitive Impairment in Retired Male Professional Soccer Players. *JAMA Network Open*. 2023;6:e2323822.

[3] Macnab, T.M.P., Espahbodi, S., Hogervorst, E., **Thanoon, A**., Fernandes, G.S., Millar, B., Duncan, A., Goodwin, M., Batt, M., Fuller, C.W. and Fuller, G. Cognitive Impairment and Self-Reported Dementia in UK Retired Professional Soccer Players: A Cross-Sectional Comparative Study. *Sports Medicine Open* 2023;9:43

Manuscript under review

[1] **Thanoon, A.A.**, Espahbodi, S., Shuaib, M.A., Millar, B., Duncan, A., Bowen, C., O'Neill, T.W., Wakefield, R.J., Watt, F.E., Walsh, D.A., Fuller, C., Fuller, G., Batt, M.E., Parekh, S.M., Fernandes, G.S., Doherty, M. and Zhang, W. Prevalence of foot/ankle osteoarthritis and pain in retired male professional footballers compared to general population male controls: A cross-sectional study. *Under Review in Sports Medicine - Open*, 2025.

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Other abstracts:

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Other presentations:

[1] **Ahmed Thanoon,** 2021. Foot/ankle OA and Cognitive Impairment in UK Soccer FOCUS. Oral presentation at the 7th Annual Showcase of the UK Research in Musculoskeletal Epidemiology (UK-RiME) partnership, funded by Versus Arthritis, hosted at the University of Bristol, 2nd-3rd September 2021.

[2] **Ahmed Thanoon**, 2022. Foot/ankle Pain and Osteoarthritis in Retired Ex-Professional Footballers. Oral presentation (ten-minute talk with three minutes of discussion) at the Sue Watson PGR Oral Presentation Event, hosted at the University of Nottingham on 26th April 2022.

Collaborations

[1] I coordinated the Foot and Ankle Osteoarthritis and Cognitive impairment in retired UK Soccer players (FOCUS) project in the second year of my PhD that included two conditions: (1) foot and ankle OA with radiographic assessment related to my thesis and (2) dementia and cognitive impairment, involving a telephone assessment. I am a co-author for all publications relating to this work and I have coordinated the collection, entry, cleaning and management of the data.

[2] I was involved with Ashley Duncan (PhD student) in her project “Investigating the association between knee pain, anxiety, and depression during the COVID-19 pandemic: Utilising the Knee Pain and Related Health in the Community Survey (KPIC)”. I helped her pack and sent out more than 900 questionnaires during the pandemic.

[3] I was involved in supervision meetings for Monirah Shuaib (PhD student) in her project “The incidence of knee pain and multimorbidity in male ex-professional footballers compared to men in the general population".

[4] I have also been involved in developing and managing the FOCUS database and providing the FOCUS data to other users, including other PhD students and researchers both within and outside the University.

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List of Abbreviations

ACR	American College of Rheumatology
aOR	Adjusted odds ratio
aRR	Adjusted relative risks
AT	Ahmed Thanoon
BMI	Body Mass Index
BPM	Body Pain Mannequin
CASF	Clinical Assessment Study of the Foot
CI	Confidence interval
CMJ	Cuneo-metatarsal joint
CSB	Clinical Sciences Building
DOB	Date of birth
EULAR	European Alliance of Associations for Rheumatology
FA	Football Association
FHSQ	Foot Health Status Questionnaire
FIFA	Fédération Internationale de Football Association
FOCUS	Foot/ankle Osteoarthritis and Cognitive impairment in UK Soccer players
FSST	Four Square Step Test
GDPR	General Data Protection Regulation
GP	General Practitioner
HRQOL	Health-related quality of life
IASP	International Association for the Study of Pain
IMD	Index of Multiple Deprivation
JSN	Joint space narrowing
KL	Kellgren and Lawrence
KOA	Knee osteoarthritis
KPIC	Knee Pain and related health In the Community
LTFA	La Trobe Foot Atlas
MRI	Magnetic resonance imaging
MS	Monirah Shuaib
MSU	Monosodium urate
MTPJ	Metatarsophalangeal joint
N1st CJ	Navicular-first cuneiform joint
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OA	Osteoarthritis
OP	Osteophyte
OR	Odds-ratio
PCQ	Pain Catastrophizing Scale
PDQ	Pain Detect Questionnaire
PFA	Professional Footballers' Association
PIS	Participant's information sheet
PPI	Patient and public involvement
QoL	Quality of life
RKOA	Radiographic knee osteoarthritis
ROA	Radiographic osteoarthritis

SES	Socioeconomic Status
SF-36	Short Form 36 Health Survey
sROA	Symptomatic radiographic osteoarthritis
TNJ	Talonavicular joint
UK	United Kingdom
UoN	University of Nottingham
10-MWT	10-metre walk test

Chapter : 1 Introduction

1.1 Osteoarthritis

Osteoarthritis (OA) is a term derived from the Greek word *osteo*, meaning bone and *arthros* meaning joint, with the suffix *itis* implying inflammation (Brandt et al., 2008). The term "degenerative joint disease" is often used to describe OA. However, this is a misleading term because OA is not simply a process of wear and tear but involves active remodelling of joint tissues driven by a host of inflammatory mediators within the affected joint (Loeser et al., 2012). The National Institute for Health and Care Excellence (2022) defines OA as “a disorder of synovial joints which occurs when damage triggers repair processes leading to structural changes within a joint”. OA occurs in synovial (diarthrodial) joints and leads to focal loss of articular cartilage with narrowing of the articular space, bone remodelling, and marginal new bone formation (osteophytes) (Doherty et al., 2016b).

1.1.1 The phylogenetic and evolutionary preservation of OA

The study of ancient skeletal remains suggests that OA has accompanied mankind throughout our evolutionary history (Hutton, 1987, Ruffer and Rietti, 1911). Structural changes equivalent to OA are also found in other animals with synovial joints that fuse their epiphyses in the adult form. Indeed, archaeological evidence supports the evolutionary antiquity of the condition in many species, including dinosaurs, which suggests that OA is not necessarily ‘all bad’ and may have been conserved throughout

animal evolution for a reason, for example, as an adaptive response to joint injury (Rothschild, 1990, Ruffer and Rietti, 1911).

One major issue when studying archaeological skeletons is the lack of data and the uncertainty about how representative the collected skeletons are of the population they come from. For instance, certain burial sites may contain a high concentration of a particular group, such as the clergy or the most wealthy individuals, which may not reflect the wider population (Rothschild, 1990, Ruffer and Rietti, 1911). Additionally, accurately determining the age of skeletons is challenging, as the methods used by biological anthropologists tend to be imprecise, only allowing for age estimation within a decade after the skeletal maturity period and with no differentiation after the age of 50 in most cases (Rothschild, 1990, Ruffer and Rietti, 1911). As a result, it is difficult to make accurate comparisons between the prevalence of OA in ancient and modern populations.

1.1.2 Dynamic nature of OA

OA is a metabolically active process that affects all tissues in the joint and is characterised by the growth of new bone (readily apparent as osteophytes), synovial hyperplasia, and thickening of the joint capsule (Doherty et al., 2016a). Although loss of cartilage is a key feature, chondrocytes in an OA joint initially multiply in number and increase their activity, producing more matrix components and becoming hypertrophic (Doherty et al., 2016a). New fibrocartilage is also formed at the joint

margins which then undergoes ossification to form osteophytes (Figure 1-1).



Figure 1-1. Knee radiograph showing severe patellofemoral narrowing, abundant large osteophytes, and multiple osteochondral bodies anteriorly in the suprapatellar pouch and posteriorly in the popliteal fossa. Produced with permission (Doherty et al., 2016a).

In the synovium, synoviocytes can transform into chondroid cells that produce fibrocartilage. This fibrocartilage may ossify and create slowly growing osteochondral (“loose”) bodies (Glyn-Jones et al., 2015). The biochemical changes in OA cartilage differ from those during the natural ageing process. In OA, there is an increased turnover of various cartilage matrix components and the expression of chondroitin epitopes that are typically seen in young or growing cartilage. Similar dynamic processes occur in other OA tissues, such as bone and synovium (Hunter and Bierma-Zeinstra, 2019). These features suggest that all joint components

are attempting to produce new tissue in response to joint insults, thus negating the old term ”degenerative joint disease” (Doherty et al., 2016a).

OA can affect any synovial joint but most commonly affects the knees, hips, first carpometacarpal (CMCJs), interphalangeal finger joints (IPJs), first metatarsophalangeal (1st MTPJ) (bunion) joints, and apophyseal facet joints of the lower cervical and lower lumbar spine. Figure 1-2 illustrates the joints commonly affected by OA (Abhishek and Doherty, 2013).

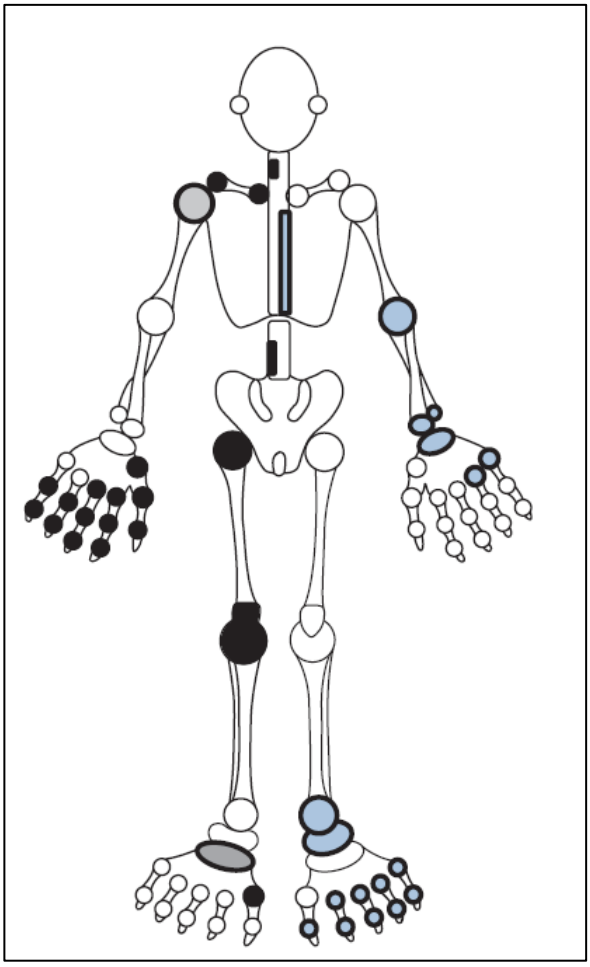


Figure 1-2 Targeted distribution of osteoarthritis in humans. Common target sites are shown on the left in black, less common sites in older age are shown in grey, and relatively spared sites are shown on the right in blue. Produced with permission (Doherty et al., 2016a).

1.1.3 Discordance between structural changes and symptoms

It is worth noting that clinical and radiographic signs of OA can often be present without symptoms or compromised function (Doherty et al., 2016a). Asymptomatic OA is particularly common in certain sites, such as finger joints and lower cervical, and lumbar apophyseal joints, but it can also occur in large weight-bearing joints. Most of us develop OA in some part of our body as we age, but this does not usually lead to any noticeable issues in the majority of cases (Hunter and Bierma-Zeinstra, 2019). Therefore, there is a significant difference between the disease OA (which involves structural changes that can be identified through imaging or clinical examination) and the illness OA (which involves symptoms that patients report) (Doherty et al., 2016a).

1.1.4 Generally good outcome of OA

Although the impact of symptomatic OA on an individual's health can be significant, it is not always progressive (Doherty et al., 2016a). Many people with OA experience periods of time when their symptoms worsen but then gradually improve over time (Doherty et al., 2016a). These episodes, known as "flares," are common among people with OA (Doherty et al., 2016a). Intermittent flares occur especially when nodal OA is first developing in finger interphalangeal joints, but may also occur in hips and knees with OA (Hunter and Bierma-Zeinstra, 2019).

Although the symptoms may resolve, the structural changes of OA persist and stabilise. The lost hyaline cartilage cannot be replaced (Doherty et

al., 2016a). However, in rare cases, radiographs may show improvement with remodelling of bony contours and limited fibrocartilage replacement, which may increase inter-bone distance (Doherty et al., 2016a).

1.2 Nature of Osteoarthritis

OA is by far the most prevalent joint disorder affecting any synovial joint (Doherty et al., 2016a). Established OA manifests as a blend of tissue loss and new tissue formation, leading to the classic triad of focal loss of hyaline articular cartilage with focal joint space narrowing (JSN), local-bone remodelling, and marginal osteophyte development (Glyn-Jones et al., 2015). The combination of focal articular cartilage loss and marginal osteophytosis fundamentally defines OA from the pathological perspective (Glyn-Jones et al., 2015). However, it is important to note that other typical pathological changes occur in all joint tissues in OA, underscoring it as a condition that encompasses the entire joint. Recently, there has been a growing interest in the alterations observed in the synovial tissues of people with OA and how they may contribute to cartilage changes in those with progression of OA (Roemer et al., 2010).

Bone is an active tissue that maintains balance through continuous breakdown (resorption) and formation undertaken by osteoclasts and osteoblasts, respectively (Doherty et al., 2016b). However, in OA, this balance is disrupted, favouring increased bone formation, which leads to bone outgrowth (osteophytes) at the joint margins, hardening of the subchondral tissues (sclerosis), and bone remodelling (Doherty et al.,

2016b). This remodelling is primarily a response to mechanical pressure and other OA-related changes. The bone adapts to increased mechanical stress from the narrowed cartilage and changes its shape, internal architecture, and thickness to allow the compromised OA joint to cope better with mechanical loading (Roemer et al., 2010).

Subchondral bone, a highly adaptable and dynamic tissue, can reshape itself in response to local mechanical pressure. This part of the bone plays a crucial role in the development of OA. The changes observed in the subchondral bone due to OA include bone remodelling, microfractures, isolated areas of osteonecrosis, and thickening of the trabecular bone, and formation of osteophytes at the joint margin (Doherty et al., 2016b). Radin and Rose (1986) first proposed subchondral bone abnormalities preceding issues with the articular cartilage in OA pathology. However, the stress experienced by articular cartilage may gradually cause microfractures in the trabecular bone over time. The subsequent healing of these microfractures may lead to an increase in subchondral bone rigidity, thus hampering its ability to function as a shock absorber and increasing the forces across the joint (Radin and Rose, 1986, Doherty et al., 2016a).

In severe OA, full-thickness cartilage loss can expose the underlayer of bone (subchondral bone), which is most prone to sclerosis. The mechanical friction between the two adjacent bone ends may give the bone a smooth, polished appearance (known as 'eburnation'), often with deep grooves reflecting the wear pattern and assisting joint stability.

Eburnation of the articular surfaces is shown on imaging by the bone density increase in the areas affected (Doherty et al., 2016b). Also, cysts in the subchondral bone can form beneath remodelled joint surfaces, usually close to where the cartilage is missing (Doherty et al., 2016b). These cysts may develop from localised small breaks (microfractures) and dead bone tissue (osteonecrotic lesions) caused by increased mechanical pressure (Doherty et al., 2016b). Alternatively, joint fluid may infiltrate the subchondral bone via small cracks in hardened cartilage, leading to fluid-filled cavities analogous to a hernia. The death of the bone tissue near the surface is thought to result from increased local mechanical stress (Li et al., 2013).

1.2.1 Pathology

Pathologically, OA is characterised by focal areas of articular cartilage damage centred on the maximum load-bearing sites within the joint (Lane et al. (2011). Osteophytosis, changes in the subchondral bone, varying degrees of synovial hyperplasia, and capsular thickening (Figure 1-3). (Glyn-Jones et al., 2015). OA is often asymptomatic and may be diagnosed incidentally during clinical or radiographic examinations, or it may be a relatively temporary cause of symptoms or a progressive, painful, and disabling joint condition (Abhishek and Doherty, 2013).

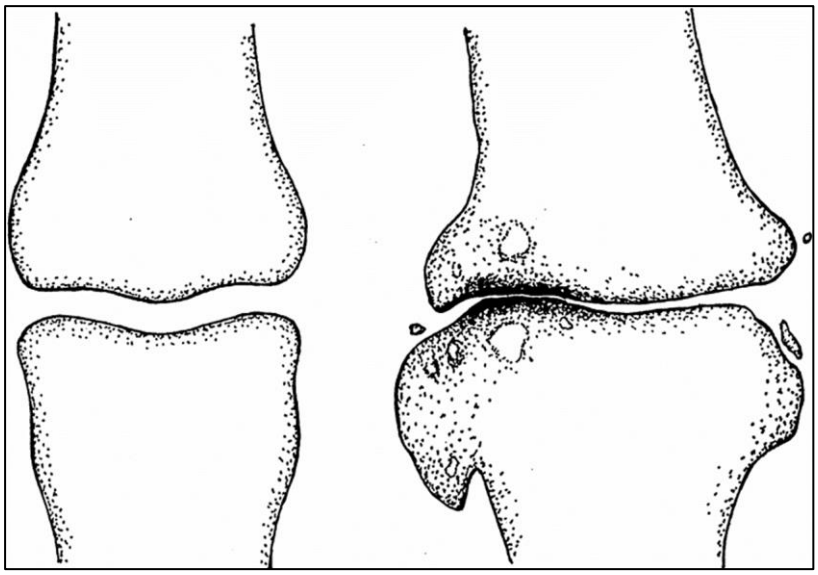


Figure 1-3. Diagrammatic features of the changes that occur in a joint with OA that may be evident on a radiograph.

Normal joint (left) versus an osteoarthritic joint (right) with joint space narrowing, subchondral sclerosis, osteophyte, cysts, and osteochondral bodies. Produced with permission (Doherty et al., 2016a).

Articular hyaline cartilage acts as a smooth, low-friction surface, allowing bones to move easily against each other within a joint. In OA, the cartilage weakens, and fragments break away from the articular surface, creating initial vertical clefts (fibrillation) and eventual loss of cartilage thickness (predominantly localised). In severe cases, cartilage loss can lead to the opposing bones rubbing directly on each other (Lane et al., 2011).

Inflammation of the synovial lining membrane (synovitis) is increasingly considered an important factor in OA pathology (Loeser et al., 2012). This inflammation could be linked to pain by generating pro-inflammatory cytokines, which can make nerves more sensitive to increased pressure within the joint capsule. The synovium is rich in blood and nerves (Roemer et al., 2010). It produces synovial fluid that lubricates the

articular cartilage surfaces, and aids in delivering nutrients and oxygen to cartilage cells (chondrocytes) and removes waste products via draining lymphatic tissue (Doherty et al., 2016a). However, the inflammatory reaction of the synovium in OA is generally much less intense than that in rheumatoid arthritis. Also, synovial inflammation is the first pathological abnormality in Rheumatoid arthritis, is widespread throughout the joint, and causes marginal bone erosion and eventual generalised cartilage loss, with periarticular osteopenia and no new bone response. In contrast, in OA, synovial thickening tends to be localised within an already abnormal joint, and marginal bone erosion is not a feature (Doherty et al., 2016a).

Normal synovial fluid is highly viscous and comprises an ultrafiltrate of plasma that has been enhanced by the secretion of hyaluronic acid and other synovium-produced molecules (Hoff et al., 2013). It contains almost no cells and appears pale yellow or colourless. In OA, the synovial fluid volume increases, whereas its viscosity decreases owing to a reduction in hyaluronic acid and other macromolecules. The ligaments and the capsule within the joint provide essential support and stability (Sun et al., 2014). In OA, these structures undergo pathological changes, including thickening of the joint and tightening capsule and intra-articular ligaments. These changes may help stabilise the affected OA joint, especially when narrowing of the joint space occurs as part of the attempted repair process (Sun et al., 2014).

Tears and scar tissue can be observed microscopically in OA ligaments and capsular tissue. Although thickening and contraction are common, the ligaments and capsule may lose some stabilising potential, contributing to further joint pathology. An increase in synovial fluid in the joint can trigger capsule distortion, whereas changes in the capsule itself may impair fluid movement within the joint cavity (Sun et al., 2014). Bony outgrowths at the attachment points of the capsule, ligaments, and tendons (enthesophytes) may also be more prevalent in OA, indicating a bone-forming phenotype (Doherty et al., 2016a). Local cartilage, synovium, and subchondral bone may play crucial roles in OA pathogenesis, and systemic inflammation may also contribute to this condition (Scanzello and Goldring, 2012).

1.2.2 Pathophysiology

OA is characterised by focal damage, cartilage loss, subarticular bone attrition, osteophytes, muscle weakness, and synovial inflammation (Arden and Nevitt, 2006). This complexity makes it challenging to identify specific causes and mechanisms of OA, thus requiring further research.

1.2.3 Osteophytes

Osteophytes, also known as bone spurs, are cartilaginous and bony growths that primarily develop along the edge of a joint (Doherty et al., 2016b). However, they can also occur centrally (for example, in the inter-condylar site and tibial 'spiking' at the knee and bone 'buttons' emerging into the cartilage from the subchondral bone (Doherty et al., 2016a). OA

causes specific changes in joint tissues that differ from those caused by ageing. These changes vary in severity and tend to occur slowly over time. OA is characterised by the growth of new tissue and the loss of existing tissue, which typically results in the focal loss of articular cartilage, bone remodelling, and the formation of osteophytes (Doherty et al., 2016a, Allen et al., 2022).

Osteophytosis primarily occurs through endochondral ossification, in which an initial fibrocartilaginous outgrowth at the joint margin undergoes calcification and then ossification, which is the same process that allows bones to elongate during growth (van der Kraan and van den Berg, 2007). At the hip joint, osteophytes may develop from the periosteum along the inferior aspect of the femoral neck. This unique type of periosteal osteophyte (known as femoral 'buttressing') may appear as a separate, distinct layer from the underlying bone (Doherty et al., 2016a).

Bone morphogenetic protein, in combination with transforming growth factor beta (TGFβ) and basic fibroblast growth factor (bFGF), could play a significant role in the development of osteophytes (Menkes and Lane, 2004). Osteophytes develop in specific locations within a joint and may act as a protective mechanism to stabilise an osteoarthritic joint (van der Kraan and van den Berg, 2007). Osteophytes are fibrocartilage growths in the periosteum at the junction of bone and cartilage that then undergo ossification in the lower part, which grows and advances outwards with more new bone formation in the bottom part of the fibrocartilage (Menkes and Lane, 2004).

Osteophytosis occurs at joint margins, and during the development of osteophytes, hypertrophic chondrocytes are replaced by osteoblasts through chondrogenesis (Zuscik et al., 2008). As a result, bony outgrowths become visible on diagnostic imaging (Menkes and Lane, 2004). In addition, in large joints (hips and knees), recovery of joint space may occur through the formation of large osteophytes, which help to stabilise the joint (Wong et al., 2016). However, the purpose of these structural changes remains unclear. Although osteophytes can occur in anyone, they are more common in older adults and those with OA (Menkes and Lane, 2004).

1.2.4 Joint space narrowing

Synovial joints are composed of two bone ends with hyaline cartilage endplates within a soft synovial membrane (the inner part of the capsule) that secretes synovial fluid (Dieppe and Lohmander, 2005). Hyaline cartilage is a low-friction material that distributes weight across the joint surface while being wear-resistant (Dieppe and Lohmander, 2005). At the molecular level, OA is caused by several mechanisms, including articular cartilage degradation, bone remodelling, and synovial inflammation (Pearle et al., 2005). The extracellular matrix provides an articular structure consisting of collagen and aggrecan. Cartilage is aneural and, therefore, cannot be directly responsible for joint pain (Pearle et al., 2005). Therefore, pain originates from other tissues such as bone, synovium, capsule, or peri-articular tissues (bursitis, enthesitis) involved secondarily in altered joint functioning (Dieppe and Lohmander, 2005).

In summary, OA is a repair process triggered by joint insults, involving responses from all joint tissues, and resulting in variable outcomes. OA causes pathological changes in all joint tissues, which can vary in severity and usually occur slowly. It is characterised by both new tissue production and tissue attrition, which result in focal loss of articular cartilage, bone remodelling, and marginal osteophyte formation. Additionally, the features of varying degrees of synovial hyperplasia, inflammation, increased synovial fluid volume, and capsular thickening are recognised. OA can also lead to calcium crystal deposition in cartilage (chondrocalcinosis), local muscle atrophy, and enthesophyte formation in the periarticular areas.

Most joints with OA are asymptomatic because their changes compensate for the various insults that have triggered the requirement for repair. However, when there is an overwhelming or continuous insult, or the repair process is compromised, the OA joint may no longer be able to compensate for the triggering insults and then is more likely to associate with symptoms and disabilities – i.e. a situation of “joint failure” Figure 1-4) (Doherty et al., 2016a).

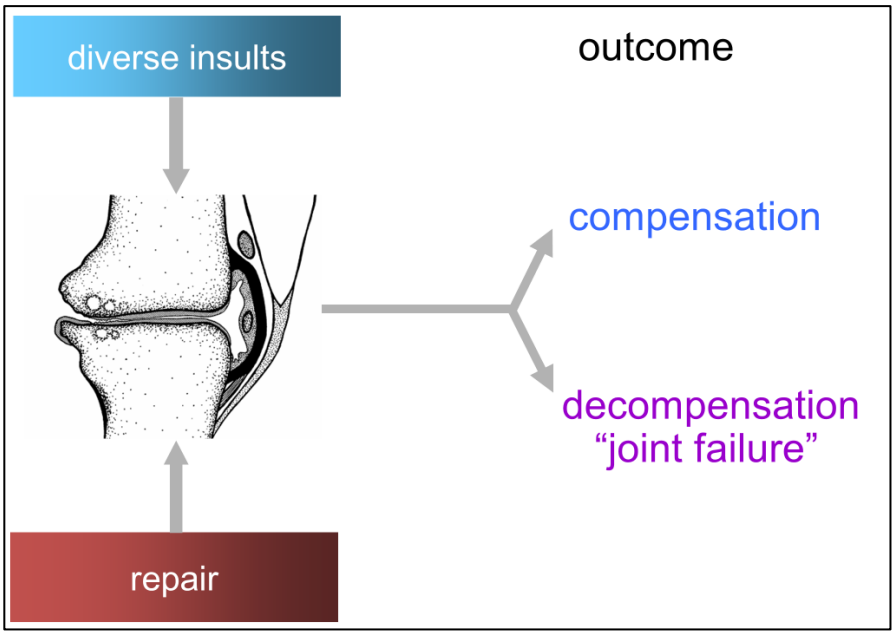


Figure 1-4. Joint failure

1.3 Risk factors for OA

OA is a complex disorder with multiple genetic, constitutional, and environmental risk factors, which may interact variably with each other. Researchers are still striving to fully understand its underlying causes and mechanisms (Hunter et al., 2020). Figure 1-5 outlines the risk factors.

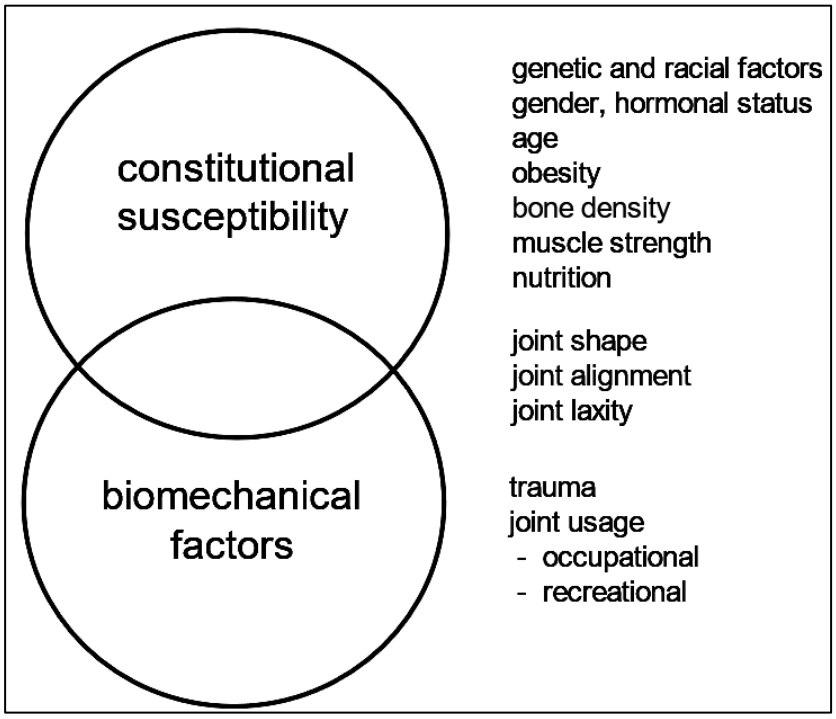


Figure 1-5. Potential risk factors for the common complex disorder of OA. Produced with permission (Doherty et al., 2016a)

1.3.1 Genetic

The genetic risk for OA has been examined in family, twin, and sibling studies, as well as in population-based genome-wide association studies (Allen and Golightly, 2015, Kalichman and Hernández-Molina, 2014, Wilder et al., 2005b). Joint-specific differences in OA heritability have been observed in twin and family studies (MacGregor and Spector,

1999). Heritability estimates for OA have been reported to be 40% for the knee, 60% for the hip, 65% for the hand, and approximately 70% for the spine (Spector and MacGregor, 2004).

The Clearwater Osteoarthritis Study reported a co-occurrence of 1st MTPJ OA with hand or knee OA, even after adjusting for age, body mass index (BMI), and occupational history, suggesting a potential genetic risk (Wilder et al., 2005b). To date, 16 families with MTPJ OA have undergone genomic analysis, and the results indicate that alterations in inflammatory signalling are a major risk factor for developing 1st MTPJ OA. One family has been associated with early onset OA of the 1st MTPJ due to a rare allele of receptor-interacting protein kinase 2 (RIPK2) (p.Asn104Asp) (Jurynec et al., 2018). Further research is needed to identify the genes and pathways that are significant risk factors for foot /ankle OA, which may contribute to a better understanding of the disease mechanisms and the development of therapeutics that could modify the course of OA.

1.3.2 Ethnicity

The prevalence of foot pain was similar between African Caribbean and white people in the Clinical Assessment Study of the Foot (CASF) study (Roddy et al., 2011), with the highest prevalence in Africans and the lowest in Asians. However, these findings should be interpreted with caution because only 2% of the sample was from racial/ethnic minority groups (Roddy et al., 2011). The prevalence of foot pain among white

participants ranges from 13% to 36% in different studies (Jordan, 2015, Roddy et al., 2011, Dufour et al., 2009, Hart and Spector, 1993). African Americans and white individuals reported similar foot pain frequencies (36% and 35%, respectively) in the Johnston County Osteoarthritis Study (Jordan, 2015). In the CASF study (Roddy et al., 2011), foot pain was most prevalent among African Americans (38%) compared to only 10% among Asian participants.

It is worth noting that most studies have largely focused on white populations. For example, the Chingford 1000 Women Study and Framingham Foot Study primarily involved white participants, and the results cannot be generalised to other races or ethnicities (Jordan, 2015, Roddy et al., 2011, Dufour et al., 2009, Hart and Spector, 1993).

1.3.3 Gender

Women are more likely than men to develop OA in all sites, such as foot, knee, hand and cervical spine, apart from the hip which shows overall a similar prevalence in both sexes (Johnson and Hunter, 2014). Menz et al. (2009a) found that women had a higher median number of foot joints with ROA than men among 197 participants aged 62–94 recruited from an Australian retirement village and a university clinic. Similarly, Roddy et al. (2015a) concluded that the prevalence of symptomatic radiographic OA (sROA) of the foot in the UK was higher in all evaluated foot joints in women than in men among 9334 adults aged above 50 years. The role of oestrogen and its reduced levels following menopause have been

suggested to influence and mediate the risk factors for female-specific OA (Spector et al., 1996).

Women may also be more likely to experience foot and ankle pain due to sex-related differences in footwear characteristics (Buldt and Menz, 2018). Heel elevation and a narrower forefoot in women's footwear have been associated with disorders such as hallux valgus, hammertoe, claw toe, and plantar keratotic lesions (Menz and Morris, 2005b). However, women are also more likely to report musculoskeletal pain in other body regions, possibly because of various biological, psychological, or social factors that contribute to differences in pain sensitivity and perception (Fillingim et al., 2009). In five cohort studies investigating multiple international populations, women reported more foot pain than men in all cohorts (Jordan, 2015, Roddy et al., 2011, Grant et al., 2009, Dufour et al., 2009, Hart and Spector, 1993).

1.3.4 Age

Age appears to be the strongest risk factor for foot/ankle OA (Roddy et al., 2015a, Downes et al., 2018, Thomas et al., 2015a). Although age may not directly cause OA and the prevalence and incidence of sROA foot/ankle increase sharply with age (Golightly and Gates, 2020, Menz, 2016, Roddy and Menz, 2018). The prevalence of foot pain generally increases with age and is much lower in younger participants (20–44 years) than in those older than 45 years (Jordan, 2015, Roddy et al., 2011, Grant et al., 2009, Dufour et al., 2009, Hart and Spector, 1993).

Roddy et al. (2015a) demonstrated that sROA foot in the UK affecting the 1st MTPJ occurs in 7.8% of community-dwelling individuals over 50 years. However, the exact mechanisms underlying the increased prevalence of foot OA with age are not fully understood. With age, the increased risk of OA may result from cumulative exposure to multiple risk factors and biological changes that occur with ageing (Kalichman and Hernández-Molina, 2014). Older adults may suffer from various articular issues, such as cartilage thinning, reduced proprioception and weaker muscle strength (Johnson and Hunter, 2014). This effect of ageing may be mediated by excess joint loading due to obesity, a reduction in joint repair capacity, and impaired muscle function (Hunter and Bierma-Zeinstra, 2019).

1.3.5 2D:4D digit ratio

The 2D:4D digit ratio is the ratio of the length of the second digit (index finger, 2D) to that of the fourth digit (ring finger, 4D) (Paul et al., 2006). This finger pattern is genetically determined and appears from an early age (Paul et al., 2006). There are three possible patterns: type 1 (index finger is longer than the ring finger), type 2 (index finger equal to the ring fingers) and type 3 (index finger shorter than the ring finger) (Robertson et al., 2008).

Zhang et al. (2008) found that individuals with a pattern 3-digit ratio had a higher risk of developing knee OA (OR 1.94, 95% CI 1.54-2.44) compared to those with patterns 1 or 2. Additionally, women with a

pattern 3-digit ratio (OR 3.05, 95% CI 2.08-4.47) had a significantly higher risk of knee OA than men (OR 1.45, 95% CI 1.08-1.95). It is important to note that in this study, all participants with knee and hip OA had clinically severe OA and were referred for total joint replacement. Therefore, these results may not be generalisable to individuals with less severe OA or different joint types. Furthermore, no study has investigated whether the pattern 3-digit ratio is associated with foot/ankle OA, and further study is needed.

The pattern 3 2D:4D digit length ratio is associated with higher athletic performance, higher testosterone levels, "maleness" characteristics, and generalised nodal OA (Paul et al., 2006, Hönekopp et al., 2006). Moreover, according to Islam and Kundu (2020), footballers with pattern 3 perform significantly better than those with pattern 1 in terms of soccer passing accuracy and other aspects such as dribbling, controlling, turning decision-making, and cognition.

Hanna et al. (2005) suggested that the association between a pattern 3-digit ratio and the development of OA could be related to increased activity and performance in sports requiring physical activity. Additionally, increased testosterone levels may contribute to the hormonal modulation of the metabolism of joint connective tissue, including the activity of chondrocytes and osteoblasts (Hanna et al., 2005). Furthermore, the link to HOX genes involved in developmental segmentation might also influence joint morphology and contribute to OA development and progression (Hanna et al., 2005).

1.3.6 Gout

A significant association exists between the joint sites affected by acute gout flares and the presence of clinically assessed OA (Stewart et al., 2016). Roddy et al. (2007a) found an association between gout and 1st MTPJ (aOR 2.06; 95% CI 1.28, 3.30), midfoot (aOR 2.85; 95% CI 1.34, 6.03), and distal interphalangeal joints (aOR 12.67; 95% CI 1.46, 109.91), respectively, after adjusting for confounding variables. Numerous mechanisms have been proposed to explain the correlation between acute gout flares and OA sites. These mechanisms include mechanical damage, synovial proteoglycans, changes in cartilage, cartilage fragments, epitaxial monosodium urate (MSU) crystal formation, and temporary increases in urate concentration during the resolution of synovial effusions (Wilcox and Khalaf, 1975, Perricone and Brandt, 1978). This can be attributed to the varying permeability of the synovium to urate and water, which may facilitate MSU crystal nucleation and precipitation. Further studies are needed to understand this association's causal aspects and mechanisms.

1.3.7 Nodal OA

A finger node is a firm to hard dorsal swelling over the finger interphalangeal joints, appearing as a single transverse bar or as two separate dorsolateral swellings (Rees et al., 2012). The occurrence of nodes is associated with underlying interphalangeal OA and an increased risk of generalised OA at other distant joint sites (McGonagle et al., 2008). Nodes located in the distal interphalangeal (DIP) joints are

known as Heberden's nodes and are easily discernible, whereas those in the proximal interphalangeal (PIP) joints are Bouchard's nodes and are less prominent (Figure 1-6). Nodes are more common in women and may be intermittently symptomatic when they slowly appear and enlarge, usually around middle age, just prior to or following the onset of menopause, but once established, they are usually asymptomatic (McGonagle et al., 2008).

According to Wright et al. (1998), nodal OA occurs when nodes are present on at least two rays in each hand. Blagojevic et al. (2010) conducted a systematic review that found nodal OA was a risk factor for knee OA (pooled OR 1.49, 95% CI 1.05-2.10). However, Thomas et al. (2015a) observed no association between nodal interphalangeal joint OA and the risk of symptomatic midfoot OA. Further research is required to investigate the relationship between nodal OA and foot /ankle OA.

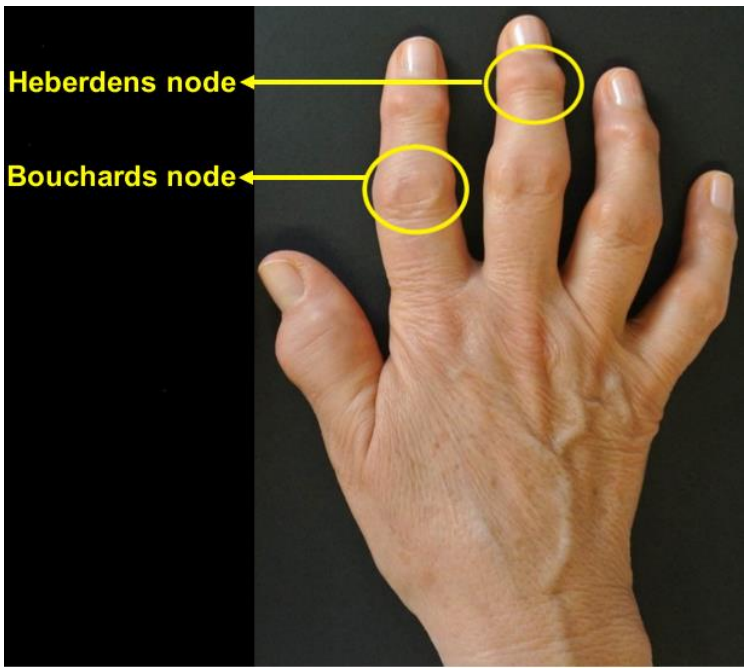


Figure 1-6. Heberden's and Bouchard's Nodes
Produced with permission (Doherty et al., 2016a)

1.3.8 Obesity

Body mass index (BMI) determines whether a person is underweight or overweight (World Health Organization, 2023). BMI is calculated by dividing a person's weight (in kilograms) by the square of their height (in metres): ***BMI (kg/m2) = Weight (kg) / Height (m)^2***

Table 1-1. WHO BMI Classification

BMI (kg/m2) Classification	**BMI (kg/m2) 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 Organization (WHO) body mass index (BMI) was used to determine obesity. BMI is the weight (kg) divided by the square of the height (in metres).

Being overweight or obese is an accepted strong risk factor for the development of knee and hip OA, and increased BMI and fat mass are also associated with a higher prevalence of foot pain (Shaw et al., 2006, Butterworth et al., 2012). Tanamas et al. (2012) demonstrated an association between foot pain and increased fat mass rather than body mass alone. Butterworth et al. (2013) suggested that increased fat mass predicts incident foot pain due to systemic metabolic and inflammatory mediators produced by adipose tissue, which can cause detrimental changes to the connective tissues essential for anatomic foot integrity and promote foot pain.

In five cohort studies, the prevalence of foot pain was highest in participants classified as obese (BMI >30.0 kg/m2) (Jordan, 2015, Roddy et al., 2011, Grant et al., 2009, Dufour et al., 2009, Hart and Spector,

1993). Moreover, Menz et al. (2009a) found that midfoot OA was associated with a higher BMI than controls, although the exact association between obesity and OA remains unclear.

A systematic review and cross-sectional study confirmed the relationship between increased BMI, body composition, and the prevalence of foot pain (Butterworth et al., 2012, Tanamas et al., 2012). Frey and Zamora (2007) demonstrated that overweight and obese people with a BMI ≥ 25 kg/m2 have a 1.5 times higher chance of developing ankle OA ($p<0.05$, 95% CI 0.986–2.274). Moreover, several other studies have shown that increased BMI is a risk factor for ankle OA (Frey and Zamora, 2007, Richmond et al., 2013, Lementowski and Zelicof, 2008). However, no studies have investigated the efficacy of weight loss interventions for ankle OA.

Obesity is associated with greater foot pain severity and increased disability in individuals with symptomatic first MTPJ OA. A cross-sectional study of 151 participants with symptomatic radiographic first MTPJ OA found that higher BMI was independently associated with more severe symptoms and reduced function, although the relationship with radiographic severity was not assessed (Munteanu et al., 2012). However, Menz et al. (2015b) found no association between BMI and radiographic severity of first MTPJ OA. These findings support the importance of weight management in clinical care for individuals with symptomatic first MTPJ OA.

1.3.9 Nutritional factors

A review of clinical studies has reported that vitamin D deficiency is associated with an increased risk of OA, particularly in the hip and knee joints, due to its role in cartilage metabolism (Garfinkel et al., 2017). This suggests that decreased cartilage thickness may be associated with vitamin D insufficiency, which could contribute to OA development. The role of vitamin D supplementation in OA remains uncertain. Further study is needed to clarify these findings and investigate whether similar associations exist for foot/ankle joints.

1.3.10 Smoking

According to the Framingham study, smoking is a significant risk factor for cardiovascular disease (Freund et al., 1993) but a protective factor for knee OA (Hui et al., 2011). However, a systematic review in 2011 found that smoking was not protective for OA at the knee, hip, hand and spine (Hui et al., 2011) and that smoking is not a significant risk factor for the development of OA. A subsequent systematic review conducted in 2013 also found that smoking did not play an important role in the development or progression of OA (OR, 0.92; 95% CI 0.83, 1.02) (Pearce et al., 2013). The negative association observed from the Framingham study and other studies is likely due to selection bias or the left-censorship, where smokers died earlier than non-smokers before they developed OA (Hui et al., 2011). The results were confirmed by another systematic review where smoking did not play a significant role in total joint replacement due to knee/hip OA (OR, 0.92; 95% CI 0.83, 1.02) (Pearce et al., 2013).

However, whether smoking is associated with foot/ankle OA has not been reported.

1.3.11 Injuries

Traumatic joint injury is a significant risk factor for OA of the hip, knee and foot/ankle joints (Salzmann et al., 2017b, Allen and Golightly, 2015). Two retrospective cohort studies from the general population showed that 70–78% of ankle OA cases were associated with a previous ankle injury (Valderrabano et al., 2009, Saltzman et al., 2005), including fractures, isolated osteochondral defects of the talus, and ankle ligament injuries. Saltzman et al. (2005) reported that single and recurrent lateral ankle sprains were the most common association with post-traumatic ankle OA in the general population. However, further research is needed to understand the effects of significant single or frequent minor ankle injuries on the prevalence of ankle OA.

1.3.12 Footwear

Appropriate footwear and shoe sizes are crucial for foot health (Buldt and Menz, 2018) and suboptimal footwear has been linked to the development of foot pain and structural foot disorders such as hallux valgus and lesser toe deformities (Buldt and Menz, 2018).

Footwear is recognised as a significant modifiable risk factor for the development and progression of hallux valgus, particularly in women (Menz et al., 2016, Menz and Morris, 2005a). A narrow forefoot or ill-fitting

footwear, especially shoes with elevated heels and tight toe regions, may increase pressure across the medial forefoot, contributing to joint deformity over time (Menz and Morris, 2005a). Hallux valgus is strongly associated with structural changes in the first MTPJ and may contribute to the development or worsening of OA via altered joint loading and cartilage damage (Ulus et al., 2023, Roddy, 2011). However, the exact mechanisms underlying these conditions and the sequence in which they occur are not yet fully understood. Further study is needed to clarify the biomechanical pathways underlying the association between footwear, hallux valgus, and first MTPJ OA.

Deformities of the lesser toe include hammertoe and mallet toe. These are usually caused by an imbalance between the muscles and tendons toe. These changes are usually flexible but can become fixed in their new position over time (Buldt and Menz, 2018). Eight studies have examined the association between incorrectly fitted footwear and foot disorders (López-López et al., 2016, McHenry et al., 2015, Schwarzkopf et al., 2011, de Castro et al., 2010, Nixon et al., 2006, Menz and Morris, 2005b, Burns et al., 2002, Frey et al., 1993). Schwarzkopf et al. (2011) found that ill-fitting footwear was associated with foot pain. Tight footwear was strongly associated with foot pain, with 84% of participants in Frey et al. (1993) and 91% in McHenry et al. (2015) reporting pain while wearing tight shoes. However, the characteristics of the recruited participants may have influenced the results.

Too tight or narrow shoes with high heels or a lack of adequate support can increase joint pressure and exacerbate foot pain (de Castro et al., 2010). Wearing inappropriate footwear during physical activity or sports can also increase the risk of injury, which may lead to OA development over time (Buldt and Menz, 2018). Footwear that provides adequate support, cushioning, and stability is essential for reducing the risk of foot pain and managing symptoms. Several studies have noted an association between ill-fitting footwear and a poor quality of life (QoL) (López-López et al., 2016, McHenry et al., 2015, Schwarzkopf et al., 2011, Burns et al., 2002).

The type of footwear best suited for each person depends on factors such as the severity of their symptoms, the location and extent of joint damage, and their gait mechanics (Schwarzkopf et al., 2011). It may be helpful for individuals with foot/ankle conditions to consult a podiatrist specialising in foot/ankle conditions to determine the best type of footwear for their needs (Buldt and Menz, 2018).

1.4 Foot/ ankle OA

Foot OA can cause foot pain and deformities, resulting in poor balance and an increased risk of falling (Roddy and Menz, 2018, Roddy et al., 2015a). Foot OA can significantly negatively impact physical mobility and QoL (Kalichman and Hernández-Molina, 2014, Arnold et al., 2019). Some authors have suggested that structural and biomechanical factors can play a role in foot OA (Menz et al., 2010, Zammit et al., 2009). For

instance, hallux limitus (reduced movement) or hallux rigidus (lack of movement), which associates with OA of the 1st MTPJ of the foot, might be caused by joint compression on the dorsal aspect during the propulsive phase of gait in individuals with an excessively wide first metatarsal, wide proximal phalanx, or long sesamoids (Zammit et al., 2009). Similarly, joint compression while walking could also lead to OA development in the tarsometatarsal joints when there is an excessively long second metatarsal (Zammit et al., 2009).

Ankle OA is characterised by JSN, OP, subchondral bone loss, loose bodies, and deformity (Valderrabano et al., 2009) (Figure 1-7). The progression of ankle OA may lead to reduced articular cartilage thickness and reduced range of motion (KHLOPAS et al., 2019).



Figure 1-7. Radiograph showing severe ankle OA with complete loss of joint space, subchondral sclerosis and cyst formation, and marginal osteophyte.

There is a distinction between primary and secondary ankle OA. Primary ankle OA is an idiopathic condition predominantly associated with ageing that affects previously healthy joints without any apparent local cause or initiating factor (KHLOPAS et al., 2019). Secondary ankle OA is OA that results from a recognised predisposing and initiating factor, such as prior trauma that damage cartilage and repetitive strain, especially in athletes and footballers (KHLOPAS et al., 2019).

The primary cause of ankle OA in football players, accounting for 75-80% of all cases, is fractures around the ankle area (Herrera-Pérez et al., 2021). The remaining 16% are caused by unresolved chronic ligament injuries, particularly those affecting the lateral collateral ligament (which some authors call “ligamentary ankle OA”).

1.4.1 First metatarsophalangeal joint OA

The first metatarsophalangeal joint (1st MTPJ) is essential for body transfer during the propulsive phase of gait (Canseco et al., 2008, Zammit et al., 2008). 1st MTPJ OA is most commonly asymptomatic and usually occurs bilaterally, but may cause localised big toe pain during standing and ambulation (Bowen et al., 2019). The characteristic radiographic features of 1st MTPJ OA include JSN, osteophyte proliferation along the metatarsal head and proximal phalanx, subchondral sclerosis, subchondral cysts, and local sesamoid hypertrophy (Figure 1-8) (Menkes and Lane, 2004, Pearle et al., 2005).



Figure 1-8. Radiograph of 1st MTPJ OA.

The arrows indicate severe joint space narrowing in the 1st MTPJ affected by OA.

1st MTPJ OA has been described as either hallux limitus or hallux rigidus, which are terms that relate to the degree of loss of movement (Bowen et al., 2019). The term used depends on the degree of the joint affected by OA and the amount of joint motion available (Hunter and Bierma-Zeinstra, 2019). Hallux limitus is characterised by restricted sagittal plane motion, particularly in dorsiflexion. Sometimes, the joint becomes stiff and does not move, resulting in hallux rigidus. The 1st MTPJ may have bony enlargement and deformities, such as hallux valgus, where the big toe points towards the midline of the foot (Abhishek and Doherty, 2013). Hallux valgus and bony enlargement of the 1st MTPJ are often associated with bursitis and other periarticular fibrous tissue reactions (“bunion”) in the medial aspect of the 1st MTPJ (Figure 1-9). Hallux valgus may be a constitutional deformity present in early adulthood,

which is a risk factor for subsequent 1st MTPJ OA or occurs secondary to OA at the joint.



Figure 1-9. Hallux valgus with mild OA

1.4.2 Anatomy of foot and ankle joint

Foot and ankle joints are complex systems that allow for a range of controlled movement. The foot consists of 26 bones, 33 joints, 112 ligaments, and 13 extrinsic and 21 intrinsic muscles (Aparisi Gómez et al., 2019). The foot is conventionally divided up into three regions: (i) Hindfoot – talus and calcaneus (including ankle and subtalar joints); (ii) Midfoot – navicular, cuboid, and cuneiforms; and (iii) Forefoot – metatarsals and phalanges (Aparisi Gómez et al., 2019) (Figure 1-10).



Figure 1-10. Regions of the foot

The hindfoot consists of the talus and calcaneus. The talus is an ankle bone that articulates with the tibia and fibula, and the calcaneus is the heel bone (Chaitow and DeLany, 2011). The midfoot includes the navicular, cuboid, and cuneiforms. The navicular is a boat-shaped bone that connects the talus to the cuneiforms. The cuboid is a cube-shaped bone connecting the calcaneus to the cuneiform. The cuneiforms are three long, narrow bones that form a triangle (Chaitow and DeLany, 2011).

The midfoot joints play a critical role in the formation of the arches of the foot, which provide a spring and act as a shock absorber during walking or running (Chaitow and DeLany, 2011). The midfoot joints form a functional composite that principally allows forefoot inversion and eversion, though some forefoot abduction and adduction are also possible. Five tarsometatarsal joints connect the midfoot to the forefoot (Omar et al., 2023). The forefoot consists of the metatarsals and phalanges. Metatarsals are five long bones that connect the cuneiforms to the toes. The phalanges are the bones of the toes (Omar et al., 2023).

The ankle joint, also known as the talocrural joint, is a synovial hinge joint connecting the lower leg to the foot (Hernández-Díaz et al., 2012). It permits dorsi-flexion and plantar flexion and plays a crucial role in weight-bearing, walking, and maintaining balance. The ankle joint consists of three bones, specifically the tibia and fibula (lower leg bones) and the talus (foot bone) (Aparisi Gómez et al., 2019). The lower end of the tibia forms the medial malleolus, and the lower end of the fibula forms the lateral malleolus of the joint. The talus is between these two malleoli (Mojica and Early, 2019).

The ankles, hindfoot, and midfoot are inter-related complex anatomical structures with biomechanical loads that enable fine balance while walking on uneven ground (Mojica and Early, 2019). The subtalar joint is between the concave under the talus's surface and the calcaneus's posterior convex facet. It has a very tight capsule and, together with the

talocalcaneal portion of the talocalcaneonavicular joint, allows inversion and eversion of the hindfoot (Figure 1-11).

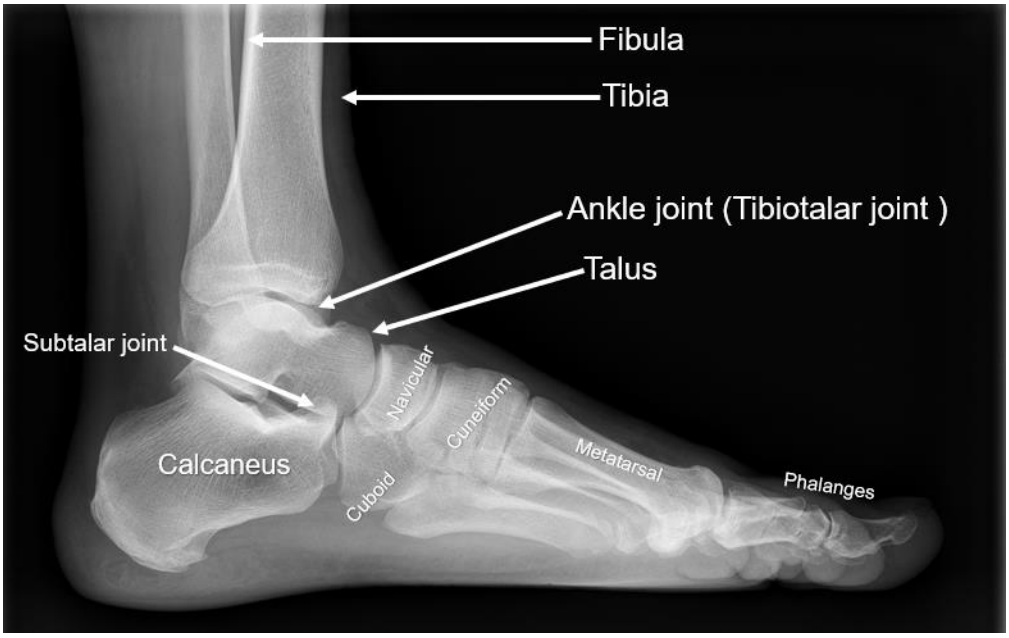


Figure 1-11. Foot /ankle bones

1.5 Clinical diagnosis of OA

According to the NICE guidelines, OA can be diagnosed clinically without investigation by imaging or blood tests (NICE, 2022). A clinical diagnosis of OA can be made if a patient is 45 years or older, has joint pain related to activity, and either no morning stiffness or stiffness lasting less than 30 minutes (NICE, 2022). The American College of Rheumatology (ACR) criteria for the diagnosis of OA are the most commonly used method in many studies (Altman et al., 1986). These criteria include clinical features plus one blood test (for rheumatoid factor).

- being 40 years or older,
- Crepitus or bony swelling,

- Pain most days of the month,
- Morning stiffness of less than half an hour
- Negative serum Rheumatoid Factor.

The European League Against Rheumatism (EULAR) deduced a simple clinical diagnosis of knee OA, focusing on three key symptoms and three physical signs. The three symptoms included persistent knee pain, short-lived morning stiffness, and functional knee limitation. The three physical signs were crepitus (palpable and sometimes audible crunching sensation in the anterior aspect of the knee during movement), restricted movement and bony enlargement around the joint (Zhang et al., 2010). It is important to note that symptoms may not always accompany radiographic changes in joints, so relying on radiographic screening alone cannot accurately identify clinical cases of OA. Clinical or symptomatic OA can be diagnosed solely based on symptoms and clinical assessment (Kalichman and Hernández-Molina, 2014).

1.5.1 Foot/ankle OA diagnosis

Clinical definitions for knee, hip, and hand OA have been established for decades, but a clear definition for clinical foot/ankle still needs to be established (Paterson and Arnold, 2021, Zhang et al., 2010, Zhang et al., 2009). Although some definitions of symptomatic radiographic foot OA have been proposed, there is no consensus on whether a separate clinical definition is necessary or feasible (Roddy and Menz, 2018). Roddy et al. (2015a) defined symptomatic radiographic foot OA as

observed radiographic OA in the foot with pain in the corresponding area. Whether separate clinical definitions are required for different foot/ankle regions remains unclear (Paterson and Arnold, 2021).

Zammit et al. (2011) developed a clinical diagnostic rule for identifying radiographic 1st MTPJ OA. Long-standing pain, crepitus, osteophyte, restricted range of motion, and hard end-feel (feeling of resistance when the range of motion of the joint is fully utilised) had good diagnostic accuracy for identifying radiographic 1st MTPJ OA, with excellent specificity and sensitivity (Zammit et al., 2011). However, this study had several limitations, including a small sample size and lack of other imaging modalities.

Clinical diagnosis of midfoot OA is difficult because the midfoot joints are in close proximity, making it challenging to isolate and evaluate tenderness, stiffness, and deformities (Kalichman and Hernández-Molina, 2014). Clinical assessments of the midfoot, including the range of motion, foot posture, and palpable dorsal osteophytes, perform poorly in identifying radiographic OA in people with midfoot pain (Thomas et al., 2015c). The diagnosis of midfoot OA depends on palpation or provocation of the suspected joint in conjunction with diagnostic imaging, most commonly plain radiographs (Wilder et al., 2005b). Further evidence and validated clinical tests are required to evaluate the presence of midfoot OA and establish a consensus definition (Arnold et al., 2022a).

Roddy et al. (2011) recommended a collection of static assessments from pre-study consensus work, including a range of motion, foot posture measures, palpation and observation. None of these could distinguish between individuals with or without structural radiographic midfoot changes (Thomas et al., 2015c). The ankle/subtalar joint version and ankle joint dorsiflexion range of motion significantly correlated with radiographic 1st MTPJ OA (Menz et al., 2015a).

In summary, some physical examinations may need to be revised to distinguish the presence or absence of symptomatic foot/ankle OA. Further investigations are necessary to determine the reliability and validity of these measures and other clinical assessments to differentiate between the presence and absence of symptomatic OA in all identifiable foot joints. Paterson and Arnold (2021) confirmed that a validated clear definition for foot/ankle OA might help reduce patient burden, healthcare costs, and reliance on radiographs in clinical practice. Although a few guidelines exist for foot/ankle OA, they do not provide clinical diagnostic criteria and imaging remains the gold standard for diagnosis (Zammit et al., 2011, Arnold et al., 2022a). Currently, there is no consensus or evidence-based classification criteria for foot/ankle OA.

1.5.2 Symptoms and signs of foot/ankle OA

OA symptoms depend on the location and severity of the condition. In many cases, it may not cause any symptoms, but in other cases, it can cause pain, stiffness, swelling, and reduced range of motion in the affected joint (Dieppe and Lohmander, 2005).

Midfoot OA can result in persistent foot pain, difficulty walking and climbing stairs, and deformity (Rathod et al., 2016, Thomas et al., 2015a). Symptoms can vary over time, and symptoms may change as time progresses. When midfoot OA persists for more than 18 months, it often leads to ongoing pain in the foot and can result in disability (Downes et al., 2018).

Symptomatic 1st MTPJ OA can be debilitating, with nearly three-quarters of affected individuals describing their pain as "disabling" (Munteanu et al., 2011, Kadakia and Molloy, 2011). Symptomatic 1st MTPJ OA is associated with difficulty obtaining suitable footwear, diminished foot function, and increased foot pain, as measured using the Foot Health Status Questionnaire (Bergin et al., 2012). Additionally, individuals with 1st MTPJ OA have significant difficulties performing weight-bearing activities, which can have a negative impact on their QoL (Bergin et al., 2012).

1.6 Imaging diagnosis of foot/ankle OA

1.6.1 Conventional radiography

The EULAR recommendations favour plain radiography as the first-line diagnostic modality before considering other modalities for OA (Sakellariou et al., 2017). Radiographs are most commonly used to investigate structural changes related to OA because they can be obtained quickly, are inexpensive, and are widely available in hospitals compared to magnetic resonance imaging (MRI) (Nieminen et al., 2019). Bony osteophytes or spurs at the joint margin and focal loss of cartilage observed as a loss of interosseous distance or JSN are the two key characteristics of radiographic changes in OA (Wong et al., 2016). Both features are identifiable on radiographs, and the severity of the changes reflects the progression of OA (Braun and Gold, 2012). Large osteophytes, marked JSN, bone sclerosis, cysts, and deformities are radiographic evidence of more severe OA (Hayashi et al., 2019).

The current radiographic diagnosis of OA typically uses the Kellgren and Lawrence (KL) system (Kellgren and Lawrence, 1957a), which was developed primarily for knees, hips and hands OA and may not be appropriate and valid for foot OA (Spector et al., 1993, Menz et al., 2009a). Table 1-2 shows the KL criteria for OA (Kellgren and Lawrence, 1957b).

Table 1-2. Criteria for osteoarthritis using the Kellgren Lawrence

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

1.6.2 The La Trobe Foot Atlas

Studies on foot OA are limited because of the lack of foot-specific grading systems for defining radiographic foot OA. However, Menz et al. (2007a) addressed this by publishing the 2007 La Trobe Foot Atlas (LTFA), which provides an ordinal grading system for the radiographic features of five-foot joints (Table 1-3) (Menz et al., 2007a). The LTFA was used to assess five joints, including the 1st MTPJ, first cuneo-metatarsal joint (1st CMJ), second cuneo-metatarsal joint (2nd CMJ), navicular-1st cuneiform joint (N1st CNJ) and talo-navicular joint (TNJ).

Table 1-3. Scoring system using La Trobe radiographic foot atlas

Osteophytes		Joint space narrowing	
Grade	**Score**	**Grade**	**Score**
Absent	0	None	0
Small	1	Definite	1
Moderate	2	Severe	2
Severe	3	bone on bone at least one point	3

Menz et al. (2007a) found that the dorso-plantar view identified almost all cases of 1st MTPJ OA (94.6%), but its sensitivity was poor (31%) when evaluating the other four joints. In contrast, the lateral view identified all cases of OA except for the 1st MTPJ and 1st tarsometatarsal joints. The authors reported that the atlas had moderate to excellent intra-rater

reliability and fair to excellent inter-rater reliability. However, using only one view and one radiographic feature (osteophytes or JSN) had low sensitivity for OA at all joint sites (ranging from 14.3% to 63%). It is important to note that the atlas was limited to images obtained from dorso-planar and lateral views.

Several key limitations of using LTFA must be recognised. First, the Atlas only identifies certain joints and fails to account for the occurrence of OA in other joints, such as the subtalar and interphalangeal joints (Trivedi et al., 2010). Another limitation of the atlas is its focus on osteophytes and JSN while excluding other common OA features, such as subchondral sclerosis and cysts (Menz et al., 2007a). The images produced by the La Trobe Foot Atlas can also be difficult to interpret because of the overlap of bones, particularly in the 2nd CMJ. Additionally, the reliability and repeatability of the atlas may be influenced by unknown racial variations, sex, age, and the health status of the population used for the images (Menz et al., 2007a).

The following recommendations address the limitations of the LTFA. First, written guidelines should be developed for the atlas with justifications for items that must be included. Second, the pictures should be consistent and any variables that may affect the findings of the measured aspect should be removed. Finally, additional information on demographic variations and deformities in patients with foot OA should be provided (Menz et al., 2007a).

1.6.3 Magnetic resonance imaging

MRI provides images of all the joint tissues and can detect changes in OA joints earlier than standard radiography (Allen and Golightly, 2015). However, MRI is typically more expensive, time-consuming to undertake and examine the images, and less widely available when compared to plain radiography (Mathiessen et al., 2013). A systematic review by Hunter et al. (2011) investigated the validity of MRI in OA and concluded that it is the most valuable imaging tool for assessing OA because of its ability to visualise various individual tissue pathologies related to pain and other clinical outcomes. Halstead et al. (2017) published the first definitive scoring MRI system for foot OA. Although MRI has become more established as an imaging modality at other sites, such as the hip and knee, the foot remains under studied (Guermazi et al., 2013).

Moreover, no validated and reliable foot atlases are available for MRI (Menz et al., 2009a). Conventional radiography is the most appropriate method to diagnose OA in the foot at this stage based on epidemiological studies (Menz et al., 2007a, Roddy et al., 2015a, Thomas et al., 2015a).

1.6.4 Ultrasound

Ultrasound is a reliable tool for evaluating synovial hypertrophy, power Doppler signal and joint effusion. However, further experiments are required to determine its potential in assessing cartilage damage and osteophytes (Zabotti et al., 2019). Ultrasound can visualise important diagnostic information on the foot's soft tissue and bony structures.

Indeed, a significant limitation of the US is related to the incomplete evaluation of hyaline cartilage, considered the target tissue in OA. In contrast to plain radiography, it can detect inflammation and cartilage reduction (Riente et al., 2006). Compared to MRI, the US has excellent sensitivity and specificity in detecting osteophytes in various joint regions (Wakefield et al., 2000, Szkudlarek et al., 2004, Mathiessen et al., 2013).

1.7 Prevalence and incidence of foot/ankle OA

1.7.1 Incidence

Foot/ankle OA incidence has only been examined in a few studies (Table 1-4). In the Johnston County Osteoarthritis (JoCoOA) study, 4% of participants aged over 55 years developed incident foot radiographic OA (ROA) over a period of 3-4 years, while 28% developed incident ankle ROA over 4-5 years (Flowers et al., 2021b). In the Clearwater OA Study, approximately one-quarter of the participants aged over 40 years developed ROA in the 1st MTPJ over seven years (Mahiquez et al., 2006) (Table 1-4).

In the Chingford study, 13.5% of the women developed incidents of OA in the right 1st MTPJ and 8.3% in the left over 19 years. However, the study population was limited to older women (mean age 75.7 years, SD± 5.2 years) from a single geographical region in the UK, which may limit the generalisability of the findings (Bowen et al., 2020). Further research is needed to investigate the long-term incidence, natural history, and progression of radiographic foot and ankle OA in general populations.

1.7.2 Prevalence of foot/ankle OA

There are more prevalence estimates for foot OA than ankle OA and more in ROA than sROA of the foot in general population (Thomas et al., 2015c, Thomas et al., 2015a, Roddy et al., 2015a, Menz et al., 2015a).

The prevalence of foot ROA was much higher in retired village residents and university health sciences clinics in Australia, being 42% for the 1st MTPJ, 22% for the 1st CMJ, 60% for the 2nd CMTJ, 39% for the N1stCJ, and 32% for the TNJ (Menz et al., 2009a). The higher prevalence might be due to the mean age of 75.9 years (Menz et al., 2009a). This study focused on the presence of radiographic OA without considering its symptoms. However, a recent study reported the prevalence of sROA of the foot, defined as pain in addition to radiographic OA (Roddy et al., 2015a). The Clinical Assessment Study of the Foot (CASF) study included 5109 adults aged >50 years registered with four general practices in North Staffordshire in the UK found that the prevalence of sROA of the foot was 14.3% in male adults aged 50 years (Roddy et al., 2015a).

sROA at any of the four midfoot joints using the LTFA affected 12.0% of 560 participants, included males and females from community-dwelling older adults aged above 50 years the participants (Thomas et al., 2015a). In the midfoot, the 2nd CMJ was the most commonly affected (6.8%), followed by the TNJ (5.8%), NCJ (5.2%) and 1st CMJ (3.9%) joints (Thomas et al., 2015a).

Table 1-4. Key epidemiological studies reporting foot OA prevalence and incidence.

Study	N	Age range (mean)	Female %	Population and Country	Radiographic views	Joints assessed	Radiographic definition	Symptomatic definition
Zoetermeer Study (Van Saase et al., 1989)	6,585	19 + (NR)	53	Zoetermeer, Western Netherlands Netherlands	NR	First to fifth MTP, TMT, PIP,	KL Grade>- 2	-
Clearwater Osteoarthritis Study **(Wilder et al., 2005a)**	3.436	40-94 (62)	>69	Netherlands Pinellas County, Florida USA	WB AP	1st MTPJ	KL Grade>- 2	-
Clinical Assessment Study of the Foot (CASF) (Roddy et al., 2015a)	525	50-87 (65)	56	Four general practices, North Staffordshire UK	WB AP WB lateral	1st MTPJ, 1st CMJ, 2nd CMJ, NC, TNJ	La Trobe Foot Atlas Grade >-2 for OP and/or JSN, either view	Pain in the past 4 weeks in the corresponding region of the foot
Johnston County Osteoarthritis Project (JoCoOA) (Flowers et al., 2021a)	863	55 + (71)	68	Six communities in Johnston County, North Carolina USA	WB AP WB lateral	1st MTPJ, first CM, second CM, NC, TNJ	La Trobe Foot Atlas Grade 2 for OP and/or JSN, either view	Pain, aching or stiffness in the corresponding foot
Chingford Study (Bowen et al., 2020)	209	45 - 64 (57)	100	One general practice, Chingford, East London UK	Semi-WB AP	1st MTPJ	La Trobe Foot Atlas Grade 2 for OP and/or JSN	-

NR: not reported; KL: Kellgren and Lawrence; MTP: metatarsophalangeal joint; TMT: tarsometatarsal; PIP: proximal interphalangeal; CMJ: cuneometatatarsal joint ; NC: navicularfirst cuneiform; TN: talonavicular joint; WB: weight-bearing; AP: anteroposterior; OP: osteophytes; JSN: joint space narrowing

1.7.3 Prevalence of 1st MTPJ OA

A systematic review conducted by Trivedi et al. (2010) identified seven studies that used similar methods to estimate the prevalence of ROA affecting the 1st MTPJ (Bremner et al., 1968, Brighton et al., 1985, Solomon et al., 1976, Van Saase et al., 1989, Van Saase et al., 1988, Wilder et al., 2005b, Wilder et al., 2008). Using the K&L grade 2 or higher as the case definition of 1st MTPJ ROA, the prevalence ranged from 6.3% in rural African women aged 40 years to 28–39% in women aged 35-64 living in Wensleydale, UK. Few studies have used the same definition to provide population prevalence estimates for ROA at other sites in the foot.

The prevalence of ROA of the 1st MTPJ OA was 10% in JoCoOA (Flowers et al., 2021b) and 8% in the Clearwater OA study, ranging from less than 4% in the 20-24 age group (Wilder et al., 2005a). Similarly, 1st MTPJ sROA affected 6.7% of males and 8.8% of females in the CASF study (Roddy et al., 2015a). Van Saase et al. (1989) investigated 6,585 people in Europe above the age of 40 years and reported a 28% prevalence of OA in the 1st MTPJ, an 8% prevalence of OA in other MTPJs, and a 7% prevalence of OA in the proximal interphalangeal joints.

Wilder et al. (2005b) used a ROA case definition in Clearwater, Florida, with 3,436 people aged between 40 and 94 years, reporting a 20% prevalence of OA in the 1st MTPJ. Both studies (Wilder et al., 2005b, Van

Saase et al., 1989) focused on only a limited number of joints in the foot and used only the dorsoplantar radiographic view. Future epidemiological studies are required to combine the dorsal planter and lateral views using osteophytes and JSN to define OA in each of the five joints in the foot to avoid underestimation of the prevalence of radiographic foot OA (Menz et al., 2020).

1.7.4 Prevalence of radiographic foot OA

According to Flowers et al. (2021b), in the Johnston County Osteoarthritis Study, the prevalence of ROA of the foot in males was 29.8% and sROA was present in 23.9% of individuals aged 72.1 years or above. In contrast, the CASF study showed a prevalence of sRAO of the foot of 16.7% in adults (male and female) aged ≥ 50 years (Roddy et al., 2015a). The differences in the estimates of sROA between the JoCoOA and CASF studies may be related to the different source populations, recruitment procedures, and definitions of symptomatic foot OA. Several studies have reported on the prevalence of radiographic foot OA (Table 1-5).

The prevalence of ROA affecting the second to fifth MTP joints was estimated to be 2% in men and 5% in women in Wensleydale, UK, and 3% in both men and women in Jamaica (Van Saase et al., 1989, Van Saase et al., 1988). In the Netherlands, two studies reported the population prevalence from Zoetermeer. The prevalence of ROA in the first study was 4.3% in men and 5.4% in women at the second through to fifth MTP joints, 4.3% in men and 5.0% in women at the

tarsometatarsal joints, and 6.7% in men and 7.2% at the proximal interphalangeal joints. The second study of adults over the age of 19 years reported similar prevalence rates of 3.4% in men and 4.7% in women for the second to fifth MTP joints, 3.1% at the tarsometatarsal joints in men and 3.3% in women, and at the proximal interphalangeal joints 4.3% in men and 4.3% in women (Van Saase et al., 1989).

Table 1-5. Prevalence of radiographic foot OA. Adapted from Roddy and Menz (2018)

(First author), year	Country	Age (years)	Radiographic definition	Joint	Prevalence (%)	Prevalence in men (%)	Prevalence in women (%)
(Bremner et al., 1968)	Jamaica	35–64	K&L ⩾ 2	1st MTPJ	23	17	29
				Second to fifth MTPJ	3	3	3
(Bremner et al., 1968)	UK	35–64	K&L ⩾ 2	1st MTPJ	35	30	39
(Solomon et al., 1976)	South Africa	>35	K&L ⩾ 2	1st MTPJ	21.5	15.1	24.0
(Brighton et al., 1985)	South Africa	>18	K&L ⩾ 2	1st MTPJ	5.0	11.1	2.5
(Van Saase et al., 1988)	Netherlands	45–64	K&L ⩾ 2	1st MTPJ	33.1	28.5	37.6
				Second to fifth MTP joints	4.9	4.3	5.4
				Tarsometatarsal joints	4.7	4.3	5.0
				Toe PIP joints	7.0	6.7	7.2
(Van Saase et al., 1989)	Netherlands	19	K&L ⩾ 2	1st MTPJ	22.7	20.0	25.0
				Second to fifth MTPJ	4.1	3.4	4.7
				Tarsometatarsal joints	3.2	3.1	3.3
				Toe PIP joints	4.4	4.3	4.5
(Wilder et al., 2005b)	USA	40–94	K&L ⩾ 2	1st MTPJ	20.0	25.1	17.7
(Wilder et al., 2008)	USA	40	K&L ⩾ 2	1st MTPJ	20.0	–	–
(Menz et al., 2009a)	Australia	62–94	LFT ⩾ 2	1st MTPJ	42.4	–	–
				1st CMTJ	22.6	–	–
				2nd CMTJ	60.2	–	–
				NCJ	39.1	–	–
				TN**J**	32.7	–	–

1st MTPJ: First metatarsophalangeal joint,1st CMTJ: First cuneiform-metatarsal joints, 2nd CMTJ: Second cuneiform-metatarsal joint, TNJ: Talonavicular joint, N1st CJ: Navicular-first cuneiform joint, K&L, Kellgren and Lawrence, PIP, proximal interphalangeal joints; TN, talonavicular joint.

1.7.5 Prevalence of foot/ankle pain

Foot and ankle pain affects approximately 1 in 5 middle-aged-to-older people. (Thomas et al., 2011). A systematic review by Thomas et al. (2011) analysed 31 population-based studies with sample sizes ranging from 96 to 42,826 participants. The review reported that 24% of adults over 45 suffered foot pain (95% CI 22-25%), and 15% suffered ankle pain (95% CI 13-16%). One in ten people over 70 had experienced foot pain for over three years (Thomas et al., 2011, Hill et al., 2008). However, the comparison of the prevalence of foot pain across existing studies has been challenged due to inconsistent case definitions of foot pain (Paterson and Arnold, 2021). Of the 31 studies analysed by Thomas et al. (2011), only eight used comparable case definitions for data pooling.

There is a wide range of foot pain prevalence in different countries, with 13% in the Chingford 1000 Women Study, 18% in the Northwest Adelaide Health Study, 21% in the CASF Clinical Assessment Study of the Foot, 25% in the Framingham Foot Study, and 36% in the Johnston County Osteoarthritis Project (Jordan, 2015, Roddy et al., 2011, Grant et al., 2009, Dufour et al., 2009, Hart and Spector, 1993). Additionally, the prevalence of foot pain can be influenced by age, sex, occupation, and physical activity levels. In five cohort studies, the main limitation was the variation in questions used to determine foot pain, particularly duration and response components, as shown by the answers for the original pain questions in the Chingford 1000 Women Study. This study provides valuable comparisons of foot pain among five population cohorts.

Furthermore, to estimate pain prevalence, all components of pain, aching, or stiffness should be included in a single question. Therefore, developing a standard set of questions related to foot pain and its measures would be helpful for future studies (Table 1-6).

Table 1-6. Prevalence of foot pain across international population-based cohorts – adopted from Gates et al. (2019)

Cohort study, author, and country	Data collection time point	N	Age, mean ± SD (years)	Prevalence in men	Prevalence in women	Foot pain variables across cohorts
Johnston County Osteoarthritis **Jordan -2015-** **USA**	First follow-up visit (1999–2004)	1,619	65.8 ± 9.8	30%	Female = 39%	"On most days do you have pain, aching or stiffness in your feet?" (yes/no)
Chingford Study **Hart – 1993** **UK**	Year 15 (2003)	655	68.6 ± 5.8	None	12%	"On how many days in the last month did you get pain?" (0/1–5/6–14/15+ days)
Framingham Foot Study **Durfour-2019** **USA**	Phase 1 (2002 - 2008)	3,420	66.5 ± 10.6	19%	29%	"On most days do you have pain, aching or stiffness in your feet?" (yes/no)
Northwest Adelaide Health Study Grant – 2009 Australia	Stage 2 clinics (2004–2006)	3,145	47.6 ± 17.5	15%	19%	"Pain, aching or stiffness in the foot in the past month" (No days/few days/some days/most days/all days)
Clinical Assessment Study of the Foot **Roddy – 2011** **UK**	Baseline health survey (2010–2011)	4,490	64.9 ± 9.8	18%	22%	"Pain, aching or stiffness in the foot in the past month" (No days/few days/some days/most days/all days)

1.8 Socioeconomic burden of foot/ankle OA

The extent of the economic and social impact of foot/ankle OA has yet to be fully determined (Arnold et al., 2022a). However, given its widespread occurrence and the associated expenses for treatment, work-related costs, and disability, it is likely to be comparable to other forms of OA (Paterson and Gates, 2019b). Accurate estimation of the burden of foot/ankle OA is crucial for developing clinical and cost-effective treatment strategies (Golightly and Gates, 2020).

1.9 Risk of foot/ankle OA in professional footballers

Football is one of the most popular sports globally and is often called the "king of sports" (Koch et al., 2021b). The Fédération Internationale de Football Association (FIFA) estimates that there are over 265 million active players globally, of which 110,000 are professional male footballers (FIFA, 2023). Repetitive running, jumping, pivoting, and tackling in football can place significant stress on the feet and ankles, leading to joint damage (Koch et al., 2021b). As a result, footballers may experience pain, stiffness, swelling, and reduced mobility in their feet and ankles. However, the increased participation of footballers worldwide has led to increased injury rates, especially in the lower extremities. Professional footballers are at an increased risk of developing lower-limb OA because of the high-impact nature of sports and injuries (Paget et al., 2020a).

Several risk factors may contribute to foot/ankle OA development in professional footballers, including age, previous injuries, playing position, and training intensity (Paget et al., 2020b). The impact of foot/ankle OA is not limited to a footballer's career, as the condition can have long-lasting effects on QoL and daily activities after retirement (Paget et al., 2020b). Therefore, footballers must take a proactive approach to their joint health, even after retiring from football.

After a professional football career ends, retired football players have been reported to be at increased risk of developing OA in different joints of the lower limb, including the hip and knee, compared with the general population (Fernandes et al., 2018, Koch et al., 2021b, Alsayel et al., 2019b, Salzmann et al., 2017b).

1.9.1 Biomechanical impact of football activities on the foot/ankle joints

Professional football places substantial biomechanical demands on the lower extremities, particularly the foot/ankle joints, which collectively comprise 26 bones, 33 joints, 112 ligaments, and 34 muscles (Alsayel et al., 2019a, Walls et al., 2016). These anatomical structures often undergo acute and cumulative loading from football-specific movements, and injuries to these areas have consistently been associated with a higher risk of foot/ankle OA in later life (Paget et al., 2020b, Alsayel et al., 2019a, Walls et al., 2016).

The ankle is more likely to be injured than the foot joints through playing professional football, and such acute direct trauma may be sufficient to cause ankle OA in later life (Valderrabano et al., 2014). However, further studies are needed to determine whether repetitive football-related trauma contributes to the subsequent development of foot /ankle OA.

In addition, repetitive microtrauma may damage the repair process after injuries (Valderrabano et al., 2014). Football-related activities such as sprinting, jumping, pivoting, and tackling cause repetitive high-impact forces that place considerable stress on the foot and ankle joints and may contribute to the development of OA (Valderrabano et al., 2014). Alsayel et al. (2019a) demonstrated that during these actions, the ankle joint may experience loading forces, which can damage the cartilage, cause subchondral bone stress, and cause excessive strain on ligamentous structures. Moreover, recurrent dorsiflexion, particularly during landing, has been implicated in the development of anterior ankle impingement and osteophyte formation, which may lead to ankle OA (Nery et al., 2016). Walls et al. (2016) pointed out that rapid directional changes and tackling manoeuvres are primary mechanisms underlying for lateral ankle sprains in footballers. These injuries often result from medially applied contact forces at foot strike, which cause forced inversion and increase the risk of rupture of the anterior talofibular ligament.

Furthermore, inadequate rehabilitation may add burdens to the injured joints that can result in chronic mechanical instability and altered joint kinematics, both of which are recognised as contributing factors in the

aetiology of post-traumatic OA. (Chalidapong et al., 2024). Further study is needed to better understand the long-term biomechanical consequences of these football-specific injuries and their contribution to the development of foot/ankle OA.

1.9.2 The current evidence

Previous studies on footballers have not explored the multiple outcomes of foot/ankle OA simultaneously but have focused on either self-reported physician-diagnosed foot/ankle OA (Drawer and Fuller, 2001, Turner et al., 2000, Liam et al., 2020) or radiographic ankle OA (Armenis et al., 2011b). Six studies have reported the prevalence of either foot or ankle OA among professional footballers in terms of self-reported or ROA (Paget et al., 2020a, Prien et al., 2017, Iosifidis et al., 2015, Armenis et al., 2011b, Drawer and Fuller, 2001a, Turner et al., 2000b). However, none of these studies examined the prevalence of sROA of the foot or ankle OA (Table 1-7).

The prevalence of ankle OA 16-22 years after a professional football career has ended has been reported to be between 12% and 19% (Drawer and Fuller, 2001a, Turner et al., 2000b, Kuijt et al., 2012). In these studies, OA was determined using self-reported diagnoses. However, these studies had small sample sizes and only one study had a control group.

Iosifidis et al. (2015) investigated the prevalence of lower extremity clinical and ROA in 218 former elite male athletes with mean age 50.1

years from different sports, including football, volleyball, martial arts, track and field, basketball, and skiing. They compared them with 181 male controls with a mean age 50.7 years. They found a similar prevalence of clinical OA between former athletes (15.6%) and controls (14.4%). However, the prevalence of radiographic OA was significantly higher (p=0.03) in former athletes (36.6%) than in the controls (23.9%). Age, BMI, and occupation were identified as strong predictors of OA development in former athletes. However, this study was limited by the small number of participants in individual sports, which prevented comparison of the risk between individual subgroups.

A previous study by Armenis et al. (2011b) investigated in Greek footballers the prevalence of ROA of the ankle in male footballers who had played professional football for 8–10 years compared with a control group. The study included 170 male footballers aged between 42 and 55 years (mean 49.8, SD 7.4), while the control group (general population) included 132 men aged between 42 and 55 years (mean 50.7, SD 9.9). Based on clinical examinations and questionnaires, there was no significant difference in the occurrence of ankle OA between male footballers and the control group ($p > 0.05$). However, this study found that the prevalence of clinical OA of the ankle was slightly higher (4.1%) in footballers compared to controls (3.56%), although this difference was not significant ($p > 0.05$). Nevertheless, ROA of the ankle was significantly more prevalent in footballers than in controls (8.8% versus 3.7 %, $p < 0.05$). However, it should be noted that the study by Armenis et al.

(2011b) focused solely on the ankle joint and did not provide information about the foot joint. The limitations of this study included a lack of detail regarding the clinical assessment and radiographic assessment and the lack of specification of the radiographic protocol employed for diagnosing ROA for ankle joints.

Four studies investigated the prevalence of ankle OA and found it to range from 4 to 12% (Paget et al., 2020a, Iosifidis et al., 2015, Armenis et al., 2011b, Drawer and Fuller, 2001a). However, these studies did not investigate the foot joint and used different approaches to diagnose OA in various joints, including clinical assessment, ROA, and self-reporting ankle OA. Additionally, the definition of a professional footballer differed between studies, and some did not include details of the career and the retirement date. More information regarding playing positions and career duration also would have been of relevance. Another limitation of these studies was the small sample size of retired professionals from each country and the fact that the ex-professional footballers were recruited from just one club. It would be helpful to standardise a consistent definition of "professional footballer" in future studies.

A history of ankle injuries in national football players is reported to have a long-term negative impact on their joint health related to impaired daily activities (Ieong et al., 2019, Gouttebarge and Frings-Dresen, 2014). Ankle OA in professional football players appears strongly associated with ankle injuries (KHLOPAS et al., 2019, Paterson and Gates, 2019a). However, it remains unclear whether repetitive minor mechanical insults

associated with sprinting, jumping, running, passing, and physical contact with opponents during competition also contribute to the increased prevalence of foot/ankle OA in retired professional footballers.

Several studies have shown that long-term forceful physical activity can increase the risk of ankle OA (Paget et al., 2020b, Armenis et al., 2011a, Nery et al., 2016, Alsayel et al., 2019a) .However, these studies did not investigate specific activities that lead to ankle OA. These results are supported by previous studies that illustrated a relationship between a history of ankle sprain and structural OA changes in the ankle (Saltzman et al., 2005, Golditz et al., 2014).

The relationship between playing position in the field and injury risk in ex-professional football players has not been fully established. Although existing studies indicate no clear association (Ekstrand et al., 1983, Ekstrand and Gillquist, 1983, Hawkins and Fuller, 1999, Engström et al., 1990). There is some evidence that suggests a possible higher incidence of injuries in defenders, halfbacks, and midfielders (Fuller et al., 2012, Peterson et al., 2000). This could be attributed to modern football's defensive requirements in the forward and attacking phases of the game for defenders. Additionally, players may change positions during the season or even within a game, which could contribute to the lack of a definitive link between injury risk and specific playing positions.

Fernandes et al. (2018) investigated the prevalence of knee pain, radiographic knee OA (RKOA), and associated risk factors in male ex-

professional footballers compared to men in the general population. That study found that the prevalence of all knee OA outcomes, specifically current knee pain (aRR 1.91, 95% CI 1.77 to 2.06), KOA (aRR 2.21, 95% CI 1.92 to 2.54) and total knee replacement (aRR 3.61, 95% CI 2.90 to 4.50) were two to three times higher in ex-footballers compared with the general population. Knee injury, training, age and gout were the leading risk factors for developing KOA within the footballer group (Fernandes et al., 2018). In summary, evidence for the risk of foot/ankle OA in professional footballers over the general population is sparse and inconclusive.

Table 1-7. Previous studies that have examined ankle OA in male professional footballers.

Reference	**(Koch et al., 2021b)**	**(Paget et al., 2020a)**	**(Iosifidis et al., 2015)**	**(Armenis et al., 2011b)**	**(Drawer and Fuller, 2001a)**	**(Turner et al., 2000b)**
Country of	**Germany**	**The Netherlands-Global**	**Greece**	**Greece**	**United Kingdom**	**United Kingdom**
Study design and purpose	Cross-sectional To investigate the impact of injuries on professional footballers' careers, reasons for termination, and post-retirement	Cross-sectional To determine the prevalence of ankle OA in professional footballers and rugby players	Case-control This study aims to investigate the prevalence of clinical and radiographic OA in lower extremities in former elite male athletes and referents from the general population and examine its association with the participant's demographic characteristics.	Cross-sectional To determine the prevalence of ankle OA in male retired professional footballers compared with the male general population.	Cross-sectional To determine the prevalence of OA and pain in the lower limb joints of retired professional footballers	Cross-sectional To investigate the long-term impact of playing professional football on HRQL in former players
Assessment methods	Questionnaires	Questionnaire	Questionnaire, clinical and ROA	Questionnaire, radiographic assessment	Questionnaire	Questionnaire
Source population	Former professional footballers	Former professional footballers	218 former elite male athletes (soccer, volleyball, martial arts, track and field and basketball players, and skiers) and 181 male controls	Former professional footballers	Former professional footballers	Five former professional footballer associations (FPAs)
Outcomes measure	Self-reported ankle OA	Self-reported ankle OA	Self-reported ankle OA	Radiographic ankle OA	Self-reported ankle OA	Self-reported ankle OA
Sample size	n=126 footballers, no controls	n=401 footballers no controls	Clinical assessment: 121 footballers, 181 controls Radiographic assessment: 91 footballers, 163 controls	Clinical assessment: 105 footballers, 77 controls Radiographic assessment: 75 footballers, 70 controls	n=185 footballers and no controls	n=284 footballers and no controls

Age (years) Mean SD.	32.2. ± 4.2	36 (32–40; 25–50)	Former athletes 50.1±8.5 Controls 50.7±10	Footballers 49.8±7.4 Controls 50.7±9.9	Footballers 7.6±13.2	Footballers 56.1±11.8
Years of playing football Mean (SD)	25.6 years	13 years	15.3±6.3 (all athletes)	8-10 years	n/a	13.5 years
Method of diagnosis	Self-reported (physician-diagnosed)	Self-reported (physician-diagnosed)	Clinical examination X-ray (KL classification)	Clinical examination X-ray (osteophytes, subchondral cysts, bone sclerosis, joint space narrowing)	Self-reported (physician-diagnosed)	Self-reported (physician-diagnosed)
Prevalence of ankle OA in footballers	ankle OA 35%	ankle OA 9.2% (n=37)	Clinical ankle OA 5% Radiographic ankle OA: 8%	Radiographic ankle OA 8.8% (controls 3.7%) Ankle: Clinical: 4.1%† X-ray: 8.8% *	Right ankle OA 5.7% Left ankle OA 6.3%	Right ankle 11.6% Left ankle 7.0%
Prevalence of ankle OA in controls	N/A	N/A	Clinical X-ray Ankle: 2.7% Ankle: 3.7%	Ankle: Clinical: 3.5%† X-ray: 3.7%*	N/A	N/A
Response rate	126/200= 63%	professional football (n=401) Rugby (n=152) players were enrolled in the study (response rate of 56%)	Former elite athletes: (n=391),84,4% Controls group: (n=313), RR=86.6%	Former athletes 150/170= 88.1% Controls group 115/132=86.6%	185/500= 37%	284 / 515= 55%

HRQL: health-related quality of life. n/a: not available.

1.10 Foot/ankle OA Management

The NICE guidelines for peripheral joint OA, which are mainly based on trials for knee and hip OA, recommend that the core management of anyone with OA should include advice and education related to the nature and causes of OA, local strengthening and aerobic exercises, and weight loss if the individual is overweight or obese (National Institute for Health and Care Excellence, 2022).

Pharmacological treatments for short-term pain relief are adjuncts to management, and 1st-line drugs are topical non-steroidal anti-inflammatory drugs (NSAIDs) (National Institute for Health and Care Excellence, 2022).

The primary objectives of treating foot/ankle OA are alleviating pain, enhancing function, and improving QoL (Vina and Kwoh, 2018). Currently, no specific treatments are available to address the structural changes of foot/ankle OA (National Institute for Health and Care Excellence, 2022). NICE recommends intra-articular corticosteroid injections for short-term relief from moderate to severe OA pain (National Institute for Health and Care Excellence, 2022). These injections provide rapid pain relief that typically lasts between 2 and 10 weeks. However, most evidence focuses on larger joints, such as the knee and hip, and NICE acknowledges a lack of consistent evidence for corticosteroid injections in the foot and ankle joints (National Institute for Health and Care Excellence, 2022).

Similarly, NICE provides detailed surgical recommendations for larger joints, particularly the hip, knee, and shoulder. However, specific guidance for surgical interventions for the foot and ankle is absent (National Institute for Health and Care Excellence, 2022). In the absence of such guidance, clinicians may consider adapting recommendations from the NICE guidelines for larger joints to inform clinical practice for other joints (National Institute for Health and Care Excellence, 2022). These include surgical options, such as joint fusion (arthrodesis) and joint replacement (arthroplasty), when non-surgical treatments fail to alleviate symptoms. However, the anatomical and biomechanical differences across joints may limit the direct applicability of knee-specific guidance for the foot/ankle joints. Further research is needed to develop tailored, evidence-based guidance for the surgical management of foot/ankle OA.

Conservative management of symptomatic foot/ankle OA typically involves nonpharmacological, pharmacological, and surgical interventions (Glyn-Jones et al., 2015). Treatment options include local or systemic analgesic medication, physical therapy, foot orthoses, footwear modifications, and corticosteroid joint injections (Paterson and Gates, 2019b). Surgical intervention may be considered if conservative treatment fails (Roddy and Menz, 2018). Although there are no specific clinical guidelines for managing foot/ankle OA, recommendations for managing OA at other sites may be applicable to the foot and ankle joints, including patient education, exercise, and weight loss in overweight patients (Paterson and Gates, 2019b).

Preventative measures for foot/ankle OA in retired footballers include maintaining a healthy weight, avoiding high-impact activities, incorporating low-impact exercises into their routine, and regularly stretching and strengthening their lower limbs (Prien et al., 2017). Retired footballers should continue monitoring their joint health and seek prompt medical attention if they experience foot/ankle OA symptoms (Turner et al., 2000b).

1.11 Rationale, aim and objectives of the current thesis.

1.11.1 Rationale

The prevalence and risk factors for foot/ankle OA in footballers have been less well-studied compared to the knee joint. However, it has been shown that playing professional football is a risk factor for knee OA (Fernandes et al., 2018). Whether foot/ankle OA in professional footballers is more common than in the general population remains largely unknown. It is important to identify the prevalence and risk factors of foot/ankle OA in footballers to understand the long-term consequences of sports and to inform the development of potential preventative and treatment strategies. Such information is essential for football associations, unions, and stakeholders interested in the health of retired and current professional football players.

In addition, foot /ankle injuries account for one-fifth of all injuries sustained while playing professional football (Ekstrand et al., 2009, Chomiak et al., 2000). However, despite the high incidence of injuries to

the foot/ankle in professional footballers, there is a lack of evidence relating this to OA development and other possible associated risk factors at this site.

1.11.2 Aim of thesis

To examine whether retired male professional footballers have a higher risk of foot /ankle OA and pain than general population male controls.

1.11.3 Objectives

Primary

1- To compare the prevalence of foot/ankle OA outcomes (current foot/ankle pain, pain lasting for ≥3 months, GP-diagnosed OA, surgery and radiographic foot/ankle OA) between retired male professional footballers and general population male controls.

2- To determine football-specific risk factors associated with the increased risk of foot/ankle OA in retired male professional footballers.

Secondary

1- To determine the prevalence of self-reported neuropathic-like pain, pain catastrophizing and age of onset for current foot/ankle pain between retired male professional footballers and general population male controls.

2- To compare the quality of life and two functional tests, Four Square Step Test (FSST) and a 10-Metre Walk Test (10-MWT) undertaken in the same participants who underwent radiographic assessment between

retired male professional footballers and general population male controls.

Chapter : 2 Methods

2.1 Source population

2.1.1 Participants

Participants were recruited from a previous study, which examined the prevalence of knee osteoarthritis (KOA) in retired professional male footballers living throughout the United Kingdom (UK) and general population male controls from the East Midlands region in England (Fernandes et al., 2018).

Retired male professional footballers were identified via the Professional Footballers' Association (PFA), the League Managers Association (LMA), and former players' associations at 21 professional football clubs (Appendix 2.1). In the footballer knee OA study, eligible footballers were males aged ≥40 years who had played professionally in the top four tiers of the English Football League (Fernandes et al., 2018). General population male controls were identified from 12 general practices in the East Midlands region who participated in the Knee Pain and related health In the Community (KPIC) study, where all eligible males aged ≥40 years were identified and invited by post (Fernandes et al., 2018).

Of the 1,207 retired male professional footballers in the KOA study, 878 indicated willingness to participate in future research and were sent a postal questionnaire for the current foot/ankle OA study. Similarly, of the 1,443 general population male controls in the third follow-up of the Knee Pain and Related Health in the Community (KPIC) Study (Fernandes et

al., 2018),1060 who expressed interest in future studies were sent a postal questionnaire for the current study on foot/ankle OA (Figure 3-1).

The response rate for the knee study was 25% for footballers and 42.9% for controls (Fernandes et al., 2018). The response rate for the foot/ankle OA study was 53 %for footballers and 58% for controls. Comparison between respondents versus non-respondents for knee study was not feasible as that was the first time we approached participants, and no data were obtained for non-respondents. We therefore compared the available source population (i.e., participants who attended the knee study and indicated their willingness to participate further research in the foot/ankle study) with the participants who competed the (questionnaire or radiographic assessment) in the foot/ankle study to examine the representativeness of the study samples. These results are presented in Table 3-1.

2.1.2 Research ethics

The East Midlands-Leicester Central Research Ethics Committee and HRA (REC Ref:19/EM/0354) approved this study on 23 January 2020 (Appendix 2.2). Returning the completed questionnaire was considered implied consent for participation, while written consent was obtained before undergoing radiographic assessment and functional tests.

2.1.3 Questionnaire

The questionnaire covered demographics, current health, General Practitioner (GP) diagnosed foot/ankle OA, pain history, foot/ankle injuries, foot/ankle injections, hallux valgus, and quality of life (QoL) (Table 2-1). Footballers received additional questions related to their careers, whereas the rest of the questionnaire was identical between both groups. For footballers, additional questions related to total matches, playing position, training hours, and career duration were included.

Questionnaires for footballers and controls also contained questions related to concussion, head trauma, dementia, neurodegenerative disease, and cognitive dysfunction to determine differences between footballers and controls that might have resulted from apparent direct injury or repetitive microtrauma related to heading the football. The results of this additional study have been published elsewhere (Macnab et al., 2023, Espahbodi et al., 2023) and are not presented in this thesis.

Table 2-1. Summary of the questionnaire.

Section	Questions and instruments
1. Demographic and current health	Date of birth, height, weight, list of comorbidities including diabetes, stroke, dementia, Alzheimer's, Parkinson's, depression, anxiety, hypertension, etc. Smoking and alcohol consumption. All current medications are both prescribed and alternative/over the counter.
2. Bodily pain	Body pain mannequin for previous month's pain (current), fibromyalgia mannequin (WPI) and SSSs past week's pain.
3. Foot/ankle pain	Pain present in the feet and ankles in the past month (current) and past three months (chronic), age at pain onset, diagnosis of foot OA, region-specific significant foot pain (ankle, mid-foot, big toe, other toes) and age range at the onset of pain. Pain Detect Questionnaire and Pain Catastrophizing Scale.
4. Injuries and operations to feet and ankles	Significant football-related injury to ankles/feet/toes. Region-specific (ankle, mid-foot, big toe, other toes) total number of significant football injuries throughout career, type of injury (e.g., ligament rupture), and age. Significant non-football-related injury ever (same questions as above).
5. Hallux valgus	Current and constitutional toe alignment using line drawings (straight or degree of angulation).
6. Quality of life	Short Form- 36 (SF-36) Health Survey.

SF-36 Health Survey and Questionnaire are referenced in the main text. OA, osteoarthritis; SSS, Symptom Severity Scale; WPI, Widespread Pain Index.

2.1.3.1 Section 1. Demographics

This included date of birth, height, and weight. Participant age was calculated as the number of years between their birth date and their survey completion date. Height and weight were used to calculate BMI. This section also included details of any medical comorbidities, both current and past, as well as information about current medications (those prescribed by a doctor, as well as over-the-counter medications and supplements).

The Charlson Comorbidity Index was used to generate a summary score to assess an individual's overall health status (Charlson et al., 1987b, Quan et al., 2005). The reason for using the Charlson Comorbidity Index is its widespread use and validation in predicting outcomes and adjusting for common comorbidities in clinical research (Quan et al., 2005, de Groot et al., 2003, Charlson et al., 1987b). It comprises 17 common comorbidities which are often reported across different studies, that would permitting cross-study comparisons. The index includes 17 distinct health conditions listed in Table 2-2.

Table 2-2. Charlson Comorbidity Index conditions Quan et al. (2005)

1. Myocardial infarction
2. Congestive heart failure
3. Peripheral vascular disease
4. Cerebrovascular disease
5. Dementia
6. Chronic pulmonary disease
7. Rheumatological disease
8. Peptic ulcer disease
9. Mild liver disease
10. Diabetes without chronic complication
11. Diabetes with chronic complication
12. Hemiplegia or paraplegia
13. Renal disease
14. Any malignancy, including leukaemia and lymphoma
15. Moderate or severe liver disease
16. Metastatic solid tumour
17. Acquired immune deficiency syndrome/Human immunodeficiency virus

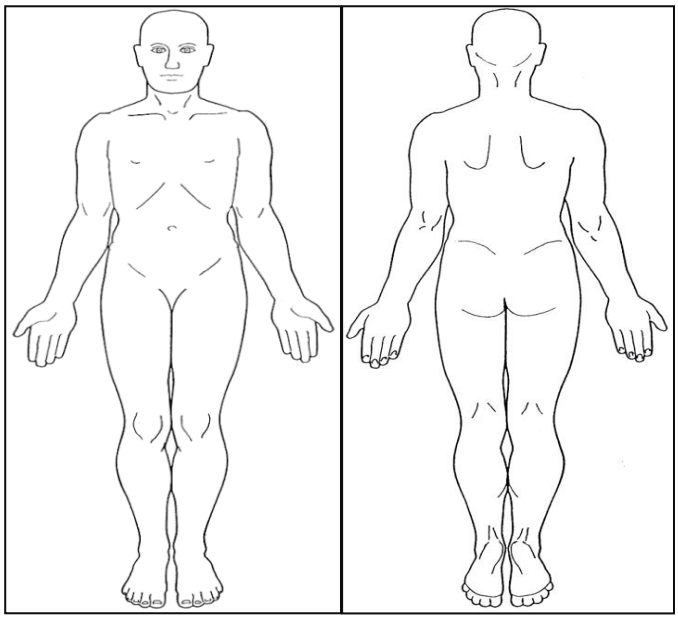
The Index of Multiple Deprivation (IMD) was used to assess Socioeconomic Status (SES) and was determined in deciles according to postcode (Gov, 2015). SES refers to an individual's or family's position relative to others based on income, education, and occupation. It comprises several factors that predict behaviours and outcomes related to health, education, and QoL. Socioeconomic status was evaluated using IMD deciles, with 1 representing the lowest and 10 the highest. A

higher socioeconomic status is generally associated with more positive outcomes and privileges, whereas a lower socioeconomic status is associated with numerous challenges and disadvantages (Gov, 2015).

2.1.3.2 Section 2. Pain anywhere in your body

This section details body pain determined using the validated Body Pain Mannequin (BPM) instrument (MacFarlane et al., 1996). Participants used the first simple diagram of the BPM to record the location of pain experienced for most days in the past month, anywhere in the body (Figure 2-1). The regional location can be classified by overlaying a template that divides the manikin into discrete areas (Appendix 2.3)

In addition to the BPM, a second diagram, which shows shaded discrete regions in the body, was used to show the site of pain experienced in the past week. Questions on the severity of tiredness, unrefreshing sleep, and difficulty in concentration in the past week were also asked, and there was also a tick list for 40 other specific symptoms experienced in the past week. The diagram and question lists can be used to score the Widespread Pain Index (WPI) to categorise the likelihood of having fibromyalgia.



A B

Figure 2-1. The body pain mannequin (BPM) tool

2.1.3.3 Section 3. Foot /ankle OA and pain

This section included three self-reported foot/ankle OA measurements. Participants were asked to respond "Yes" or "No" to the current foot/ankle pain questions: ***"Have you had significant pain in or around your feet for most days in the past month?"*** If they responded "yes", they showed where it was experienced using a set of line drawings of the feet (Figure 2-2). Foot/ankle pain for more than three months was defined by asking, ***"Have you ever had significant pain in or around your feet for most days over a three-month period? ".***

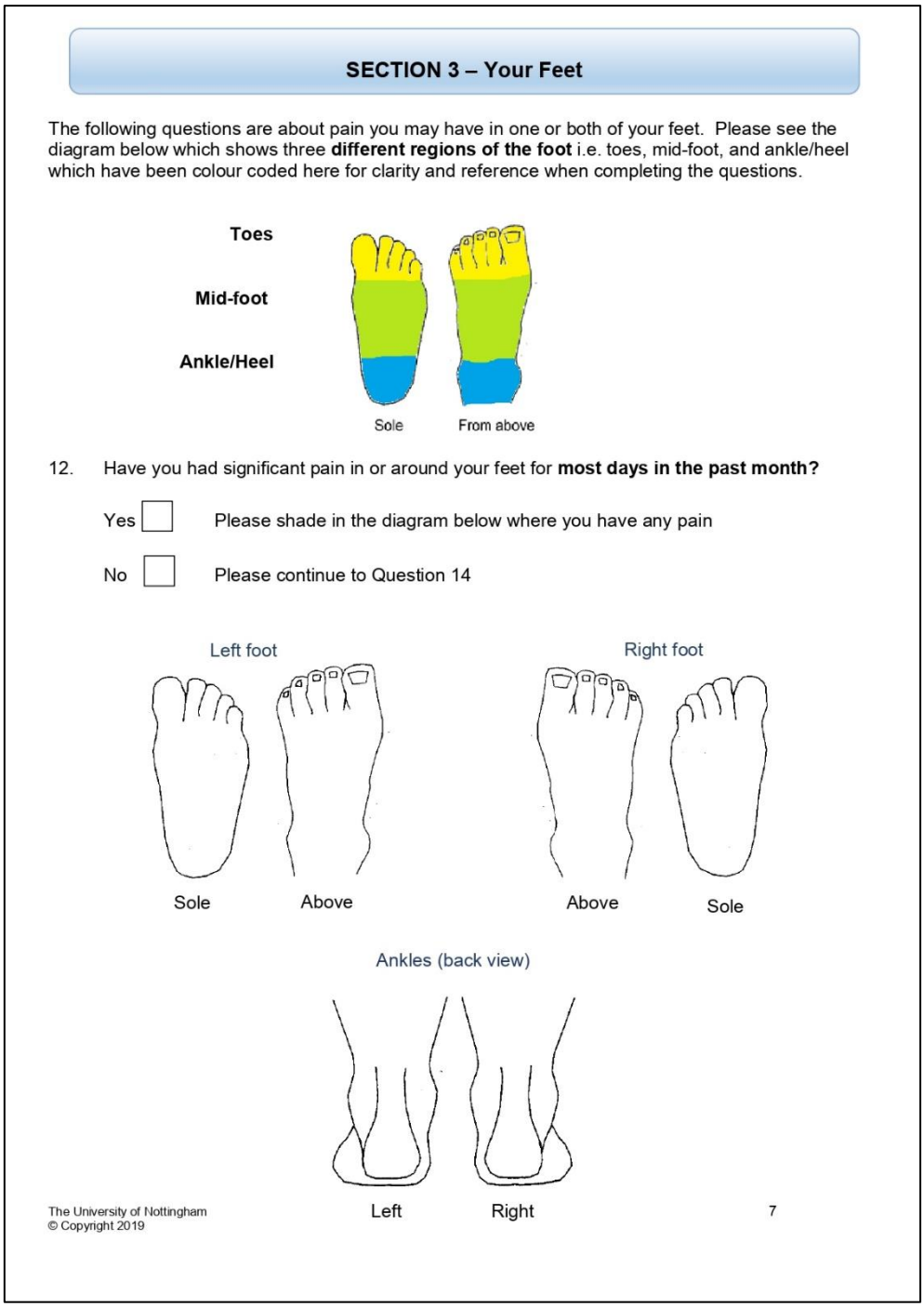


Figure 2-2. The illustrated question regarding the site of foot pain experienced for most days of the previous month.

Following the return of the questionnaire, the location of pain in any foot region that lasted most days the previous month was classified numerically using the system shown in Figure 2-3. This foot question and drawing set has been used in previous epidemiological studies, and similar foot/ankle models have been suggested for screening foot and ankle pain in clinical settings (Roddy et al., 2011, Garrow et al., 2004b, Waller et al., 2012, Chatterton et al., 2013b).

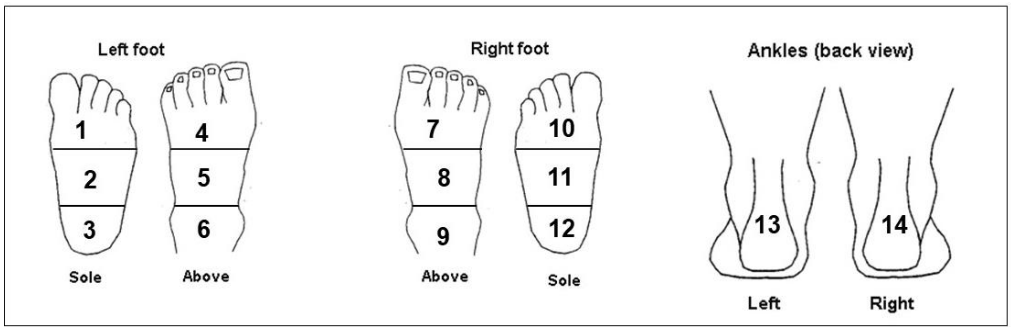


Figure 2-3. Foot manikin

Name of the site of pain in relation to numbered areas:

- Foot (1,2,4,5,7,8,10 or 11)
- Forefoot (the 5 digits/toes) (1,4,7 or 10)
- Midfoot (2,5,8 or 11)
- Hindfoot (heel) (3,6,9,12,13 or 14)
- Ankle (6,9,13 or 14)

Self-reported GP-diagnosed foot/ankle OA was determined by asking participants to respond “Yes” or “No” to the question: ***“Have you ever been diagnosed with Osteoarthritis in either of your feet by a doctor/GP?”.*** If the participants ticked “Yes,” they were asked to identify areas of included region-specific foot/ankle OA such as ankle, midfoot, big-toes, and other toes. Foot OA was defined as OA at any of the sites for the big toes, other toes, or midfoot.

The Pain Detect Questionnaire (PDQ), modified to focus solely on ankle and foot pain, was used to screen for neuropathic-like pain (Freynhagen et al., 2006a). The PDQ covered seven specific neuropathic symptoms, including burning, prickling, allodynia, attacks, thermal sensitivity, numbness, and pressure. The PDQ included 11-point numerical rating scales (NRS) to evaluate a patient's present pain level and its strongest and average levels over the past month. As part of the PDQ, nine other items were also included, including seven related to sensory responses and two related to temporal and spatial characteristics of the pain.

The Pain Catastrophising Scale (PCS) is a 13-item self-report questionnaire used to assess the presence of a catastrophising trait or state related to the participant's thoughts and feelings during their foot pain experiences (Sullivan et al., 1995b). The PCS instructions asked participants to reflect on past painful experiences and to score the degree to which they experienced each of the 13 thoughts or feelings when experiencing pain on a 5-point scale from 0 (not at all) to 4 (all the time). The total PCS scores ranged from 0-52, and the total PCS score was computed by summing the responses to all 13 items.

2.1.3.4 Section 4. Foot/ankle injuries, surgery and injections

The footballer's questionnaire included questions on significant football-related and non-football injuries to the ankles, feet, and toes. This included the region involved (ankle, midfoot, big toe, other toes), the total number of significant football injuries throughout a footballer’s career,

type of injury (e.g. ligament rupture), and age at the time of injury. A significant injury was defined as **‘*one that has caused you pain most days of the week for at least three months and has resulted in your absence from all training and matches during that period”*.**

The control questionnaire, a significant injury was identified as ***"one that has caused you pain most days of the week for at least three months and has resulted in your absence from all work and other duties during this time"*** (i.e. no mention of being related to football). A similar free-text and tick-box table was included in the footballer questionnaire, asking for information about any significant injuries to the feet, ankles, or toes unrelated to playing football.

Footballers were requested to provide information using a tick-box table concerning any injections into their ankles that they had received over their careers. The table asked for the type of injection (corticosteroid, anaesthetic, other), location, side (right or left), and the maximum number of injections in any given season. Also, they were asked to report the total number of injections they received into each ankle throughout their professional career. The questionnaire sought further details about injections elsewhere in the foot, asking participants to specify the locations and number of injections received.

Similarly, a table with free text and tick boxes queried whether the footballers had undergone forefoot/ankle surgery. The table asked about the type of surgery performed on the left and right sides of the ankle and

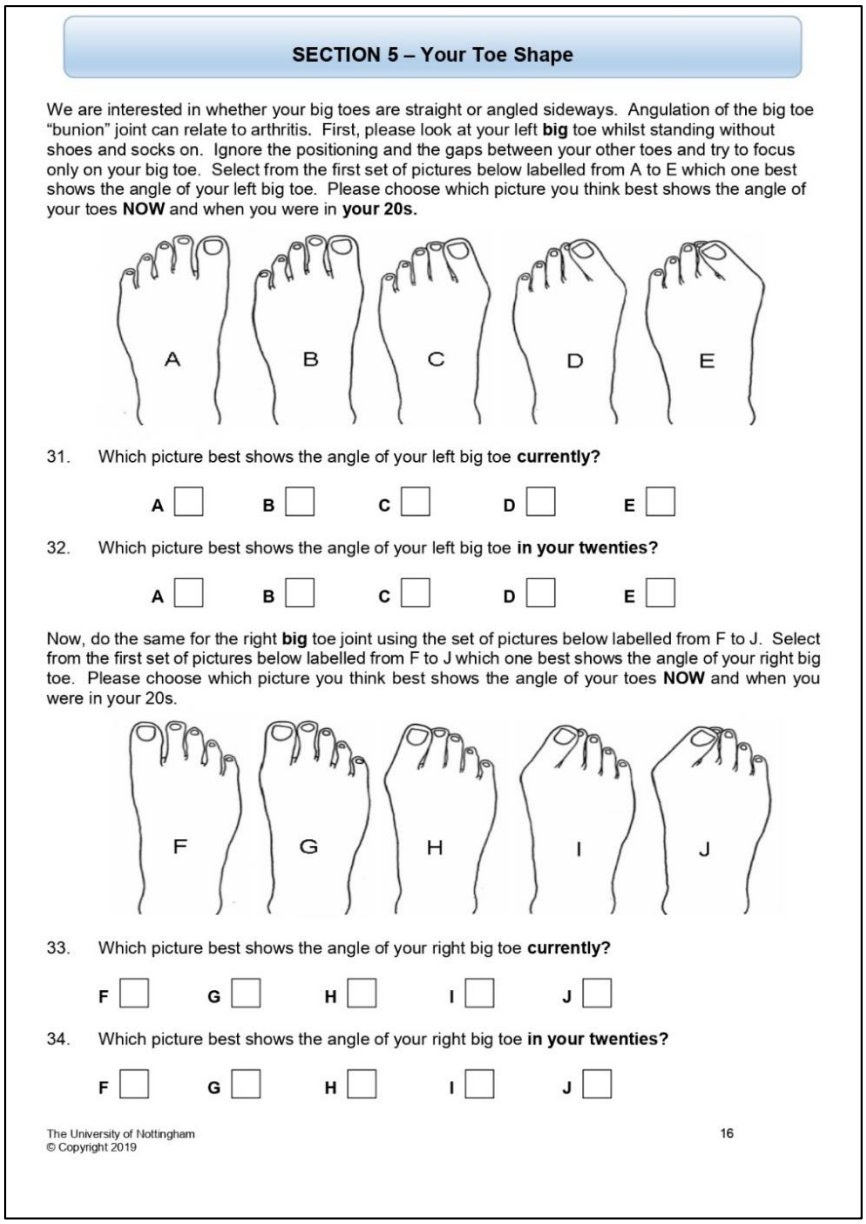
forefoot. The control group were asked the same questions about significant injuries, injections, and any ankle/toe surgery, but without any mention of football.

Having flat feet was determined by asking participants to respond “Yes” or “No” to the question: ***“Have you been told by a health professional (e.g. physiotherapist) that you have flat feet?”.***

2.1.3.5 Section 5. Hallux valgus

The current big toe alignment and the constitutional (i.e. early adult life in their 20s) were evaluated. The current big toe alignment of all participants was assessed using validated line drawings (Roddy et al., 2007c). This self-report instrument consists of a line drawing for each foot depicting normal alignment and then four 4-line drawings showing varying degrees of Hallux valgus (15˚, 30˚, 45˚, and 60˚). Each participant was instructed to compare the line drawings to their bare feet while standing and to select the picture from the questionnaires that best represented each of their left and right feet (Figure 2-4).

The severity of hallux valgus was classified as present or absent based on the three most severe grades. Specifically, 'A' or 'B' for the left foot and 'F' or 'G' for the right foot were classified as absent, whereas 'C', 'D', or 'E' for the left foot and 'H', 'I', or 'J' for the right foot were classified as present (Roddy et al., 2007c).



SECTION 5 – Your Toe Shape

We are interested in whether your big toes are straight or angled sideways. Angulation of the big toe "bunion" joint can relate to arthritis. First, please look at your left **big** toe whilst standing without shoes and socks on. Ignore the positioning and the gaps between your other toes and try to focus only on your big toe. Select from the first set of pictures below labelled from A to E which one best shows the angle of your left big toe. Please choose which picture you think best shows the angle of your toes **NOW** and when you were in **your 20s.**

31. Which picture best shows the angle of your left big toe **currently?**

A ☐ B ☐ C ☐ D ☐ E ☐

32. Which picture best shows the angle of your left big toe **in your twenties?**

A ☐ B ☐ C ☐ D ☐ E ☐

Now, do the same for the right **big** toe joint using the set of pictures below labelled from F to J. Select from the first set of pictures below labelled from F to J which one best shows the angle of your right big toe. Please choose which picture you think best shows the angle of your toes **NOW** and when you were in your 20s.

33. Which picture best shows the angle of your right big toe **currently?**

F ☐ G ☐ H ☐ I ☐ J ☐

34. Which picture best shows the angle of your right big toe **in your twenties?**

F ☐ G ☐ H ☐ I ☐ J ☐

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Figure 2-4. Line-drawing question for assessment of Hallux valgus.

2.1.3.6 Section 6. Quality of life

QoL was assessed using the well-validated RAND 36-item Health Survey 1.0 (SF-36), which was adapted to measure physical and mental health components (Framework, 1992). The two scores summarising the SF-36 subscales are the physical and mental components, representing QoL

regarding physical and mental health. The physical component score includes four subscales: physical functioning, role limitation due to physical problems, bodily pain, and general health. The mental component score includes four subscales: role limitation due to emotional problems, social functioning, mental health, and vitality (Tucker et al., 2013). For each subscale, scores range from 0 to 100, with higher scores representing better QoL. A mean score of 50 indicates average QoL, whereas a lower score indicates poor QoL (Tucker et al., 2013).

2.1.3.7 Questions related to further studies

The final page of the questionnaire presented two requests for the participants to consider. The first question asked whether the participant would be willing to undergo the radiographic assessment of the ankles and feet and the two functional assessments that would be scheduled after the survey. Participants who agreed to be contacted for these assessments were selected based on their completed and returned questionnaires, assuming that they were near Nottingham City Hospital or one of the five collaborating NHS hospitals. The second query concerned their willingness to be approached for any future studies that Academic Rheumatology would undertake at the University of Nottingham (UoN).

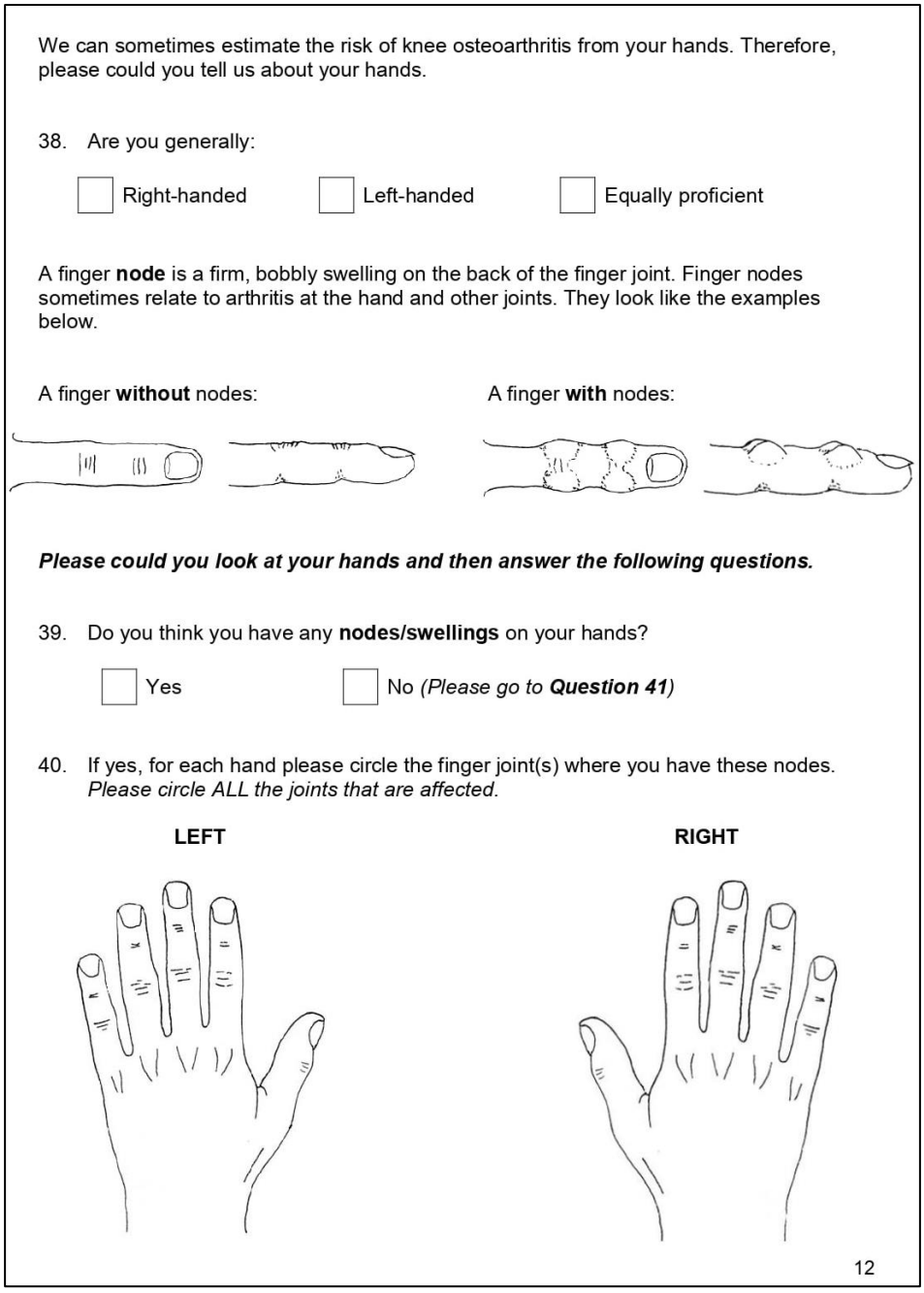
2.1.3.8 Variables obtained from the preceding knee OA questionnaire

The knee OA questionnaire (Fernandes et al., 2018), included additional variables related to controls and footballers, specifically nodal OA and index-to-ring digit (2D:4D) ratio. Specific questions regarding football-related exposures, such as position played, matches played, weekly training hours, career duration and career start and end years, were also included for the footballers only (Table 2-3). Because the variables obtained in these questions would not be expected to change over a relatively short time, these questions were not repeated in the foot/ankle OA study questionnaires to prevent redundancy and to save space.

Table 2-3. Footballer-specific variables derived from the previous knee OA study.

N	Variables	Protocol
1	Competitive (pre-professional) Football Duration (years)	=Age Started Professional Football – Age Started Competitive Football
2	Professional Career Duration (years)	= Year Retired – Year Commenced (Professional Football)
3	Total Football Duration (years)	= Competitive Football Duration + Professional Career Duration
4	Training Dose per Week (hours)	The number of hours per day spent on football training is multiplied by the number of days per week spent on football training.
5	Career Training Dose (hours)	Career training dose is the number of hours per week spent training multiplied by the number of weeks per season (average 40 weeks) and the professional career duration.
6	Position played during professional career.	[1] Goalkeeper [2] Defender [3] Midfielder [4] Forward [5] Outfielders (players other than a goalkeeper).
7	Total match	How many matches did you play for at least half the time during your professional career? Please include first-team, reserve, and international games. (e.g. 100 matches)

Nodal OA was defined as a self-reported node visible on at least two rays of both hands (Figure 2-5). A line-drawing tool was used to determine self-reported finger nodes (O'Reilly et al., 1999b).



We can sometimes estimate the risk of knee osteoarthritis from your hands. Therefore, please could you tell us about your hands.

38. 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.

39. Do you think you have any **nodes/swellings** on your hands?

☐ Yes ☐ No *(Please go to **Question 41**)*

40. 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**

12

Figure 2-5. Tool for self-reporting interphalangeal nodes.

The digit ratio is the length ratio between the index finger and ring finger, which can give three patterns: pattern 1 (A), the index finger is longer; pattern 2 (B), both fingers have the same length; and pattern 3 (C), the ring finger is longer (Caswell and Manning, 2009b) (Figure 2-6). However, it is worth noting that radiographic assessments provide a more reliable measure than visual assessments (Robertson et al., 2008).

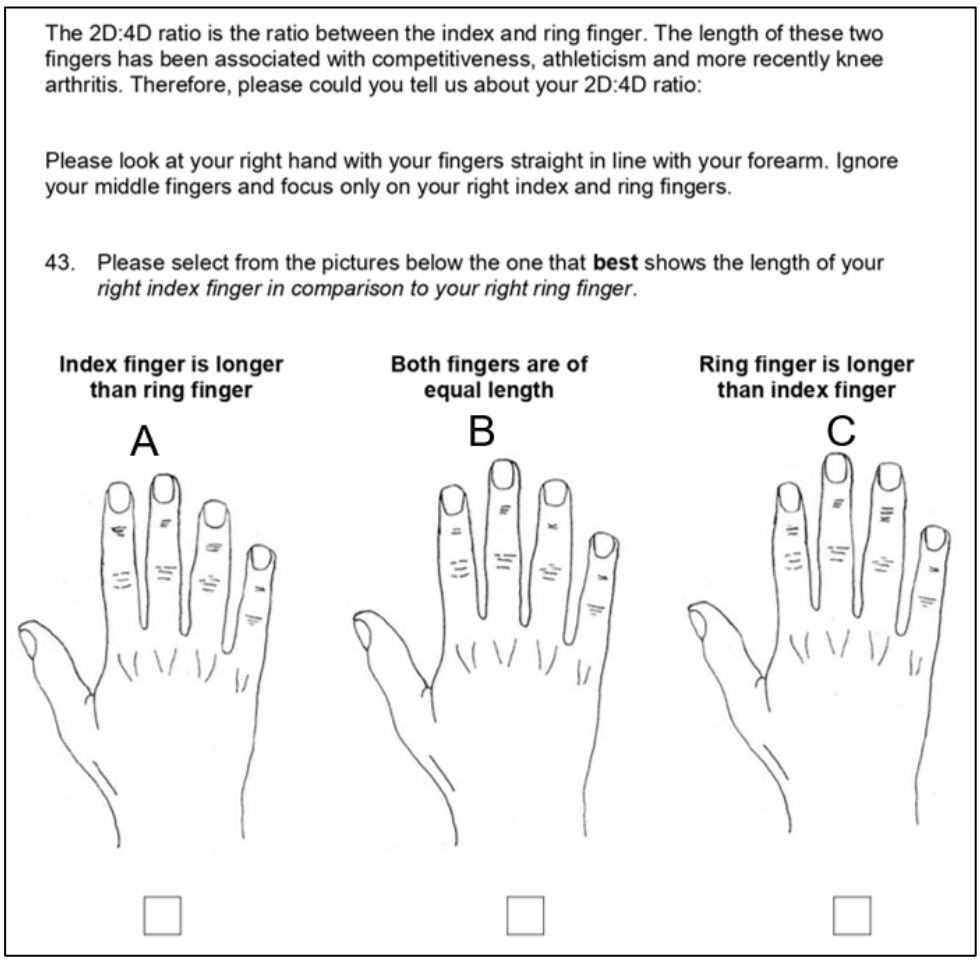


Figure 2-6. The line drawing tool to determine digit (2D:4D) ratio.

2.1.3.9 Posting questionnaires

For the footballers, the questionnaire was sent together with an invitation letter from the FA and PFA, a participant information sheet (PIS) detailing the study's objectives and importance, a prepaid return envelope, and an outer envelope with a logo. For controls, the questionnaire was sent with an invitation letter signed by the chief investigator, Professor Weiya Zhang, a PIS, and a prepaid return envelope. All questionnaires were returned to Academic Rheumatology at the Clinical Sciences Building, City Hospital, at the University of Nottingham. The full questionnaire posted to the footballers and controls are shown in Appendices 2.4-8.

A questionnaire was sent to 878 footballers in August 2020 and due to the COVID-19 pandemic and lockdown, a reminder letter was delayed and sent six months later, in February 2021, which was later than originally planned. The reminder was sent with a fresh questionnaire in case some participants could not find the previous one due to the long delay. A total of 1060 controls were sent the questionnaire in March 2021. After four weeks (April 2021), a reminder letter was sent to those who had not returned the initial questionnaire.

The questionnaire cover sheet asked for contact and personal details (e.g., names, emails, phone numbers, dates of birth, addresses). This was detached from each returned questionnaire and stored separately with the participant questionnaire's unique number to maintain participant anonymity.

Participants were given a self-addressed envelope to conveniently return the completed questionnaires to the Department of Academic Rheumatology. When received, the questionnaires were numbered consecutively with a unique code on the cover and the last page. When the completed questionnaires were received, they were given separate codes for footballers (Footballer ID) and controls (Control ID) to track responses accurately. Footballer questionnaires were printed on yellow paper, whereas those for the control group were printed on white paper. This colour differentiation aided in correctly grouping the questionnaires when they received the response and sent them to the company for data entry.

We complied fully with the General Data Protection Regulation (GDPR) (Rumbold and Pierscionek, 2017), the Data Protection Act of 2018, and the data handling guidelines of UoN and NHS. All data were collected and stored securely in locked premises within the UoN Clinical Sciences Building in the City Hospital.

2.1.4 Objective functional and radiographic assessments undertaken at the hospitals (in a sample of each group)

2.1.5 Functional assessments

The standardised instructions were provided for performing the four-step squares test (FSST) and 10-meter walk test (10-MWT) tests, which were conducted at the visit by one of two researchers (AT or MS).

2.1.5.1 Four-Step Squares Test

FSST requires a stopwatch and tape. Participants stood in square 1, facing square 2, with the tape forming a cross on the floor. They were instructed to step into each square as quickly as possible in sequences 2, 3, 4, 1, 4, 3, 2, and 1, ensuring that both feet contacted the floor in each square. This sequence involved forward, backwards, and sideways movements to the right and left. The FSST measures the time (in seconds) required to complete one complete sequence (Appendix 2.9). Participants were instructed: “Try to complete the sequence as quickly as possible without touching the tape”. Both feet must contact the floor of each square (Figure 2-7).

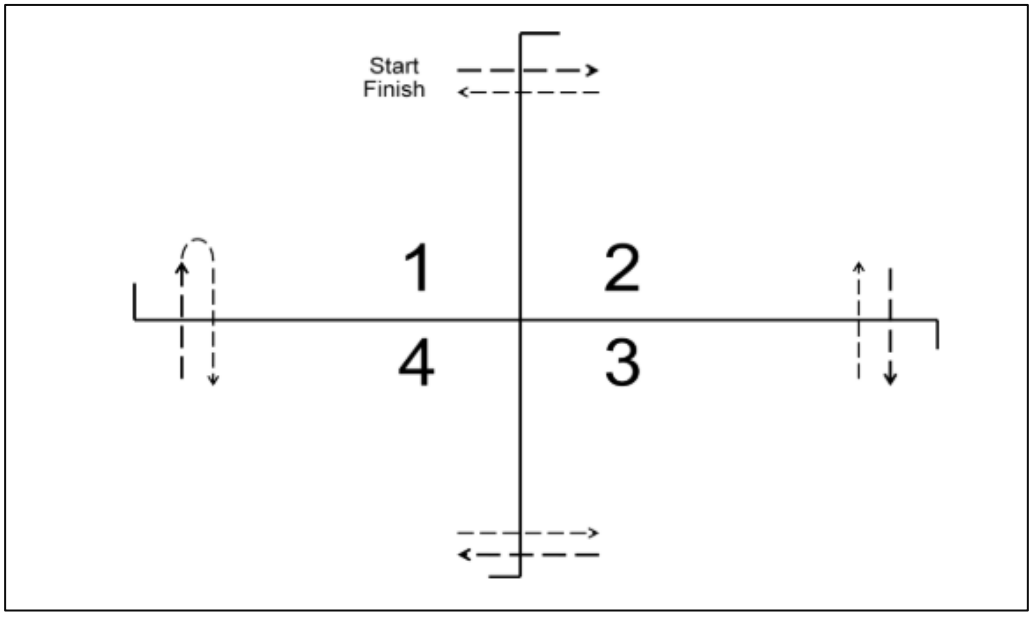


Figure 2-7. Four Square Step Test

The subject starts in square 1, facing square 2. The subject steps forward into square 2, sideway to square 3, backward to square 4, sideway to square 1, sideway to square 4, forward to square 3, sideway to square 2, and backward to square 1. The figure is adopted from Dite and Temple (2002).

The participants were instructed to face forward throughout the process to ensure a clear understanding of the sequence. They were given one

practice trial, and then the best of two FSST trials was selected as the timed score (Dite and Temple, 2002). Participants were provided standing or seated rest breaks between each FSST trial to prevent fatigue and were encouraged to rest as needed. The trial was repeated if a participant failed to complete the sequence or lost balance. Participants were allowed to turn and step forward into each square if they could not face forward throughout the sequence (Dite and Temple, 2002).

2.1.5.2 10-Metre Walk Test

The 10-MWT measures walking speed in metres per second (m/s) over a short distance. The time taken to travel 6 meters was recorded in minutes and seconds. The timer started when the toes crossed the 2-metre mark and stopped when the toes crossed the 8-metre mark (Figure 2-8).

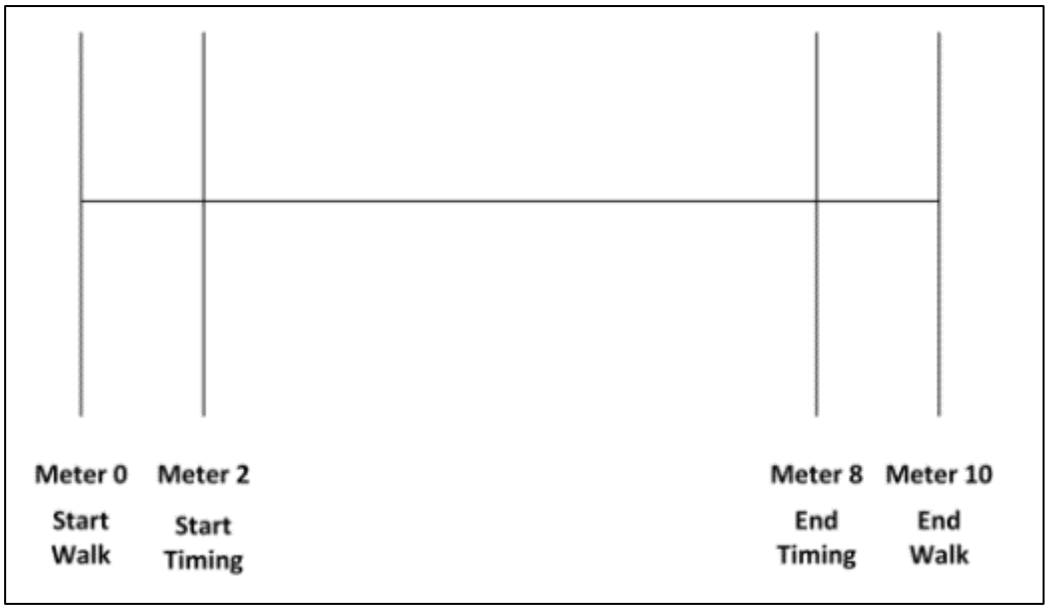


Figure 2-8. 10-Metre Walk Test

Participants were asked to complete six 10-metre trials, three at a normal speed and three at their maximum speed. Participants could use any assistive device or bracing that they were currently using, in which case the type of assistive device was documented (Appendix 2.10).

2.1.6 Radiographic assessment

A sample of footballer responders underwent radiographic assessment at one of the following five NHS collaborative sites: Nottingham University Hospital NHS Trust (City Hospital Site); Leeds Teaching Hospital NHS Trust (Chapel Allerton Hospital Site); Northern Care Alliance NHS Foundation Trust (Salford Royal Hospital Site); University Hospital Southampton NHS Foundation Trust (Southampton General Hospital Site); and Imperial College Healthcare NHS Trust (Hammersmith Hospital Site). All control participants were assessed at the City Hospital (Nottingham University Hospital NHS Trust).

Radiographic assessments were conducted for footballers and controls between November 2021 and March 2023. Participants who indicated willingness to attend and lived within 40 miles of a collaborating hospital were invited for a single visit for the radiographic and functional assessments. Communication was conducted via phone call or email to address any queries and to book and remind them of their appointment. Owing to the distance between the centres and the widespread residence of footballers in other areas of the UK, it was not feasible to invite all footballers for this assessment. Travel expenses were reimbursed for

those who participated in the assessment and any missed appointments were rescheduled.

Upon arrival at the hospital, the participants were given a folder containing the required paperwork for the assessment, along with their unique study number. Before the assessment, each participant was informed of the detailed procedures on the participant information sheet by Ahmed Thanoon (AT) or Monirah Shuaib (MS), any queries were discussed, and written consent was obtained. The two functional tests were performed, and then participants were escorted to the Radiology Department. Radiographic assessment was performed on a first-come, first-serve basis, with the convenience of nearby hospitals.

Radiographic images from the five collaborating hospitals were sent to the Academic Rheumatology department on encrypted CDs. Once received, the author (AT) reviewed the radiographic CDs and notified the hospital if any images were missing or damaged.

2.1.6.1 Views taken for all joints

The radiographic assessment protocol for the foot and ankle is detailed in (Appendix 2.11 and 2.12). Bilateral radiographs, including weight-bearing assessments, were obtained separately for the feet and ankles. The participants had to stand on the detector with their feet flat for the dorsoplantar view. The X-ray tube was angled 15° upward, with a vertical central ray centred at the base of the third metatarsal (Menz et al., 2007b).

Figure 2-9 illustrates the dorsoplantar view and the joints that were scored. The La Trobe Foot Atlas was used to assess five joints for the presence of OA, specifically the 1st MTPJ, the 1st and 2nd CMJs, the N1stCJ and the TNJ.

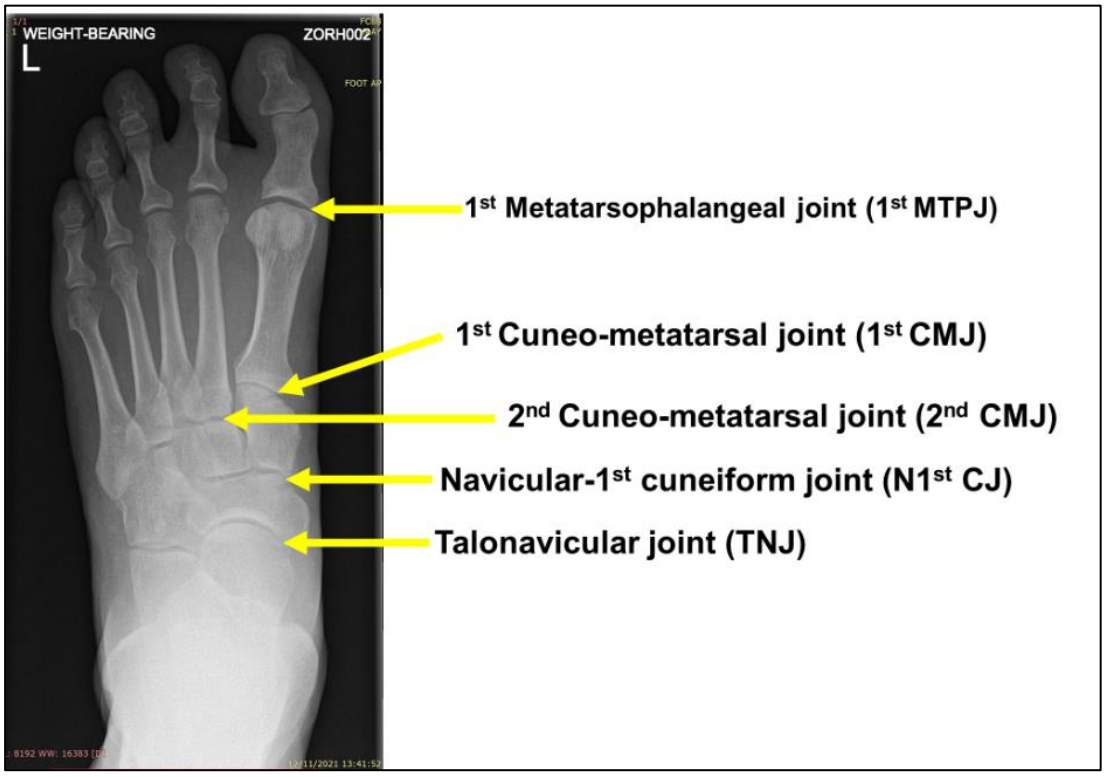


Figure 2-9. Foot radiographic dorsoplantar view.

In the lateral view, the participants stood on a low platform with the detector positioned on the side of their foot. The X-ray tube was angled at 90˚ with a central horizontal ray centred on the first metatarsal (Menz et al., 2007b). Figure 2-10 shows the lateral view of the foot.

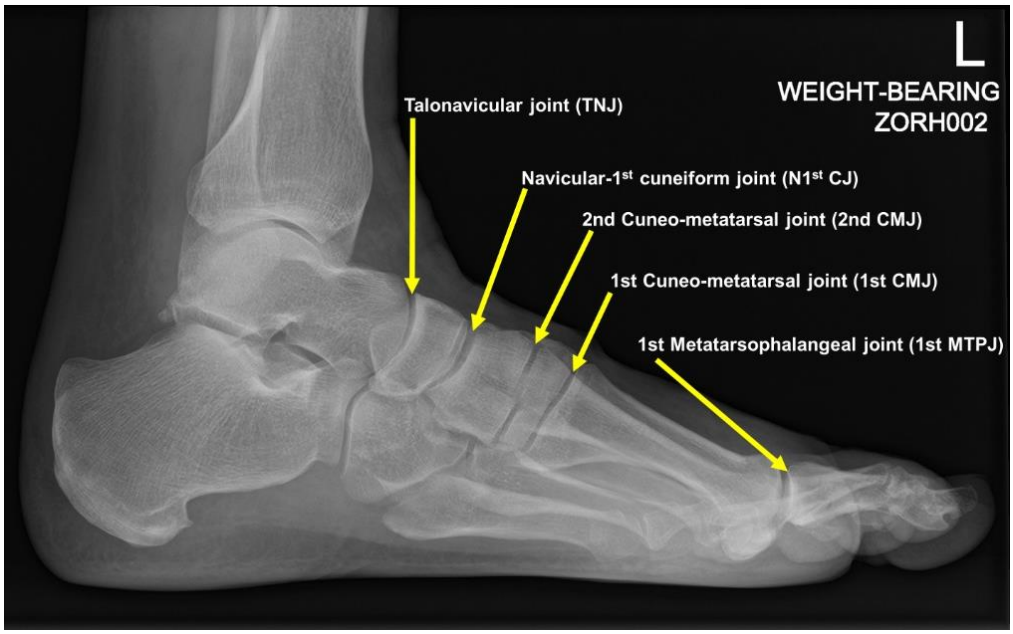
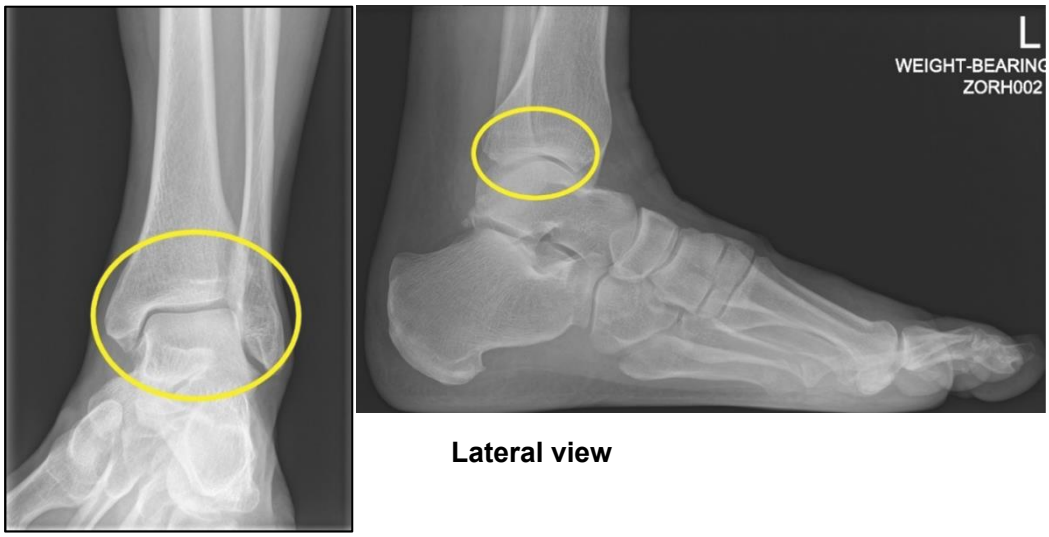


Figure 2-10. Foot radiographic lateral view.

Anteroposterior and lateral weight-bearing views of the ankle joint were obtained (Figure 2-11).



Lateral view

Anteroposterior view

Figure 2-11. Talocrural joint

Appendix 2.11 and 2.12 describe the radiographic scoring systems for foot and ankle OA, respectively (Menz et al., 2007b). Osteophytes (OP) and joint space narrowing (JSN) were scored 0-3 in each of the five-foot

joints, except for the TNJ, which was scored for JSN only. The presence of OP and JSN in each foot and ankle joint was graded as described in Table 2-4.

Table 2-4. La Trobe radiographic foot/ankle atlas scoring system.

Osteophytes		Joint space narrowing	
Grade	**Score**	**Grade**	**Score**
Absent	0	None	0
Small	1	Definite	1
Moderate	2	Severe	2
Severe	3	Bone on bone (at least at one point)	3

2.1.6.2 Scoring for foot /ankle OA

OP and JSN were assigned scores based on a conservative estimate when their interpretation and scoring were difficult. For example, if there was ambiguity in scoring an OP or JSN between 2 and 3 in a participant's joint, a lower grade of '2' was given (McQueen et al., 2017). In general, it is preferable to choose a lower score that the observer is confident about rather than a higher score for which that they are uncertain. If the scoring was impossible due to image quality issues, such as overlapping bones and excessive whiteness of the images, it was marked as '888' to indicate unreadability or difficulty in scoring.

We faced difficulties maintaining the blinding of footballers from controls during radiographic scoring. The ID system used for radiographic images, which assigned each image a specific ID to differentiate between the two sample groups, compromised the blinding process. Using 'F' (footballer) and 'C' (control) labels made it apparent to the researchers which group

each radiograph belonged to, introducing potential bias during the scoring process.

2.1.6.3 Radiographic assessment training

AT and MS underwent extensive training in foot/ankle OA scoring under the supervision of Professor Cathy Bowen, an expert in this field at the University of Southampton. After training, they spent six months practising their skills under the guidance of Professor Bowen. We practised on foot radiograph samples from Southampton and ankle radiographic samples from Keele (the CASF study images).

Our foot/ankle OA dataset was scored only after AT and MS consistently demonstrated between 80% and 90% agreement on the practice images. We measured this agreement using the kappa score for each joint in the foot and ankle radiographs from the practice samples, as outlined in Table 2-5.

Table 2-5. Kappa scores and definitions.

Kappa score	Definitions of agreement (Fleiss et al., 1981)
>0.75	Excellent agreement
0.40-0.75	Fair to good agreement
<0.40	Poor- agreement

All images were read by a single observer (AT) using RadiAnt DICOM Viewer software 2021 (Viewer, 2021). To evaluate reliability, 20 participants were randomly selected and assessed by the two observers

(AT and MS). The procedure was repeated three times with 20 different people at each time-point (starting, midpoint, and end of the study), resulting in a total of 60 participants and 120 feet and ankles being evaluated.

2.1.6.4 Case definitions of ROA foot/ankle

- **Foot ROA** was defined as the presence of OP or JSN ≥2 in either a dorsal planter or lateral view of any of the five-foot joints (1st MTPJ,1st CMJ,2nd CMJ, N1stCJ, and TNJ) (Menz et al., 2007b).

- **Midfoot ROA** was defined as OP or JSN ≥2 in either the dorsal planter or lateral view for at least one of the four midfoot joints, that is, 1st or 2nd CMJ, 1st NCJ or TNJ (Menz et al., 2007b).

- **Ankle ROA** was defined as either OP or JSN ≥2 in at least one ankle in either the anterior-posterior or lateral view (Menz et al., 2007b).

2.1.6.5 Symptomatic radiographic osteoarthritis (sROA) foot/ankle

Foot/ankle sROA was defined as the presence of both ROA and pain at the same joint using the questionnaire line-drawing foot manikin (Roddy et al., 2011, Chatterton et al., 2013a, Garrow et al., 2004a), as described below in (Table 2-6). If either or both feet were affected, individuals were defined as having sROA at each joint. Overall, sROA was defined as sROA in at least one of the five joints assessed in the foot.

Table 2-6. Definitions of symptomatic radiographic OA at foot, midfoot, and ankle joints.

Joint	Definition of sROA	Manikin Shading areas
Foot/ankle	Foot/ankle ROA and pain	(1, 2, 4, 5, 6,7,8,9,10,11,13 or 14)
Foot[1]	Foot ROA and pain	(1,2,4,5,7,8,10 or 11)
Midfoot[2]	Midfoot ROA and pain.	(2,5,8 or 11)
Ankle[3]	Ankle ROA and pain	(6,9,13 or 14)
1st MTPJ (forefoot)	1st MTPJ ROA and pain	(1,4,7 or 10)
1st CMJ	1st CMJ ROA and pain	(2,5,8 or 11)
2nd CMJ	2nd CMJ ROA and pain	(2,5,8 or 11)
N1stCJ	N1stCJ ROA and pain	(2,5,8 or 11)
TNJ	TNJ ROA and pain	(2,5,8 or 11)

[1] Foot (1st MTPJ,1st CMJ, 2nd CMJ, N1stCJ, TNJ).
[2] Midfoot (1st CMJ, 2nd CMJ, N1stCJ, TNJ)
[3] Ankle (Talocrural joint).

2.1.6.6 Coding radiographic foot/ankle OA

The coding process for the ROA and sROA definitions are presented in Appendix 2.13-16. The first step involved converting the original ROA scores of '0' or '1' to '0' to indicate the absence of ROA, while scores of '2' or '3' were converted to '1' to indicate the presence of ROA (Appendix 2.13). The second step defined ROA for each of the five-foot joints (Appendix 2.14), followed by defining ROA for foot, midfoot, and forefoot OA (Appendix 2.15). Finally, ROA for foot/ankle OA was defined by laterality (Appendix 2.16).

The coding for sensitivity analysis using a more stringent radiographic foot/ankle OA definition was made as for Grade $\geq$2 definite OP plus definite JSN anywhere in foot/ankle joints at either side is presented in Appendix 2.17.

2.1.7 Data collection and entry

The paper questionnaires and scoring sheets for the functional tests were stored in the main storage area of the Clinical Science Building at the City Hospital in UoN. Digital copies were kept in the UoN R Drive database, accessible in the Research-Rheumatology-Football-Database-Master Database.

Wyman Dillion (Bristol, England), an external organisation, entered all the questionnaire data into an Excel database. To protect the anonymity of participants, personal details, including names, emails, phone numbers, dates of birth and addresses, were removed from the questionnaires and stored separately. The questionnaires were then sent to Wyman Dillon without personal details for processing. The data were password-protected before being sent back to the Academic Rheumatology department for analysis. The paper questionnaires were sent back to Academic Rheumatology via the Post Office.

Details of personal contact information (including name, phone number, email, and address) were stored separately. A log file was created to record the contact information of the footballers and control participants. The author (AT) used Microsoft Excel 2020 (Windows 10) to enter the contact details into the database. The database was encrypted using a password to ensure data confidentiality. Access to this database was limited only to the researcher (AT) and the lead supervisor, Prof. Weiya Zhang.

AT entered the two performance tests into the master database in Microsoft Excel 2020 (Windows 10) and double-checked them using MS. The same ID number was used per participant, and AT contributed to the data cleaning process. Once data cleaning was completed, all the data used in this thesis were transferred to the Statistical Package for the Social Sciences (SPSS) for analysis.

2.1.8 Data cleaning/correction/recoding

The data provided by Wyman Dillion were re-examined to ensure its accuracy. Any unusual values (e.g., an age of over 120 years is unlikely) were replaced with missing data. After visually examining the datasets, we recorded several variables in preparation for analysis. Imputation was not considered because there was less than 10% missing data for any outcome (Hair, 2009).

2.2 Cross-sectional comparative study

This was a cross-sectional study comparing self-reported outcomes obtained by questionnaire and radiographic outcomes of foot/ankle OA between retired male professional footballers and general population male controls. The study was conducted in the UK between August 2020 and March 2023. Completion of the questionnaire was taken as implied consent, and for those invited to a subsequent hospital visit, written informed consent was obtained prior to their radiographic assessment. Those who expressed interest in undergoing foot and ankle radiographs were invited for bilateral radiographic assessment and participated in functional assessment tests, including the FSST and 10-MWT.

The study was part of the Foot/ankle Osteoarthritis and Cognitive impairment in retired UK Soccer players (FOCUS) study, the protocol of which is published (Espahbodi et al., 2022).

2.2.1 Objectives

The primary objective of this study was to compare the prevalence of foot/ankle OA and pain overall and by anatomical region (forefoot, midfoot, and ankle) between retired male professional footballers and general population male controls.

The secondary objective was to compare the laterality (left vs. right legs), summated radiographic scores (OP or JSN), self-reported neuropathic-like pain, pain catastrophizing, and age of onset for current foot/ankle

pain, as well as functional tests (10-MWT and FSST) and quality of life between the retired male professional footballers and general population male controls.

2.2.2 Inclusion /Exclusion criteria

Inclusion criteria for retired professional footballers were males aged 40 years and over who had played professionally in the top four tiers of the English Football League. Controls were males aged 40 years and over, who lived in the East Midlands and with no history of playing professional football. All participants could read and write in English, and none had known terminal illness, or inability to give informed consent or complete a questionnaire. Inclusion criteria for the radiographic assessment were similar for footballers and the controls, except those footballers needed to live within 40–50 miles of one of five collaborating NHS hospitals. Exclusion criteria for radiographs were having previously undergone bilateral ankle joint replacement or having any contraindication to having radiographs of their feet and ankles.

2.2.3 Exposure

The exposed group was defined as retired male professional footballers.

2.2.4 Comparator

The comparison group was defined as the general population male controls.

2.2.5 Outcome measures

To compare the prevalence of foot/ankle OA outcomes (current foot/ankle pain, pain lasting for ≥3 months, GP-diagnosed OA, surgery, and radiographic foot/ankle OA) between retired male professional footballers and general population male controls.

The self-reported outcomes are presented in Table 2-7, with ROA as defined in Section 2.1.6.4 and sROA as defined in Section 2.1.6.5.

Table 2-7. Self-reported outcomes for foot/ankle OA and pain.

Outcomes	Definition
Current foot/ankle pain	*"Have you had significant pain in or around your feet for most days in the past month?"*
Ever foot/ankle pain ≥3 months	*"Have you ever had significant pain in or around your feet for most days over 3-month period?"*
GP-diagnosed foot/ankle OA	*"Have you ever been diagnosed with Osteoarthritis in either of your feet by a doctor/GP?".*
Surgery forefoot/ ankle	*"Have you ever had surgery to your ankle or toe?"*

2.2.6 Confounders

Confounders were selected based on either : (1) a priori knowledge from the literature review; for example, age and socioeconomic status were considered risk factors for foot/ankle OA, as confirmed via epidemiological studies (Thomas et al., 2015b, Roddy et al., 2015b, Arnold et al., 2022b), and (2) significant in the univariate analysis, we only considered variables that showed significant differences between retired male professional footballers and general population male controls.

2.2.7 Statistical analysis

2.2.7.1 Power Calculation

The sample size was calculated according to the 14.3% prevalence of foot/ankle OA in the general population male controls and an odds ratio of 2 as a minimum clinically important difference (MCID) between footballers and general population controls (Roddy et al., 2015b). This required 250 participants per group, accounting for a 12% dropout and attrition rate to provide 90% statistical power with 5% type I error (Figure 2-12). The calculation involved using a z-test and a multiple logistic regression model with an R^2 of 0.3 between multiple covariates, as implemented in G*Power V.3.1.9.2 (Faul et al., 2009).

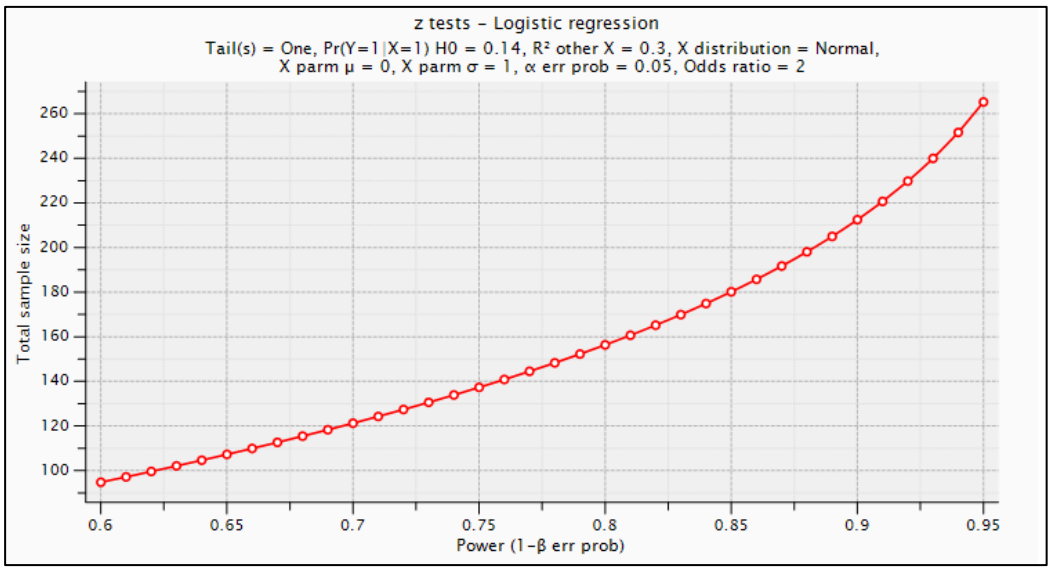


Figure 2-12. Cross-sectional study sample size calculation

- Tail(s) = One-tailed test
- Proportion ρ2 = 0.143
- α = 0.05
- Power (1-β) = 0.90
- R^2 other x = 0.3
- Sample size group 1 = 213
- Sample size group 2 = 213

2.2.7.2 Descriptive analysis

Continuous variables were presented as means and standard deviations (SDs), while categorical variables were presented as frequencies and percentages. A t-test (for continuous variables) or chi-square test (for categorical variables) was used to determine whether variable distributions differed significantly between footballers and controls. Statistical significance was defined as $p<0.05$. For comparisons across more than two groups (e.g., source population, questionnaire responders, and radiographic assessment participants), one-way ANOVA was used for normally distributed continuous variables, and the Kruskal-Wallis test was applied for non-normally distributed variables. Imputation was not performed because the overall proportion of missing data across variables was less than 10% (Dong and Peng, 2013).

The assumption of normality was checked for all continuous data. However, for well-established continuous variables such as age and BMI, the mean and SD were calculated even if they were skewed in this study based on the central limit theorem. This means that as the sample size increases, the data for these measures tends to be distributed more normally (Kwak and Kim, 2017).

The prevalence of foot/ankle OA was determined in each group by dividing the number of participants with the outcome of interest by the total number of participants in the group. This was based on a person irrespective of the number of joints affected; for example, for foot/ankle

ROA, the prevalence was calculated based on the number of participants with ROA in any foot/ankle joint on any side, divided by the total number of people per group. The prevalence of OA by anatomic region was also calculated to see which specific anatomic region of the foot/ankle joints was more likely to be affected by OA in footballers compared to controls. The prevalence between left and right within each group was also compared, and the laterality between footballers and controls was examined. Subjects with radiographs graded 0 or 1 were disease-free; those with grades 2 or 3 were cases. Agreement for intra-rater and inter-rater radiographic assessments were estimated using the kappa statistic (Fleiss et al., 1981).

2.2.7.3 Relative risk (RR)

Robust Poisson regression model was used to calculate adjusted relative risks (aRRs) with 95% confidence interval (CI) between footballers and controls (Zou, 2004, Talbot et al., 2023). The RR rather than the odds ratio (OR) was used for this analysis because (1) unlike in case-control studies, the prevalence of disease permitted a relative risk measure, allowing for the calculation of RR between groups, and (2) the outcomes were common (prevalence greater than 10%) in the population studied, making ORs suboptimal (Viera, 2008). Additionally, a relative risk measure was appropriate as a cross-sectional study comparing the prevalence of foot/ankle OA between two groups. Given that OA is common and to avoid the risk of overestimation associated with OR, Robust Poisson regression, which minimises potential overdispersion

and provides reliable and precise estimates for relative risk in binary outcomes, was used (Talbot et al., 2023, Zou, 2004). The aRR was adjusted for potential confounding factors based on existing knowledge from the literature and significant differences between footballers and controls in the univariate analysis.

2.3 Case-control study within footballers

This was a nested case-control study conducted in retired male professional footballers. Two separate nested case-control analyses were conducted: one for self-reported foot/ankle OA and another as a subgroup analysis for sROA foot/ankle.

2.3.1 Objectives

The primary objective of this study was to determine football-specific risk factors associated with the increased risk of foot/ankle OA in retired male professional footballers. To avoid the multiple testing, injury was treated as a primary risk factor, and all others as secondary risk factors.

2.3.2 Inclusion /Exclusion criteria.

Inclusion criteria for professional footballers were males aged 40 years and over living in the UK who had played professionally in the top four tiers of the English Football League. All professional footballers could read and write in English, and none had terminal illness or the inability to give informed consent or complete a questionnaire. In addition, those who returned a completed questionnaire and lived within 40 miles of one of five collaborating NHS hospitals (Nottingham, Manchester, Leeds, Southampton, and London) were invited to attend a single hospital radiology appointment for bilateral foot and ankle radiography, irrespective of their self-reported foot/ankle OA outcomes. Exclusion criteria for radiography included having previously undergone bilateral

ankle joint replacement or having any contraindication to radiography of the feet and ankles.

2.3.3 Exposure

Foot/ankle injury was the primary exposure of this case control study, which was self-reported in the questionnaire by asking professional footballers whether they had sustained significant injury during their career and how many such injuries they had experienced. For this study, we were specifically interested in significant foot/ankle injury which was defined as *"an injury which caused pain for most days over at least a 3-month period and resulted in an absence from all training and matches during this time"*.

2.3.4 Outcome measures

The primary outcome was self-reported foot/ankle OA, defined as either GP-diagnosed foot/ankle OA or a history of forefoot/ankle surgery performed at age 40 years or above. Retirement age was calculated by subtracting the date of birth from the end date of their professional football career. The age threshold of 40 was selected based on the sample's mean and median of retirement ages, and to distinguish surgery more likely related to OA from those due to acute injury before retirement (Doherty et al., 2016c). Footballers with self-reported foot/ankle OA formed the case group of this study and the remaining participants who did not fulfil this definition formed the control group. A specific joint analysis was also conducted for ankle OA, again defined as GP-

diagnosed ankle OA or a history of ankle surgery performed at age 40 years or above.

The secondary outcome was sROA foot/ankle, defined as those with both ROA and pain at any joint on the foot/ankle. Footballers with sROA foot/ankle formed the case group for this study and the remaining participants formed the control group.

2.3.5 Covariates

Covariates included demographic, constitutional, and biomechanical risk factors, as well as the career details of the footballers (Espahbodi et al., 2022). These included age, BMI, current hallux valgus (determined using a validated line drawing) was included instead of constitutional hallux valgus (assessed at the age of 20 years), which may be less reliable, to minimise recall bias (Roddy et al., 2007b). A pattern 3 2D:4D ratio (index-to-ring finger length ratio) (Caswell and Manning, 2009a) and nodal OA status were determined using validated diagrams (O'Reilly et al., 1999a). Nodal OA was classified as present in those reporting nodes on at least two rays of both hands (O'Reilly et al., 1999a). Flat-footedness was defined as present if identified by a health professional. Comorbidity was assessed using the Charlson Comorbidity Index (Charlson et al., 1987a), and the Index of Multiple Deprivations in deciles was derived from participants' postcodes (GOV.UK, 2015).

Foot/ankle injection was assessed during their playing career using the two questions, "Have you ever had any injections into your ankles?" and

“Have you ever had injections anywhere else in your foot other than in your ankle(s)?” If they replied positively, they were then asked to identify which ankle was injected and the type of injection used, with the following options: cortisone (steroid); anaesthetic (lignocaine); do not know; or other (please specify). Since we did not distinguish between intra-articular (joint) or extra-articular (soft tissue) injections, foot/ankle injection was used as a general term.

Footballers were also asked about their career training dose, career duration, weekly training hours, total matches played, and positions played (such as goalkeeper, defender, midfielder, and forward) (Espahbodi et al., 2022). Career duration was calculated as the time between the start of a professional football career (signed with a professional football club) and the date of retirement from playing professional football (end of contract or retirement). Career training was estimated by multiplying the number of hours played per week by 40 weeks (the average season) and by career duration. Weekly training hours were determined by multiplying the number of hours trained per day by the number of training days per week (Espahbodi et al., 2022).

2.3.6 Statistical analysis

2.3.6.1 Power calculation

The sample size was calculated based on a 57.5% prevalence of ankle injury in the retired male professional footballers (Paget et al., 2020b) and a minimum clinically important odds ratio of 3 for foot/ankle OA

(Eltaraboulsi et al., 2024, Parekh et al., 2021a). As a result, a minimum of 61 participants per group was required for this study to achieve 90% power with 5% Type I error (i.e., a significance level of 0.05). The calculation was performed using a z-test and a multiple logistic regression model with an R^2 of 0.3 for multiple covariates, as implemented in G*Power V.3.1.9.2 (Faul et al., 2009).

2.3.6.2 Descriptive analysis

Comparative analyses between cases and controls were conducted using the Chi-square test for categorical variables, the independent t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables. Statistical significance was defined as $p< 0.05$.

2.3.6.3 Odds ratio (OR)

Logistic regression was used to calculate the adjusted odds ratio (aOR) and 95% CI. A multivariable logistic regression model was conducted to estimate whether a risk factor was associated with foot/ankle OA, adjusting for potential confounding factors.

Univariable analysis was performed for all putative risk factors collected in this study. A multivariable logistic regression analysis was conducted using a backward stepwise approach, where all available risk factors, irrespective of their significance, were initially included in the model. This approach ensured that all putative risk factors were considered at the first step. The variables included were injury, injection, age, BMI,

socioeconomic status, Charlson Comorbidity Index, nodal OA, gout, pattern 3 of the 2D:4D digit ratio, current hallux valgus, flat feet, career training dose, career duration, total matches played, position played, and training hours per week.

Non-significant variables ($p > 0.05$) were subsequently removed from the model at one at a time, starting with the least significant, until all variables within the model remained statistically significant. The remaining variables were confirmed as independent risk factors for the outcome measure (Heinze et al., 2018). Backward stepwise selection was considered because it ensures that all relevant variables are assessed for their individual and combined impacts within a fully contextual framework (Heinze et al., 2018). Additionally, collinearity among the independent variables was examined using the variance inflation factor (VIF) to ensure that the final model was free from multicollinearity issues (O'brien, 2007). Interaction terms between two significant variables, e.g., injury*injection, were then added to the model one at a time as interested to calculate the aOR and 95% CI for interaction.

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 29.

2.3.7 Sponsor and funding

This study was sponsored by the University of Nottingham (UoN) and conducted in the Department of Academic Rheumatology. Funding was provided by Centre for Sport, Exercise and Osteoarthritis Research

Versus Arthritis, Football Association (FA) and Professional Footballers' Association (PFA).

Chapter : 3 Results Prevalence of foot/ankle OA in retired male professional footballers compared with male in the general population.

This chapter addresses the first objective, i.e., the prevalence of self-reported and ROA foot/ankle between retired male professional footballers and general population male controls. The prevalence of each foot/ankle OA outcome was compared between footballers and controls and the aRR with 95%CI was calculated using the Robust Poisson regression model.

In addition, we compared footballers and controls on the phenotypes of foot/ankle pain and the age of onset of this pain. We also compared the functional performance test (FSST and 10-metre walk test) and QoL (physical and mental component) between footballers and controls.

3.1 Recruitment

Of the postal questionnaire sent to 878 footballers and 1060 controls, completed questionnaires were returned from 468 footballers and 619 controls, giving a response rate of 53% (468/878) for footballers and 58% (619/1060) for controls. Of these, 362 footballers and 497 controls indicated willingness to undergo the radiographic examination and the two functional tests. Subsequently, 113 footballers and 319 controls completed the radiographic assessment and the functional tests (Figure 3-1). There were no differences in age, BMI, socioeconomic status, nodal OA and pattern 3 finger ratio (2D<4D) between the source population

(total available participants), questionnaire sample, and radiographic assessment sample in either the footballer or control groups (Table 3-1).

The distribution of footballers and controls in the UK who were willing to participate in radiographic assessment is presented in Appendix 3.1. For all foot/ankle radiographs obtained in the footballer and control groups, approximately 1% of radiographic images were missing. The missing data for each view of the radiographic images are presented in Appendix 3.2.

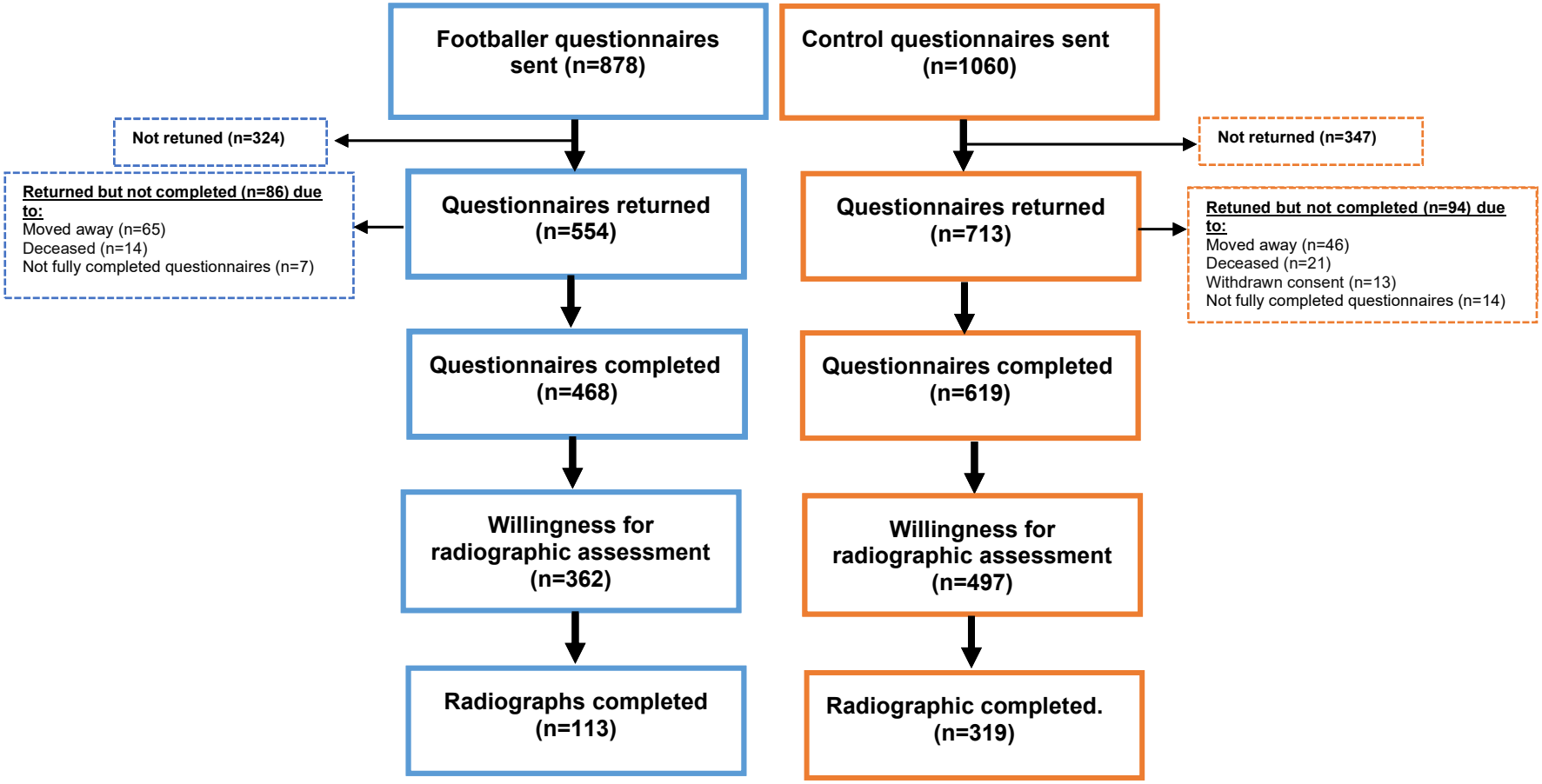


Figure 3-1. Recruitment of retired professional footballers and general population controls.

Table 3-1. Comparison among source population, questionnaire responders, and samples undergoing radiographic assessment in retired male professional footballers and general population male controls

Footballers	**Source population (n=878)**	**Questionnaires completed (n=468)**	**Radiographic assessment (n=113)**	p-value
Age (years), mean (SD)	63.40 (11.35)	63.71 (10.47)	62.38 (8.52)	0.507[a]
BMI (kg/m^2), mean (SD)	27.34 (3.00)	27.22 (2.89)	27.01 (2.66)	0.480[a]
SES, (decile), median (IQR)	8.00 (6-9)	8.00 (6-10)	9.00 (7-10)	0.173[b]
Nodal OA, n/total (%)	69/871 (7.92)	29/463 (6.26)	4/112 (3.57)	0.173[c]
Pattern 3 finger ratio (2D<4D), n/total (%)	554/846 (65.48)	300/452 (66.37)	72/109 (66.06)	0.948[c]
General population	**Source population (n=1060)**	**Questionnaires completed (n=619)**	**Radiographic assessment (n=319)**	p-value
Age (years), mean (SD)	69.51 (9.55)	69.10 (9.30)	68.17 (8.53)	0.076[a]
BMI (kg/m^2), mean (SD)	27.19 (4.27)	26.80 (4.27)	26.68 (3.71)	0.070[a]
SES, (decile), median (IQR)	6.00 (4-10)	6.50 (4-10)	6.00 (4-10)	0.092[b]
Nodal OA, n/total (%)	67/1013 (6.61)	43/598 (7.20)	26/308 (8.44)	0.545[c]
Pattern 3 finger ratio (2D<4D), n/total (%)	638/1014 (62.91)	373/598 (62.37)	203/310 (65.48)	0.637[c]

BMI: Body mass index.
SES: Socioeconomic status was measured according to postcode.
Nodal OA was defined as reporting nodes on at least two rays of both hands.
2D<4D (Pattern 3): The index finger is shorter than the ring finger.
IQR = Interquartile range.
a = ANOVA test.
b= Kruskal–Wallis test.
c = Chi-Square test.
SD: Standard deviation.

3.2 Intra- and inter-rater agreement for radiographic assessments

During the study, radiographic foot/ankle OA assessment reliability was evaluated using the intra-rater (AT) and inter-rater (AT with MS) agreement tests. The results demonstrated good to excellent agreement for both intra-rater (Table 3-2) and inter-rater reliability (Table 3-3) for OP and JSN in the foot/ankle joint.

Table 3-2. Intra-rater reliability of radiographic foot/ankle OA scoring.

View and feature	Pre-study (n=20) Kappa 95% CI	Mid-study (n=20) Kappa 95% CI	End-study (n=20) Kappa 95% CI
Foot -Dorsal view			
1st MTPJ - OP	0.69 (0.52 - 0.86)	0.92 (0.81 - 1.02)	0.94 (0.87 - 1.02)
1st MTPJ - JSN	0.76 (0.60 - 0.92)	0.88 (0.75 - 1.00)	0.91 (0.78 - 1.04)
1st CMJ - OP	0.64 (0.41 - 0.87)	0.86 (0.71 - 1.00)	0.91 (0.78 - 1.03)
1st CMJ - JSN	0.74 (0.54 - 0.94)	0.92 (0.82 - 1.02)	0.96 (0.90 - 1.03)
2nd CMJ - OP	0.69 (0.46 - 0.91)	0.90 (0.77 - 1.02)	0.95 (0.85 - 1.05)
2nd CMJ - JSN	0.81 (0.66 - 0.96)	0.89 (0.77 - 1.00)	0.96 (0.90 - 1.03)
N1stCJ - OP	0.60 (0.36 - 0.84)	0.89 (0.74 - 1.03)	0.95 (0.86 - 1.04)
N1stCJ - JSN	0.61 (0.40 - 0.82)	0.91 (0.80 - 1.01)	0.95 (0.86 - 1.04)
TNJ - JSN	0.85 (0.65 - 1.05)	0.90 (0.87 - 0.92)	1.00 (1.00 - 1.00)
Overall, the foot[1]	**0.61 (0.54 - 0.68)**	**0.91 (0.87 - 0.94)**	**0.94 (0.91 - 0.98)**
Foot - Lateral view			
1st MTPJ - OP	0.58 (0.38 - 0.77)	0.84 (0.66 - 1.02)	0.95 (0.87 - 1.04)
1st MTPJ - JSN	0.75 (0.56 - 0.93)	0.88 (0.74 - 1.01)	0.96 (0.88 - 1.04)
1st CMJ - OP	0.72 (0.49 - 0.94)	0.87 (0.72 - 1.02)	0.95 (0.86 - 1.05)
1st CMJ - JSN	0.76 (0.57 - 0.95)	0.88 (0.71 - 1.05)	0.94 (0.82 - 1.05)
2nd CMJ - OP	0.46 (0.20 - 0.71)	0.80 (0.62 - 0.98)	0.94 (0.84 - 1.05)
2nd CMJ - JSN	0.69 (0.50 - 0.87)	0.80 (0.64 - 0.96)	0.93 (0.85 - 1.02)
N1stCJ - OP	0.76 (0.57 - 0.95)	0.85 (0.69 - 1.00)	0.93 (0.80 - 1.06)
N1stCJ - JSN	0.86 (0.63 - 0.93)	0.95 (0.85 - 1.04)	0.88 (0.65 - 1.11)
TNJ - OP	0.64 (0.43 - 0.84)	0.81 (0.63 - 0.99)	0.90 (0.79 - 1.01)
TNJ - JSN	0.72 (0.51 - 0.92)	0.90 (0.77 - 1.03)	0.90 (0.70 - 1.09)
Overall, foot[1]	**0.70 (0.63 - 0.76)**	**0.87 (0.82 - 0.91)**	**0.95 (0.93 - 0.98)**
The Ankle[2]			
Anterior-posterior view			
OP	0.80 (0.62 - 0.98)	0.92 (0.81 - 1.02)	0.96 (0.90 - 1.03)
JSN	0.72 (0.58 - 0.85)	0.88 (0.75 - 1.00)	0.95 (0.86 - 1.04)
Overall ankle	**0.72 (0.58 - 0.85)**	**0.90 (0.81 - 0.98)**	**0.96 (0.91 - 1.01)**
Lateral view			
OP	0.77 (0.59 - 0.95)	0.89 (0.75 - 1.03)	0.96 (0.88 - 1.04)
JSN	0.78 (0.61 - 0.95)	0.92 (0.77 - 1.07)	0.92 (0.76 - 1.08)
Overall ankle	**0.77 (0.65 - 0.89)**	**0.90 (0.80 - 1.00)**	**0.95 (0.90 - 1.02)**

OP: Osteophytes. JSN: Joint space narrowing.
1st MTPJ 1st Metatarsophalangeal joint.1st CMJ: 1st Cuneo-metatarsal joint. 2nd CMJ: 2nd Cuneo-metatarsal joint. N1stCJ: Navicular-1st cuneiform joint. TNJ: Talonavicular joint.
[1]Foot included five joints (1st MTPJ,1st CMJ, 2nd CMJ, N1stCJ, TNJ).
[2]Ankle (Talocrural joint). AP: Anterior posterior

Table 3-3. Inter-rater reliability of radiographic foot/ankle OA scoring.

View and feature	Pre-study (n=20) Kappa 95% CI	Mid-study (n=20) Kappa 95% CI	End-study (n=20) Kappa 95% CI
Foot - Dorsal view			
1st MTPJ - OP	0.93 (0.86 - 1.00)	0.96 (0.90 - 1.03)	0.97 (0.91 - 1.02)
1st MTPJ - JSN	0.95 (0.90 - 1.00)	0.97 (0.91 - 1.02)	0.95 (0.85 - 1.04)
1st CMJ - OP	0.88 (0.75 - 0.99)	0.92 (0.88 - 1.02)	0.97 (0.91 - 1.02)
1st CMJ - JSN	1.00 (1.00 - 1.00)	0.92 (0.83 - 1.00)	0.96 (0.90 - 1.03)
2nd CMJ - OP	0.88 (0.72 - 1.00)	0.90 (0.78 - 1.02)	0.94 (0.84 - 1.05)
2nd CMJ - JSN	0.84 (0.72 - 0.97)	0.94 (0.87 - 1.01)	0.96 (0.90 - 1.03)
N1stCJ - OP	0.90 (0.79 - 1.03)	0.94 (0.83 - 1.05)	0.95 (0.86 - 1.04)
N1stCJ - JSN	0.84 (0.70 - 0.99)	0.93 (0.84 - 1.10)	0.95 (0.86 - 1.04)
TNJ - JSN	0.76 (0.52 - 1.00)	0.89 (0.69 - 1.09)	1.00 (1.00 - 1.00)
Overall, the foot[1]	**0.92 (0.88 - 0.95)**	**0.94 (0.92 - 0.97)**	**0.95 (0.92 - 0.98)**
Foot - Lateral view			
1st MTPJ - OP	0.85 (0.73 - 0.96)	0.90 (0.76 - 1.04)	0.91 (0.79 - 1.03)
1st MTPJ - JSN	0.79 (0.63 - 0.94)	0.88 (0.74 - 1.01)	0.91 (0.80 - 1.03)
1st CMJ - OP	0.89 (0.76 - 1.00)	0.91 (0.79 - 1.02)	0.90 (0.77 - 1.03)
1st CMJ - JSN	0.92 (0.81 - 1.00)	0.94 (0.82 - 1.05)	0.94 (0.82 - 1.05)
2nd CMJ - OP	0.77 (0.58 - 0.96)	0.85 (0.69 - 1.01)	0.89 (0.73 - 1.04)
2nd CMJ - JSN	0.96 (0.89 - 1.00)	0.92 (0.81 - 1.02)	0.93 (0.84 - 1.02)
N1stCJ - OP	0.86 (0.72 - 1.01)	0.90 (0.77 - 1.02)	0.93 (0.80 - 1.06)
N1stCJ - JSN	0.87 (0.73 - 1.00)	0.95 (0.86 - 1.04)	0.88 (0.64 - 1.11)
TNJ - OP	0.70 (0.50 - 0.88)	0.82 (0.66 - 0.98)	0.90 (0.79 - 1.01)
TNJ - JSN	0.86 (0.71 - 1.00)	0.90 (0.77 - 1.03)	0.88 (0.64 - 1.11)
Overall, the foot[1]	**0.83 (0.78 - 0.88)**	**0.90 (0.86 - 0.94)**	**0.93 (0.90 - 0.96)**
The Ankle[2]			
Anterior-posterior view			
OP	0.81 (0.64 - 0.99)	0.90 (0.80 - 1.01)	0.92 (0.84 - 1.01)
JSN	0.74 (0.55 - 0.93)	0.87 (0.75 - 0.99)	0.90 (0.77- 1.03)
Overall ankle[2]	**0.79 (0.67 - 0.91)**	**0.89 (0.81- 0.97)**	**0.92 (0.85 - 0.99)**
Lateral view			
OP	0.90 (0.76 - 1.03)	0.94 (0.83 - 1.04)	**0.96 (0.88 - 1.03)**
JSN	0.84 (0.67 - 1.01)	0.92 (0.77 - 1.07)	**0.92 (0.76 - 1.08)**
Overall ankle	**0.87 (0.77 - 0.98)**	**0.93 (0.84 - 1.01)**	**0.96 (0.90 - 1.02)**

OP: Osteophytes. JSN: Joint space narrowing.
1st MTPJ 1st Metatarsophalangeal joint.1st CMJ: 1st Cuneo-metatarsal joint. 2nd CMJ: 2nd Cuneo-metatarsal joint. N1stCJ: Navicular-1st cuneiform joint. TNJ: Talonavicular joint.
[1]Foot included five joints (1st MTPJ,1st CMJ, 2nd CMJ, N1stCJ, TNJ).
[2]Ankle (Talocrural joint).

The kappa statistic improved consistently for both the intra- and inter-rater agreements from before to after the study, suggesting an improvement in the reliability of the findings with increasing experience of the assessors.

3.3 Characteristics of footballers versus controls

Characteristics of participants in the questionnaire (self-reported) and those who underwent radiographic assessment are presented in (Table 3-4). Footballers were younger than controls (mean age 63.27 versus 68.42 years; $p<0.001$) and had a higher socioeconomic status (median 8.00 versus 6.50; $p<0.001$). Footballers had lower Charlson comorbidity scores (mean 1.07 versus 1.33; $p=0.048$) and less body pain (22% versus 29%; $p=0.014$), but a higher prevalence of foot/ankle injuries (44.71% versus 18.73% $p<0.001$) and foot/ankle injections (53.13% versus 6.25%; $p<0.001$) compared to controls. Footballers scored higher on the SF-36 physical component (mean 72.02 versus 69.25; $p=0.046$), with no significant difference in mental component scores (mean 77.98 versus 77.27; $p=0.559$). No other differences were observed between the two groups. The missing data for each variable related to the questionnaire data are presented in Appendix 3.3.

In the subgroup analysis based on radiographic data, footballers were 4 years younger than controls (mean 63.63 versus 68.56, $p<0.001$) and had a higher socioeconomic status (median 9.00 versus 6.00; $p=0.006$). Footballers reported more foot/ankle injuries (46.30% versus 22.40%, $p<0.001$) and foot/ankle injections (50.98% versus 8.47%; $p<0.001$) than controls. Footballers performed significantly better in the FSST than controls (8.01 seconds versus 9.30 seconds, $p < 0.001$). No other differences were observed between the two groups. The missing data for each variable are presented in Appendix 3.4.

Table 3-4. Characteristics of retired male professional footballers and general population male controls.

	Self-reported questionnaire			Radiographic examination		
	Footballers (n=468)	**Controls (n=619)**	**p-value**	**Footballers (n=113)**	**Controls (n=319)**	**p-value**
Age (years), mean (SD)	63.27 (10.46)	68.42 (9.25)	**<0.001[a*]**	63.63 (8.46)	68.56 (8.55)	**<0.001[a*]**
Body mass index (kg/m2), mean (SD)	27.16 (3.22)	26.81 (4.13)	0.124[a]	26.80 (3.01)	26.58 (3.68)	0.563[a]
Socioeconomic (decile), median (IQR)	8.00 (6-10)	6.50 (4-10)	**<0.001[c*]**	9.00 (7-10)	6.00 (4-10)	**0.006[c*]**
Charlson Comorbidity Index, mean (SD)	1.07 (2.09)	1.33 (2.28)	**0.048[a*]**	0.81 (1.83)	1.14 (2.05)	0.122[a]
SF-36[1] components summary, mean (SD)						
Physical components	72.02 (21.63)	69.25 (23.90)	**0.046[a*]**	75.03 (19.45)	71.53 (22.56)	0.143[a]
Mental components	77.98 (19.25)	77.27 (20.36)	0.559[a]	81.33 (15.83)	79.30 (18.90)	0.307[a]
Foot/ankle injury, n/total (%)	190/425 (44.71)	112/598 (18.73)	**<0.001[b*]**	50/108 (46.30)	69/308 (22.40)	**<0.001[b*]**
Foot/ankle injections, n/total (%)	221/416 (53.13)	36/576 (6.25)	**<0.001[b*]**	52/102 (50.98)	25/295 (8.47)	**<0.001[b*]**
Nodal OA, n/total (%)	29/463 (6.26)	43/598 (7.20)	0.556[b]	4/112 (3.57)	26/308 (8.44)	0.087[b]
Gout, n/total (%)	56/468 (12.00)	70/619 (11.31)	0.737[b]	18/113 (15.93)	36/318 (11.32)	0.204[b]
Pattern 3 finger ratio (2D<4D), n/total (%)	300/452 (66.37)	373/598 (62.37)	0.181[b]	72/109 (66.06)	203/310 (65.48)	0.914[b]
Current hallux valgus, n/total (%)	118/454 (25.99)	159/607 (26.19)	0.941[b]	32/111 (28.83)	69/316 (21.84)	0.136[b]
Constitutional (aged 20years), n/total (%)	27/428 (6.31)	39/568 (6.90)	0.710[b]	10/105 (9.52)	15/297 (5.05)	0.103[b]
Flat feet, n/total (%)	39/443 (8.80)	55/600 (9.17)	0.840[b]	10/109 (9.17)	32/314 (10.19)	0.760[b]
Body pain, n/total (%)	103/468 (22.00)	177/619 (29.00)	**0.014[b*]**	20/113 (17.70)	84/318 (26.42)	0.063[b]
Performance test, mean (SD)						
FSST[2], (seconds), mean (SD)	n/a	n/a	n/a	8.01 (2.22)	9.30 (3.00)	**<0.001[a*]**
10-MWT[3] - normal speed, (seconds), mean (SD)	n/a	n/a	n/a	4.30 (1.11)	4.42 (1.11)	0.340[a]
10-MWT[3] - fastest speed, (seconds), mean (SD)	n/a	n/a	n/a	3.18 (1.02)	3.40 (1.01)	0.068[a]

*p ≤ 0.05 is defined as significant and marked in bold.
[1] The SF-36 scores range from 0 to 100, with lower scores indicating poorer health status and higher scores indicating better health status.
[2] FSST: Four Square Step Test. Lower scores (faster times) indicate better balance and agility, whereas higher scores (slower times) may indicate poor balance and agility.
[3] 10-MWT: 10-Meter Walk Test.
Socioeconomic status was measured according to the postcode.
Nodal OA was defined as reporting nodes on at least two rays of both hands.
2D<4D (pattern 3): The index finger is shorter than the ring finger.
a = Independent sample T-test. b = Chi-Square test. c = Mann-Whitney U test.
IQR = Interquartile range. SD = Standard deviation. n = number. n/a = not available.

3.4 Prevalence of foot/ankle OA in footballers versus controls

Current foot/ankle pain at any foot/ankle joint or side was 35% in footballers versus 26% in controls (p=0.003), whereas GP-diagnosed foot/ankle OA was 13% in footballers versus 8% in controls (p=0.011). Footballers were three times more likely to undergo forefoot/ankle surgery than controls (24% versus 7%, respectively; p<0.001).

The aRR was adjusted for the significant potential confounding factors identified from the univariate analysis (Table 3-4). After adjusting for age, socioeconomic status and Charlson comorbidity index, footballers had a significantly higher risk of current foot/ankle pain (aRR 1.33, 95% CI 1.09-1.62), GP-diagnosed foot/ankle OA (aRR 1.77, 95%CI 1.22-2.57) and forefoot/ankle surgery (aRR 2.80, 95% CI 2.04-3.84) (Table 3-5). However, no significant differences were observed between footballers and controls for ever foot/ankle pain for ≥ 3 months.

The prevalence of ROA at any foot/ankle joint or side was 99.11% in footballers versus 97.17% in controls (p=0.072), whereas the prevalence of sROA was 39.82% in footballers versus 29.81% in controls (p=0.022). After adjusting for age and socioeconomic status, footballers had a significantly higher risk of foot/ankle ROA (aRR 1.04, 95% CI 1.01-1.07) and sROA (aRR 1.63, 95% CI 1.21-2.19) than controls.

Table 3-5. Prevalence of foot/ankle OA in retired male professional footballers versus general population male controls.

	Prevalence, n (%)		
Self-reported outcomes	**Footballers (n=468)**	**Controls (n=619)**	**aRR[1] (95% CI)**
Current foot/ankle pain	150/429 (35.00)	150/574 (26.00)	**1.33 (1.09 - 1.62)***
Ever foot/ankle pain ≥3 months	133/438 (30.00)	160/590 (27.00)	1.15 (0.93 - 1.41)
GP-diagnosed foot/ankle OA	55/424 (13.00)	47/581 (8.00)	**1.77 (1.22 - 2.57)***
Surgery forefoot/ ankle	103/426 (24.18)	47/595 (7.90)	**2.80 (2.04 -3.84)****
Radiographic outcomes	**(n=113)**	**(n=319)**	**aRR[2] (95% CI)**
ROA foot[3]/ankle[4] OA	112/113 (99.11)	309/318 (97.17)	**1.04 (1.01 - 1.07)***
sROA foot/ankle OA	45/113 (39.82)	90/318 (28.21)	**1.63 (1.21 - 2.19)****
ROA foot OA	98/112 (87.50)	295/317 (93.06)	0.97 (0.90 - 1.05)
sROA foot OA	38/112 (33.63)	78/318 (24.45)	1.02 (0.85 - 1.23)

* p<0.05. ** p<0.001.CI is defined as significant and is marked in bold.
[1]Adjusted for age, socioeconomic status and Charlson Comorbidity Index.
[2]Adjusted for age and socioeconomic status.
[3]Foot included only five joints (1st Metatarsophalangeal joint, 1st Cuneo-metatarsal joint, 2nd Cuneo-metatarsal joint, Navicular-1st cuneiform joint and Talonavicular joint).
[4]Ankle (Talocrural joint). GP = General practitioner
ROA = Radiographic osteoarthritis. sROA = Symptomatic radiographic osteoarthritis.
n = number.
The prevalence with 95% confidence intervals is shown in Appendix 3.5.

Furthermore, footballers had higher summated osteophyte scores for the foot /ankle than controls (mean 1.12 versus 0.86, p<0.001) but not higher summated JSN scores (0.96 versus 0.99, p=0.447) (Table 3-6).

Table 3-6. Summated radiographic foot/ankle features in retired male professional footballers versus general population male controls.

Summated ROA scores	**Footballers (n=113)**	**Controls (n=319)**	**p-value**
Foot/ankle			
Osteophytes, mean (SD)	1.12 (0.40)	0.86 (0.25)	**<0.001[a*]**
Joint space narrowing, mean (SD)	0.96 (0.42)	0.99 (0.25)	0.447[a]
Foot[1]			
Osteophytes, mean (SD)	0.99 (0.43)	0.77 (0.27)	**<0.001[a*]**
Joint space narrowing, mean (SD)	0.86 (0.47)	0.97 (0.29)	**0.027[a*]**

The summated score based on La Trobe atlas (scale 0-3) for the foot/ankle joint.
[1]Foot included only five joints (1st Metatarsophalangeal joint, 1st Cuneo-metatarsal joint, 2nd Cuneo-metatarsal joint, Navicular-1st cuneiform joint and Talonavicular joint).
*p ≤ 0.05 is defined as significant and marked in bold. a = Independent sample T-test.

3.5 Laterality of foot/ankle OA in footballers and controls

Table 3-7 shows the prevalence of foot/ankle OA in each leg (i.e., left, right). The prevalence of self-reported and radiographic foot/ankle OA outcomes was similar between right and left legs in both footballers and controls. However, the prevalence of current pain, surgery and sROA was higher in footballers than controls for both the right and left foot/ankle. Within both the footballers and the controls, the left and right legs appeared to be equally affected by foot/ankle OA. In other words, both sides appear to be equally affected by foot/ankle OA within each group.

Table 3-7. Prevalence of foot/ankle OA between retired male professional footballers versus general population male controls in left and right legs.

		Prevalence (%)		
	Side	Footballers (n=468)	Controls (n=619)	aRR[1] (95% CI)
Self-reported outcomes				
Current pain	Left	134/468 (28.63)	130/619 (21.00)	**1.41 (1.13 - 1 .76)***
	Right	130/468 (27.78)	126/619 (20.36)	**1.36 (1.08 - 1.71)***
	p	0.617	0.762	
Ever pain≥3 months	Left	98/468 (20.94)	121/619 (19.55)	1.07 (0.83 - 1.37)
	Right	111/468 (23.72)	122/619 (19.71)	1.27 (1.00 - 1.61)
	p	0.193	1.000	
GP-diagnosis OA	Left	n/a	n/a	n/a
	Right	n/a	n/a	n/a
	p	-	-	-
Surgery	Left	51/468 (10.90)	31/619 (5.01)	**1.90 (1.22 - 2.97)***
	Right	69/468 (14.74)	26/619 (4.20)	**3.34 (2.18 - 5.13)****
	p	0.050	0.511	
Radiographic outcomes	**Side**	**(n=113)**	**(n=319)**	**aRR[2] (95% CI)**
ROA	Left	108/112 (96.43)	293/318 (92.14)	1.06 (1.00 - 1.13)
	Right	109/112 (97.32)	296/318 (93.08)	**1.08 (1.03 - 1.13)***
	p	0.771	1.000	
sROA	Left	31/113 (27.43)	62/319 (19.44)	**1.78 (1.22 - 2.61)***
	Right	32/113 (28.32)	62/319 (19.44)	**1.68 (1.15 - 2.46)***
	p	1.000	1.000	

* p<0.05.** p<0.001. CI is defined as significant and is marked in bold.
[1]Adjusted for age, socioeconomic status and Charlson Comorbidity Index
[2]Adjusted for age and socioeconomic status.
GP = General practitioner.
ROA = Radiographic osteoarthritis.
sROA = Symptomatic radiographic osteoarthritis.
n = number
n/a = not available.

Furthermore, footballers had higher summated osteophyte scores than controls on the left leg (mean 0.89 versus 0.67, p<0.001) and the right leg (mean 1.17 versus 0.87, p<0.001) but not higher summated JSN scores (Table 3-8).

Table 3-8. Summated foot/ankle scores by left and right legs in retired male professional footballers versus general population male controls.

Summated ROA scores	side	Footballers (n=113)	Controls (n=319)	P-value
Osteophytes, mean (SD)	Left	0.89 (0.36)	0.67 (0.26)	**<0.001**[a*]
	Right	1.17 (0.47)	0.87 (0.27)	**<0.001**[a*]
Joint space narrowing, mean (SD)	Left	0.76 (0.42)	0.83 (0.27)	0.106[a]
	Right	0.99 (0.45)	0.98 (0.27)	0.891[a]

The summated score based on La Trobe atlas (scale 0-3) for the foot/ankle joint.
*p ≤ 0.05 is defined as significant and marked in bold.
a = Independent sample T-test.

3.6 Anatomic region of foot/ankle OA between footballers and controls

Table 3-9 summarises the prevalence of foot/ankle OA outcomes by anatomical region between footballers and controls. When the analysis was focused on a specific site, the hindfoot/ankle was the only region more likely to be affected by OA in footballers than controls across all self-reported and ROA outcomes. The aRR was significant for current pain in the hindfoot region (aRR 1.57, 95% CI 1.22-2.02), ever pain ≥ 3 months in the hindfoot region (aRR 1.42, 95% CI 1.09-1.86), GP-diagnosed ankle OA (aRR 2.39, 95% CI 1.50-3.79), ankle surgery (aRR 4.36, 95% CI 2.71-7.44), ROA ankle (aRR 1.52, 95% CI 1.37-1.96) and sROA ankle (aRR 3.40, 95% CI 2.04-5.65) in footballers compared to controls.

Significant associations were also found for current pain in the forefoot (aRR 1.35, 95% CI 1.03-1.76) and ROA (aRR 1.30, 95% CI 1.06-1.60) in footballers compared to controls.

Table 3-9. Prevalence according to anatomical region of the foot in retired male professional footballers and general population male controls.

Self-reported outcomes	Region	Prevalence (%)		aRR[1] (95% CI)
		Footballers (n=468)	Controls (n=619)	
Current pain	Forefoot	97/468 (20.73)	93/619 (15.02)	**1.35 (1.03 - 1.76)***
	Midfoot	55/468 (11.75)	71/619 (11.47)	1.15 (0.83 - 1.60)
	Hindfoot^	113/468 (24.15)	97/619 (15.67)	**1.57 (1.22 - 2.02)***
Ever pain ≥3 months	Forefoot	69/468 (14.74)	85/619 (13.73)	1.10 (0.81 - 1.50)
	Midfoot	47/468 (10.04)	65/619 (10.50)	1.12 (0.78 - 1.59)
	Hindfoot^	99/468 (21.15)	92/619 (14.86)	**1.42 (1.09 - 1.86)***
GP diagnosed OA	Forefoot	33/468 (7.05)	29/619 (4.68)	1.58 (0.72 - 3.45)
	Midfoot	17/468 (3.63)	17/619 (2.75)	1.45 (0.74 - 2.84)
	Ankle	46/468 (9.83)	28/619 (4.52)	**2.39 (1.50 - 3.79)****
Surgery	Forefoot	26/468 (5.56)	26/619 (4.20)	1.28 (0.80 - 2.05)
	Midfoot	n/a	n/a	n/a
	Ankle	82/468 (17.52)	22/619 (3.55)	**4.36 (2.71 - 7.44)****
Radiographic outcomes	**Region**	**(n=113)**	**(n=319)**	**aRR[2] (95% CI)**
ROA	Forefoot[3]	61/112 (54.56)	147/314 (46.82)	**1.30 (1.06 - 1.60)***
	Midfoot[4]	94/112 (83.93)	286/317 (90.22)	0.97 (0.89 - 1.06)
	Ankle[5]	107/112 (95.54)	206/315 (65.40)	**1.52 (1.37 - 1.96)****
sROA	Forefoot	14/113 (12.38)	26/319 (8.15)	1.74 (0.91 - 3.31)
	Midfoot	12/113 (10.62)	37/319 (11.60)	1.10 (0.60 - 2.04)
	Ankle	25/113 (22.12)	29/319 (9.09)	**3.40 (2.04 - 5.65)****

* p<0.05.** p<0.001. CI is defined as significant and is marked in bold.
1Adjusted for age, socioeconomic status and Charlson Comorbidity Index
2Adjusted for age and socioeconomic status.
3Forefoot (1st Metatarsophalangeal joint)
[4]Midfoot included only four joints (1st Cuneo-metatarsal joint, 2nd Cuneo-metatarsal joint, Navicular-1st cuneiform joint and Talonavicular joint)
[5]Ankle (Talocrural joint)
^Hindfoot pain refers to pain in the foot's posterior region, including the heel and ankle area.
GP = General practitioner.
ROA = Radiographic osteoarthritis.
sROA = Symptomatic radiographic osteoarthritis.
n = number
n/a = not available.

With respect to individual radiographic features of OA, footballers had higher summated osteophyte and JSN scores for the midfoot and ankle joints, but not the forefoot joints, than controls (Table 3-10).

Table 3-10. Summated ROA score by anatomical region in retired male professional footballers versus general population male controls.

Summated ROA score	Region	Footballers (n=113)	Controls (n=319)	p-value
Osteophyte, mean (SD)	Forefoot	1.07 (0.66)	0.93 (0.45)	**0.015**[a]
	Midfoot	0.93 (0.46)	0.67 (0.29)	**<0.001**[a*]
	Ankle	1.73 (0.52)	1.27 (0.37)	**<0.001**[a*]
Joint space narrowing, mean (SD)	Forefoot	0.91 (0.69)	0.92 (0.50)	0.896[a]
	Midfoot	0.84 (0.48)	0.98 (0.30)	**0.004** [a*]
	Ankle	1.41 (0.50)	1.07 (0.27)	**<0.001**[a*]

The summated score based on La Trobe atlas (scale 0-3) for the foot/ankle joint.
*p ≤ 0.05 is defined as significant and marked in bold.
a = Independent sample T-test.

Further analysis focusing on specific joints within the midfoot found that the talonavicular joint was also at a higher risk of ROA in footballers than in controls (aRR 2.00, 95% CI 1.60-2.50), whereas the risk was lower in the second cuneometatarsal joint, compared with controls (aRR 0.82, 95% CI 0.70-0.96) (Table 3-11).

Table 3-11. Prevalence of ROA and sROA in specific midfoot joints in retired male professional footballers versus general population male controls.

	Prevalence, n (%)		aRR[1] (95% CI)
	Footballers (n=113)	Controls (n=319)	
ROA			
1st Cuneo-metatarsal joint	48/112 (42.86)	136/315 (43.17)	1.19 (0.92 - 1.53)
2nd Cuneo-metatarsal joint	68/112 (60.71)	259/317 (81.70)	**0.82 (0.70 - 0.96)***
Navicular-1st cuneiform joint	59/112 (52.68)	188/315 (59.68)	1.00 (0.82 - 1.21)
Talonavicular joint	66/112 (58.93)	104/315 (33.02)	**2.00 (1.60 - 2.50)****
sROA			
1st Cuneo-metatarsal joint	7/113 (6.19)	18/319 (5.64)	1.40 (0.60 - 3.27)
2nd Cuneo-metatarsal joint	10/113 (8.85)	35/319 (11.00)	1.03 (0.53 - 2.03)
Navicular-1st cuneiform joint	10/113 (8.85)	26/319 (8.15)	1.43 (0.72 - 2.84)
Talonavicular joint	9/113 (8.00)	15/319 (4.70)	2.16 (0.93 - 5.02)

* p<0.05.** p<0.001. CI is defined as significant and is marked in bold.
[1]Adjusted for age and socioeconomic status.
ROA = Radiographic osteoarthritis.
sROA = Symptomatic radiographic osteoarthritis.
n = number.

3.7 Sensitivity analysis using a more stringent radiographic foot/ankle OA definition

Prevalence of ROA foot/ankle, foot and midfoot OA was not different between footballers and controls according to Menz's definition but was significantly different when both osteophyte and JSN ≥2, i.e., "definite moderate osteophyte and severe narrowing" were used. This result suggests that Menz's criteria were too sensitive and less specific, resulting in almost all participants having ROA of the ankle/foot (99% footballers and 97% controls) (Table 3-12). In contrast, if both "definite osteophyte plus definite narrowing" were used to define OA, the prevalence of foot/ankle OA was 81% in footballers and 58% in controls.

Table 3-12. Menz criteria compared to definite osteophytes and joint space narrowing for foot/ankle OA in retired male professional footballers versus general population male controls.

Radiographic	Prevalence, n (%)		p-value	aRR (95% CI)
	Footballers (n=113)	Controls (n=319)		
ROA Menz criteria (definite OP or definite JSN)[1]				
Foot[2]/ankle[3]	112/113 (99.11)	309/318 (97.17)	0.072[b]	**1.04 (1.01 - 1.07)***
Foot	98/112 (87.50)	295/317 (93.06)	0.068[b]	0.97 (0.90 - 1.05)
Ankle	107/112 (95.54)	206/315 (65.40)	**<0.001[b*]**	**1.52 (1.37 - 1.96)****
Forefoot[4]	61/112 (54.56)	147/314 (46.82)	0.164[b]	**1.30 (1.06 - 1.60)***
Midfoot[5]	94/112 (83.93)	286/317 (90.22)	0.072[b]	0.97 (0.89 - 1.06)
Definite OP plus definite JSN[6]				
Foot/ankle	91/112 (81.25)	180/312 (57.69)	**<0.001[b*]**	**1.51 (1.32 - 1.73)****
Foot	65/112 (58.04)	140/313 (44.73)	**0.016[b*]**	**1.46 (1.19 - 1.78)****
Ankle	75/112 (66.96)	77/312 (24.68)	**<0.001[b*]**	**2.91 (2.27 - 3.73)****
Forefoot	29/112 (25.89)	79/313 (25.24)	0.892[b]	1.18 (0.81 - 1.72)
Midfoot	53/112 (47.32)	85/313 (27.16)	**<0.001[b*]**	**2.16 (1.65 - 2.82)****

* p<0.05.** p<0.001. CI is defined as significant and is marked in bold.
[1]Menz criteria grade=>2 was defined as severe in JSN or moderate in OP anywhere in foot/ankle joints at either side
[2]Foot included only five joints (1st Metatarsophalangeal joint,1st Cuneo-metatarsal joint,2nd Cuneo-metatarsal joint, Navicular-1st cuneiform joint and Talonavicular joint).
[3]Ankle (Talocrural joint)
[4]Forefoot (1st Metatarsophalangeal joint).
[5]Midfoot included only four joints (1st Cuneo-metatarsal joint,2nd Cuneo-metatarsal joint, Navicular-1st cuneiform joint and Talonavicular joint).
[6]Grade =>2 definite (osteophyte AND joint space narrowing) anywhere in foot/ankle joints at either side.
aRR: adjusted for age and socioeconomic status.
b = Chi-Square test.
OP: Osteophytes.
JSN: Joint space narrowing.

3.8 Comparison of phenotypes of pain between footballers and controls

Table 3-13 compares the proportions of footballers and controls who reported neuropathic-like pain and pain catastrophizing. No significant differences were observed between footballers and controls for neuropathic-like pain, defined as a total score of ≥19 (13.61% versus 8.05%, respectively; p=0.124) or pain catastrophizing, defined as a score of >30) (4% versus 3.47%, respectively; p=0.686).

Table 3-13. Neuropathic-like pain and catastrophizing in retired male professional footballers and general population male controls.

Condition	Footballers (n=150)	Controls (n=150)	p-value
Neuropathic-like pain, n/total (%)	20/147 (13.61)	12/149 (8.05)	0.124[b]
Pain catastrophizing, n/total (%)	6/136 (4.41)	5/144 (3.47)	0.686[b]

Neuropathic-like pain is defined as Pain Detect Score ≥19 (Freynhagen et al., 2006b).
Pain catastrophizing is defined as Pain Catastrophizing Scale score >30 (Sullivan et al., 1995a)
b = Chi-Square test

3.9 Age of onset for pain

Table 3-14 shows that footballers reported a significantly younger mean age of onset of current foot/ankle and regional pain (all p<0.001). On average, the age of developing current foot/ankle pain was 11 years younger, while current midfoot and hindfoot pain onsets were 13-14 years younger in footballers than controls.

Table 3-14. Age of onset of current foot/ankle pain in retired male professional footballers versus general population male controls.

Region	Footballers (n=468)	Controls (n=619)	p-value
Age of onset in years, mean (SD)			
Foot/ankle	45.24 (16.36)	56.98 (15.31)	**<0.001**[a**]
Forefoot	44.02 (17.41)	57.07 (15.15)	**<0.001**[a**]
Midfoot	44.91 (16.77)	58.43 (14.18)	**<0.001**[a**]
Hindfoot^	43.28 (14.41)	55.94 (15.66)	**<0.001**[a**]

**p ≤ 0.01 is defined as significant and marked in bold.
a = Independent sample T-test.
^Hindfoot pain refers to pain in the foot's posterior region, including the heel and ankle area.

In summary, professional footballers were more likely to report current foot/ankle pain, GP-diagnosed foot/ankle OA, forefoot/ankle surgery, foot/ankle ROA and sROA than the general population. The ankle joint appeared to be more commonly affected by both self-reported and radiographic OA in footballers than controls. For specific joints in the midfoot, footballers had a higher risk of ROA in the talonavicular joint and a lower risk in the second cuneometatarsal joint, compared with controls. Whilst there was no difference in the phenotypes of current foot/ankle pain, footballers reported current foot/ankle pain a decade earlier than controls.

Chapter : 4 Results: Risk factors associated with foot/ankle OA in retired male professional footballers

This chapter describes a case-control study nested within footballers to identify football-specific risk factors related to foot/ankle OA. Logistic regression was used to calculate the aOR and 95% CI.

4.1 Risk factors associated with self-reported foot/ankle OA within footballers

The self-reported foot/ankle OA cases were defined as a footballer having either GP-diagnosed foot/ankle OA or a history of forefoot/ankle surgery performed at age 40 years or above. Controls were footballers without GP-diagnosed foot/ankle OA and no history of foot/ankle surgery. We focused on GP-diagnosed foot/ankle OA and surgery as hard outcomes, as these are more specific than self-reported pain and may also increase the number of identified cases (Duryea et al., 2003).

4.2 Characteristics of footballers with (cases) and without (controls) foot/ankle OA

Based on self-reported foot/ankle OA in the questionnaire, 63 cases and 361 controls were identified. Cases played more matches during their careers compared to controls (532.03 versus 454.89, respectively; p=0.028). In addition, a greater proportion of cases than controls had experienced foot/ankle injury (73.33% versus 42.55%, respectively; p<0.001), and had reported a history of any type of foot/ankle injection

(75.00% versus 48.44%, respectively; p<0.001), ankle injection (61.29% versus 36.63%, respectively; p<0.001), and corticosteroid ankle injection (57.14% versus 32.13%, respectively; p<0.001). The maximum number of ankle corticosteroid injections per season was 22 in cases and 12 in controls, with means of 4.21 and 3.09, respectively. Furthermore, cases were also more likely to have nodal OA (16.13% versus 5.34%; p=0.002), gout (19.05% versus 10.25%; p=0.044), and current hallux valgus (36.07% versus 22.75%; p=0.026) compared to controls. No other differences were observed between cases and controls (Table 4-1).

Table 4-1. Characteristics of footballers with (cases) and without (controls) foot/ankle OA

	Cases (n=63)	Controls (n=361)	p-value
Age (years), mean (SD)	63.22 (9.25)	63.08 (10.57)	0.457[a]
Body mass index (kg/m2), mean (SD)	27.70 (3.85)	27.09 (2.97)	0.240[a]
Socioeconomic decile, median (IQR)	8.00 (6-9)	8.00 (6-10)	0.711[c]
Charlson Comorbidity Index, mean (SD)	1.25 (2.03)	1.06 (2.14)	0.498[a]
Nodal OA, n/total (%)	10/62 (16.13)	19/356 (5.34)	**0.002**[b*]
Gout, n/total (%)	12/63 (19.05)	37/361 (10.25)	**0.044**[b*]
Pattern 3 2D:4D finger ratio, n/total (%)	43/62 (69.35)	228/350 (65.14)	0.519[b]
Current hallux valgus, n/total (%)	22/61 (36.07)	81/356 (22.75)	**0.026**[b*]
Flat feet, n/total (%)	7/61 (11.48)	29/342 (8.48)	0.450[b]
Foot/ankle injury, n/total (%)	44/60 (73.33)	140/329 (42.55)	**<0.001**[b*]
Foot/ankle injection (any injectable)[1], n/total (%)	45/60 (75.00)	155/320 (48.44)	**<0.001**[b*]
Foot injection, n/total (%)	18/58 (31.03)	62/324 (19.14)	**0.040**[b*]
Ankle injection, n/total (%)	38/62 (61.29)	126/344 (36.63)	**<0.001**[b*]
Ankle corticosteroid injections, n/total (%)	36/63 (57.14)	116/361 (32.13)	**<0.001**[b*]
Number of ankle corticosteroid injections per season, mean (maximum)	4.21 (22.00)	3.09 (12.00)	0.159[a]
Career training dose (hours) mean (SD)[2]	8407.00 (4444.81)	7608.34 (4020.70)	0.197[a]
Career duration (years), mean (SD)[3]	14.11 (4.48)	13.64 (5.57)	0.466[a]
Total matches played, mean (SD)[4]	532.03 (252.02)	454.89 (240.11)	**0.028**[a*]
Training hours/week, mean (SD)[5]	15.24 (6.18)	14.38 (5.03)	0.300[a]
Position played, n (%)			
Goalkeeper	9 (14.29)	321 (8.86)	
Outfielders[6]	54 (85.71)	329 (91.14)	0.179[b]
Defender	21 (33.33)	140 (38.78)	0.411[b]
Midfielder	17 (26.98)	85 (23.55)	0.556[b]
Forward	15 (23.81)	103 (28.53)	0.440[b]

p≤ 0.05 is defined as significant and marked in bold.
[1] Includes any of the following: cortisone (steroid) or anaesthetic (lignocaine) or “don’t know”.
[2] Career training dose calculated by multiplying hours per week trained, number of weeks per season (40), and career duration.
[3] Professional career duration is the difference in years between commencing and retiring from professional football.
[4] Number of matches played during the professional career.
[5] Hours per week calculated by multiplying hours per day and days per week.
[6] Outfielders was any player other than a goalkeeper.
a = Independent sample T-test.
b = Chi-Square test.
c= Mann-Whitney U test.
IQR = Interquartile range.
SD= standard deviation.
n= number

Table 4-2 shows the results of the univariable analysis, indicating that several variables, such as nodal OA, gout, current hallux valgus, foot/ankle injury and injection and total matches played, demonstrated a statistically significant association with foot/ankle OA ($p < 0.05$).

Table 4-2. Univariable analysis of potential risk factors for self-reported foot/ankle OA in footballers.

Sample size	**(63 cases vs 361 controls)**
Exposures	**OR (95% CI), p-value**
Age (years)	1.00 (0.98 - 1.03), p = 0.922
Body mass index	1.06 (0.98 - 1.15), p = 0.159
Socioeconomic	0.99 (0.88 - 1.11), p = 0.816
Charlson Comorbidity Index	1.04 (0.92 - 1.17), p = 0.512
Nodal OA	3.41 (1.50 - 7.74), p = 0.003
Gout	2.06 (1.01 - 4.21), p = 0.047
Pattern 3 2D:4D digit ratio	1.21 (0.68 - 2.17), p = 0.520
Current hallux valgus	1.92 (1.07 - 3.42), p = 0.028
Flat feet	1.40 (0.58 - 3.35), p = 0.452
Foot/ankle injury	3.71 (2.01 - 6.85), p < 0.001
Foot/ankle injection	3.19 (1.71 - 5.96), p < 0.001
Career training dose(hours)	1.00 (1.00 - 1.00), p = 0.165
Career duration (years)	1.02 (0.97 - 1.07), p = 0.529
Total matches played	1.001 (1.000 - 1.002), p = 0.022
Training hours/week	1.03 (0.98 - 1.08), p = 0.229
Position played	0.90 (0.68 - 1.18), p = 0.430
Position played (overall)	- p= 0.430[1]
Defender versus Goalkeeper	0.53 (0.22 - 1.27), p= 0.157
Midfielder versus Goalkeeper	0.71 (0.29 - 1.76), p= 0.460
Forward versus Goalkeeper	0.52 (0.21 - 1.30), p= 0.159

[1]Overall p-value from the Likelihood Ratio test.
Position played was analysed as a categorical variable (goalkeeper, defender, midfielder, forward) with goalkeeper as the reference category. The overall p-value reflects the likelihood ratio test, and individual odds ratios represent comparisons with the goalkeeper position.
There were two hallux valgus assessments, and the current (not constitutional) one was used for this analysis.

Table 4-3 shows that all variables had a VIF below 10, indicating no severe multicollinearity (O'brien, 2007).

Table 4-3. Variance inflation factor for self-reported foot/ankle OA in footballers.

Sample size	**(63 cases vs 361 controls)**
Exposures	**Variance inflation factor**
Age (years)	1.43
Body mass index	1.19
Socioeconomic	1.09
Charlson Comorbidity Index	1.20
Nodal OA	1.15
Gout	1.08
Pattern 3 2D:4D digit ratio	1.04
Current hallux valgus	1.12
Flat feet	1.10
Foot/ankle injury	1.21
Foot/ankle injection	1.27
Career training dose (hours)	2.03
Total matches played	1.75
Training hours/week	1.71
Position played	1.14

There were two hallux valgus assessments, and the current (not constitutional) one was used for this analysis.
Career duration (VIF=9.79) was excluded due to high collinearity with career training dose (VIF= 8.95), which was included.

Of the 16 available risk factors included in the logistic regression model, only two (injury and injection) remained significant in the model after the backward stepwise selection. The aORs (95% CI) were 4.23 (1.88-9.48) for foot/ankle injury and 2.62 (1.19-5.78) for foot/ankle injection, respectively (Table 4-4). Although there was a strong correlation between injury and injection ($p<0.001$), both remained in the model as independent risk factors. A subgroup analysis focusing on ankle OA showed that the aORs and (95% CI) were 2.16 (95% CI: 1.03-4.56) for ankle injury and 3.59 (95% CI: 1.66-7.76) for ankle injection respectively. Appendix 4.1 outlines all the analytical steps for the backward stepwise selection model in the multivariable logistic regression of self-reported foot/ankle OA in footballers.

Table 4-4. Multivariable logistic regression model for self-reported foot/ankle OA in footballers (backward stepwise selection model).

Sample size	**(63 cases vs 361 controls)**
Exposures	**Adjusted OR (95% CI), p-value**
Foot/ankle injury	4.23 (1.88 - 9.48), <0.001*
Foot/ankle injection	2.62 (1.19 - 5.78), 0.017*

Adjusted for (injury, injection, age, BMI, socioeconomic status, Charlson Comorbidity Index, nodal OA, gout, pattern 3 of the 2D:4D digit ratio, current hallux valgus, flat feet, career training dose, total matches played, position played, and training hours per week)

Furthermore, the interaction between foot/ankle injury and injection was examined but the result was not significant (aOR 1.29, 95%CI 0.32-5.15).

4.3 Type of foot/ankle injections in footballers

Corticosteroid injections were reported more frequently than anaesthetic injections (Figure 4-1), and injections of corticosteroids were reported by 82% of footballers. Other injections included anaesthetics (16%) and unknown (2%). Furthermore, there was a strong correlation between injuries and injections ($p<0.001$), which suggests that injuries in the foot/ankle region are closely linked to the subsequent administration of injections.

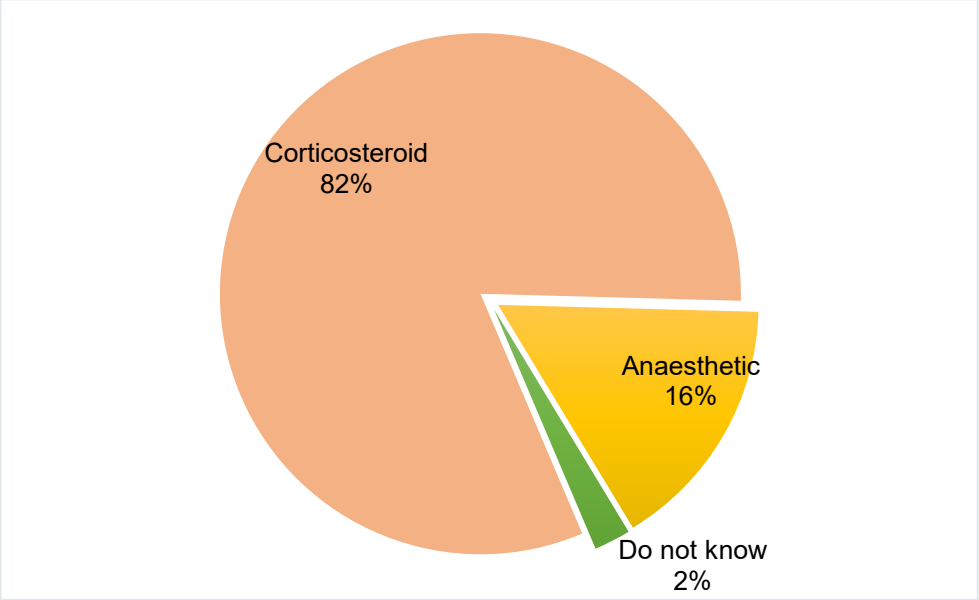


Figure 4-1. Type of ankle injections in professional footballers

Injection categories were obtained from the questionnaire. Percent (%) reported per population (468 footballers)

Table 4-5 shows associations between playing position and risk of foot/ankle injuries and injections in footballers. Although playing position was not significantly associated with foot/ankle injuries ($p=0.352$), outfield players (i.e., defenders, midfield players and forwards combined) had significantly higher injection rates than goalkeepers ($p=0.020$).

Table 4-5. Risk of foot/ankle injuries and injections in footballers according to playing position.

Playing position	Foot/ankle injuries % (n=417)	p-value	Foot/ankle injections % (n=414)	p-value
Goalkeeper	36.84	0.352[b]	32.43	**0.020***[b]
Defender	44.72		55.48	
Midfield	51.55		60.78	
Forward	50.41		49.14	

Percentages were calculated by dividing the number of occurrences (injuries or injections) by the total number of footballers in each playing position.
b = Chi-Square test.
n= number

4.4 Risk factors associated with symptomatic radiographic foot/ankle OA in footballers

This subgroup analysis investigated risk factors for foot/ankle sROA instead of ROA. This is because we were unable to do ROA, as, according to Menz's definition, almost all footballers would be classified as ROA (99%). In contrast, using foot/ankle sROA allowed for reasonable number of cases and controls for this analysis.

4.5 Characteristics of footballers with (cases) and without (controls) foot/ankle sROA

A total of 45 cases and 68 controls with and without foot/ankle sROA were identified. Cases showed a higher prevalence of gout (24.4% versus 10.3%, p=0.044) and foot/ankle injections (61.9% versus 42.4%, p=0.042) than controls but no other differences were observed between cases and controls (Table 4-6).

Table 4-6. Characteristics of the footballers with (cases) and without (controls) foot/ankle sROA

	Cases (n=45)	Controls (n=68)	p-value
Age (years), mean (SD)	64.36 (9.70)	63.15 (7.56)	0.460[a]
Body mass index (kg/m2), mean (SD)	26.72 (3.45)	26.85 (2.71)	0.828[a]
Socioeconomic decile, median (IQR)	8.00 (6-10)	9.00 (7-9)	0.847[c]
Charlson Comorbidity Index, mean (SD)	1.18 (2.12)	0.56 (1.57)	0.078[a]
Nodal OA, n/total (%)	2/45 (4.44)	2/67 (3.00)	0.683[b]
Gout, n/total (%)	11/45 (24.44)	7/68 (10.29)	**0.044[b*]**
Pattern 3 2D:4D digit ratio, n/total (%)	29/43 (67.44)	43/66 (65.15)	0.805[b]
Flat feet footed, n/total (%)	4/45 (8.89)	6/64 (9.38)	0.931[b]
Current hallux valgus, n/total (%)	16/44 (36.36)	16/67 (23.88)	0.156[b]
Constitutional (aged20years)	5/42 (11.90)	5/63 (7.94)	0.497[b]
Foot/ankle injury, n/total (%)	26/42 (62.79)	28/64 (43.75)	0.067[b]
Foot/ankle injections, n/total (%)	27/43 (61.90)	25/59 (42.37)	**0.042[b*]**
Career training dose(hours) mean (SD)[1]	7285.50 (3193.75)	7322.08 (4077.51)	0.961[a]
Career duration, mean (SD)[2]	13.09 (4.43)	13.33 (5.67)	0.808[a]
Total matches played, mean (SD)[3]	477.27 (219.58)	467.03 (267.52)	0.833[a]
Training hours/week, mean (SD)[4]	14.83 (5.33)	14.32 (5.26)	0.625[a]
Position played, n (%)			
Goalkeeper	5 (11.63)	3 (4.55)	
Outfielders[5]	38 (88.37)	63 (95.45)	0.166[b]
Defender	19 (44.2)	28 (41.8)	0.588[b]
Midfielder	11 (25.58)	17 (25.37)	0.980[b]
Forward	8 (18.60)	18 (26.87)	0.490[b]

p≤ 0.05 is defined as significant and marked in bold.
[1] Career training dose was calculated by multiplying hours per week trained, the number of weeks per season (40), and career duration.
[2]Professional career duration is the difference in years between commencing and retiring from professional football.
[3] Number of matches played during the professional career.
[4] Hours per week calculated by multiplying hours per day and days per week.
[5] Outfielders was any player other than a goalkeeper.
a = Independent sample T-test.
b = Chi-Square test.
c = Mann-Whitney U test.
IQR = Interquartile range.
SD = standard deviation

Table 4-7 shows the results of the univariable analysis, indicating that several variables gout and foot/ankle injection demonstrated a statistically significant association with the outcome ($p < 0.05$).

Table 4-7. Univariable analysis of risk factors for foot/ankle sROA in footballers.

Sample size	**(45 cases vs 68 controls)**
Exposures	**Crude OR (95% CI), p-value**
Age	1.02 (0.97-1.06), 0.564
Body mass index	0.99 (0.87 - 1.12), 0.826
Socioeconomic	0.98 (0.82 - 1.16), 0.791
Charlson Comorbidity Index	1.21 (0.97 - 1.50), 0.092
Nodal OA	0.98 (0.16 -6.09), 0.980
Gout	2.82 (1.00 - 7.95), 0.050*
Pattern 3 2D:4D digit ratio	1.11 (0.49 - 2.50), 0.805
Current hallux valgus	1.82 (0.79 - 4.19), 0.158
Flat feet	0.94 (0.25 - 3.55), 0.931
Foot/ankle injury	2.09 (0.94 - 4.63), 0.069
Foot/ankle injection	2.29 (1.03 - 5.14), 0.043*
Career duration	0.99 (0.92 - 1.07), 0.816
Total matches played	1.00 (1.00 - 1.00), 0.831
Training hours/week	1.02 (0.95 - 1.10), 0.620
Position played,	0.77 (0.51 - 1.18), 0.228

There were two hallux valgus assessments, and the current (not constitutional) one was used for this analysis.

All variables had a VIF less than 10, suggesting no severe multicollinearity (Table 4-8) (O'brien, 2007).

Table 4-8. Variance inflation factor for foot/ankle sROA in footballers

Sample size	**(45 cases vs 68 controls)**
Exposures	**Variance inflation factor**
Age	1.64
Body mass index	1.25
Socioeconomic status	1.28
Charlson Comorbidity Index	1.33
Nodal OA	1.26
Gout	1.24
Pattern 3 2D:4D digit ratio	1.23
Current hallux valgus	1.21
Flat feet	1.12
Foot/ankle injury	1.41
Foot/ankle injections	1.52
Career duration	1.87
Total matches played	1.78
Training hours/week	1.30
Position played,	1.26

There were two hallux valgus assessments, and the current (not constitutional) one was used for this analysis.
Career training dose was excluded due to high multicollinearity with career duration (VIFs: 13.23 and 13.33, respectively).

Of the 16 available risk factors included in the logistic regression model, only one risk factor, foot/ankle injury (aOR=3.33 95% CI 1.31-8.45, p=0.011), remained significant in the model (Table 4-9). Appendix 4.2 details all the analysis steps for the backward stepwise selection model in the multivariable logistic regression for sROA foot/ankle.

Table 4-9. Multivariable logistic regression model for foot/ankle sROA in footballers (backward stepwise selection model).

Sample size	**(cases 45 vs controls 68)**
Exposures	**Adjusted OR (95% CI), p-value**
Foot/ankle injury	3.33 (1.31 - 8.45), 0.011*

Adjusted for (injury, injection, age, BMI, socioeconomic status, Charlson Comorbidity Index, nodal OA, gout, pattern 3 of the 2D:4D digit ratio, current hallux valgus, flat feet, career duration, total matches played, position played, and training hours per week).

In summary, foot/ankle injury and injection were independent risk factors for the development of self-reported foot/ankle OA in retired UK male professional footballers. Whether they are associated with foot/ankle sROA independently remains to be confirmed.

Chapter : 5 Discussion

This is by far the largest study in the UK to compare the prevalence of foot/ankle OA in retired male professional footballers with male controls in the general population and to identify the risk factors of foot/ankle OA within professional footballers. To our knowledge, this is the first comprehensive study to examine the risk factors for OA in retired professional footballers in all three regions of the foot.

5.1 Key findings

[1] Compared to the general population, retired professional footballers were more likely to have current foot/ankle pain, GP-diagnosed foot/ankle OA, forefoot/ankle surgery, foot/ankle ROA and sROA.

[2] The ankle appeared to be the joint most affected by OA in professional footballers compared to the general population.

[3] Footballers experienced foot/ankle pain a decade earlier than the general population.

[4] Football-related foot/ankle injuries and injections were the two major risk factors associated with self-reported foot/ankle OA in footballers. Although injuries and injections were correlated, they were independently associated with foot/ankle OA. The most common agent injected was corticosteroid.

[5] Despite the higher risk of foot/ankle OA, footballers had better QoL (i.e., better physical capability and similar mental capability) and better objective physical performance in the FSST than controls from the general population.

5.2 Comparison with the literature

The prevalence of self-reported GP-diagnosed ankle OA in retired footballers (9.83%) closely aligns with a previous study that reported a 9.2% (37/401) prevalence of self-reported physician-diagnosed ankle OA in retired male professional footballers from multiple countries (Paget et al., 2020a). Both studies had similar sample sizes and used the same OA definition defined by medical professionals. However, our study included a control group of men from the general population, which made direct risk comparison possible.

The prevalence of ankle ROA was significantly higher in footballers (95.54%) than in controls (65.40%), which is consistent with a previous study that reported a higher prevalence of ankle ROA in former Greek footballers (8.8%) compared to controls (3.7%) (Armenis et al., 2011b). The prevalence rates in that study were clearly much lower than in our study, which may be due to the sensitivity of Menz's criteria and the limited experience of both scorers in scoring foot/ankle ROA, which may have led to an overestimation of its prevalence. When a more stringent definition (i.e., both osteophyte ≥ 2 and JSN ≥ 2) has been used, the prevalence reduced to 81.25% in footballers and 57.69% in controls. This stricter definition of ROA, requiring the presence of both osteophyte ≥ 2 and JSN ≥ 2, was based on the approach used by Nagaosa et al. (2000) to enhance diagnostic specificity and minimise overestimation of ROA prevalence at the knee.

The prevalence of foot ROA affecting at least one of five joints in the general population was 93.1% (295/317), which is the same as that reported by Menz et al. (2009a) 93% (184/197). Also, the prevalence of ROA on individual joints in the general population was similar but slightly higher than that reported by Menz et al. (2009a) at the 1st MTPJ (46.82% versus 42.4%, respectively) the 1st CMJ (43.2% versus 22.6%, respectively), 2nd CMJ (81.70% versus 60.2%, respectively) and the NCJ (59.68% versus 39.1%, respectively), but the same at the TNJ (33.02% versus 32.7%, respectively). However, it is worth mentioning that Menz's study included both men and women and our study included only men.

The prevalence of foot sROA affecting at least one of five joints in the general population control men was 24.45%, higher than the 14.3% reported in men by Roddy et al. (2015a). The prevalence of OA for individual joints for foot sROA in the general population control men was similar but slightly higher than that in men reported by Roddy et al. (2015a) at the 1st MTPJ (8.15% versus 6.7%, respectively), the 1st CMJ (5.6% versus 3.6%,respectively), 2nd CMJ (11% versus 5%, respectively) and the NCJ (8.1% versus 3.8%, respectively), but the same for the TNJ (4.7% versus 5%, respectively). Roddy et al. (2015a) found sROA to be more prevalent in individuals with a lower socioeconomic status, which can affect access to healthcare, lifestyle choices and psychosocial stress, and socioeconomic differences may in part, explain the modest variance in prevalence rates between the two

studies (Thomas et al., 2015a). Another reason may be due to the mean age in our study being 68 years, which is 8 years older than that in Roddy et al. (2015a), whose mean age was approximately 60 years for the male population.

A different pattern of joint-specific prevalence, particularly within the midfoot, for both ROA and sROA was observed in our general population controls compared with published data from general population studies in Australia and the UK (Menz et al., 2009b, Roddy et al., 2015b). These differences may reflect variations in population characteristics (e.g. age and BMI), case definitions, sampling methods and outcome measures. Therefore, direct comparisons with previous studies may have limited value.

The prevalence of self-reported hallux valgus in the male control group was 26.2%, which was higher than the 21% in adults aged >30 years in the Nottingham Gout Study conducted in the UK (Roddy et al., 2008) and lower than the 36% reported by Menz et al. (2011) in adults aged ≥50 years, which included both males and females. However, the present study included only males. Therefore, variations in age distribution and population characteristics may account for the differences in prevalence observed across studies. The prevalence of self-reported doctor-diagnosed gout in the male control group was 11.2%. This was higher than the 6.2% reported Roddy et al. (2007a), in a UK community sample aged ≥30 years, which included both males and females. However, the

higher prevalence in the present study may be due to the older age of participants and the inclusion of only males.

Studies on retired athletes have previously shown that injury is a risk factor for OA of the hip, knee, and ankle (Prien et al., 2017, Gwen Sascha et al., 2018, Dale et al., 2018, Kujala et al., 1995, Parekh et al., 2021b). This study confirmed this association and suggested that the risk of foot/ankle injury for self-reported foot/ankle (aOR, 4.23) is greater than that previously reported in retired elite German female footballers (self-reported ankle aOR 1.13). The reasons for these differences are unclear, but they may be due to geographical definition of OA, and sport-related factors, such as the type of sport (single versus multi-sport) and the level of intensity of participation (Prien et al., 2017).

As we used the same population as in our previous knee OA study (Parekh et al., 2021b), the higher aOR between injury and self-reported foot/ankle OA (aOR 4.23) than RKOA (aOR 2.88) at least suggests that the foot/ankle joint may be more vulnerable to injury in football games. However, caution must be taken as our study only relied on self-reported foot/ankle OA, while Parekh et al. (2021b) measured radiographic knee OA.

5.3 Biological explanation

Injury is a well-recognised major risk factor contributing to the increased risk of foot/ankle OA and the findings from this study are consistent with those of previous studies that have highlighted this factor in the lower limbs of footballers (Gouttebarge and Kerkhoffs, 2015, Koch et al., 2021a, Paget et al., 2020b, Turner et al., 2000a).

A strong association exists between significant foot/ankle injuries with self-reported foot/ankle OA (aOR=4.23, 95% CI 1.88-9.48, p<0.001). This finding aligns with the pathophysiological understanding that acute severe injury can cause direct articular damage, which may lead to subsequent OA changes (Valderrabano et al., 2009). In addition to the high acute injury risk in professional footballers, repetitive use of the foot/ankle joints during football training and matches may lead to repetitive micro-trauma (Paget et al., 2020a). Although such microtrauma may not cause symptoms or problems at the time, the cumulative effects of this lesser injury over a professional footballer's career may eventually result in foot/ankle OA in later life (Drawer and Fuller, 2001b, Gouttebarge and Kerkhoffs, 2015, Paget et al., 2020b).

The association between injury and foot/ankle OA in male retired footballers in this study is not surprising given that prior injury is a recognised risk factor for OA at the knee (Poulsen et al., 2019, Gelber et al., 2000), hip (Gelber et al., 2000) and ankle (Valderrabano et al., 2008, Saltzman et al., 2005) in the general population.

A notable finding was the significant association between injections and self-reported foot/ankle OA in footballers. Although there was a strong correlation between injury and injection ($p<0.001$), both remained in the model as independent risk factors. After adjusting for injury, the association with injection reduced but remained significant (aOR=2.62, 95%CI 1.19-5.78, $p=0.017$), suggesting that injection is a risk factor independent of injury. The prevalence of footballers who received foot/ankle injections (53.13%) was much greater than that in general population controls (6.25%) and this may have untoward consequences concerning the structures within a joint, resulting in ROA foot/ankle. Furthermore, footballers with foot/ankle OA reported a maximum number of 22 injections into any ankle during a single season, with many reporting more than the currently recommended maximum number of 4 corticosteroid injections per year (Uson et al., 2021, de la Torre-Aboki et al., 2022). The potential harms of such high number of corticosteroid injections into the same joint during a short-time period deserve further investigation.

This raises concerns about the long-term consequences of commonly used treatments, such as corticosteroid injections, which might lead to repeated or accelerate joint damage not just due to direct possible deleterious effects of the corticosteroid on joint tissues, but also because players would be able to carry on with high physical activities that may further damage the injured joint, as injection may mask underlying joint pathology, increasing the likelihood of recurrent microtrauma and further

joint damage (Gultekin et al., 2021). This finding calls for a cautious approach to injections in managing foot/ankle injuries in footballers, advocating a balance between immediate pain relief and long-term joint health.

About 82% of the footballers reported receiving corticosteroid injections in both ankles, and many players received a large number of injections even within the same season. Such high usage should be reconsidered given the findings of this study.

Apart from having a higher risk of foot/ankle OA following retirement, we also found that footballers experienced foot /ankle pain a decade earlier than general population controls (mean age 45.24 versus 56.98, $p<0.001$). This suggests that professional footballers are not only at higher risk of foot/ankle OA than the general population after retirement, but they may also develop foot/ankle pain 10 years earlier than the general population, some of them may not yet have retired.

Despite the higher prevalence of foot/ankle OA and pain in footballers than in the general population, we found no differences in the type of pain experienced in each group, as reflected by the prevalence of neuropathic-like pain or catastrophising state or trait. It is often assumed that foot/ankle OA in footballers is predominantly “secondary” to severe acute or repetitive low-grade trauma (including fracture and ligamentous instability - post-traumatic OA) (Valderrabano et al., 2014). In contrast, in the general population, it is regarded as more “primary” and resulting

from multiple genetic, constitutional, and environmental risk factors rather than a single type of joint insult (Doherty et al., 2016b). Our findings suggest that the type of pain experienced from foot/ankle OA may be similar in footballers and the general population irrespective of the cause. Recent evidence also indicates that neuropathic-like pain is common in first MTPJ OA in the general population, with 31% of individuals reporting possible or likely neuropathic pain (Menz et al., 2023). However, previous studies suggest that the type of pain may differ between primary and post-traumatic OA due to different pathogenesis and underlying mechanisms (Maia et al., 2023, Leonardo et al., 2016). The absence of a significant difference in type of pain in our study may be due to the small sample size and recall bias.

The findings of this study call for targeted intervention in sports medicine. These include preventive strategies, early OA detection, and tailored post-career medical support (Zakaria, 2022). The prevalence of self-reported and radiographic OA was significantly higher in the hindfoot/ankle region in footballers than general population controls and the only other joint with more ROA was the midfoot talonavicular joint. This may be because the ankle is more likely to be injured than other foot joints in professional footballers, sufficiently to result in ankle OA (Alsayel et al., 2019a, Nery et al., 2016, Salzmann et al., 2017a). Ankle ligament strains (especially lateral strains) are very common because of swerving and being tackled by the opponent's hard boots, which may cause instability and subsequent OA (Kolokotsios et al., 2021, Liam et al.,

2020). In contrast, the second cuneometatarsal joint showed a lower risk of ROA in footballers compared to controls. The reason for this joint-specific difference remains unknown and warrants further investigation. Moreover, although footwear helps protect the midfoot and forefoot, professional football boots are very open at the back and offer no secure protection for the ankle. Prevention measures are needed to prevent acute injuries and the long-term effects of injuries such as OA (Valderrabano et al., 2014). Football organizations should allow optimal conservative management and recovery time before players return to play after injury (FIFA, 2024).

In the footballer-only case-control study, footballers with sROA of the foot/ankle had a higher prevalence of gout than controls (24.4% versus 10.3%, respectively, p=0.044). It is a well-recognized clinical observation that acute flares of gout and tophaceous deposits often occur at joints also affected by OA. Two controlled studies have found that joints affected by acute gout flares are more likely to display clinical or radiographic features of OA than joints that have not been the site of acute gout (Roddy et al., 2007a, Kawenoki-Minc et al., 1974). Several mechanisms may explain a causal relationship between monosodium urate (MSU) crystal deposition and OA in the same joint, including the possibility that MSU crystals deposit more readily in osteoarthritic cartilage due to increased promotors and reduced inhibitors in OA cartilage matrix, and conversely deposition of MSU crystals leads to progressive joint damage (Roddy and Doherty, 2012).

The overall summated osteophytes score of foot/ankle OA was higher in footballers than in the general population. Higher osteophyte scores reflect dynamic movements of the foot and chronic joint overloading, triggering bony adaptive processes that attempt to stabilise damaged regions in the joint (Drawer and Fuller, 2001a). This may be due to the repetitive impact and microtrauma experienced by professional football players during their careers. These effects are believed to initiate bony adaptations and accelerate joint remodelling changes, including osteophytosis (Turner et al., 2000b). Radiographs are not very sensitive at detecting cartilage loss, especially when it is focal, as in OA. In contrast, osteophytes, which protrude as a new feature, are often the first abnormalities to be evident on plain radiographs (Guermazi et al., 2011).

Footballers appear to have a better QoL related to physical components than the general population. This may reflect the potential benefits of being physically active (Snyder et al., 2010). No previous studies have compared differences in FSST between male footballers and the general population. Footballers were shown to have better FSST than the general population, presumably because of rigorous training, superior agility, and balance. The FSST measures dynamic balance and requires quick and coordinated movement. Long-term participation in football leads to neuromuscular adaptations that enhance coordination and balance (Zemková and Zapletalová, 2022). Jaakkola et al. (2017) highlighted the effects of training on postural control and agility in elite athletes, leading

to improved neuromuscular control, which is crucial in balance tests such as the FSST.

The absence of a significant difference in the 10-MWT between footballers and the general population may be due to its focus on basic gait speed, a fundamental motor function that remains preserved in most healthy individuals (Lozano-Meca et al., 2024). Given that this test does not depend on complex balance or directional control, it is less likely to distinguish between trained and untrained populations (Lozano-Meca et al., 2024). Further study is needed to investigate whether FSST and 10-MWT performance differ between footballers with and without foot/ankle OA and whether these functional tests are associated with OA.

5.4 Limitations

This study has several limitations. Importantly, observational studies such as cross-sectional, case-control and cohort studies cannot establish a causal association between exposure and outcome. Although we controlled for common measurable confounding factors, the study's observational design limits causal inference. Further studies are needed to establish causal relationships between exposure and outcome. In addition, due to logistical reasons, not all participants underwent radiographic assessment, which raises the question of the representativeness of the footballers and controls samples. However, a comparison between footballers and controls, available source populations, questionnaire samples, and radiographic assessment samples showed no differences in age, BMI, socioeconomic status, nodal OA, or pattern 3 finger ratio (2D<4D) among the three groups of footballers and controls, suggesting that the questionnaire sample and radiographic assessments sample are representative of the source population.

Recall bias was acknowledged in the assessment of constitutional hallux valgus at age 20. However, because this is a morphological feature, the likelihood of significant recall bias is lower compared to other subjective conditions, such as footwear habits, where individuals may not accurately recall the type of shoes they frequently wore. Although individuals may recall obvious deformities from early adulthood, the self-report line-drawing instrument was validated by comparing self-reported current

hallux valgus against contemporaneous clinician assessment, but objective assessment of self-reported constitutional alignment was not possible (Roddy et al., 2007b). Therefore, the possibility of recall bias with respect to self-reported early adult alignment remains. Further study is needed to validate the assessment of hallux valgus at age 20.

In addition, footballers with foot/ankle OA may have been more likely to recall and report past injuries and injections than those without OA, potentially introducing differential recall bias.

Furthermore, as in any retrospective self-reported questionnaire study, there is potential for recall bias, leading to overestimation or underestimation of the frequency of various exposures or outcomes. However, comparing the prevalence of foot/ankle OA with previous studies may have limited value. This is due to differences that may reflect variations in population characteristics (e.g., age and BMI), case definitions, sampling methods, radiographic assessment and outcome measures.

This study is prone to misclassification bias as the definition of foot/ankle OA was self-reported. In addition, the small number of cases also limited the ability to perform joint-specific analyses on the foot (e.g., first MTPJ and midfoot OA) to identify region-specific risk factors in footballers. Further studies with a large sample size are needed to identify risk factors specific to different foot regions in footballers.

Foot posture was assessed using a single self-report question regarding flat feet, which captures only one aspect of a complex, multi-dimensional construct. In addition to the radiographic assessment of foot/ankle OA, only two objective functional assessments, the FSST and the 10-MWT, were conducted. These tests evaluate balance and mobility but do not assess structural foot characteristics. The absence of more detailed objective assessments, such as the Foot Posture Index, Arch Index and Navicular height, limits the ability to evaluate foot posture comprehensively (Menz et al., 2012, Cavanagh and Rodgers, 1987). Further study is needed to include objective assessment of foot posture and explore its association with foot/ankle OA.

The control group had a higher response rate in both the questionnaire and radiographic assessment than footballers, potentially because of the larger sample size, as they lived locally and had been more frequently contacted for other studies undertaken by Academic Rheumatology. Footballers who lived everywhere in England had to travel to five different NHS clinics for radiographic assessment, which led to more logistical difficulties in recruiting. Another issue was that due to COVID-19 restrictions, non-responder controls were sent a reminder after just one month according to the protocol, whereas footballers were sent a reminder after six months. Due to the lockdown, researchers were required to register with the department and obtain approval before being granted access to the site. No more than 2-3 PhD students were permitted to work in an office for only two days per week and were

required to maintain a distance separation of 2-3 metres. In addition, delays were caused by the post office's time limit restrictions for collecting and sending questionnaires.

Systematic reviews have identified several strategies that may improve response rates (Edwards et al., 2002, Edwards et al., 2023). These include shorter well designed and not crowded questionnaires, personalised cover letters, pre-contacting participants, follow-up reminders, stamped return envelopes, and recorded delivery. Additional methods include offering non-monetary incentives (e.g., a pen), using electronic or SMS reminders, assuring confidentiality and using single-sided printing or the university affiliation.

Risk factors associated with foot/ankle sROA in footballers remain to be confirmed. This may be due to insufficient power, as there were only (45 cases and 68 controls). The sROA was investigated rather than ROA because defining cases and controls for ROA was not possible. This was due to the sensitivity of Menz's criteria and the limited experience of the two scorers, which may have affected the sensitivity of scoring foot/ankle ROA and led to an overestimation of its prevalence.

Subgroup analysis showed a significant association between foot/ankle injury and sROA foot/ankle (aOR 3.33, 95% CI 1.31–8.45). In contrast, injections were not associated with this outcome, despite their observed association with self-reported foot/ankle OA. This discrepancy may be due to a limited sample size and insufficient statistical power. Given this

uncertainty, the findings should be interpreted as exploratory rather than confirmatory. Further studies with larger samples are required to confirm these associations.

It is noteworthy that using the La Trobe radiographic atlas and the Menz et al definition of OA according to a single OA feature (either osteophyte ≥2 or JSN≥2), the prevalence of foot/ankle ROA was extremely high (almost saturated) and did not significantly differ between footballers (99.11%) and controls (97.17%) (p=0.072) (Menz et al., 2007c). These results suggest that the Menz et al definition may be too sensitive, and further study concerning the optimal radiographic assessment for foot/ankle ROA is warranted (Menz et al., 2007c). In addition to the sensitivity of Menz's criteria, the scorers' experience may have affected the sensitivity of the scoring. Both scorers were at their first time to score radiographic OA. Although they had been trained by an experienced senior scorer and their inter-rater reliability was moderate to excellent (weighted kappa ranged from 80% to 90%). The inter-rater reliability with the senior scorer was not done due to the logistic reason. This might have led to an overestimation of foot/ankle ROA prevalence. This methodological limitation should be considered when interpreting the findings. Furthermore, the omission of the subtalar joint from the La Trobe atlas, which limits assessment of the hindfoot, is also noteworthy and merits further consideration (Menz et al., 2007c). The medial oblique view, which is required, especially for scoring the 2nd CMJ, was not considered.

In addition, no significant differences were observed between footballers and general population controls in some forefoot and midfoot outcomes. However, some outcomes, such as GP-diagnosed forefoot OA and forefoot sROA, showed an elevated aRR, although not statistically significant. This may reflect small sample sizes and limited power, increasing the risk of Type II error (failure to detect a true effect). Further studies with larger samples are needed to confirm these potential associations.

The time taken from the receipt of the questionnaire to the radiographic assessment varied for footballers, ranging from 8 to 30 months (with a mean of 19.84 ± 5.16 months), while it ranged from 4 to 20 months (with a mean of 12.00 ± 3.69 months) for controls. However, since radiographic changes in OA usually occur slowly at all joint sites, it is acceptable for the radiographs to be up to 1-2 years after the self-reported data, as it is unlikely to make a difference to the findings (Goldring and Goldring, 2006, Doherty et al., 2016a).

To adjust for confounding, we selected potential confounding factors that were significant in the univariate analysis to avoid over-adjustment (Schisterman et al., 2009). We only included significant factors from the characteristics of the study population to maintain statistical power. If non-significant factors were included as confounding factors, the power of the study to detect differences could have been reduced, especially if the sample size was small, especially in radiographic samples. Adding one more factor to the model requires at least 30-50 more participants to

maintain the study's power (Schisterman et al., 2009). According to the sample size calculation, we should include 250 retired professional football players and 250 men from the general population to participate in our radiographic assessment study (Espahbodi et al., 2022). However, we were unable to achieve our desired sample size due to financial constraints and logistics difficulties as described above.

The results on radiographic foot/ankle OA are yet to be confirmed, as the number of participants with radiographic assessment (113 footballers and 319 controls) did not meet the calculated minimum required sample size of 250 per group, due to logistical issues caused by the COVID-19 pandemic and subsequent strikes.

This study exclusively focused on male football players. Female professional games are less widespread and have only relatively recently started, meaning that the source population for an equivalent study in post-retirement women, at an age when OA may be prevalent, would be harder to organise. Furthermore, differences in physical demands and gameplay between genders mean that findings for males may not directly apply to females. Also, this study was restricted to professional footballers in the UK who played football several decades ago, and the generalisability of the findings to footballers in other countries and under current rules and circumstances remains to be determined.

5.5 Future work

Ideally, a prospective longitudinal observational study should be conducted in the form of a cohort study over a long period of time. Compared to the current cross-sectional case-control study, the advantages of a cohort study are that participants can be followed up over time, and the incidence of the outcome of interest and the temporal association between exposure, such as injury and injection and foot/ankle OA can be determined.

Moreover, there is no consensus definition of RAO foot (Roddy et al., 2021). Further studies are needed to develop robust definitions of radiographic foot OA that incorporate pain at specific joint sites within the foot and individual radiographic findings (Roddy et al., 2021). Further studies also are needed to determine the optimal scoring method for assessing ROA of the foot, given the caveats of the Menz OA definition and assessment protocol (Menz et al., 2007a).

A notable finding was the significant association between injections and foot/ankle OA in footballers. Further studies are needed to determine the number, type, and frequency of intra-articular injections administered to current retired professional footballers, their potential role in the development of post-career foot/ankle OA, and to inform strategies to minimise injection use during the course of a professional football career.

In addition to plain radiography, ultrasound can be a useful adjunct to plain radiography in showing soft tissue changes and some of the

structural changes of OA. MRI may be used to show three-dimensional soft tissue structures, bone details, and early changes in foot/ankle OA.

Ours is the first study to examine and compare differences in FSST between male footballers and the general population. The test showed a difference between footballers and controls, suggesting that it is a reasonable tool to use more widely in research and clinical practice. Further study is needed to examine the association between the FSST and foot/ankle OA in football players, since foot/ankle OA and pain can affect the gait pattern and reduce walking speed (Batting and Barker, 2019).

5.6 Conclusion

Retired UK male professional footballers were more likely to have current foot/ankle pain, GP-diagnosed OA, forefoot/ankle surgery, foot/ankle ROA and sROA than general population male controls in their later life. The ankle appeared to be the joint most affected by OA in footballers compared to general population. Injury and injection were the two major risk factors associated with an increased risk of foot/ankle OA in professional footballers. Further studies are needed to develop preventive strategies to reduce the risk of foot and ankle OA in current and future professional footballers.

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Appendixes

Appendix 2.1. Number of Clubs

n	Clubs
1	Arsenal FC
2	Bolton Wanderers FC
3	Chelsea FC
4	Coventry City FPA
5	Derby County FC
6	Ipswich Town FC
7	Liverpool FC
8	Luton Town FC
9	Manchester City FPA
10	Manchester United FC
11	Newport County FPA
12	Northampton Town FC
13	Norwich City FC
14	Notts County FC
15	Portsmouth FC / FPA
16	Reading FPA
17	Sheffield Wednesday FC
18	Stoke City FPA
19	Walsall FPA
20	West Bromwich Albion FPA
21	West Ham United FC

Appendix 2.2. Letter Of Approval.

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Weiya Zhang
Academic Rheumatology
Clinical Sciences Building
Nottingham City Hospital
NG5 1PB

Email: hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

23 January 2020

Dear Professor Zhang

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Investigation into the Prevalence of Foot/Ankle Osteoarthritis, Pain, Cognitive and Neurological Impairment in Former Professional UK Male Footballers. The FOCUS (Foot Osteoarthritis & Concussion in Uk Soccer) Study.**
IRAS project ID:	**261168**
Protocol number:	**19063**
REC reference:	**19/EM/0354**
Sponsor	**University of Nottingham**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **261168**. Please quote this on all correspondence.

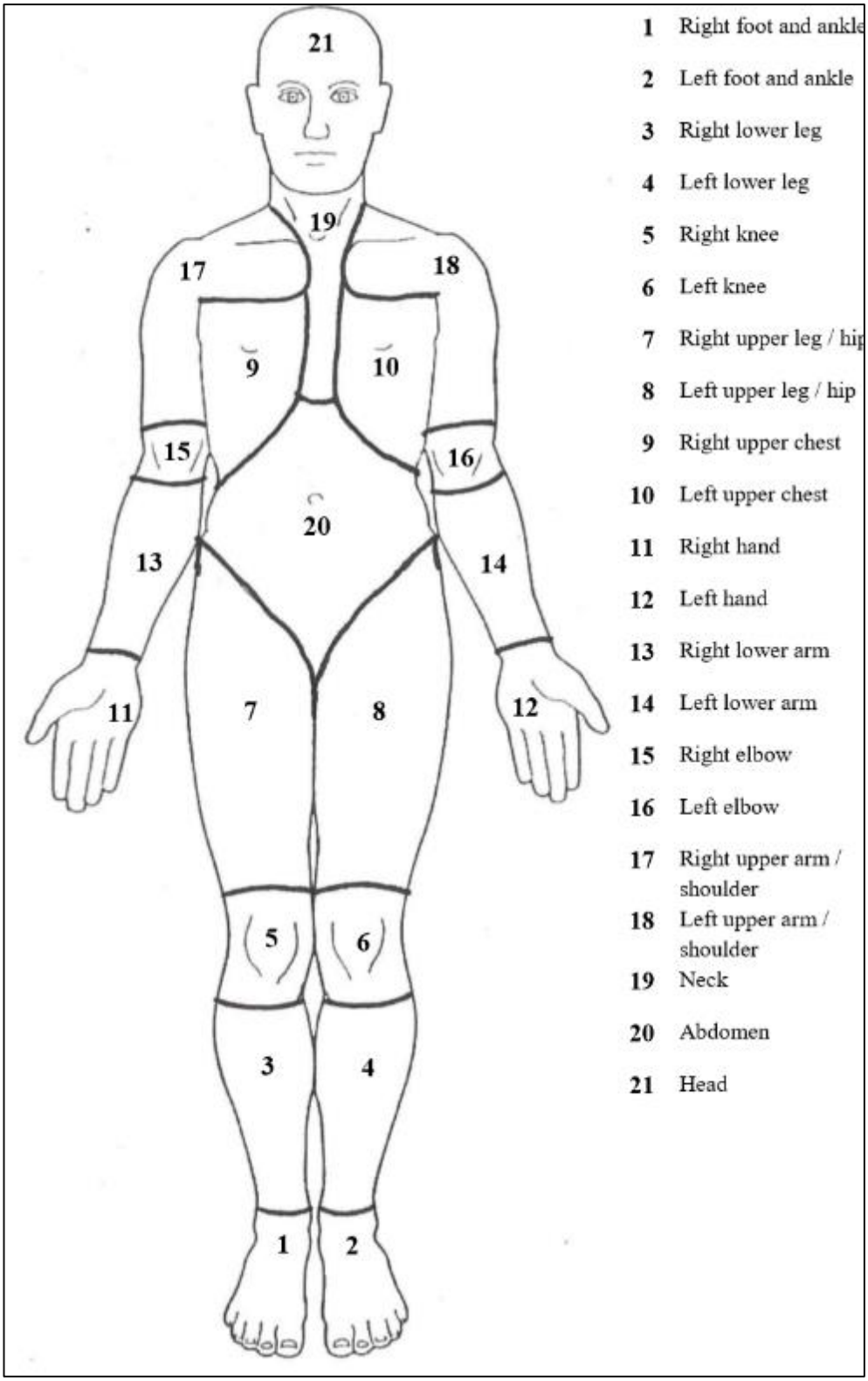
Yours sincerely,
Barbara Cuddon

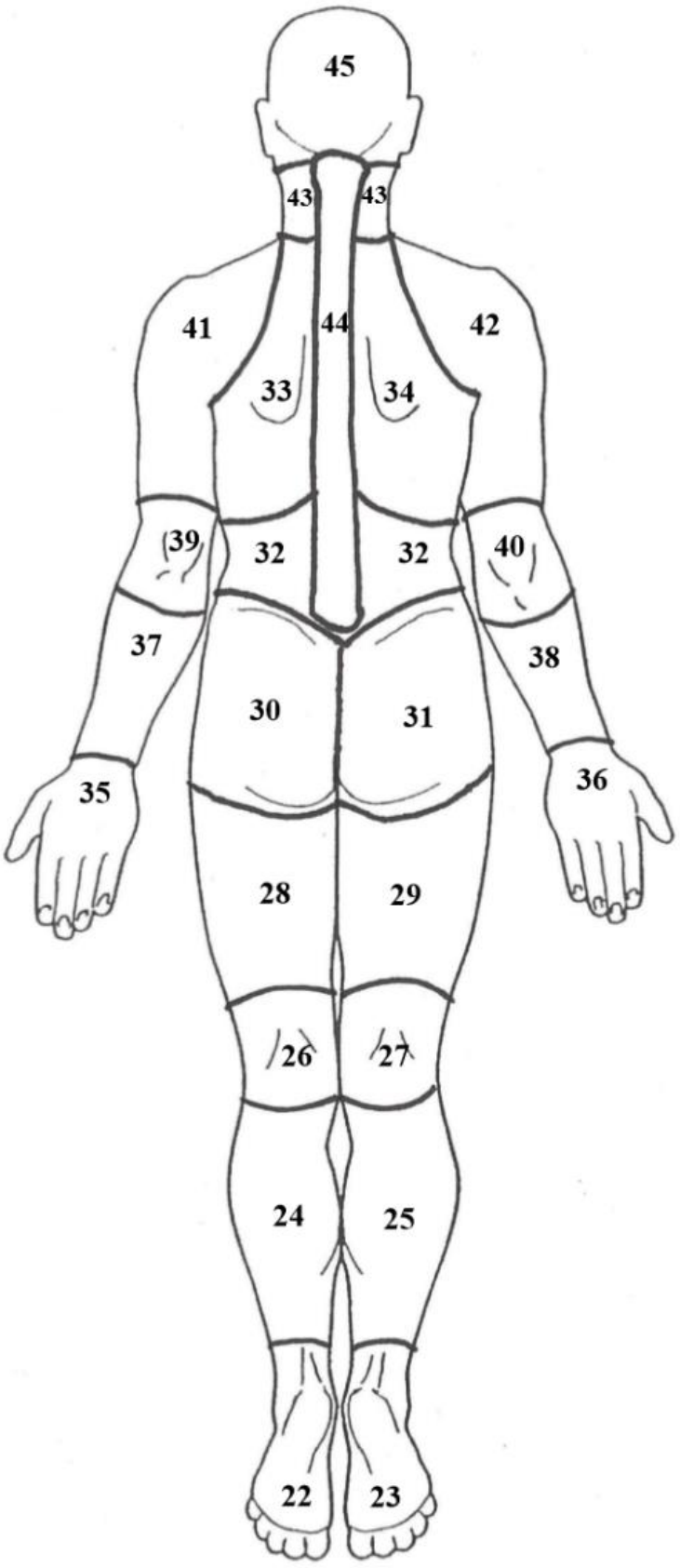
Approvals Specialist

Email: hra.approval@nhs.net

Copy to: *Ms Angela Shone*

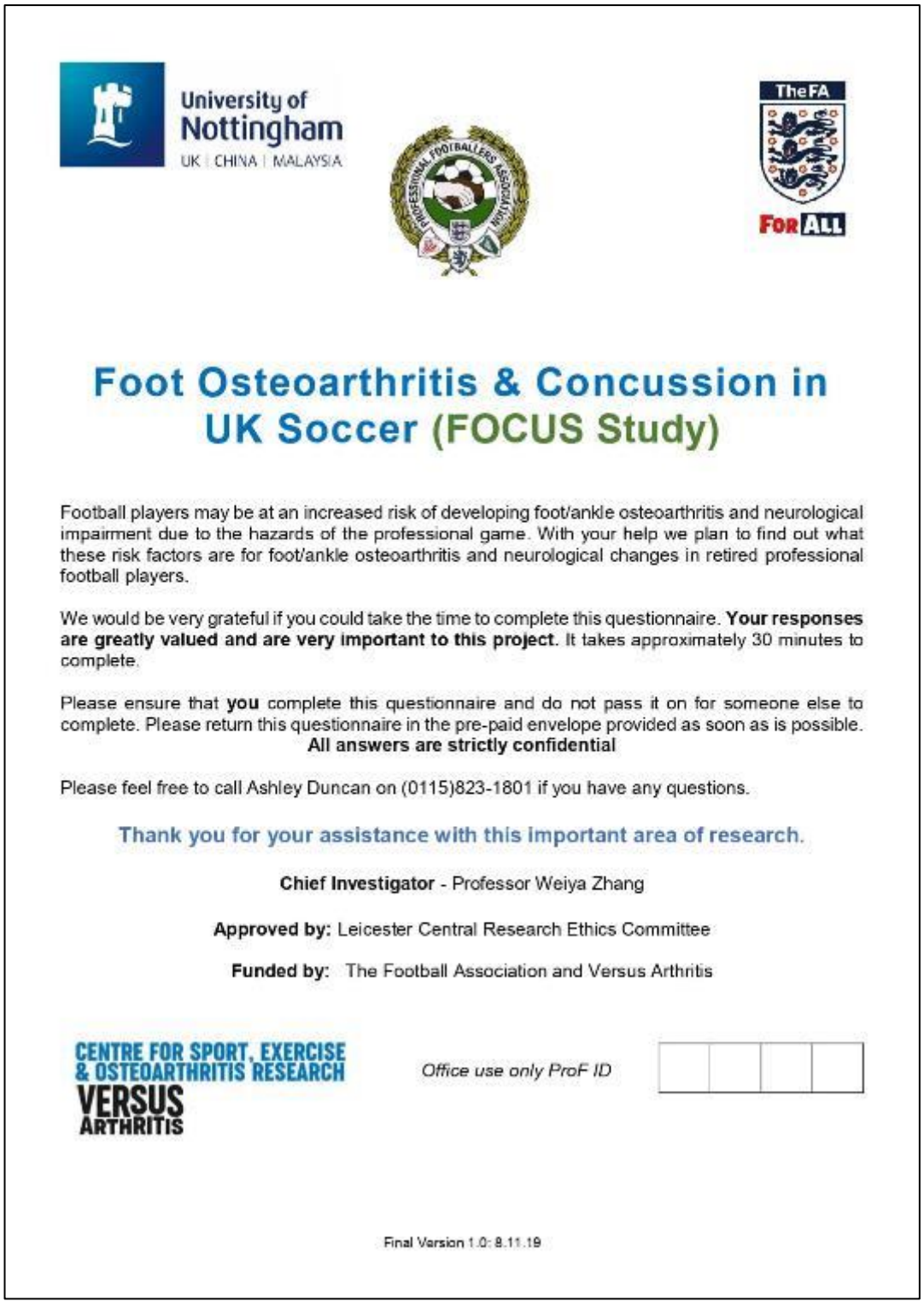
Appendix 2.3. Body Pain Mannequin (BPM) Classification





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

Appendix 2.4. Footballers Questionnaires.



University of Nottingham
UK | CHINA | MALAYSIA

The FA
FOR ALL

Foot Osteoarthritis & Concussion in UK Soccer (FOCUS Study)

Football players may be at an increased risk of developing foot/ankle osteoarthritis and neurological impairment due to the hazards of the professional game. With your help we plan to find out what these risk factors are for foot/ankle osteoarthritis and neurological changes in retired professional football players.

We would be very grateful if you could take the time to complete this questionnaire. **Your responses are greatly valued and are very important to this project.** It takes approximately 30 minutes to complete.

Please ensure that **you** complete this questionnaire and do not pass it on for someone else to complete. Please return this questionnaire in the pre-paid envelope provided as soon as is possible.
All answers are strictly confidential

Please feel free to call Ashley Duncan on (0115)823-1801 if you have any questions.

Thank you for your assistance with this important area of research.

Chief Investigator - Professor Weiya Zhang

Approved by: Leicester Central Research Ethics Committee

Funded by: The Football Association and Versus Arthritis

CENTRE FOR SPORT, EXERCISE & OSTEOARTHRITIS RESEARCH
VERSUS ARTHRITIS

Office use only ProF ID

Final Version 1.0: 8.11.19

SECTION 1 – You and Your Current Health

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. 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
☐ Circulation Problems in legs	☐ Rheumatoid Arthritis	☐ Gout	☐ Fibromyalgia
☐ Parkinson's	☐ Alzheimer's	☐ Dementia	☐ Stroke
☐ Transient Ischaemic Attack	☐ Depression	☐ Anxiety	☐ Hearing Loss
☐ Anaemia	☐ Ankylosing Spondylitis	☐ Asthma	☐ Back Pain (non-traumatic)
☐ Cardiac Arrhythmias	☐ Cholesterol Problems	☐ Chronic Skin Disease	☐ Colitis
☐ Chronic Heart Failure	☐ COPD/Chronic Lung Conditions	☐ Coronary Heart Disease	☐ Epilepsy
☐ Fatigue	☐ Gall bladder stone	☐ Gastritis	☐ Hepatitis B

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- [ ] HIV/AIDS
- [ ] Irritable bowel syndrome (IBS)
- [ ] Liver disease
- [ ] Lupus
- [ ] Lymphatic Disease
- [ ] Migraine
- [ ] Multiple Sclerosis
- [ ] Nutritional Problems (Obesity)
- [ ] Osteoporosis
- [ ] Peptic Ulcer Disease
- [ ] Prostate
- [ ] Psoriasis
- [ ] Psychosis
- [ ] Renal Disorders
- [ ] Schizophrenia
- [ ] Sjögren's Syndrome
- [ ] Sleep Disorder
- [ ] Thyroid disorder
- [ ] Tuberculosis
- [ ] Valvular Heart Disease
- [ ] Vision Problem
- [ ] Vitamin D Deficiency
- [ ] Other, *please specify:* _____
- [ ] Not Applicable

5. What is your current smoking status?

- [ ] Never smoked
- [ ] Previous smoker
- [ ] Current smoker
- [ ] Number per day

6. Please indicate if you drink alcoholic beverages?

- [ ] Yes, MORE than 2-3 alcoholic beverages per day
- [ ] Yes, LESS than 2-3 alcoholic beverages per day
- [ ] Almost every day
- [ ] Sometimes
- [ ] Rarely
- [ ] Never

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7. Please list **all your current medications**, including those prescribed by your doctor and those bought by yourself over the counter, and state the approximate date you started taking each one.

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 _____

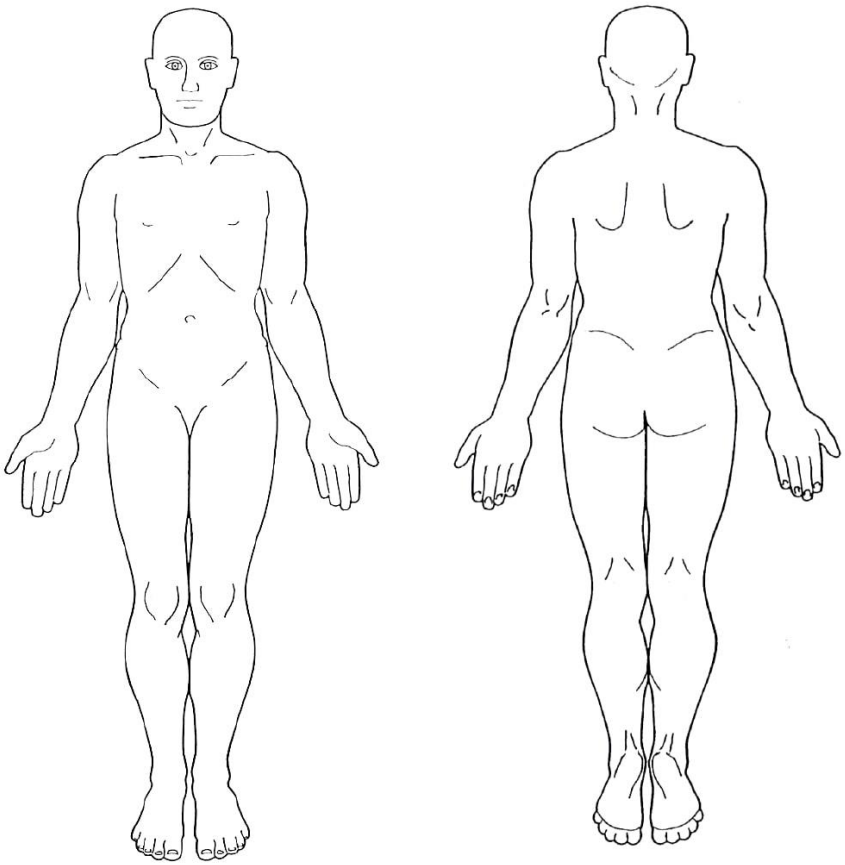
Name of Medicine .....Date Started _____

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SECTION 2 – Pain anywhere in your Body

8. 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 the flu.

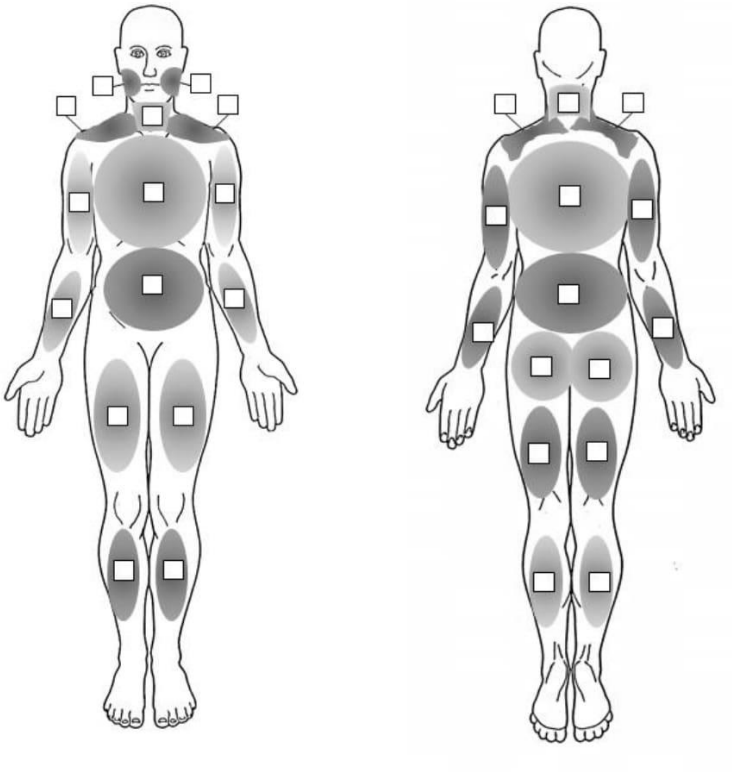
If you **have not** had any body pain lasting for most days in the previous month, *please tick this box* ☐



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9. We are also interested in your body pain experience particularly **in the past one week**. Please can you think of your pain and symptoms but **exclude any** that have been due to known illnesses such as arthritis, lupus etc.

In the diagrams below, please tick the boxes ☐ where you have experienced pain in the region indicated by the shaded areas. Please tick all relevant boxes (the boxes are either placed in the area itself or joined to the area by a line).



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10. Please indicate below your level of symptom severity over the **past week** using the following scale.

	0 = No problem	1 = Slight or mild problems; generally mild or intermittent	2= Moderate; considerable problems; often present and/or at a moderate level	3= Severe: pervasive, continuous, life disturbing problems
a) Tiredness	☐	☐	☐	☐
b) Waking Unrefreshed	☐	☐	☐	☐
c) Concentration (Forgetfulness and problem solving)	☐	☐	☐	☐

11. Lastly, which of the following symptoms have you experienced <u>in the past 1 week</u>? Please tick all that apply.

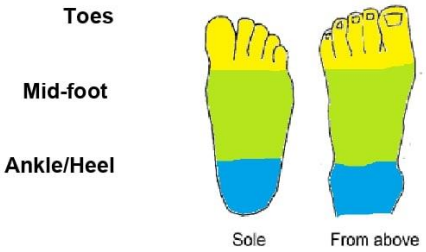
☐ Muscle Pain	☐ Diarrhoea	☐ Headache	☐ Itching
☐ Muscle weakness	☐ Dry mouth	☐ Dizziness	☐ Raynaud's*
☐ Numbness/tingling	☐ Vomiting	☐ Depression	☐ Hives**
☐ Fever	☐ Heartburn	☐ Nervousness	☐ Rash
☐ Irritable bowel Syndrome	☐ Oral ulcers	☐ Blurred vision	☐ Sun sensitivity
☐ Pain/cramps in abdomen	☐ Loss/change in taste	☐ Fits	☐ Easy bruising
☐ Constipation	☐ Loss of appetite	☐ Chest pain	☐ Hair loss
☐ Pain in upper abdomen	☐ Fatigue/tiredness	☐ Wheezing	☐ Frequent urination
☐ Nausea	☐ Thinking/ problems remembering	☐ Shortness of breath	☐ Painful urination
☐ Ringing in ears	☐ Dry eyes	☐ Hearing difficulties	☐ Bladder pain

**Raynaud's: Sudden painful whitening of several fingers with numbness and tingling*
***Hives: normally raised itchy small pale skin swellings which come and go quickly*

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SECTION 3 – Your Feet

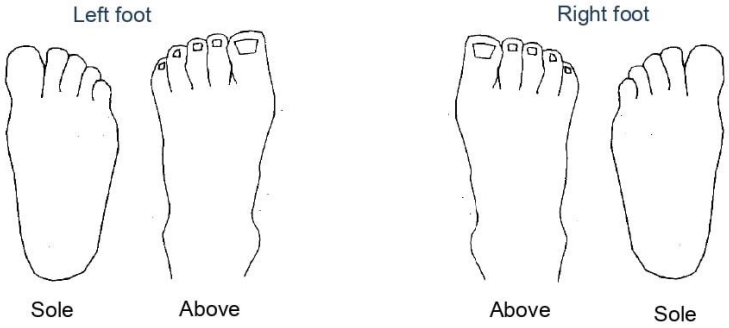
The following questions are about pain you may have in one or both of your feet. Please see the diagram below which shows three **different regions of the foot** i.e. toes, mid-foot, and ankle/heel which have been colour coded here for clarity and reference when completing the questions.

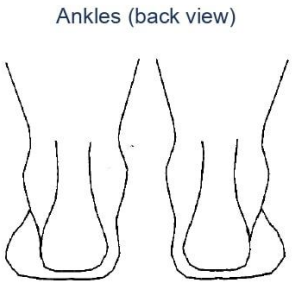


12. Have you had significant pain in or around your feet for **most days in the past month?**

Yes ☐ Please shade in the diagram below where you have any pain

No ☐ Please continue to Question 14





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13. At what age did you first notice this type of pain in your foot/feet?

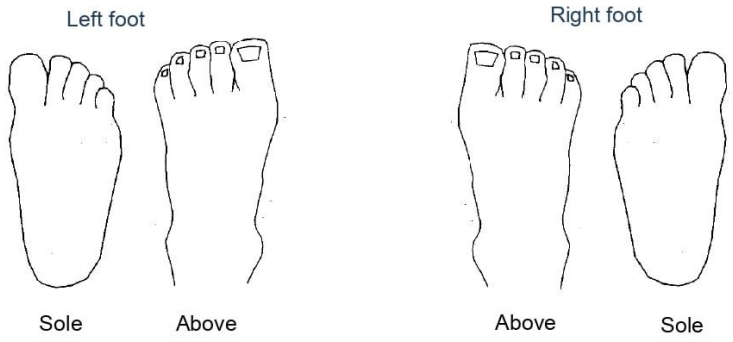
Ankle/Heel: ☐ years old Mid-feet: ☐ years old

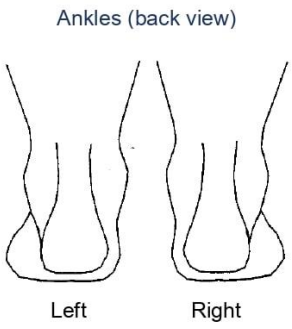
Big Toe(s): ☐ years old Other Toe(s): ☐ years old

14. Have you **ever** had significant pain in or around your feet for **most days over a three month period?**

Yes ☐ Please shade in the diagram below where this has occurred.

No ☐ Please continue to Question 15.





15. Have you ever been diagnosed with **Osteoarthritis** in either of your feet by a doctor/GP?

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Yes ☐ No ☐ **If yes**, please state the foot region and your age when diagnosed:

Ankle ☐ years old Mid-feet ☐ years old Big-Toes ☐ years old Other Toes ☐ years old

16. Please tick-box the region in your feet in which you experienced **significant pain** and at what age(s) it affected you? *By significant pain, we mean pain that you have had for most days for **at least a three month period**. Please tick all that apply.*

Age(years)	Right sided Pain				Left sided Pain			
	Ankle	Mid-foot	Big Toe	Other Toes	Ankle	Mid-foot	Big Toe	Other Toes
10-15	☐	☐	☐	☐	☐	☐	☐	☐
16-20	☐	☐	☐	☐	☐	☐	☐	☐
21-30	☐	☐	☐	☐	☐	☐	☐	☐
31-40	☐	☐	☐	☐	☐	☐	☐	☐
41-50	☐	☐	☐	☐	☐	☐	☐	☐
51-60	☐	☐	☐	☐	☐	☐	☐	☐
61-70	☐	☐	☐	☐	☐	☐	☐	☐
71-80	☐	☐	☐	☐	☐	☐	☐	☐
81-90	☐	☐	☐	☐	☐	☐	☐	☐

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17. This question is on the pattern of your pain in the **most painful region in your foot.** Which of the 4 different options below is the one that best describes the pattern of your worst ankle/foot/toe pain over the past month? (Tick one box)

☐  Persistent pain with slight fluctuations

☐  Persistent pain with pain attacks

☐  Pain attacks without pain between them

☐  Pain attacks with pain between them

18. Please select the response that best describes the **type of pain in your most painful** foot region over the **past month**. Please tick only one box per question and do not leave any questions blank.

	Never	Hardly noticed	Slightly	Moderate	Strongly	Very strongly
a. Do you suffer from a burning sensation (e.g. stinging nettles) in or around your most painful foot?	☐	☐	☐	☐	☐	☐
b. Do you have a tingling or prickling sensation in the area of your most painful ankle/foot ' (e.g. like crawling ants or electrical tingling)?	☐	☐	☐	☐	☐	☐
c. Is light touching (clothing, a blanket) in this area painful?	☐	☐	☐	☐	☐	☐
d. Do you have sudden pain attacks in the area of your most painful foot, like electrical shocks?	☐	☐	☐	☐	☐	☐
e. Is cold or heat (bath water) in this area occasionally painful?	☐	☐	☐	☐	☐	☐
f. Do you suffer from a sensation of numbness in or around your most painful foot?	☐	☐	☐	☐	☐	☐
g. Does slight pressure in this area, (e.g. with a finger), trigger pain?	☐	☐	☐	☐	☐	☐

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19. We are interested in the types of thoughts and feelings 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 in your foot/feet.

	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	☐	☐	☐	☐	☐

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SECTION 4 – Injuries and Operations to your Ankles/Feet

20. Have you ever had a **significant** football-related **injury** to your ankles, feet, toe(s)? *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 23**)

21. Please state the **total** number of significant football related **injuries** you have had through your professional football career in both your right and left ankles, feet, and toes.

Right ankle	☐ injuries	Left ankle	☐ injuries
Right mid-foot	☐ injuries	Left mid-foot	☐ injuries
Right big toe	☐ injuries	Left big toe	☐ injuries
Right other toe(s)	☐ injuries	Left other toe(s)	☐ injuries

22. If you **have** suffered a significant football related injury *(e.g. ligament rupture, tendon tear, or fracture)*, please state the type of injury, tick-box the foot-region that was affected and approximately how old you were when it occurred.

Type of football injury	Right side				Left side				Age
	Ankle	Mid-foot	Big Toe	Other Toes	Ankle	Mid-foot	Big Toe	Other Toes	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	

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	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	

23. Similarly, if you **have** suffered a significant **NON-football** related injury, please could you state the type of injury, which foot-region was affected and your approximate age when it occurred.

Type of NON-football injury	Right side				Left side				Age
	Ankle	Mid-foot	Big Toe	Other Toes	Ankle	Mid-foot	Big Toe	Other Toes	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	

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24. Have you **ever** had any injections into your ankles?

☐ Yes ☐ No *(Please go to* **Question 27***)*

25. If you **have had injections** into your ankles, please indicate which injection(s) you have had into each ankle. *Please tick all that apply*.

Type of injection	Right Ankle	Left Ankle
Cortisone (Steroid)	☐	☐
Anaesthetic (Lignocaine)	☐	☐
Don't Know	☐	☐
Other, *please specify*		

26. We would like to know the greatest number of injections you have had into each ankle.

a) What is the greatest number of injections you had into each ankle in any **season?**

Right ankle ☐ injections Left ankle ☐ injections

b) What is the **total number** of injections you have into each ankle over the course of your professional career?

Right ankle ☐ injections Left ankle ☐ injections

27. Have you ever had injections anywhere else in your foot other than in your ankle(s)?

☐ Yes ☐ No

If yes, please state where and how many? _____

28. Have you ever had surgery to your ankle or toe(s)?

☐ Yes ☐ No (*Please go to* **Question 30**)

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29. If you have had any surgery (e.g. ankle joint replacement, fracture fixation, or key hole surgery), please state what type of procedure you had, which ankle or toe(s) was affected and your age when the surgery occurred.

Type of surgery	Right side		Left side		Age
	Ankle	Toes	Ankle	Toes	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	

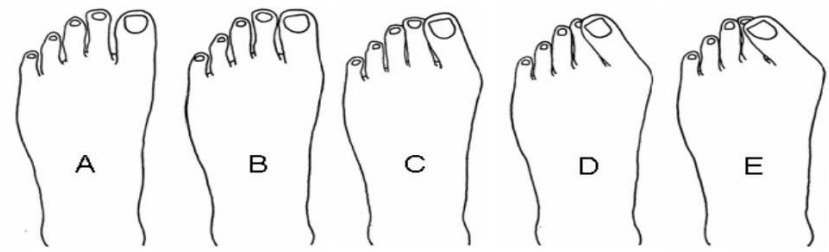
30. We are interested in whether you are flat-footed. This can relate to arthritis. Have you been told by a health professional (e.g. physiotherapist) that you have flat feet?

☐ Yes ☐ No

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SECTION 5 – Your Toe Shape

We are interested in whether your big toes are straight or angled sideways. Angulation of the big toe "bunion" joint can relate to arthritis. First, please look at your left **big** toe whilst standing without shoes and socks on. Ignore the positioning and the gaps between your other toes and try to focus only on your big toe. Select from the first set of pictures below labelled from A to E which one best shows the angle of your left big toe. Please choose which picture you think best shows the angle of your toes **NOW** and when you were in **your 20s.**



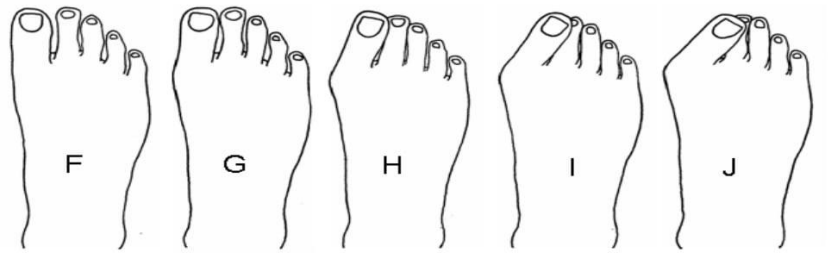
31. Which picture best shows the angle of your left big toe **currently?**

A ☐ **B** ☐ **C** ☐ **D** ☐ **E** ☐

32. Which picture best shows the angle of your left big toe **in your twenties?**

A ☐ **B** ☐ **C** ☐ **D** ☐ **E** ☐

Now, do the same for the right **big** toe joint using the set of pictures below labelled from F to J. Select from the first set of pictures below labelled from F to J which one best shows the angle of your right big toe. Please choose which picture you think best shows the angle of your toes **NOW** and when you were in your 20s.



33. Which picture best shows the angle of your right big toe **currently?**

F ☐ **G** ☐ **H** ☐ **I** ☐ **J** ☐

34. Which picture best shows the angle of your right big toe **in your twenties?**

F ☐ **G** ☐ **H** ☐ **I** ☐ **J** ☐

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SECTION 6 – The Way You Feel

35. The following questions are designed to help us know how you feel. Please read each item below and 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 as if I am slowed down
☐ nearly all the time
☐ very often
☐ sometimes
☐ not at all

b. I get a sort of frightened feeling like 'butterflies' in the stomach
☐ not at all
☐ occasionally
☐ quite often
☐ very often

c. 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

d. I feel restless as if I have to be on the move
☐ very much indeed
☐ quite a lot
☐ not very much
☐ not at all

e. 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

f. I get sudden feelings of panic
☐ very often indeed
☐ quite often
☐ not very often
☐ not at all

g. I can enjoy a good book or radio or television programme
☐ often
☐ sometimes
☐ not often
☐ very seldom

h. I feel tense or 'wound up'
☐ most of the time
☐ a lot of the time
☐ from time to time, occasionally
☐ not at all

i. I still enjoy the things I used to enjoy
☐ definitely as much
☐ not quite so much
☐ only a little
☐ hardly at all

j. 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

k. 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

l. Worrying thoughts go through my mind
☐ a great deal of the time
☐ a lot of the time
☐ not too often
☐ very little

m. I feel cheerful
☐ never
☐ not often
☐ sometimes
☐ most of the time

n. I can sit at ease and feel relaxed
☐ definitely
☐ usually
☐ not often
☐ not at all

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SECTION 7 – Your Quality of Life

The following questions are regarding your health-related quality of life. We are able to assess the impact that 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.***

36. In general, would you say your health currently is:

☐ *Excellent* ☐ *Very Good* ☐ *Good* ☐ *Fair* ☐ *Poor*

37. **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*
☐	☐	☐	☐	☐

38. 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 a lot	*Yes, Limited a little*	*Not, limited at all*
Walking **half a mile**	☐	☐	☐
Walking **100 yards** *(approximately 100 metres)*	☐	☐	☐
Bathing and dressing yourself	☐	☐	☐

39. 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)	☐	☐

40. During the **past month**, have you had any of the following problems with 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	☐	☐

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41. 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* ☐

42. How much **physical** pain have you had during the **past month**?

None ☐ *Very Mild* ☐ *Mild* ☐ *Moderate* ☐ *Severe* ☐ *Very Severe* ☐

43. 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* ☐

44. 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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45. 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*
☐	☐	☐	☐	☐

46. 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	☐	☐	☐	☐	☐

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SECTION 8 – Heading during your professional football play

We are interested in how often you headed the ball during your professional football career.

47. In general, please indicate how frequently you 'headed' the ball during a typical professional **football match**?

☐ 0-5 times ☐ 6-15 times ☐ More than 15 times

48. In general, please indicate how frequently you 'headed' the ball during a typical professional football **training session**?

☐ 0-5 times ☐ 6-15 times ☐ More than 15 times

49. During your professional football career please tick below which statement best describes your play during a match.

Heading was a *minor* part of my play ☐

Heading was a *moderate* part of my play ☐

Heading was a *major* part of my play ☐

50. Did you have professional training sessions that were specifically for **'Only Heading'**?

☐ Yes ☐ No

If yes, please estimate how often this occurred:

Pre-season ☐ times per week

During the season ☐ times per week

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51. Please indicate the type of football that was used for professional matches during your football career. Please tick all that apply.

- ☐ Leather with panels and laces (1930s-1940s)
- ☐ Leather with panels and stitching (1950s-1960s)
- ☐ Leather and synthetic stitched (1960s-1970s)
- ☐ Synthetic stitched (1986-1990s)
- ☐ Synthetic/Latex stitched (1990s-2000s)
- ☐ Latex moulded (2006 onwards)

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SECTION 9 – Concussion and Head Injuries

Please read the definition of concussion to help you answer the following questions.

Definition of Concussion

A concussion can be caused by a direct or indirect blow to the head, face, or neck causing impact to the brain, followed by a variety of symptoms that may include any of the following:

Headache, dizziness, loss of balance, blurred vision, "seeing stars", feeling in a fog or slowed down, memory problems, poor concentration, and nausea or throwing up.

Getting "knocked out" or being unconscious does NOT always occur with concussion.

52. Have you ***ever*** been **diagnosed** with 'Concussion' as a result of playing professional football (including training and matches) by a Doctor/ Health Professional?

☐ Yes ☐ No **If yes**, how many times? ☐

If yes, how many times did the concussion(s) cause any of the following?

Loss of consciousness ☐ Loss of memory ☐ Hospitalisation ☐

53. Have you ***ever*** been **diagnosed** with 'Concussion' for any other reason e.g. an accident, a fall, etc.?

☐ Yes ☐ No **If yes**, how many times? ☐

If yes, how many times did the concussion(s) cause any of the following?

Loss of consciousness ☐ Loss of memory ☐ Hospitalisation ☐

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54. Have you ***ever*** suffered a **serious** head injury/impact that needed medical care/hospitalisation?

☐ Yes ☐ No **If yes**, how many times? ☐

If yes, please briefly describe it including your diagnosis

.....

.....

.....

.....

55. During your professional football career, how frequently did you have an impact to the head, **separate to heading** that **did NOT** cause concussion symptoms?

For example, an elbow or knee to the head, heads clashed, kicked in the head, fallen to the ground, hit goal post, or struck by the ball.

☐ Rarely ☐ Occasionally ☐ Often

56. During your **professional football career**, do you think you may have experienced any of the concussion symptoms (described in the definition above), whether or not you reported it or told your team's medical staff?

☐ Yes ☐ No **If yes**, how many times did this occur? ☐

In general, please indicate how many times the concussion symptom(s) resulted in any of the following?

Loss of consciousness ☐ Memory Loss ☐ Another symptom above ☐

57. During your life **outside of professional football**, do you think you may have experienced any concussion symptom(s) e.g. from a fall, fight, or other incident, even if you did not report it?

☐ Yes ☐ No **If yes**, how many times did this occur? ☐

In general, please indicate how many times the concussion symptom(s) resulted in any of the following?

Loss of consciousness ☐ Memory Loss ☐ Another symptom above ☐

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SECTION 10 – Your Memory and Thinking

58. Please indicate if you have problems with your memory and how these started?

- ☐ I have no problems
- ☐ Yes, the problems started slowly
- ☐ Yes, the problems started suddenly (e.g. after a stroke or fall or death of a loved one)

59. Please indicate if the memory problems have been getting worse?

☐ Yes ☐ No

60. Please indicate if these problems make it difficult for you to function socially or to work or function in your daily activities

☐ Yes ☐ No

61. The following is a short standard test called Test Your Memory (TYM). It is widely used to help assess functions of memory and thinking. Please complete the following series of questions on your own and in one go. Please do not look at the last page of the test until you have completed the first page.

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Test Your Memory
The TYM test

PLEASE WRITE YOUR FULL NAME……..……..

TODAY IS ……..DAY

TODAY'S DATE IS THE: ……..… OF ……(MONTH) 20……

HOW OLD ARE YOU? ……..YEARS

ON WHAT DATE WERE YOU BORN? ……. / ……(MONTH) 19……

PLEASE COPY THE FOLLOWING SENTENCE:

GOOD CITIZENS ALWAYS WEAR STOUT SHOES

……..

PLEASE READ THE SENTENCE AGAIN AND TRY TO REMEMBER IT

WHO IS THE PRIME MINISTER? …… ……..

IN WHAT YEAR DID THE 1ST WORLD WAR START ……

Sums

20 – 4 = …….
16 + 17 = ……
8 x 6 = ……
4 + 15 - 17 = ……

PLEASE LIST FOUR CREATURES BEGINNING WITH "S" e.g. SHARK

1 S……
2 S……
3 S……
4 S……

WHY IS A CARROT LIKE A POTATO?……

WHY IS A LION LIKE A WOLF ? ……

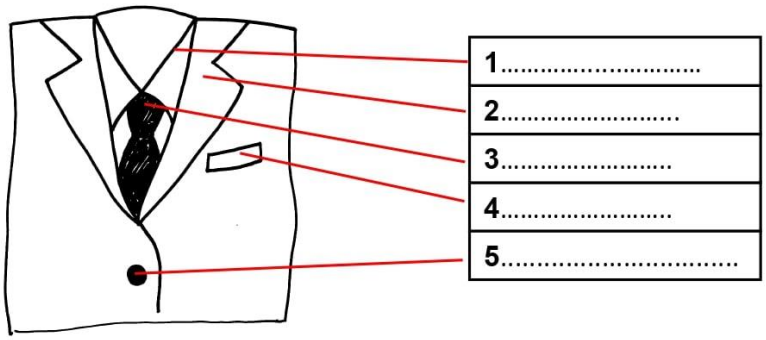
REMEMBER: GOOD CITIZENS ALWAYS WEAR STOUT SHOES

Please Turn Over

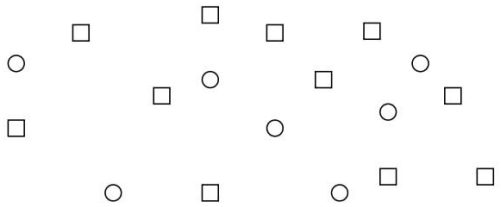
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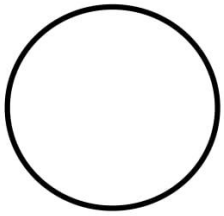
PLEASE NAME THESE ITEMS



PLEASE JOIN THE CIRCLES TOGETHER TO FORM A LETTER
- IGNORE THE SQUARES



PLEASE DRAW IN A CLOCK FACE, PUT IN THE NUMBERS 1 – 12 AND PLACE THE HANDS AT 9.20



WITHOUT TURNING BACK THE PAGE, PLEASE WRITE DOWN THE SENTENCE YOU COPIED EARLIER:

.....

©Jmbrown 2008

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).

Your data will be **anonymised** in all further analyses.

We would like to invite some questionnaire responders to participate in further stages of this study, irrespective of their question responses, which will involve the following:

In the next few weeks, a telephone call for a short assessment of your memory, thinking and concentration. This will last less than 30 minutes.

Please **tick** this box if you might be interested in this telephone assessment ☐

Much later in 2021, if it becomes feasible given the Covid-19 crisis and logistical issues, a single visit to a hospital in your region to have foot/ankle X-rays to look for changes of osteoarthritis.

Please **tick** this box if you might be interested in having foot/ankle x-rays ☐

More detailed information on these 2 assessments is provided in the Patient Information Sheet. If you have ticked any box above and are selected, we will re-contact you to discuss any questions you may have. You will then be able to decide whether you would like to participate.

Academic Rheumatology may also wish to contact you in the future regarding other studies related to your health.

Please tick this box if you are interested to hear of new studies ☐

Please complete your details below so that we will be able to contact you:

Full name: _____

Address: _____

Best Daytime Phone Number: _____

If you are happy for us to email you, please provide you email address below:

Email address: _____@_____

Thank you for your time

Office use only ProF ☐☐☐☐

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Appendix. 2.5. Footballers Participants Information Sheets.

PIS Footballers IRAS ID: 261168

CENTRE FOR SPORT, EXERCISE & OSTEOARTHRITIS RESEARCH
VERSUS ARTHRITIS

University of Nottingham
UK | CHINA | MALAYSIA

Nottingham University Hospitals NHS
NHS Trust

PROFESSIONAL FOOTBALLERS ASSOCIATION

The FA

Foot/Ankle Osteoarthritis, Cognitive and Neurological Impairment in Former Professional UK Male Footballers

Acronym: **FOCUS** (Foot Osteoarthritis & Concussion in UK Soccer)

PARTICIPANT INFORMATION SHEET

Chief Investigator: Weiya Zhang, Professor of Epidemiology

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 FOCUS study?

Osteoarthritis and dementias (e.g. Alzheimer's) are a major cause of pain, physical and mental disability, and reduced quality of life for millions of sufferers. Professional footballers may be at higher risk of developing both these conditions because of injuries sustained during their careers. Our previous study showed that professional footballers are 2-3 times more likely to develop knee osteoarthritis (OA) compared to other men in the general population.

Foot/ankle injuries are very common amongst players and can lead to foot/ankle OA. Symptoms range from severe pain, impaired function, disturbed sleep, depression and a reduced quality of life. There is no cure - medical treatments may improve symptoms but many people eventually need joint surgery.

Final Version 1.1: 29.07.20

Likewise, injuries/impacts to the head are common and may develop over time causing concussion or sub-concussive trauma to the brain. Symptoms can be subtle and range from headaches to loss of consciousness. However even subtle symptoms may over time contribute to problems with memory, attention and general mood. There is still much debate and controversy about the long-term effects of head impacts on the brains of footballers and research so far has been inconclusive.

This is the first comprehensive study investigating from 'Top to Toe' the effects of both head and feet injuries in footballers.

This study involves the following three components:

- a **Postal Questionnaire** contained in this pack. It has been sent to nearly one thousand footballers registered with the UK Professional Footballers Association (PFA) to determine the frequency of: (1) pain, symptoms, injuries and operations related to your feet/ankles; and (2) concussions, head injuries/impacts, memory, thinking, and general health.

- a **Telephone Assessment** involving some questions, which lasts under 30 minutes. This is to obtain more detailed information on your brain health and any neurological changes that may be present.

- Then later in 2021, only if it becomes feasible, we may contact you to invite you for **foot/ankle x-rays** to look for changes of osteoarthritis. Several NHS Trusts will be taking part in this assessment and you will be invited to the most convenient location to have this done.

The purpose of this study is to determine if footballers are more likely to develop foot/ankle osteoarthritis, and/or neurological diseases (e.g. Alzheimer's and Parkinson's). Also, if there are specific risks with playing professional football that contribute to developing these conditions. The results of these detailed tests from the footballers will then be compared to age-matched men from the general population for biomechanical, neurological, cognitive, physical, and pain profiles.

Part of this study is being conducted as an educational project for a PhD by Mr. Ahmed Thanoon.

Why have I been invited?
You have already kindly taken part in our previous study on knee osteoarthritis and general health in professional footballers. During this you indicated that you would be willing to receive further information in the future about other upcoming studies which involved general health, which is why we are contacting you now. You should read this information sheet in detail before deciding whether you wish to take part or not. We aim to receive 540 responses to the Questionnaire and recruit 250 participants for the Telephone Assessment, irrespective of their responses to the postal questionnaire.

Do I have to take part?

No. You should only take part if you want to. It is entirely up to you whether or not to take part. If you do decide to take part in the survey then completion and return of the enclosed Questionnaire can be taken as consent.

If you decide to take part in the Telephone Assessment you will be asked to give verbal consent over the phone. In this pack is a copy of the consent form which will be read out to you by one of our colleagues when they call you. After you have given verbal consent this will be documented on the form and kept in the study files. If you request a copy we can email/post it to you.

If you decide to participate 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. This participant information sheet is for you to keep.

What will happen to me if I take part?

The first part of the study involves completing the enclosed paper Questionnaire and returning it to us in the pre-paid addressed envelope. You can complete the Questionnaire at home in your own time – it will take about 30-45 minutes.

Then, on the last page of the Questionnaire you will be able to tick a box to indicate if you would like to have a Telephone Assessment. If you have ticked it, you will be contacted by phone by an assessor who will arrange/conduct a series of questions over the phone with you which takes less than 30 minutes.

Much later, in 2021, ***if it becomes feasible*** to perform x-rays, you will be contacted again by the research team to find out if you are still interested in having x-rays. If you are, then an appointment will be made at the nearest NHS Hospital to see the study researchers. This appointment at the NHS Hospital will take around 1 hour.

When you arrive at the NHS Hospital, the researcher will first discuss any remaining questions you may have about the study and the consent procedure. If you are still willing to participate in the study, you will be asked to sign two copies of the consent form, one to be kept by you and one for the researcher to keep in the study records.

Following this, x-rays of both of your feet and ankles will be taken by NHS staff in the Radiology Department. Your x-rays will be taken in two positions, both times when you are fully weight-bearing and standing.

What are the possible disadvantages and risks of taking part?

In general, there are no risks or disadvantages in taking part in the Questionnaire survey or the Telephone Assessment.

If in 2021 it is feasible to conduct the x-rays and you decide to participate, then this would involve exposure to a small amount of x-radiation. As part of everyday living everyone is exposed to naturally occurring background radiation. The x-rays from this

trial would give an exposure equivalent to less than one day of background radiation received by an average UK resident. At this dose level no harmful effects of radiation have been demonstrated and the risk is believed to be negligible.

What are the possible benefits of taking part?

By taking part in this research study, you will be helping us to understand if professional footballers are more likely (at risk) to develop foot/ankle osteoarthritis and problems with memory/thinking/organisation when compared with men in the general population of the same age. It will allow us to estimate the risks for footballers and eventually reduce these risks through appropriate screening, therapeutic and rehabilitation strategies. It may also have an impact on the way professional players currently train, practice and play football.

What if there is a problem?

If you have a concern about any aspect of this study, please speak to Ashley Duncan who will do her best to answer your questions (telephone number: 0115-823 1801). If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service in confidence at Nottingham City Hospital on 0115 969 1169 (extension 59671) or on pals@nuh.nhs.uk.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will any genetic tests be done?

No genetic testing will be done.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you during the course of the research. This information will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database at the University of Nottingham. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally identifiable information possible.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations 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.

Where possible information about you which leaves the Department of Academic Rheumatology will have your name and address removed and a unique code will be used so that you cannot be recognised from it. However, sometimes we need to ensure that we can recognise you to link the research data with your medical records (for the foot x-rays) so in these instances we will need to know your name and date of birth. We will also need this information if we need to follow up your medical records as part of the research, where we may need to ask the Government services that hold medical information about you (such as NHS Digital, the Office for National Statistics, among others) to provide this information to us. By signing the consent form you agree to the above.

Your contact information will continue to be kept by the University of Nottingham after the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies as previously agreed (unless you advise us that you do not wish to be contacted). We will contact you regularly to confirm that you are happy for your details to be kept for this purpose but you can ask for them to be removed at any time by contacting the study team on the contact details given below. This information will be kept separately from the research data collected and only those who need to will have access to it. All other data (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, and only members of the research team who have been given permission by the data custodian will have access to your personal data.

In accordance with the policies of the University of Nottingham, the Government and our funders, we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is anonymised (so that you could not be identified).

Although what you say to us is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

The hospital taking your x-rays may need to create a health record, including the x-ray taken and your associated personal data, but this will be kept confidential in common with all medical records (only if this becomes feasible in 2021).

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw we will no longer collect any information about you or from you. However, we will keep the information about you that we have already obtained as we are not allowed to tamper with study records and this information may have already been used in some analyses and may still be used in the final study analyses. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Will I be paid for participation in this study?

Participation in this study is entirely voluntary. You will receive no payment for your participation in completing the Questionnaire and/or the Telephone Assessment. However, your travel costs to and from the NHS Trust Hospital will be reimbursed if this visit becomes feasible in 2021 and you decide to participate.

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 neurological impairment and foot/ankle osteoarthritis and help guide future management of these common health problems in footballers. Results of the study will be presented nationally and internationally and will also be published in international medical journals. Your anonymity will always be maintained, and no reference will ever be made to personal identifiers in any of our published results. Sections of the study results pertaining to foot/ankle osteoarthritis will be written up as a PhD thesis by one of our research students. Please let us know if you would like a copy of any of the publications and we shall be happy to provide it when it is available. We will also provide you with a summary of the results if you wish.

What happens when the research study stops?

When this study has finished your data will be statistically analysed along with data from others who have also participated, in order to determine the overall results of the research. We will compare the results from the footballer group with those from the general population male volunteers. All data will be anonymised and there will be no reference to personal identifiable details. The results will be published in peer reviewed medical journals and at your request you will be provided with any such publications.

Who is organising and funding the research?

This study is organised by staff in Academic Rheumatology, a department of the University of Nottingham based at the City Hospital. The study is being funded both by Versus Arthritis, an arthritis medical research charity, and the Football Association (FA), the UK governing body of association football.

Who has reviewed the study?

All research in healthcare is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by Leicester Central Research Ethics Committee.

Further information and contact details

Study Contact:

Miss Ashley Duncan, PhD student, Academic Rheumatology,
Clinical Sciences Building, Nottingham City Hospital,
Nottingham, NG5 1PB.
Tel: 0115 8231801

Chief Investigator: Professor Weiya Zhang, Professor of Epidemiology, Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, Nottingham, NG5 1PB
Tel: 0115 8231750

Research Contacts: Mrs Helen Richardson, Operations Manager, Room B103
Clinical Sciences Building, Nottingham City Hospital,
Nottingham NG5 1PB
Tel: 0115 823 3172

Appendix 2.6. Footballers Consent Form

Consent Form Footballers IRAS ID: 261168

ProF ID number: ☐☐☐☐







CONSENT FORM
(Final version 1.1: 29.07.20)

Title of Study: Foot/Ankle Osteoarthritis, Cognitive and Neurological Impairment in Former Professional Footballers (FOCUS STUDY)

REC Project ID: 261168

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the participant information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any 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 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 and agree that participating in this study will involve a study researcher calling me to conduct a telephone assessment with me. ☐
5. This is OPTIONAL and ONLY if it becomes feasible in 2021.
   I understand and agree that I might be invited to attend an NHS Trust Hospital to have x-rays of my feet/ankles undertaken by a radiographer. **(Only if feasible in 2021)** ☐
6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature

This will be verbally agreed by the participant and a copy of this completed consent form will be emailed/posted upon request.

Name of Person taking consent	Date	Signature

1

Appendix 2.6. Controls Questionnaires

University of Nottingham
UK | CHINA | MALAYSIA

The FA FOR ALL

Foot Osteoarthritis & Concussion in UK Soccer (FOCUS Study)

- A comparative study with the general population

Football players may be at an increased risk of developing foot/ankle osteoarthritis and neurological impairment due to the hazards of the professional game. With your help we plan to find out what these risk factors are for foot/ankle osteoarthritis and neurological changes in retired professional football players in comparison with the general population.

You have been selected from the general population for this comparison. We would be very grateful if you could take the time to complete this questionnaire. **Your responses are greatly valued and are very important to this project.** It takes approximately 30 minutes to complete.

Please ensure that **you** complete this questionnaire and do not pass it on for someone else to complete. Please return this questionnaire in the pre-paid envelope provided as soon as possible.

All answers are strictly confidential

Please feel free to call Ashley Duncan on (0115) 823-1801 if you have any questions.

Thank you for your assistance with this important area of research.

Chief Investigator - Professor Weiya Zhang

Approved by: Leicester Central Research Ethics Committee

Funded by: The Football Association and Versus Arthritis

CENTRE FOR SPORT, EXERCISE & OSTEOARTHRITIS RESEARCH
VERSUS ARTHRITIS

Office use only GMP ID | | | | |

Final Version 1.0 8.11.19

SECTION 1 – You and Your Current Health

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. 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
☐ Circulation Problems in legs	☐ Rheumatoid Arthritis	☐ Gout	☐ Fibromyalgia
☐ Parkinson's	☐ Alzheimer's	☐ Dementia	☐ Stroke
☐ Transient Ischaemic Attack	☐ Depression	☐ Anxiety	☐ Hearing Loss
☐ Anaemia	☐ Ankylosing Spondylitis	☐ Asthma	☐ Back Pain (non traumatic)
☐ Cardiac Arrhythmias	☐ Cholesterol Problems	☐ Chronic Skin Disease	☐ Colitis
☐ Chronic Heart Failure	☐ COPD/ Chronic Lung Condition	☐ Coronary Heart Disease	☐ Epilepsy
☐ Fatigue	☐ Gall bladder stone	☐ Gastritis	☐ Hepatitis B

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☐ HIV/AIDS ☐ IBS ☐ Liver disease ☐ Lupus

☐ Lymphatic Disease ☐ Migraine ☐ Multiple Sclerosis ☐ Nutritional Problems (Obesity)

☐ Osteoporosis ☐ Peptic Ulcer Disease ☐ Prostate ☐ Psoriasis

☐ Psychosis ☐ Renal Disorders ☐ Schizophernia ☐ Sjögren's Syndrome

☐ Sleep Disorder ☐ Thyroid disorder ☐ Tuberculosis ☐ Valvular Heart Disease

☐ Vision Problem ☐ Vitamin D Deficiency

☐ Other, *please specify:* _____

☐ Not Applicable

5. What is your current smoking status?

☐ Never smoked ☐ Previous smoker ☐ Current smoker ☐ Number per day

6. Please indicate if you drink alcoholic beverages?

☐ Yes, MORE than 2-3 alcoholic beverages per day

☐ Yes, LESS than 2-3 alcoholic beverages per day

☐ Almost everyday ☐ Sometimes

☐ Rarely ☐ Never

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7. Please list **all your current medication** including those prescribed by your doctor and those bought yourself over the counter, and 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 _____

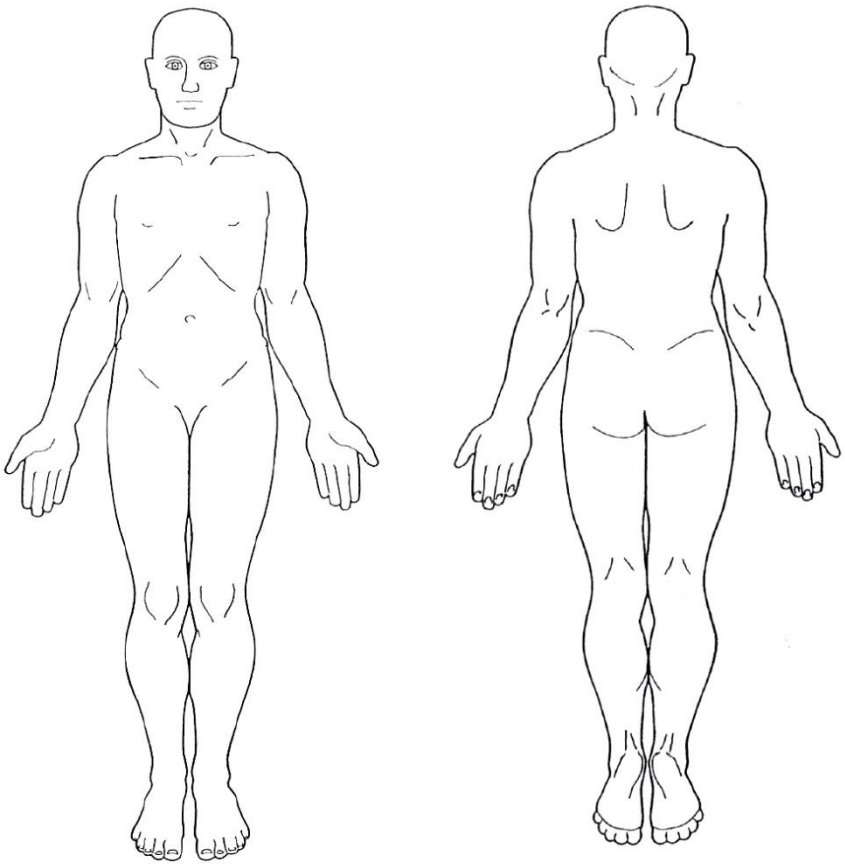
Name of Medicine .....Date Started _____

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SECTION 2 – Pain anywhere in your Body

8. 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 the flu.

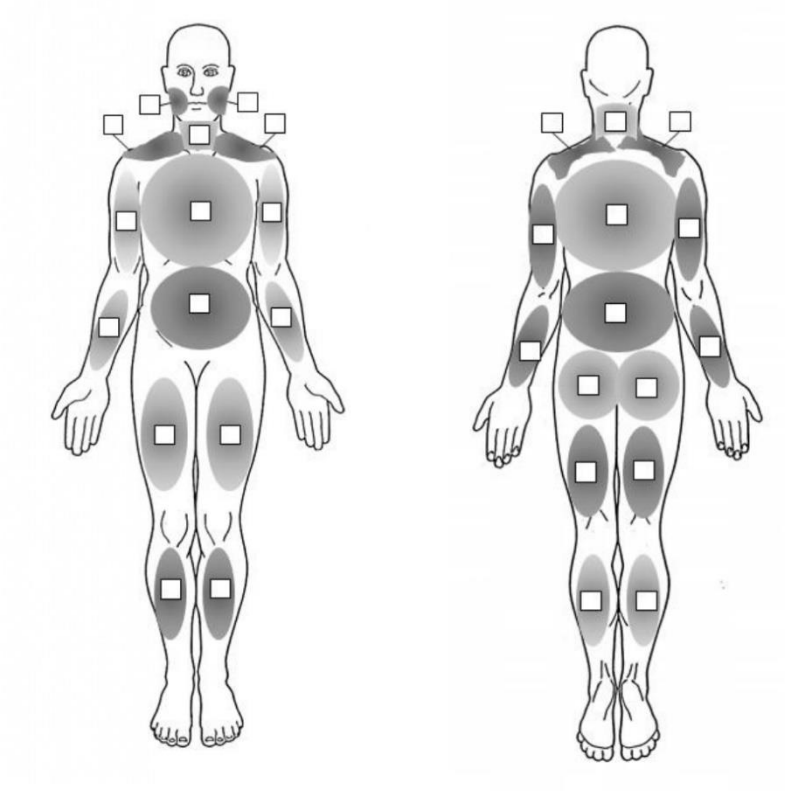
   If you **have not** had any body pain lasting for most days in the previous month, *please tick this box* ☐



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9. We are also interested in your body pain experience particularly **in the past one week**. Please can you think of your pain and symptoms but **exclude any** that have been due to known illnesses such as arthritis, lupus etc.

In the diagrams below, please tick the boxes ☐ where you have experienced pain in the region indicated by the shaded areas. Please tick all relevant boxes (the boxes are either placed in the area itself or joined to the area by a line).



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10. Please indicate below your level of symptom severity over the **past week** using the following scale.

	0 = No problem	1 = Slight or mild problems; generally mild or intermittent	2= Moderate; considerable problems; often present and/or at a moderate level	3= Severe: pervasive, continuous, life disturbing problems
a) Tiredness	☐	☐	☐	☐
b) Waking Unrefreshed	☐	☐	☐	☐
c) Concentration (Forgetfulness and problem solving)	☐	☐	☐	☐

11. Lastly, which of the following symptoms have you experienced in the past 1 week? Please tick all that apply.

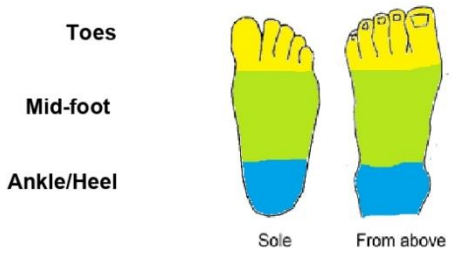
☐ Muscle Pain	☐ Diarrhoea	☐ Headache	☐ Itching
☐ Muscle weakness	☐ Dry mouth	☐ Dizziness	☐ Raynaud's*
☐ Numbness/tingling	☐ Vomiting	☐ Depression	☐ Hives**
☐ Fever	☐ Heartburn	☐ Nervousness	☐ Rash
☐ Irritable bowel Syndrome	☐ Oral ulcers	☐ Blurred vision	☐ Sun sensitivity
☐ Pain/cramps in abdomen	☐ Loss/change in taste	☐ Fits	☐ Easy bruising
☐ Constipation	☐ Loss of appetite	☐ Chest pain	☐ Hair loss
☐ Pain in upper abdomen	☐ Fatigue/tiredness	☐ Wheezing	☐ Frequent urination
☐ Nausea	☐ Thinking/ problems remembering	☐ Shortness of breath	☐ Painful urination
☐ Ringing in ears	☐ Dry eyes	☐ Hearing difficulties	☐ Bladder pain

**Raynaud's: Sudden painful whitening of several fingers with numbness and tingling*
***Hives: normally raised itchy small pale skin swellings which come and go quickly*

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SECTION 3 – Your Feet

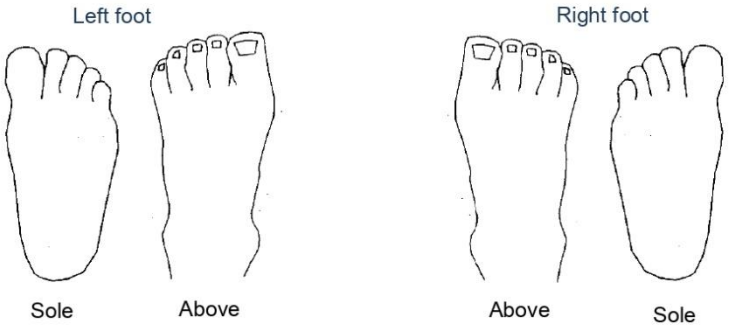
The following questions are about pain you may have in one or both of your feet. Please see the diagram below which shows three **different regions of the foot** i.e. toes, mid-foot, and ankle/heel which have been colour coded for clarity and reference when completing the questions.

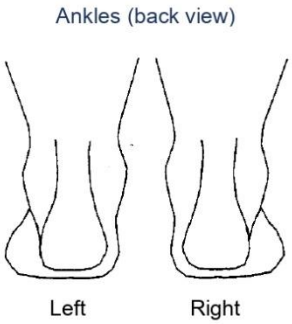


12. Have you had significant pain in or around your feet for **most days in the past month?**

Yes ☐ Please shade in the diagram below where you have any pain

No ☐ Please continue to Question 14





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13. At what age did you first notice this type of pain in your foot/feet?

Ankle/Heel: ☐ years old Mid-feet: ☐ years old

Big Toe(s): ☐ years old Other Toe(s): ☐ years old

14. Have you **ever** had significant pain in or around your feet for **most days over a three month period?**

Yes ☐ Please shade in the diagram below where this has occurred.

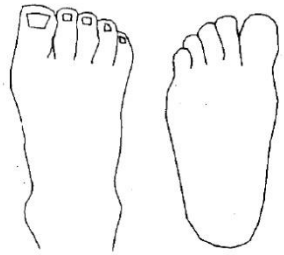
No ☐ Please continue to Question 15.

Left foot



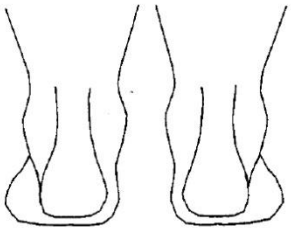
Sole Above

Right foot



Above Sole

Ankles (back view)



Left Right

15. Have you ever been diagnosed with **Osteoarthritis** in either of your feet by a doctor/GP?

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Yes ☐ No ☐ **If yes**, please select the foot region and state your age when diagnosed:

Ankle ☐ years old Mid-feet ☐ years old Big-Toes ☐ years old Other Toes ☐ years old

16. Please tick-box the region in your feet in which you experienced **significant pain** and at what age(s) it affected you? *By significant pain, we mean pain that you have had for most days for **at least a three month period**. Please tick all that apply.*

Age(years)	Right sided Pain				Left sided Pain			
	Ankle	Mid-foot	Big Toe	Other Toes	Ankle	Mid-foot	Big Toe	Other Toes
10-15	☐	☐	☐	☐	☐	☐	☐	☐
16-20	☐	☐	☐	☐	☐	☐	☐	☐
21-30	☐	☐	☐	☐	☐	☐	☐	☐
31-40	☐	☐	☐	☐	☐	☐	☐	☐
41-50	☐	☐	☐	☐	☐	☐	☐	☐
51-60	☐	☐	☐	☐	☐	☐	☐	☐
61-70	☐	☐	☐	☐	☐	☐	☐	☐
71-80	☐	☐	☐	☐	☐	☐	☐	☐
81-90	☐	☐	☐	☐	☐	☐	☐	☐

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17. This question is on the pattern of your pain in the **most painful region in your foot.** Which of the 4 different options below is the one that best describes the pattern of your worst ankle/foot/toe pain over the past month? (Tick one box)

☐  Persistent pain with slight fluctuations

☐  Persistent pain with pain attacks

☐  Pain attacks without pain between them

☐  Pain attacks with pain between them

18. Please select the response that best describes the **type of pain in your most painful** foot region over the **past month**. Please tick only one box per question and do not leave any questions blank.

	Never	Hardly noticed	Slightly	Moderate	Strongly	Very strongly
a. Do you suffer from a burning sensation (e.g. stinging nettles) in or around your most painful foot?	☐	☐	☐	☐	☐	☐
b. Do you have a tingling or prickling sensation in the area of your most painful ankle/foot (e.g. like crawling ants or electrical tingling)?	☐	☐	☐	☐	☐	☐
c. Is light touching (clothing, a blanket) in this area painful?	☐	☐	☐	☐	☐	☐
d. Do you have sudden pain attacks in the area of your most painful foot, like electrical shocks?	☐	☐	☐	☐	☐	☐
e. Is cold or heat (bath water) in this area occasionally painful?	☐	☐	☐	☐	☐	☐
f. Do you suffer from a sensation of numbness in or around your most painful foot?	☐	☐	☐	☐	☐	☐
g. Does slight pressure in this area, (e.g. with a finger), trigger pain?	☐	☐	☐	☐	☐	☐

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19. We are interested in the types of thoughts and feelings 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 in your foot/feet.

	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	☐	☐	☐	☐	☐

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SECTION 4 – Injuries and Operations to your Ankles/Feet

20. Have you ever had a **significant injury** to your ankles, feet, toe(s)? *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 work and other duties during this time.*

☐ Yes ☐ No (Please go to **Question 23**)

21. Please state the **total** number of significant **injuries** you have had through your life in both your right and left ankles, feet, and toes.

Right ankle	☐	injuries	Left ankle	☐	injuries
Right mid-foot	☐	injuries	Left mid-foot	☐	injuries
Right big toe	☐	injuries	Left big toe	☐	injuries
Right other toe(s)	☐	injuries	Left other toe(s)	☐	injuries

22. If you **have** suffered a significant injury to your feet/ankles *(e.g. ligament rupture, tendon tear, or fracture)*, please state the type of injury, tick-box the foot-region that was affected and approximately how old you were when it occurred.

Type of injury	Right side				Left side				Age
	Ankle	Mid-foot	Big Toe	Other Toes	Ankle	Mid-foot	Big Toe	Other Toes	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	

	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	☐	☐	☐	

23. Have you **ever** had any injections into your ankles?

☐ Yes ☐ No *(Please go to* **Question 26***)*

24. If you **have had injections** into your ankles, please indicate which injection(s) you have had into each ankle. *Please tick <u>all</u> that apply*.

Type of injection	Right Ankle	Left Ankle
Cortisone (Steroid)	☐	☐
Anaesthetic (Lignocaine)	☐	☐
Don't Know	☐	☐
Other, *please specify*		

25. We would like to know the <u>greatest number of injections</u> you have had into each ankle.

a) What is the <u>greatest number</u> of injections you had into each ankle in <u>any</u> **year?**

Right ankle ☐ injections Left ankle ☐ injections

b) What is the **total number** of injections you have into each ankle over the course of your life?

Right ankle ☐ injections Left ankle ☐ injections

26. Have you ever had injections anywhere else in your foot other than in your ankle(s)?

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☐ Yes ☐ No

If yes, please state where and how many? _____

27. Have you ever had surgery to your ankle or toe(s)?

☐ Yes ☐ No (*Please go to* **Question 29**)

28. If you have had any surgery (e.g. ankle joint replacement, fracture fixation, or key hole surgery), please state what type of procedure you had, which ankle or toe(s) was affected and your age when the surgery occurred.

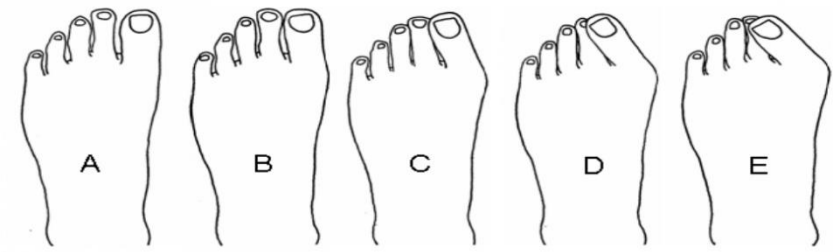
Type of surgery	Right side		Left side		Age
	Ankle	Toes	Ankle	Toes	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	

29. We are interested in whether you are flat-footed. This can relate to arthritis. Have you been told by a health professional (e.g. physiotherapist) that you have flat feet?

☐ Yes ☐ No

SECTION 5 – Your Toe Shape

We are interested in whether your big toes are straight or angled sideways. Angulation of the big toe "bunion" joint can relate to arthritis. First, please look at your left **big** toe whilst standing without shoes and socks on. Ignore the positioning and the gaps between your other toes and try to focus only on your big toe. Select from the first set of pictures below labelled from A to E which one best shows the angle of your left big toe. Please choose which picture you think best shows the angle of your toes **NOW** and when you were in **your 20s.**



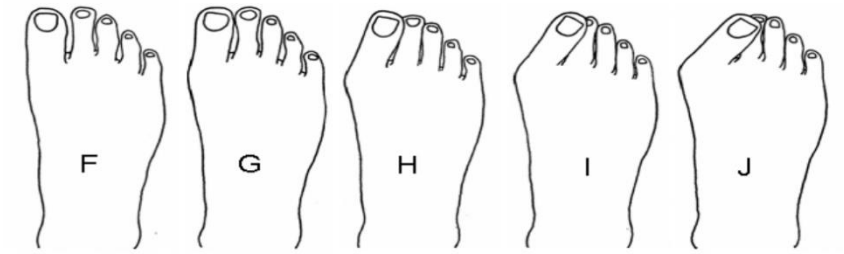
30. Which picture best shows the angle of your left big toe **currently?**

A ☐ **B** ☐ **C** ☐ **D** ☐ **E** ☐

31. Which picture best shows the angle of your left big toe **in your twenties?**

A ☐ **B** ☐ **C** ☐ **D** ☐ **E** ☐

Now, do the same for the right **big** toe joint using the set of pictures below labelled from F to J. Select from the first set of pictures below labelled from F to J which one best shows the angle of your right big toe. Please choose which picture you think best shows the angle of your toes **NOW** and when you were in your 20s.



32. Which picture best shows the angle of your right big toe **currently?**

F ☐ **G** ☐ **H** ☐ **I** ☐ **J** ☐

33. Which picture best shows the angle of your right big toe **in your twenties?**

F ☐ **G** ☐ **H** ☐ **I** ☐ **J** ☐

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SECTION 6 – The Way You Feel

34. The following questions are designed to help us know how you feel. Please read each item below and 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 as if I am slowed down
☐ nearly all the time
☐ very often
☐ sometimes
☐ not at all

b. I get a sort of frightened feeling like 'butterflies' in the stomach
☐ not at all
☐ occasionally
☐ quite often
☐ very often

c. 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

d. I feel restless as if I have to be on the move
☐ very much indeed
☐ quite a lot
☐ not very much
☐ not at all

e. 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

f. I get sudden feelings of panic
☐ very often indeed
☐ quite often
☐ not very often
☐ not at all

g. I can enjoy a good book or radio or television programme
☐ often
☐ sometimes
☐ not often
☐ very seldom

h. I feel tense or 'wound up'
☐ most of the time
☐ a lot of the time
☐ from time to time, occasionally
☐ not at all

i. I still enjoy the things I used to enjoy
☐ definitely as much
☐ not quite so much
☐ only a little
☐ hardly at all

j. 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

k. 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

l. Worrying thoughts go through my mind
☐ a great deal of the time
☐ a lot of the time
☐ not too often
☐ very little

m. I feel cheerful
☐ never
☐ not often
☐ sometimes
☐ most of the time

n. I can sit at ease and feel relaxed
☐ definitely
☐ usually
☐ not often
☐ not at all

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SECTION 7 – Your Quality of Life

The following questions are regarding your health-related quality of life. We are able to assess the impact that 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.***

35. In general, would you say your health currently is:

☐ *Excellent* ☐ *Very Good* ☐ *Good* ☐ *Fair* ☐ *Poor*

36. **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*
☐	☐	☐	☐	☐

37. 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 a lot	*Yes, Limited a little*	*Not, limited at all*
Walking **half a mile**	☐	☐	☐
Walking **100 yards** *(approximately 100 metres)*	☐	☐	☐
Bathing and dressing yourself	☐	☐	☐

38. 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)	☐	☐

39. During the **past month**, have you had any of the following problems with 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	☐	☐

40. 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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☐ ☐ ☐ ☐ ☐

41. How much **physical** pain have you had during the **past month**?

None	*Very Mild*	*Mild*	*Moderate*	*Severe*	*Very Severe*
☐	☐	☐	☐	☐	☐

42. 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*
☐	☐	☐	☐	☐

43. 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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44. 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*
☐	☐	☐	☐	☐

45. 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	☐	☐	☐	☐	☐

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SECTION 8 – Concussion and Head Injuries

Please read the definition of concussion to help you answer the following questions.

Definition of Concussion

A concussion can be caused by a direct or indirect blow to the head, face, or neck causing impact to the brain, followed by a variety of symptoms that may include any of the following:

Headache, dizziness, loss of balance, blurred vision, "seeing stars", feeling in a fog or slowed down, memory problems, poor concentration, and nausea or throwing up.

Getting "knocked out" or being unconscious does NOT always occur with concussion.

46. Have you ***ever*** been **diagnosed** with 'Concussion' by a Doctor/ Health Professional?

☐ Yes ☐ No **If yes**, how many times? ☐

If yes, how many times did the concussion(s) cause any of the following?

Loss of consciousness ☐ Loss of memory ☐ Hospitalisation ☐

47. Have you ***ever*** suffered a **serious** head injury/impact that needed medical care/hospitalisation?

☐ Yes ☐ No **If yes**, how many times? ☐

If yes, please briefly describe it including your diagnosis

.....

.....

.....

.....

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48. At any point during your life **e.g. from a fall, accident, fight, contact-sports play**, do you think you may have experienced any of the concussion symptoms (described in the definition box), whether or not you reported it or told medical staff?

☐ Yes ☐ No **If yes**, how many times did this occur? ☐

In general, please indicate how many times the concussion symptom(s) resulted in any of the following?

Loss of consciousness ☐ Memory Loss ☐ Another symptom ☐

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SECTION 9 – Your Memory and Thinking

49. Please indicate if you have problems with your memory and how these started?

- ☐ I have no problems
- ☐ Yes, the problems started slowly
- ☐ Yes, the problems started suddenly (e.g. after a stroke or fall or death of a loved one)

50. Please indicate if the memory problems have been getting worse?

☐ Yes ☐ No

51. Please indicate if these problems make it difficult for you to function socially or to work or function in your daily activities

☐ Yes ☐ No

52. The following is a short standard test called Test Your Memory (TYM). It is widely used to help assess functions of memory and thinking. Please complete the TYM questions on your own and in one go. Please do not look at the last page of the test until you have completed the first page.

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Test Your Memory

The TYM test

PLEASE WRITE YOUR FULL NAME……

TODAY IS ……..DAY

TODAY'S DATE IS THE: ……. OF ……..(MONTH) 20……

HOW OLD ARE YOU? ……..YEARS

ON WHAT DATE WERE YOU BORN? ……. / ……..(MONTH) 19……

PLEASE COPY THE FOLLOWING SENTENCE:

GOOD CITIZENS ALWAYS WEAR STOUT SHOES

……

PLEASE READ THE SENTENCE AGAIN AND TRY TO REMEMBER IT

WHO IS THE PRIME MINISTER? …… ……..

IN WHAT YEAR DID THE 1ST WORLD WAR START ……

Sums

20 – 4 = …….
16 + 17 = ……
8 x 6 =……
4 + 15 - 17 =……

PLEASE LIST FOUR CREATURES BEGINNING WITH "S" e.g. SHARK

1 S……
2 S……
3 S……
4 S……

WHY IS A CARROT LIKE A POTATO?……

WHY IS A LION LIKE A WOLF ? ……

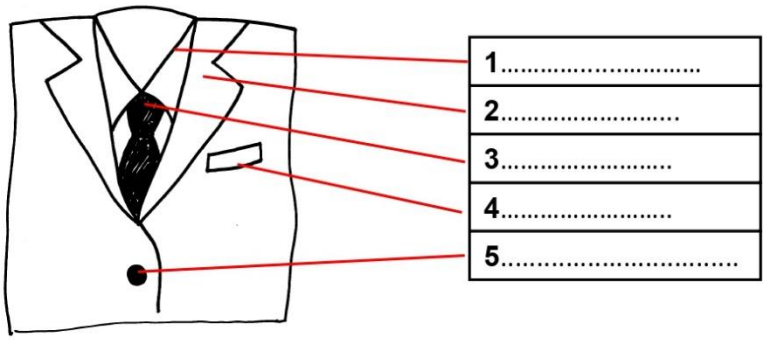
REMEMBER: GOOD CITIZENS ALWAYS WEAR STOUT SHOES

Please Turn Over

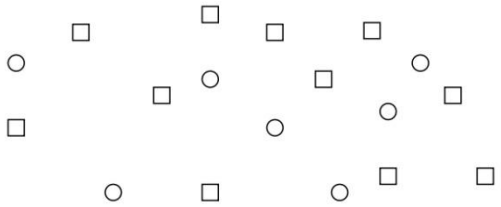
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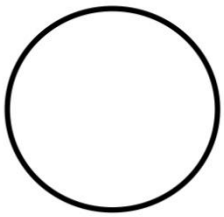
PLEASE NAME THESE ITEMS



PLEASE JOIN THE CIRCLES TOGETHER TO FORM A LETTER
- IGNORE THE SQUARES



PLEASE DRAW IN A CLOCK FACE, PUT IN THE NUMBERS 1 – 12 AND PLACE THE HANDS AT 9.20



WITHOUT TURNING BACK THE PAGE, PLEASE WRITE DOWN THE SENTENCE YOU COPIED EARLIER :

.....

©Jmbrown 2008

Thank you very much for taking the time to complete this questionnaire.

Please ensue 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).

Your data will be **anonymised** in all further analyses.

We would like to invite some questionnaire responders to participate in further stages of this study, irrespective of their question responses, which will involve the following:

In the next few weeks, a telephone call for a short assessment of your memory, thinking and concentration. This will last less than 30 minutes.

Please **tick** this box if you might be interested in this telephone assessment ☐

Much later in 2021, if it becomes feasible given the Covid-19 crisis and logistical issues, a single visit to a hospital in your region to have foot/ankle X-rays to look for changes of osteoarthritis.

Please **tick** this box if you might be interested in having foot/ankle x-rays ☐

More detailed information on these 2 assessments is provided in the Patient Information Sheet. If you have ticked any box above and are selected, we will re-contact you to discuss any questions you may have. You will then be able to decide whether you would like to participate.

Academic Rheumatology may also wish to contact you in the future regarding other studies related to your health.

Please tick this box if you are interested to hear of new studies ☐

Please complete your details below so that we will be able to contact you:

Full name: _____

Address: _____

Best Daytime Phone Number: _____

If you are happy for us to email you, please provide you email address below:

Email address: _____@_____

Thank you for your time

Office use only GMP | | | | |

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Appendix.2.7. Controls Participants Information Sheets

PIS Control IRAS ID: 261168

Foot/Ankle Osteoarthritis, Cognitive and Neurological Impairment in Former Professional UK Male Footballers versus the general population

Acronym: **FOCUS** (Foot Osteoarthritis & Concussion in UK Soccer)

PARTICIPANT INFORMATION SHEET

Chief Investigator: Weiya Zhang, Professor of Epidemiology

You are invited to take part in this research from the general population for comparison purpose. 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 FOCUS study?

Osteoarthritis and dementias (e.g. Alzheimer's) are a major cause of pain, physical and mental disability, and reduced quality of life for millions of sufferers. Professional footballers may be at higher risk of developing both these conditions because of injuries sustained during their careers. Our previous study showed that professional footballers are 2-3 times more likely to develop knee osteoarthritis (OA) compared to other men in the general population.

Foot/ankle injuries are very common amongst players and can lead to foot/ankle OA. Symptoms range from severe pain, impaired function, disturbed sleep, depression and a reduced quality of life. There is no cure - medical treatments may improve symptoms but many people eventually need joint surgery.

Final Version 1.1: 29.07.20

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw we will no longer collect any information about you or from you. However, we will keep the information about you that we have already obtained as we are not allowed to tamper with study records and this information may have already been used in some analyses and may still be used in the final study analyses. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Will I be paid for participation in this study?

Participation in this study is entirely voluntary. You will receive no payment for your participation in completing the Questionnaire and/or the Telephone Assessment. However, your travel costs to and from the NHS Trust Hospital will be reimbursed if this visit becomes feasible in 2021 and you decide to participate.

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 neurological impairment and foot/ankle osteoarthritis and help guide future management of these common health problems in footballers. Results of the study will be presented nationally and internationally and will also be published in international medical journals. Your anonymity will always be maintained, and no reference will ever be made to personal identifiers in any of our published results. Sections of the study results pertaining to foot/ankle osteoarthritis will be written up as a PhD thesis by one of our research students. Please let us know if you would like a copy of any of the publications and we shall be happy to provide it when it is available. We will also provide you with a summary of the results if you wish.

What happens when the research study stops?

When this study has finished your data will be statistically analysed along with data from others who have also participated, in order to determine the overall results of the research. We will compare the results from the footballer group with those from the general population male volunteers. All data will be anonymised and there will be no reference to personal identifiable details. The results will be published in peer reviewed medical journals and at your request you will be provided with any such publications.

Who is organising and funding the research?

This study is organised by staff in Academic Rheumatology, a department of the University of Nottingham based at the City Hospital. The study is being funded both by Versus Arthritis, an arthritis medical research charity, and the Football Association (FA), the UK governing body of association football.

Who has reviewed the study?

All research in healthcare is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by Leicester Central Research Ethics Committee.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations 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.

Where possible information about you which leaves the Department of Academic Rheumatology will have your name and address removed and a unique code will be used so that you cannot be recognised from it. However, sometimes we need to ensure that we can recognise you to link the research data with your medical records (for the foot x-rays) so in these instances we will need to know your name and date of birth. We will also need this information if we need to follow up your medical records as part of the research, where we may need to ask the Government services that hold medical information about you (such as NHS Digital, the Office for National Statistics, among others) to provide this information to us. By signing the consent form you agree to the above.

Your contact information will continue to be kept by the University of Nottingham after the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies as previously agreed (unless you advise us that you do not wish to be contacted). We will contact you regularly to confirm that you are happy for your details to be kept for this purpose but you can ask for them to be removed at any time by contacting the study team on the contact details given below. This information will be kept separately from the research data collected and only those who need to will have access to it. All other data (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, and only members of the research team who have been given permission by the data custodian will have access to your personal data.

In accordance with the policies of the University of Nottingham, the Government and our funders, we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is anonymised (so that you could not be identified).

Although what you say to us is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

The hospital taking your x-rays may need to create a health record, including the x-ray taken and your associated personal data, but this will be kept confidential in common with all medical records (only if this becomes feasible in 2021).

trial would give an exposure equivalent to less than one day of background radiation received by an average UK resident. At this dose level no harmful effects of radiation have been demonstrated and the risk is believed to be negligible.

What are the possible benefits of taking part?

By taking part in this research study, you will be helping us to understand if professional footballers are more likely (at risk) to develop foot/ankle osteoarthritis and problems with memory/thinking/organisation when compared with men in the general population of the same age. It will allow us to estimate the risks for footballers and eventually reduce these risks through appropriate screening, therapeutic and rehabilitation strategies. It may also have an impact on the way professional players currently train, practice and play football.

What if there is a problem?

If you have a concern about any aspect of this study, please speak to Ashley Duncan who will do her best to answer your questions (telephone number: 0115-823 1801). If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service in confidence at Nottingham City Hospital on 0115 969 1169 (extension 59671) or on pals@nuh.nhs.uk.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will any genetic tests be done?

No genetic testing will be done.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you during the course of the research. This information will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database at the University of Nottingham. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally identifiable information possible.

Do I have to take part?

No. You should only take part if you want to. It is entirely up to you whether or not to take part. If you do decide to take part in the survey then completion and return of the enclosed Questionnaire can be taken as consent.

If you decide to take part in the Telephone Assessment you will be asked to give verbal consent over the phone. In this pack is a copy of the consent form which will be read out to you by one of our colleagues when they call you. After you have given verbal consent this will be documented on the form and kept in the study files. If you request a copy we can email/post it to you.

If you decide to participate 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. This participant information sheet is for you to keep.

What will happen to me if I take part?

The first part of the study involves completing the enclosed paper Questionnaire and returning it to us in the pre-paid addressed envelope. You can complete the Questionnaire at home in your own time – it will take about 30-45 minutes.

Then, on the last page of the Questionnaire you will be able to tick a box to indicate if you would like to have a Telephone Assessment. If you have ticked it, you will be contacted by phone by an assessor who will arrange/conduct a series of questions over the phone with you which takes less than 30 minutes.

Much later, in 2021, ***if it becomes feasible*** to perform x-rays, you will be contacted again by the research team to find out if you are still interested in having x-rays. If you are, then an appointment will be made at the nearest NHS Hospital to see the study researchers. This appointment at the NHS Hospital will take around 1 hour.

When you arrive at the NHS Hospital, the researcher will first discuss any remaining questions you may have about the study and the consent procedure. If you are still willing to participate in the study, you will be asked to sign two copies of the consent form, one to be kept by you and one for the researcher to keep in the study records.

Following this, x-rays of both of your feet and ankles will be taken by NHS staff in the Radiology Department. Your x-rays will be taken in two positions, both times when you are fully weight-bearing and standing.

What are the possible disadvantages and risks of taking part?

In general, there are no risks or disadvantages in taking part in the Questionnaire survey or the Telephone Assessment.

If in 2021 it is feasible to conduct the x-rays and you decide to participate, then this would involve exposure to a small amount of x-radiation. As part of everyday living everyone is exposed to naturally occurring background radiation. The x-rays from this

Likewise, injuries/impacts to the head are common and may develop over time causing concussion or sub-concussive trauma to the brain. Symptoms can be subtle and range from headaches to loss of consciousness. However even subtle symptoms may over time contribute to problems with memory, attention and general mood. There is still much debate and controversy about the long-term effects of head impacts on the brains of footballers and research so far has been inconclusive.

This is the first comprehensive study investigating from 'Top to Toe' the effects of both head and feet injuries in footballers.

This study involves the following three components:

- a **Postal Questionnaire** contained in this pack. It has been sent to nearly one thousand footballers registered with the UK Professional Footballers Association (PFA) to determine the frequency of: (1) pain, symptoms, injuries and operations related to your feet/ankles; and (2) concussions, head injuries/impacts, memory, thinking, and general health.

- a **Telephone Assessment** involving some questions, which lasts under 30 minutes. This is to obtain more detailed information on your brain health and any neurological changes that may be present.

- Then later in 2021, only if it becomes feasible, we may contact you to invite you for **foot/ankle x-rays** to look for changes of osteoarthritis. Several NHS Trusts will be taking part in this assessment and you will be invited to the most convenient location to have this done.

The purpose of this study is to determine if footballers are more likely to develop foot/ankle osteoarthritis, and/or neurological diseases (e.g. Alzheimer's and Parkinson's). Also, if there are specific risks with playing professional football that contribute to developing these conditions. The results of these detailed tests from the footballers will then be compared to age-matched men from the general population for biomechanical, neurological, cognitive, physical, and pain profiles.

Part of this study is being conducted as an educational project for a PhD by Mr. Ahmed Thanoon.

Why have I been invited?
You have already kindly taken part in our previous study on knee osteoarthritis and general health in professional footballers versus the general population. During this you indicated that you would be willing to receive further information in the future about other upcoming studies which involved general health, which is why we are contacting you now. You should read this information sheet in detail before deciding whether you wish to take part or not. We aim to receive 540 responses to the Questionnaire and recruit 250 participants for the Telephone Assessment, irrespective of their responses to the postal questionnaire.

Further information and contact details

Study Contact:

Miss Ashley Duncan, PhD student, Academic Rheumatology,
Clinical Sciences Building, Nottingham City Hospital,
Nottingham, NG5 1PB.
Tel: 0115 8231801

Chief Investigator: Professor Weiya Zhang, Professor of Epidemiology, Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, Nottingham, NG5 1PB
Tel: 0115 8231750

Research Contacts: Mrs Helen Richardson, Operations Manager, Room B103
Clinical Sciences Building, Nottingham City Hospital,
Nottingham NG5 1PB
Tel: 0115 823 3172

Appendix 2.8. Controls Consent Form.

Consent Form Controls IRAS ID: 261168

GPM ID number: ☐☐☐☐







CONSENT FORM
(Final version 1.1: 29.07.20)

Title of Study: Foot/Ankle Osteoarthritis, Cognitive and Neurological Impairment in Former Professional Footballers versus the general population (FOCUS STUDY)

REC Project ID: 261168

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the participant information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any 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 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 and agree that participating in this study will involve a study researcher calling me to conduct a telephone assessment with me. ☐
5. This is OPTIONAL and ONLY if it becomes feasible in 2021.
   I understand and agree that I might be invited to attend an NHS Trust Hospital to have x-rays of my feet/ankles undertaken by a radiographer. **(Only if feasible in 2021)** ☐
6. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature

This will be verbally agreed by the participant and a copy of this completed consent form will be emailed/posted upon request.

_____	_____	_____
Name of Person taking consent	Date	Signature

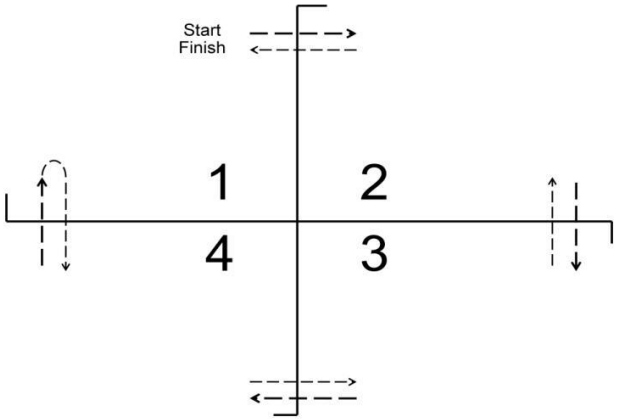
Appendix 2.9. Four-Step-Square-Test.

Four Step Square Test Instructions

General Information:

- The patient is instructed to stand in square 1 facing square number 2 (see figure below)
- The patient is required to step as fast as possible into each square in the following sequence: 2, 3, 4, 1, 4, 3, 2, and 1
  - requires the patient to step forward, backward, and sideway to the right and left
- Equipment required for the FSST includes a stopwatch and 4 canes.

Set-up (derived from Dite and Temple 2002): A square is formed with the 4 canes by resting them flat on the floor.



Patient Instructions (derived from Dite and Temple 2002):

- "Try to complete the sequence as fast as possible without touching the sticks. Both feet must make contact with the floor in each square. If possible, face forward during the entire sequence."
- Demonstrate the sequence to the patient.
- Ask the patient to complete one practice trial to ensure the patient knows the sequence. Repeat the trial if the patient is unsuccessful

Downloaded from www.rehabmeasures.org
Test instructions provided courtesy of Wayne Dite

at completing the sequence, loses balance, or contacts a cane during the trial.

- Two FSST are completed with the best time taken as the score.
- A score is still provided if the patient is unable to face forward during the entire sequence.

Scoring:

- the best time of two FSST is the score
- stopwatch starts when the first foot contacts the floor in square 2
- stopwatch finishes when the last foot comes back to touch the floor in square 1

Downloaded from www.rehabmeasures.org
Test instructions provided courtesy of Wayne Dite

Four Step Square Test (FSST)

Name:_____

Assistive Device and/or Bracing Used:_____

Date:_____

Trial 1_____sec.___ Trial 1_____sec.___

FSST Score (best timed trial):_____sec.___

Date:_____

Trial 1_____sec.___ Trial 1_____sec.___

FSST Score (best timed trial):_____sec.___

Date:_____

Trial 1_____sec.___ Trial 1_____sec.___

FSST Score (best timed trial):_____sec.___

Date:_____

Trial 1_____sec.___ Trial 1_____sec.___

FSST Score (best timed trial):_____sec.___

Downloaded from www.rehabmeasures.org
Test instructions provided courtesy of Wayne Dite

References:

Dite, W. and Temple, V. A. (2002). "A clinical test of stepping and change of direction to identify multiple falling older adults." Arch Phys Med Rehabil **83**(11): 1566-1571.

Downloaded from www.rehabmeasures.org
Test instructions provided courtesy of Wayne Dite

Appendix 2.10. 10 Meter Walk Test

Study ID: Date: Tester Initials:

10-meter walk test

A. Time For First Walk Test

Time for 10m: sec

If participant did not attempt test or failed, circle why:

Tried but unable	1
Participant could not walk unassisted	2
Not attempted, you felt unsafe	3
Not attempted, participant felt unsafe	4
Participant unable to understand instructions	5
Other (Specify)	6
Participant refused	7

Aids used:

Comments:

B. Time For Second Walk Test

Time for 10m: sec

If participant did not attempt test or failed, circle why:

Tried but unable	1
Participant could not walk unassisted	2
Not attempted, you felt unsafe	3
Not attempted, participant felt unsafe	4
Participant unable to understand instructions	5

Other (Specify)	6
Participant refused	7

Aids used:

Comments:

C. Time For Third Walk Test

Time for 10m: sec

If participant did not attempt test or failed, circle why:

Tried but unable	1
Participant could not walk unassisted	2
Not attempted, you felt unsafe	3
Not attempted, participant felt unsafe	4
Participant unable to understand instructions	5
Other (Specify)	6
Participant refused	7

Aids used:

Comments:

What is the time for the fastest of the three walks?

Record the shortest of the three times: sec

If only 1 walk done, record that time: sec

Average time of three walks sec

Average velocity m/s

Appendix 2.11. Protocol foot/ankle Radiographic Assessment

Standard Operating Procedure for Foot x-rays:

Part 2: Radiographic Positioning and Evaluation of the Foot and Ankle joints:

Part II will be conducted at each respective NHS Trust hospital (participating centres) (footballers) and at Academic Rheumatology (University of Nottingham) with only the x-rays being performed at Nottingham City Hospital (NUH Trust) for controls. Participants will be asked whether or not they have had x-rays in the previous 12 months outside of Academic Rheumatology.

Plain radiographs of both the foot and ankle will be obtained for all participants in accordance with the following well defined protocols by Menz et al (2007).

Positioning

The participant will be asked to stand in a relaxed position with the participant's body weight distributed equally. A relaxed position will be achieved by asking the participant to walk on the spot for a few steps and then stand relaxed.

Summary of purpose of x-rays

The x-rays are being taken to determine the presence of radiographic OA for this study and will be assessed for OA using the Australian Foot Atlas (A.F.A.). The anteroposterior and medial oblique views will enable more robust detail to be extracted relative to OA within all the individual foot joints.

NB: All X-rays are fully weight-bearing.

Procedure

1. Foot x-rays should coincide with the clinical assessments (i.e. same day) or as close as possible.
2. Participants to remove all footwear and hosiery items.
3. Participants should be standing comfortably with both feet flat and touching the floor.
4. Once the participant is correctly positioned digital x-rays of both feet to be undertaken.
5. Dorso-plantar (DP) view x-rays of both feet and Antero-posterior views of both ankle joints. Medial oblique and Lateral view x-rays carried out for feet individually; x-rays to be taken fully weight-bearing (see notes for specific detailing) according to recommended procedure (*Roddy et al 2011*). Total of 7 x-ray images per patient.

General notes regarding patient positioning

Ensure ground contact exists between the three key points of the foot in a tripod formation and also with the toes (where possible).



Finally, ensure the feet (heel to toe) and knees are a parallel distance apart (approximately 2 inches apart).



Appendix 4 Foot X-rays SOP and Scoring

1) Fully weight-bearing Dorso-plantar (DP) views of both feet

Position of patient and image receptor

- Patient is standing with both feet on image receptor.
- Image receptor should be lowered in accordance with the height and tilted appropriately in order to achieve aforementioned anatomical angles.

Direction and centring of x-ray beam

- Central ray is directed over the cuboid-navicular tuberosity, midway between the navicular tuberosities of both feet.
- X-ray tube is angled 15° cranially when the image receptor is flat on the table.

Essential image characteristics

- Tarsal and metatarsal joints should be demonstrated when the whole foot is examined.
- The kVp selected should reduce the difference in subject contrast between the thickness of the toes and the tarsus to give a uniform radiographic contrast over the range of foot densities.

Additional Considerations

- A wedge filter can be used to compensate for the difference in tissue thickness.





2) Weight-bearing Medial oblique views of both feet (Standing oblique)

Position of patient and image receptor

- From the basic dorsoplantar view, tilt the limb of interest medially on image receptor to achieve an angle of 30-45 ° (each foot x-rayed individually).
- A non-opaque angled pad is placed beneath the foot to maintain the position whilst using the contra-lateral limb supporting the limb of interest if the participants standing. To be carried out with patient standing and as much as possible to evenly distribute pressure between both limbs.

Direction and centring of x-ray beam

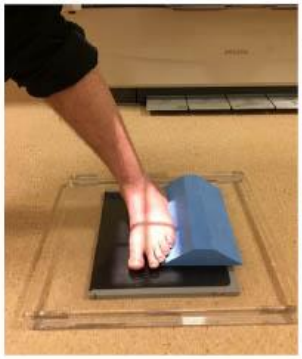
- The vertical central ray is directed over the cuboid-navicular joint.

Essential image characteristics

- Medial oblique should demonstrate the inter-tarsal and tarsometatarsal joints.
- The projection should allow the alignment of the metatarsals with the distal row of the tarsus to be assessed.
- The base of the fifth metatarsal should be clearly seen.

Additional considerations

- None of significance.





3) Fully Weight-bearing Lateral views of both feet

Position of patient and image receptor

- Patient stands on a low platform with the image receptor to the lateral aspect of the foot
- To maintain this position, a vertical support should be provided for participant to rest their forearms, with foot stool placed behind for the contralateral foot to rest on.
- Each foot is x-rayed separately.

Direction and centring of x-ray beam

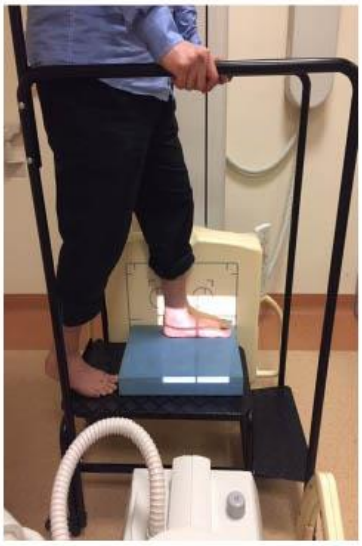
- The horizontal central ray is directed towards the tubercle of the first metatarsal.

Essential image characteristics

- The image should include the distal phalanges and calcaneum.
- The ankle joint and soft tissue margins of the plantar aspect of the foot should be included.
- The longitudinal arches of the feet should be clearly demonstrated.

Additional considerations

- Images should be labelled as 'standing' or 'weight-bearing'.



4) Fully Weight-bearing antero-posterior views of both ankle joints

Position of patient and image receptor

- Patient standing on raised platform to the required height of the receptor distributing weight equally between both limbs.
- The ankle should be at a 90° dorsiflexed angle.
- The assessed limb is rotated medially (approx. 20°) until the medial and lateral malleoli are equidistant from the image receptor.
- Each ankle joint should be assessed separately
- The lower edge of the image receptor is positioned just below the plantar aspect of the heel.

Direction and centering of x-ray beam

- Centre midway between the medial and lateral malleoli with the vertical central ray at 90° to an imaginary line joining the malleoli.

Essential image criteria

- Lower third of the tibia and fibula should be included.
- A clear joint space between the tibia, fibula and talus should be demonstrated (mortice view).

Additional considerations

- Insufficient dorsiflexion = calcaneum superimposed on lateral malleolus
- Insufficient internal rotation = overlapping of the tibiofibular joint.



Scope

This Standard Operating procedure (SOP) applies to all individuals involved in the acquisition or interpretation of x-ray imaging, recorded as part of the Nottingham Footballer study FOCUS project.

Scoring of Radiographs

Plain radiographs will be scored by a single reader, (PhD student) who will be blinded to all other information regarding the participant. The two validated grading systems used to score the x-rays will be the Menz (2007)

Foot

Menz et al's (2007) radiographic atlas of five foot joints was published online in 2007 for scoring osteophytes and joint space narrowing of the first metatarsophalangeal joint (MTPJ), the first cuneo-metatarsal joint (CMJ), the second cuneo-metatarsal, the navicular-first cuneiform joint (NCJ) and the talonavicular joint (TNJ).

(i) Osteophytes and joint space narrowing at the 1st MTPJ, 1st and 2nd CMJs, NCJ and TNJ will be scored (0-3) according to the validated atlas by Menz et al (2007). The presence of osteophytes is graded as absent (score=0), small (score=1), moderate(score=2), severe (score=3). The presence of joint space narrowing is graded as none (score=0), definite (score=1), severe (score=2), or joint fusion at least one point (score=3). Radiographic OA at each individual joint is defined as a score of 2 or more for both osteophytes or joint space narrowing on either AP or lateral views.

Both AP/DP and lateral views will be used to assess osteophyte and joint space width except for the TNJ. For the TNJ only the lateral view will be used as the dorsal aspect of the joint, where osteophytes most commonly develop, is not easily seen on the AP/DP view.

Ankle

Ankle OA will be assessed by radiographic grading of the articulation between the talus, tibia, and fibula.

(i) The presence of osteophytes and joint space narrowing will be graded on a (0-3) scale in both views. This standardised atlas was developed as an extension of one recently developed for the foot, due to the lack of an appropriate scoring system for assessing individual radiographic features in ankle OA (Roddy 2018). The presence of osteophytes at the ankle joint will be graded as: absent (score=0), small (score=1), moderate (score=2), and severe (score=3). The presence of joint space narrowing will be graded as none (score=0), definite (score=1), severe (score=2) and joint fusion at one point or more (score=3). Radiographic ankle OA will be defined as a grade more than or equal to 2 for either osteophyte or joint space narrowing on either view.

References

1. Menz HB, Munteanu SE, Landorf KB, Zammit GV, Cicuttini FM: Radiographic classification of osteoarthritis in commonly affected joints of the foot. Osteoarthritis Cartilage 2007, 15:1333-1338.

2. Whitley AS, Sloanne C, Hoardley G, Moore AD, Alsop CW: Clark's positioning in radiography London: Holder Arnold; 2005.

4. Kraus VB, Kilfoil TM, Hash TW, McDaniel G, Renner JB, Carrino JA. Atlas of radiographic features of osteoarthritis of the ankle and hindfoot. Osteoarthritis Cartilage. 2015; 23(12): 2059–2085.

Appendix.2.11. Radiographic La Trobe Foot Atlas

Radiographic classification of osteoarthritis in commonly affected joints of the foot

Supplementary data: atlas of radiographic images

S1. Scoring system
S2. First metatarso-phalangeal joint (dorsal): osteophytes
S3. First metatarso-phalangeal joint (lateral): osteophytes
S4. First metatarso-phalangeal joint (dorsal): joint space narrowing
S5. First metatarso-phalangeal joint (lateral): joint space narrowing
S6. First cuneo-metatarsal joint (dorsal): osteophytes
S7. First cuneo-metatarsal joint (lateral): osteophytes
S8. First cuneo-metatarsal joint (dorsal): joint space narrowing
S9. First cuneo-metatarsal joint (lateral): joint space narrowing
S10. Second cuneo-metatarsal joint (dorsal): osteophytes
S11. Second cuneo-metatarsal joint (lateral): osteophytes
S12. Second cuneo-metatarsal joint (dorsal): joint space narrowing
S13. Second cuneo-metatarsal joint (lateral): joint space narrowing
S14. Navicular-first cuneiform joint (dorsal): osteophytes
S15. Navicular-first cuneiform joint (lateral): osteophytes
S14. Navicular-first cuneiform joint (dorsal): joint space narrowing
S15. Navicular-first cuneiform joint (lateral): joint space narrowing
S16. Talo-navicular joint (lateral): osteophytes
S17. Talo-navicular joint (dorsal): joint space narrowing
S18. Talo-navicular joint (lateral): joint space narrowing

Scoring system

Osteophytes

0	absent
1	small
2	moderate
3	severe

Joint space narrowing

0	none
1	definite
2	severe
3	joint fusion at at least one point

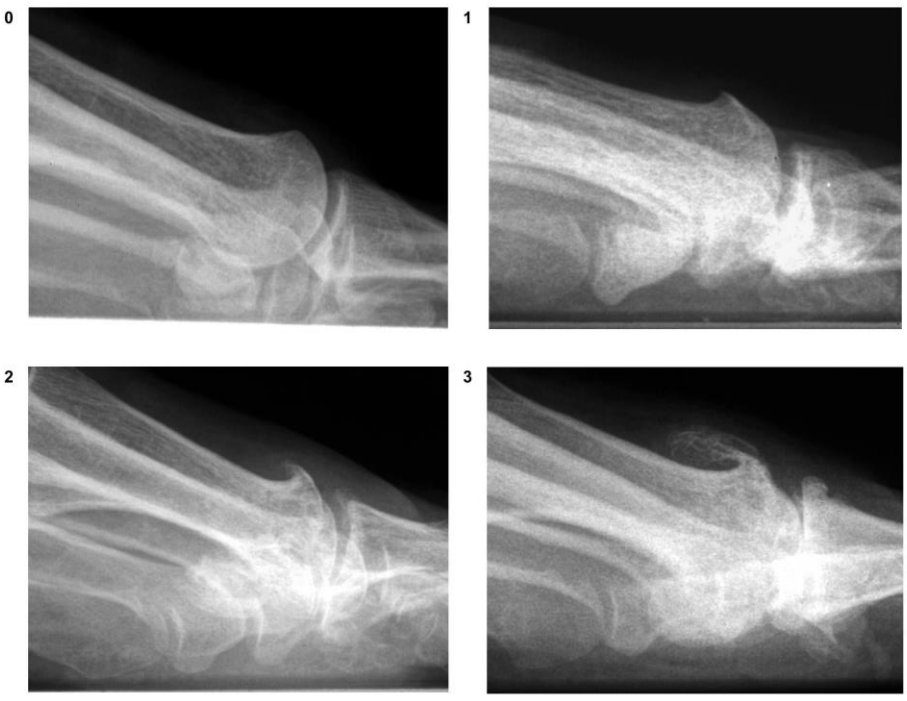
Case definition of foot osteoarthritis in individual joints

> Radiographic OA can be considered to be present if a score of 2 or above is documented for *either* osteophytes or joint space narrowing, from *either* the dorso-plantar or lateral view



First metatarso-phalangeal joint (dorsal): osteophytes

2



First metatarso-phalangeal joint (lateral): osteophytes

3



First metatarso-phalangeal joint (dorsal): joint space narrowing

4



First metatarso-phalangeal joint (lateral): joint space narrowing



First cuneo-metatarsal joint (dorsal): osteophytes

6



First cuneo-metatarsal joint (lateral): osteophytes

7



First cuneo-metatarsal joint (dorsal): joint space narrowing

8



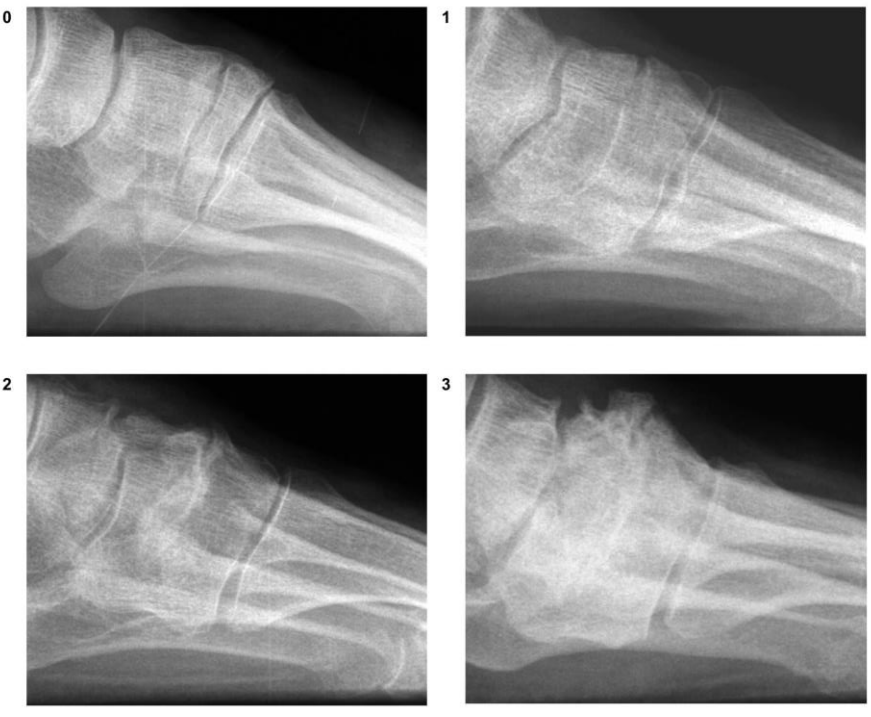
First cuneo-metatarsal joint (lateral): joint space narrowing

9



Second cuneo-metatarsal joint (dorsal): osteophytes

10



Second cuneo-metatarsal joint (lateral): osteophytes

11



Second cuneo-metatarsal joint (dorsal): joint space narrowing

12



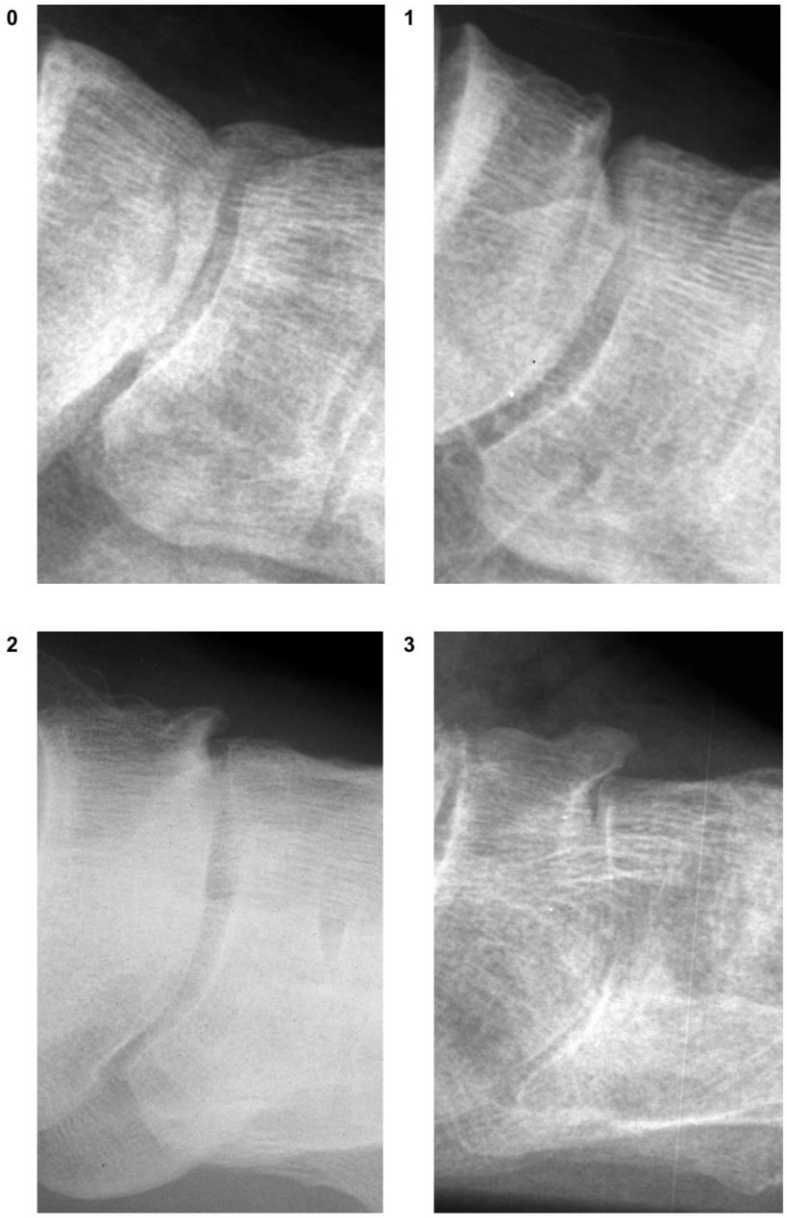
Second cuneo-metatarsal joint (lateral): joint space narrowing

13



Navicular-first cuneiform joint (dorsal): osteophytes

14



Navicular-first cuneiform joint (lateral): osteophytes

15



Navicular-first cuneiform joint (dorsal): joint space narrowing

16

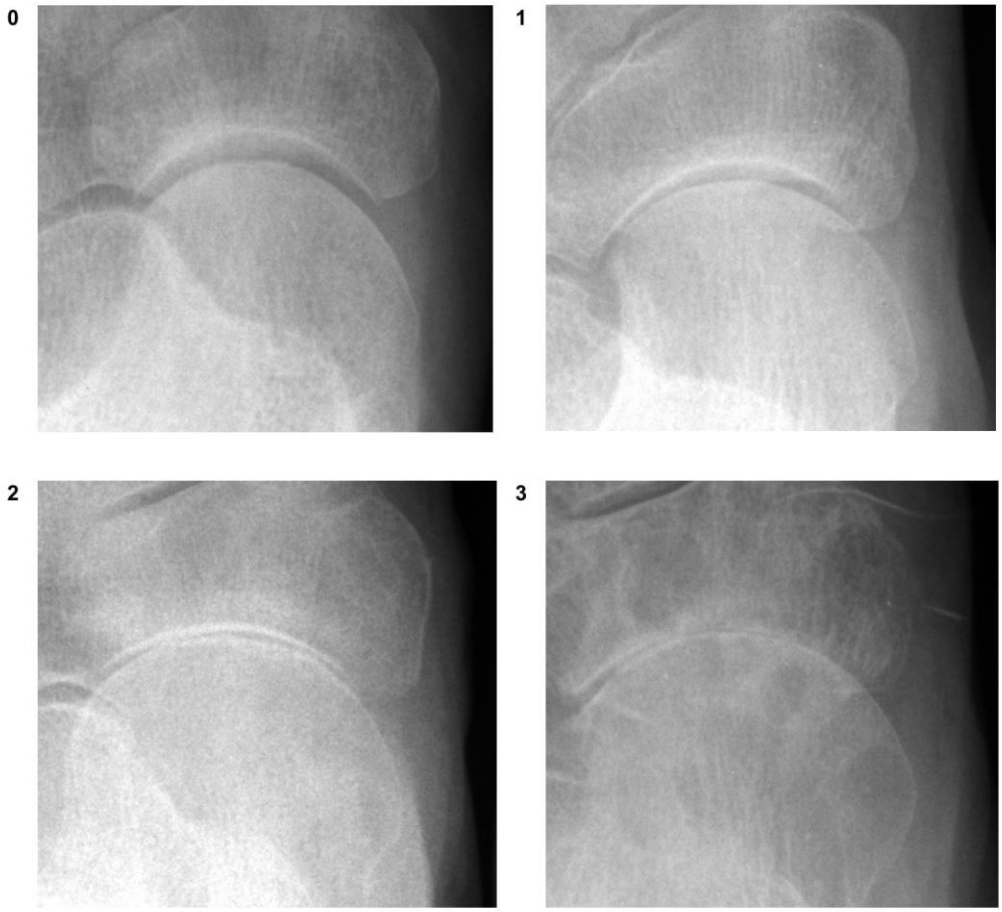


Navicular-first cuneiform joint (lateral): joint space narrowing 17



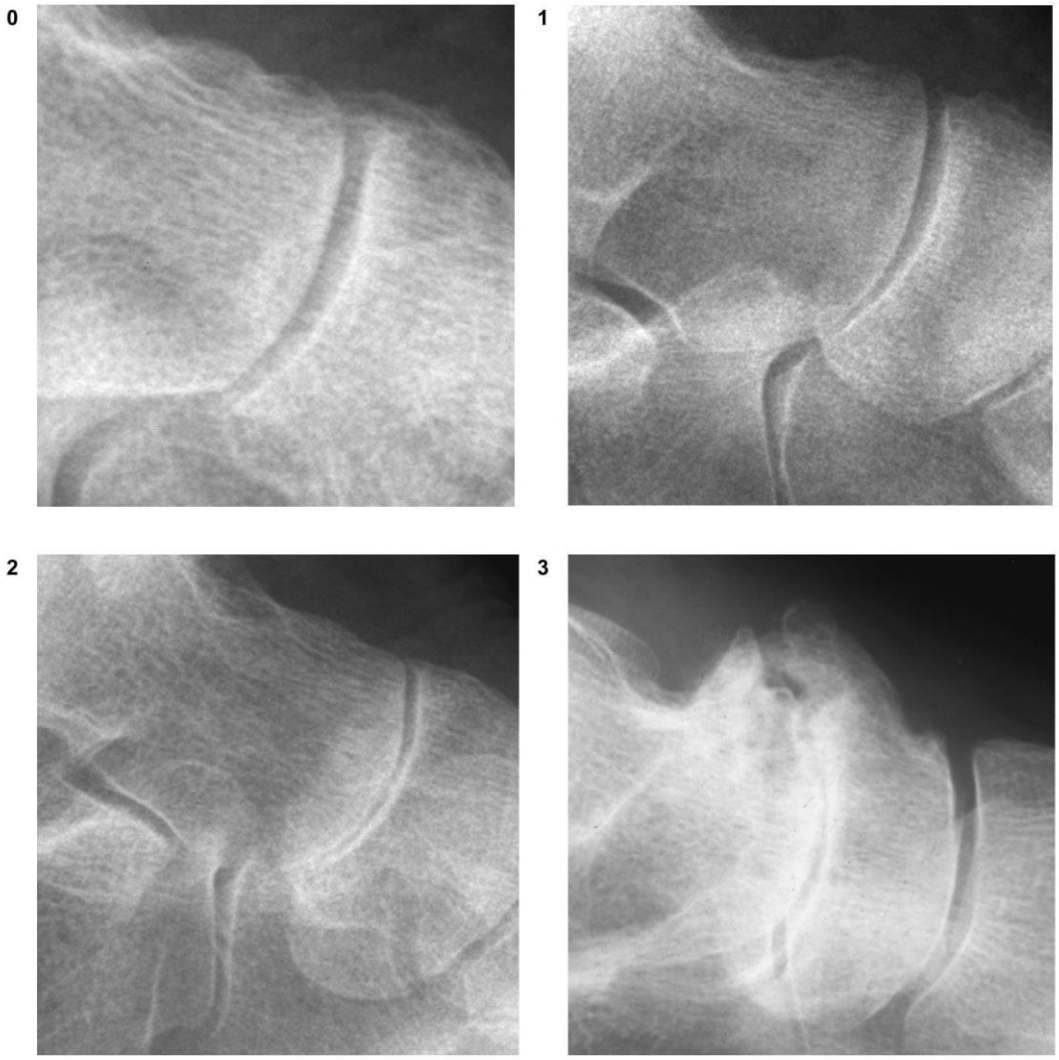
Talo-navicular joint (lateral): osteophytes

18



Talo-navicular joint (dorsal): joint space narrowing

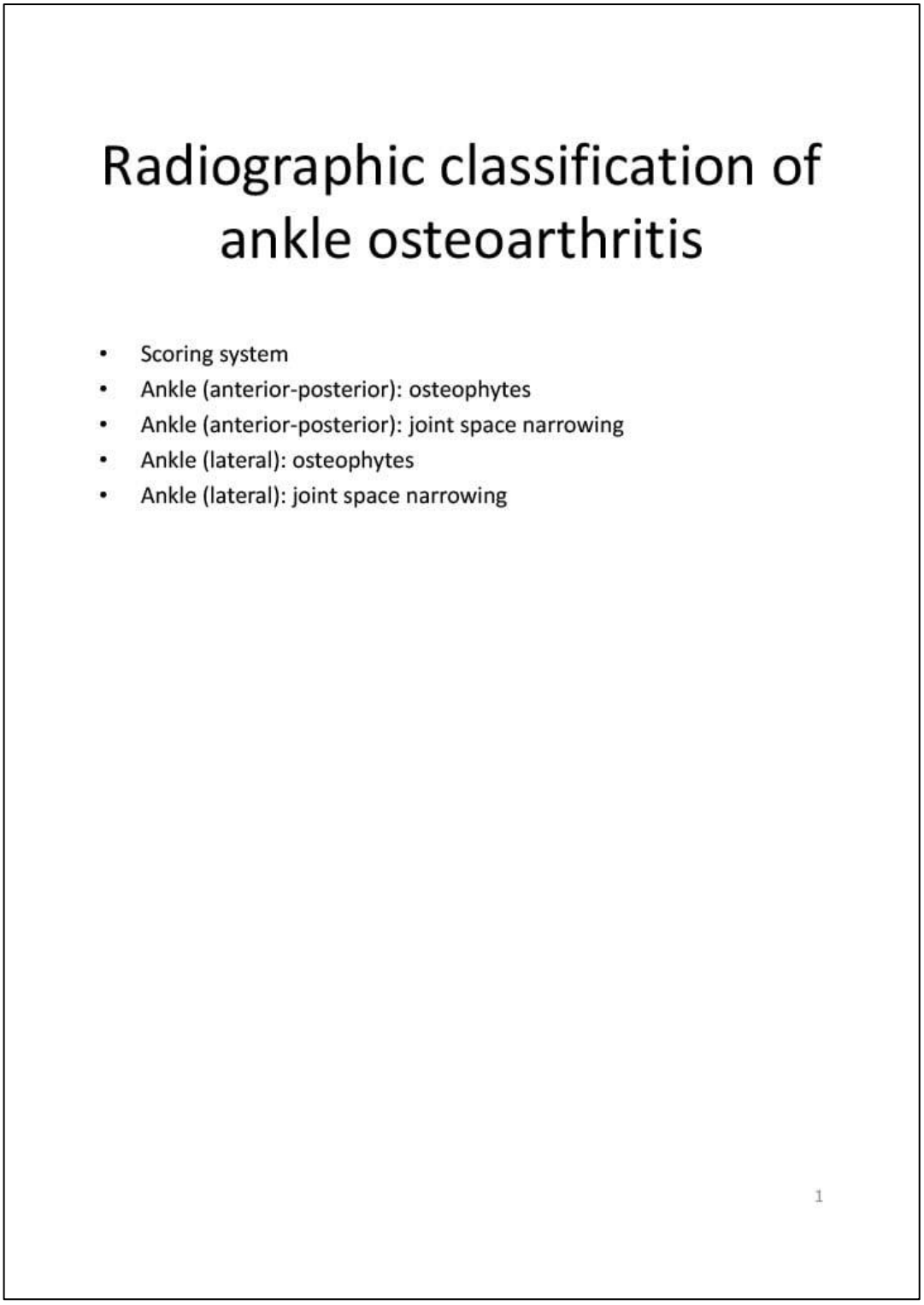
19



Talo-navicular joint (lateral): joint space narrowing

20

Appendix.2.12. The Ankle-OA-Scoring-System



Scoring system

Osteophytes

- 0 - absent
- 1 - small
- 2 - moderate
- 3 - severe

Joint space narrowing

- 0 - none
- 1 - definite
- 2 - severe
- 3 - joint fusion at least one point

Case definition of ankle osteoarthritis in individual joints

- Radiographic OA can be considered to be present if a score of 2 or above is documented for either osteophytes or joint space narrowing, from either the anterior-posterior or lateral view

2

Anterior-posterior view - osteophytes



0 1



2 3

3

Anterior-posterior view – joint space narrowing

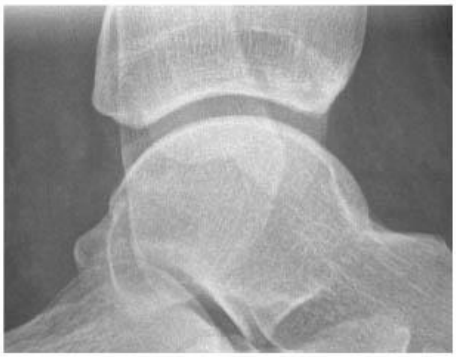


0 1

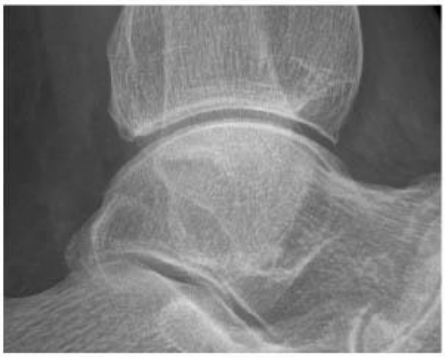
2 3

4

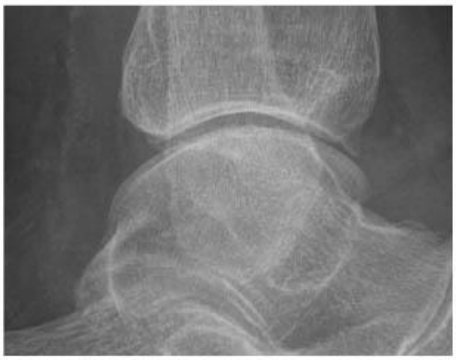
Lateral view - osteophytes



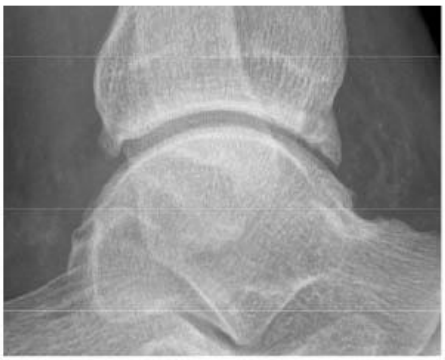
0



1



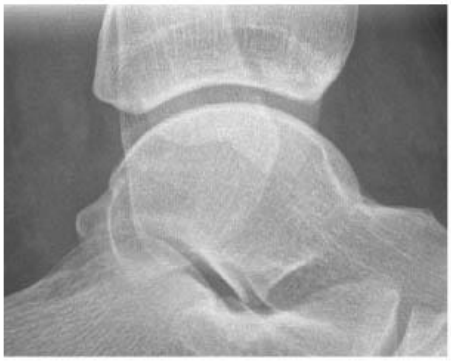
2



3

5

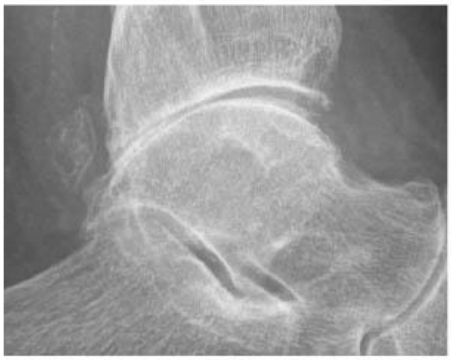
Lateral view – joint space narrowing



0



1



2



3

6

Appendix 2.13. Coding Radiographic Foot/Ankle OA

Foot rOA

Original Variable	Original Codes	New Variable After Recoding	Recoded Values	Foot OA
L_DP_1stMTPJ_OP	0, 1	L_DP_1stMTPJ_OP_r	0	No OA
	2, 3		1	Present OA
L_DP_1stMTPJ_JSN	0, 1	L_DP_1stMTPJ_JSN_r	0	No OA
	2, 3		1	Present OA
L_DP_1stCMJ_OP	0, 1	L_DP_1stCMJ_OP_r	0	No OA
	2, 3		1	Present OA
L_DP_1stCMJ_JSN	0, 1	L_DP_1stCMJ_JSN_r	0	No OA
	2, 3		1	Present OA
L_DP_2ndCMJ_OP	0, 1	L_DP_2ndCMJ_OP_r	0	No OA
	2, 3		1	Present OA
L_DP_2ndCMJ_JSN	0, 1	L_DP_2ndCMJ_JSN_r	0	No OA
	2, 3		1	Present OA
L_DP_N1stCJ_OP	0, 1	L_DP_N1stCJ_OP_r	0	No OA
	2, 3		1	Present OA
L_DP_N1stCJ_JSN	0, 1	L_DP_N1stCJ_JSN_r	0	No OA
	2, 3		1	Present OA
L_DP_TNJ_JSN	0, 1	L_DP_TNJ_JSN_r	0	No OA
	2, 3		1	Present OA
R_DP_1stMTPJ_OP	0, 1	R_DP_1stMTPJ_OP_r	0	No OA
	2, 3		1	Present OA
R_DP_1stMTPJ_JSN	0, 1	R_DP_1stMTPJ_JSN_r	0	No OA
	2, 3		1	Present OA
R_DP_1stCMJ_OP	0, 1	R_DP_1stCMJ_OP_r	0	No OA
	2, 3		1	Present OA
R_DP_1stCMJ_JSN	0, 1	R_DP_1stCMJ_JSN_r	0	No OA
	2, 3		1	Present OA
R_DP_2ndCMJ_OP	0, 1	R_DP_2ndCMJ_OP_r	0	No OA
	2, 3		1	Present OA
R_DP_2ndCMJ_JSN	0, 1	R_DP_2ndCMJ_JSN_r	0	No OA
	2, 3		1	Present OA
R_DP_N1stCJ_OP	0, 1	R_DP_N1stCJ_OP_r	0	No OA
	2, 3		1	Present OA
R_DP_N1stCJ_JSN	0, 1	R_DP_N1stCJ_JSN_r	0	No OA
	2, 3		1	Present OA
R_DP_TNJ_JSN	0, 1	R_DP_TNJ_JSN_r	0	No OA
	2, 3		1	Present OA
L_LAT_1stMTPJ_OP	0, 1	L_LAT_1stMTPJ_OP_r	0	No OA
	2, 3		1	Present OA
L_LAT_1stMTPJ_JSN	0, 1	L_LAT_1stMTPJ_JSN_r	0	No OA
	2, 3		1	Present OA
L_LAT_1stCMJ_OP	0, 1	L_LAT_1stCMJ_OP_r	0	No OA
	2, 3		1	Present OA
L_LAT_1stCMJ_JSN	0, 1	L_LAT_1stCMJ_JSN_r	0	No OA
	2, 3		1	Present OA
L_LAT_2ndCMJ_OP	0, 1	L_LAT_2ndCMJ_OP_r	0	No OA
	2, 3		1	Present OA
L_LAT_2ndCMJ_JSN	0, 1	L_LAT_2ndCMJ_JSN_r	0	No OA
	2, 3		1	Present OA
L_LAT_N1stCJ_OP	0, 1	L_LAT_N1stCJ_OP_r	0	No OA
	2, 3		1	Present OA
L_LAT_N1stCJ_JSN	0, 1	L_LAT_N1stCJ_JSN_r	0	No OA
	2, 3		1	Present OA
L_LAT_TNJ_OP	0, 1	L_LAT_TNJ_OP_r	0	No OA
	2, 3		1	Present OA
L_LAT_TNJ_JSN	0, 1	L_LAT_TNJ_JSN_r	0	No OA
	2, 3		1	Present OA
R_LAT_1stMTPJ_OP	0, 1	R_LAT_1stMTPJ_OP_r	0	No OA
	2, 3		1	Present OA
R_LAT_1stMTPJ_JSN	0, 1	R_LAT_1stMTPJ_JSN_r	0	No OA
	2, 3		1	Present OA

Ankle rOA

Original Variable	Original Codes	New Variable After Recoding	Recoded Values	Ankle OA
L_AnkleAP_OP	0, 1	L_Ankle_LAT_OP_01	0	No OA
	2, 3		1	Present OA
L_AnkleAP_JSN	0, 1	L_Ankle_LAT_JSN_01	0	No OA
	2, 3		1	Present OA
R_AnkleAP_OP	0, 1	R_Ankle_LAT_OP_01	0	No OA
	2, 3		1	Present OA
R_AnkleAP_JSN	0, 1	R_Ankle_LAT_JSN_01	0	No OA
	2, 3		1	Present OA
L_Ankle_LAT_OP	0, 1	L_AnkleAP_OP_01	0	No OA
	2, 3		1	Present OA
L_Ankle_LAT_JSN	0, 1	L_AnkleAP_JSN_01	0	No OA
	2, 3		1	Present OA
R_Ankle_LAT_OP	0, 1	R_AnkleAP_OP_01	0	No OA
	2, 3		1	Present OA
R_Ankle_LAT_JSN	0, 1	R_AnkleAP_JSN_01	0	No OA
	2, 3		1	Present OA

Please note that :We used the Transform in SPSS - Recode into Different Variables method, which assigns values to different ranges. In our case, we assigned the range (0,1) to 0, indicating no OA, and 2,3 to 1, indicating present OA. Additionally, the click generates new variables that include the view and name of joints, with 0 being assigned to No OA and 1 being assigned to Yes OA.

Appendix.2.14. Defined-Radiographic-OA-in-Five-Foot-Joints

1stMTPJ Joint:			Prevalence of 1st MTPJ_rOA_01 (Forefoot)
New Variable After Recoding	**Recoded Values**	**Foot OA**	**Cases** IF (L_DP_1stMTPJ_OP_r = 1 OR L_DP_1stMTPJ_JSN_r = 1 OR R_DP_1stMTPJ_OP_r = 1 OR R_DP_1stMTPJ_JSN_r = 1 OR L_LAT_1stMTPJ_OP_r = 1 OR L_LAT_1stMTPJ_JSN_r = 1 OR R_LAT_1stMTPJ_OP_r = 1 OR R_LAT_1stMTPJ_JSN_r = 1). This creates a variable called First_MTPJ_rOA_01 that is coded 1 if OA evidence is present in any of them. I Will code the same variable "0" to get Controls (with no OA) as you can see below in the formal: **Controls** IF(L_DP_1stMTPJ_OP_r = 0 AND L_DP_1stMTPJ_JSN_r = 0 AND R_DP_1stMTPJ_OP_r = 0 AND R_DP_1stMTPJ_JSN_r = 0 AND L_LAT_1stMTPJ_OP_r = 0 AND L_LAT_1stMTPJ_JSN_r = 0 AND R_LAT_1stMTPJ_OP_r = 0 AND R_LAT_1stMTPJ_JSN_r = 0).
L_DP_1stMTPJ_OP_r	0	No OA	
	1	Present OA	
L_DP_1stMTPJ_JSN_r	0	No OA	
	1	Present OA	
R_DP_1stMTPJ_OP_r	0	No OA	
	1	Present OA	
R_DP_1stMTPJ_JSN_r	0	No OA	
	1	Present OA	
L_LAT_1stMTPJ_OP_r	0	No OA	
	1	Present OA	
L_LAT_1stMTPJ_JSN_r	0	No OA	
	1	Present OA	
R_LAT_1stMTPJ_OP_r	0	No OA	
	1	Present OA	
R_LAT_1stMTPJ_JSN_r	0	No OA	
	1	Present OA	
1stCMJ Joint:			**Prevalence of 1st CMJ_rOA_01**
New Variable After Recoding	**Recoded Values**	**Foot OA**	**Cases** IF (L_DP_1stCMJ_OP_r = 1 OR L_DP_1stCMJ_JSN_r = 1 OR R_DP_1stCMJ_OP_r = 1 OR R_DP_1stCMJ_JSN_r = 1 OR L_LAT_1stCMJ_OP_r = 1 OR L_LAT_1stCMJ_JSN_r = 1 OR R_LAT_1stCMJ_OP_r = 1 OR R_LAT_1stCMJ_JSN_r = 1) This creates a variable called 1stCMJ_OA that is coded 1 if OA evidence present in any of them. I Will code the same variable "0" to get Controls (with no OA) as you can see below in the formal: **Controls** IF(L_DP_1stCMJ_OP_r = 0 AND L_DP_1stCMJ_JSN_r = 0 AND R_DP_1stCMJ_OP_r = 0 AND R_DP_1stCMJ_JSN_r = 0 AND L_LAT_1stCMJ_OP_r = 0 AND L_LAT_1stCMJ_JSN_r = 0 AND R_LAT_1stCMJ_OP_r = 0 AND R_LAT_1stCMJ_JSN_r = 0).
L_DP_1stCMJ_OP_r	0	No OA	
	1	Present OA	
L_DP_1stCMJ_JSN_r	0	No OA	
	1	Present OA	
R_DP_1stCMJ_OP_r	0	No OA	
	1	Present OA	
R_DP_1stCMJ_JSN_r	0	No OA	
	1	Present OA	
L_LAT_1stCMJ_OP_r	0	No OA	
	1	Present OA	
L_LAT_1stCMJ_JSN_r	0	No OA	
	1	Present OA	
R_LAT_1stCMJ_OP_r	0	No OA	
	1	Present OA	
R_LAT_1stCMJ_JSN_r	0	No OA	
	1	Present OA	
2ndCMJ Joint:			**Prevalence of 2st CMJ_rOA_01**
New Variable After Recoding	Recoded Values	Foot OA	**Cases** IF (L_DP_2ndCMJ_OP_r = 1 OR L_DP_2ndCMJ_JSN_r = 1 OR R_DP_2ndCMJ_OP_r = 1 OR R_DP_2ndCMJ_JSN_r = 1 OR L_LAT_2ndCMJ_OP_r = 1 OR L_LAT_2ndCMJ_JSN_r = 1 OR R_LAT_2ndCMJ_OP_r = 1 OR R_LAT_2ndCMJ_JSN_r = 1) This creates a variable called 2stCMJ_OA that is coded 1 if OA evidence is present in any of them. I Will code the same variable "0" to get Controls (with no OA), as you can see below in the formal: **Controls** IF (L_DP_2ndCMJ_OP_r = 0 AND L_DP_2ndCMJ_JSN_r = 0 AND R_DP_2ndCMJ_OP_r = 0 AND R_DP_2ndCMJ_JSN_r = 0 AND L_LAT_2ndCMJ_OP_r = 0 AND L_LAT_2ndCMJ_JSN_r = 0 AND R_LAT_2ndCMJ_OP_r = 0
L_DP_2ndCMJ_OP_r	0	No OA	
	1	Present OA	
L_DP_2ndCMJ_JSN_r	0	No OA	
	1	Present OA	
R_DP_2ndCMJ_OP_r	0	No OA	
	1	Present OA	
R_DP_2ndCMJ_JSN_r	0	No OA	
	1	Present OA	
L_LAT_2ndCMJ_OP_r	0	No OA	
	1	Present OA	
L_LAT_2ndCMJ_JSN_r	0	No OA	
	1	Present OA	
R_LAT_2ndCMJ_OP_r	0	No OA	
	1	Present OA	
R_LAT_2ndCMJ_JSN_r	0	No OA	
	1	Present OA	
N1stCJ Joint:			**Prevalence of N1stCJ_rOA_01**
New Variable After Recoding	Recoded Values	Foot OA	**Cases** IF (L_DP_N1stCJ_OP_r = 1 OR L_DP_N1stCJ_JSN_r = 1 OR R_DP_N1stCJ_OP_r = 1 OR R_DP_N1stCJ_JSN_r = 1 OR L_LAT_N1stCJ_OP_r = 1 OR L_LAT_N1stCJ_JSN_r = 1 OR R_LAT_N1stCJ_OP_r = 1 OR R_LAT_N1stCJ_JSN_r = 1). This creates a variable called N1stCJ_rOA_01 that is coded 1 if OA evidence is present in any of them. I Will code the same variable "0" to get Controls (with no OA), as you can see below in the formal: **Controls** IF (L_DP_N1stCJ_OP_r = 0 AND L_DP_N1stCJ_JSN_r = 0 AND R_DP_N1stCJ_OP_r = 0 AND R_DP_N1stCJ_JSN_r = 0 AND L_LAT_N1stCJ_OP_r = 0 AND L_LAT_N1stCJ_JSN_r = 0 AND R_LAT_N1stCJ_OP_r = 0 AND R_LAT_N1stCJ_JSN_r = 0).
L_DP_N1stCJ_OP_r	0	No OA	
	1	Present OA	
L_DP_N1stCJ_JSN_r	0	No OA	
	1	Present OA	
R_DP_N1stCJ_OP_r	0	No OA	
	1	Present OA	
R_DP_N1stCJ_JSN_r	0	No OA	
	1	Present OA	
L_LAT_N1stCJ_OP_r	0	No OA	
	1	Present OA	
L_LAT_N1stCJ_JSN_r	0	No OA	
	1	Present OA	
R_LAT_N1stCJ_OP_r	0	No OA	
	1	Present OA	
R_LAT_N1stCJ_JSN_r	0	No OA	
	1	Present OA	
TNJ Joint:			**Prevalence of TNJ_rOA_01**
New Variable After Recoding	Recoded Values	Foot OA	**Cases** IF (L_DP_TNJ_JSN_r = 1 OR R_DP_TNJ_JSN_r = 1 OR L_LAT_TNJ_OP_r = 1 OR L_LAT_TNJ_JSN_r = 1 OR R_LAT_TNJ_OP_r = 1 OR R_LAT_TNJ_JSN_r = 1) This creates a variable called TNJ_rOA_01 that is coded 1 if OA evidence is present in any of them. I Will code the same variable "0" to get Controls (with no OA) as you can see below in the formal: **Controls** IF (L_DP_TNJ_JSN_r = 0 AND R_DP_TNJ_JSN_r = 0 AND L_LAT_TNJ_OP_r = 0 AND L_LAT_TNJ_JSN_r = 0 AND R_LAT_TNJ_OP_r = 0 AND R_LAT_TNJ_JSN_r = 0)
L_DP_TNJ_JSN_r	0	No OA	
	1	Present OA	
R_DP_TNJ_JSN_r	0	No OA	
	1	Present OA	
L_LAT_TNJ_OP_r	0	No OA	
	1	Present OA	
L_LAT_TNJ_JSN_r	0	No OA	
	1	Present OA	
R_LAT_TNJ_OP_r	0	No OA	
	1	Present OA	
R_LAT_TNJ_JSN_r	0	No OA	
	1	Present OA	
Ankle Joints			**Prevalence of Ankle_rOA_01**
New Variable After	Recoded	Ankle OA	**Cases** IF (L_Ankle_LAT_OP_01 = 1 or L_Ankle_LAT_JSN_01 = 1 or L_AnkleAP_OP_01 = 1 or L_AnkleAP_JSN_01 = 1 or R_Ankle_LAT_OP_01 = 1 or R_Ankle_LAT_JSN_01 = 1 or R_AnkleAP_OP_01 = 1 or R_AnkleAP_JSN_01 = 1 This creates a variable called Ankle_rOA_01 that is coded 1 if OA evidence is present in any of them. I Will code the same variable "0" to get Controls (with no OA) as you can see below in the formal: **Controls** IF(L_Ankle_LAT_OP_01 = 0 AND L_Ankle_LAT_JSN_01 = 0 AND L_AnkleAP_OP_01 = 0 AND L_AnkleAP_JSN_01 = 0 AND R_Ankle_LAT_OP_01 = 0 AND R_Ankle_LAT_JSN_01 = 0 AND R_AnkleAP_OP_01 = 0 AND R_AnkleAP_JSN_01 = 0).
L_Ankle_LAT_OP_01	0	No OA	
	1	Present OA	
L_Ankle_LAT_JSN_01	0	No OA	
	1	Present OA	
R_Ankle_LAT_OP_01	0	No OA	
	1	Present OA	
R_Ankle_LAT_JSN_01	0	No OA	
	1	Present OA	
L_AnkleAP_OP_01	0	No OA	
	1	Present OA	
L_AnkleAP_JSN_01	0	No OA	
	1	Present OA	
R_AnkleAP_OP_01	0	No OA	
	1	Present OA	
R_AnkleAP_JSN_01	0	No OA	
	1	Present OA	

Appendix 2.15. Defined radiographic foot, midfoot and forefoot OA.

Foot rOA			Midfoot_rOA			Forefoot rOA		
n	View/ Cases	View/ Controls	n	View/ Cases	View/ Controls	n	View/ Cases	View/ Controls
1	L_DP_1stMTPJ_OP_r = 1 OR	L_DP_1stMTPJ_OP_r = 0 AND	1	L_DP_1stCMJ_OP_r = 1 OR	L_DP_1stCMJ_OP_r = 0 AND	1	L_DP_1stMTPJ_OP_r = 1 OR	L_DP_1stMTPJ_OP_r = 0 AND
2	L_DP_1stMTPJ_JSN_r = 1 OR	L_DP_1stMTPJ_JSN_r = 0 AND	2	L_DP_1stCMJ_JSN_r = 1 OR	L_DP_1stCMJ_JSN_r = 0 AND	2	L_DP_1stMTPJ_JSN_r = 1 OR	L_DP_1stMTPJ_JSN_r = 0 AND
3	L_DP_1stCMJ_OP_r = 1 OR	L_DP_1stCMJ_OP_r = 0 AND	3	L_DP_2ndCMJ_OP_r = 1 OR	L_DP_2ndCMJ_OP_r = 0 AND	3	R_DP_1stMTPJ_OP_r = 1 OR	R_DP_1stMTPJ_OP_r = 0 AND
4	L_DP_1stCMJ_JSN_r = 1 OR	L_DP_1stCMJ_JSN_r = 0 AND	4	L_DP_2ndCMJ_JSN_r = 1 OR	L_DP_2ndCMJ_JSN_r = 0 AND	4	R_DP_1stMTPJ_JSN_r = 1 OR	R_DP_1stMTPJ_JSN_r = 0 AND
5	L_DP_2ndCMJ_OP_r = 1 OR	L_DP_2ndCMJ_OP_r = 0 AND	5	L_DP_N1stCJ_OP_r = 1 OR	L_DP_N1stCJ_OP_r = 0 AND	5	L_LAT_1stMTPJ_OP_r = 1 OR	L_LAT_1stMTPJ_OP_r = 0 AND
6	L_DP_2ndCMJ_JSN_r = 1 OR	L_DP_2ndCMJ_JSN_r = 0 AND	6	L_DP_N1stCJ_JSN_r = 1 OR	L_DP_N1stCJ_JSN_r = 0 AND	6	L_LAT_1stMTPJ_JSN_r = 1 OR	L_LAT_1stMTPJ_JSN_r = 0 AND
7	L_DP_N1stCJ_OP_r = 1 OR	L_DP_N1stCJ_OP_r = 0 AND	7	L_DP_TNJ_JSN_r = 1 OR	L_DP_TNJ_JSN_r = 0 AND	7	R_LAT_1stMTPJ_OP_r = 1 OR	R_LAT_1stMTPJ_OP_r = 0 AND
8	L_DP_N1stCJ_JSN_r = 1 OR	L_DP_N1stCJ_JSN_r = 0 AND	8	R_DP_1stCMJ_OP_r = 1 OR	R_DP_1stCMJ_OP_r = 0 AND	8	R_LAT_1stMTPJ_JSN_r = 1 OR	R_LAT_1stMTPJ_JSN_r = 0 AND
9	L_DP_TNJ_JSN_r = 1 OR	L_DP_TNJ_JSN_r = 0 AND	9	R_DP_1stCMJ_JSN_r = 1 OR	R_DP_1stCMJ_JSN_r = 0 AND			
10	R_DP_1stMTPJ_OP_r = 1 OR	R_DP_1stMTPJ_OP_r = 0 AND	10	R_DP_2ndCMJ_OP_r = 1 OR	R_DP_2ndCMJ_OP_r = 0 AND			
11	R_DP_1stMTPJ_JSN_r = 1 OR	R_DP_1stMTPJ_JSN_r = 0 AND	11	R_DP_2ndCMJ_JSN_r = 1 OR	R_DP_2ndCMJ_JSN_r = 0 AND			
12	R_DP_1stCMJ_OP_r = 1 OR	R_DP_1stCMJ_OP_r = 0 AND	12	R_DP_N1stCJ_OP_r = 1 OR	R_DP_N1stCJ_OP_r = 0 AND			
13	R_DP_1stCMJ_JSN_r = 1 OR	R_DP_1stCMJ_JSN_r = 0 AND	13	R_DP_N1stCJ_JSN_r = 1 OR	R_DP_N1stCJ_JSN_r = 0 AND			
14	R_DP_2ndCMJ_OP_r = 1 OR	R_DP_2ndCMJ_OP_r = 0 AND	14	R_DP_TNJ_JSN_r = 1 OR	R_DP_TNJ_JSN_r = 0 AND			
15	R_DP_2ndCMJ_JSN_r = 1 OR	R_DP_2ndCMJ_JSN_r = 0 AND	15	L_LAT_1stCMJ_OP_r = 1 OR	L_LAT_1stCMJ_OP_r = 0 AND			
16	R_DP_N1stCJ_OP_r = 1 OR	R_DP_N1stCJ_OP_r = 0 AND	16	L_LAT_1stCMJ_JSN_r = 1 OR	L_LAT_1stCMJ_JSN_r = 0 AND			
17	R_DP_N1stCJ_JSN_r = 1 OR	R_DP_N1stCJ_JSN_r = 0 AND	17	L_LAT_2ndCMJ_OP_r = 1 OR	L_LAT_2ndCMJ_OP_r = 0 AND			
18	R_DP_TNJ_JSN_r = 1 OR	R_DP_TNJ_JSN_r = 0 AND	18	L_LAT_2ndCMJ_JSN_r = 1 OR	L_LAT_2ndCMJ_JSN_r = 0 AND			
19	L_LAT_1stMTPJ_OP_r = 1 OR	L_LAT_1stMTPJ_OP_r = 0 AND	19	L_LAT_N1stCJ_OP_r = 1 OR	L_LAT_N1stCJ_OP_r = 0 AND			
20	L_LAT_1stMTPJ_JSN_r = 1 OR	L_LAT_1stMTPJ_JSN_r = 0 AND	20	L_LAT_N1stCJ_JSN_r = 1 OR	L_LAT_N1stCJ_JSN_r = 0 AND			
21	L_LAT_1stCMJ_OP_r = 1 OR	L_LAT_1stCMJ_OP_r = 0 AND	21	L_LAT_TNJ_OP_r = 1 OR	L_LAT_TNJ_OP_r = 0 AND			
22	L_LAT_1stCMJ_JSN_r = 1 OR	L_LAT_1stCMJ_JSN_r = 0 AND	22	L_LAT_TNJ_JSN_r = 1 OR	L_LAT_TNJ_JSN_r = 0 AND			
23	L_LAT_2ndCMJ_OP_r = 1 OR	L_LAT_2ndCMJ_OP_r = 0 AND	23	R_LAT_1stCMJ_OP_r = 1 OR	R_LAT_1stCMJ_OP_r = 0 AND			
24	L_LAT_2ndCMJ_JSN_r = 1 OR	L_LAT_2ndCMJ_JSN_r = 0 AND	24	R_LAT_1stCMJ_JSN_r = 1 OR	R_LAT_1stCMJ_JSN_r = 0 AND			
25	L_LAT_N1stCJ_OP_r = 1 OR	L_LAT_N1stCJ_OP_r = 0 AND	25	R_LAT_2ndCMJ_OP_r = 1 OR	R_LAT_2ndCMJ_OP_r = 0 AND			
26	L_LAT_N1stCJ_JSN_r = 1 OR	L_LAT_N1stCJ_JSN_r = 0 AND	26	R_LAT_2ndCMJ_JSN_r = 1 OR	R_LAT_2ndCMJ_JSN_r = 0 AND			
27	L_LAT_TNJ_OP_r = 1 OR	L_LAT_TNJ_OP_r = 0 AND	27	R_LAT_N1stCJ_OP_r = 1 OR	R_LAT_N1stCJ_OP_r = 0 AND			
28	L_LAT_TNJ_JSN_r = 1 OR	L_LAT_TNJ_JSN_r = 0 AND	28	R_LAT_N1stCJ_JSN_r = 1 OR	R_LAT_N1stCJ_JSN_r = 0 AND			
29	R_LAT_1stMTPJ_OP_r = 1 OR	R_LAT_1stMTPJ_OP_r = 0 AND	29	R_LAT_TNJ_OP_r = 1 OR	R_LAT_TNJ_OP_r = 0 AND			
30	R_LAT_1stMTPJ_JSN_r = 1 OR	R_LAT_1stMTPJ_JSN_r = 0 AND	30	R_LAT_TNJ_JSN_r = 1	R_LAT_TNJ_JSN_r = 0			
31	R_LAT_1stCMJ_OP_r = 1 OR	R_LAT_1stCMJ_OP_r = 0 AND						
32	R_LAT_1stCMJ_JSN_r = 1 OR	R_LAT_1stCMJ_JSN_r = 0 AND						
33	R_LAT_2ndCMJ_OP_r = 1 OR	R_LAT_2ndCMJ_OP_r = 0 AND						
34	R_LAT_2ndCMJ_JSN_r = 1 OR	R_LAT_2ndCMJ_JSN_r = 0 AND						
35	R_LAT_N1stCJ_OP_r = 1 OR	R_LAT_N1stCJ_OP_r = 0 AND						
36	R_LAT_N1stCJ_JSN_r = 1 OR	R_LAT_N1stCJ_JSN_r = 0 AND						
37	R_LAT_TNJ_OP_r = 1 OR	R_LAT_TNJ_OP_r = 0 AND						
38	R_LAT_TNJ_JSN_r = 1	R_LAT_TNJ_JSN_r = 0						

Appendix 2.16. Defined radiographic foot/ankle OA, left and right foot/ankle OA and ankle OA

Foot_ankle_rOA_01		
n	View/ Cases	View/ Controls
1	L_DP_1stMTPJ_OP_r = 1 OR	L_DP_1stMTPJ_OP_r = 0 AND
2	L_DP_1stMTPJ_JSN_r = 1 OR	L_DP_1stMTPJ_JSN_r = 0 AND
3	L_DP_1stCMJ_OP_r = 1 OR	L_DP_1stCMJ_OP_r = 0 AND
4	L_DP_1stCMJ_JSN_r = 1 OR	L_DP_1stCMJ_JSN_r = 0 AND
5	L_DP_2ndCMJ_OP_r = 1 OR	L_DP_2ndCMJ_OP_r = 0 AND
6	L_DP_2ndCMJ_JSN_r = 1 OR	L_DP_2ndCMJ_JSN_r = 0 AND
7	L_DP_N1stCJ_OP_r = 1 OR	L_DP_N1stCJ_OP_r = 0 AND
8	L_DP_N1stCJ_JSN_r = 1 OR	L_DP_N1stCJ_JSN_r = 0 AND
9	L_DP_TNJ_JSN_r = 1 OR	L_DP_TNJ_JSN_r = 0 AND
10	R_DP_1stMTPJ_OP_r = 1 OR	R_DP_1stMTPJ_OP_r = 0 AND
11	R_DP_1stMTPJ_JSN_r = 1 OR	R_DP_1stMTPJ_JSN_r = 0 AND
12	R_DP_1stCMJ_OP_r = 1 OR	R_DP_1stCMJ_OP_r = 0 AND
13	R_DP_1stCMJ_JSN_r = 1 OR	R_DP_1stCMJ_JSN_r = 0 AND
14	R_DP_2ndCMJ_OP_r = 1 OR	R_DP_2ndCMJ_OP_r = 0 AND
15	R_DP_2ndCMJ_JSN_r = 1 OR	R_DP_2ndCMJ_JSN_r = 0 AND
16	R_DP_N1stCJ_OP_r = 1 OR	R_DP_N1stCJ_OP_r = 0 AND
17	R_DP_N1stCJ_JSN_r = 1 OR	R_DP_N1stCJ_JSN_r = 0 AND
18	R_DP_TNJ_JSN_r = 1 OR	R_DP_TNJ_JSN_r = 0 AND
19	L_LAT_1stMTPJ_OP_r = 1 OR	L_LAT_1stMTPJ_OP_r = 0 AND
20	L_LAT_1stMTPJ_JSN_r = 1 OR	L_LAT_1stMTPJ_JSN_r = 0 AND
21	L_LAT_1stCMJ_OP_r = 1 OR	L_LAT_1stCMJ_OP_r = 0 AND
22	L_LAT_1stCMJ_JSN_r = 1 OR	L_LAT_1stCMJ_JSN_r = 0 AND
23	L_LAT_2ndCMJ_OP_r = 1 OR	L_LAT_2ndCMJ_OP_r = 0 AND
24	L_LAT_2ndCMJ_JSN_r = 1 OR	L_LAT_2ndCMJ_JSN_r = 0 AND
25	L_LAT_N1stCJ_OP_r = 1 OR	L_LAT_N1stCJ_OP_r = 0 AND
26	L_LAT_N1stCJ_JSN_r = 1 OR	L_LAT_N1stCJ_JSN_r = 0 AND
27	L_LAT_TNJ_OP_r = 1 OR	L_LAT_TNJ_OP_r = 0 AND
28	L_LAT_TNJ_JSN_r = 1 OR	L_LAT_TNJ_JSN_r = 0 AND
29	R_LAT_1stMTPJ_OP_r = 1 OR	R_LAT_1stMTPJ_OP_r = 0 AND
30	R_LAT_1stMTPJ_JSN_r = 1 OR	R_LAT_1stMTPJ_JSN_r = 0 AND
31	R_LAT_1stCMJ_OP_r = 1 OR	R_LAT_1stCMJ_OP_r = 0 AND
32	R_LAT_1stCMJ_JSN_r = 1 OR	R_LAT_1stCMJ_JSN_r = 0 AND
33	R_LAT_2ndCMJ_OP_r = 1 OR	R_LAT_2ndCMJ_OP_r = 0 AND
34	R_LAT_2ndCMJ_JSN_r = 1 OR	R_LAT_2ndCMJ_JSN_r = 0 AND
35	R_LAT_N1stCJ_OP_r = 1 OR	R_LAT_N1stCJ_OP_r = 0 AND
36	R_LAT_N1stCJ_JSN_r = 1 OR	R_LAT_N1stCJ_JSN_r = 0 AND
37	R_LAT_TNJ_OP_r = 1 OR	R_LAT_TNJ_OP_r = 0 AND
38	R_LAT_TNJ_JSN_r = 1 OR	R_LAT_TNJ_JSN_r = 0 AND
39	L_Ankle_LAT_OP_01 = 1 OR	L_Ankle_LAT_OP_01 = 0 AND
40	L_Ankle_LAT_JSN_01 = 1 OR	L_Ankle_LAT_JSN_01 = 0 AND
41	L_AnkleAP_OP_01 = 1 OR	L_AnkleAP_OP_01 = 0 AND
42	L_AnkleAP_JSN_01 = 1 OR	L_AnkleAP_JSN_01 = 0 AND
43	R_Ankle_LAT_OP_01 = 1 OR	R_Ankle_LAT_OP_01 = 0 AND
44	R_Ankle_LAT_JSN_01 = 1 OR	R_Ankle_LAT_JSN_01 = 0 AND
45	R_AnkleAP_OP_01 = 1 OR	R_AnkleAP_OP_01 = 0 AND
46	R_AnkleAP_JSN_01 = 1	R_AnkleAP_JSN_01 = 0

Left_Foot_ankle_rOA_01		
n	View/ Cases	View/ Controls
1	L_DP_1stMTPJ_OP_r = 1 OR	L_DP_1stMTPJ_OP_r = 0 AND
2	L_DP_1stMTPJ_JSN_r = 1 OR	L_DP_1stMTPJ_JSN_r = 0 AND
3	L_DP_1stCMJ_OP_r = 1 OR	L_DP_1stCMJ_OP_r = 0 AND
4	L_DP_1stCMJ_JSN_r = 1 OR	L_DP_1stCMJ_JSN_r = 0 AND
5	L_DP_2ndCMJ_OP_r = 1 OR	L_DP_2ndCMJ_OP_r = 0 AND
6	L_DP_2ndCMJ_JSN_r = 1 OR	L_DP_2ndCMJ_JSN_r = 0 AND
7	L_DP_N1stCJ_OP_r = 1 OR	L_DP_N1stCJ_OP_r = 0 AND
8	L_DP_N1stCJ_JSN_r = 1 OR	L_DP_N1stCJ_JSN_r = 0 AND
9	L_DP_TNJ_JSN_r = 1 OR	L_DP_TNJ_JSN_r = 0 AND
10	L_LAT_1stMTPJ_OP_r = 1 OR	L_LAT_1stMTPJ_OP_r = 0 AND
11	L_LAT_1stMTPJ_JSN_r = 1 OR	L_LAT_1stMTPJ_JSN_r = 0 AND
12	L_LAT_1stCMJ_OP_r = 1 OR	L_LAT_1stCMJ_OP_r = 0 AND
13	L_LAT_1stCMJ_JSN_r = 1 OR	L_LAT_1stCMJ_JSN_r = 0 AND
14	L_LAT_2ndCMJ_OP_r = 1 OR	L_LAT_2ndCMJ_OP_r = 0 AND
15	L_LAT_2ndCMJ_JSN_r = 1 OR	L_LAT_2ndCMJ_JSN_r = 0 AND
16	L_LAT_N1stCJ_OP_r = 1 OR	L_LAT_N1stCJ_OP_r = 0 AND
17	L_LAT_N1stCJ_JSN_r = 1 OR	L_LAT_N1stCJ_JSN_r = 0 AND
18	L_LAT_TNJ_OP_r = 1 OR	L_LAT_TNJ_OP_r = 0 AND
19	L_LAT_TNJ_JSN_r = 1 OR	L_LAT_TNJ_JSN_r = 0 AND
20	L_Ankle_LAT_OP_01 = 1 OR	L_Ankle_LAT_OP_01 = 0 AND
21	L_Ankle_LAT_JSN_01 = 1 OR	L_Ankle_LAT_JSN_01 = 0 AND
22	L_AnkleAP_OP_01 = 1 OR	L_AnkleAP_OP_01 = 0 AND
23	L_AnkleAP_JSN_01 = 1	L_AnkleAP_JSN_01 = 0

Right_Foot_ankle_rOA_01		
1	R_DP_1stMTPJ_OP_r = 1 OR	R_DP_1stMTPJ_OP_r = 0 AND
2	R_DP_1stMTPJ_JSN_r = 1 OR	R_DP_1stMTPJ_JSN_r = 0 AND
3	R_DP_1stCMJ_OP_r = 1 OR	R_DP_1stCMJ_OP_r = 0 AND
4	R_DP_1stCMJ_JSN_r = 1 OR	R_DP_1stCMJ_JSN_r = 0 AND
5	R_DP_2ndCMJ_OP_r = 1 OR	R_DP_2ndCMJ_OP_r = 0 AND
6	R_DP_2ndCMJ_JSN_r = 1 OR	R_DP_2ndCMJ_JSN_r = 0 AND
7	R_DP_N1stCJ_OP_r = 1 OR	R_DP_N1stCJ_OP_r = 0 AND
8	R_DP_N1stCJ_JSN_r = 1 OR	R_DP_N1stCJ_JSN_r = 0 AND
9	R_DP_TNJ_JSN_r = 1 OR	R_DP_TNJ_JSN_r = 0 AND
10	R_LAT_1stMTPJ_OP_r = 1 OR	R_LAT_1stMTPJ_OP_r = 0 AND
11	R_LAT_1stMTPJ_JSN_r = 1 OR	R_LAT_1stMTPJ_JSN_r = 0 AND
12	R_LAT_1stCMJ_OP_r = 1 OR	R_LAT_1stCMJ_OP_r = 0 AND
13	R_LAT_1stCMJ_JSN_r = 1 OR	R_LAT_1stCMJ_JSN_r = 0 AND
14	R_LAT_2ndCMJ_OP_r = 1 OR	R_LAT_2ndCMJ_OP_r = 0 AND
15	R_LAT_2ndCMJ_JSN_r = 1 OR	R_LAT_2ndCMJ_JSN_r = 0 AND
16	R_LAT_N1stCJ_OP_r = 1 OR	R_LAT_N1stCJ_OP_r = 0 AND
17	R_LAT_N1stCJ_JSN_r = 1 OR	R_LAT_N1stCJ_JSN_r = 0 AND
18	R_LAT_TNJ_OP_r = 1 OR	R_LAT_TNJ_OP_r = 0 AND
19	R_LAT_TNJ_JSN_r = 1 OR	R_LAT_TNJ_JSN_r = 0 AND
20	R_Ankle_LAT_OP_01 = 1 OR	R_Ankle_LAT_OP_01 = 0 AND
21	R_Ankle_LAT_JSN_01 = 1 OR	R_Ankle_LAT_JSN_01 = 0 AND
22	R_AnkleAP_OP_01 = 1 OR	R_AnkleAP_OP_01 = 0 AND
23	R_AnkleAP_JSN_01 = 1	R_AnkleAP_JSN_01 = 0

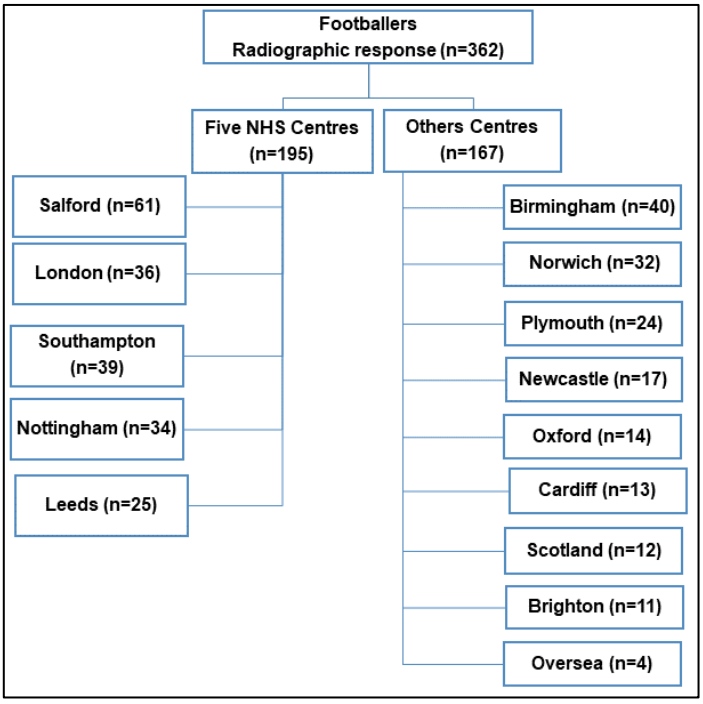
Bilateral_foot_ankle_rOA_01	
Left_Foot_ankle_rOA_01 = 1 AND Right_Foot_ankle_rOA_01	Left_Foot_ankle_rOA_01 = 0 and Right_Foot_ankle_rOA_01 = 0

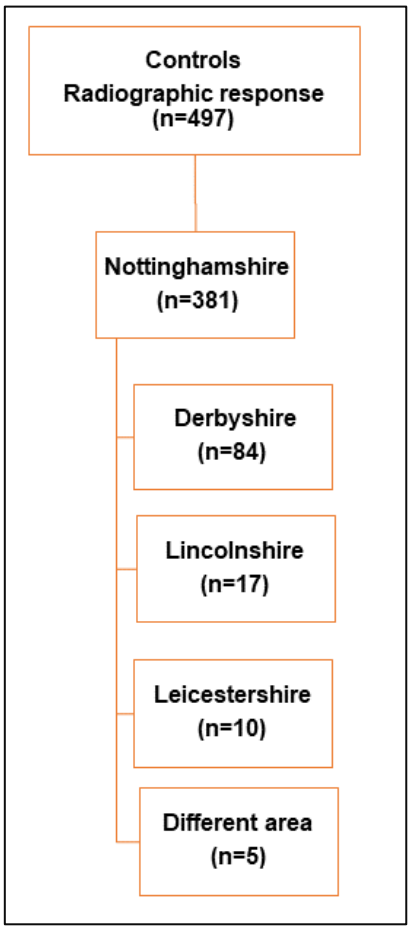
Ankle_rOA_01		
n	View/ Cases	View/ Controls
1	L_Ankle_LAT_OP_01 = 1 OR	L_Ankle_LAT_OP_01 = 0 AND
2	L_Ankle_LAT_JSN_01 = 1 OR	L_Ankle_LAT_JSN_01 = 0 AND
3	L_AnkleAP_OP_01 = 1 OR	L_AnkleAP_OP_01 = 0 AND
4	L_AnkleAP_JSN_01 = 1 OR	L_AnkleAP_JSN_01 = 0 AND
5	R_Ankle_LAT_OP_01 = 1 OR	R_Ankle_LAT_OP_01 = 0 AND
6	R_Ankle_LAT_JSN_01 = 1 OR	R_Ankle_LAT_JSN_01 = 0 AND
7	R_AnkleAP_OP_01 = 1 OR	R_AnkleAP_OP_01 = 0 AND
8	R_AnkleAP_JSN_01 = 1	R_AnkleAP_JSN_01 = 0

Appendix.2.17. Grade =>2 definite (OP ANDJSN) anywhere in foot/ankle joints at either side

This code uses definite OP and definite JSN to define radiographic foot/ankle OA. The yellow colour represents OP plus definite JSN for each joint.		
First_MTPJ_rOA_OP_overall	Cases =1	L_DP_1stMTPJ_OP_r = 1 OR R_DP_1stMTPJ_OP_r = 1 OR L_LAT_1stMTPJ_OP_r = 1 OR R_LAT_1stMTPJ_OP_r = 1
	Controls= 0	L_DP_1stMTPJ_OP_r = 0 AND R_DP_1stMTPJ_OP_r = 0 AND L_LAT_1stMTPJ_OP_r = 0 AND R_LAT_1stMTPJ_OP_r = 0
First_MTPJ_rOA_JSN_overall	Cases =1	L_DP_1stMTPJ_JSN_r = 1 OR R_DP_1stMTPJ_JSN_r = 1 OR L_LAT_1stMTPJ_JSN_r = 1 OR R_LAT_1stMTPJ_JSN_r = 1
	Controls= 0	L_DP_1stMTPJ_JSN_r = 0 AND R_DP_1stMTPJ_JSN_r = 0 AND L_LAT_1stMTPJ_JSN_r = 0 AND R_LAT_1stMTPJ_JSN_r = 0
First_MTPJ_rOA_mMenz	Cases =1	First_MTPJ_rOA_OP_overall = 1 AND First_MTPJ_rOA_JSN_overall = 1
	Controls= 0	First_MTPJ_rOA_OP_overall = 0 OR First_MTPJ_rOA_JSN_overall = 0
First_CMJ_rOA_OP_overall	Cases =1	L_DP_1stCMJ_OP_r = 1 OR R_DP_1stCMJ_OP_r = 1 OR L_LAT_1stCMJ_OP_r = 1 OR R_LAT_1stCMJ_OP_r = 1
	Controls= 0	L_DP_1stCMJ_OP_r = 0 AND R_DP_1stCMJ_OP_r = 0 AND L_LAT_1stCMJ_OP_r = 0 AND R_LAT_1stCMJ_OP_r = 0
First_CMJ_rOA_JSN_overall	Cases =1	L_DP_1stCMJ_JSN_r = 1 OR R_DP_1stCMJ_JSN_r = 1 OR L_LAT_1stCMJ_JSN_r = 1 OR R_LAT_1stCMJ_JSN_r = 1
	Controls= 0	L_DP_1stCMJ_JSN_r = 0 AND R_DP_1stCMJ_JSN_r = 0 AND L_LAT_1stCMJ_JSN_r = 0 AND R_LAT_1stCMJ_JSN_r = 0
First_CMJ_rOA_mMenz	Cases =1	First_CMJ_rOA_OP_overall = 1 AND First_CMJ_rOA_JSN_overall = 1
	Controls= 0	First_CMJ_rOA_OP_overall = 0 OR First_CMJ_rOA_JSN_overall = 0
Second_CMJ_rOA_OP_overall	Cases =1	L_DP_2ndCMJ_OP_r = 1 OR R_DP_2ndCMJ_OP_r = 1 OR L_LAT_2ndCMJ_OP_r = 1 OR R_LAT_2ndCMJ_OP_r = 1
	Controls= 0	L_DP_2ndCMJ_OP_r = 0 AND R_DP_2ndCMJ_OP_r = 0 AND L_LAT_2ndCMJ_OP_r = 0 AND R_LAT_2ndCMJ_OP_r = 0
Second_CMJ_rOA_JSN_overall	Cases =1	L_DP_2ndCMJ_JSN_r = 1 OR R_DP_2ndCMJ_JSN_r = 1 OR L_LAT_2ndCMJ_JSN_r = 1 OR R_LAT_2ndCMJ_JSN_r = 1
	Controls= 0	L_DP_2ndCMJ_JSN_r = 0 AND R_DP_2ndCMJ_JSN_r = 0 AND L_LAT_2ndCMJ_JSN_r = 0 AND R_LAT_2ndCMJ_JSN_r = 0
Second_CMJ_rOA_mMenz	Cases =1	Second_CMJ_rOA_OP_overall = 1 AND Second_CMJ_rOA_JSN_overall = 1
	Controls= 0	Second_CMJ_rOA_OP_overall = 0 OR Second_CMJ_rOA_JSN_overall = 0
N1stCJ_rOA_OP_overall	Cases =1	L_DP_N1stCJ_OP_r = 1 OR R_DP_N1stCJ_OP_r = 1 OR L_LAT_N1stCJ_OP_r = 1 OR R_LAT_N1stCJ_OP_r = 1
	Controls= 0	L_DP_N1stCJ_OP_r = 0 AND R_DP_N1stCJ_OP_r = 0 AND L_LAT_N1stCJ_OP_r = 0 AND R_LAT_N1stCJ_OP_r = 0
N1stCJ_rOA_JSN_overall	Cases =1	L_DP_N1stCJ_JSN_r = 1 OR R_DP_N1stCJ_JSN_r = 1 OR L_LAT_N1stCJ_JSN_r = 1 OR R_LAT_N1stCJ_JSN_r = 1
	Controls= 0	L_DP_N1stCJ_JSN_r = 0 AND R_DP_N1stCJ_JSN_r = 0 AND L_LAT_N1stCJ_JSN_r = 0 AND R_LAT_N1stCJ_JSN_r = 0
N1stCJ_rOA_mMenz	Cases =1	N1stCJ_rOA_OP_overall = 1 AND N1stCJ_rOA_JSN_overall = 1
	Controls= 0	N1stCJ_rOA_OP_overall = 0 OR N1stCJ_rOA_JSN_overall = 0
TNJ_rOA_JSN_overall	Cases =1	L_DP_TNJ_JSN_r = 1 OR R_DP_TNJ_JSN_r = 1 OR L_LAT_TNJ_JSN_r = 1 OR R_LAT_TNJ_JSN_r = 1
	Controls= 0	L_DP_TNJ_JSN_r = 0 AND R_DP_TNJ_JSN_r = 0 AND L_LAT_TNJ_JSN_r = 0 AND R_LAT_TNJ_JSN_r = 0
TNJ_rOA_OP_overall	Cases =1	L_LAT_TNJ_OP_r = 1 OR R_LAT_TNJ_OP_r = 1
	Controls= 0	L_LAT_TNJ_OP_r = 0 AND R_LAT_TNJ_OP_r = 0
TNJ_rOA_mMenz	Cases =1	TNJ_rOA_JSN_overall = 1 AND TNJ_rOA_OP_overall = 1
	Controls= 0	TNJ_rOA_JSN_overall = 0 OR TNJ_rOA_OP_overall = 0
Ankle_rOA_OP_overall	Cases =1	L_Ankle_LAT_OP_01 = 1 OR R_Ankle_LAT_OP_01 = 1 OR L_AnkleAP_OP_01 = 1 OR R_AnkleAP_OP_01 = 1
	Controls= 0	L_Ankle_LAT_OP_01 = 0 AND R_Ankle_LAT_OP_01 = 0 AND L_AnkleAP_OP_01 = 0 AND R_AnkleAP_OP_01 = 0
Ankle_rOA_JSN_overall	Cases =1	L_Ankle_LAT_JSN_01 = 1 OR R_Ankle_LAT_JSN_01 = 1 OR L_AnkleAP_JSN_01 = 1 OR R_AnkleAP_JSN_01 = 1
	Controls= 0	L_Ankle_LAT_JSN_01 = 0 AND R_Ankle_LAT_JSN_01 = 0 AND L_AnkleAP_JSN_01 = 0 AND R_AnkleAP_JSN_01 = 0
Ankle_rOA_mMenz	Cases =1	Ankle_rOA_OP_overall = 1 AND Ankle_rOA_JSN_overall = 1
	Controls= 0	Ankle_rOA_OP_overall = 0 OR Ankle_rOA_JSN_overall = 0
Foot_rOA	Cases =1	First_MTPJ_rOA_mMenz = 1 OR First_CMJ_rOA_mMenz = 1 OR Second_CMJ_rOA_mMenz = 1 OR N1stCJ_rOA_mMenz = 1 OR TNJ_rOA_mMenz = 1
	Controls= 0	First_MTPJ_rOA_mMenz = 0 AND First_CMJ_rOA_mMenz = 0 AND Second_CMJ_rOA_mMenz = 0 AND N1stCJ_rOA_mMenz = 0 AND TNJ_rOA_mMenz = 0
Foot_ankle_rOA_mMenz	Cases =1	Ankle_rOA_mMenz = 1 OR Foot_mMenz = 1
	Controls= 0	Ankle_rOA_mMenz = 0 AND Foot_mMenz = 0

Appendix 3.1. Distribution of footballers and controls in the UK who were able to undergo radiographic assessment.





Appendix 3.2. Number of missing views for radiographic images in footballers and controls for foot/ankle joints.

	Foot joint	Missing view, n	
n	**View and Description**	**Footballers (n=113)**	**Controls (n=319)**
	Dorsal-planer view		
1	Left dorsal-plantar 1st metatarsophalangeal joint: Osteophytes	1	4
2	Left dorsal-plantar 1st metatarsophalangeal joint: JSN	1	4
3	Left dorsal-plantar 1st cuneo-metatarsal joint: Osteophytes	1	4
4	Left dorsal-plantar 1st cuneo-metatarsal joint (dorsal): JSN	1	4
5	Left dorsal-plantar 2ndcuneo-metatarsal joint: Osteophytes	1	4
6	Left dorsal-plantar 2ndcuneo-metatarsal joint: JSN	1	4
7	Left dorsal-plantar navicular-1st cuneiform: Osteophytes	1	4
8	Left dorsal-plantar navicular-1st cuneiform: JSN	1	4
9	Left dorsal-plantar talo-navicular joint: JSN	1	4
10	Right dorsal-plantar 1st metatarsophalangeal joint: Osteophytes	1	4
11	Right dorsal-plantar 1st metatarsophalangeal joint: JSN	1	4
12	Right dorsal-plantar 1stcuneo-metatarsal joint: Osteophytes	1	4
13	Right dorsal-plantar 1stcuneo-metatarsal joint: JSN	1	4
14	Right dorsal-plantar 2ndcuneo-metatarsal joint: Osteophytes	5	4
15	Right dorsal-plantar 2ndcuneo-metatarsal joint: JSN	4	4
16	Right dorsal-plantar navicular-1st cuneiform: Osteophytes	4	4
17	Right dorsal-plantar navicular-1st cuneiform: JSN	1	4
18	Right dorsal-plantar talo-navicular joint: JSN	1	4
	Lateral view		
19	Left lateral 1st metatarsophalangeal joint: Osteophytes	1	5
20	Left lateral 1st metatarsophalangeal joint: JSN	1	5
21	Left lateral 1st cuneo-metatarsal joint: Osteophytes	1	4
22	Left lateral 1st cuneo-metatarsal joint: JSN	1	4
23	Left lateral 2nd cuneo-metatarsal joint: Osteophytes	2	4
24	Left lateral 2nd cuneo-metatarsal joint: JSN	2	4
25	Left lateral navicular-1st cuneiform: Osteophytes	1	4
26	Left lateral navicular-1st cuneiform: JSN	1	4
27	Left lateral talo-navicular joint: Osteophytes	1	4
28	Left lateral talo-navicular joint: JSN	1	4
29	Right lateral 1st metatarsophalangeal joint: Osteophytes	3	3
30	Right lateral 1st metatarsophalangeal joint: JSN	3	3
31	Right lateral 1st cuneo-metatarsal joint: Osteophytes	1	3
32	Right lateral 1st cuneo-metatarsal joint : JSN	1	3
33	Right lateral 2nd cuneo-metatarsal joint: Osteophytes	1	3
34	Right lateral 2nd cuneo-metatarsal joint: JSN	1	3
35	Right lateral navicular-1st cuneiform: Osteophytes	1	3
36	Right lateral navicular-1st cuneiform: JSN	1	3
37	Right lateral talo-navicular joint: Osteophytes	1	3
38	Right lateral talo-navicular joint: JSN	1	3

Ankle joint		Missing view, n	
N	**View and Description**	**Footballers (n=113)**	**Controls (n=319)**
1	Left anteroposterior weight-bearing osteophytes ankle view	1	4
2	Left anteroposterior weight-bearing JSN ankle view	1	4
3	Right anteroposterior weight-bearing osteophytes ankle view	1	4
4	Right anteroposterior weight-bearing JSN ankle view	1	4
5	Left lateral weight-bearing osteophytes ankle view	1	4
6	Left lateral weight bearing JSN ankle view	1	4
7	Right lateral weight-bearing osteophytes ankle view	1	3
8	Right lateral weight bearing JSN ankle view	1	3

Appendix 3.3. Questionnaires - Missing data

	Missing Data, n (%)	
	Footballers (n=468)	**Controls (n= 619)**
Age, n	0	4
BMI, n (%)	9 (1.92)	33 (5.33)
Socioeconomic status, n (%)	53 (11.32)	6 (1.00)
Nodal OA, n (%)	21 (3.39)	5 (1.07)
Pattern 3-digit ratio, n (%)	16 (3.42)	21 (3.39)
Flat footed, n (%)	25 (5.34)	19 (3.07)
Self-reported outcomes		
Current foot/ankle pain (1 month), n (%)	39 (8.33)	45 (7.27)
Chronic foot/ankle pain (≥3 months), n (%)	30 (6.41)	29 (4.68)
GP- diagnosed foot/ankle OA, n (%)	44 (9.40)	38 (6.14)
Ankle/toe surgery, n (%)	42 (8.97)	24 (3.88)

Appendix 3.4. Radiographic - Missing data

	Missing Data, n (%)	
Radiographic assessment completed	**Footballers (n=113)**	**Controls (n= 319)**
Age, n	0	0
BMI, n (%)	1 (0.88)	17 (5.33)
Socioeconomic status, n (%)	3 (2.65)	1 (0.31)
Nodal OA, n (%)	1 (0.88)	11 (3.45)
Pattern 3-digit ratio, n (%)	4 (3.54)	9 (2.82)
Flat footed, n (%)	4 (3.54)	5 (1.57)
Body pain, n (%)	4 (3.54)	5 (1.57)
Gout, n (%)	0	1 (0.31)
FSST, n (%)	13 (11.50)	7 (2.19)
10-MWT, n (%)	13 (11.50)	7 (2.19)

Appendix 3.5. Prevalence of foot/ankle OA with 95% confidence intervals in retired male professional footballers and general population male controls.

	Prevalence, % (95%CI)	
Self-reported outcomes	**Footballers (n=468)**	**Controls (n=619)**
Current foot/ankle pain	35.0 (95%CI: 29.7 - 39.5)	26.0 (95%CI: 21.4 - 28.9)
Ever foot/ankle pain ≥3 months	30.0 (95%CI: 26.6 - 36.1)	27.0 (95%CI: 21.8 - 29.3)
GP-diagnosed foot/ankle OA	13.0 (95%CI: 9.1 - 15.9)	8.0 (95%CI: 4.3 - 8.5)
Surgery to forefoot/ankle	24.2 (95%CI: 19.3 - 28.1)	7.9 (95%CI: 5.3 - 9.8)
Radiographic outcomes	**(n=113)**	**(n=319)**
ROA foot[1]/ankle[2] OA	99.1 (95%CI: 95.2 - 99.8)	97.2 (95%CI: 94.7 - 98.5)
sROA foot/ankle OA	39.8 (95%CI: 31.3 - 49.0)	28.3 (95%CI: 23.6 - 33.5)
ROA foot OA	87.5 (95%CI: 80.1 - 92.4)	93.1 (95%CI: 89.7 - 95.4)
sROA foot OA	33.6 (95%CI: 25.8 - 43.1)	24.5 (95%CI: 20.1 - 29.5)

[1]Foot included only five joints (1st Metatarsophalangeal joint, 1st Cuneo-metatarsal joint, 2nd Cuneo-metatarsal joint, Navicular-1st cuneiform joint and Talonavicular joint).
[2]Ankle (Talocrural joint).
GP = General practitioner
ROA = Radiographic osteoarthritis.
sROA = Symptomatic radiographic osteoarthritis.
n = number.

Appendix 4.1. Backward stepwise selection model in the multivariable logistic regression of self-reported foot/ankle OA

		Variables in the Equation							
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	0.010	0.021	0.213	1	0.644	1.010	0.969	1.052
	Current_BMI	-0.016	0.058	0.080	1	0.777	0.984	0.878	1.102
	Index of Multiple Deprivation Decile	-0.063	0.079	0.628	1	0.428	0.939	0.805	1.097
	Charlson_score_full	0.072	0.085	0.707	1	0.400	1.074	0.909	1.270
	ACRCriteriaNodalOA	0.824	0.625	1.737	1	0.187	2.280	0.669	7.767
	Gout_01	0.185	0.549	0.114	1	0.736	1.203	0.411	3.525
	2d4d ratio	0.376	0.401	0.882	1	0.348	1.457	0.664	3.195
	Currently_big_toe	0.077	0.435	0.031	1	0.859	1.080	0.460	2.535
	Flat_foot_01	0.675	0.589	1.315	1	0.252	1.965	0.619	6.234
	Foot_ankles_injury_01	1.448	0.432	11.251	1	0.001	4.253	1.825	9.910
	Foot_Ankle_Injections_01	0.955	0.432	4.898	1	0.027	2.599	1.115	6.057
	Calculated: traindoseweek*careerdur*40 (weeks/season)	0.000	0.000	0.209	1	0.648	1.000	1.000	1.000
	matches	0.001	0.001	2.708	1	0.100	1.001	1.000	1.003
	Training dose per week Calculated: Q15_Hours* Q15_Days	0.041	0.043	0.897	1	0.344	1.042	0.957	1.134
	position	0.052	0.195	0.071	1	0.791	1.053	0.718	1.544
	Constant	-4.514	2.251	4.020	1	0.045	0.011		
Step 2[a]	Age	0.011	0.020	0.267	1	0.605	1.011	0.971	1.052
	Current_BMI	-0.016	0.058	0.080	1	0.778	0.984	0.879	1.102
	Index of Multiple Deprivation Decile	-0.064	0.079	0.664	1	0.415	0.938	0.804	1.094
	Charlson_score_full	0.071	0.085	0.695	1	0.405	1.074	0.908	1.269
	ACRCriteriaNodalOA	0.831	0.625	1.765	1	0.184	2.295	0.674	7.816
	Gout_01	0.190	0.548	0.120	1	0.729	1.209	0.413	3.538
	2d4d ratio	0.370	0.399	0.860	1	0.354	1.448	0.662	3.167

	Flat_foot_01	0.689	0.583	1.396	1	0.237	1.992	0.635	6.249
	Foot_ankles_injury_01	1.446	0.432	11.215	1	0.001	4.247	1.822	9.902
	Foot_Ankle_Injections_01	0.954	0.432	4.884	1	0.027	2.597	1.114	6.055
	Calculated: traindoseweek*careerdur*40 (weeks/season)	0.000	0.000	0.233	1	0.629	1.000	1.000	1.000
	matches	0.001	0.001	2.727	1	0.099	1.001	1.000	1.003
	Training dose per week Calculated: Q15_Hours* Q15_Days	0.041	0.043	0.899	1	0.343	1.042	0.957	1.134
	position	0.049	0.195	0.064	1	0.801	1.050	0.717	1.538
	Constant	-4.518	2.249	4.037	1	0.045	0.011		
Step 3[a]	Age	0.011	0.020	0.330	1	0.565	1.012	0.973	1.052
	Current_BMI	-0.016	0.057	0.075	1	0.784	0.984	0.879	1.102
	Index of Multiple Deprivation Decile	-0.065	0.079	0.677	1	0.410	0.937	0.804	1.093
	Charlson_score_full	0.071	0.085	0.704	1	0.401	1.074	0.909	1.269
	ACRCriteriaNodalOA	0.802	0.614	1.707	1	0.191	2.231	0.669	7.435
	Gout_01	0.200	0.545	0.135	1	0.713	1.222	0.420	3.553
	2d4d ratio	0.369	0.399	0.857	1	0.355	1.446	0.662	3.159
	Flat_foot_01	0.705	0.580	1.474	1	0.225	2.023	0.649	6.309
	Foot_ankles_injury_01	1.449	0.432	11.267	1	0.001	4.261	1.828	9.932
	Foot_Ankle_Injections_01	0.967	0.430	5.068	1	0.024	2.631	1.133	6.106
	Calculated: traindoseweek*careerdur*40 (weeks/season)	0.000	0.000	0.213	1	0.644	1.000	1.000	1.000
	matches	0.001	0.001	2.680	1	0.102	1.001	1.000	1.003
	Training dose per week Calculated: Q15_Hours* Q15_Days	0.041	0.043	0.880	1	0.348	1.041	0.957	1.134
	Constant	-4.446	2.230	3.976	1	0.046	0.012		
Step 4[a]	Age	0.012	0.020	0.351	1	0.553	1.012	0.973	1.052
	Index of Multiple Deprivation Decile	-0.065	0.079	0.689	1	0.407	0.937	0.803	1.093
	Charlson_score_full	0.069	0.085	0.658	1	0.417	1.071	0.907	1.264
	ACRCriteriaNodalOA	0.777	0.607	1.639	1	0.200	2.175	0.662	7.150
	Gout_01	0.163	0.529	0.095	1	0.758	1.177	0.417	3.317
	2d4d ratio	0.351	0.392	0.800	1	0.371	1.420	0.658	3.064
	Flat_foot_01	0.684	0.576	1.412	1	0.235	1.981	0.641	6.121
	Foot_ankles_injury_01	1.448	0.432	11.255	1	0.001	4.253	1.826	9.908
	Foot_Ankle_Injections_01	0.956	0.427	5.003	1	0.025	2.601	1.126	6.010
	Calculated: traindoseweek*careerdur*40 (weeks/season)	0.000	0.000	0.188	1	0.664	1.000	1.000	1.000
	matches	0.001	0.001	2.626	1	0.105	1.001	1.000	1.003

	Training dose per week Calculated: Q15_Hours* Q15_Days	0.037	0.042	0.800	1	0.371	1.038	0.957	1.126
	Constant	-4.816	1.773	7.383	1	0.007	0.008		
Step 5[a]	Age	0.012	0.020	0.369	1	0.543	1.012	0.973	1.053
	Index of Multiple Deprivation Decile	-0.067	0.078	0.737	1	0.391	0.935	0.802	1.090
	Charlson_score_full	0.070	0.085	0.678	1	0.410	1.072	0.908	1.265
	ACRCriteriaNodalOA	0.784	0.605	1.680	1	0.195	2.189	0.669	7.161
	2d4d ratio	0.356	0.392	0.823	1	0.364	1.427	0.662	3.079
	Flat_foot_01	0.674	0.575	1.374	1	0.241	1.962	0.636	6.058
	Foot_ankles_injury_01	1.460	0.431	11.496	1	0.001	4.306	1.852	10.014
	Foot_Ankle_Injections_01	0.945	0.426	4.916	1	0.027	2.573	1.116	5.934
	Calculated: traindoseweek*careerdur*40 (weeks/season)	0.000	0.000	0.183	1	0.669	1.000	1.000	1.000
	matches	0.001	0.001	2.588	1	0.108	1.001	1.000	1.003
	Training dose per week Calculated: Q15_Hours* Q15_Days	0.038	0.042	0.818	1	0.366	1.038	0.957	1.127
	Constant	-4.810	1.774	7.353	1	0.007	0.008		
Step 6[a]	Age	0.011	0.020	0.308	1	0.579	1.011	0.973	1.051
	Index of Multiple Deprivation Decile	-0.072	0.077	0.876	1	0.349	0.930	0.799	1.082
	Charlson_score_full	0.065	0.084	0.605	1	0.437	1.068	0.905	1.259
	ACRCriteriaNodalOA	0.794	0.605	1.725	1	0.189	2.212	0.676	7.234
	2d4d ratio	0.347	0.391	0.787	1	0.375	1.415	0.657	3.046
	Flat_foot_01	0.694	0.573	1.464	1	0.226	2.001	0.651	6.155
	Foot_ankles_injury_01	1.463	0.430	11.547	1	0.001	4.317	1.857	10.036
	Foot_Ankle_Injections_01	0.927	0.424	4.787	1	0.029	2.527	1.101	5.796
	matches	0.001	0.001	2.566	1	0.109	1.001	1.000	1.003
	Training dose per week Calculated: Q15_Hours* Q15_Days	0.028	0.035	0.647	1	0.421	1.028	0.961	1.100
	Constant	-4.676	1.745	7.177	1	0.007	0.009		
Step 7[a]	Index of Multiple Deprivation Decile	-0.079	0.076	1.078	1	0.299	0.924	0.796	1.073
	Charlson_score_full	0.079	0.080	0.984	1	0.321	1.083	0.925	1.267
	ACRCriteriaNodalOA	0.867	0.592	2.142	1	0.143	2.380	0.745	7.602
	2d4d ratio	0.327	0.389	0.706	1	0.401	1.386	0.647	2.971
	Flat_foot_01	0.625	0.558	1.257	1	0.262	1.869	0.626	5.579
	Foot_ankles_injury_01	1.463	0.430	11.560	1	0.001	4.318	1.858	10.034
	Foot_Ankle_Injections_01	0.904	0.420	4.629	1	0.031	2.471	1.084	5.631
	matches	0.001	0.001	2.640	1	0.104	1.001	1.000	1.003

	Training dose per week Calculated: Q15_Hours* Q15_Days	0.026	0.034	0.570	1	0.450	1.026	0.960	1.097
	Constant	-3.897	1.016	14.704	1	0.000	0.020		
Step 8[a]	Index of Multiple Deprivation Decile	-0.083	0.076	1.204	1	0.272	0.920	0.793	1.068
	Charlson_score_full	0.090	0.078	1.324	1	0.250	1.094	0.939	1.276
	ACRCriteriaNodalOA	0.877	0.590	2.207	1	0.137	2.404	0.756	7.645
	2d4d ratio	0.314	0.388	0.657	1	0.418	1.369	0.640	2.929
	Flat_foot_01	0.606	0.556	1.186	1	0.276	1.832	0.616	5.449
	Foot_ankles_injury_01	1.504	0.426	12.434	1	0.000	4.498	1.950	10.375
	Foot_Ankle_Injections_01	0.901	0.419	4.616	1	0.032	2.462	1.082	5.602
	matches	0.001	0.001	2.258	1	0.133	1.001	1.000	1.002
	Constant	-3.459	0.829	17.424	1	0.000	0.031		
Step 9[a]	Index of Multiple Deprivation Decile	-0.085	0.076	1.257	1	0.262	0.919	0.792	1.066
	Charlson_score_full	0.086	0.078	1.231	1	0.267	1.090	0.936	1.270
	ACRCriteriaNodalOA	0.918	0.583	2.485	1	0.115	2.505	0.800	7.849
	Flat_foot_01	0.677	0.549	1.520	1	0.218	1.968	0.671	5.773
	Foot_ankles_injury_01	1.503	0.427	12.410	1	0.000	4.496	1.948	10.378
	Foot_Ankle_Injections_01	0.888	0.418	4.514	1	0.034	2.430	1.071	5.510
	matches	0.001	0.001	2.729	1	0.099	1.001	1.000	1.003
	Constant	-3.277	0.792	17.130	1	0.000	0.038		
Step 10[a]	Index of Multiple Deprivation Decile	-0.091	0.076	1.453	1	0.228	0.913	0.787	1.059
	ACRCriteriaNodalOA	1.049	0.571	3.371	1	0.066	2.853	0.932	8.739
	Flat_foot_01	0.647	0.546	1.403	1	0.236	1.910	0.655	5.572
	Foot_ankles_injury_01	1.488	0.424	12.331	1	0.000	4.426	1.930	10.153
	Foot_Ankle_Injections_01	0.860	0.414	4.309	1	0.038	2.363	1.049	5.323
	matches	0.001	0.001	2.673	1	0.102	1.001	1.000	1.003
	Constant	-3.100	0.770	16.214	1	0.000	0.045		
Step 11[a]	Index of Multiple Deprivation Decile	-0.091	0.076	1.449	1	0.229	0.913	0.788	1.059
	ACRCriteriaNodalOA	0.975	0.566	2.964	1	0.085	2.652	0.874	8.047
	Foot_ankles_injury_01	1.492	0.422	12.500	1	0.000	4.448	1.945	10.174
	Foot_Ankle_Injections_01	0.882	0.412	4.592	1	0.032	2.416	1.078	5.415
	matches	0.001	0.001	2.348	1	0.125	1.001	1.000	1.002
	Constant	-3.007	0.762	15.591	1	0.000	0.049		
Step 12[a]	ACRCriteriaNodalOA	1.015	0.562	3.266	1	0.071	2.760	0.918	8.302

	Foot_ankles_injury_01	1.472	0.418	12.384	1	0.000	4.359	1.920	9.897
	Foot_Ankle_Injections_01	0.880	0.409	4.637	1	0.031	2.411	1.082	5.373
	matches	0.001	0.001	2.316	1	0.128	1.001	1.000	1.002
	Constant	-3.682	0.544	45.869	1	0.000	0.025		
Step 13[a]	ACRCriteriaNodalOA	1.082	0.555	3.802	1	0.051	2.952	0.994	8.762
	Foot_ankles_injury_01	1.487	0.417	12.694	1	0.000	4.423	1.952	10.022
	Foot_Ankle_Injections_01	0.887	0.407	4.747	1	0.029	2.428	1.093	5.391
	Constant	-3.195	0.416	58.837	1	0.000	0.041		
Step 14[a]	Foot_ankles_injury_01	1.442	0.412	12.235	1	0.000	4.228	1.885	9.485
	Foot_Ankle_Injections_01	0.964	0.403	5.722	1	0.017	2.622	1.190	5.778
	Constant	-3.115	0.409	57.866	1	0.000	0.044		

a. Variable(s) entered on step 1: Age, Current_BMI, Index of Multiple Deprivation Decile, Charlson_score_full, ACRCriteriaNodalOA, Gout_01, 2d4d ratio, Currently_big_toe, Flat_foot_01, Foot_ankles_injury_01, Foot_Ankle_Injections_01, Calculated: traindoseweek*careerdur*40 (weeks/season), matches, Training dose per week Calculated: Q15_Hours* Q15_Days , position.

Appendix 4.2. Backward stepwise selection model in the multivariable logistic regression of sROA foot/ankle

		Variables in the Equation							
								95% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1[a]	Current_Age	-.046	.041	1.240	1	.265	.955	.882	1.035
	Current_BMI	-.077	.095	.667	1	.414	.926	.769	1.114
	Index of Multiple Deprivation Decile	-.297	.146	4.122	1	.042	.743	.558	.990
	Charlson_score_full	.106	.161	.433	1	.511	1.112	.811	1.525
	ACRCriteriaNodalOA	.476	1.262	.143	1	.706	1.610	.136	19.094
	Gout_01	.446	.765	.341	1	.560	1.563	.349	6.996
	2d4d ratio	-.432	.625	.479	1	.489	.649	.191	2.208
	Currently_big_toe	.624	.645	.937	1	.333	1.866	.527	6.603
	Flat_foot_01	-.998	1.072	.866	1	.352	.369	.045	3.016
	Ankle_foot_toes_injury_01	1.041	.594	3.069	1	.080	2.832	.884	9.077
	Foot_ankle_Injections_0111	1.309	.659	3.944	1	.047	3.704	1.017	13.488
	Career duration : calculated: Q9_To-Q9_From	-.033	.075	.195	1	.659	.967	.835	1.121
	matches	.000	.002	.000	1	.987	1.000	.997	1.003
	Training dose per week Calculated: Q15_Hours* Q15_Days	-.036	.056	.416	1	.519	.965	.865	1.076
	position	-.015	.311	.002	1	.960	.985	.535	1.812
	Constant	6.739	4.149	2.638	1	.104	844.587		
Step 2[a]	Current_Age	-.045	.040	1.283	1	.257	.956	.883	1.034
	Current_BMI	-.077	.094	.678	1	.410	.926	.770	1.112
	Index of Multiple Deprivation Decile	-.297	.146	4.141	1	.042	.743	.558	.989
	Charlson_score_full	.106	.159	.441	1	.506	1.111	.814	1.518
	ACRCriteriaNodalOA	.476	1.260	.142	1	.706	1.609	.136	19.032
	Gout_01	.447	.765	.341	1	.559	1.563	.349	6.996
	2d4d ratio	-.431	.620	.483	1	.487	.650	.193	2.189
	Currently_big_toe	.624	.645	.937	1	.333	1.866	.528	6.602
	Flat_foot_01	-1.001	1.063	.885	1	.347	.368	.046	2.956
	Ankle_foot_toes_injury_01	1.042	.590	3.121	1	.077	2.836	.892	9.012
	Foot_ankle_Injections_0111	1.310	.659	3.956	1	.047	3.706	1.019	13.477

	Career duration : calculated: Q9_To-Q9_From	-.032	.059	.301	1	.583	.968	.863	1.087
	Training dose per week Calculated: Q15_Hours* Q15_Days	-.036	.056	.416	1	.519	.965	.865	1.076
	position	-.017	.304	.003	1	.956	.983	.543	1.783
	Constant	6.728	4.101	2.692	1	.101	835.868		
Step 3[a]	Current_Age	-.046	.040	1.331	1	.249	.955	.884	1.033
	Current_BMI	-.077	.094	.680	1	.410	.926	.770	1.112
	Index of Multiple Deprivation Decile	-.298	.145	4.229	1	.040	.742	.558	.986
	Charlson_score_full	.105	.158	.439	1	.507	1.110	.815	1.512
	ACRCriteriaNodalOA	.493	1.224	.162	1	.687	1.637	.149	18.009
	Gout_01	.444	.763	.339	1	.561	1.559	.349	6.954
	2d4d ratio	-.431	.619	.483	1	.487	.650	.193	2.189
	Currently_big_toe	.628	.641	.958	1	.328	1.873	.533	6.580
	Flat_foot_01	-1.009	1.054	.916	1	.339	.365	.046	2.878
	Ankle_foot_toes_injury_01	1.041	.589	3.120	1	.077	2.832	.892	8.991
	Foot_ankle_Injections_0111	1.309	.658	3.953	1	.047	3.701	1.019	13.444
	Career duration : calculated: Q9_To-Q9_From	-.032	.059	.303	1	.582	.968	.863	1.086
	Training dose per week Calculated: Q15_Hours* Q15_Days	-.036	.055	.430	1	.512	.964	.865	1.075
	Constant	6.724	4.102	2.686	1	.101	832.062		
Step 4[a]	Current_Age	-.040	.037	1.185	1	.276	.961	.894	1.033
	Current_BMI	-.076	.094	.661	1	.416	.927	.771	1.113
	Index of Multiple Deprivation Decile	-.305	.144	4.468	1	.035	.737	.555	.978
	Charlson_score_full	.098	.157	.386	1	.534	1.103	.810	1.500
	Gout_01	.418	.759	.304	1	.582	1.519	.343	6.722
	2d4d ratio	-.406	.617	.434	1	.510	.666	.199	2.230
	Currently_big_toe	.602	.638	.889	1	.346	1.825	.523	6.376
	Flat_foot_01	-1.035	1.053	.965	1	.326	.355	.045	2.800
	Ankle_foot_toes_injury_01	1.034	.587	3.103	1	.078	2.813	.890	8.890
	Foot_ankle_Injections_0111	1.329	.654	4.123	1	.042	3.776	1.047	13.618
	Career duration : calculated: Q9_To-Q9_From	-.030	.058	.257	1	.612	.971	.866	1.088
	Training dose per week Calculated: Q15_Hours* Q15_Days	-.036	.055	.424	1	.515	.965	.866	1.075
	Constant	6.360	3.977	2.557	1	.110	577.959		

Step 5[a]	Current_Age	-.042	.036	1.331	1	.249	.959	.893	1.030
	Current_BMI	-.077	.094	.679	1	.410	.926	.770	1.112
	Index of Multiple Deprivation Decile	-.303	.143	4.485	1	.034	.738	.558	.978
	Charlson_score_full	.091	.157	.337	1	.562	1.095	.806	1.489
	Gout_01	.378	.756	.249	1	.618	1.459	.331	6.422
	2d4d ratio	-.435	.614	.501	1	.479	.648	.195	2.156
	Currently_big_toe	.631	.634	.991	1	.320	1.880	.542	6.513
	Flat_foot_01	-1.045	1.051	.988	1	.320	.352	.045	2.760
	Ankle_foot_toes_injury_01	1.070	.582	3.378	1	.066	2.915	.931	9.123
	Foot_ankle_Injections_0111	1.216	.611	3.960	1	.047	3.374	1.018	11.175
	Training dose per week Calculated: Q15_Hours* Q15_Days	-.027	.051	.271	1	.602	.974	.880	1.077
	Constant	6.044	3.885	2.420	1	.120	421.762		
Step 6[a]	Current_Age	-.038	.035	1.145	1	.285	.963	.899	1.032
	Current_BMI	-.074	.093	.629	1	.428	.929	.774	1.115
	Index of Multiple Deprivation Decile	-.311	.141	4.871	1	.027	.733	.556	.966
	Charlson_score_full	.092	.156	.344	1	.557	1.096	.807	1.489
	2d4d ratio	-.447	.611	.535	1	.465	.640	.193	2.118
	Currently_big_toe	.582	.623	.871	1	.351	1.789	.527	6.070
	Flat_foot_01	-1.094	1.048	1.090	1	.297	.335	.043	2.611
	Ankle_foot_toes_injury_01	1.115	.575	3.758	1	.053	3.048	.988	9.406
	Foot_ankle_Injections_0111	1.214	.605	4.021	1	.045	3.366	1.028	11.023
	Training dose per week Calculated: Q15_Hours* Q15_Days	-.029	.051	.327	1	.568	.971	.878	1.074
	Constant	5.846	3.831	2.328	1	.127	345.770		
Step 7[a]	Current_Age	-.033	.034	.932	1	.334	.968	.906	1.034
	Current_BMI	-.081	.093	.754	1	.385	.922	.768	1.107
	Index of Multiple Deprivation Decile	-.301	.140	4.656	1	.031	.740	.563	.973
	Charlson_score_full	.095	.157	.360	1	.548	1.099	.807	1.497
	2d4d ratio	-.412	.605	.464	1	.496	.662	.202	2.167
	Currently_big_toe	.626	.615	1.038	1	.308	1.871	.561	6.244
	Flat_foot_01	-1.124	1.049	1.149	1	.284	.325	.042	2.538
	Ankle_foot_toes_injury_01	1.059	.564	3.526	1	.060	2.884	.955	8.712

	Foot_ankle_Injections_0111	1.182	.600	3.886	1	.049	3.261	1.007	10.564
	Constant	5.216	3.637	2.057	1	.152	184.262		
Step 8[a]	Current_Age	-.027	.032	.682	1	.409	.974	.914	1.037
	Current_BMI	-.072	.092	.622	1	.430	.930	.777	1.113
	Index of Multiple Deprivation Decile	-.301	.139	4.694	1	.030	.740	.564	.972
	2d4d ratio	-.492	.590	.697	1	.404	.611	.192	1.941
	Currently_big_toe	.566	.605	.878	1	.349	1.762	.539	5.762
	Flat_foot_01	-1.099	1.039	1.119	1	.290	.333	.043	2.552
	Ankle_foot_toes_injury_01	1.113	.557	3.994	1	.046	3.044	1.022	9.069
	Foot_ankle_Injections_0111	1.175	.598	3.856	1	.050	3.237	1.002	10.452
	Constant	4.726	3.549	1.773	1	.183	112.818		
Step 9[a]	Current_Age	-.028	.032	.764	1	.382	.972	.913	1.035
	Index of Multiple Deprivation Decile	-.278	.135	4.239	1	.040	.758	.582	.987
	2d4d ratio	-.479	.579	.682	1	.409	.620	.199	1.929
	Currently_big_toe	.599	.602	.990	1	.320	1.820	.560	5.917
	Flat_foot_01	-1.257	1.042	1.454	1	.228	.285	.037	2.194
	Ankle_foot_toes_injury_01	1.120	.554	4.091	1	.043	3.064	1.035	9.071
	Foot_ankle_Injections_0111	1.057	.568	3.460	1	.063	2.879	.945	8.772
	Constant	2.737	2.423	1.276	1	.259	15.447		
Step 10[a]	Current_Age	-.022	.031	.505	1	.477	.978	.920	1.040
	Index of Multiple Deprivation Decile	-.257	.131	3.822	1	.051	.773	.598	1.001
	Currently_big_toe	.615	.595	1.069	1	.301	1.849	.577	5.932
	Flat_foot_01	-1.353	1.042	1.684	1	.194	.258	.034	1.994
	Ankle_foot_toes_injury_01	1.084	.548	3.919	1	.048	2.956	1.011	8.646
	Foot_ankle_Injections_0111	1.048	.563	3.471	1	.062	2.852	.947	8.591
	Constant	1.887	2.173	.754	1	.385	6.598		
Step 11[a]	Index of Multiple Deprivation Decile	-.259	.132	3.831	1	.050	.772	.596	1.000
	Currently_big_toe	.506	.576	.774	1	.379	1.659	.537	5.125
	Flat_foot_01	-1.246	1.025	1.478	1	.224	.288	.039	2.144
	Ankle_foot_toes_injury_01	1.079	.547	3.894	1	.048	2.941	1.007	8.588
	Foot_ankle_Injections_0111	1.036	.561	3.407	1	.065	2.818	.938	8.464
	Constant	.536	1.051	.260	1	.610	1.710		
Step 12[a]	Index of Multiple Deprivation Decile	-.268	.130	4.274	1	.039	.765	.593	.986

	Flat_foot_01	-1.088	.981	1.231	1	.267	.337	.049	2.303
	Ankle_foot_toes_injury_01	1.091	.544	4.025	1	.045	2.976	1.025	8.639
	Foot_ankle_Injections_0111	1.055	.556	3.603	1	.058	2.873	.966	8.545
	Constant	.717	1.014	.500	1	.480	2.048		
Step 13[a]	Index of Multiple Deprivation Decile	-.248	.126	3.866	1	.049	.780	.609	.999
	Ankle_foot_toes_injury_01	1.033	.539	3.675	1	.055	2.810	.977	8.079
	Foot_ankle_Injections_0111	1.013	.551	3.371	1	.066	2.753	.934	8.112
	Constant	.526	.985	.285	1	.593	1.693		
Step 14[a]	Index of Multiple Deprivation Decile	-.205	.117	3.069	1	.080	.814	.647	1.025
	Ankle_foot_toes_injury_01	1.376	.501	7.533	1	.006	3.961	1.482	10.584
	Constant	.568	.948	.359	1	.549	1.765		
Step 15[a]	Ankle_foot_toes_injury_01	1.204	.475	6.435	1	.011	3.333	1.315	8.450
	Constant	-1.003	.352	8.102	1	.004	.367		

a. Variable(s) entered on step 1: Current_Age, Current_BMI, Index of Multiple Deprivation Decile, Charlson_score_full, ACRCriteriaNodalOA, Gout_01, 2d4d ratio, Currently_big_toe, Flat_foot_01, Ankle_foot_toes_injury_01, Foot_ankle_Injections_0111, Career duration : calculated: Q9_To-Q9_From , matches, Training dose per week Calculated: Q15_Hours* Q15_Days , position.

Appendix 5.1 Impact of COVID-19 pandemic on my study and myself

Due to the COVID-19 pandemic and lockdown, all non-COVID-related research studies that required face-to-face assessment of participants in the UK were paused to protect the National Health Services (NHS) from increasing COVID-related patients from May 2020 until November 2021. Our study also required face-to-face assessment, such as radiographic examinations, which resulted in a delay of over a year in my study. Additionally, despite my study delay, my wife and I were infected with coronavirus during the pandemic while we had a newborn baby (My son Yousef), born on 13 September 2020 which added to the burden in our lives. Our supervisor supported and helped me during the infection period, which lasted for one month. I spent that time recovering and deeply appreciated their support and help during the pandemic.

Despite the pandemic and lockdown, I attended the office 1-2 times weekly, following the university's COVID guidance. I sent 2000 questionnaires to footballers and controls, received the completed questionnaires, developed a database, and entered and validated the data. Furthermore, due to the research fellow leaving after I finished the first year of my PhD, I took over the role of the project coordinator. This involved research ethics amendments, data acquisition, telephone assessment allocation, and data management. Because of this, I gained more skills than I could have gained without the pandemic.