



**University of
Nottingham**

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Osteoarthritis and Multimorbidity in Male Retired Professional Footballers compared to Men in the General Population

Thesis submitted to the University of Nottingham for the degree of
Doctor of Philosophy

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Declaration

I hereby declare that this PhD thesis is the result of original research. It has been conducted substantially by myself with assistance as outlined below. It has not already been accepted for any degree, diploma or other qualification. All authors and works to which reference has been made are fully acknowledged.

Supervision of this thesis was provided by Professor Weiya Zhang (Principal supervisor), Professor Michael Doherty, Dr Michelle Hall and Dr Subhashisa Swain.

Study design, literature search, searching abstract and full text articles for eligibility for the systematic review and meta-analysis were conducted primarily by myself with the support from my supervisors. Nouf Al-Otaibi provided support as a second reviewer for the literature search, searching abstracts and full text articles for eligibility and for quality assessment of all included studies.

Professors Weiya Zhang and Michael Doherty, Dr Colin Fuller, Dr Gordon Fuller and Prof. Mark Batt conceptualised and designed the baseline knee osteoarthritis (OA) study. Professors Weiya Zhang and Michael Doherty, Dr Gwen Fernandes and Dr Sanjay Parekh obtained ethical approval and were involved in recruitment, questionnaire distribution, data collection and assessment and scoring of radiographic knee OA.

Professors Weiya Zhang and Michael Doherty, Ahmed Thanoon (AT), Dr Bonnie Miller and Shima Espahbodi were involved in the design of the “Foot/ankle Osteoarthritis and Cognitive impairment in United Kingdom Soccer players” (FOCUS) study, ethical approval, questionnaire distribution and data collection. I was responsible for obtaining the socioeconomic status of the participants using their post-code at the follow-up. Prof. David Walsh (Nottingham), Prof. Catherine Bowen (Southampton), Prof. Terence O’Neil (Manchester), Dr Richard Wakefield (Leeds) and Prof. Fiona Watts (London) were principal investigators at 5 National Health Service (NHS) collaborating sites. The FOCUS administrative team were led by Dr Bonnie Miller and comprised Tom Gray, Deri Fitzpatrick and Sean Mcloughlin. They provided accessibility and assistance in arranging the radiography appointments for all footballers and control participants in the Radiology Departments of the five collaborating NHS sites.

AT and I were the main researchers to recruit participants at 5 NHS sites with help from Dr Bonnie Miller. Prof. Catherine Bowen from the University of Southampton trained AT and I on how to score radiographic features of foot and ankle OA. AT was responsible for scoring the radiographs for both the footballers and the controls. AT also conducted inter-observer reliability with me at three time points.

Patient-public involvement inputs were obtained with the help from the FOCUS administrative team (Dr. Bonnie Miller and Tom Gray) for footballers, and from

the Pain Centre administrative team (Rose Bentley and Maggie McPhee) for the general population.

I was responsible for the development of the cohort using the two cross-sectional databases over 6 years focusing on the incidence of knee pain and multimorbidity in professional footballers compared with the general population control men. I undertook data management and cleaning and analysis for the whole of the thesis, coding for long-term conditions at baseline and multimorbidity at follow-up for the cohort study, and for data management and coding for the radiographic association between knee OA and foot/ankle OA.

Table of contents

Declaration	i
Abstract.....	xiii
Conferences/meetings	xix
Acknowledgments	xxi
List of Abbreviations.....	xxiii
List of Figures	xxv
List of Tables.....	xxix
Chapter 1 Introduction.....	1
1.1 Osteoarthritis	1
1.1.1 Definition of Osteoarthritis	1
1.1.2 Nature of Osteoarthritis	1
1.1.3 Pathophysiology of Osteoarthritis.....	4
1.1.4 Signs and symptoms of Osteoarthritis.....	7
1.1.4.1 Knee Osteoarthritis	7
1.1.4.2 Foot/ankle Osteoarthritis	9
1.1.5 Diagnosis of Osteoarthritis	11
1.1.5.1 Classification Criteria for Osteoarthritis	11
1.1.5.2 Knee Osteoarthritis	12
1.1.5.3 Foot/ankle Osteoarthritis	15
1.1.6 Epidemiology of Osteoarthritis	22
1.1.6.1 Prevalence of Osteoarthritis.....	22
1.1.6.2 Incidence of osteoarthritis	25
1.1.6.3 Risk factors for Osteoarthritis.....	28
1.1.6.3.1 Genetic risk factors.....	29
1.1.6.3.2 Constitutional risk factors.....	40
1.1.6.3.3 Environmental risk factors	46
1.1.6.4 Risk Factors for Knee Osteoarthritis Pain	47
1.1.6.5 Risk factors for foot/ankle OA	53

1.1.7	Impact and burden of Osteoarthritis	58
1.1.8	Management of Osteoarthritis	59
1.2	Multimorbidity.....	63
1.2.1	Definition of Multimorbidity	63
1.2.2	Types of Multimorbidity	63
1.2.3	Epidemiology of Multimorbidity.....	65
1.2.3.1	Prevalence of Multimorbidity	65
1.2.3.2	Incidence of Multimorbidity.....	69
1.2.3.3	Risk factors for Multimorbidity	71
1.2.4	Burden and impact of Multimorbidity	72
1.2.5	Management of multimorbidity	73
1.2.6	Multimorbidity and Osteoarthritis.....	75
1.2.7	Association between osteoarthritis at the knee and foot/ankle joints 77	
1.3	Professional Footballers	79
1.3.1	Knee Pain in Professional Footballers	80
1.3.2	Foot/ankle Osteoarthritis in Professional Footballers	84
1.3.3	Multimorbidity in Professional Footballers	88
1.4	Justification of the Research.....	92
1.5	Aim	93
1.6	Objectives	94
1.7	Structure of the thesis	94
Chapter 2	Multimorbidity and long-term conditions and related risk factors in professional footballers compared to the general population: a systematic review and meta-analysis of observational studies	96
2.1	Introduction	96
2.2	Materials and methods	96
2.2.1	Study selection.....	96
2.2.2	Data sources and searches.....	98

2.2.3	Data extraction and management	100
2.2.4	Quality assessment.....	101
2.2.5	Validation	103
2.2.6	Data synthesis and analysis.....	103
2.3	Results.....	105
2.3.1	Search results and study quality	105
2.3.2	Study characteristics	107
2.3.3	Quality assessments	110
2.3.4	Prevalence, incidence and associated risk factors of multimorbidity and long-term conditions.....	116
2.3.4.1	Osteoarthritis.....	116
2.3.4.2	Back pain	128
2.3.4.3	Psychological conditions	129
2.3.4.4	Cardiovascular conditions	133
2.3.4.5	Respiratory conditions.....	135
2.3.4.6	Neurological disease.....	136
2.3.4.7	Endocrine disease	139
2.3.4.8	Vision	141
2.3.4.9	Other types of conditions/diseases and their related risk factors 142	
2.4	Discussion	144
2.4.1	Long-term conditions in footballers	144
2.4.2	Quality assessment.....	150
2.4.3	Limitations/strengths	150
2.4.4	Conclusion	151
Chapter 3	Methods for the longitudinal cohort study examining the incidence of knee pain and multimorbidity	152
3.1	Introduction	152
3.2	Study Design	152
3.2.1	Initial cross-sectional study	154

3.2.2	The subsequent follow-up study.....	156
3.3	Participants	157
3.4	Questionnaires.....	158
3.4.1	Baseline postal questionnaire:	160
3.4.2	General questions	160
3.4.3	Football-related questions	163
3.4.4	Follow-up postal questionnaire:.....	164
3.5	Exposure.....	165
3.6	Comparator.....	165
3.7	Outcome	166
3.7.1	Knee Pain.....	166
3.7.2	Multimorbidity	168
3.8	Covariates.....	172
3.9	Sample Size Calculation	173
3.10	Statistical Analysis	174
3.10.1	Descriptive analysis	174
3.10.2	Incidence of knee pain and multimorbidity	175
3.10.3	Incidence of specific groups of conditions	180
3.10.4	Risk factors associated with incident knee pain and multimorbidity 180	
3.10.5	Association between baseline knee pain and incident multimorbidity 181	
Chapter 4	Results and discussion of the longitudinal cohort study examining the incidence of knee pain and related risk factors among retired male professional footballers compared to men in the general population	182
4.1	Introduction	182
4.1	Results.....	182
4.1.1	Eligible population for knee pain	182

4.1.2	Study population for incident knee pain	183
4.1.2.1	Incidence of knee pain	184
4.1.3	Risk factors for incident knee pain within groups	186
4.1.3.1	Characteristics between footballers with versus those without incident knee pain	186
4.1.3.2	Characteristics between controls with versus those without incident knee pain	188
4.1.3.3	Risk factors related to incident knee pain.....	189
4.1.4	Knee pain and its association with incident multimorbidity	191
4.2	Discussion	194
4.2.1	Incidence of knee pain	194
4.2.2	Risk factors related to incident knee pain.....	197
4.2.3	Knee pain and its association with incident multimorbidity	200
4.2.4	Limitations.....	201
4.2.5	Conclusion	202
Chapter 5	Results and discussion of the longitudinal cohort study examining incident multimorbidity and its related risk factors in male retired professional footballers compared to men in the general population.....	203
5.1	Introduction.....	203
5.2	Results.....	203
5.2.1	Eligible population for multimorbidity.....	203
5.2.2	Study population for incident multimorbidity	204
5.2.2.1	Incidence of Multimorbidity.....	205
5.2.2.2	Incidence of specific groups of conditions.....	206
5.2.3	Risk factors for incident multimorbidity within group.....	208
5.2.3.1	Characteristics of footballers with versus those without incident multimorbidity	208
5.2.3.2	Characteristics of controls with versus those without incident multimorbidity	210
5.2.3.3	Risk factors related to incident multimorbidity	211

5.3	Discussion	214
5.3.1	Incidence of multimorbidity.....	214
5.3.2	Incidence of specific groups of medical conditions.....	215
5.3.3	Risk factors related to incident multimorbidity	219
5.3.4	Limitations.....	223
5.3.5	Conclusion	225
Chapter 6 Association between radiographic knee and foot/ankle		
osteoarthritis in male retired professional footballers and men in the general		
population: an observational study.....		
6.1	Introduction	226
6.2	Methods.....	226
6.2.1	Study design	226
6.2.2	Participants	227
6.2.3	Questionnaires	228
6.2.4	Recruitment.....	230
6.2.5	Radiographic assessment.....	231
6.2.5.1	Knee osteoarthritis	231
6.2.5.2	Foot/ankle osteoarthritis.....	232
6.2.5.3	Scoring techniques	238
6.2.6	Data management and cleaning	239
6.2.7	Statistical analysis.....	240
6.2.7.1	Descriptive analysis	240
6.2.7.2	Association between OA at the knee and foot and/or ankle... ..	242
6.2.7.3	Association between summated scores of OP and JSN at the knee and foot and/or ankle	243
6.3	Results.....	244
6.3.1	Inter/intra rater reliability.....	244
6.3.2	Characteristics of the study population	248
6.3.3	Association between radiographic knee OA and foot/ankle OA	250

6.3.4	Association between radiographic knee OA and foot OA and ankle OA	254
6.3.5	Association between summated score of structural changes between knee OA and foot/ankle OA	258
6.4	Discussion	261
6.4.1	Limitations	265
6.4.2	Conclusion	266
Chapter 7	Patient and public involvement and engagement	267
7.1	Introduction	267
7.2	Aims.....	267
7.3	Methods.....	267
7.4	Results.....	269
7.5	Discussion	274
7.5.1	Challenges	275
7.5.2	Limitations.....	275
7.5.3	Conclusion	275
Chapter 8	General discussion and conclusion	277
8.1	Introduction	277
8.2	Main findings and interpretation.....	277
8.3	Novel findings	284
8.4	Strengths and Limitations	284
8.5	Clinical Implications	286
8.6	Future research recommendations	287
8.7	Conclusion.....	290
References.....		292
Appendices		345

Appendix A: FOCUS newsletter	345
Appendix B: Data request for baseline data of the questionnaire	347
Appendix C: Baseline questionnaire for footballers (C-1) and controls (C-2) ..	359
Appendix (C-1): baseline questionnaire for footballers.....	359
Appendix (C-2) baseline questionnaire for controls	380
Appendix D: Follow-up questionnaire for footballers (D-1) and controls (D-2)	403
Appendix (D-1) follow-up questionnaire for footballers.....	403
Appendix (D-2) follow-up questionnaire for controls	433
Appendix E: Goodness of fit of the model and variance inflation factor for logistic regression of incident knee pain; validation of the results using “backward-stepwise regression”	460
Appendix F: Goodness of fit of the model and variance inflation factor for logistic regression of incident multimorbidity and specific long-term condition; validation of the results using “backward-stepwise regression”	462
Appendix G: Incidence of specific conditions in the study population during 2014-2020.....	467
Appendix H: Study population recruited for foot/ankle radiographic assessment in 5 NHS sites	468
Appendix I: Details for all data management and cleaning of foot and/or ankle OA.....	469
Appendix J: Goodness of fit of the model and variance inflation factor for logistic regression of association between knee OA and foot and/or ankle OA	472
Appendix K: Variance inflation factors in linear regression between summated scores of OP and JSN in knee OA and summated scores of OP and JSN in foot/ankle OA	475
Appendix L: Responses of footballers and Pain Centre people to the first patient public involvement questions	476

Appendix M: GANTT chart for delivery of each of the studies undertaken in this
PhD 480

Abstract

Background: Football is one of the most popular sports world-wide.

Professional footballers are at higher risk of injuries of lower limb joints and the head due to the nature of the game. This can lead to short- and long-term health consequences such as osteoarthritis (OA) and cognitive disorders. However, whether footballers are at higher risk of developing knee pain, multimorbidity and OA of the foot/ankle after retirement remains unknown.

Objectives: [1] to systematically review published observational studies on multimorbidity and long-term conditions in professional footballers only or compared to the general population; [2] to examine the incidence of knee pain in male retired professional footballers (referred to as footballers) compared to men in the general population (referred to as controls) and associated risk factors in each group; [3] to examine the association between knee pain at baseline and incidence of multimorbidity at follow-up in footballers and controls; [4] to examine the incidence of multimorbidity in footballers compared to controls and associated risk factors in each group; and [5] to examine the association between radiographic knee OA and foot and/or ankle OA in footballers and controls.

Method: *A systematic literature review* of observational studies for multimorbidity in professional footballers was undertaken in 3 databases in addition to the Google Scholar until 31st December 2021. The Newcastle-Ottawa

Scale was used to assess the quality of the observational studies. The prevalence, incidence and associated risk factors of multimorbidity, or specific long-term conditions were extracted or calculated for footballers compared to the general population. The pooled prevalence of multimorbidity and each long-term condition and 95% confidence interval (CI) were calculated.

An observational cohort study was undertaken in retired male professional footballers and aged matched general population controlled men aged ≥ 40 years using a postal questionnaire to examine the incidence of knee pain and multimorbidity over the 6-year period, and radiographic examination in a sample from each group to examine the association between radiographic knee and foot/ankle OA. Knee pain was defined as anterior knee pain experienced for most days of the previous month using body pain mannequin. Multimorbidity was defined as having at least 2 long-term conditions in an individual from 45 conditions included. Risk factors for incident knee pain and multimorbidity were examined per group. Radiographic knee OA was defined using Kellgren and Lawrence grade ≥ 2 in either tibiofemoral or patellofemoral compartments irrespective of the side. Foot and/or ankle OA was defined using the La Trobe Atlas (i.e., the presence of at least ≥ 2 in osteophytes (OP) plus joint space narrowing (JSN) at any joint of foot/ankle). Incidence (%) of knee pain and multimorbidity was estimated for both groups and adjusted odd ratio (aOR) and 95% CI was calculated using logistic regression. Risk factors for knee pain and multimorbidity were examined using multivariable logistic regression. OR and

95% CI was calculated using logistic regression for association between radiographic OA at the knee and foot/ankle joints. Correlation coefficient β was calculated using linear regression for summated radiographic OP and JSN scores at both sites.

Results

56 studies (42 cross-sectional studies, 4 case-control studies, 8 cohort studies, and 2 mixed design studies (cross-sectional and case-control)) were eligible for the systematic review from 18 different countries. There were 24 studies for footballers versus controls, and 32 studies for footballers only. The age ranged from 18 to 93 years old. Quality of included studies was regarded as medium quality. Most of the retrieved studies focused on a single long-term condition, and some studies reported on more than one long-term condition but did not report on multimorbidity. OA was found to be the most common condition being investigated, followed by neurodegenerative diseases, hip or knee pain, psychological and cardiovascular diseases. Methods used to examine long-term conditions or their risk factors were highly heterogenous. Of the 14 studies provided prevalence of knee OA in footballers, the pooled prevalence was 31% in male retired footballers (95% CI 20 – 42%). Of the 6 studies provided prevalence of knee OA, the pooled prevalence was 26% in male controls (95% CI 7 – 44%). Of the 4 studies provided prevalence of knee pain in footballers, the pooled prevalence was 53% in male retired footballers (95% CI 0 – 100%). Of the two studies provided prevalence of knee pain, the pooled prevalence was

27% in male controls (95% CI 26 – 28%). Of the 4 studies provided prevalence of ankle OA, the pooled prevalence was 9% (95% CI 7 - 10%) in male retired footballers. Of the 7 studies provided prevalence of hip OA in footballers, the pooled prevalence was 7% (95% CI 4 - 11%) in male retired footballers. Of the two studies provided prevalence of hip OA in controls, the pooled prevalence was 2% (95% CI 1 - 4%) in controls. Joint injury was the major risk factor associated with the increased risk of OA in footballers. For neurodegenerative disease, only one comparative study was identified from the literature, the incidence of neurodegenerative disease was higher in footballers (5.0%) compared to the general population controls (1.6%) over 18 years follow-up ($p<0.001$). Playing position (midfielder and defender), head injury and career duration might increase risk for neurodegenerative disease. For the following conditions, only one comparative study was identified from the literature, the prevalence of self-reported acute myocardial infarction was 3.08% in male retired footballers and 9.46% in controls ($p<0.001$), hypertension was 22.98% in footballers and 34% in controls ($p<0.001$), and diabetes was 3.77% in footballers and 11.47% in controls ($p<0.001$).

Of 486 footballers and 610 controls with data collected at two waves, 222 footballers and 402 controls were at risk for knee pain. There was no significant difference in the incidence of knee pain between footballers and controls (24.0% and 28.8% respectively, $p=0.18$) (aOR 0.77, 95% CI 0.52 – 1.16). Whilst body mass index (BMI) (aOR 1.17, 95% CI 1.04 – 1.31) and football-related knee

injury (aOR 2.42, 95% CI 1.22 – 4.79) were risk factors for incident knee pain in footballers, BMI (aOR 1.08, 95% CI 1.01 – 1.14) and higher socioeconomic status (aOR 0.88, 95% CI 0.81 – 0.95) were associated with incident knee pain in controls. No association was observed between knee pain at baseline and incidence of multimorbidity at follow-up in footballers and controls.

A total of 317 footballers and 362 controls were at risk for multimorbidity. The incidence of multimorbidity was lower in footballers (37.5%) than controls (52.0%) ($p < 0.001$) (aOR 0.64, 95% CI 0.45 - 0.89). Whilst age (aOR 1.04, 95% CI 1.01 – 1.07), the presence of one condition at baseline (aOR 2.98, 95% CI 1.78 – 4.99) and analgesic use (aOR 2.88, 95% CI 1.53 – 5.40) were risk factors for incidence of multimorbidity in footballers, age (aOR 1.05, 95% CI 1.03 – 1.08), the presence of one condition at baseline (aOR 2.73, 95% CI 1.73 – 4.31) and higher socioeconomic status (aOR 0.88, 95% CI 0.81 – 0.95) were associated with the incidence of multimorbidity in controls.

A total of 72 footballers and 147 controls underwent radiographs for both knee and foot/ankle joints. The association between knee OA and foot/ankle OA was not statistically significant in footballers (aOR 4.13, 95% CI 0.72 – 23.66; $p = 0.111$), but was significant in controls (aOR 2.57, 95% CI 1.01 – 6.53; $p = 0.046$). Similar findings were observed using the linear regression analysis for summated radiographic scores of OP and JSN.

Conclusions

Although professional footballers may be more likely to develop OA and neurodegenerative disease, they may be less likely to develop other long-term conditions, such as diabetes and cardiovascular diseases, and multimorbidity. In addition to the constitutional risk factors such as BMI, football-related head and joint injuries may explain the additional risks of OA and neurodegenerative disease. However, the general health and physical fitness may also explain the lower risk of other conditions and multimorbidity in footballers compared to controls. The results of this PhD project suggest the preventative strategy should be tailored to the population specifications to mitigate the specific risks and improve the general health status.

Conferences/meetings

PhD work

1. The British Association of Sport and Exercise Medicine (Manchester, 2023 5th-6th Oct). Incidence of Knee pain and Multimorbidity in Male ex-professional footballers compared to men in the General Population: A retrospective cohort study (Poster Presentation).
2. UK-Rime (Keele, 4th-5th Sept 2024). Association between radiographic knee and foot/ankle osteoarthritis in male retired professional footballers and men in the general population: an observational study (Oral Presentation).
3. I have contributed to the overall FOCUS newsletter (Appendix A).

Non-PhD work

1. The 65th Annual Scientific Meeting of the British Pain Society (Glasgow, 9th - 11th May 2023). Nouf AlOtaibi, **Monirah Ali Shuaib**, Subhashisa Swain, Michael Doherty, Weiya Zhang, Michelle Hall. Epidemiology of chronic shoulder pain in people aged 40 or older: a systematic review and meta-analysis of observational studies (Oral and poster presentation).
2. The European Alliance of Associations for Rheumatology (EULAR) Conference (Vienna, 12th-15th June 2024). Thanoon, A., Espahbodi, S., **Shuaib, M. A.**, Miller, B., Duncan, A., Bowen, C., O'Neill, T., Wakefield, R., Watt, F., Walsh, D., Fuller, C., Fuller, G., Batt, M., Parekh, S., Fernandes, G., Doherty, M., Zhang, W. *Prevalence and risk factors of foot/ankle osteoarthritis in retired male professional footballers compared with general population controls: a cross-sectional study* (Publication, AB1574-HPR).

Collaborations:

1. I have been involved in the Nouf Al-Otaibi (PhD student) systematic review and meta-analysis (“Epidemiology of chronic shoulder pain in people aged 40 or older: a systematic review and meta-analysis of observational studies”) as a second reviewer to extract and validate data and to assess the quality of all included studies.

2. I have been involved in research by Ahmed Thanoon (PhD student):
 - a. Prevalence of foot and ankle pain and radiographic osteoarthritis in retired professional footballers compared with men in the general population: a cross-sectional study.
 - b. Risk factors for foot and ankle osteoarthritis in retired professional footballers compared to men in the general population: a case-control study.

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List of Abbreviations

1 st CMJ	First cuneo-metatarsal joint
1 st MTPJ	First metatarsophalangeal joint,
2D:4D ratio	The length ratio between the second digit (2D) and the fourth digit (4D)
2 nd CMJ	Second cuneo-metatarsal joint
ACL	Anterior cruciate ligament
ACR	The American College of Rheumatology
ALS	Amyotrophic lateral sclerosis
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
EULAR	The European Alliance of Associations for Rheumatology
FL	First league
FOCUS	Foot/ankle Osteoarthritis and Cognitive impairment in UK Soccer players Study
GOAL	Nottingham Genetics of Osteoarthritis and Lifestyle
GP	General practitioner
HDL	High density lipoprotein
HR/aHR	Hazard ratio/adjusted hazard ratio
IQR	Interquartile range
JSN	Joint space narrowing
K-L	Kellgren-Lawrence
Kg	Kilograms
KPIC	Knee Pain and related Health in the Community Study
m	Meter
MCAR	Missing completely at random

MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
N1 st CJ	Navicular-first cuneiform joint
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OP	Osteophytes
OR/aOR	Odds ratio/adjusted odds ratio
PPI	Patient-public involvement
PPIE	Patient and public involvement and engagement
PRC	Proportional risk contribution
RKOA	Radiographic knee OA
ROM	Range of motion
RR/aRR	Relative risk/adjusted relative risk
SD	Standard deviation
SE	Standard error
SIR	Standardised incidence rate
SMR	Standardised mortality ratio
TKR	Total knee replacement
TNJ	Talonavicular joint
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WOMAC	The Western Ontario and McMaster Universities Arthritis Index
YLD	Years lived with disability

List of Figures

Figure 1. Joints often affected by osteoarthritis are shown in the left (black). Relatively spared joints of involvement are shown on the right (stippled). Produced with permission from Prof. Michael Doherty.....	2
Figure 2. An illustration of osteoarthritis as an inherent repair process that is triggered by a variety of insults and results in varying outcomes (adapted from Doherty et al., 2016). OA – osteoarthritis	4
Figure 3. Pathogenic features of OA. Produced with permission from Prof. Michael Doherty	5
Figure 4. the La Trobe Foot Atlas to examine radiographic features of foot osteoarthritis in five joints across two views. OP – osteophyte; JSN – joint space narrowing	19
Figure 5. Five feet joints in the dorso-plantar view in both feet	20
Figure 6. Foot and ankle joints scored in the lateral view.....	21
Figure 7. The ankle (talocrural) joint seen in the antero-posterior view.....	21
Figure 8. Overall prevalence of osteoarthritis according to joint sites using primary care data in the United Kingdom. OA – osteoarthritis (adapted from Swain et al., 2020 study for illustration purpose).....	23
Figure 9. Prevalence of symptomatic radiographic osteoarthritis according to joint sites using community-based study in the United Kingdom. OA – osteoarthritis (adapted from Peat et al., 2020 and Murray et al., 2018 studies for illustration purpose).....	24
Figure 10. Incidence of osteoarthritis at any joint by age and sex in 2017 in the UK. Produced with permission from Dr Subhashisa Swain.....	26
Figure 11. Possible risk factors for osteoarthritis development	29
Figure 12. Femoral shaft/neck angle – high on the left, low on the right. Produced with permission from Prof. Michael Doherty.....	32
Figure 13. Measurement of the femoral head-to-femoral neck ratio and the neck shaft angle. NSA – neck shaft angle. Produced with permission from Prof. Michael Doherty	32

Figure 14. Centre edge angle (CEA) and acetabular depth (AD) angles used to estimate the risk for hip osteoarthritis. Produced with permission from Dr Daniel McWilliams	34
Figure 15. Genes have a large influence in early skeletal growth and shape that predispose to osteoarthritis. Produced with permission from Dr Cindy Boer.....	36
Figure 16. Knee malalignment (A and B indicate varus), C is normal and (D and E indicate valgus).....	37
Figure 17. Three patterns of finger ratio	39
Figure 18. Summary of NICE recommendations. The core consists of the basic recommendations that everyone with symptomatic OA should be given. Analgesics should be considered as adjuncts if the core treatments alone are insufficient. (Data from Osteoarthritis – national clinical guideline for care and management in adults. NICE and Royal College of Physicians Guidelines on Osteoarthritis. 2022).....	62
Figure 19. PRISMA Flow Diagram	106
Figure 20. Forest plot showing pooled prevalence of knee osteoarthritis in male retired footballers, random effects model. CI – confidence interval.....	117
Figure 21. Asymmetrical Funnel plot showing pooled prevalence of knee OA in male retired footballers in studies	118
Figure 22. Forest plot showing pooled prevalence of knee osteoarthritis in male controls, random effects model. CI – confidence interval.....	118
Figure 23. Forest plot showing pooled prevalence of knee pain in male retired footballers, random effects model. CI – confidence interval.....	122
Figure 24. Forest plot showing pooled prevalence of knee pain in male controls, fixed effects model. CI – confidence interval.....	122
Figure 25. Forest plot showing the pooled prevalence of ankle osteoarthritis in male retired footballers, fixed effects model. CI – confidence interval	124
Figure 26. Forest plot showing the pooled prevalence of hip osteoarthritis in male retired footballers, random effects model. CI – confidence interval	126
Figure 27. Forest plot showing the pooled prevalence of hip osteoarthritis in controls, fixed effects model. CI – confidence interval	126

Figure 28. Summary of prevalence of osteoarthritis in male retired footballers only or/and retired footballers versus controls. OA – osteoarthritis. Other include osteoarthritis at the elbow, wrist, hand and shoulder	128
Figure 29. Forest plot showing the pooled prevalence of depression in female current footballers, random effects model. CI – confidence interval.....	130
Figure 30. Forest plot showing the pooled prevalence of depression in male retired footballers, random effects model. CI – confidence interval.....	131
Figure 31. Forest plot showing the pooled prevalence of hypertension in male retired footballers, random effects model. CI – confidence interval.....	135
Figure 32. Forest plot showing the pooled prevalence of diabetes in male retired footballers, random effects model. CI – confidence interval.....	140
Figure 33. Forest plot showing the pooled prevalence of gout in male retired footballers, fixed effects model. CI – confidence interval	140
Figure 34. Summary of study population including footballers and general population in 2014 and 2020. PF - professional footballers; OA – osteoarthritis; KPIC - Knee Pain and Related Health In the Community Study; FOCUS - Foot/ankle Osteoarthritis and Cognitive impairment in UK Soccer players	155
Figure 35. Mapping for common questions in the baseline and follow-up questionnaires for the study population.....	159
Figure 36. The line drawing tool to determine nodal osteoarthritis	162
Figure 37. Hand diagram for participant to indicate the presence of nodes in each finger joint(s) for both hands.....	162
Figure 38. Body mannequin to determine self-reported anterior knee pain and pain for most days in the past month at any other region.....	167
Figure 39. Incidence of specific groups of conditions in footballers and controls between 2014-2020. * Bonferroni adjusted p-value ≤ 0.0038	207
Figure 40. Participant position for bilateral foot radiograph in the dorsoplantar view.....	233
Figure 41. Participant position for unilateral foot radiograph in the medial-oblique view.....	234

Figure 42. Participant position for unilateral foot and ankle radiographs in the lateral view	235
Figure 43. Participant position for unilateral ankle radiograph in the antero-posterior view	236
Figure 44. The medial-oblique view for the foot providing a clearer view to score the 2nd cuneo-metatarsal joint.....	283

List of Tables

Table 1. Symptoms and signs of knee osteoarthritis.....	8
Table 2. Signs and symptoms of foot and ankle osteoarthritis	11
Table 3. Different criteria to diagnose knee osteoarthritis	14
Table 4. Kellgren and Lawrence grading system for osteoarthritis.....	15
Table 5. The radiographic scoring for the foot using the La Trobe Foot Atlas...	18
Table 6. Details of studies examined foot and ankle osteoarthritis	54
Table 7. Examples of studies that have examined multimorbidity prevalence in the United Kingdom.....	68
Table 8. Risk factors for knee osteoarthritis related outcomes in male retired professional footballers (Parekh et al. 2021).....	84
Table 9. Search strategy in MEDLINE database.....	99
Table 10. Characteristics of the included studies	109
Table 11. Quality of cross-sectional studies by Newcastle-Ottawa Scale	111
Table 12. Quality of case-control studies by Newcastle-Ottawa Scale	114
Table 13. Quality of cohort studies by Newcastle-Ottawa Scale	115
Table 14. Long-term conditions included in assessment of multimorbidity in footballers and controls	168
Table 15. Specific long-term conditions listed in the baseline questionnaire in footballers versus controls	171
Table 16. Covariates for knee pain and multimorbidity	173
Table 17. Questionnaire missing data for incident knee pain in footballers and controls	178
Table 18. Questionnaire missing data for incident multimorbidity in footballers and controls	179
Table 19. Characteristics of the study populations at baseline for the incident knee pain study.....	184
Table 20. Incidence of knee pain by age between 2014 and 2020	185
Table 21. Odds ratio of incident knee pain in footballers compared to controls	186

Table 22. Comparison between footballers with (cases) and without (controls) incident knee pain	187
Table 23. Characteristics of the study population for incident knee pain in the general population	189
Table 24. Risk factors related to incident knee pain in footballers versus the general population	191
Table 25. The association between baseline knee pain and incident multimorbidity between 2014-2020	193
Table 26. Characteristics of study population having no or just one condition at baseline.....	204
Table 27. Incidence of multimorbidity by age between 2014 and 2020.....	205
Table 28. Odds ratio of multimorbidity in footballers compared to controls	206
Table 29. Comparison between footballers with and without incident multimorbidity	209
Table 30. Comparison between the general population with and those without incident multimorbidity.....	211
Table 31. Risk factors related to incident multimorbidity in the footballers and the general population	213
Table 32. The Kellgren and Lawrence radiographic scoring system	231
Table 33. The radiographic scoring for foot and ankle osteoarthritis using the La Trobe Atlas.....	237
Table 34. Missing data for variables in the questionnaire and radiographic assessment for the study population.....	241
Table 35. Inter-rater reliability between two observers for radiographic assessment of knee osteoarthritis.....	245
Table 36. Intra-rater reliability of radiographic foot/ankle osteoarthritis	246
Table 37. Inter-rater reliability of radiographic foot/ankle osteoarthritis	247
Table 38. Characteristics of the study population at baseline	249
Table 39. Association between radiographic knee osteoarthritis and foot/ankle osteoarthritis	252

Table 40. Association between radiographic knee osteoarthritis and foot/ankle osteoarthritis	253
Table 41. Interaction between being a footballer and knee OA for the risk of foot/ankle OA	254
Table 42. Association between radiographic knee osteoarthritis and foot osteoarthritis	256
Table 43. Association between radiographic knee osteoarthritis and ankle osteoarthritis	257
Table 44. Linear regression between summated knee radiographic scores and summated foot/ankle radiographic scores.....	260
Table 45. Summary of the responses from the footballers and Pain Centre volunteers	271
Table 46. Summary of the responses from the footballers and Pain Centre volunteers to the newsletter email.....	273

Chapter 1 Introduction

This chapter provides the background and rationale for the studies undertaken for this PhD thesis. It commences with an overview of osteoarthritis (OA) and multimorbidity. Then, a review of studies examining knee pain, foot/ankle OA and multimorbidity in professional footballers. Finally, the rationale, aim and objectives, and structure of the thesis are presented.

1.1 Osteoarthritis

1.1.1 Definition of Osteoarthritis

OA is the most common type of chronic arthritis worldwide (Johnson and Hunter, 2014). It used to be thought that OA was a degenerative ‘wear and tear’ disease of cartilage (Millerand et al., 2019). However, OA is now widely regarded as a metabolically active, dynamic process that involves all joint tissues, characterised by both tissue damage and new tissue production, which might be induced by a range of mechanical and biochemical joint insults (Doherty et al., 2016).

1.1.2 Nature of Osteoarthritis

OA is a common complex disorder confined to synovial joints. Although it most commonly affects the hand, foot, knee, hip and spinal apophyseal joints it can affect any synovial joint (Figure 1) (O'Neill et al., 2018). OA is a leading cause of joint pain and disability in middle-aged and older individuals (Doherty et al., 2016).

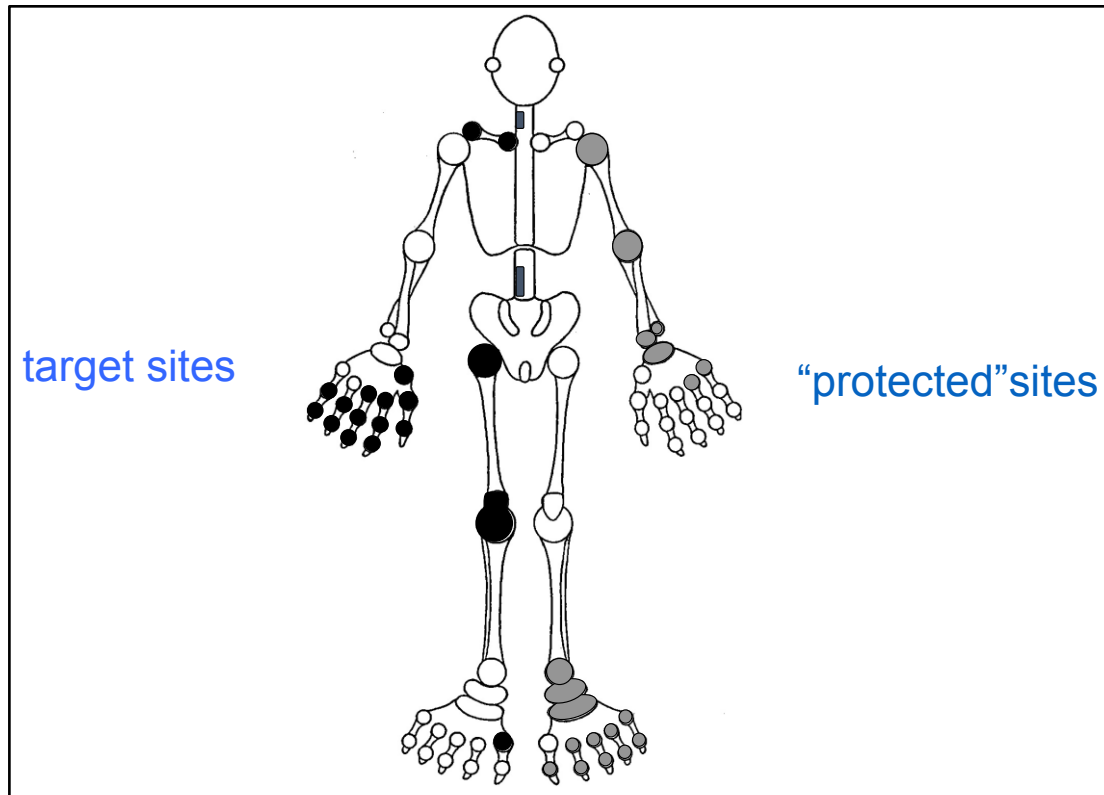


Figure 1. Joints often affected by osteoarthritis are shown in the left (black). Relatively spared joints of involvement are shown on the right (stippled).
Produced with permission from Prof. Michael Doherty

OA has been conserved throughout our evolutionary history and it is also present in other animals that have synovial joints (Hutton, 1987, Jurmain and Kilgore, 1995). Most OA never causes any symptoms and the majority of people who do develop symptoms in joints with OA have phases of pain and disability that eventually may improve and even resolve completely (Atkinson, 1996). This is particularly true with nodal OA of the hands which typically causes several years of intermittent pain and stiffness in middle-age, especially in women (“menopausal OA”), when some of the distal and proximal interphalangeal joints are developing structural OA, but once the finger swellings/nodes are fully

formed the OA joints usually become pain-free and function is no worse than in other people of the same age without hand OA. Such a good outcome also commonly occurs at other sites, the site with the worse prognosis being the hip (Brandt et al., 2003, Pattrick et al., 1989, Danielsson, 1964, Hernborg and Nilsson, 1977). The evolutionary and phylogenetic preservation of OA, its pathophysiological activity, the common absence of any symptoms and the generally good outcome of symptomatic OA all suggests that OA is the inherent repair process of synovial joints, which may be triggered by diverse insults including genetic, constitutional and environmental risk factors (Figure 2) (Bland and Cooper, 1984, Radin and Burr, 1984).

The slow natural history of OA allows for an inherent repair process of synovial joints to occur (Brandt et al., 2003, Doherty et al., 2016). The initial insult that necessitated joint repair is frequently made up for by the remodeling and production of new bone as well as the mechanical adaptations of the joint tissues (known as “compensated OA”). However, for some, the overwhelming insult(s) or continued microtrauma in the joint, along with the mediating influence of personal risk factors, prevent the joint from successfully compensating. This more frequently results in symptoms and loss of function (also known as “decompensated OA”) (Figure 2) (Brandt et al., 2003, Doherty et al., 2016).

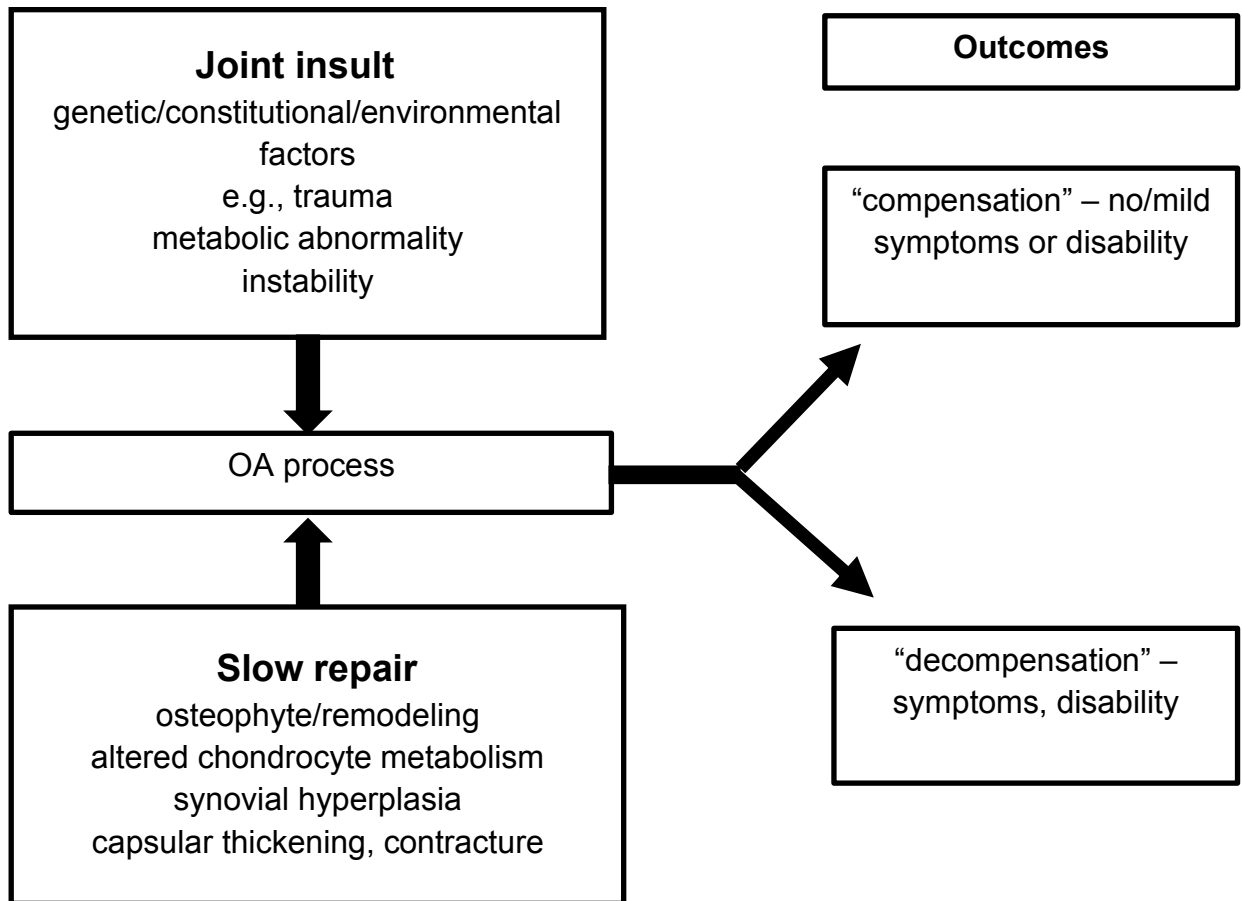


Figure 2. An illustration of osteoarthritis as an inherent repair process that is triggered by a variety of insults and results in varying outcomes (adapted from Doherty et al., 2016). OA – osteoarthritis

1.1.3 Pathophysiology of Osteoarthritis

OA is a whole joint condition involving structural changes in the subchondral and marginal bone, hyaline articular cartilage, fibrocartilage in joints with menisci (such as the knee), synovium/capsule, ligaments and periarticular tissue including muscles (Figure 3) (Brandt et al., 2006). Although the pathogenesis of OA is still unclear, it is widely accepted that OA is multifactorial in origin (Lespasio et al., 2017). OA is an active dynamic process involving both damage and attempted repair of joint tissues (Prieto-Alhambra et al., 2014a).

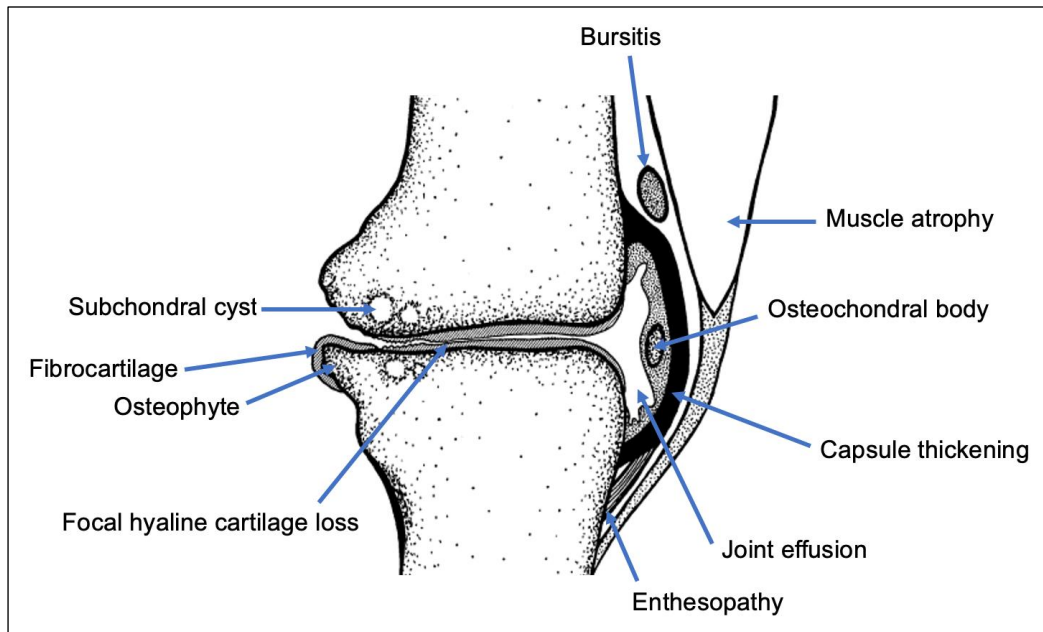


Figure 3. Pathogenic features of OA. Produced with permission from Prof. Michael Doherty

During the OA process (Hunter and Bierma-Zeinstra, 2019):

- Cartilage loses its integrity and its composition changes, resulting in reduced biomechanical resilience and making it more susceptible to adverse physical forces.
- Cartilage slowly develops surface fibrillation and loss of tissue and later deeper vertical cartilage fissures followed by the enlargement of the calcified cartilage zone.
- Cartilage cells (chondrocytes) increase their number and synthetic activity, taking on a hypertrophic phenotype, in an attempt to repair. However, by doing so, matrix degradation products and proinflammatory

mediators are generated, which deregulate chondrocyte function and act on the adjacent synovium stimulating proliferative and pro-inflammatory responses. Proliferating synoviocytes also release proinflammatory products. This process is accompanied by tissue hypertrophy and increased vascularity.

- Bone turnover is increased in the subchondral bone, and vascular invasion occurs from the subchondral bone through the tidemark and even into the cartilage. The development of subchondral bone marrow lesions is linked to this bone remodeling and repair. Bone marrow lesions are often visualised with magnetic resonance imaging (MRI) in OA assessment (Lepage et al., 2019). They were initially called “bone bruising” and are thought to represent mechanical bone injury and subsequent attempted repair – if it fails it may result in bone cysts (Lepage et al., 2019).
- Development of osteophytes at the joint margins occurs through the process of endochondral ossification (i.e., production of new fibrocartilage which undergoes calcification and ossification – the same process that allows bones to grow and elongate during development). This is stimulated by inflammatory factors and by altered biomechanical loading of the joint.

1.1.4 Signs and symptoms of Osteoarthritis

1.1.4.1 Knee Osteoarthritis

The main symptoms of knee OA are usage-related knee pain, stiffness, function limitation and participation restriction, and reduced quality of life (Yunus et al., 2020). Physical signs that may be present on examination include decreased range of motion, joint-line tenderness on palpation, muscle weakness and later wasting, crepitus, bony swelling, mild or modest effusion and malalignment (Table 1) (Abhishek and Doherty, 2013, Sharma et al., 2016). Chronic pain and difficulties undertaking activities of daily living (e.g., walking, climbing stairs, performing household duties) may have a negative psychological impact and contribute to a lower quality of life and cause people to seek medical advice (Paskins et al., 2013, Lespasio et al., 2017).

Table 1. Symptoms and signs of knee osteoarthritis

Symptoms	Signs
• stiffness • functional impairment • pain	• reduced range of motion • joint-line tenderness • bony enlargement • crepitus (coarse grating on palpation during movement, sometimes with audible cracking) • muscle weakness or wasting • joint instability • deformity/ malalignment • small to modest effusion

Chronic knee pain is considered a significant indicator for OA progression (Zhang et al., 2011). Usage-related joint pain, relieved by rest, is the most common symptom, and is felt anteriorly, often localised according to the compartments affected (i.e., anterior localised over the kneecap with patellofemoral OA, antero-medial with medial tibiofemoral OA, and antero-lateral with lateral tibiofemoral OA). Secondary peri-articular lesions (e.g., inferior medial tibiofemoral enthesopathy, anserine bursitis) may also accompany knee OA and cause well-localised pain over the involved structure, away from the joint-line (Zhang et al., 2011, Abhishek and Doherty, 2013). Pain may be sharp

or dull, persistent or intermittent, and vary in severity from mild to severe (Lespasio et al., 2017). Any change in symptoms typically occurs slowly.

1.1.4.2 Foot/ankle Osteoarthritis

People with structural first metatarsophalangeal joint (1st MTPJ) OA walk with altered foot biomechanics, presenting with reduced joint range of motion and greater maximum force and peak plantar pressures below the hallux, which may contribute to the severity of the symptoms (Zammit et al., 2008, Menz et al., 2018). 1st MTPJ OA is associated with reduced range of motion of 1st MTPJ dorsiflexion (Halstead and Redmond, 2006). All of these contribute to the patient adopting pain avoidance gait patterns (Menz et al., 2018, Canseco et al., 2008). Also, it might contribute to the development of inter-phalangeal joint hypertension and secondary calluses (Menz et al., 2015, Zammit et al., 2008).

Midfoot OA is associated with several symptoms such as pain in the midfoot (Thomas et al., 2015b), weakness of foot and leg muscles (Arnold et al., 2021), midfoot deformity (reduction of the dorsal arch and bony enlargement on the dorsal surface), and difficulty in climbing stairs and walking (Rathod et al., 2016, Rao et al., 2009). Pain is experienced predominantly on the dorsal aspect of the midfoot, and is aggravated by weight-bearing activity and triggered by footwear pressure in severe cases (Patel et al., 2010). Pain severity is also correlated with the flatter feet and higher midfoot plantar pressure during barefoot walking

manifested in people with midfoot OA deformity (Menz et al., 2010c, Thomas et al., 2015a, Rao et al., 2011).

Ankle OA is associated with usage related pain localised predominantly anteriorly and laterally around the joint line, significant deficiencies in gait, reduced stability during stair climbing, persistent instability, worse postural control, greater reported disability, and altered plantar pressure (Horisberger et al., 2009, Valderrabano et al., 2007, Valderrabano et al., 2006a, Wikstrom and Anderson, 2013). People with unilateral or asymmetric ankle OA also exhibit reduced activation of lower leg muscles and atrophy for ankle muscles flexors and extensors (Nüesch et al., 2012, Valderrabano et al., 2006b, Wiewiorski et al., 2012). Table 2 summarises the signs and symptoms of OA in different areas of the foot and ankle.

Table 2. Signs and symptoms of foot and ankle osteoarthritis

1 st MTPJ OA	Midfoot OA	Ankle OA
• pain • ↓ ROM • pain avoidance gait pattern	• pain • ↓ strength of foot and lower leg muscles • difficulty walking and climbing stairs	• pain • deficiencies in gait • persistent instability • reduced stability during climbing stairs • worse postural control • reduced lower leg muscle strength

OA – osteoarthritis; 1st MTPJ – first-metatarsophalangeal joint

ROM – range of motion

1.1.5 Diagnosis of Osteoarthritis

1.1.5.1 Classification Criteria for Osteoarthritis

OA is a common complex disorder with variable interaction between genetic, constitutional and environmental risk factors (Lespasio et al., 2017). It is rare for OA to be caused by just one factor (e.g., monogenic joint dysplasia). OA classification criteria traditionally has been divided into primary OA, which is caused mainly by genetic and constitutional factors, and secondary OA, which occurs when there is an overt cause of joint damage (Herrero-Beaumont et al., 2009).

“Secondary” OA may result from monogenic congenital or developmental disorders, trauma, and other joint or bone disorders such as gout, septic arthritis, Paget’s disease of bone, osteonecrosis and rheumatoid arthritis (Herrero-Beaumont et al., 2009). However, distinction between primary and secondary OA is often blurred, and it has been shown that despite a severe joint injury, people who develop post-traumatic knee OA have the same genetic risk profile as those who develop primary knee OA (Valdes et al., 2013).

1.1.5.2 Knee Osteoarthritis

The clinical diagnosis of knee OA can be made by typical symptoms and physical examination findings alone (Altman et al., 1986). In addition, routine laboratory tests for inflammation (such as serum C-reactive protein and erythrocyte sedimentation rate) are not elevated by knee OA, and plain radiographs (although relatively insensitive) can demonstrate the presence of typical structural OA changes (Heidari, 2011, Lespasio et al., 2017). However, there is no single clinical manifestation that is highly specific or sensitive.

Typically, conventional radiography is the standard imaging that can be used to help to confirm the presence of structural changes of knee OA, and can also be employed to rule out other suspected diagnoses or if the presentation is atypical (Sakellariou et al., 2017). However, the European Alliance of Associations for Rheumatology (EULAR), the National Institute for Health and Care Excellence (NICE) and the American College of Rheumatology (ACR) suggest that knee

OA can be diagnosed on clinical features alone without radiographic evidence of OA (Altman et al., 1986, Zhang et al., 2010).

Details of each ACR, EULAR and NICE criteria to diagnose people with knee OA are shown in Table 3 (Altman et al., 1986, Zhang et al., 2010, NICE, 2022b). ACR criteria are the most widely used in clinical diagnosis in reporting people with knee OA (Altman et al., 1986). According to EULAR evidence-based recommendations, the probability of having radiographic knee OA increased to 99% when all six symptoms and signs are presented (Table 3) (Zhang et al., 2010). The NICE OA guideline states that imaging should not be used routinely to diagnose OA unless there are atypical features that require further investigation (NICE, 2022b).

Table 3. Different criteria to diagnose knee osteoarthritis

ACR			EULAR	NICE
Clinical	Clinical and laboratory	Clinical and radiographic	aged ≥ 40 years	aged ≥45 years
knee pain + at least 3 of 6	knee pain + at least 5 of 9	knee pain + at least 1 of 3	persistent knee pain limited morning stiffness	activity-related joint pain have either no or < 30 minutes of morning stiffness
age >50 years	age >50 years	age > 50 years	reduced function	
stiffness < 30 min crepitus	stiffness < 30 min crepitus	stiffness < 30 min crepitus		
bony tenderness bony enlargement	bony tenderness bony enlargement	+ osteophytes		
no palpable warmth	no palpable warmth ESR (Westergren) < 40 mm/hour serum rheumatoid factor < 1:40 synovial fluid signs of OA (clear, viscous, and/or white blood cell count < 2,000/mm ³)			

ACR – the American College of Rheumatology; EULAR – the European Alliance of Associations for Rheumatology; NICE – National Institute for Health and Care Excellence; ESR - Erythrocyte sedimentation rate; Crepitus on active movement in ACR

Plain radiographic findings of OA depend on the presence of the following: focal narrowing of joint space, subchondral cysts, subchondral sclerosis and marginal osteophyte formation (Schiphof et al., 2008). Details are given in Table 4. The disease severity of knee OA can be graded following the ordinal Kellgren-Lawrence (K-L) system of radiographic findings using four grades (I-IV), which was described in 1957 (Kellgren and Lawrence, 1957). Grade 2 is often taken as the minimal requirement for definition of radiographic OA in epidemiological studies.

Table 4. Kellgren and Lawrence grading system for osteoarthritis

Grade	Description
Grade 0	Normal
Grade 1	Doubtful narrowing of joint space, possible osteophyte
Grade 2	Definite osteophyte, possible narrowing (mild OA)
Grade 3	Moderate multiple osteophytes, definite narrowing, some sclerosis, possible deformity of bone ends (moderate OA)
Grade 4	Large osteophytes, marked narrowing, severe sclerosis, definite deformity of bone ends (severe OA)

OA – osteoarthritis

1.1.5.3 Foot/ankle Osteoarthritis

There is no accepted clinical definition of foot/ankle OA even though clinical definitions of OA in other joints including the hip, knee and hands have existed for several decades (International FAO Consortium et al., 2022). The necessity

and feasibility of a stand-alone clinical definition, and whether different clinical definitions for each foot and ankle region are necessary, remains unclear.

However, an agreed definition could reduce reliance on imaging.

Only one previous study has developed a clinical diagnostic rule for identifying people with 1st MTPJ pain OA in the presence or absence of radiographs (Zammit et al., 2011). This had good diagnostic accuracy for identifying radiographic OA, with excellent sensitivity and specificity, and included the following features:

- presence of longstanding pain
- palpable dorsal joint osteophyte
- crepitus
- a hard “end-feel” described as “the examiner grasped the proximal phalanx and proceeded to dorsiflex the hallux until movement was no longer possible. A positive test result was concluded if a hard osseous end-feel was determined as opposed to a gradual end-feel of joint motion”
- restricted range of motion

Assessing midfoot OA, however, is more difficult and challenging due to the complexity of having multiple small joints in close proximity and the difficulty in palpating or moving them individually to assess for tenderness, deformity, stiffness and restricted movement. Clinical diagnostic assessments of midfoot OA in one study were undetermined as they involved poorly identified

symptomatic radiographic midfoot OA (Thomas et al., 2015b). Therefore, the proposed clinical diagnosis of midfoot OA is reliant on palpation and reproduction of pain by longitudinal rotation of the midfoot while holding the calcaneum, in conjunction with diagnostic imaging, particularly plain radiographs (International FAO Consortium et al., 2022).

There is no established clinical definition for ankle OA. As a consequence, the diagnosis relies on a range of clinical signs and symptoms, with or without imaging (Barg et al., 2013). Post-traumatic ankle OA accounts for the majority of ankle OA cases (International FAO Consortium et al., 2022). It is therefore necessary to consider post-traumatic ankle OA as a distinct entity, perhaps requiring a separate clinical management strategy to prevent progression of post-traumatic ankle OA (Delco et al., 2017).

A widely known tool for diagnosing radiographic foot and ankle OA is the La Trobe Foot Atlas (Table 5 and Figure 4) (Menz et al., 2007, Kraus et al., 2015). Radiographic features observed in dorso-plantar and lateral views are scored for five of the foot joints, specifically the 1st MTPJ, the 1st cuneo-metatarsal joint (1st CMJ), the 2nd cuneo-metatarsal joint (2nd CMJ), the navicular-first cuneiform joint (N1st CJ) and the talonavicular joint (TNJ) (Figures 5-6). The radiographic features observed in antero-posterior and lateral views are scored for the ankle joint, specifically the talocrural joint (Figures 6-7). The scores for both foot and ankle joints for osteophytes and joint space narrowing range from 0 to 3, and

details of each definition are shown in Table 5 (Menz et al., 2007, Kraus et al., 2015).

Table 5. The radiographic scoring for the foot using the La Trobe Foot Atlas

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

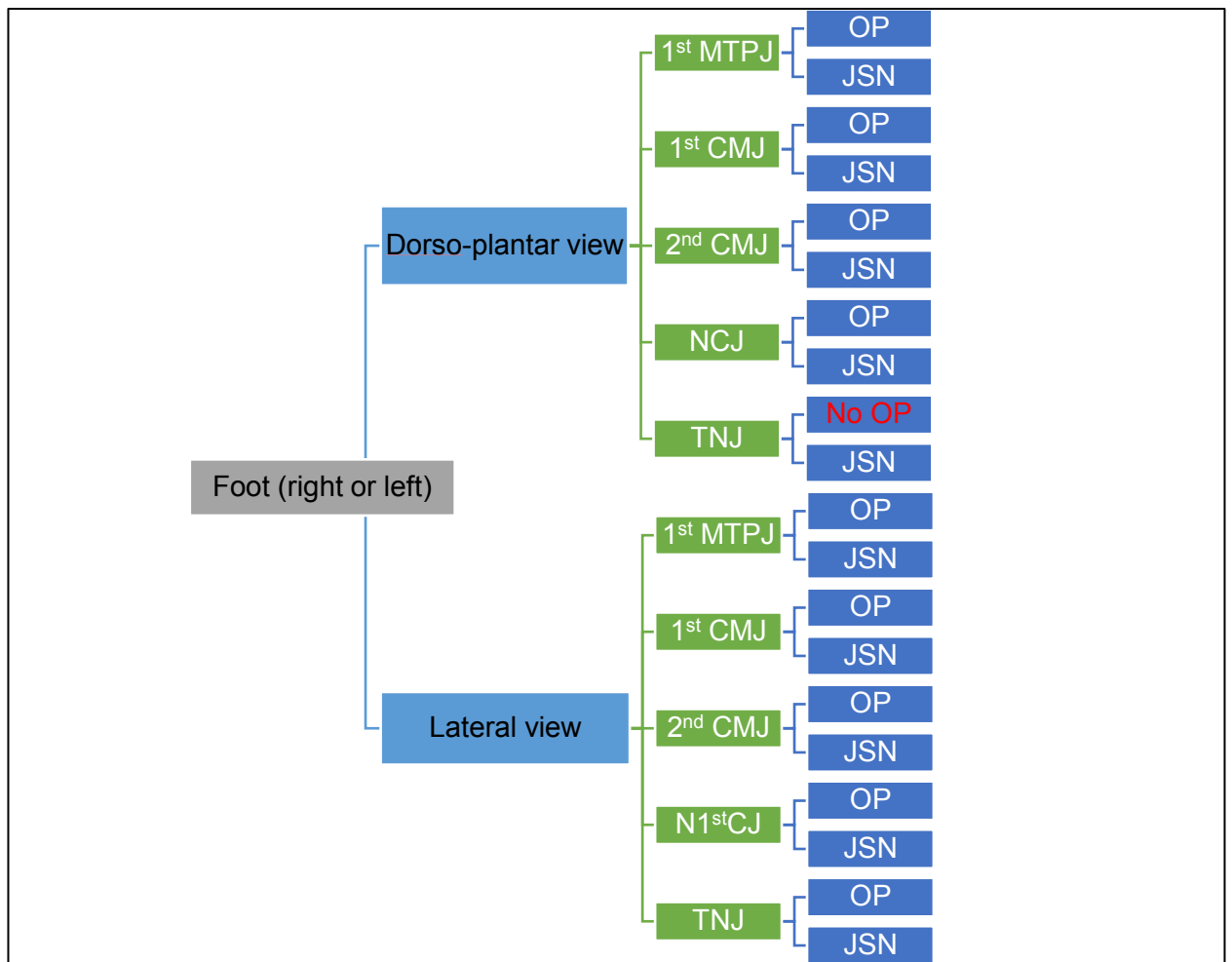


Figure 4. the La Trobe Foot Atlas to examine radiographic features of foot osteoarthritis in five joints across two views. OP – osteophyte; JSN – joint space narrowing

1st MTPJ – first metatarsophalangeal joint; 1st CMJ – first cuneo-metatarsal joint; 2nd CMJ - second cuneo-metatarsal joint; N1st CJ – navicular-first cuneiform joint; and TNJ - talonavicular joint

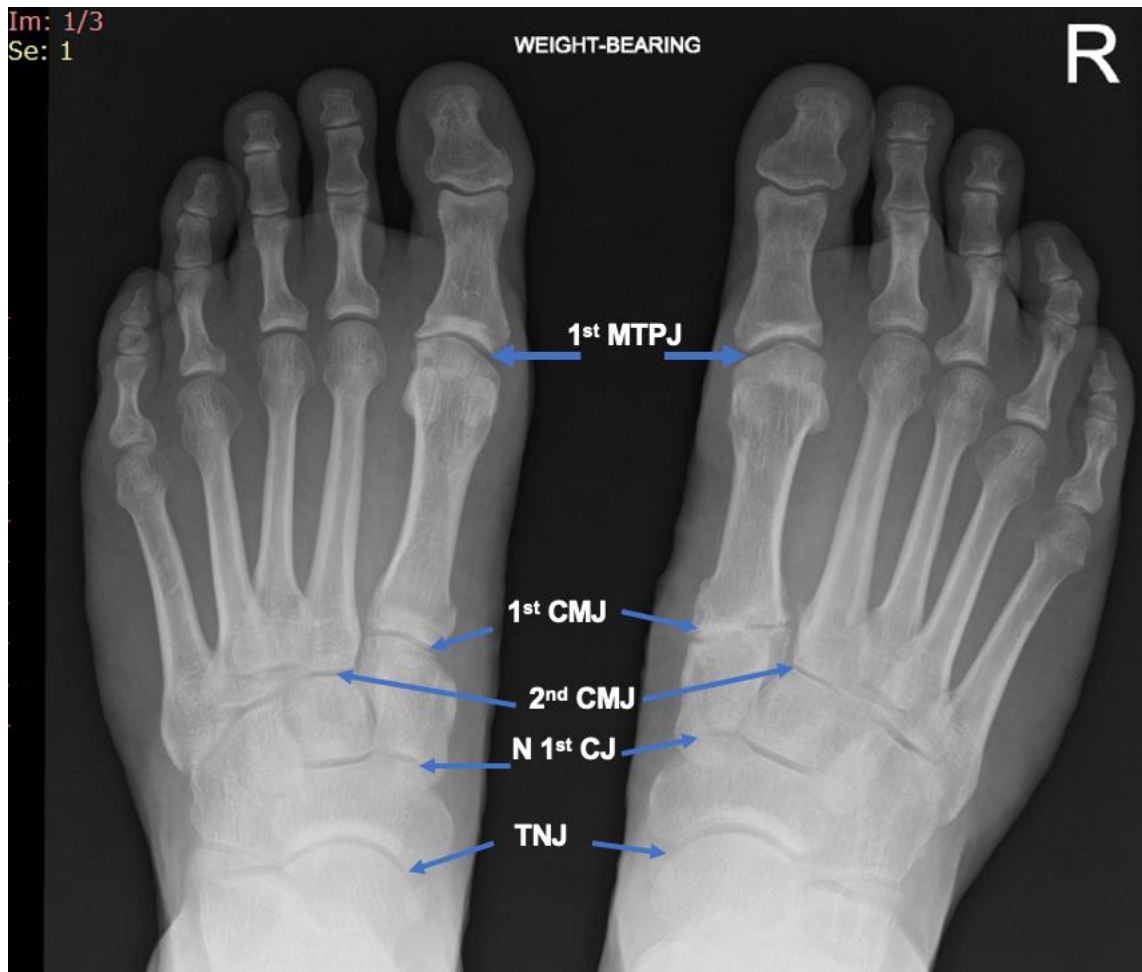


Figure 5. Five foot joints in the dorso-plantar view in both feet

Scored foot joints include the 1st MTPJ – first metatarsophalangeal joint; 1st CMJ – first cuneo-metatarsal joint; 2nd CMJ - second cuneo-metatarsal joint; N1st CJ – navicular-first cuneiform joint; and TNJ - talonavicular joint

The left 1stMTPJ shows focal narrowing, osteophyte and subchondral sclerosis, and the right 1st CMJ shows marked narrowing (bone-on-bone), osteophyte and subchondral sclerosis

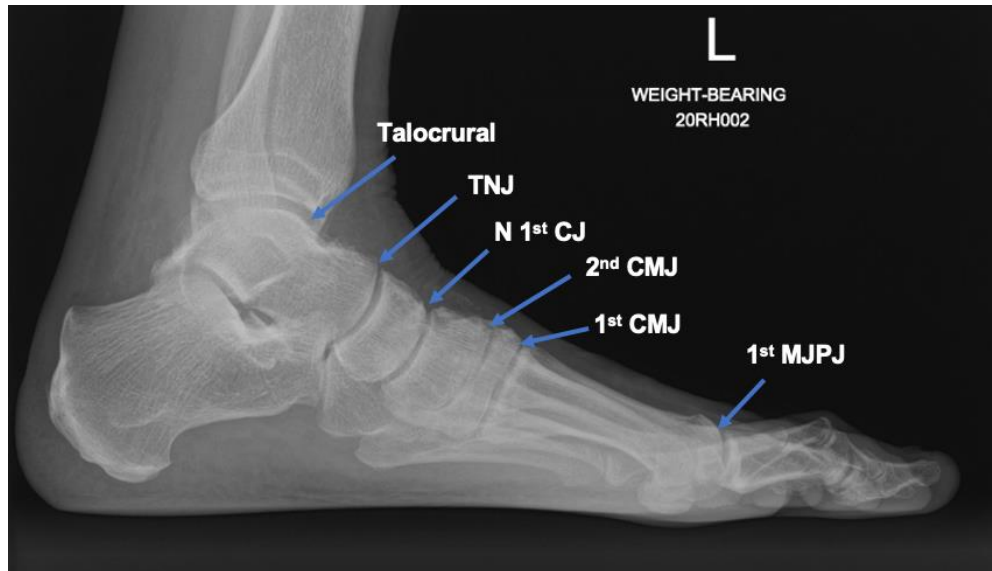


Figure 6. Foot and ankle joints scored in the lateral view

Foot joints include: 1st MTPJ – first metatarsophalangeal joint; 1st CMJ – first cuneo-metatarsal joint; 2nd CMJ - second cuneo-metatarsal joint; N1st CJ – navicular-first cuneiform joint; TNJ - talonavicular joint; and the ankle (talocrural) joint. The 2nd CMJ shows marked uneven narrowing with possible osteophytes



Figure 7. The ankle (talocrural) joint seen in the antero-posterior view

The talocrural joint shows marked uneven narrowing

1.1.6 Epidemiology of Osteoarthritis

The reported prevalence and incidence of OA varies according to a number of factors, including the definition of OA (clinical and radiographic criteria), the joint site affected by OA, the country of study, and the sex and age group examined (Pereira et al., 2011). This section presents an overview of prevalence and incidence of OA worldwide, with a focus on specific data in the United Kingdom (UK), particularly on knee OA and foot/ankle OA, and some results for non-UK countries.

1.1.6.1 Prevalence of Osteoarthritis

From the Global Burden of Diseases Study, OA was estimated to affect around 595 million adults in 2020, representing an increase of 132.2% since 1990, with high body mass index (BMI) contributing to 20.4% of OA cases (Steinmetz et al., 2023). Knee OA presented the highest burden for age-standardised prevalence of OA for most regions except for eastern Europe and central Asia where hand OA was the predominant burden (Steinmetz et al., 2023).

A UK-based study in 2017 conducted within the Clinical Practice Research Datalink (CPRD), a large nationally representative primary care database, found an overall prevalence of OA of 10.8%, being higher in women (12.8%) than men (8.6%) across all age groups (Swain et al., 2020). Approximately one in ten adults had symptomatic OA based on a clinical diagnosis, with the knee having the highest reported prevalence, followed by the hip, wrist/hand and foot/ankle

(Figure 8) (Swain et al., 2020). West Midlands, Scotland and Northern Ireland had the highest prevalence compared to other country regions (Swain et al., 2020).

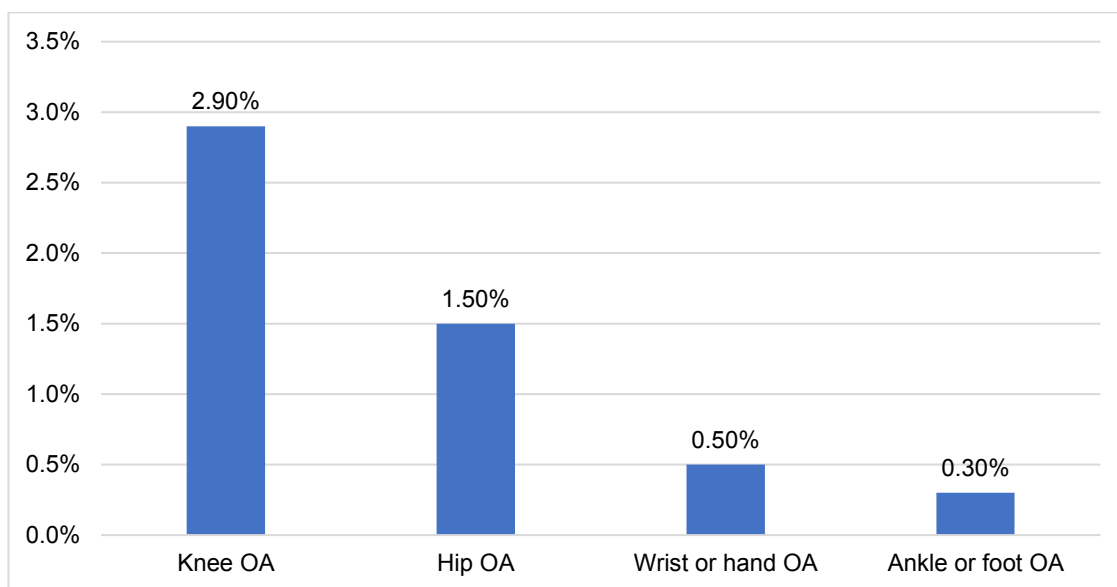


Figure 8. Overall prevalence of osteoarthritis according to joint sites using primary care data in the United Kingdom. OA – osteoarthritis (adapted from Swain et al., 2020 study for illustration purpose)

Data from a UK study that included clinical and radiographic assessment of 8,984 adults aged 50 years and older, reported that the prevalence of symptomatic and radiographic knee OA was 17.7% and foot OA was 15.9% (Figure 9) (Peat et al., 2020). Another study using a similar data source showed that the prevalence of symptomatic radiographic (K-L grade ≥ 2) ankle OA was 3.4% (Figure 9) (Murray et al., 2018).

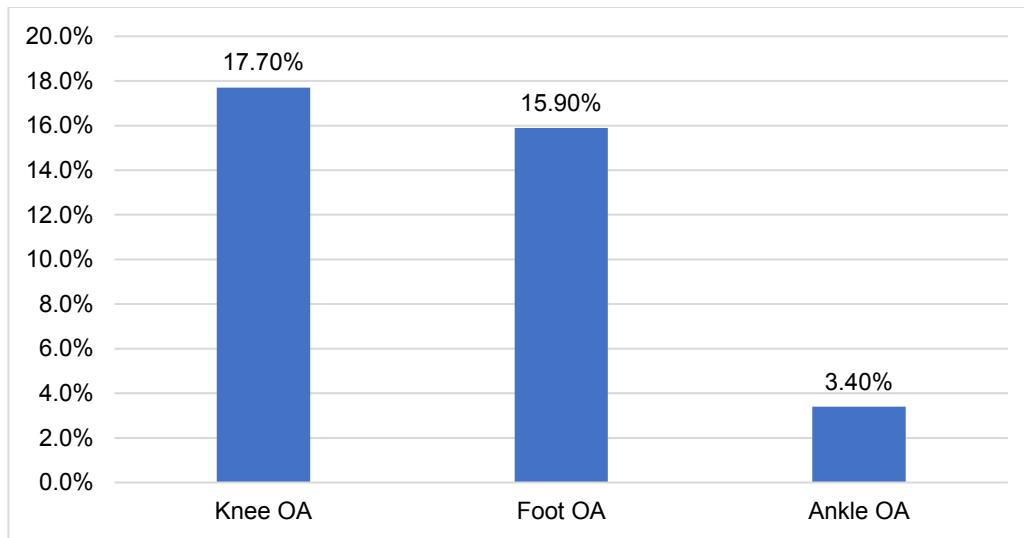


Figure 9. Prevalence of symptomatic radiographic osteoarthritis according to joint sites using community-based study in the United Kingdom. OA – osteoarthritis (adapted from Peat et al., 2020 and Murray et al., 2018 studies for illustration purpose)

A review of prevalence of OA affecting the midfoot and forefoot reported considerable variation in the prevalence estimates for midfoot and forefoot OA, ranging from 0.1 – 61.0%, based on age, sex, and joint(s) being examined (Kalichman and Hernández-Molina, 2014). Other non-UK community studies reported that the prevalence of midfoot and forefoot OA ranged from 6% to 56% (Beaudart et al., 2023, Berto et al., 2021, Blanco et al., 2020, Fuchs et al., 2017). This variation revealed the differences in the population characteristics (i.e., age, sex, BMI), the joint(s) being studied and the assessment used to determine OA.

1.1.6.2 Incidence of osteoarthritis

According to data from the Global Burden of Disease Study from 1990 to 2017, there was a notable increase in the age standardised annual incidence rate of OA from 8.2% to 9.6%, respectively, and also an increase in years lived with disability (YLD) due to increased life expectancy and an increasingly aged global population (Safiri et al., 2020). Globally, the age-standardised incidence rate of OA in 2017 was 181.2 (95% uncertainty intervals 162 to 202.4) cases per 100,000 population with a variation ranging from 99.5 to 316.9 cases per 100,000 population across countries. The United States (US), Kuwait and Qatar had the highest age-standardised incidence rate of OA, whereas Taiwan, North Korea and Madagascar had the lowest rate (Safiri et al., 2020).

In the UK, data from the CPRD reported that there were 494,716 incident cases of clinical OA in people aged ≥ 20 years between 1997 and 2017, corresponding to 6.8 per 1000 person-years (Swain et al., 2020). The incidence of clinical OA in 2017 was 0.08 per 1000 person-years in both genders with a gradual increase according to age as shown in Figure 10. The East Midlands and the North East had the highest incidence of OA compared to other country regions in 2014. Among all OA types, knee OA had the highest reported incidence, followed by hip, wrist/hand and foot/ankle (Swain et al., 2020).

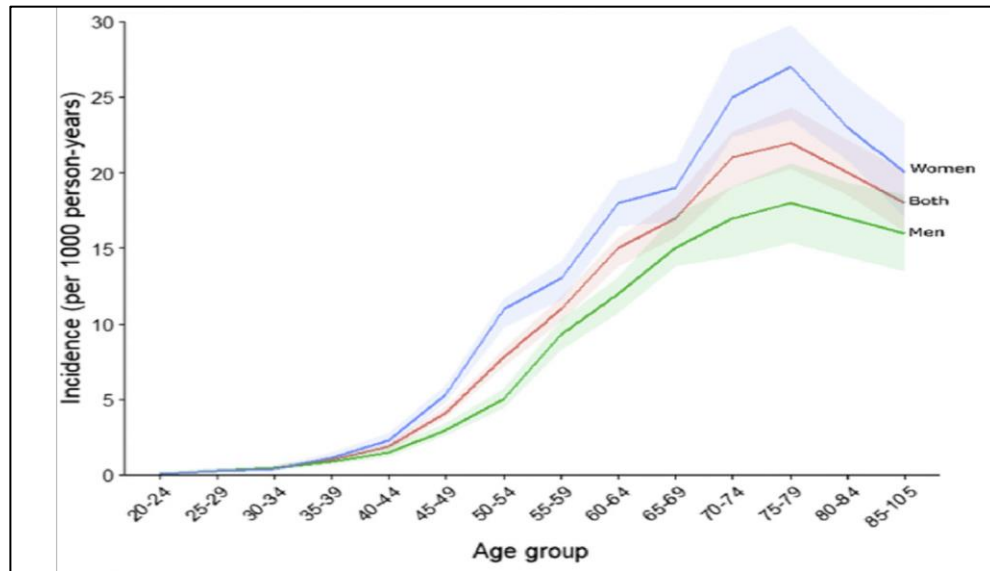


Figure 10. Incidence of osteoarthritis at any joint by age and sex in 2017 in the UK. Produced with permission from Dr Subhashisa Swain

Another UK-based study examining secondary-care data on 3,143,928 people with OA derived from the National Health Service Hospital Episode Statistics Database in England reported the incidence of the hip, knee, foot and hand from 2000/01 to 2017/18 (Morgan et al., 2019). The results showed that there were significant increases in the incidence of OA at the hip (3.8%), knee (2.9%), foot “1st MTPJ” (3.8%) and hand 1st carpometacarpal joint (10.9%) per year from 2000/01 to 2017/18. During the same period, a greater proportion of women were diagnosed with OA. However, a higher incidence in men was estimated for hip and hand OA. There was a significant increase of hip OA in younger adults, and knee OA decreased in all age groups in 2012/13 to 2017/18. The incidence of hand and foot OA were particularly high among those aged ≥ 75 years (Morgan et al., 2019).

According to the Chingford Study in the UK, the cumulative 5-years incidence of radiographic knee OA in women aged between 45 to 64 years was 17.6% (Driban et al., 2020). Another study using the same data source, estimated the incidence of radiographic 1st MTPJ OA of 21.7% in either foot over a 19-year period (Bowen et al., 2020).

There are wide variations in reporting the incidence of OA for non-UK countries. For example, Spain primary care records showed that knee and hip OA increased steadily with age, with the highest female to male rate ratios at 70-75 years with a median of 4.45 years follow-up. Female hand OA risk peaked at 60-64 years of age. Among 3,266,826 individuals, the incidence rate for knee, hip and hand OA was 6.5, 2.1 and 2.4 (per 1000 person-years), respectively (Prieto-Alhambra et al., 2014b). Based on data from the Fallon Community Health Plan in Central Massachusetts, the age and gender-standardised incidence of hip OA was 88/100,000 person years, knee OA was 240/100,000 person years, and hand OA was 100/100,000 person years in 1991. The incidence rate of hip, knee and hand OA increased with ageing, and women had the greater rate compared to males, particularly beyond the age of 50 (Oliveria et al., 1995). Rahman et al. (2014) examined a random sample of 640,000 people from Canadian health records of visits to health professionals and hospital admissions for OA diagnosis in any joint except the spine, either generalised or localised. 49.1% were male, 50.9% were female and their mean age at follow-up was 48.6 years. Age-standardised rates of OA varied from 12.1 to 13.2 (per

1000 person-years) in men, and from 16 to 17.4 (per 1000 person-years) in women over 17 years follow-up (Rahman et al., 2014). This variation was due to a different study population, the joint being assessed, the method used to examine OA and the follow-up duration.

1.1.6.3 Risk factors for Osteoarthritis

OA is a common complex disorder with multiple risk factors. Risk factors can be divided broadly into genetic, constitutional and environmental (Brandt et al., 2003). For example, constitutional joint alignment/shape is genetic whereas occupation is environmental (Figure 11) (Doherty et al., 2016). However, there is some overlap between these groups, for example, gender is constitutional but is determined genetically, and obesity and metabolic syndrome also have some genetic basis. Among these risk factors, some can be considered modifiable risk factors, such as obesity and diet, which may be targets for treatment strategies, and some factors such as age and sex are considered unmodifiable risk factors (Vina and Kwok, 2018).

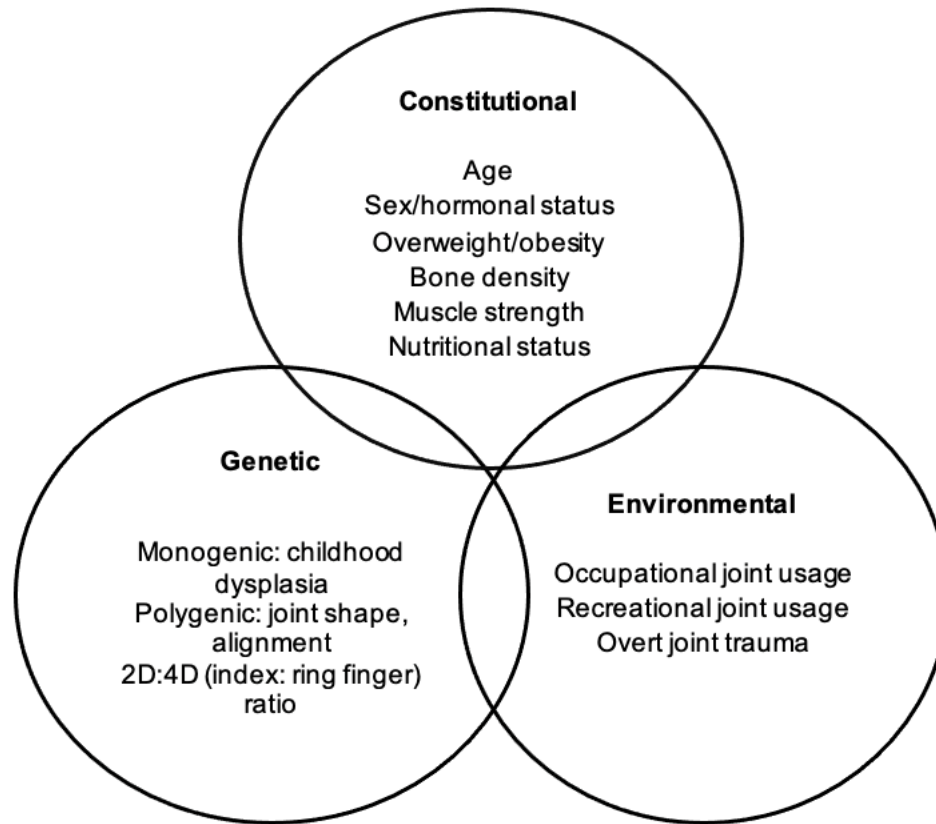


Figure 11. Possible risk factors for osteoarthritis development

1.1.6.3.1 Genetic risk factors

Genetics

OA is known to be influenced by genetic factors (Warner and Valdes, 2016).

The heritability of OA varies according to joint site in twin studies, being 39-65% for radiographic knee OA, approximately 60% for radiographic hip OA and 69-80% for radiographic knee OA progression in female twins (Spector et al., 1996, MacGregor et al., 2000, Zhai et al., 2007). A 20-year longitudinal study including a total of 59,970 participants (concordant or discordant pairs of female and male

twins aged ≥ 35 years), reported that the heritability of physician-diagnosed hand OA was 48%, 86% and 87% for both the distal and proximal interphalangeal joint OA, the first carpometacarpal joint, and hand OA (any joint), respectively (Magnusson et al., 2022). All these estimates suggest a heritability of 50% or greater for OA, indicating that genetic factors can explain half of the variation in susceptibility to OA. Familial clustering has been recognised since the earliest description of OA. Familial clustering of Heberden's nodes of the fingers was first formally identified in 1941, and later familial clustering of both knee and hand OA ("generalised OA") also was identified (Stecher, 1941, Kellgren et al., 1963). All these associations were determined after accounting for the effect of constitutional risk factors such as age, sex and BMI.

According to a recent large genetic review, certain genes such as Growth Differentiating Factor 5, Collagen type XI, Parathyroid hormone-like hormone and Astrotactin 2, might be associated with constitutional joint shape that predisposes to OA (Wilkinson and Zeggini, 2021). Within this study, genes that influence early skeletal growth and shape form one of the largest groupings of known genes that predispose to OA, suggesting that constitutional morphology is an important mechanism/mediator of genetic risk of OA (Boer et al., 2021).

Constitutional Joint shape of the hip and knee

Four cross-sectional case-control studies of hip and knee constitutional morphology have been undertaken within the Nottingham Genetics of

Osteoarthritis and Lifestyle (GOAL) cohort which includes men and women aged >45 years with clinically severe knee OA or hip OA and people without knee or hip OA living in or around Nottingham. The first study aimed to examine whether femoral head shape and angle were associated with hip OA (Figure 12). First, the morphological features were assessed in 1108 asymptomatic people with no hip OA (controls) and were shown to be symmetrical on the right and left sides (Doherty et al., 2008). The features were then examined in the unaffected hip in 566 individuals with unilateral hip OA (cases), on the assumption that the unaffected hip would reflect the constitutional morphology of the affected hip before it developed OA (Doherty et al., 2008). It was found that the prevalence of pistol grip deformity (nonspherical femoral head shape) was higher in the unaffected hip of cases (17.71%) compared to controls (3.61%) with an adjusted odd ratio (aOR) of 6.95 (95% confidence interval (CI) 4.64 – 10.41). Similarly, a higher prevalence of abnormal femoral head-to-femoral neck ratio (Figure 13) was found in cases (24.27%) than in controls (3.70%) with an aOR of 12.08 (95% CI 8.05 – 18.15). It was found also that as the femoral head-to-femoral neck ratio decreased, the risk of hip OA increased (p-trend <0.001) (Doherty et al., 2008).



Figure 12. Femoral shaft/neck angle – high on the left, low on the right.
Produced with permission from Prof. Michael Doherty

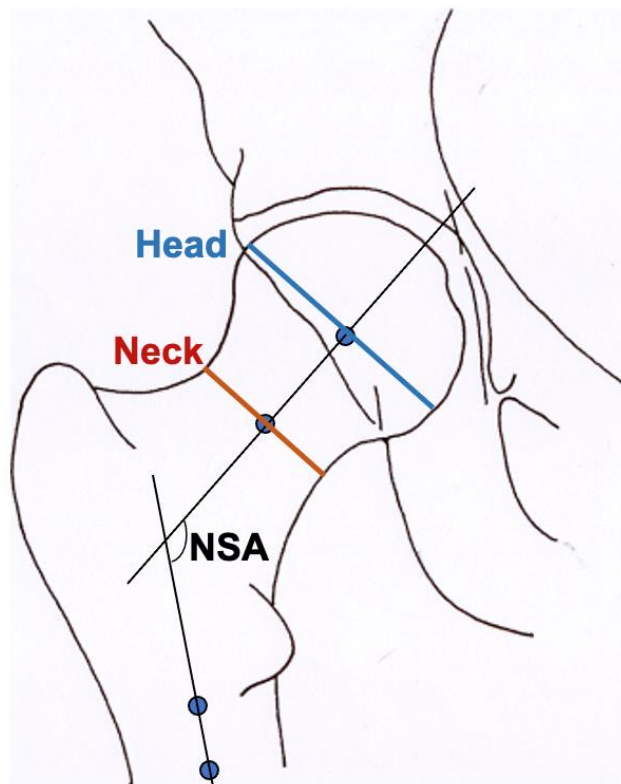


Figure 13. Measurement of the femoral head-to-femoral neck ratio and the neck shaft angle. NSA – neck shaft angle. Produced with permission from Prof. Michael Doherty

A second study embedded within the GOAL cohort, using the same study design and 566 cases and 1108 controls, examined whether mild acetabular dysplasia might be a risk factor for clinically severe onset of hip OA by measuring the centre edge and acetabular depth angles of the hip (Figure 14) (McWilliams et al., 2010b). The results showed that, irrespective of side, there was a decrease in both the centre edge and acetabular depth angles in the unaffected hip of people with unilateral hip OA compared to controls. The lowest tertile of acetabular depth angle in the cases was associated with a 2.5-fold risk of hip OA, whereas the lowest tertile of the centre edge angle was associated with an eight-fold risk of hip OA. The risk of hip OA increased significantly with decreasing acetabular depth and centre edge angles (McWilliams et al., 2010b).

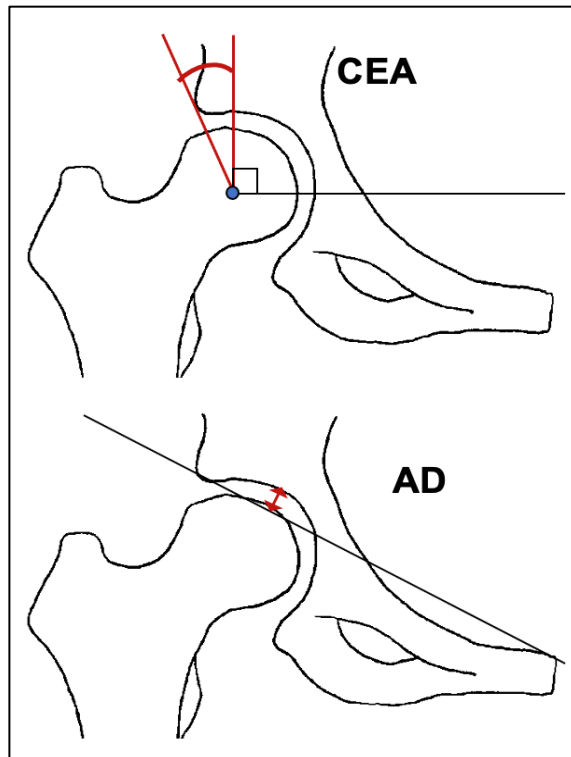


Figure 14. Centre edge angle (CEA) and acetabular depth (AD) angles used to estimate the risk for hip osteoarthritis. Produced with permission from Dr Daniel McWilliams

A third study in GOAL, using the same study design and participants, examined 14 morphological features (including 10 not studied in the previous studies) (Abdulrahim et al., 2021). Again, all features showed right-left symmetry and each feature was associated with hip OA after adjusting for age, sex and BMI. Increased sourcil angle showed the strongest association (aOR 6.93, 95% CI 5.16 - 9.32). Furthermore, 3 clusters were identified, and several variants could contribute to the same morphological feature. The proportional risk contribution (PRC) varied between individual features and between clusters, and the PRC for all 14 features combined contributed to 34.95% (95% CI 30.93 - 39.65) of the

hip OA which was greater than the PRC of 25% (95% CI 8.62 - 24.21) for all other recognised risk factors combined (Abdulrahim et al., 2021).

The fourth case-control study conducted in GOAL comprised 315 people with unilateral knee OA (cases), in which the unaffected knees had no knee pain or radiographic OA, and 408 controls with no symptoms or radiographic OA in either knee (Nair et al., 2023). This found that of the 12 measures studied, five showed independent associations with knee OA, specifically a narrower sulcus angle and condylar angle (patello-femoral OA), increasing distal femoral tilt and proximal tibial tilt, and varus angulation (tibio-femoral OA) (Nair et al., 2023).

Therefore, the results from the four GOAL studies produce strong circumstantial evidence for the importance of constitutional morphology in development of hip and knee OA, in line with the conclusion from the genetic study by Boer et al. (2021) (Figure 15). However, although right-left symmetry of all features was found in the controls, the assumption that the unaffected joint represents the morphology of the contralateral affected side is open to question, especially since bone remodeling can be a very early imaging abnormality in OA and biomechanical changes in the affected joint could lead to changes in the apparently unaffected side. Therefore, prospective studies are required to confirm these findings.

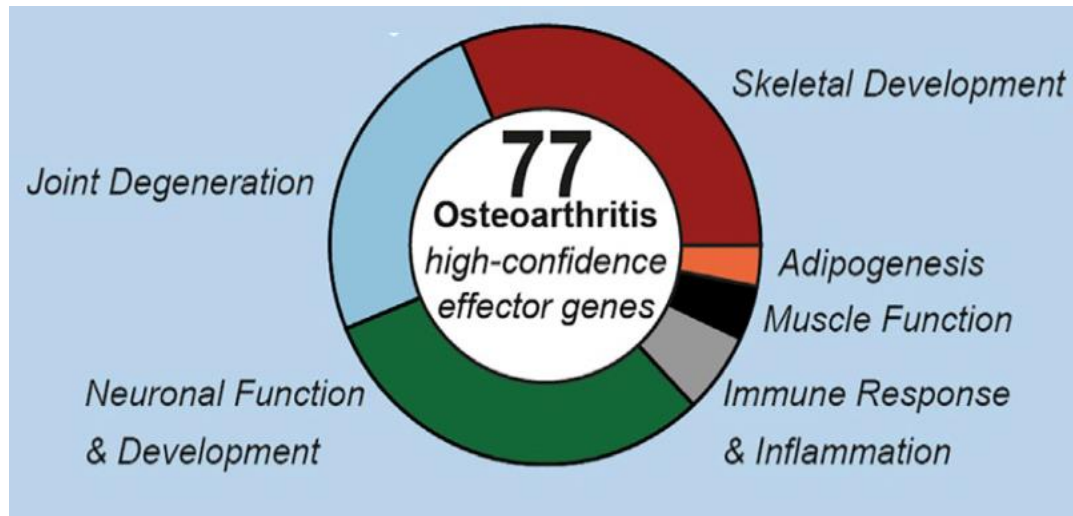


Figure 15. Genes have a large influence in early skeletal growth and shape that predispose to osteoarthritis. Produced with permission from Dr Cindy Boer

Knee malalignment, including both varus and valgus, is associated with increased structural degradation in the relevant tibiofemoral compartment due to greater compressive stress (Figure 16) (Sharma et al., 2001, Ingham et al., 2010). In a case-control study, people with varus malalignment had an increase in the coronal tibial slope which was associated with incident medial tibiofemoral OA (Driban et al., 2016). Varus malalignment increased the risk of incidence of radiographic tibiofemoral knee OA by almost 1.49 times compared to normal alignment (Sharma et al., 2010). Presence of varus-aligned knees with thrust, which relates to joint instability during walking, results in abrupt onset or dynamic deterioration of bow-leg (varus) alignment as the limb accepts weight (known as stance phase), followed by a return to a more neutral alignment (less varus) during lift-off and the non-weightbearing phase (known as swing phase) of the gait (Wink et al., 2017). Over 2 years in people with a mean age of 67.4

years, this increased the odds of incident and worsening medial bone marrow lesions as well as worsening medial tibiofemoral cartilage loss compared to those with varus-aligned knees without thrust (Wink et al., 2017).

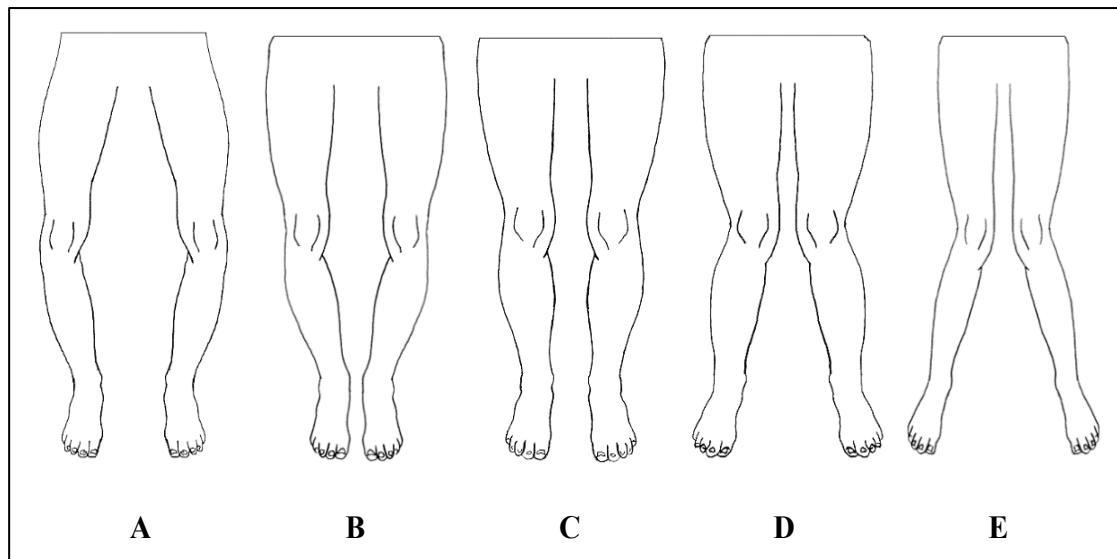


Figure 16. Knee malalignment (A and B indicate varus), C is normal and (D and E indicate valgus)

An association has been found in the UK between self-reported constitutional knee malalignment (varus or valgus) during early adulthood and the risk of development of radiographic knee OA later in life (McWilliams et al., 2010a). Varus alignment was more common than valgus alignment and associated with increased risk of medial tibiofemoral OA, but a higher risk was found in those with valgus alignment which associated with risk of both lateral tibiofemoral and lateral patellofemoral OA (McWilliams et al., 2010a).

Second to fourth digit (2D:4D) ratio

The 2D:4D ratio is the length ratio between the second digit (2D) and the fourth digit (4D), that is, between the index finger and the ring finger, when the middle finger is in line with the forearm (Figure 17) (Robertson et al., 2008, Zhang et al., 2008). There are three patterns: in pattern 1 the index finger is longer than the ring finger; in pattern 2 “index” and “ring” fingers lengths are equal, and in pattern 3, the ring finger is longer than the index finger (Robertson et al., 2008). The 2D:4D ratio has been associated with HOX genes that are involved in early segmentation and development of gonads, fingers and toes in many species (Manning et al., 2003). The 2D:4D ratio relates to prenatal testosterone levels, and men typically have a shorter index finger compared with the ring finger (pattern 3), while the fingers have more equal length in women (pattern 2) (Manning et al., 1998). Pattern 3 has been shown to be more prevalent in men and women who are involved in sports, and this might indicate “maleness” in terms of better physical fitness and better athletic skills (Hönekopp et al., 2006, Eklund et al., 2020, Islam and Kundu, 2020).

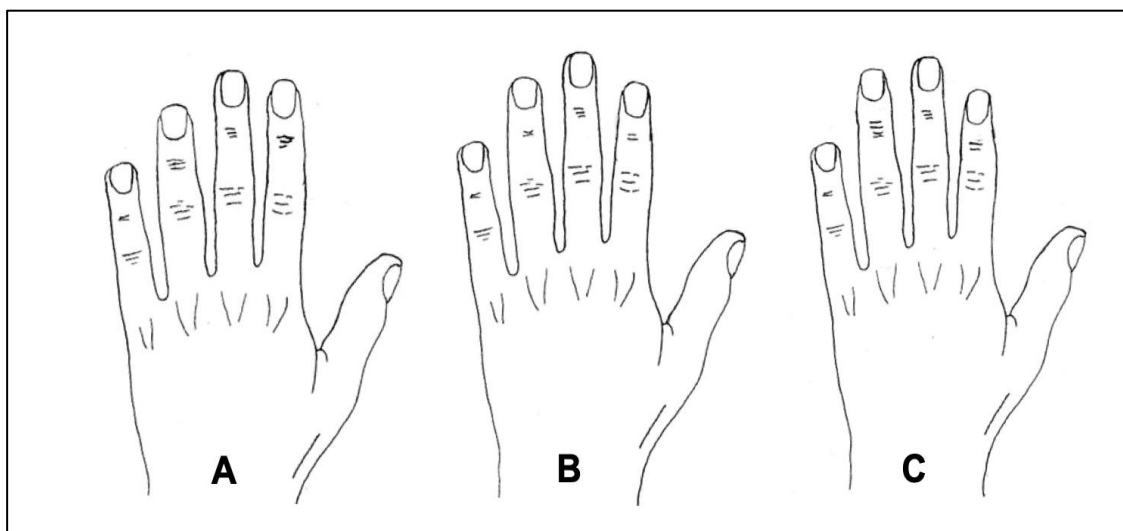


Figure 17. Three patterns of finger ratio

A: Pattern 1 - index finger longer than ring finger

B: Pattern 2 - both fingers are of equal length

C: Pattern 3 - ring finger is longer than index finger

Pattern 3 finger ratio has been shown in the UK to be associated with knee OA, hip OA and generalised OA (finger interphalangeal nodes and OA at the knee or/and hip), and this association was greater in women than in men (Zhang et al., 2008). The risk of knee OA in people with pattern 3 was nearly two times higher than in those without this pattern (Zhang et al., 2008). Similarly, data from the Clearwater Osteoarthritis Study in the US revealed a significant association between pattern 3 and radiographic knee OA, and again women demonstrated a stronger association than men (Ferraro et al., 2010). In Iceland, pattern 3 was associated with total knee replacement in older men and women (Sigurjonsdottir et al., 2013). However, Data from the Framingham study in the US showed no association between pattern 3 and radiographic knee OA for both men and

women (Haugen et al., 2011). It has been suggested that in women with hand OA, pattern 3 could be a consequence rather than a cause of OA due to finger joint malalignment and shortening (Haugen et al., 2011). However, the length ratio of the 2nd and 4th metacarpal bones (measured on hand radiographs) aligns very strongly with the constitutional 2D:4D ratio within individuals and is less prone to alterations due to arthritis, trauma and finger positioning, and can be used as an alternative when radiographs are available (Robertson et al., 2008). Pattern 3 was associated with severe knee OA that required total knee replacement in a cohort study over 10.5 years in Australian men and women (Hussain et al., 2014).

1.1.6.3.2 Constitutional risk factors

Age

Age is considered to be the main risk factor for OA at all joint sites (Felson et al., 2000, Doherty et al., 2016). A combination of biological changes and various risk factors that occur with increasing age might explain the mechanism behind its association with OA (Anderson and Loeser, 2010). These include decline in basic cellular mechanisms that maintain tissue homeostasis, thinning of cartilage, oxidative damage, muscle weakening and reduction in balance and proprioception (Anderson and Loeser, 2010). A recent systematic review and meta-analysis has confirmed that age is a risk factor for the onset and progression of knee OA (Dong et al., 2023). Results for meta-analysis revealed that the pooled odd ratio (OR) for knee OA in people aged ≥ 40 years was 1.02

(95% CI 1.01 - 1.03) (Dong et al., 2023). However, there is some difficulty in synthesising by meta-analysis the overall risk from age due to variation in age ranges and categories for the population studied and the study design used.

Sex

Numerous studies have shown that OA risk is greater in women than men at all sites apart from the hip (Allen et al., 2022, Doherty et al., 2016). Women are more likely to have knee and hand OA than men, and the incidence of OA rises around the menopause (Srikanth et al., 2005, Tschon et al., 2021). Hip OA is more common in men at younger ages (<45 years), but women become more commonly affected after age 55 and overall the prevalence in the population is fairly equal (Lane and Schnitzer, 2012). Sex may also influence the severity of OA and make it more severe in women (Tschon et al., 2021, Srikanth et al., 2005). This is due to the role of oestrogen, particularly in postmenopausal women, which was found to have an impact in mediating the development of OA (Spector and Campion, 1989). Oestrogen deficiency can contribute to OA progression by increasing muscle mass loss, after which muscle function is impaired leading to joint instability, inequality of mechanical load (uneven mechanical loading), and ultimately to cartilage damage (Sipilä, 2003, Peshkova et al., 2022). Oestrogen deficiency might also activate bone loss by direct effects on cells (e.g., osteoblasts, osteoclasts and osteocytes), and adversely affect bone remodeling. This may result in structural and mineral alternations and bone resorption, the main factors of postmenopausal osteoporosis

(Mohamad et al., 2020). Pooled ORs have shown that women were 1.04 times more likely than men to develop knee OA (Dong et al., 2023). There is a 3.5-fold greater risk of hand OA for women aged 50-60 compared to men of similar age group (Prieto-Alhambra et al., 2014b).

BMI

Overweight (defined as a BMI > 25 kg/m²) and obesity (defined as a BMI > 30 kg/m²) are clearly associated with increased risk for OA, particularly at the knee (Doherty et al., 2016, Chen et al., 2020a). People who are overweight are almost 1.59 times more likely to develop knee OA compared to people with normal BMI (Zhou et al., 2014). Obesity has been reported to increase the incidence of radiographic patellofemoral knee OA approximately 2-fold over 8 years (Hart et al., 2020). A dose–response relationship has been demonstrated between obesity and risk of knee OA in which for every 5-unit increase in BMI, the associated increased risk of knee OA was 35%, with the magnitude of the association being significantly greater in women than in men (Jiang et al., 2012). It is known that obesity contributes to an inflammatory systemic environment that has a catabolic effect on cartilage metabolism. This involves the presence of high levels of cytokines and adipokines in obese people, which have been associated with cartilage degradation (Azamar-Llamas et al., 2017, Wang and He, 2018). A recent study found that, even after controlling for BMI, metabolic syndrome and low levels of high density lipoprotein (HDL) were associated with an increase in bone marrow lesion size and loss of medial compartment

cartilage volume (Pan et al., 2020c). Additionally, some components of metabolic syndrome are associated with worse knee pain (Valdes, 2020, Pan et al., 2020a, Li et al., 2020).

Bone density

According to several studies, high bone mineral density (BMD) has been found to be associated with higher risk or progression of OA in weight-bearing and non-weight-bearing joints (Cai et al., 2020, Bergink et al., 2019, Jiang et al., 2023, Gregson et al., 2017). In these studies, higher local subchondral BMD was associated with an increased risk of knee replacement, while higher systemic BMD was associated with increased risk of hip replacement over a 12-year period in Australians with a mean age of 63 years (Cai et al., 2020). A causal association was found between higher systemic total body BMD and risk of hip OA (Jiang et al. 2019). A recent UK cohort study found an association between BMD and knee and hip replacement, and BMD was associated with progression of osteophyte in men and women over an 8-year period (Hartley et al., 2020). A higher systemic BMD was associated with increased early knee cartilage damage, particularly in the medial and lateral tibiofemoral compartments, and with accelerated loss of lateral tibial cartilage volume in middle-aged people without clinical knee OA (Teichtahl et al., 2017). Another UK study found that high BMD was associated also with radiographic hand OA, and specifically osteophyte, in people with high bone mass compared to family

controls, who were unaffected first degree spouses or relatives (Gregson et al., 2017).

Muscle strength

The role of muscle strength and knee OA has been extensively studied (Øiestad et al., 2015, Neelapala et al., 2020). Sarcopenia was found to be associated with higher incidence of symptomatic knee OA (46.9%) in women and men in the US over 4 years, the risk being 2.29 times higher compared to those without sarcopenia (Veronese et al., 2021). Poor muscle quality (i.e., increased intramuscular fat) has been associated also with greater cartilage volume loss and radiographic knee OA progression in women aged 62 and older (Kemnitz et al., 2018).

A meta-analysis of 15 studies including > 8,000 people reported that lower strength of knee extensor muscles was associated with an increased risk of knee symptoms and functional decline over the next 1.5 to 8 years (Culvenor et al., 2017). A recent systematic review and meta-analysis of cohort studies evaluating the association between low knee muscle strength and risk of knee structural worsening reported that low knee extensor and flexor strength increased the risk of worsening tibiofemoral OA, whereas low knee extensor strength increased the risk of worsening patellofemoral OA (Patterson et al., 2023). Greater isometric strength of hip and thigh muscle groups has been

associated with better self-reported physical function in people with hip OA in one cross-sectional study (Hall et al., 2017).

Nutritional status

Various dietary factors and nutritional status might have a role in the development of OA (Sanghi et al., 2009). People with knee OA who consistently maintained sufficient serum vitamin D levels by supplementation over a 2-year period reported a beneficial impact on cartilage loss, effusion-synovitis and physical function compared to those who did not (Zheng et al., 2017). Other studies indicate that vitamin D supplementation might positively affect foot pain and depression symptoms among people with knee OA (Tu et al., 2021, Zheng et al., 2019). People who had high vitamin C intake also had a reduced risk for radiographic knee OA progression compared to those with lowest vitamin C intake (Joseph et al., 2020). Vitamin E supplementation might help in stimulating the growth of cartilage cells and delay the progression of OA (Li et al., 2016, Chin and Ima-Nirwana, 2018). Some other studies have found that Vitamin E supplementation mitigates oxidative stress conditions in people with advanced knee OA, and can effectively improve clinical symptoms (Tantavisut et al., 2017, Chin and Ima-Nirwana, 2018). A recent study indicated that glutathione and its precursor N-acetylcysteine can significantly protect against the effects of prolonged, exacerbated oxidative stress, common in chronic inflammatory musculoskeletal disorders including OA (Setti et al., 2021).

1.1.6.3.3 Environmental risk factors

Occupation

The risk of OA has been reported to be increased by strenuous and physically demanding occupations (Canetti et al., 2020). A systematic review and meta-analysis of 25 observational studies (2 cohort, 10 case-controls and 16 cross-sectional) showed that construction workers, brick/floor layers, farmers and service personnel were at high risk of developing OA at the hip and knee (Canetti et al., 2020). In addition, hand OA has also been associated with occupational activities that require heavy manual labour and repetitive use of the hands (Kalichman and Hernández-Molina, 2010, Plotz et al., 2021).

Participation in certain competitive sports has been found to increase the risk of OA. A systematic review of studies investigating professional sport activities and risk of hip OA later in life found that elite handball players, soccer players and hockey players were at an increased risk of hip OA with estimated odds ranging from 5- to 9-fold compared to matched controls (Vigdorchik et al., 2017).

Another systematic review investigating the association between knee OA and participation in certain sports, found that participation in elite soccer, long-distance running, wrestling and competitive weight lifting was associated with a higher prevalence of knee OA compared to non-elite controls (Driban et al., 2017). A recent meta-analysis revealed that a high risk of hip, knee and ankle OA was associated with participation in American football, handball, wrestling,

ice hockey, shooting and bobsleigh but the relative risks were not adjusted for confounding factors (Bestwick-Stevenson et al., 2021).

Injury

Prior traumatic joint injury is recognised as a risk factor for OA (Doherty et al., 2016). The majority of evidence for post-traumatic OA exists for the knee (Whittaker et al., 2022, Webster and Hewett, 2022). Direct articular damage, anterior cruciate ligament (ACL) injury and meniscal tear following injury have all been linked to subsequent development of knee OA (Kramer et al., 2011). A recent systematic review and meta-analysis reported that the odds for knee OA were 4 times higher after isolated ACL injury, and 6 times higher after isolated meniscus injury and when ACL and meniscus injuries were combined compared to those without knee injury (Poulsen et al., 2019). A cohort study in the US with a 5-year follow-up revealed that ankle injury was associated with increased subsequent incidence of radiographic ankle OA in 541 men and women with a mean age of 69.4 years (Jaleel et al., 2021).

1.1.6.4 Risk Factors for Knee Osteoarthritis Pain

Risk factors for knee OA pain may be different from, or be the same, as those for knee OA, including:

1- Psychological factors

Psychological factors such as anxiety and depression, and catastrophising trait or state have been shown to be associated with occurrence and severity of knee OA pain and physical impairments (Axford et al., 2010, Van Baar et al., 1998). These also adversely influence the quality of life and associate with increased pain level, likelihood of neuropathic-like knee pain (often described as burning, present even at rest, and diffuse rather than localised), higher pain medication use, more frequent hospital visits, and less optimal patient-centered outcomes (Sharma et al., 2016). Depression is prevalent and affects 20% of people with OA (Stubbs et al., 2016). However, depression is not a risk factor for structural radiographic knee OA incidence or progression (Rathbun et al., 2020).

A recent systematic review and meta-analysis examined the association between pain severity and levels of depression and anxiety in people with OA, with knee OA being the most studied (Fonseca-Rodrigues et al., 2022). It included a total of 30,085 participants with a mean age of 64.3 years, 63% being females, from 121 included studies. Results of the meta-analysis showed significant positive correlations between pain severity and both depression and anxiety (Fonseca-Rodrigues et al., 2022). In those with physician-diagnosed knee OA sleep was independently associated with pain and depression at the baseline. The sleep-pain relationship was found to be mediated by depression symptoms in which poor sleep interacted with pain to exacerbate depression in those who experienced severe pain. After one year follow-up, sleep disturbance

at baseline predicted increases in both depression and disability (Parmelee et al., 2015).

2- Diabetes

Diabetes-related mechanisms have been proposed to increase the pathophysiological processes of OA resulting in inflammation, degradation and destabilisation of joint structures thus both causing and aggravating OA processes (Berenbaum, 2012). For example, advanced glycation end products play an important role in prolonging the inflammatory process throughout the joint (Chowdhury et al., 2022). As a result of this increased inflammation, breakdown of cells and tissues occurs and result in OA progression. Thus, people with OA and poor glycemic control are more likely to have greater OA pain compared to people with OA alone (Chowdhury et al., 2022).

Diabetes (unspecified as type 1 or 2) has been found to have an impact on knee pain, with the likelihood of higher pain severity and distribution of unilateral and bilateral knee pain being increased 2.45 to 2.55 times in diabetic individuals with knee OA compared to those with knee OA but no diabetes (Alenazi et al., 2020). Diabetes, however, not only has a significant impact on knee OA pain but also on the components of the Medical Outcome Study Short Form 12 (SF-12) questionnaire including physical status and mental status (Eitner et al., 2021). Moreover, diabetes and HbA1c levels were found to be predictors for incidence of symptomatic knee OA over 5 years follow-up (Zheng et al., 2023). Diabetes

regardless of HbA1c level significantly increased the risk almost 1.37 time higher for symptomatic knee OA, and those with a HbA1c level of $\geq 7\%$ were almost 2 times more likely to develop symptomatic knee OA compared to those without (Zheng et al., 2023). These studies suggest that diabetes negatively impacts patient-related outcomes.

3- Catastrophising trait

Pain catastrophising is one of the psychological factors that has been associated consistently with poor OA-related outcomes (Terry et al., 2020, Luong et al., 2012). Pain sensitisation via peripheral or central pain pathways appears to be present in a substantial proportion of people with OA (Fu et al., 2018). It was found that the presence of high levels of neuropathic pain and central sensitisation were significant predictors for poorer functional ability in people with knee OA (Elsehrawy et al., 2023). The Self-reported Central Mechanism Trait questionnaire score, derived from eight components including catastrophising, anxiety, depression, fatigue, neuropathic-like pain, sleep disturbance, pain distribution and cognitive impact, was a predictor for both knee pain persistence and knee pain severity in people with knee pain over one year in adults aged 40 years and older (Akin-Akinyosoye et al., 2020). Among those eight components, the self-report trait of catastrophising measured by the Pain Catastrophising Scale (ranging from 0 – 52) was found to increase pain persistence almost two-fold higher in people with knee pain at baseline compared to those who had resolved knee pain at one year follow-up (adjusted

relative risk (aRR) 1.94, 95% CI 1.29 – 2.93), and to predict pain severity (β 0.49, 95% CI 0.32 – 0.65; $p < 0.001$) (Akin-Akinyosoye et al., 2020).

A systematic review and meta-analysis found that pain sensitisation in people with OA was higher than in healthy individuals when objectively measured by quantitative sensory testing of pain pressure thresholds, temporal summation, flexor withdrawal responses and conditioned pain modulation (Fingleton et al., 2015). Moreover, it showed that those with knee OA having high symptom severity had lower pressure pain thresholds compared to those with low symptom severity (Fingleton et al., 2015). Thus, changes in nociceptive processing in the central and/or peripheral nervous systems might play a role in explaining the wide range of clinical pain manifestations associated with knee OA.

4- Non-restorative sleep

The quality of sleep is viewed as another measure that influences pain levels in those with knee OA (Campbell et al., 2015). Poor quality of sleep, especially short-lasting or fragmented sleep, may enhance pain sensitivity in those with knee OA and might be exacerbated by pain catastrophising (Smith et al., 2009, Campbell et al., 2015). Sleep disturbance affected 58.1% of those with knee OA at least three nights per week (Wilcox et al., 2000). An Australian prospective cohort study, comprising 1,099 people (51% females) with a mean age of 63 years, revealed that persistent sleep disturbance was significantly associated

with persistent knee pain (aRR 1.90, 95% CI 1.26 – 2.87) after adjustment for age, sex, BMI and other confounding factors (Pan et al., 2020b). Conversely, persistent knee pain was associated with persistent sleep disturbance (aRR 1.99, 95% CI 1.23 – 3.24) after adjustment for age, sex, BMI and other confounding factors (Pan et al., 2020b).

Another 8-year cohort study in the US aimed to identify restless sleep trajectories and its association with people with or at high risk for knee OA aged 45-79 years (n=4,359) (Song et al., 2021). Those experiencing restless sleep for 3 or more nights/week were classified into a worsening trajectory group characterised by a low baseline probability of restless sleep followed by increasing probabilities over time, and a good trajectory group characterised by the lowest probabilities of restless sleep over time. It was revealed that in those with knee OA who had restless sleep, the worsening trajectory group had an increased likelihood of knee pain (aOR 1.04, 95% CI 1.00 – 1.07) after adjustment for sociodemographic and other health and behavioural factors (Song et al., 2021). These studies suggest that there is a bidirectional relationship between pain experience and quality of sleep (Smith et al., 2009, Song et al., 2021, Campbell et al., 2015, Pan et al., 2020b). Thus, to improve pain and disability in those experiencing painful knee OA it is important to take into account the quality of their sleep.

1.1.6.5 Risk factors for foot/ankle OA

Risk factors contributing to foot/ankle OA vary according to whether the assessment used was self-reported or radiographic, the joint being assessed and the population studied (International FAO Consortium et al., 2022). Most studies investigating risk factors for foot and/or ankle OA have been cross-sectional and there are only two cohort studies (International FAO Consortium et al., 2022). Table 6 summarises the studies that have examined risk factors for foot and ankle OA.

Table 6. Details of studies examined foot and ankle osteoarthritis

Study	Country	Study design	Joint	Sample	Age	Risk factors
Foot OA						
Flowers et al. (2021)	US	Community based cross-sectional	Symptomatic radiographic foot OA	864 (68.2% were female)	≥ 55 years	Radiographic foot OA Older age (aOR 1.03, 95% CI 1.01 - 1.06) Obese people (aOR 2.27, 95% CI 1.34-3.86) Symptomatic radiographic foot OA Obese people (aOR 5.13, 95% CI 1.49 - 17.7)
Rathod et al. (2016)	UK	Cross-sectional (from 4 general practices)	Radiographic polyarticular (multi-joint) foot OA	533 (60% were female)	≥ 50 years	Age (aOR 67.3, 95% CI 65.4 – 69.2) BMI (aOR 32.5, 95% CI 31.2 – 33.8) Radiographic nodal OA (aOR 0.34, 95% CI 0.24 – 0.44) More pain (aOR 0.38, 95% CI 0.28 – 0.47) Functional limitation (aOR 37.2, 95% CI 34.2 – 40.1)
First MTPJ						
Rathod et al. (2016)	UK	Cross-sectional (from 4 general practices)	Radiographic 1 st MTPJ OA	533 (60% were female)	≥ 50 years	Age (aOR 66.1, 95% CI 64.6 – 67.7) BMI (aOR 30.1, 95% CI 29.1 – 31.2)
Wilder et al. (2005)	US	Community based cross-sectional	Radiographic 1 st MTPJ OA	3436 (69% were female)	≥ 40 years	Radiographic hand OA (aOR 3.6, 95% CI 3.0 - 4.4) Radiographic knee OA (aOR 3.7, 95% CI 3.0 – 4.5)

Mahiquez et al. (2006)	US	Community based cohort with 7-years follow-up	Incidence of radiographic 1 st MTPJ OA	1,592 men and women	≥ 40 years	Pronated foot posture (hindfoot valgus) (aRR 1.23, 95% CI 1.06 – 1.42)
Bernard et al. (2010)	US	Community based cross-sectional	Radiographic 1 st MTPJ OA	3,548 (69% were women)	≥ 40 years	Occupational stair-climbing (>5 times/day) in males only (aOR 1.61, 95% CI 1.11 – 2.32)
Cherry et al. (2020)	UK	Population base cohort with 6-years follow-up	Radiographic 1 st MTPJ OA	209 female	45-64 years	Lifetime occupations was not associated with ROA of 1 st MTPJ (aOR 1.02, 95% CI 0.79 – 1.31)
Mid-foot OA and ankle OA						
Thomas et al. (2015a)	UK	Cross-sectional (from 4 general practices)	Symptomatic radiographic midfoot OA	525 men and women	≥ 50 years	Obesity (aOR 2.02, 95% CI 1.32 – 3.08)
						One or more previous forefoot fracture (aOR 2.06, 95% CI 1.14 – 3.71)
						Having pain in other weight-loaded joints (aOR 8.53, 95% CI 2.63 – 27.71)
Arnold et al. (2021)	UK	Cross-sectional (from 4 general practices)	Symptomatic radiographic midfoot OA	52 people with symptomatic midfoot OA (73% female)	≥ 40 years	Ankle invertor muscle strength was negatively and independently associated with foot pain (β -0.026, 95% CI -0.051 to -0.001)
				36 asymptomatic controls (66% were female)		

Golightly et al. (2019)	US	Community based cross-sectional	Radiographic OA of TNJ Symptomatic radiographic ankle OA	848 (68% were female)	≥ 55 years	Knee hypermobility was significantly associated with: 1.Radiographic OA of TNJ (aOR 3.05, 95% CI 1.10 – 8.51) 2.Symptomatic radiographic ankle OA (aOR 5.34, 95% CI 1.37 – 20.79) 3.Foot symptoms (aOR 2.40, 95% CI 1.15 – 5.04) 4.Ankle symptoms (aOR 4.41, 95% CI 2.06 – 9.44)
Menz et al. (2010c)	Australian	Cross-sectional Based community and health clinics	Radiographic OA in the TNJ and N1 st CJ	205 people (65.3% were female)	61-94 years	Pronated foot posture (flat feet) was associated with radiographic OA of the TNJ and N1 st CJ during walking (OR 1.07, 95% CI 1.02 – 1.13)
Thomas et al. (2015b)	UK	Cross-sectional (from 4 general practices)	Symptomatic radiographic midfoot OA	525 men and women	≥ 50 years	Pronated foot posture low arch (>0.28) (aOR 3.25, 95% CI 1.36 – 7.76)

UK – United Kingdom; US – United States; OA – osteoarthritis; BMI – body mass index; aOR – adjusted odd ratio; CI – confidence interval; 1st MTPJ – First metatarsophalangeal joint, TNJ - Talonavicular joint and N1stCJ - Navicular-first cuneiform joint

Cherry et al. (2020) classified the occupation into sedentary (higher manager/profession, admin/secretary/clerical), light manual (housewife, skilled manager/teacher/nurse, cleaning/domestic) and heavy manual (skilled manual, unskilled manual)

All radiographic OA was defined as (grade ≥ 2) and pain was assessed using foot mannequin or a question

Symptomatic radiographic foot OA was associated with older age and increased BMI (Flowers et al., 2021). Obesity was significantly associated with increased odds to almost 5 times greater for symptomatic radiographic foot OA, and to almost 2 times greater for radiographic foot OA compared to normal weight in an adjusted model (Flowers et al., 2021). Polyarticular (multi-joint) foot OA was associated with age, radiographic nodal OA, increased BMI, and more pain and functional limitation compared to the other classes, which include no or minimal foot OA and isolated 1st MTPJ OA after adjustment for age and sex (Rathod et al., 2016).

As regards 1st MTPJ OA, pronated foot posture (hindfoot valgus) was associated with the incidence of radiographic 1st MTPJ OA (Mahiquez et al., 2006). Radiographic 1st MTPJ OA was associated with occupational stair-climbing (>5 times/day) in males (Bernard et al., 2010). However, it was not associated with lifetime occupation in a cohort study involving women only (Cherry et al., 2020). Radiographic OA of the hand and the knee were associated with radiographic 1st MTPJ OA (Wilder et al., 2005). Age and BMI were associated with radiographic 1st MTPJ OA (Rathod et al., 2016).

Symptomatic midfoot OA was associated with obesity, one or more previous forefoot fracture, and having pain in other weight-loaded joints such as the lower back, hip, knee, hindfoot/ankle and forefoot (Thomas et al., 2015a). People with symptomatic midfoot OA were more likely to report diabetes (Thomas et al.,

2015a), and have weaker ankle invertor muscles compared with people with asymptomatic midfoot OA (Arnold et al., 2021). Knee hypermobility was significantly associated with radiographic OA of the TNJ and with foot symptoms (Golightly et al., 2019). Pronated foot posture was associated with radiographic OA of the TNJ and N1stCJ during walking in older people (Menz et al., 2010c), and symptomatic radiographic midfoot OA (Thomas et al., 2015b). Knee hypermobility was associated with both ankle symptoms and symptomatic radiographic ankle OA (Golightly et al., 2019).

1.1.7 Impact and burden of Osteoarthritis

According to the 2021 Global Burden of Disease, OA ranked the 14th highest contributor cause of YLD worldwide, and the 7th leading cause of YLD in those aged 70 years and older in 2020 (Steinmetz et al., 2023). Knee OA is a common condition, and years lived with this disability increased by 57% between 1990 and 2020 (Steinmetz et al., 2023). It has been reported that physical impairment associated with ankle OA is equivalent to that resulting from congestive heart failure and end-stage kidney disease (Saltzman et al., 2006). The most disabling form of foot OA is midfoot OA which impacts walking, standing and performing daily activities (Rathod et al., 2016). OA can co-exist with, and negatively impact, other long-term conditions (Swain et al., 2021). Therefore, OA tends to increase the burden at both personal and healthcare system levels.

Previous studies in Norway, Sweden, Finland, Italy and Denmark have shown increased utilisation of primary and specialist healthcare by people with OA compared to controls ranging from 6% to 15% (Hallberg et al., 2023, Colombo et al., 2021). Primary care appears to have high consultation rates for ankle and/or foot musculoskeletal complaints in the UK, Netherlands and Australia (Menz et al., 2010a, Menz et al., 2010b, van der Waal et al., 2006, Menz et al., 2022). Data from the CPRD in the UK showed increased annual primary consultations after the index date in people with OA compared to those without OA ($p < 0.05$). Specifically within the OA group, 12.38% of consultations were for hip OA, 12.15% for knee OA and 11.66% for foot/ankle OA (Swain et al., 2023). There were significant increases in the median number of annual consultations with increasing age in both sexes (Swain et al., 2023). Hospitalisation was also found to be higher in people with OA compared to controls in the UK, US, Sweden and Italy (Swain et al., 2023, Wright et al., 2010, Colombo et al., 2021, Kiadaliri and Englund, 2021).

1.1.8 Management of Osteoarthritis

The recommended management for knee OA or foot/ankle OA should involve individualised, shared decision-making and have non-pharmacological interventions as the core treatments and pharmacological and surgical interventions as adjunctive treatments (Mora et al., 2018, National Clinical Guideline, 2014, International FAO Consortium et al., 2022). Optimal management of knee OA or foot/ankle OA pain should include, where feasible,

the addressing of modifiable risk factors such as obesity and muscle weakness in the treatment plan (Georgiev and Angelov, 2019, Morley et al., 2021). Figure 18, is an example of NICE recommendations for OA which are applicable for OA at any site (NICE, 2022a).

The non-pharmacological core interventions for knee OA or foot/ankle OA include: patient education on OA (its causes, associations, outcomes and treatment options); weight loss if overweight or obese; exercise prescription including strengthening and aerobic fitness; and reduction in adverse mechanical factors (e.g., pacing of activities, footwear modification) (Lim and Doherty, 2011).

Medications for short-term pain relief are adjuncts in the treatment plan, with topical non-steroidal anti-inflammatory drugs (NSAIDs) being the first-line agents before consideration of oral systemic analgesics (e.g., paracetamol, NSAIDs, opioids). If the pain is resistant to other treatments, intra-articular corticosteroids may also be considered (Lim and Doherty, 2011, Nelson et al., 2014a, NICE, 2022a).

Surgical interventions for knee OA include osteotomy and total joint arthroplasty. Despite arthroplasty being the most suitable option to consider for those with continuing chronic pain, disability and reduced quality of life because of their

knee OA, it is notable that at least 20% of people still experience chronic knee pain after total joint arthroplasty (Wylde et al., 2018).

As regards surgical intervention for the foot, two randomised control trials compared total joint replacement to arthrodesis in people with 1st MTPJ OA (Gibson and Thomson, 2005, Stone et al., 2017). In both, significant improvement in pain was reported in favour of arthrodesis at 2 and 15 years (Gibson and Thomson, 2005, Stone et al., 2017). The surgical options for midfoot OA are midfoot arthrodesis (fusion), a hybrid plating system, and fixation devices including staples and a plate screw (Kurup and Vasukutty, 2020). For the ankle, the main options are fusion and total ankle replacement, which may result in improvement in pain, functions and quality of life both short- and long-term, with most improvement being provided by total ankle arthroplasty (Norvell et al., 2019, Wood et al., 2009, Nunley et al., 2019).

Any management plan must be re-evaluated and possibly modified in accordance with the outcomes, so follow-up and intermittent review of people with OA is important (Figure 18) (NICE, 2022a). A full, holistic assessment for someone with OA, enquiry and discussion of their illness perceptions about OA, individualisation of the management plan and involvement of the patient in shared decision-making is recommended best practice (Lim and Doherty, 2011).

Management of osteoarthritis

Explain that:

- osteoarthritis is diagnosed clinically and usually does not need imaging to confirm diagnosis
- management is guided by symptoms and physical function
- the core treatments are therapeutic exercise and weight management, alongside information and support.

Exercise	Weight management	Information and support
• For all people with osteoarthritis, offer therapeutic exercise tailored to their needs (for example, local muscle strengthening, general aerobic fitness). • Consider supervised therapeutic exercise sessions. • Advise people it may initially cause pain or discomfort but long-term adherence to an exercise plan will benefit the joints, reduce pain and improve function. • Consider combining therapeutic exercise with an education programme or behaviour change approaches in a structured treatment package.	For people who are living with overweight or obesity: • advise them that weight loss will improve quality of life and physical function, and reduce pain • support them to choose a weight loss goal • explain that any weight loss is likely to be beneficial, but losing 10% is likely to be better than 5%. For guidance and information on weight management, including interventions for weight loss, see NICE's topic page on obesity.	• Tailor information to the person's individual needs and ensure it is in an accessible format. • Advise where people can find further information on: ◦ the condition and information that challenges common misconceptions ◦ specific types of exercise ◦ managing their symptoms ◦ how to access additional information and support ◦ benefits and limitations of treatment.

Manual therapy Only consider for hip and knee osteoarthritis and alongside therapeutic exercise.	Devices Consider walking aids for lower limb osteoarthritis.	Do not offer: • acupuncture or dry needling • electrotherapy treatments • insoles, braces, tape, splints or supports routinely.

This is a summary of the recommendations on managing osteoarthritis in [NICE's guideline on osteoarthritis in over 16s: diagnosis and management](#)

NICE National Institute for Health and Care Excellence

Referral for joint replacement

Consider referring people with hip, knee or shoulder osteoarthritis for joint replacement if:

- joint symptoms are substantially impacting their quality of life **and**
- non-surgical management is ineffective or unsuitable.

Do not exclude people from referral for joint replacement because of age, sex or gender, smoking, comorbidities, or overweight or obesity.

Pharmacological management

If needed, use:

- alongside non-pharmacological treatments and to support therapeutic exercise
- the lowest effective dose for the shortest possible time.

Review with the person whether to continue treatment. Base frequency of reviews on clinical need.

- Offer a topical non-steroidal anti-inflammatory drug (NSAID) for knee osteoarthritis.
- Consider a topical NSAID for other osteoarthritis-affected joints.

Consider an oral NSAID if topical medicines are ineffective or unsuitable and offer a gastroprotective treatment alongside.

Do not offer:

- paracetamol or weak opioids routinely, unless:
 - used infrequently for short-term pain relief
 - all other treatments are ineffective or unsuitable
- glucosamine
- strong opioids
- intra-articular hyaluronan injections.

Consider intra-articular corticosteroid injections for short-term relief when other pharmacological treatments are ineffective or unsuitable or to support therapeutic exercise.

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Figure 18. Summary of NICE recommendations. The core consists of the basic recommendations that everyone with symptomatic OA should be given. Analgesics should be considered as adjuncts if the core treatments alone are insufficient. (Data from Osteoarthritis – national clinical guideline for care and management in adults. NICE and Royal College of Physicians Guidelines on Osteoarthritis. 2022)

1.2 Multimorbidity

1.2.1 Definition of Multimorbidity

Multimorbidity is a global health concern because it has a substantial impact on individuals and their family, healthcare system and society (Skou et al., 2022). It is defined as the occurrence of two or more long-term conditions in an individual simultaneously, including physical or mental health conditions (van den Akker et al., 1996). It is associated with deterioration in quality of life, a rise in health-care costs and a greater burden on health care systems (Violán et al., 2014, Fortin et al., 2007, Bähler et al., 2015).

1.2.2 Types of Multimorbidity

Broadly, different types of multimorbidity have been classified based on the pathophysiology and common shared risk factors for the conditions (Lappenschaar et al., 2012). Multimorbidity has been divided into random and associative as listed below:

1. Random multimorbidity

This refers to a random co-occurrence of diseases where there is no direct causation of one to the other, no shared risk factors, and their coexistence has occurred by chance. It is known also as independent multimorbidity (Lappenschaar et al., 2012) and is similar to the concept of non-aetiological association (Kraemer, 1995, Valderas et al., 2009). Occurrence of OA and asthma in an individual is an example of a random multimorbidity (Piette and

Kerr, 2006). Other examples of random multimorbidity in an individual are diabetes with asthma or irritable bowel syndrome or mental illness including depression symptoms (Aung et al., 2015, Magnan et al., 2015), and chronic kidney disease with heart failure or dementia or chronic obstructive pulmonary disease or cancer (Hall et al., 2020).

2. Associative multimorbidity

This is the opposite of random/independent multimorbidity in which there is some relationship between the two or multiple diseases that causes disease co-occurrence more often than would be predicted by chance (Lappenschaar et al., 2012). This could be a shared or linked pathophysiology, occurrence of common risk factors, or caused by a treatment from one to another. For example, diabetes and cardiovascular conditions because metabolic abnormalities including insulin resistance and impaired glucose tolerance or impaired fasting glycaemia can damage blood vessels and this could lead to cardiovascular events in addition to both conditions having shared risk factors such as obesity, hypertension and dyslipidemia (Piette and Kerr, 2006, Leon and Maddox, 2015, Eckel et al., 2005). There are a number of medications that are associated with increased risk of other condition such as NSAIDs (including selective COX-2 inhibitors) used for OA pain to myocardial infarction (Laine et al., 2008), antipsychotics are associated with increased risk of dyslipidemia and diabetes (Newcomer, 2007), and medications with anticholinergic effects are associated

with increased risk of cognitive impairment/dementia and cardiovascular events (Hanlon et al., 2020).

1.2.3 Epidemiology of Multimorbidity

1.2.3.1 Prevalence of Multimorbidity

With an increasing, and increasingly aged, global population, the prevalence of multimorbidity is expected to rise (Afshar et al., 2015). A recent systematic review and meta-analysis aimed to examine the prevalence of multimorbidity across the World Health Organisation geographic regions in adults (Chowdhury et al., 2023). A total of 126 peer-reviewed studies were included from 54 countries around the world, comprising nearly 15.4 million people with a weighted mean age of 56.94 years and 67.9% being female. Results showed that multimorbidity occurs in 37.2% of the global population, affecting mainly those aged over 60 years (Chowdhury et al., 2023). The lowest prevalence of multimorbidity was found in Asia (35%), followed by North America (43.1%) and then Europe (39.2%), and South America had the highest prevalence (45.7%) (Chowdhury et al., 2023).

A whole population study in England, using the National Bridges to Health Segmentation dataset, estimated the prevalence of multimorbidity to be 14.8%, being 0.9% in the young age group (0-19 years) and 68.2% in the older age group (≥ 80 years) (Valabhji et al., 2024). Age was strongly associated with multimorbidity specifically in the ≥ 80 age group compared to the 50-59 age

group. Men had higher odds of multimorbidity compared to women. The effect of deprivation increased relative to age until the 50-59 years age group (aOR 2.76, 95% CI 2.73 – 2.78), then decreased thereafter with deprivation effect being the smallest in the 70-79 years age group (aOR 1.95, 95% CI 1.93 – 1.97) (Valabhji et al., 2024).

Another British study used the CPRD between 2004 and 2019 in England, and reported the prevalence of multimorbidity by types as basic (≥ 2 chronic conditions) and complex (≥ 3 chronic conditions) (Head et al., 2021). The prevalence of basic multimorbidity was 52.8%, while that of complex multimorbidity was 32.7%. Women had a higher prevalence than men of both basic and complex multimorbidity in all age groups, apart from the prevalence of complex multimorbidity in the 70-79 age group (Head et al., 2021). The prevalence of both multimorbidity types increased by age and in the most deprived areas. Subsequently, another study using the CPRD estimated the projected prevalence of cases in England from 2019 to 2049 according to the index of multiple deprivation, age group and sex (Head et al., 2024). It estimated that the prevalence of multimorbidity (basic or complex) is predicted to increase by 34% from 53.8% in 2019 to 71.9% (95% uncertainty interval 71.8 – 72) in 2049 (Head et al., 2024). This rise represents an increase of 84% in the number of people with multimorbidity from 19.2 million in 2019 to 35.3 million in 2049, with the greatest increase occurring in the most deprived quintile, predominantly

in women but with similar relative increases over the age of 30 years between the sexes and those aged ≤ 65 (Head et al., 2024).

Furthermore, another study using the CPRD in Scotland reported a prevalence of multimorbidity of 23.2% in 2007 (Barnett et al., 2012). Prevalence of multimorbidity increased significantly with age, particularly among people aged ≥ 65 years, and women had higher rates of multimorbidity than to men. It was also determined that the onset of multimorbidity occurred 10-15 years earlier in young and middle-aged adults living in the most deprived areas and having socioeconomic deprivation compared to those living in the most affluent areas (Barnett et al., 2012).

In all the UK studies mentioned above, age and socioeconomic deprivation were associated with a higher prevalence of multimorbidity. Women were more likely to have multimorbidity compared to men, except the study by Valabhji et al. (2023) which reported that men were more likely to have multimorbidity than women, though the differences were small. Table 7 summarises the studies conducted in the UK. The reported prevalence of multimorbidity in non-UK countries ranges from 7.9% to 73%. This wide variation arises through study of different age groups, the characteristics of the populations studied and the definition of multimorbidity (Alvarez-Galvez et al., 2023, Chen et al., 2020b, Amirzada et al., 2023, Hernández et al., 2019).

Table 7. Examples of studies that have examined multimorbidity prevalence in the United Kingdom

Study	Data source	Age group	Definition of multimorbidity	Prevalence of multimorbidity
Valabhji et al. (2023)	The National Bridges to Health Segmentation dataset (England)	0 - ≥ 80	≥ 2 chronic conditions	Overall prevalence (14.8%) Aged 0-19 years (0.9%) Aged ≥ 80 years (68.2%)
Head et al. (2021)	CPRD 1 st Jan 2004 until 31 st Dec 2019 (England)	≥ 18	Basic multimorbidity (≥2 chronic conditions) Complex multimorbidity (≥3 chronic conditions)	Basic multimorbidity (52.8%) Complex multimorbidity (32.7%)
Barnett et al. (2012)	CPRD As of March 2007 (Scotland)	0 - ≥ 85	≥ 2 chronic conditions	23.2%

CPRD - Clinical Practice Research Datalink

Basic multimorbidity defined as having ≥2 chronic conditions

Complex multimorbidity defined as having ≥3 chronic conditions

1.2.3.2 Incidence of Multimorbidity

A 2021 systematic review of the incidence of multimorbidity included 32 studies from 19 countries comprising a sample of 390 to >5 million people aged from childhood through to older adults (men and women) (Kudesia et al., 2021). It was found that among five studies the incidence rate of multimorbidity ranged from 1.26 to 68.5 per 1,000 person-years with a median incidence of 30.7 per 1,000 person-years (interquartile range (IQR) 39.5 per 1,000 person-years). Across ten studies, the overall cumulative incidence of multimorbidity ranged from 1.3% to 61% with a median cumulative incidence of multimorbidity of 2.8% (IQR 28.7%) (Kudesia et al., 2021). This systematic review highlighted the heterogeneity among studies regarding reporting incidence due to the variation in length of follow-up, in criteria used to define multimorbidity, and in study populations, as some included the general population while others included patient populations with a particular baseline condition. The remaining 17 incidence studies reported incidence stratified by sociodemographic (e.g., age, sex, race/ethnicity, and medical factors such as number of diseases at baseline). Notably, incidence of multimorbidity was greater in those who were older and who had one condition at baseline (Kudesia et al., 2021).

In England, the age-standardised incidence of basic multimorbidity (≥ 2 chronic conditions) changed little between 2004 and 2019. However, the incidence of complex multimorbidity (≥ 3 chronic conditions) was 497/10,000 person-years in men and 546/10,000 person-years in women in 2019, with an increase of 19%

in men and 14.6% in women since 2004 (Head et al., 2021). Between 2004 and 2019 the age of onset of basic multimorbidity fell from 56 years to 46 years, and of complex multimorbidity from 66 years to 55 years. Older age, being female, and living in the most deprived regions were associated with an increased risk for both multimorbidity types (Head et al., 2021). Another study using the CPRD estimated the projected incidence of multimorbidity inequalities in England between 2019 - 2049, and found 1.07 million cumulative incident cases of basic multimorbidity and approximately 0.70 million cases of complex multimorbidity, especially in those < 65 years and in the most deprived quintile (Head et al., 2024).

In a retrospective cohort study of 826,936 adults aged ≥ 18 years registered in general practices in one inner London Borough and followed for a median of 4.2 years, 76% entered the study with no condition, 15% had one condition, 5% had 2 conditions and 4% had ≥ 3 conditions (Bisquera et al., 2022). At the follow-up, 24% developed ≥ 1 long-term condition and 3% had died (Bisquera et al., 2022). Being female, having higher deprivation and being of black ethnicity were independently associated with an increased risk of transitioning from one to two long-term conditions, and a shorter period of time spent in a healthy state (Bisquera et al., 2022).

The incidence of multimorbidity in non-UK countries has been estimated in two studies to range from 12.6 to 34.2 per 100 person-years over three years of follow-up (Melis et al., 2014, Hussin et al., 2019), and in two other studies to

range from 1.3% to 23.7% over one to nine years of follow-up (Van den Akker et al., 1998, Shang et al., 2020). These variation in incidence are due to differences in the study populations and their characteristics (i.e., age, sex, BMI, socioeconomic status) and whether they already had one condition at baseline or were free of diseases.

1.2.3.3 Risk factors for Multimorbidity

Several risk factors have been associated with likelihood of multimorbidity, including lower socioeconomic class, low physical activity levels, alcohol consumption, higher BMI and smoking habits (Fortin et al., 2014, Cassell et al., 2018). Notably, age is a well recognised determinant of multimorbidity along with relative deprivation (Barnett et al., 2012, Head et al., 2021). Furthermore, pre-existing medical conditions such as hypertension, hypercholesterolemia and osteoporosis were associated as common risk factors for multimorbidity (Willadsen et al., 2016). Recently, it has been reported that low educational level, high loneliness, self-reporting fair/poor health, disability and low quality of life were strongly associated with multimorbidity among adults in 17 European countries (Bezerra de Souza et al., 2021).

Depression might also be a risk factor for development of subsequent long-term conditions (multimorbidity ≥ 2 chronic condition), as found by a 10-year follow-up study in Canada of 29,838 adults, of whom 51% were females aged 18 and older (Li et al., 2021). At baseline 8% of women and 4% of men had depression

and this was associated with an increased risk of subsequent development of a “first” chronic condition with an adjusted hazard ratio (aHR) of 1.16 (95% CI 1.07 – 1.26) for women and 1.20 (95% CI 1.07 – 1.36) for men after adjustment for demographic, behavioral and socioeconomic factors (Li et al., 2021).

1.2.4 Burden and impact of Multimorbidity

In primary care in England one in two consultations involve people with multimorbidity, and health care costs of an individual increase almost exponentially according to the number of long-term conditions that they have (Salisbury et al., 2011). In the UK, people with multimorbidity had more primary care visits (aOR 2.56, 95% CI 2.48 – 2.64), and a higher number of hospitalisations (aOR 4.33, 95% CI 3.63 – 5.17) compared to people without multimorbidity (Cassell et al., 2018, Wang et al., 2015). In 16 European countries it was also found that healthcare utilisations were higher in people with multimorbidity of both sexes and with a median age of 66 years (Palladino et al., 2016). Specifically, there was an increase in the mean number of general practitioner (GP) visits annually from 4.8 in people without long-term condition to 9.9 for people with multimorbidity. An increase in the number of a long term conditions was linked with increased secondary care utilisation, an increased possibility of being hospitalised, an increased number of hospitalisations and a more prolonged hospital stay (Palladino et al., 2016).

Multimorbidity has a significant impact on both the patient and the health care system, and its consequences are wide-ranging as it is associated with:

- poor health-related quality of life (Walker et al., 2016)
- presence of polypharmacy (Calderón-Larrañaga et al., 2012)
- longer stays in hospital and higher potential of re-admission (Librero et al., 1999)
- increased functional decline (Calderón-Larrañaga et al., 2019)
- increased mortality rate (Menotti et al., 2001)

Although these consequences might have psychological and physical impacts on an individual, whether medical support might be required depends primarily on the combination of diseases and their severity. However, support for a single disease is more likely to be available than for those with multimorbidity (Smith and O'Dowd, 2007). This indicates an increased burden on health care services and places financial strain on both patients and the healthcare system.

1.2.5 Management of multimorbidity

Management burden refers to the workload of self-management and the increased medical treatment and healthcare services that are required, which are all strongly linked to the number of conditions that someone has (Barnett et al., 2012). The management of multimorbidity is often challenging for healthcare professionals and patients (Wallace et al., 2015). This is due to complex organisational problems in terms of accessibility to care, coordination and consultation time (Liddy et al., 2014). Involvement of drugs may result in

polypharmacy with its associated risks (Duerden et al., 2013, Guthrie et al., 2011). People with multimorbidity have a high treatment burden in terms of understanding and self-managing the long-term conditions, attending numerous medical appointments, and managing complex medication regimens (Skou et al., 2022).

Some healthcare organisations have published guidance on the management of people with multimorbidity, for example in the UK (Farmer et al., 2016), Europe (Palmer et al., 2018, Muth et al., 2014) and the US (Health and Services, 2010, Multimorbidity, 2012). All of these share a consensus about the key components of an approach based on the Patient-Centred Care Model and the Chronic Care Model (Stewart et al., 2013, Bodenheimer et al., 2002). These key components include a regular comprehensive review of people problems according to their individualised circumstances, shared decision-making with patients, tailoring treatment plans based on each patient's priorities, focusing on disease control and quality of life and function, balancing risks and benefits of treatment in order to mitigate treatment burden particularly in those with inappropriate polypharmacy, encouraging self-management, and developing a personalised care plan (Stewart et al., 2013, Bodenheimer et al., 2002).

A multidisciplinary team should provide these services for people with multimorbidity. This could be achieved with one clearly designated professional responsible for healthcare coordination. In order to facilitate system re-design,

an efficient user-friendly clinical information system is required to enable information sharing among healthcare practitioners (Salisbury et al., 2018).

1.2.6 Multimorbidity and Osteoarthritis

Multimorbidity is reported to be a common problem in people with OA who are seen in general practice in the UK and the Netherlands (Kadam et al., 2004, Van Oostrom et al., 2014). The components of multimorbidity that have been associated with knee and hip OA include cardiovascular diseases, chronic obstructive pulmonary disease, diabetes, and sinusitis (Reeuwijk et al., 2010). Conversely, OA is also very common in people living with multimorbidity (Ran et al., 2021). This is due primarily to the shared increased prevalence of long-term conditions with aging, and shared multiple risk factor such as obesity, medication use, physical inactivity and the potential role of inflammation in multimorbidity that could contribute to OA, and vice versa (Chudasama et al., 2019, Friedman et al., 2015).

Recently, Swain and colleagues in a CPRD study found that those with OA in the UK are more likely to have other chronic conditions both prior to and after the first diagnosis of OA during 1997 to 2017. For example, those with OA had a higher risk for the development of chronic conditions such as heart failure, dementia, liver disease, irritable bowel syndrome and gastrointestinal bleeding following OA diagnosis. On the other hand, chronic conditions such as back

pain, fibromyalgia, gout and ankylosing spondylitis were more likely to be present prior to OA diagnosis (Swain et al., 2021).

A Swedish longitudinal study investigated 548,681 adults aged 35 and older for the risk of developing comorbidities in individuals with physician-diagnosed hip or knee OA from 2010 to 2017 (Dell'Isola et al., 2022). This study found that individuals with newly physician-diagnosed hip or knee OA had a significant increased risk of developing cardiovascular diseases, osteoporosis, back pain and depression compared to those with no hip or knee OA physician-diagnosis. However, those with new knee OA diagnosis alone were additionally at significantly higher risk of developing diabetes mellitus, lung cancer and Alzheimer's disease compared to those with no knee OA diagnosis (Dell'Isola et al., 2022).

A previous meta-analysis aimed to evaluate musculoskeletal conditions and the risk of developing chronic diseases in a total of 2,686,113 mid-older aged adults using cohort studies from Taiwan, Spain, US, Norway, Netherlands, UK, Canada, Italy, and Australia (Williams et al., 2018). Musculoskeletal conditions referred to one or a combination of back or neck pain or knee or hip OA, whereas chronic diseases included cancer, diabetes, cardiovascular disease, obesity or chronic respiratory disease. Results showed that individuals with musculoskeletal conditions had a 17% increase in the risk of developing chronic diseases compared to those without musculoskeletal conditions (hazard ratio

(HR) 1.17, 95% CI 1.13 – 1.22) (Williams et al., 2018). Another meta-analysis that examined the relationship between OA and cardiovascular diseases in mid-older aged adults found statistically significant increases in relative risk (RR) of ischaemic heart disease (RR 1.78, 95% CI 1.18 – 2.69) and heart failure (RR 2.80, 95% CI 2.25 – 3.49) in people with OA compared to those without OA (Hall et al., 2016).

1.2.7 Association between osteoarthritis at the knee and foot/ankle joints

OA may affect multiple joint sites within an individual (O'Neill et al., 2018). Generalised OA is a common condition and it has an impact on activity limitation and health related quality of life (Nelson et al., 2014b, Cuperus et al., 2015). The term "generalised OA" is used particularly in people with nodal hand OA in conjunction with other joint sites including OA at the synovial apophyseal joints of the spine, knee or hip joints (Kraus et al., 2007). No previous study has examined the specific association between radiographic OA occurring at the knee and the foot/ankle joint sites. However, a positive association between symptomatic radiographic knee OA with foot and/or ankle pain has been reported ($p < 0.05$) in a study using data from the OA Initiative (OAI) (Paterson et al., 2015). This study found that foot and/or ankle pain negatively affected general outcomes such as the SF-12 (mental and physical components) and knee-related outcomes including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (pain, stiffness, function), 20-metres walk test (meter/second) and repeated chair stand pace (stands/second)

compared to those with only symptomatic radiographic knee OA (Paterson et al., 2015).

Another study based within the OAI cohort found that foot and/or ankle pain associated with the development of incident symptomatic radiographic knee OA over a four year period (aOR 3.28, 95% CI 1.69 – 6.37) and with knee symptoms including pain, stiffness or aching in or around the knee on most days of the month for at least one month in the past year (aOR 1.55, 95% CI 1.10 – 2.19) (Paterson et al., 2017b). A subsequent OAI study also reported that foot and/or ankle pain associated with worsening knee pain in those with symptomatic radiographic knee OA (aOR 1.54, 95% CI 1.25 – 1.91) (Paterson et al., 2017a). These OAI studies enrolled people with evidence of knee OA or at high risk of developing knee OA, so there is some inherent bias towards developing knee OA. Moreover, a community-based 7-year cohort study including middle to older aged adults in the UK found that ankle pain with and without foot pain was significantly associated with risk of incident symptomatic radiographic knee OA and frequent knee pain with aORs of 2.30 (95% CI 1.13-4.66) and 2.53 (95% CI 1.34 - 4.80), respectively (Perry et al., 2021).

Irrespective of the joint affected, OA is the inherent repair process of synovial joints that may be triggered by various insults resulting from genetic, constitutional and environmental risk factors (Doherty et al., 2016, Brandt et al., 2003). Age, sex and higher BMI could have an influence on the development of

OA both at the knee and foot/ankle joints (Doherty et al., 2016). From a biomechanical perspective, previous studies have indicated that alterations in ankle biomechanics are associated with knee OA (Astegh et al., 2008, Ro et al., 2019, Robon et al., 2000). This could be viewed also as a bidirectional relationship as knee OA has been proposed to have a negative impact on ankle biomechanics (Ro et al., 2019).

1.3 Professional Footballers

Football is one of the most popular sports in the world. There are approximately 130,000 professional footballers worldwide (FIFA, 2021). Professional football is a high-performance sport that requires players to be able to combine physical, tactical, technical and mental abilities at a high level (Barnes et al., 2014, Bloomfield et al., 2007). This demand for prolonged and heavy physical activities during training and competitions, exposes footballers to sport-related health risks (Kuijt et al., 2012). Musculoskeletal injuries and head trauma in particular are the most common sport-related health risks, which may increase the risk both of OA, cognitive dysfunction and dementia (Carmody et al., 2022, Macnab et al., 2023). Apart from overt acute injury, repetitive microtrauma can also damage musculoskeletal tissues and the brain and be a risk factor for OA and cognitive dysfunction (Sui et al., 2022, Lappenschaar et al., 2012). This section presents an overview of studies of knee pain and foot/ankle OA in professional footballers, followed by a section on the development of long-term conditions in professional footballers.

1.3.1 Knee Pain in Professional Footballers

Professional football has a high injury rate and the knee is involved in 16%, and the thigh in 42% of all injuries (Fares et al., 2023). These injuries can result in short-term and long-term effects such as chronic knee pain and the development of knee OA (Tran et al., 2016, Heun and Pringle, 2018). Most of the previous studies on this were cross-sectional in nature and presented the prevalence, but not the incidence, of knee pain in professional footballers. There are four main studies on knee pain in professional footballers:

1. *Knee osteoarthritis in professional football is related to severe knee injury and knee surgery.* (Gouttebarga et al., 2018a)

The prevalence of knee OA, knee OA associated factors and consequences of knee OA on physical knee function in current and retired male professional footballers was examined in a cross-sectional study by means of questionnaires in 2500 footballers (70% current; 30% former) in the Netherlands. The footballers were recruited by the World Players' Union aged between 18 and 50 years. A history of severe knee injury and related surgery during a career as a professional footballer was examined through a single question where participants were advised to consult their team doctor or medical records. Physical knee function was examined by the Knee injury and Osteoarthritis Outcome Score Physical Function Short Form. Of the 2500 footballers, 1360 (54%, including 964 current and 396 former) completed the questionnaire. The

study indicated that the prevalence of knee OA was higher in retired footballers (28%) compared to current footballers (13%) with increasing age being a significant risk factor for a higher prevalence of knee OA in both groups ($p<0.01$). Every additional severe knee injury and knee surgery sustained during a professional footballer's career nearly doubled the risk of knee OA in each group. Both current and retired professional footballers with knee OA showed detrimental effects on physical knee function compared to players without knee OA ($p<0.01$).

2. *Osteoarthritis of the hip and knee in former male professional soccer players.*
(Petrillo et al., 2018)

This systematic review aimed to determine whether the prevalence of hip OA and knee OA in male retired professional footballers is higher than in gender and age matched general population controls across five databases. The systematic review found 10 studies which reported a higher prevalence of clinical, radiographic OA and sonographic OA of the knee in retired professional footballers (14.6%, 53.7% and 52%, respectively), compared to the controls (12.9%, 31.9% and 33%, respectively). Likewise, a higher prevalence of both clinical (8.6%) and radiographic hip OA (21.2%) was found in retired professional footballers compared to controls (5.6% and 9.8%, respectively).

3. *Prevalence of knee pain, radiographic osteoarthritis and arthroplasty in retired professional footballers compared with men in the general population: a cross-sectional study.* (Fernandes et al., 2018)

The prevalence of knee pain, radiographic knee OA (RKO), radiographic chondrocalcinosis defined as the presence of cartilage calcification in the hyaline or fibrocartilage of any compartment, and total knee replacement (TKR) were compared in a cross-sectional case-control study between 1207 retired male professional footballers who had played in the English league and 4085 men in the general population, all of whom had completed a postal questionnaire. Radiographs of both knees were obtained in a sample from each group (470 footballers and 491 general population controls). Pain in or around the knees on most days in the previous month was regarded as current knee pain. Presence and severity of RKO were examined on standardised radiographs using the Nottingham Line Drawing Atlas. In the retired professional footballers, all outcomes of knee OA were two to three times higher than in the general population controls after adjusting for BMI and age, and the primary attributable factor was knee injury. The prevalence of current knee pain was higher in footballers than in controls (52.2% versus 26.9%, respectively) with an aRR 1.48 (95% CI 1.38 – 1.63), prevalence of physician-diagnosed knee OA was higher in footballers than in controls (28.3% versus 12.2%, respectively) with an aRR 2.69 (95% CI 2.36 – 3.07), and prevalence of TKR was higher in footballers than in controls (11.1% versus 3.8%, respectively) with an aRR 2.33 (95% CI 1.84 – 2.95). Prevalence of chondrocalcinosis was higher in footballers

than in controls (24.3% versus 8.8%, respectively) with an aRR 2.63 (95% CI 1.84 – 3.75). When compared to the general population, retired footballers had considerably greater RKOA in their right, left and both knees (12.2%, 10.1% and 5.6%) (27.2%, 34.6% and 14.4%), respectively. RKOA was more common in the left knee compared to the right knee of the retired footballers, and most joint space narrowing was in the patellofemoral compartment in footballers compared to the tibiofemoral compartment in controls.

4. *Risk factors for knee osteoarthritis in retired professional footballers: a cross-sectional study.* (Parekh et al., 2021)

This was a nested study within the cross-sectional study by Fernandes et al (2018) undertaken to determine the risk factors related to outcomes of knee OA, specifically knee pain, RKOA and TKR, among the 1207 retired male professional footballers who had responded to the study questionnaire, 470 of whom had also undergone radiographs of both knees. The study identified risk factors that were specific to footballers (e.g., knee injury and training dose). Football-related injury was a significant risk factor for knee pain (aOR 4.22, 95% CI 3.26 – 5.48), RKOA (aOR 2.88, 95% CI 1.81 – 4.59) and TKR (aOR 4.83, 95% CI 2.87 – 8.13). Career training dose (per 1000 hour) was a risk factor for RKOA (aOR 1.07, 95% CI 1.01 – 1.12). The study found also risk factors that were nonspecific (e.g., age, BMI, nodal OA, family history, malalignment, pattern

3 2D:4D finger ratio and gout). Details of each risk factors and associated outcomes are shown in Table 8.

Table 8. Risk factors for knee osteoarthritis related outcomes in male retired professional footballers (Parekh et al. 2021)

	Knee pain	RKOA	TKR
Age		✓	✓
BMI	✓		✓
Pattern 3 digit ratio	✓		
Nodal OA			✓
Familial OA	✓		
Goat	✓	✓	✓
Constitutional malalignment			✓

RKOA – radiographic knee osteoarthritis; TKR – total knee replacement; BMI – body mass index; OA – osteoarthritis

1.3.2 Foot/ankle Osteoarthritis in Professional Footballers

It is known that professional footballers have a high injury rate in the lower limbs (Jones et al., 2019). Ankle injuries account for 13.5% and foot injuries for 11.1% of all injuries (Fares et al., 2023). These injuries could increase the risk of OA at foot and ankle joints (Carmody et al., 2022). There are five main studies on foot and/or ankle OA in professional footballers:

1. *Ankle osteoarthritis and its association with severe ankle injuries, ankle surgeries and health-related quality of life in recently retired professional*

male football and rugby players: a cross-sectional observational study.

(Paget et al. 2020)

The prevalence of ankle OA in retired male footballers compared to retired male rugby players and the association between ankle injury or surgery with ankle OA in male retired footballers were examined in a cross-sectional study by means of questionnaires in a total of 401 male footballers and 152 male rugby players in the Netherlands. Retired footballers were recruited by the Football Players Worldwide, whereas rugby players were recruited by the International Rugby Players. Ankle OA was assessed by the question *“Have you been diagnosed with ankle osteoarthritis by a medical professional?”*. A history of a severe ankle injury or ankle-related surgery during their professional football career was examined through a single question asking for the sequential recording of single or multiple injury events or surgery over time. A severe injury was defined as an injury that involved the ankle, occurred during team activities (training or match), and led to absence from either training or a match for more than 28 days. The study concluded that the self-reported prevalence of ankle OA was 9.2% (95% CI 6.4 – 12.1) in retired footballers and 4.6% (95% CI 1.2 – 8.0) in retired rugby players. The odds of developing ankle OA increased significantly in male retired professional footballers who sustained severe ankle injury (aOR 1.33, 95% CI 1.14 - 1.55; $p < 0.001$) and those who underwent ankle surgery (aOR 2.09, 95% CI 1.4 - 3.08; $p < 0.001$) after adjustment for age and BMI.

2. *Propensity for osteoarthritis and lower limb joint pain in retired professional soccer players. (Drawer and Fuller, 2001)*

This was a UK cross-sectional study that aimed to determine the prevalence of ankle OA in 500 male retired professional footballers using a self-reported questionnaire without a comparison group. Information on ankle OA was obtained if they had been diagnosed with ankle OA by a physician. The response rate was 185 (37%), and the mean age was 47.6 years. Results showed that the prevalence of ankle OA was 6.0% in footballers.

3. *Long term health impact of playing professional football in the United Kingdom. (Turner et al. 2000)*

The prevalence of foot and ankle OA was examined in a cross-sectional study by means of questionnaire in a total of 515 male retired professional footballers with a mean age of 56.1 years, without a comparison group. The response rate was 55% (284 footballers). OA diagnosis was obtained by a question that asked if they had been diagnosed with foot and ankle OA by a physician. Results showed that the prevalence of ankle OA was 19% (7% for the right ankle and 12% for the left ankle) and the prevalence of foot OA was 4.2% (2.1% for both right and left foot).

4. *Lower limb clinical and radiographic osteoarthritis in former elite male athletes. (Iosifidis et al. 2015)*

This study determined the prevalence of clinical and radiographic OA of the lower limbs in retired male athletes in Greece (volleyball, martial arts, soccer, skiers, track and field and basketball players) compared to the general population. However, for the purpose of this section, only data on footballers will be mentioned. Information on OA was obtained using a questionnaire enquiring about pain and physician-diagnosis of ankle OA and clinical assessment that included crepitus, joint range of motion and malalignment. Positive radiographic OA was defined as grade ≥ 2 using the K-L classification. A total of 121 footballers and 181 controls aged 40 and older were included. Results showed that the prevalence of clinical ankle OA was 4.13%, and the prevalence of radiographic ankle OA was 6.61% in retired male footballers, whereas a lower prevalence of clinical ankle OA (2.76%) and radiographic ankle OA (3.68%) was found in controls (p-value is not available between footballers and controls because the study included all types of former elite athletes in one group).

5. *Osteoarthritis of the Ankle and Foot Complex in Former Greek Soccer Players. (Armenis et al. 2011)*

This study examined the prevalence of OA of the ankle-foot complex in 170 male retired professional footballers compared to 132 men in the general population using questionnaires, clinical and radiographic examinations. The

response rate was 88.1% (n=150) in footballers and 86.6% (n=115) in controls. The clinical assessments were considered favourable for diagnosis if two of the following features were present: pain during movement or palpation, range of motion, deformity and crepitus. The radiographic findings included presence of osteophytes, bone sclerosis, subchondral cysts and joint space narrowing. Results showed a higher prevalence of radiographic ankle-foot complex OA in footballers (8.8%) than in the general population controls (3.7%) ($p<0.05$) but a similar prevalence of clinical manifestations of OA in both groups (4.1% versus 3.5%, respectively; $p>0.05$).

1.3.3 Multimorbidity in Professional Footballers

No studies have examined the effect of sport on multimorbidity among professional footballers but some studies have examined the impact of recreational sport on multimorbidity or comorbidity. Previous studies have demonstrated that playing recreational football can help people of all ages improve their health, allowing a range of chronic non-communicable diseases to be better prevented and managed (Krustrup and Krustrup, 2018, Krustrup et al., 2018). Data from a 14 year cohort study of community-dwelling older adults in Hong Kong reported that strenuous sport/recreational activities might reduce depressive symptoms in people with multimorbidity (aRR 0.99, 95% CI 0.98 – 0.99; $p=0.001$) (Liang et al., 2021). In that study, a total of 1,056 people were included, of whom 50.7% had multimorbidity. Multimorbidity was defined as having ≥ 2 long-term conditions from a list of 19 conditions and depressive

symptoms were obtained by the Geriatric Depression Scale (15-item version), which is based on an interviewer-administered questionnaire (scores ranging from 0 to 15), with higher scores indicating increased depressive symptoms (Liang et al., 2021).

Furthermore, performance variables and indicators of cardiovascular health were examined in 11 elderly football players compared to 7 untrained male age-matched controls aged from 65 to 85 years (Randers et al., 2014). Results showed that compared to untrained controls elderly football players had a significantly longer time to exhaustion, lower fat percentage measured by the skinfold method, higher heart rate reserve, and higher number of capillaries per fiber determined from vastus lateralis biopsy ($p < 0.05$) (Randers et al., 2014). Although the study had a very small sample size it supported the beneficial effect of physical activity in older adults.

Most previous studies have focused on OA and psychological conditions in professional footballers, though recently the focus has shifted to neurodegenerative diseases and cognitive impairment and their association with concussion and head trauma (Macnab et al., 2023, Carmody et al., 2022, Wållgren et al., 2024, Woods et al., 2022). Multimorbidity, however, is common in the general population (Chowdhury et al., 2023, Head et al., 2021) and has not been evaluated in male retired professional footballers. The conditions that may affect current and retired professional footballers include the following:

- *Musculoskeletal problems such as OA of the hip, knee and ankle joints.*

These may be linked to serious traumatic injuries and operations throughout their career (Kuijt et al., 2012, Gouttebarga et al., 2015b, Parekh et al., 2021, Carmody et al., 2022).

- *Psychological conditions.* A high level of mental and psychosocial health issues including low self-esteem, adverse nutrition behavior, alcohol abuse, smoking, distress and burnout have been reported in current and retired footballers (Gouttebarga et al., 2015a). These might result from the nature of the sport, the pressure of maintaining a high level of performance during training and competitions and it might also result from early retirement due to injury (McLoughlin et al., 2021, Koch et al., 2021). A recent narrative review revealed that the symptoms of common mental disorders is higher in current female footballers than current male footballers, and similarly more frequently reported in retired footballers compared to current players (Woods et al., 2022). Also it was found that being retired and having sustained an injury were associated with symptoms of common mental disorders in professional footballers (Woods et al., 2022).

- *Neurodegenerative diseases including mild cognitive impairment, dementia and Parkinson's disease.* These could result from football-related concussion and repetitive head micro-trauma from heading the ball (Ramsay et al., 2023, Macnab et al., 2023). It was found that being a retired professional footballer significantly increased the risk of developing medically diagnosed

neurodegenerative disease compared to general population controls (aOR 3.46, 95% CI 1.25 – 9.63; $p=0.02$) after adjustment for age, BMI, education, concussion, and other covariates (Macnab et al., 2023). The same study also reported a higher prevalence of self-reported dementia/Alzheimer's (2.8% versus 0.3; $p<0.001$) and neurodegenerative diseases (2.8% versus 0.9%; $p=0.02$) in male retired footballers than men in the general population (Macnab et al., 2023).

- *Cardiovascular conditions.* As a result of regular athletic training, footballers undergo a complex process of structural functional and electrical remodeling that leads to cardiac chamber enlargement (Prior and La Gerche, 2012). However, the risk for death due to cardiovascular conditions might arise from pre-existing coronary artery abnormalities, undetected congenital heart disease and hypertrophic cardiomyopathy which has led to consideration of early screening in adolescent footballers (Malhotra et al., 2018). Sudden death occurring during football-specific activity or up to one hour afterwards was examined in a prospective study from 2014 to 2018 worldwide (Egger et al., 2022). A total of 617 footballers were included with a mean age of 34 years, of whom 96% were men from 67 countries (Egger et al., 2022). They found that coronary artery disease was the leading cause of death (76%, 50 of 66 cases) in footballers aged >35 years. The most common cause of sudden cardiac death in footballers aged ≤ 35 years varied by region, being cardiomyopathy in South America (42% of deaths), coronary artery anomaly in North America (33% of deaths), and sudden unexplained death in Europe

(26% of deaths) (Egger et al., 2022). Conversely, male retired professional footballers may be physically much fitter and less obese than population controls, so may be at less risk of some comorbidities such as diabetes, heart attack and hypertension (Fernandes et al., 2019).

1.4 Justification of the Research

Although football is regarded as a healthy activity due to its positive impact on physical and mental health (Krustrup and Krustrup, 2018), there might be some conditions that are causally associated with playing professional football such as OA and neurodegenerative diseases (Carmody et al., 2022). The incidence of knee pain and multimorbidity are associated with mid-older age, and have been reported in adults in the general population (Ingham et al., 2011a, Shang et al., 2020). However, whether the benefits of being fitter and less obese in early life influence the development of multimorbidity in retired professional footballers remains unknown. An association between foot and/or ankle symptoms has been reported in people with radiographic knee OA in the general population (Perry et al., 2021, Paterson et al., 2017b). However, the association between radiographic OA at the knee and foot/ankle joints has not been examined in footballers. OA is predominantly injury-related in footballers and such OA may not be associated with development of OA at other joint sites as in the general population in whom OA risk factors are predominantly constitutional, genetics and obesity. It is not clear whether radiographic knee OA is associated with foot and/or ankle OA (using the K-L system or summated scoring for osteophytes

and joint space narrowing), and whether the association is different between people at higher risk of joint injury versus the general population.

The association of footballers with possible short- and long-term health consequences, including knee pain, multimorbidity and foot/ankle OA after retirement, is an important concern due to its impact on their health, well-being and quality of life. Accordingly, injury prevention and management in footballers is often debated. However, to develop preventive strategies, update policies of treatment and management, and reduce the burden of such long-term conditions, a better understanding of conditions related to footballers is required, since the incidence of knee pain and multimorbidity, and association between radiographic OA at the knee and foot/ankle remain substantially unknown. A group of patient-public involvement (PPI) were involved to provide their views on the importance of research questions.

1.5 Aim

To examine the incidence of knee pain and multimorbidity and their associated risk factors in male retired professional footballers (referred to as footballers) compared to men in the general population (referred to as controls) in the UK.

1.6 Objectives

1. To systematically review published observational studies of the prevalence and incidence of multimorbidity and long-term conditions in professional footballers, either alone or compared to general population controls.
2. To examine the incidence of knee pain and its related risk factors in footballers and controls.
3. To examine the association between knee pain and multimorbidity within footballers and controls.
4. To examine incidence of multimorbidity and its related risk factors in footballers compared to controls.
5. To examine the association between radiographic knee and foot/ankle OA in footballers and controls.

1.7 Structure of the thesis

Chapter 2 is the systematic review and meta-analysis presented as an independent chapter including methods, results and discussion (objective 1).

Chapter 3 describes the overall method for the cohort study to examine the incidence of knee pain and multimorbidity in footballers compared to controls (objectives 2-4).

Chapter 4 presents the results and discussion of the incidence of knee pain and its related risk factors in footballers compared to controls and the association between baseline knee pain and incident multimorbidity (Objectives 2 and 3).

Chapter 5 presents the results and discussion of the incidence of multimorbidity and its related risk factors in footballers and controls (Objective 4).

Chapter 6 is an independent chapter, including method, results and discussion, of the association between radiographic knee OA and foot/ankle OA in footballers and controls (Objective 5).

Chapter 7 describes my work with the PPI group who were involved in the studies involving the footballers and general populations controls.

Chapter 8 presents the overall discussion and conclusion of the thesis work.

Chapter 2 Multimorbidity and long-term conditions and related risk factors in professional footballers compared to the general population: a systematic review and meta-analysis of observational studies

2.1 Introduction

This chapter presents the methods, results and discussion of the first objective of the thesis, specifically “to systematically review the literature on multimorbidity and long-term conditions and related risk factors in professional footballers”. The aim was to have a better understanding of the long-term conditions and multimorbidity that associate with professional footballers during and after their career and to identify the gaps in the research.

2.2 Materials and methods

This systemic review protocol was registered with PROSPERO (CRD42021256440) (Moher et al., 2010). The aim of this study was to systematically review published observational studies of multimorbidity and long-term conditions in professional footballers examined either alone or in comparison to the general population.

2.2.1 Study selection

All types of observational, cross-sectional, case-control and cohort studies in professional footballers were included in the study. The following eligibility criteria were used to select studies:

Participants: studies including footballers aged ≥ 18 years old alone (cases-only) and/or footballers versus general population controls (comparative) were included in the study. There were no limitations regarding the status of footballers with regards to gender, the country in which they played, and whether they were active or retired.

Exposure: being professional footballers was the exposure.

Comparator: studies including general population controls aged ≥ 18 years old who were not exposed to professional football.

Outcomes: prevalence, incidence, risk factors, RR, HR, or OR of multimorbidity and long-term conditions. Long-term conditions were defined as any chronic physical or mental medical condition.

There was no language limitation in the search or restrictions in publication date. Moreover, there were no restrictions as to whether studies used self-reported, radiographic, physician-diagnosis or other diagnostic tool for the outcome assessment. Studies were excluded if they were a narrative review article, book chapter or conference abstract.

2.2.2 Data sources and searches

Relevant studies were identified through a systematic literature search from inception of each database to December 2021 in MEDLINE (1946-), Embase (1974-) and SPORTDiscus (2004-) (the latter is for sports and sports medicine related research databases). Additionally, “comorbidities and professional footballers” was searched in Google Scholar search engine (2004-), and the first 1,000 articles were screened for eligibility independently by one reviewer (MS).

According to the database being examined, the search strategy was built upon three search domains and their synonyms, specifically chronic condition, study design and population. The search terms in each domain were combined using the Boolean operator “OR”. Three domains of searches were combined using the Boolean operator ‘AND’. Reference lists of relevant studies were read for potentially relevant studies. Details of the electronic search strategy of the MEDLINE electronic database are given in Table 9. A similar search strategy with slight modification was applied to fit with the structure and terminology of other databases.

Table 9. Search strategy in MEDLINE database

1.	((Chronic or long term) and (illness or disease or condition)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2.	Comorbidit*.mp.
3.	Multimorbidit*.mp
4.	1 or 2 or 3
5.	Cohort stud*.mp.
6.	cross sectional stud*.mp.
7.	case control stud*.mp.
8.	(Retrospective stud* or prospective stud*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9.	Epidemiology.mp. or Epidemiology/
10.	5 or 6 or 7 or 8 or 9
11.	(Professional or Elite).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12.	(Football or soccer players).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13.	footballers.mp.
14.	11 or 12 or 13
15.	4 and 10 and 14

The search strategy was piloted initially and amended by the team. A systematic search in the three databases was conducted independently by one reviewer (MS). Based on the stated inclusion/exclusion criteria, all studies identified by

the title and abstract were gathered and imported into EndnoteX9. Duplicated studies were removed. All the titles and abstracts were reviewed by two reviewers independently (MS and NA) based on the eligibility criteria. Full-text articles were obtained to confirm suitability for inclusion, and those meeting the eligibility criteria were retained for data extraction and quality assessment.

2.2.3 Data extraction and management

A customised data extraction form was used to extract data from all included studies. The data were managed using the Covidence program (Babineau, 2014) which aims to improve the efficiency of the evidence synthesis process. An overall study characteristics table was constructed to show the total number of included studies, total number of participants, comparator (footballers only or versus controls), age range, study design, country or region of the study, and the conditions investigated. Furthermore, detailed information for each study was extracted, including:

- Author names, study design, year of publication
- Participant mean/median age and BMI
- Criteria for identifying conditions/diseases
- Results, including prevalence, incidence, OR and standard error (SE) or CI

2.2.4 Quality assessment

The Newcastle-Ottawa Scale (NOS) checklist for observational studies was used by two reviewers (MS and NA) to independently assess the study quality (Wells et al., 2000). The NOS tool includes a scoring scale divided into three sections, specifically, the selection of study groups, the comparability of study groups, and the assessment of exposure or outcome. The quality score is based on a star system from 0-10 stars for cross-sectional studies:

1. Selection

- Representativeness of the sample (maximum one star)
- Sample size (maximum one star)
- Non-respondents (maximum one star)
- Ascertainment of the exposure (risk factor) (maximum two stars)

2. Comparability (maximum two stars)

3. Outcome

- Assessment of outcome (maximum two stars)
- Statistical test (maximum one star)

For case-control studies, from 0-9 stars are awarded for each item as follows:

1- Selection

- Is the case definition adequate (maximum one star)
- Representative of the cases (maximum one star)
- Selection of controls (maximum one star)
- Definition of controls (maximum one star)

2- Comparability (maximum two stars)

3- Exposure

- Ascertainment of exposure (maximum one star)
- Same method of ascertainment for cases and controls (maximum one star)
- Non-response rate (maximum one star)

For cohort studies, from 0-9 stars are awarded as follows:

1- Selection

- Representativeness of the exposed cohort (maximum one star)
- Selection of the non-exposed cohort (maximum one star)
- Ascertainment of exposure (maximum one star)
- Demonstration that the outcome of interest was not present at the start of the study (maximum one star)

2- Comparability (maximum two stars)

3- Outcome

- Assessment of outcome (maximum one star)
- Was follow-up long enough for outcomes to occur (maximum one star)
- Adequacy of follow-up of cohorts (maximum one star)

The NOS scores were divided into three categories, specifically: high risk of bias (low quality) (0 to 3 NOS points); medium risk of bias (medium quality) (4 to 6 NOS points); and low risk of bias (high quality) (7 to 10 NOS points).

2.2.5 Validation

Study selection and data extraction were validated by a second reviewer (NA) in a random sample of 10% of the included studies using the Rayyan platform (Couban, 2016). Any disagreement between reviewers (MS and NA) in the study selection and data extraction were recorded and resolved by discussion with a third reviewer (WZ). The acceptable level of agreement was considered to be above 80% between the two reviewers (MS and NA) (Belur et al., 2021, Furlan et al., 2011). If there was less than 80% agreement, the reason for the disagreements would be further investigated and an additional 10% of full-text articles would be screened as appropriate. For quality assessment, all the included studies were assessed independently by two reviewers (MS and NA). Again, the acceptable level of agreement was considered to be at least 80% between the reviewers (Belur et al., 2021) and if there was less than 80% agreement, the reason for the disagreements would be further investigated with a third reviewer (WZ).

2.2.6 Data synthesis and analysis

Descriptive characteristics of the studies were expressed as medians/means and/or frequencies, as appropriate, depending on the distribution of variables.

Incidence/prevalence and SE were extracted or calculated for each study. For studies that reported both right and left sided prevalence in any joint, the higher prevalence was chosen. RR, OR, or HR and 95% CI were extracted or calculated to present the association between risk factors and multimorbidity or long-term conditions. A value of $p < 0.05$ was considered statistically significant. The framework of presenting the results of each long-term condition would commence with total number of studies related to each long-term condition, followed by meta-analysis or narration as appropriate.

For the pooled prevalence, the 'inverse variance weighted' method was used to pool the data (Barendregt et al., 2013). The SE of the prevalence was calculated as follows:

$$SE = \sqrt{p(1 - p)/n}$$

where n is the total population for the prevalence and p is the proportion of a specific long-term condition.

Heterogeneity estimates between studies were quantified by the I^2 (%) and Q test (p -value) (Higgins, 2008). An I^2 value ranging from 25% to 49% was considered low heterogeneity, an I^2 value of 50% to 74% was deemed moderate heterogeneity (Higgins et al., 2003), and an I^2 value exceeding 75% was regarded as considerable heterogeneity (Higgins et al., 2023). Results were pooled using the random-effects model if the heterogeneity was statistically

significant, otherwise a fixed effect model was used (Higgins, 2008, Borenstein et al., 2010).

Publication bias was assessed using funnel plots and Egger's test if there were at least 10 included studies, whereas the Harbord or Begg's test was used if there were less than 10 studies (Van Enst et al., 2014). All statistical analyses were performed using R Statistical Software.

2.3 Results

2.3.1 Search results and study quality

The initial electronic databases search identified 11,295 articles from the 3 databases. Of these, 8,258 studies remained after removal of duplicates.

Following review of the title and abstract of these studies, 47 studies were retrieved for full-text article screening. Justifications for excluding the other studies are summarised in Figure 19. After reading the full text, 31 articles were eligible for inclusion. An additional 21 studies were added after searching the reference list of the included studies, and 4 studies were added from a scoping review on the topic of health conditions in retired footballers (Carmody et al., 2022). Overall, 56 studies were finally included in the analysis.

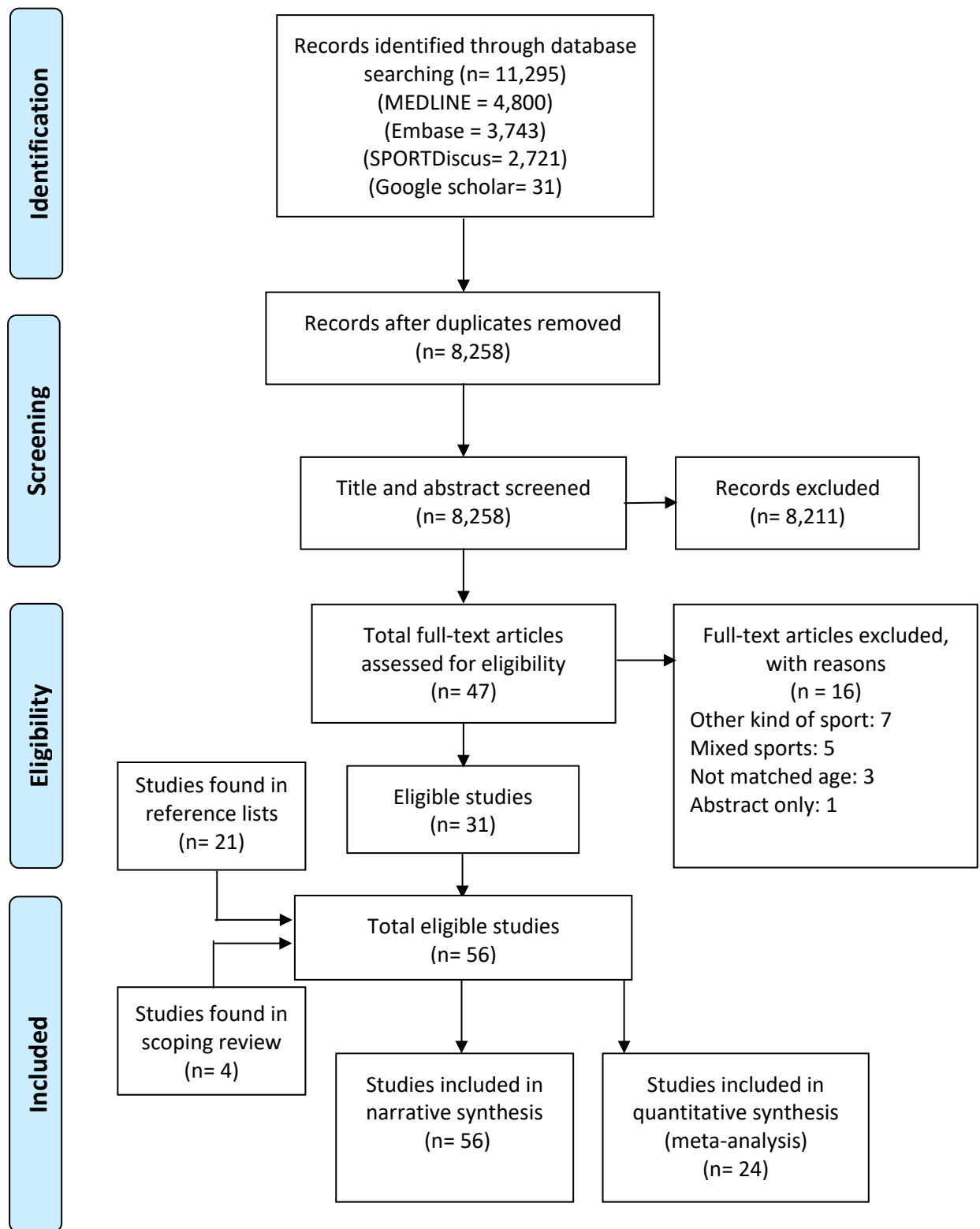


Figure 19. PRISMA Flow Diagram

2.3.2 Study characteristics

Of the 56 eligible studies included, there were 42 cross-sectional studies, 4 case-control studies, 8 cohort studies, and 2 mixed design studies (cross-sectional and case-control), none were for multimorbidity but all were for a single long-term condition. These studies were published between 1980 and December 2021. Ages ranged from 18 to 93 years for footballers and controls. The study populations included either footballers only or footballers versus controls. Characteristics of the included studies are summarised in Table 10.

The vast majority of studies were of male retired footballers and only five focused on female retired footballers. However, eleven studies examined current male professional footballers, three examined current female footballers and five examined retired female footballers. Most of the studies reported prevalence, four studies reported incidence, four studies reported HRs, five studies reported ORs, and two reported RR.

Cross-sectional studies were used to extract data for prevalence of long-term conditions. Case-control studies were used to extract data for risk factors of long-term conditions. OA was reported by the majority of the studies. The sample size ranged from 27 to 1207 footballers, and from 20 to 4,085 controls.

For the cohort studies, seven studies focused on male retired footballers aged 40 years and older, providing data from 30 to 23,586 male retired footballers

and from 28 to 23,028 general population controls. In addition, there was one study that provided data on 84 current and retired female footballers aged from 26 to 40 years.

Table 10. Characteristics of the included studies

Number of studies	56
Number of participants	79,337
Men (%)	77,896 (98.2%)
Women (%)	1,441 (1.8%)
Age range (years)	
Professional footballers	18 – 93
Controls	18 - 88
Comparison	
Footballers versus control	24
Footballers only	32
Type of studies	
Cross-sectional	42
Case control	4
Cohort	8
Mixed (cross-sectional and case-control)	2
Study location	
Europe	44
South America	5
Asia	5
Africa	2
Conditions investigated	
Musculoskeletal: Osteoarthritis	28
Gout	3
Chondrocalcinosis	1
Knee or hip pain	5
Back pain	3
Neurological diseases	8
Cardiovascular diseases	5
Psychological conditions	5
Endocrine diseases	3
Respiratory diseases	3
Vision	2
Mental health disorders	1
Dermatological diseases	1
Cancer	1
Oral	1
Multimorbidity	0

Validation

There were no disagreements in study selection and data extraction. However, in quality assessment there were twelve disagreements that were resolved by consensus between the two reviewers, and in two others the third reviewer WZ was involved to reach consensus.

2.3.3 Quality assessments

The quality of cross-sectional studies varied with 25 studies having scores that varied from 4 to 6, which is deemed medium risk of bias (medium quality), and 19 studies had scores that varied from 7 to 9 which represents low risk of bias (high quality). A summary of the risk of bias checklists with their domains are shown in Table 11.

The quality of the case-control studies varied with two studies having a score of 6, which is deemed a medium risk of bias (medium quality), and the remaining four studies having a score of 7-9, which represents low risk of bias (high quality) (Table 12).

The quality of cohort studies was as follows: two studies had a score of 4-6, which is deemed a medium risk of bias (medium quality); and six studies had a score of 8, which represents low risk of bias (high quality) (Table 13).

Table 11. Quality of cross-sectional studies by Newcastle-Ottawa Scale

Study	Selection				Comparability: (Maximum 2 stars)	Outcome: (Maximum 3 stars)		
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor):	The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.	Assessment of the outcome:	Statistical test:	Total NOS score
Chantraine (1985)	*	—	—	**	—	**	*	6
Sortland and Tysvaer (1989)	*	—	—	**	—	**	*	6
Lindberg et al. (1993)	*	—	—	**	—	**	*	6
Roos et al. (1994)	*	—	—	**	—	**	*	6
Kujala et al. (1995)	*	—	*	**	**	**	*	9
Kujala et al. (1996)	*	—	*	**	—	*	*	6
Turner et al. (2000)	*	—	*	**	—	*	*	6
Drawer and Fuller (2001)	*	—	—	**	—	*	*	5
Matser et al. (2001)	*	—	—	*	**	**	*	7
Shepard et al. (2003)	*	—	*	**	—	**	*	7
Von Porat et al. (2004)	*	—	—	**	—	**	*	6

Purim et al. (2005)	*	—	—	**	—	**	*	6
Elleuch et al. (2008)	*	—	—	**	—	**	*	6
Ozturk et al. (2008)	*	—	*	**	—	**	*	7
Krajnc et al. (2010)	*	—	—	**	—	**	*	6
Armenis et al. (2011)	*	—	*	**	—	**	*	7
Wilson et al. (2012)	*	—	—	**	*	**	*	7
Jones et al. (2014)	*	—	—	**	—	*	*	5
Arliani et al. (2014a)	*	*	*	**	—	**	*	8
Arlaini et al. (2014b)	*	—	—	**	—	**	*	6
Branci et al. (2015)	*	—	—	**	—	**	*	6
Tunas et al. (2015)	*	—	*	**	*	*	*	7
Needleman et al. (2015)	*	—	*	**	—	**	*	7
Pereira et al. (2015)	*	—	—	**	—	**	*	6
Junge and Feddermann- Demont (2016)	*	—	—	**	—	*	*	6
Prinz et al. (2016)	*	—	*	**	—	*	*	6
Paxinos et al. (2016)	*	—	—	**	—	**	*	6
Wegmann et al. (2016)	*	—	—	**	—	**	*	6
Prien et al. (2017)	*	—	*	*	—	*	*	5

Sanders and Stevinson (2017)	*	—	—	**	—	*	*	5
Fernandes et al. (2018)	*	*	—	**	**	**	*	9
Gouttebarga et al. (2018b)	*	*	*	**	—	*	*	7
Gouttebarga et al. (2018a)	*	*	*	**	*	*	*	8
Lv et al. (2018)	*	—	—	**	**	**	*	8
Fernandes et al. (2019)	*	*	—	**	**	*	*	8
Ka et al. (2019)	*	—	—	**	—	**	*	6
Toledo et al. (2019)	*	—	—	**	—	**	*	6
Akkurt et al. (2020)	—	—	—	*	—	**	*	4
Emran et al. (2020)	*	—	—	**	—	**	*	6
Fernandes et al. (2020)	*	—	*	*	**	**	*	8
Prien et al. (2020a)	*	—	—	**	**	**	*	8
Paget et al. (2020)	*	*	*	**	**	*	*	9
Parekh et al. (2021)	*	*	—	**	*	**	*	8
van den Noort et al. (2021)	*	*	*	**	—	*	*	7

Bold indicates low risk of bias (high quality) (7 to 10 NOS points); NOS - Newcastle-Ottawa Scale

Table 12. Quality of case-control studies by Newcastle-Ottawa Scale

Selection			Comparability			Exposure			Total NOS score
Study	case definition adequate ?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Klunder et al. (1980)	*	*	—	*	—	*	*	*	6
Sortland et al. (1982)	*	*	*	*	—	*	*	-	6
Iosifidis et al. (2015)	*	*	*	*	**	*	*	-	8
Fernandes et al. (2019)	*	*	*	*	**	-	*	—	7
Prien et al. (2020b)	*	*	*	*	**	*	*	-	9
Parekh et al. (2021)	*	*	*	*	**	-	*	-	7

Bold indicates low risk of bias (high quality) (7 to 10 NOS points); NOS - Newcastle-Ottawa Scale

Table 13. Quality of cohort studies by Newcastle-Ottawa Scale

Study	Selection				Comparability		Outcome		Total NOS score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Lundin et al. (2000)	*	*	—	*	—	*	*	*	6
Lohmander et al. (2004)	*	—	*	*	**	*	*	*	8
Chio et al. (2005)	*	*	*	*	—	*	*	*	7
Tveit et al. (2012)	*	*	*	*	*	*	—	*	4
Mackay et al. (2019)	*	*	*	*	*	*	*	*	8
Pupillo et al. (2020)	*	*	*	*	—	*	*	*	7
Russell et al. (2020)	*	*	*	*	*	*	*	*	8
Russell et al. (2021)	*	*	*	*	**	*	*	*	9

Bold indicates low risk of bias (high quality) (7 to 10 NOS points); NOS - Newcastle-Ottawa Scale

2.3.4 Prevalence, incidence and associated risk factors of multimorbidity and long-term conditions

None of the retrieved studies examined multimorbidity in footballers only or compared to controls. Most of the studies focused on prevalence of single long-term conditions, some studies reported on more than one long-term condition but did not report on multimorbidity and a limited number of studies examined incidence of long-term conditions.

2.3.4.1 Osteoarthritis

Twenty-eight studies reported on OA in various joints in current and retired footballers. The method used to diagnosis OA varied across studies and included self-reporting by participants, clinical assessment, imaging (radiographs, ultrasonography and MRI), physician-diagnosis of OA, or a combination of such methods.

Knee osteoarthritis

Fourteen studies (n= 3,405) reported knee OA in male retired footballers. Of these studies, only seven compared male retired footballers to general population controls, and only one study also reported the prevalence of knee OA among male current footballers with a mean age of 26 years, which was 13%, without comparison to controls (Gouttebarga et al., 2018a). Two additional studies (n=201) reported knee OA in female retired footballers determined by different diagnostic assessments (Prien et al., 2017, Prien et al., 2020a).

The pooled prevalence of knee OA was 31% in male retired footballers (95% CI 20 – 42%) and 26% in male controls (95% CI 7 – 44%) (Figure 20 and 22). High heterogeneity was observed across the included studies for male retired footballers ($I^2=96\%$, $p<0.01$) (Figure 20). The funnel plot was asymmetric in male retired footballers (Figure 21), and the result of the Egger test ($t=1.95$, $p=0.074$) indicating no publication bias. High heterogeneity was found in male controls ($I^2=98\%$, $p<0.01$) (Figure 22), the Begg test ($z=-0.19$, $p=0.851$) indicating no publication bias. However, in female retired footballers the prevalence of knee OA ranged from 14% to 69.4% (Prien et al., 2017, Prien et al., 2020a).

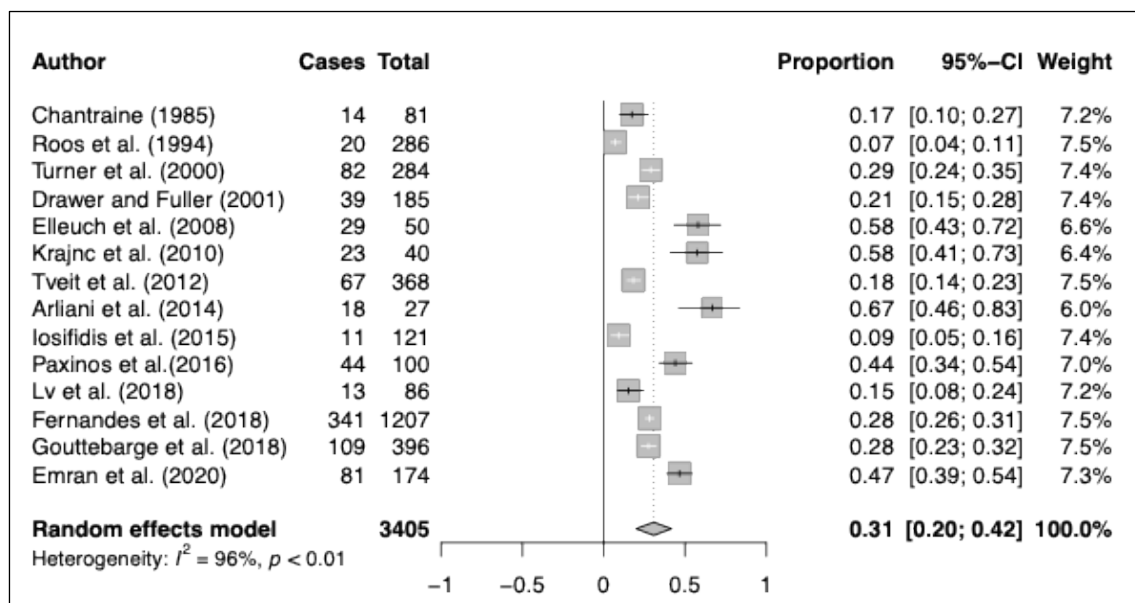


Figure 20. Forest plot showing pooled prevalence of knee osteoarthritis in male retired footballers, random effects model. CI – confidence interval

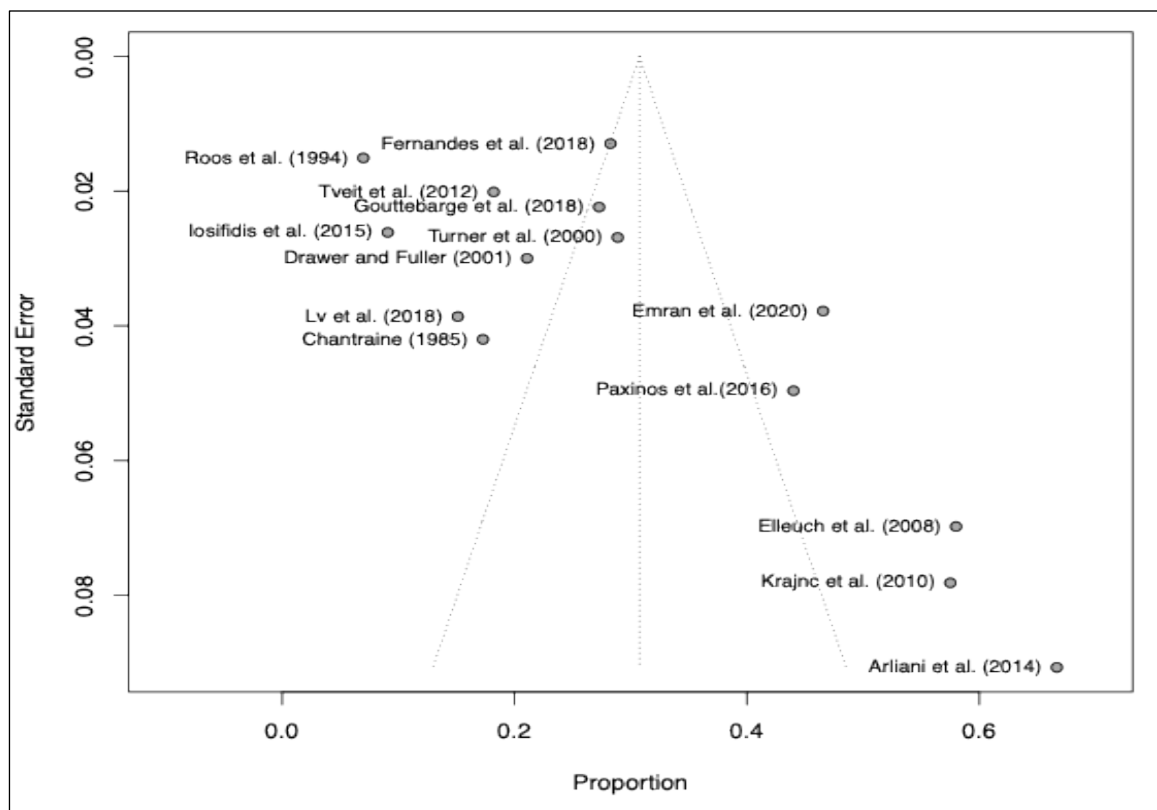


Figure 21. Asymmetrical Funnel plot showing pooled prevalence of knee OA in male retired footballers in studies

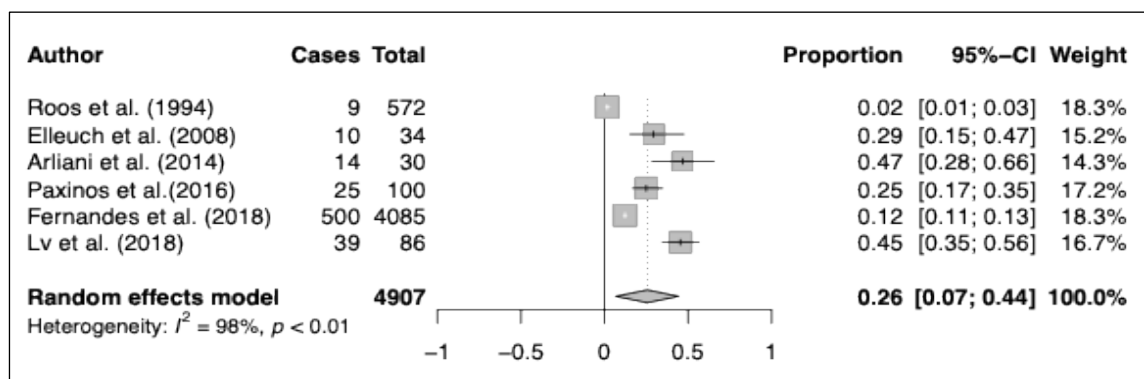


Figure 22. Forest plot showing pooled prevalence of knee osteoarthritis in male controls, random effects model. CI – confidence interval

Five additional studies reported the prevalence of tibiofemoral and patellofemoral knee OA, knee chondrocalcinosis and the prevalence of knee OA after injury. The prevalence of unilateral radiographic tibiofemoral knee OA was 7% in male retired footballers and 1.75% in controls, whereas the prevalence of bilateral radiographic tibiofemoral knee OA was 1.7% in male retired footballers and 7% in controls. Similarly, the prevalence of unilateral radiographic patellofemoral OA was 3.5% in male retired footballers and 0% in controls, whereas the prevalence of bilateral radiographic patellofemoral OA was 7% in male retired footballers and 8.7% in controls (Klunder et al., 1980). Another study reported the prevalence of 26% for tibiofemoral OA and 16% for patellofemoral joint OA in male retired footballers (Kujala et al., 1995). Male retired footballers were more likely to have radiographic knee chondrocalcinosis compared to controls (24.3% versus 8.8%, respectively) with an aRR 2.63 (95% CI 1.84 - 3.75) after adjustment for age, BMI, injury and football status (Fernandes et al., 2018). Von Porat et al. (2004) examined the knees of male retired footballers 14 years after an ACL tear, and found that 41% had radiographic knee OA, defined as K-L grade ≥ 2 , in the injured knee, whereas only 4% had radiographic OA in the contralateral knee (Von Porat et al., 2004). Lohmander et al. (2004) reported that the prevalence of symptomatic radiographic knee OA using K-L grade ≥ 2 was 75% in female retired footballers assessed 12 years after ACL injury. Moreover, the prevalence of symptomatic radiographic knee OA was 46% in female retired footballers who had undergone

ACL reconstruction surgery compared to 35% in those who had not undergone surgery assessed 12 years after ACL injury (Lohmander et al., 2004).

Risk factors of knee osteoarthritis

Three studies examined risk factors for knee OA in male current and retired footballers (Gouttebarga et al., 2018a, Lv et al., 2018, Parekh et al., 2021)

Only one study examined risk factors for self-reported (physician-diagnosed) knee OA among male current and retired footballers (Gouttebarga et al., 2018a).

A history of severe knee injury and related surgery during a career as a professional footballer was examined through a single question where participants were advised to consult their team doctor or medical records.

Severe knee injury was defined as injury to the knee that occurred during team activities either during training or a match that resulted in more than 28 days absence from training or matches. Each additional severe knee injury increased the risk of knee OA by 74% (aRR 1.74, 95% CI 1.50 - 2.01) in male current footballers and by 87% (aRR 1.87, 95% CI 1.61 – 2.13) in male retired footballers after adjustment for age and BMI. Each additional surgical operation increased the risk nearly two-fold in both current and retired footballers (aRR 1.96, 95% CI 1.66 – 2.29) (aRR 1.72, 95% CI 1.50 – 1.95), respectively.

Two additional studies reported risk factors for radiographic knee OA (K-L grade ≥ 2) in male retired footballers (Lv et al., 2018, Parekh et al., 2021). Parekh et al. (2021) found that increasing age (aOR 1.08, 95% CI 1.05 – 1.10), ≥ 5 significant knee injuries (aOR 4.78, 95% CI 2.42 - 9.46), gout (aOR 2.71, 95% CI 1.13 -

6.49) and every 1000 hours of career training dose for footballers (aOR 1.07, 95% CI 1.01 - 1.12) were associated with radiographic knee OA (K-L grade ≥ 2) in male retired footballers after adjustment for age and BMI. They defined career training dose as the number of hours per week spent training multiplied by the number of weeks per season (average of 40 weeks) multiplied by the professional career duration (Parekh et al., 2021). Lv et al. (2018) found that osteoporosis, defined as body mass density being ≤ -2.5 , (aOR 8.17, 95% CI 1.90 - 35.07) was associated with radiographic knee OA after adjustment for age and occupation.

Knee pain

Two studies reported the prevalence of knee pain in male retired footballers only (Kujala et al., 1995, Arliani et al., 2014). Two reported the prevalence of knee pain in male retired footballers compared to controls (Fernandes et al., 2018, Elleuch et al., 2008). The pooled prevalence of knee pain was 53% in male retired footballers (95% CI 0 – 100%) and 27% in male controls (95% CI 26 – 28%) (Figure 23 and 24). High heterogeneity was observed across the included studies for male retired footballers ($I^2=99\%$, $p<0.01$) (Figure 23), and the result of the Begg test ($z=0.68$, $p=0.496$) indicating no publication bias. Low heterogeneity was found in male controls ($I^2=9\%$, $p=0.29$) (Figure 24).

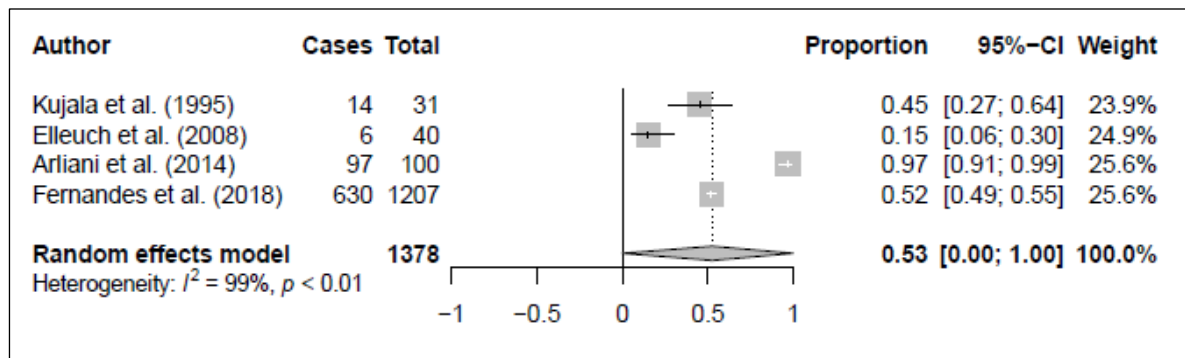


Figure 23. Forest plot showing pooled prevalence of knee pain in male retired footballers, random effects model. CI – confidence interval

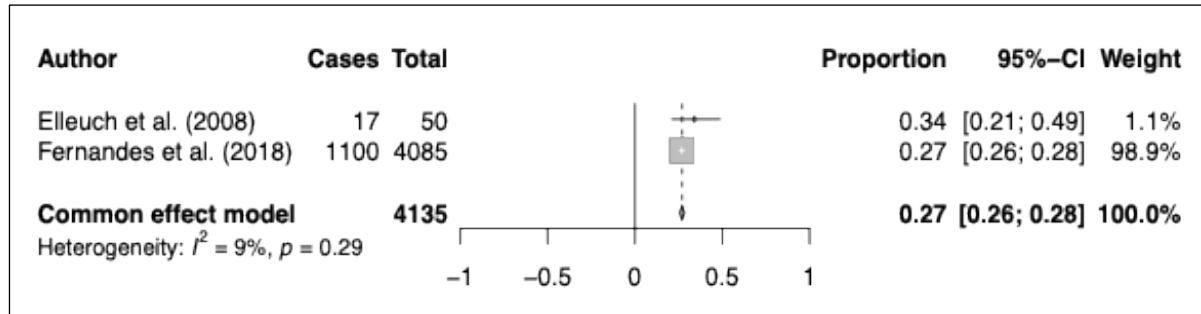


Figure 24. Forest plot showing pooled prevalence of knee pain in male controls, fixed effects model. CI – confidence interval

Risk factors for knee pain

Two studies examined risk factors for knee pain in male retired footballers (Parekh et al., 2021, Fernandes et al., 2020). Parekh et al. (2021) reported risk factors for knee pain based on a sample of 1207 male retired footballers and found that after adjustment for age and BMI knee pain was associated with age (aOR 0.99, 95% CI 0.98 – 1.00), obesity (aOR 2.28, 95% CI 1.55 – 3.33), familial OA (aOR 1.51, 95% CI 1.17 – 1.94), type 3 finger ratio (aOR 1.34, 95% CI 1.05 – 1.72), gout (aOR 2.16, 95% CI 1.46 – 3.20) and ≥ 5 significant knee

injuries (aOR 12.97, 95% CI 7.92 - 21.26). Significant knee injury was defined as *“one which caused you pain for most days of at least a 3-month period and resulted in an absence from all training and matches during this time”*.

Furthermore, receiving a knee intra-articular injection during their professional career in male retired footballers was significantly associated with knee pain (aOR 1.81, 95% CI 1.40 - 2.34) and TKR (aOR 2.21, 95% CI 1.43 - 3.42) compared to those without knee injections (adjusted for age, BMI and knee injury) (Fernandes et al., 2020). However, it was not associated with radiographic knee OA (aOR 1.30, 95% CI 0.85 – 2.01). These data were obtained using postal questionnaire (n=1207) and subsequent knee radiographs in a sample of questionnaire responders, irrespective of knee pain status (n=470).

Foot and ankle osteoarthritis

Six studies reported the prevalence of either foot and/or ankle OA among retired footballers, one in female retired footballers and five in male retired footballers (Iosifidis et al., 2015, Paget et al., 2020, Drawer and Fuller, 2001, Turner et al., 2000, Prien et al., 2017, Armenis et al., 2011). Of these, one study reported the prevalence of ankle OA to be 7.2% in female retired footballers (n=152) (Prién et al., 2017). One study reported a prevalence of 2.11% of foot OA in male retired footballers with no comparison to controls (Turner et al., 2000). Another study reported the prevalence of clinical ankle-foot complex OA was similar

(4.1%) among male retired footballers compared to controls (3.56%) ($p>0.05$) (Armenis et al., 2011). However, the prevalence of radiographic ankle-foot complex OA was higher in male retired footballers compared to controls (8.8% versus 3.7%, respectively; $p<0.05$) (Armenis et al., 2011).

The pooled prevalence of self-reported ankle OA in male retired footballers was 9% (95% CI 7 - 10%) (Figure 25). Low heterogeneity was observed across the included studies ($I^2=38\%$, $p=0.18$) (Figure 25), the Begg test ($z=0.00$, $p=1.00$) indicating no publication bias.

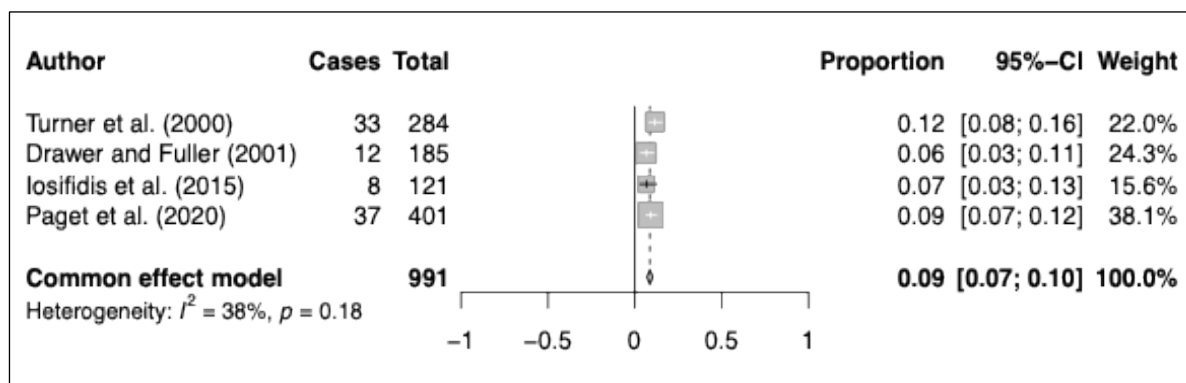


Figure 25. Forest plot showing the pooled prevalence of ankle osteoarthritis in male retired footballers, fixed effects model. CI – confidence interval

Risk factors for ankle osteoarthritis

This was examined in one study (Paget et al., 2020). Male retired footballers who sustained severe ankle injury and those who underwent ankle surgery had significantly increased odds of developing ankle OA (aOR 1.33, 95% CI 1.14 -

1.55) (aOR 2.09, 95% CI 1.41 - 3.08), respectively after adjustment for age and BMI. This was determined by questionnaire among 401 male retired footballers.

Hip osteoarthritis

Eight studies determined the prevalence of hip OA in male retired footballers (Iosifidis et al., 2015, Van den Noort et al., 2021, Turner et al., 2000, Drawer and Fuller, 2001, Tveit et al., 2012, Lindberg et al., 1993, Shepard et al., 2003, Klünder et al., 1980). Of these, only two studies compared prevalence of hip OA in male retired footballers to controls (Shepard et al., 2003, Lindberg et al., 1993), and one study also examined self-reported (physician-diagnosed) hip OA in male current footballers, and found it to occur in 2% (Van den Noort et al., 2021).

The pooled prevalence of hip OA was 7% (95% CI 4 - 11%) in male retired footballers and 2% (95% CI 1 - 4%) in controls (Figures 26 and 27). High heterogeneity was observed across the included studies of male retired footballers ($I^2=83\%$, $p<0.01$) (Figure 26), the Begg test ($z=1.05$, $p=0.293$) indicating no publication bias.

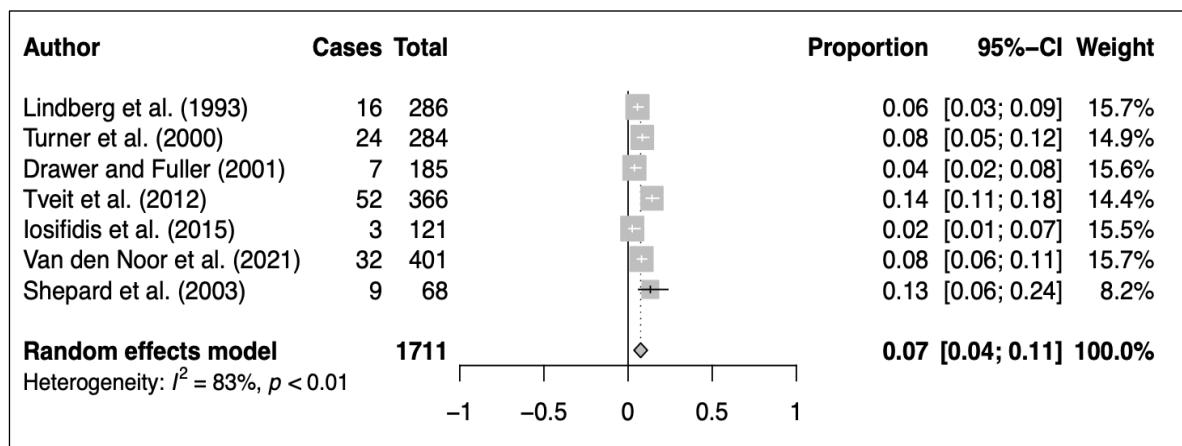


Figure 26. Forest plot showing the pooled prevalence of hip osteoarthritis in male retired footballers, random effects model. CI – confidence interval

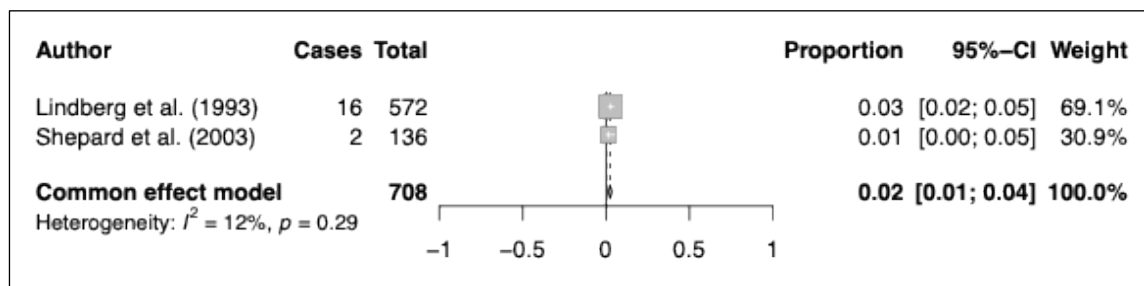


Figure 27. Forest plot showing the pooled prevalence of hip osteoarthritis in controls, fixed effects model. CI – confidence interval

One further study in male retired footballers determined hip OA based on it being unilateral or bilateral. In that study, the prevalence of unilateral hip OA was higher (16%) in male retired footballers than controls (5.3%) and that of bilateral hip OA was 33.3% in male retired footballers compared to 21% in controls ($p < 0.05$), defined using radiographic signs of OA (i.e., reduction in joint space with sclerosis and/or subchondral cyst formation), as described by Danielsson et al. (1964) (Klunder et al., 1980).

Other site of osteoarthritis

One study also reported the prevalence of self-reported OA in other joint sites among male retired footballers, and found that 9% reported lumbar OA, 8% neck OA and 5.3% OA at other sites including the elbow, wrist, hand and shoulder with no comparison to controls (Turner et al., 2000). Self-reported lower extremity OA occurred in 33% of male retired footballers, with knee OA accounting for most (75%) of the cases with no comparison to controls (Gouttebarga et al., 2018b).

One study investigated the prevalence of radiographic degenerative cervical spine changes in male retired footballers. They found that the prevalence of slight or moderate scoliosis in retired footballers was 32.6% and in controls was 37.2% (p-value is not available), but a similar prevalence of moderate anterolisthesis (vertebral slipping) at one level in both groups (4.7% versus 4.7%, respectively). Nine (21%) male retired footballers reported having a long history of neck complaints, including stiffness and pain (Sortland et al., 1982).

Figure 28 presents summary data for the prevalence of OA at different sites in retired professional footballers only or/and in comparison to controls.

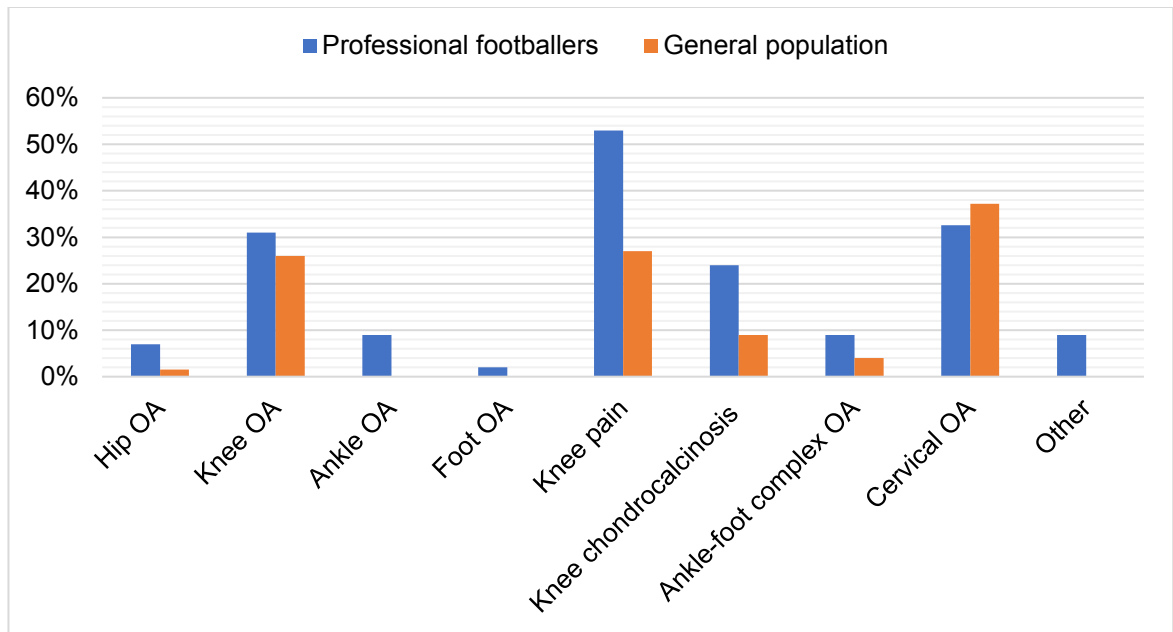


Figure 28. Summary of prevalence of osteoarthritis in male retired footballers only or/and retired footballers versus controls. OA – osteoarthritis. Other include osteoarthritis at the elbow, wrist, hand and shoulder

2.3.4.2 Back pain

Two studies reported the prevalence of back pain among footballers, one being in female current footballers and one in male retired footballers (Tunås et al., 2015, Fernandes et al., 2019), and one further study examined incidence of back pain in male retired footballers (Lundin et al., 2001).

The prevalence of back pain was almost identical, being 30.18% in male retired footballers compared to 29.38% in controls (aRR 1.00, 95% CI 0.76 to 1.32) after adjustment for age and BMI (Fernandes et al., 2019). Similarly, the prevalence of low back pain in the previous 12 months was 57% among female

current footballers (n=277), and 60% in female controls (n=167) using a questionnaire (p=0.85) (Tunås et al., 2015).

One additional single cohort study with a mean follow-up of 13.4 years determined the incidence of back pain in 30 male retired footballers, 28 male wrestlers, 28 male tennis players, 24 male gymnasts, and 28 male non-athletes with no previous or current back injuries or symptoms using a questionnaire (Lundin et al., 2001). Only data related to footballers will be mentioned. This study found that the incidence of moderate back pain to be 16.7% in male retired footballers and 28.6% in non-athletes, whereas severe back pain occurred in 36.7% of male retired footballers, and 32.1% of non-athletes (no p-value was reported between footballers and non-athletes) (Lundin et al., 2001).

2.3.4.3 Psychological conditions

Depression during active career

Depression during the active career period was determined in two studies (Prinz et al., 2016, Junge and Feddermann-Demont, 2016). Both studies used a modified version of the Centre of Epidemiologic Studies Depression Scale (Radloff, 1977), which is a self-reported scale measuring the severity of depression symptoms experienced in the last week based on answers to 20 items on a scale (0-3). The depression scores ranged between 0 and 60, with a cut-off score of 16 for mild-moderate depression, and of > 21 for major depression.

The pooled prevalence of depression during active career in female footballers was 18% (95% CI 0 - 100%) (Figure 29). High heterogeneity was observed across the included studies ($I^2=98\%$, $p<0.01$) (Figure 29).

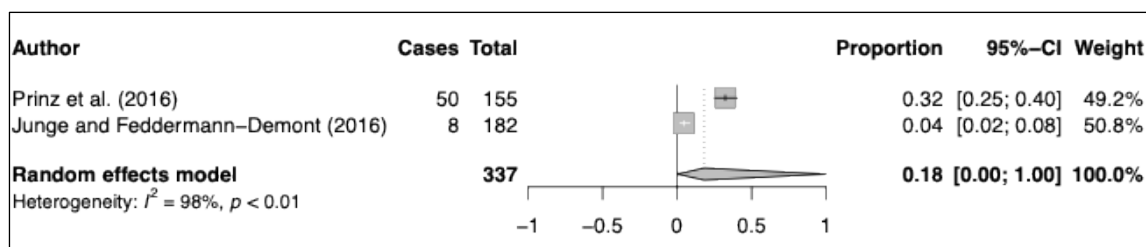


Figure 29. Forest plot showing the pooled prevalence of depression in female current footballers, random effects model. CI – confidence interval

Prinz et al. (2016) also reported that during their professional football career, 25.2% (n=39) reported mild or moderate depression (p-value was not available in the study, and the prevalence was reported descriptively) (Prinz et al., 2016). It was found that the average depression scores varied significantly by position played, with goalkeepers and forwards being at the highest risk compared to other positions ($F=2.75$; $p<0.05$) (Prinz et al., 2016). Junge and Feddermann-Demont (2016) also examined depression involving 211 male first league (FL) players and 182 female FL players compared to matched controls in the general population (394 men and 474 women). They found that the prevalence of average depression scores was significantly lower in male FL (5.5%) compared to female FL players (8.5%) ($p<0.001$), but no statistically significant differences when compared to male (5.0%) and females (7.6%) controls (Junge and Feddermann-Demont, 2016).

Prevalence of depression in retired professional footballers

Three studies determined the prevalence of depression among retired footballers (Fernandes et al., 2019, Prinz et al., 2016, Sanders and Stevinson, 2017). One of these reported the prevalence of depression in female retired footballers and found it to be 8.5% (n=13 of 153 female footballers) in their first two years after their professional career (Prinz et al., 2016).

The pooled prevalence of depression in male retired footballers in the other two studies was 11% (95% CI 0 - 73%) (Figure 30). High heterogeneity was observed across the included studies ($I^2=95\%$, $p<0.01$) (Figure 30). Of these only one study compared the prevalence of depression in male retired footballers to that in controls (5.66% versus 5.76, $p=0.94$) (Fernandes et al., 2019).

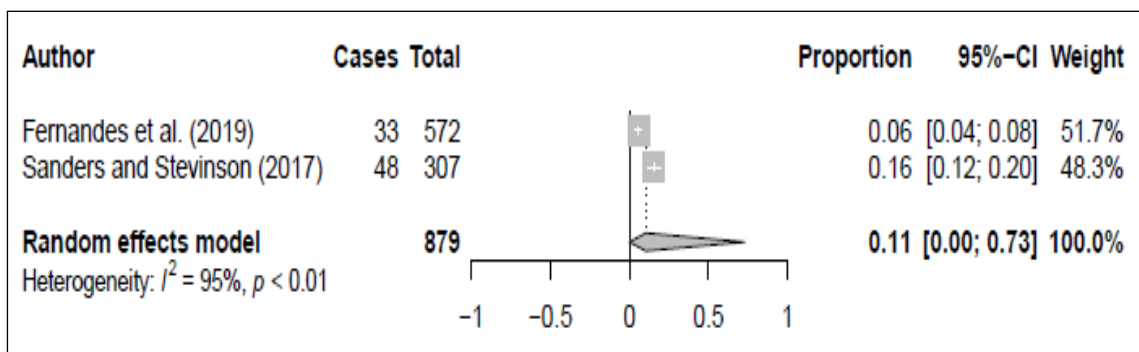


Figure 30. Forest plot showing the pooled prevalence of depression in male retired footballers, random effects model. CI – confidence interval

Risk factors for Depression

Only one study reported that retirement due to injury increased the odds of being depressed in male retired footballers (n=307) (OR 3.44, 95% CI 1.39 – 8.51), for each unit increase in the intensity of chronic pain (OR 1.38, 95% CI 1.02 – 1.86) and for each unit increase in the athletic identity score (OR 1.28, 95% CI 1.14 – 1.44) (Sanders and Stevinson, 2017). In sports people, athletic identity refers to the extent to which they identify with their athlete role and includes perceptions of values and social networks measured by the 10-item Athletic Identity Measurement Scale devised by Brewer et al. (1993).

Anxiety

Two studies determined the prevalence of anxiety in male retired footballers and female current footballers (Junge and Feddermann-Demont, 2016, Fernandes et al., 2019). The prevalence of a score ≥ 11 (the suggested cut-off to define clinical anxiety) on the Hospital Anxiety and Depression Scale was no higher in male retired footballers compared to controls (12.01% versus 10.29%, respectively, $p=0.34$) in the study by Fernandes et al (2019). In the study by Junge and Feddermann-Demont (2016), the prevalence of average anxiety measured by the Generalised Anxiety Disorder-7 questionnaire was significantly lower in female current FL players (1.1%) than female controls (4.7%) ($p<0.001$). Similarly, current male FL players had lower average anxiety (0.5%) than male controls (4.7%) ($p<0.001$) (Junge and Feddermann-Demont, 2016).

One further study examined the risk of hospitalisation among 7,676 male retired footballers matched with 23,028 general population controls using individual-level records of hospital admission. They found that compared to matched population controls after adjustment for age male retired footballers had a lower risk of hospitalisation for the most common mental health disorders such as depression (0.50% versus 0.73%, respectively) (aHR 0.64, 95% CI 0.44 - 0.92; $p=0.02$), bipolar and affective disorders (0.27% versus 0.49%, respectively) (aHR 0.55, 95% CI 0.34 - 0.88; $p=0.01$) and anxiety and stress-related disorders (0.35% versus 0.96%, respectively) (aHR 0.37, 95% CI 0.25 - 0.55; $p<0.001$) (Russell et al., 2020).

2.3.4.4 Cardiovascular conditions

Five studies examined cardiovascular conditions in male footballers, three being in male retired footballers and two in current male footballers. The prevalence of self-reported acute myocardial infarction was lower in male retired footballers compared to controls (3.08% versus 9.46%, $p<0.001$) after adjustment for age and BMI with an aRR of 0.43 (95% CI 0.26 - 0.73) (Fernandes et al., 2019). Male retired footballers with ischemic heart disease showed a significantly lower mortality rate (2.3%) than matched controls (2.5%) (aHR 0.80, 95% CI 0.66 - 0.97; $p=0.02$) after adjustment for age (Mackay et al., 2019). This was analysed using death certificates in a large retrospective cohort study of 7676 retired footballers and 23,028 general population controls matched for age, sex and degree of social deprivation (Mackay et al., 2019).

Risk factors for cardiovascular disease

One study estimated that the overall risk for an average 10-years for cardiac events was 6% in male current footballers using the Framingham risk score (Wegmann et al., 2016). This study also reported a prevalence of 35% for an elevated total cholesterol level, 39% for a lowered HDL level and 23% for an elevated low density lipoproteins level in male current footballers (Wegmann et al., 2016). One study reported that the prevalence of dyslipidemia was 2% among male retired footballers (Ka et al., 2019). Moreover, Wilson et al. (2012) examined the cardiovascular risk factors in 100 current male footballers of West-Asian (Middle East and Gulf Countries) descent and 90 of Black African descent competing in the 2010/11 in Qatar Stars League using physical examination and blood sample for total cholesterol and HDL (Wilson et al., 2012). They reported that West-Asian footballers had significantly higher total cholesterol levels (43% versus 37%, $p=0.038$) and lower HDL levels (1.3 versus 1.4 mmol/L, $p=0.004$) than Black African footballers (without control group). The difference remained significant in West-Asian footballers after adjusting for family history of coronary heart disease and for total cholesterol ($t=2.4$, 95% CI 0.046 – 0.494; $p=0.019$) and lower HDL levels ($t=2.8$, 95% CI 0.028 – 0.162; $p=0.001$) (Wilson et al., 2012).

Prevalence of hypertension

Three studies reported the prevalence of hypertension among male footballers (Fernandes et al., 2019, Ka et al., 2019, Wegmann et al., 2016). The pooled

prevalence of hypertension in male retired footballers was 39% (95% CI 0 – 100%). High heterogeneity was observed across the two studies ($I^2=97\%$, $p<0.01$) (Figure 31). Of these, only one study compared footballers to controls (22.98% versus 34.00%, respectively), reporting that footballers had a significantly lower risk of hypertension (aRR 0.79, 95% CI 0.65 - 0.96) after adjustment for age and BMI (Fernandes et al., 2019). Only one study reported the prevalence of hypertension among male current footballers, which was 66%, without comparison to controls (Wegmann et al., 2016).

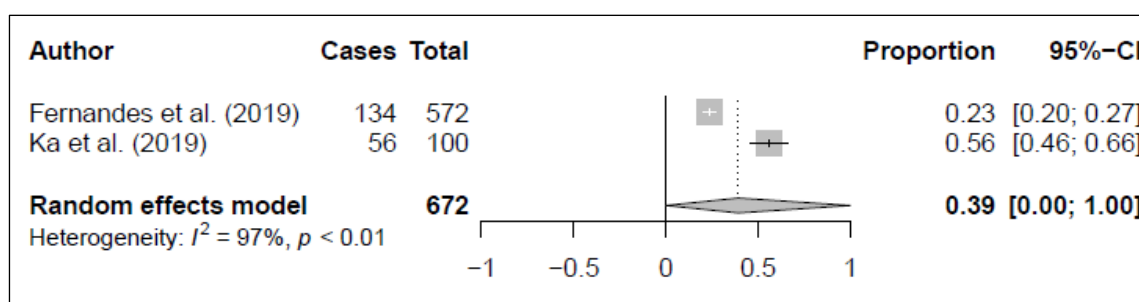


Figure 31. Forest plot showing the pooled prevalence of hypertension in male retired footballers, random effects model. CI – confidence interval

2.3.4.5 Respiratory conditions

Two studies examined the prevalence of respiratory conditions in male footballers (Kujala et al., 1996, Ka et al., 2019), and one study examined incidence of lung cancer mortality in male footballers (Mackay et al., 2019). One studied the prevalence of current respiratory diseases in 159 male retired footballers between 1920 and 1965 using questionnaire (self-reported physician-diagnosis) and found that chronic bronchitis occurred in 11%, asthma in 1%,

emphysema in 7% and allergic rhinitis in 14% (Kujala et al., 1996). The other study by Ka et al. (2019) reported in retired male footballers that the prevalence of self-reported asthma was 10.7% during their football career with no comparison to controls. Another study reported that the incidence of lung cancer mortality was significantly lower in male retired footballers (1.0%) than matched controls (1.6%) (aHR 0.53, 95% CI 0.40 - 0.70; $p < 0.001$) after adjustment for age (Mackay et al., 2019). This study used death certificates in a large retrospective cohort study of 7676 male retired footballers and 23,028 general population controls matched for age, sex and degree of social deprivation (Mackay et al., 2019).

2.3.4.6 Neurological disease

Eight studies examined neurological conditions, six being in male retired footballers, one in female retired footballers and one in current male footballers. One study reported that 33% of the 33 male retired footballers studied had brain atrophy on cerebral Computed Tomography Scan (Sortland and Tysvaer, 1989). It was also reported that 9% of male retired footballers aged between 54 to 66 years had moderate cerebellar atrophy (Sortland and Tysvaer, 1989). In addition, the prevalence of memory problems was 63.6% in female retired footballers (n=66) using a computerised neurocognitive test and four written tests (Prien et al., 2020b). Furthermore, one study reported a prevalence of 11% for mild cognitive impairment (MCI) in 92 male retired footballers with no comparison to controls (Jones et al., 2014).

The incidence of neurodegenerative disease mortality was analysed using death certificates in a large retrospective cohort study of 7676 retired footballers and 23,028 general population controls matched for age, sex and degree of social deprivation (Mackay et al., 2019). Retired footballers with neurodegenerative disease showed a significantly higher mortality rate (1.7%) than matched controls (0.5%) (aHR 3.45, 95% CI 2.11 - 5.62), $p < 0.001$) after adjustment for age, competing risks of death from ischemic heart disease and death from cancer (Mackay et al., 2019).

Furthermore, Russell et al. (2021) examined the incidence of neurodegenerative disease in 7676 male retired footballers compared to 23,028 general population using the Scottish Morbidity Record and death certification information (Russell et al., 2021). The incidence of neurodegenerative disease over a median of 18 years follow-up was significantly higher in male retired footballers (5.0%) than matched controls (1.6%) (HR 3.66, 95% CI 2.88 – 4.65) (Russell et al., 2021). It was also found that outfielders (defenders, midfielders and forwards) showed higher risk of neurodegenerative disease than men in the general population (5.6% versus 1.6%) (aHR 4.48, 95% CI 3.67 – 5.48) after adjustment for the competing risk of deaths from causes other than neurodegenerative disease (Russell et al., 2021). Risk of neurodegenerative disease varied among outfield player positions in male retired footballers compared to the general population. Defenders had the highest risk of having neurodegenerative diseases (HR 4.98, 95% CI 3.18 – 7.79), whereas forwards had the lowest (HR 2.79, 95% CI 2.06 –

3.78). In terms of career length, male retired footballers with professional career length of more than 15 years were at significantly higher risk of neurodegenerative disease than men in the general population (7.4% versus 1.2%) (HR 5.20, 95% CI 3.17 – 8.51) (Russell et al., 2021).

In addition, Pupillo et al. (2020) reported the association between professional football related factors and the risk of amyotrophic lateral sclerosis (ALS) in 23,586 male retired footballers using archives of an Italian soccer players and ALS association (Pupillo et al., 2020). They found that the incidence of ALS increased significantly in footballers in the age group < 45 years (standardised incidence rate (SIR) 4.66, 95% CI 2.66 – 7.57), footballers who started their career between 1975 and 1984 (SIR 3.97, 95% CI 1.91 – 7.31), midfielders (SIR 2.37, 95% CI 1.32 – 3.90) and footballers who played in first division A (SIR 5.69, 95% CI 2.73 – 10.47) (Pupillo et al., 2020).

Risk factors for neurological diseases

Two studies examined risk factors for cognitive impairment, one in male retired and one in male current footballers (Jones et al., 2014, Matser et al., 2001). Of these, one study showed a positive association between age and positive screening tests for MCI in male retired footballers (HR 1.13, 95% CI 1.03 - 1.25; $p=0.01$) (Jones et al., 2014). However, Matser et al. (2001) examined the impact of concussion on cognitive impairment in 84 current male footballers using neuropsychological testing (Matser et al., 2001). They reported a significant

association between soccer-related concussion and poorer performance on tests measuring focused attention and verbal/visual memory (all $p < 0.05$). The results were adjusted for age, alcohol intake, number of concussions not sustained in football, number of procedures requiring general anesthetics and level of education.

In addition, the associations between ALS and football related factors were significantly higher in 7,325 male retired footballers with career duration > 5 years (standardised mortality ratios (SMR) 15.2, 95% CI 3.1 – 44.4), and who played midfield position (SMR 12.2, 95% CI 3.3 – 31.2) based on death certificates, archives of the major Italian ALS centres and the ALS association (Chio et al., 2005).

2.3.4.7 Endocrine disease

Diabetes

Two studies reported the prevalence of diabetes in male retired footballers (Fernandes et al., 2019, Ka et al., 2019). The pooled prevalence of diabetes was 7% (95% CI 0 - 59%). High heterogeneity was observed across the two studies ($I^2 = 83\%$, $p = 0.01$) (Figure 32). One of the studies compared the prevalence of diabetes in male retired footballers to controls (3.8% versus 11.47%, respectively) and after adjustment for age and BMI, the aRR was 0.39 (95% CI 0.24 - 0.63) (Fernandes et al., 2019).

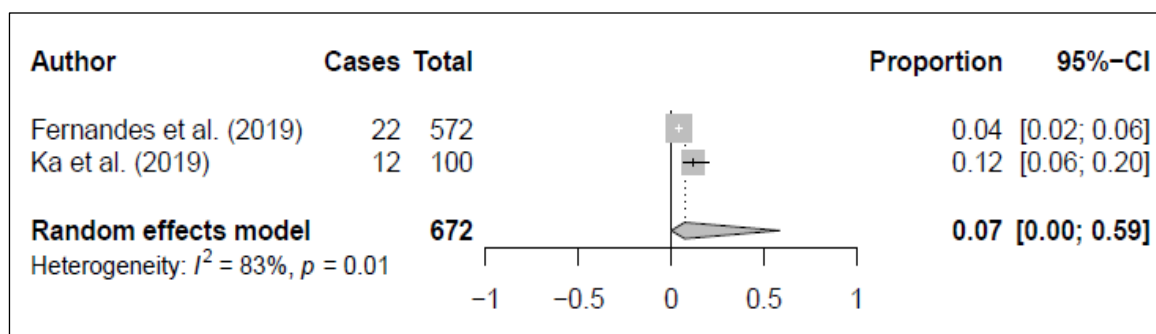


Figure 32. Forest plot showing the pooled prevalence of diabetes in male retired footballers, random effects model. CI – confidence interval

Gout

Two studies reported the prevalence of gout in male retired footballers with no comparison to controls (Parekh et al., 2021, Emran et al., 2020). The pooled prevalence of gout was 11% (95% CI 10 – 13%). Low heterogeneity was observed across the two studies ($I^2=45\%$, $p=0.18$) (Figure 33). Another study with no controls reported a 2% prevalence of hyperuricemia, but no data on gout, in 100 male retired footballers with a mean age of 57 ± 9.6 years (36 to 75 years) (Ka et al., 2019).

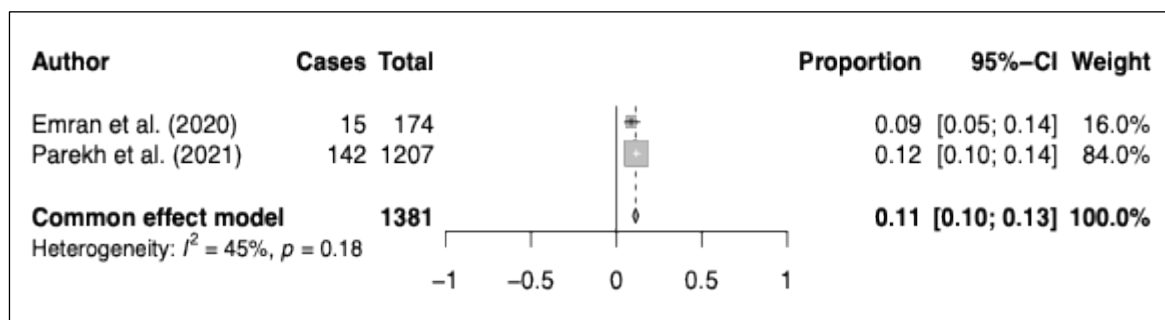


Figure 33. Forest plot showing the pooled prevalence of gout in male retired footballers, fixed effects model. CI – confidence interval

Pituitary dysfunction

One study examined the impact of heading and concussion on pituitary function in 32 male retired footballers compared to 26 sedentary career individuals using questionnaire and blood samples (Akkurt et al., 2020). No difference was found in the occurrence of low levels of growth hormone (hypopituitarism), which was identified in 9.2% of retired footballers (16% of whom had experienced concussion during their professional career), and 10% of sedentary career individuals.

2.3.4.8 Vision

Two studies examined ophthalmology related conditions in current male footballers. Toledo et al. (2019) determined that the prevalence of pinguecula was 63% and pterygium occurred in 17% of current male footballers (n=84) using questionnaire and ophthalmology examinations (Toledo et al., 2019).

Pereira et al (2015) evaluated peripheral visual field retinal sensitivity, using the Humphrey peripheral 60-4 threshold test program, in 29 male current footballers compared to 26 age and gender-matched non-athletes. They found that the footballers had significantly higher retinal sensitivity than the non-athletes in both inferior right (27.09 ± 1.44 decibel (dB) versus 25.58 ± 2.15 dB, $p=0.004$) and inferior left quadrants (27.29 ± 1.18 dB versus 26.10 ± 1.97 dB, $p=0.011$) (Pereira et al., 2015).

2.3.4.9 Other types of conditions/diseases and their related risk factors

One study reported a prevalence of cancer was 6.86% in male retired footballers versus 8.58% in controls (aRR 0.88, 95% CI 0.59 - 1.30) after adjustment for age and BMI using questionnaire (Fernandes et al., 2019). The same study also found more widespread body pain in male retired footballers than controls (8.40% versus 4.60%, respectively) (aRR 1.88, 95% CI 1.15 - 3.09%). However, the prevalence of fibromyalgia was similar in retired footballers (0.51%) compared to (0.20%), with an aRR 3.08 (95% CI 0.31 - 31.02%) (Fernandes et al., 2019). Additionally, retired footballers consumed more NSAIDs compared to controls (8.6% versus 4.2%) (aRR 1.94, 95% CI 1.19 - 3.20), and more other over-the-counter analgesics (24% versus 14%) (aRR 1.86, 95% CI 1.44 - 2.43). However, opioid use was similar in retired footballers (4%) and controls (6.4%) with an aRR of 0.64 (95% CI 0.37 - 1.10) (Fernandes et al., 2019).

Radiographic changes in the lumbar spine were examined in 70 male retired footballers compared to 59 male controls (Öztürk et al., 2008). A significant increase in the total number of osteophytes in the thoraco-lumbar spine was observed in retired footballers compared to controls at levels T12 (27.1% versus 5.4%, $p=0.001$), at level L1 (27.1% versus 5.49%, $p=0.001$), L2 (24.3% versus 7.1%, $p=0.01$) and at level L4 (51.4% versus 28.6%, $p=0.01$). Further analysis was undertaken to examine the disc height and concavity index according to playing position. They found that the mean disc height of T12–L1 in goalkeepers

was significantly higher than in forward footballers ($p=0.019$), and the mean concavity index of L1 in forward players was lower than in defenders ($p= 0.018$) (Öztürk et al., 2008).

Ka et al. (2019) reported the prevalence of self-reported phlebitis (3.5%) and sciatica (3.5%) in retired male professional footballers during their career with no comparison to controls (Ka et al., 2019). Moreover, Forte et al. found that the prevalence of tinea pedis was 15.7% in current Brazilian footballers and 20.8% in controls (p-value was not available) using physical and dermatological examinations (Purim et al., 2005).

Branci et al. (2015) reported no difference in MRI-defined adductor longus 'tendinopathy' in current soccer players with or without symptoms (72% versus 71%, respectively). However, both were higher than the 27% prevalence in asymptomatic non-soccer players ($p=0.007$) (Branci et al., 2015).

Oral health was examined in 187 active male footballers by clinical examination and a questionnaire. Of these, 5% had moderate-severe irreversible periodontal disease, and 53.1% had dental erosion, for whom severity in the most affected tooth was moderate to severe in anterior teeth in 20.9% of cases and in posterior teeth in 20.6% of cases (Needleman et al., 2016).

In summary, none of the retrieved studies examined multimorbidity in retired footballers compared to the general population. Footballers potentially had a higher prevalence of OA and neurodegenerative disease but they may be less likely to develop diabetes and cardiovascular diseases

2.4 Discussion

To our knowledge, this is the first systematic review and meta-analysis of the literature to examine the prevalence and incidence of multimorbidity and long-term conditions and their associated risk factors in professional footballers compared to the general population. The main findings were: (1) no study has examined multimorbidity in retired footballers compared to the general population; (2) footballers were more likely to have OA and neurodegenerative diseases; (3) injury (joint and head) was the major risk factor associated with the increased risk of OA and neurodegenerative diseases in footballers; and (4) playing position (midfielder and defender), head injury and career duration might increase risk for neurodegenerative disease.

2.4.1 Long-term conditions in footballers

The current study found that retired footballers particularly are at higher risk of developing OA in lower limb joints, especially the knee. The most common studied condition in professional footballers is OA (Migliorini et al., 2022). The pooled prevalence of knee OA was 31% in male footballers, and 26% in male controls. In a previous systematic review, 54.7% of retired footballers presented

with knee OA compared to 31.9% of controls (Petrillo et al., 2018). The pooled prevalence of knee pain was 53% in male retired footballers, and 27% in male controls. The prevalence in the male controls accords with previous evidence from community populations, namely 32.2% in men, and 58.0% in women aged ≥ 50 (Kim et al., 2011). Similarly, we found that the pooled prevalence of hip OA was (7%) in retired footballers, and (2%) in controls. This accords with previous studies reporting that hip OA ranged from 2% to 60% in former elite athletes and was higher than in controls (Gouttebarger et al., 2015b, Petrillo et al., 2018). In the current study, the pooled prevalence of ankle OA was 9%, which was higher than the previous study, which reported a prevalence of ankle OA of 3.4% in adults aged 50 years and older (Murray et al., 2018). The pooled prevalence of gout was 11% in male retired footballers, while the previous reported global prevalence ranged from <1% to 6.8% (Dehlin et al., 2020).

One significant risk factor for OA in professional athletes is sport-related contact and non-contact injuries (Salzmann et al., 2017). The injury rate is considerably increased during matches in professional footballers, especially in lower limbs (López-Valenciano et al., 2020). The risk factors for developing OA (i.e., age, injury and gout) stated in this study agree with the existing evidence (O'Neill et al., 2018, Doherty et al., 2016).

Other long-term conditions (e.g., neurodegenerative diseases) were identified to be more common in professional footballers. This might be explained by the nature of football, as it is a physically demanding and potentially traumatic sport,

resulting in short and long term effects (Reilly and Ekblom, 2005, Melzer et al., 2004).

The current study found that the prevalence of MCI among male retired footballers was 11%, and the prevalence of MCI among the general population increased with age being 6.7% in those aged 60–64 years and 25.2% in those aged 80–84 years (Petersen et al., 2018). Both memory problems and MCI are often an early manifestations of dementia (Duong et al., 2017). It is estimated that approximately 5% to 15% of people with MCI progress to dementia each year (Dunne et al., 2021).

The current study also found that the incidence of neurodegenerative disease was higher in male retired footballers (5.0%) than matched controls (1.6%) over a median of 18 years follow-up. Footballers are exposed to repeated head injuries from heading the ball, distributed predominantly over the front of the head, which might increase the development of neurodegenerative diseases. This is similar to the situation in boxing (Neal et al., 2022, Naunheim et al., 2000). There is evidence to support that footballers might be more susceptible to develop dementia in later life due to frequent concussion effects from heading the ball (Gouttebarga, 2021). In addition, one study found that self-reported heading frequency (>15 times per match or training session) in retired male professional footballers was associated with an increased risk of cognitive impairment which was 3.5 times greater compared to footballers with reduced

heading frequency (0-5 times per match or training session (Espahbodi et al., 2022).

A positive association between age and positive screening tests for MCI in male retired footballers aligns with previous studies undertaken in the general population (Jia et al., 2020, Hou et al., 2019). Two of the studies from this systematic review highlighted that playing in a midfield position was particularly associated with neurodegenerative diseases.

Head injury and concussion might also be a risk for eye conditions and pituitary dysfunction, though few studies have investigated these conditions in footballers. Concussion often results in disturbance in pupillary ability to focus or to move the eyes together, and this occurs due to damage to areas of the brain that control focusing activities (Tator, 2013, Gunasekaran et al., 2019). The severity of hormonal disturbance is correlated with the severity of traumatic brain injury. However, pituitary dysfunction can be exacerbated by minor head injuries as well (Benvenga et al., 2000, Casanueva et al., 2005). This is also similar to boxing, which is known to cause repetitive head trauma and thereby cause pituitary dysfunction (Kelestimur et al., 2004). One retrieved study reported 10% of pituitary dysfunction in male footballers, while previous evidence reported a prevalence of pituitary dysfunction of 37.5% in individuals with mild traumatic brain injury and a prevalence of 59.3% in those with severe traumatic brain injury (Bondanelli et al., 2004).

Only one study reported a prevalence of cardiovascular conditions including self-reported heart attack that was lower in male retired footballers (3.1%) than controls (9.4%), and lower than previous population estimates (9.1%) (Otiniano et al., 2003). Likewise, the prevalence of dyslipidemia was lower among retired footballers (2%), the recent standardised prevalence of dyslipidemia in adults aged ≥ 18 years being 31.5% (Qiu et al., 2021). Similarly, male retired footballers seem to have a lower prevalence of hypertension compared to controls (23% versus 34%), the standardised prevalence of hypertension in adults aged ≥ 18 years being 29% (Qiu et al., 2021).

The current study found no difference in the prevalence of anxiety in retired footballers (12.0%) and in general population controls (10.3%). However, current footballers have significantly lower anxiety than controls. It is estimated that up to 34% of people experience an anxiety disorder during their lifetime, based on a large population-based survey (Bandelow and Michaelis, 2022). On the other hand, depression occurred in 11% of retired footballers. Globally, the estimated prevalence of depression is 5% in all adults and 6% in adults older than 60 years (World Health Organisation, 2021). Furthermore, one included study merely highlighted risk factors for depression, namely chronic pain as well as retirement due to injury. The association with chronic pain might be explained by the effects of analgesics use, which might result in lower mood (Sheng et al., 2017).

The prevalence of the following conditions was determined by a single study for each condition. Tinea pedis was 15.7% in footballers and this accords with previous population estimates that range from 4% to 35% (Rasul et al., 2022). Fibromyalgia occurred in 0.51% of male retired footballers, which is lower than the reported fibromyalgia prevalence in the general population (2.48% in women, and 1.06% in men) (Walitt et al., 2015). Male retired footballers seem to have a lower prevalence of diabetes compared to controls (3.8% versus 11.47%), and globally, the estimated prevalence of diabetes is 19.9% in all adults aged 65-79 years (Saeedi et al., 2019). Furthermore, widespread body pain occurred in 8.40% of retired footballers, which accords with a previous systematic review showing that the prevalence of chronic widespread pain ranged from 1.4% to 24% of the general population (Andrews et al., 2018). Asthma occurred in 11% of footballers during their football career, which is higher than the global prevalence of doctor-diagnosed asthma, which was 4.3% for adults aged 18 to 45 years from 70 countries (To et al., 2012).

While most of the included studies involved male professional footballers, women's football is becoming more professionalised and popular, and hence efforts should be made to better understand the gender-specific issues experienced by female footballers. Further studies examining neurodegenerative disease related risk factors including lifestyle and comorbidities, and the possible association between head injuries and pituitary dysfunction and vision disorders appear to be warranted. Also, multimorbidity is a global health priority and merits study in professional footballers, to provide

better understanding and potential preventive strategies for professional footballers during and after their professional football career.

2.4.2 Quality assessment

Based on the cut-off points for the NOS checklists for all study designs, 29 studies were deemed to have a high quality, whereas 29 were considered to have medium quality. Therefore, it appears that the overall quality of the included studies was medium-high.

2.4.3 Limitations/strengths

There are several limitations to this study. First, the search strategy aimed primarily to include studies involving multimorbidity in footballers, with long-term conditions as a secondary objective. Therefore, predominantly general terms related to long-term conditions were searched for “chronic or long term” and “illness or disease or condition”, so some studies examining specific long-term conditions might have been missed. Second, there might be uncertainty in the results due to the observed high heterogeneity in the pooled prevalence resulting from a diversity of methodologies, demographics of the participants (i.e., age and BMI), definition and assessment used for each outcome. Third, 28 of the retrieved studies reported solely on OA in footballers. This may be because OA is the most common condition in footballers.

Despite these limitations, this systematic review included 56 studies across 18 different countries, with a range of long-term conditions in both male and female footballers either currently active or retired, with some comparisons to the general population. This review has highlighted gaps for future research and identified two major long-term conditions, specifically OA and neurodegenerative conditions, in professional footballers which require consideration of preventative strategies.

2.4.4 Conclusion

In summary, this systematic review provides consistent evidence that footballers are at higher risk of developing OA and neurodegenerative diseases, which might be explained by the repetitive physical nature of football and the required intensive training, as well as an obvious risk from overt direct injury.

Furthermore, it highlights the limited data that are available on such long-term conditions and no studies have examined multimorbidity in footballers of both genders. Future high-quality, adequately powered and appropriately designed studies involving a multinational population of footballers are warranted to provide a better understanding of long-term conditions and multimorbidity. This would be especially helpful if standardised criteria were used to assess the long-term conditions and risk factors were collected and compared to those in the general population.

Chapter 3 Methods for the longitudinal cohort study examining the incidence of knee pain and multimorbidity

3.1 Introduction

This chapter presents the methods used for the cohort study. It includes the aim and objectives, study design, information about participants, descriptions of baseline and follow-up questionnaires, exposures, comparator and study outcomes (knee pain and multimorbidity). Data management and cleaning, and the statistical analyses undertaken are also described.

3.2 Study Design

The study was a secondary data analysis of two previous cross-sectional studies (2014 and 2020) conducted in Academic Rheumatology, University of Nottingham, before my studentship. Both studies were undertaken in the same population of male retired footballers (referred to as the footballer group) and age matched and adjusted general population controls (referred to as the control group). The current study utilised the existing data obtained in the two cross-sectional studies to form a cohort of footballers and controls with 6 years follow-up.

Aim

To examine the incidence of knee pain and multimorbidity and their associated risk factors in footballers compared to controls.

Objectives

1. To examine the incidence of knee pain and its related risk factors in footballers and controls.
2. To examine the association between knee pain and multimorbidity within footballers and controls.
3. To examine incidence of multimorbidity and its related risk factors in footballers compared to controls.

Both previous studies conducted in 2014 and 2020 were cross-sectional in design. This allowed the prevalence of the outcomes to be measured (i.e., knee pain, physician-diagnosed knee OA, TKR, neurodegenerative disease and foot/ankle OA) in a proportion of footballers and controls who had a specific outcome at a specific time point. However, the cross-sectional study design limited the ability to examine how the outcomes evolved. Confounding factors (e.g., age, BMI, injury) were collected at the same time as the outcome, making it difficult to determine whether the exposure led to the outcome or vice versa. In contrast, the cohort study provided longitudinal data in which exposures (e.g., age, BMI, injury and analgesic use) were measured and preceded the outcome of interest (knee pain or multimorbidity). This made it possible to track changes over time (6-years) and to measure the risk of developing multiple outcomes (knee pain or multimorbidity). The cohort study allowed the temporal relationship between exposure and outcome to be examined and therefore the association

between knee pain and incident multimorbidity, which would provide better understanding of disease progression and causation.

3.2.1 Initial cross-sectional study

The initial cross-sectional study was conducted in 2014 by a research fellow Dr Gwen Fernandes and a PhD student, Sanjay Parekh, under the supervision of Professor Michael Doherty, Professor Weiya Zhang. Footballers were recruited from the “Footballer study for knee OA”, and general population men were recruited from the Knee Pain and related Health in the Community Study (KPIC) as shown in Figure 34 (Fernandes et al., 2018). The primary aim of the Footballer study for knee OA was to examine the prevalence and associated risk factors for knee OA and its outcomes, including knee pain, RKOA and TKR in retired male professional footballers versus general population male controls (Fernandes et al., 2018). Baseline data of the questionnaire was requested (Appendix B). The following is a summary of the main findings of the initial cross-sectional study (Fernandes et al., 2018, Parekh et al., 2021, Fernandes et al., 2019):

1. Footballers had a higher prevalence of knee pain, knee OA and TKR than controls.
2. Age, BMI and knee injury were the main risk factors for knee pain, knee OA and TKR in footballers.
3. Footballers had a lower prevalence of diabetes, heart attacks and hypertension than controls.

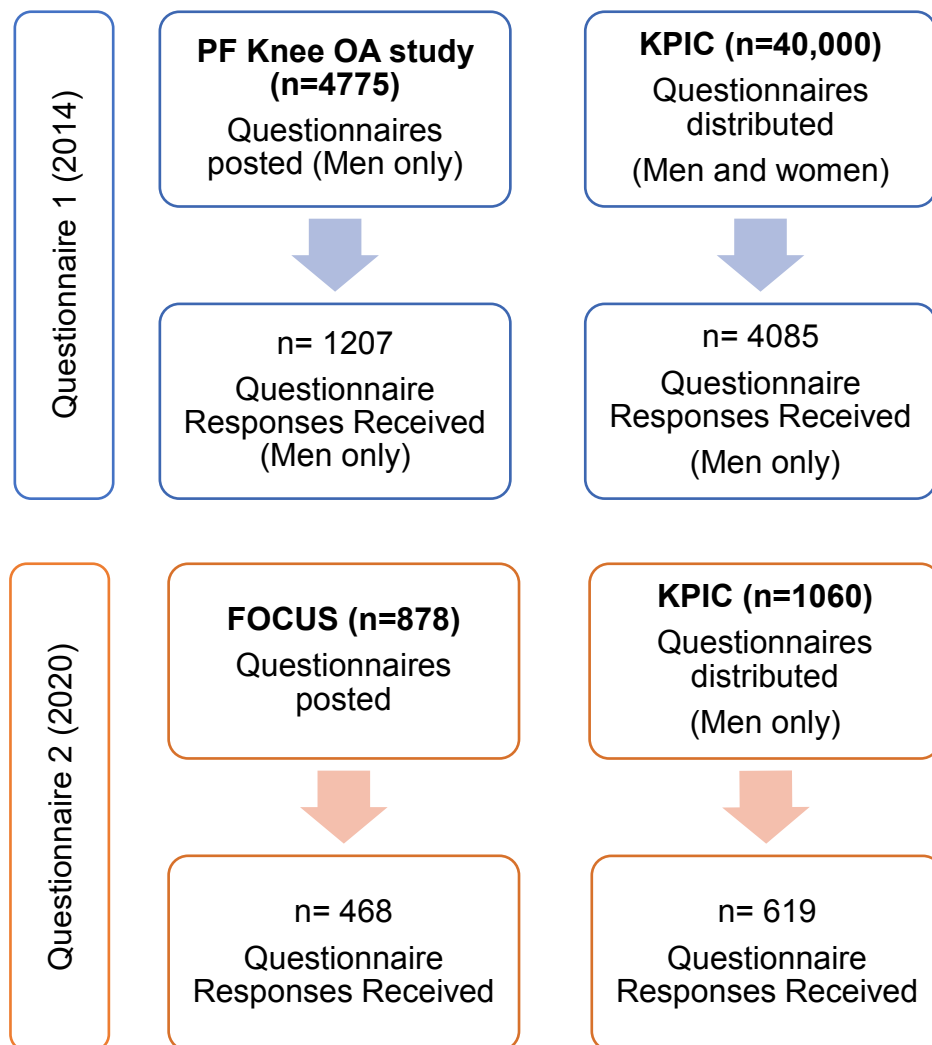


Figure 34. Summary of study population including footballers and general population in 2014 and 2020. PF - professional footballers; OA – osteoarthritis; KPIC - Knee Pain and Related Health In the Community Study; FOCUS - Foot/ankle Osteoarthritis and Cognitive impairment in UK Soccer players

3.2.2 The subsequent follow-up study

The subsequent follow-up study of the same participants, conducted in 2020, was the “Foot/ankle Osteoarthritis and Cognitive impairment in United Kingdom Soccer players” (FOCUS) study (Espahbodi et al., 2022). This study was conducted by a research fellow Dr Shima Espahbodi and a PhD student, Ahmed Thanoon, under the supervision of Professor Weiya Zhang and Professor Michael Doherty. I was involved in scoring the outcome of radiographic foot/ankle OA, and also had the responsibility for obtaining the socioeconomic status of the participants using their post-code. The primary aim of the FOCUS study was to examine the prevalence and associated risk factors for symptomatic and radiographic foot/ankle OA in retired footballers compared to men in the general population. It also aimed to determine the prevalence of cognitive impairment including dementia and Parkinson’s disease. The secondary aim was to identify specific football-related risks factors such as foot/ankle injuries for chronic symptomatic foot/ankle OA, and head impact/concussion for neurodegenerative conditions. The following is a summary of the main findings of the follow-up study (Espahbodi et al., 2023, Macnab et al., 2023):

1. Neurodegenerative disease prevalence was higher in footballers than in controls.
2. Heading/concussion was an independent risk factor for cognitive impairment.
3. Foot/ankle OA prevalence was higher in footballers compared to controls.

4. Injury was an independent risk factor for foot/ankle OA.

Both baseline and follow-up studies were approved by the Nottingham Research Ethics Committee 1 and 2 (Refs 14/EM/0045 and 14/EM/0015) (RCF 261168). All participants (referred to as footballers and controls) gave implied consent by responding to the questionnaires. Those who indicated in their returned questionnaire willingness to undergo additional radiographic assessment, and who lived close enough to attend one of the radiographic centres involved in the study, were invited for a single visit to undergo radiographs of both their knees (1st study) or both ankles and feet (2nd study). Written informed consent was obtained prior to having the radiographs.

3.3 Participants

Footballers were retired male football players aged 40 years and older living at different locations within the UK. All had played professionally in the top four tiers of the English Football League and were registered with one or more of the Professional Footballer's Association, the Former Players' Association and the Club Player Association (League level). The baseline questionnaire for the knee study was sent to footballers by Football Associations. Return of the completed questionnaire was taken as implicit consent to participate, and if responders gave their contact details and agreed to be recontacted directly by the research team about having radiographs and or receiving information about future studies then communication was made directly to them from Academic Rheumatology.

The control group comprised male controls aged 40 years and older who were registered with General Practices in the East Midlands region of the UK. The questionnaire was sent directly from their General Practice with an explanatory letter and a stamped addressed envelope (as with the footballers). All participants (footballers and controls) needed to have the ability to write in English, to not be terminally ill, and to be able to give informed consent.

For the follow-up questionnaire, all participants were approached by the FOCUS administrative team in the Academic Rheumatology, University of Nottingham using contact details from the master database, following the UK General Data Protection Regulation guidance.

3.4 Questionnaires

The baseline postal questionnaire was based on previously published questionnaires undertaken in Academic Rheumatology (O'Reilly et al., 1996, Ingham et al., 2011a). Both baseline and follow-up questionnaires sent to footballers were different from those sent to controls in terms of the football-specific questions such as position played, training hours and matches played, determination of injury and concussion during matches. However, they shared similar structures and identical questions relating to OA and multimorbidity outcomes. An overview of the common questions to both footballers and controls, and the football-related questions in both the baseline and follow-up questionnaires is shown in Figure 35.

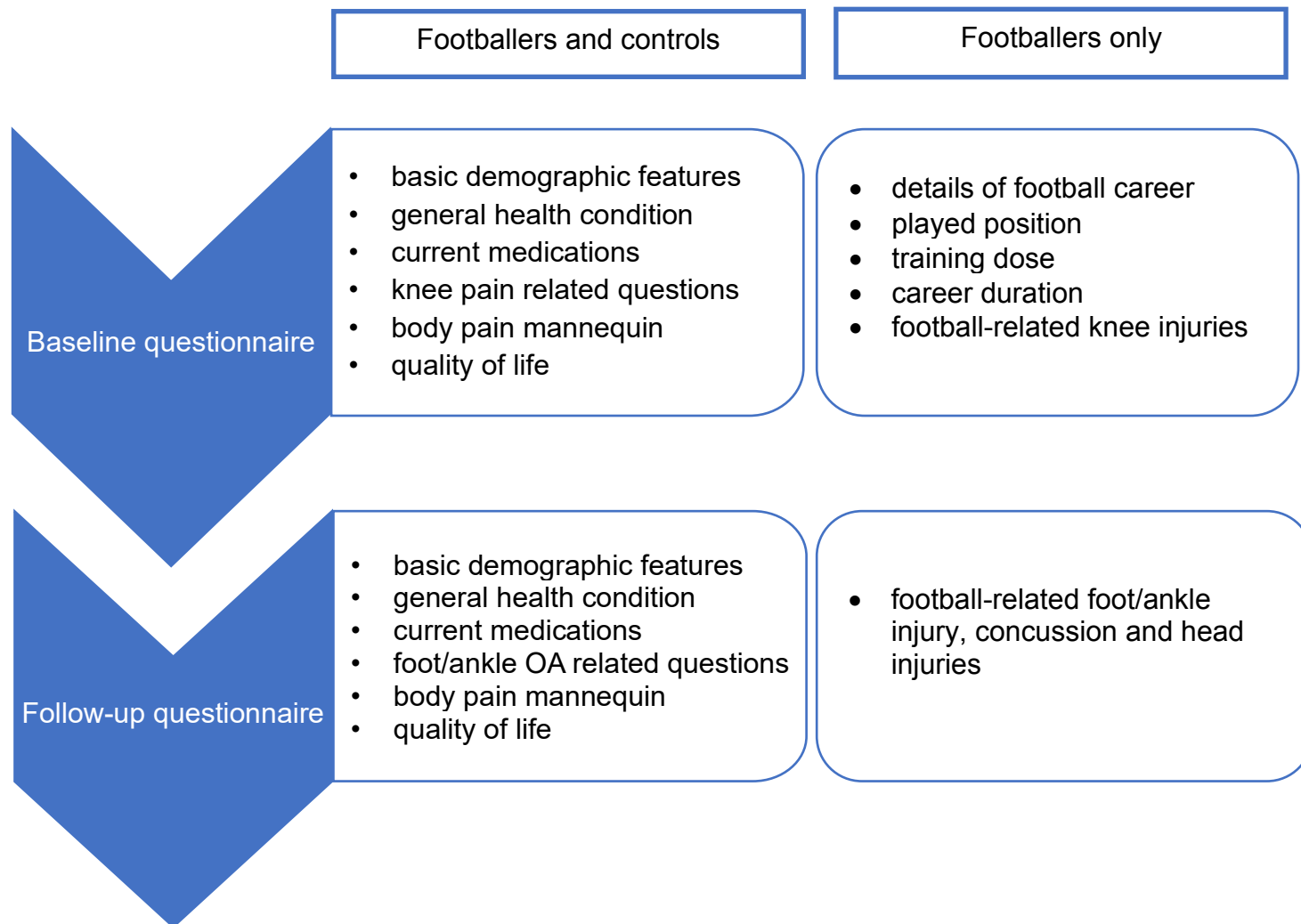


Figure 35. Mapping for common questions in the baseline and follow-up questionnaires for the study population

3.4.1 Baseline postal questionnaire:

Baseline questionnaire sent to all participants asked for information on current and past knee pain, knee surgery and knee OA risk factors. Information on basic demographic features, general health, current medications and occupational history were also collected. A body pain mannequin was used to locate pain that lasted for most days of the previous month in any body region. The questionnaire also asked if they would be willing to undergo bilateral knee radiographs to assess presence of RKOA and chondrocalcinosis. Only those who indicated such willingness were sent a subsequent postal invitation, which for footballers was dependent on them living within 40 miles of the nearest collaborating medical centre (Spire Healthcare). For controls, all radiographs were undertaken at the City Hospital, Nottingham. Further details of the questionnaire for footballers and controls are shown in Appendix C.

3.4.2 General questions

The following exposures/variables were determined at the baseline to characterise the study population:

- Age was calculated by calculating the interval between the participant date of birth and the date of the last day of the baseline survey (01/12/2015).
- BMI was calculated as self-reported weight in kilograms (kg) divided by the square of the height in metres (m), i.e., $BMI = kg/m^2$.

- Postcode information was used to measure socioeconomic status (decile) employing the Index of Multiple Deprivation and English Indices of Deprivation (2019). On this index, 1 is the lowest socioeconomic level and 10 is the highest socioeconomic level (Ministry of Housing, 2019).
- Self-reported current use of oral analgesics, including any prescribed oral NSAID, paracetamol or opioids, and also self-purchased over-the-counter oral analgesics (paracetamol, ibuprofen). This was obtained by the question *“please list all your current medication including those prescribed by your doctor and those you bought yourself over the counter”*.
- Knee injury in controls was defined by the question *“Have you ever suffered significant injury to either of your knees?”*.
- Physician-diagnosed knee OA was determined by the question *“Have you ever been diagnosed with osteoarthritis in your knees by a physician (for example, your GP)?”*.
- Nodal OA was determined using a validated diagram (Figure 36) devised in Academic Rheumatology (Rees et al., 2012) and classified as present in those reporting nodes on at a least two rays of each hand (Zhang et al., 2009). Specific nodes on each hand were obtained by a question *“for each*

hand please circle the finger joint(s) where you have these nodes. Please circle ALL joints that are affected” (Figure 37).

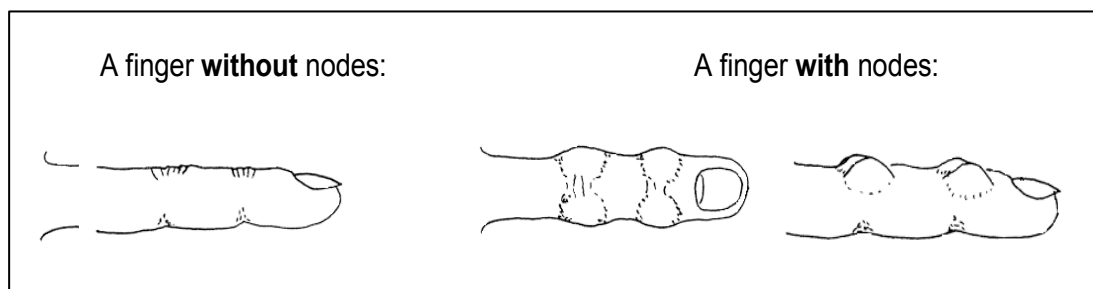


Figure 36. The line drawing tool to determine nodal osteoarthritis

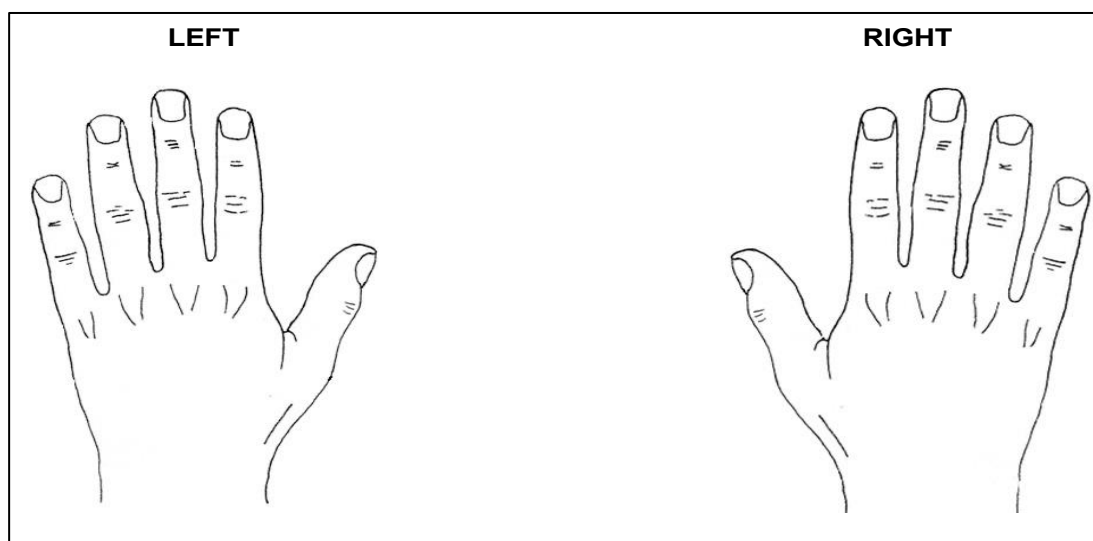


Figure 37. Hand diagram for participant to indicate the presence of nodes in each finger joint(s) for both hands

- The 2D:4D finger ratio was assessed using validated line drawings (refer to Figure 17, page 39) (Zhang et al., 2008). The three possible finger length patterns are shown in Figure 17 (page 39).

3.4.3 Football-related questions

Football-specific details obtained in the baseline questionnaire to footballers only included the following:

- Career duration was determined by the question “*For how long did you or have you played professional football*”, e.g. 1986 – 1999.
- Playing position was examined by “*What position did you mainly play during your professional career?*”. followed by “Tick one” box for the following:
☐Goalkeeper ☐Defender ☐Midfielder ☐Forward
- New variable named “outfielder” was subsequently derived from this response and included the positions played as defender or midfielder or forward (i.e., non-goalkeeper positions).
- The number of matches played was obtained by the question “*Approximately how many matches did you take part in during your professional career including first team, reserve and international games*”. (e.g., 100 matches).

- Average weekly training duration was examined by *“On average, during your professional career, how many hours per day and how many days per week did you spend training?”*.
- Career training dose was calculated by multiplying the number of hours played per week by 40 (i.e., an average season in one year) and then by the number of years they were a professional footballer. It was classified into five as follows: <1000, 1000-3999, 4000-6999, 7000-9999 and >10000.
- Significant knee injury was defined as *“one which caused pain for most days for at least a 3-month period and resulted in an absence from all training and matches during this time”*.

3.4.4 Follow-up postal questionnaire:

All participants who indicated willingness in the first questionnaire to participate in further studies were sent a second postal questionnaires in 2020 to obtain information primarily on self-reported foot/ankle OA, foot/ankle OA risk factors, head injury/concussion, and memory. There were also questions on basic demographic features (date of birth, height, weight), general health, quality of life using the SF-36, current medications and occupational history. A manikin was used to locate any current regional pain lasting most days of the previous month, and a foot line-drawing was used to locate in more detail any current foot

pain. An invitation to undergo foot and ankle radiographs, irrespective of any foot pain, was sent to a sample of participants (footballers and controls) who indicated willingness to undergo a single hospital visit and who also lived reasonably close to Nottingham City Hospital or one of the five collaborating hospitals. Further details of the questionnaire for footballers and controls are shown in Appendix D.

For the current study, relevant data relating to knee pain and multimorbidity contained in the baseline and follow-up questionnaires were extracted from the two retired footballers and KPIC databases and combined into a single database using SPSS software.

3.5 Exposure

The primary exposure for this cohort study was having previously been a professional footballer. We also examined specific risk factors related to football such as playing position, training hours per week, career length, football-related injury and joint injections. Self-reported knee pain was considered as an exposure for incident multimorbidity.

3.6 Comparator

For the incidence of knee pain and multimorbidity a cohort study was undertaken where the exposure was defined as people who had been a

professional footballer whereas the comparator was defined as a male, matched general population group. For risk factors related to incident knee pain or multimorbidity per group (footballers or controls), a case control study was undertaken within footballers or controls, where the case was defined as people who developed knee pain or multimorbidity, whereas the comparator was defined as those who did not develop knee pain or multimorbidity at the follow-up.

Footballer related risk factors for incident knee pain and multimorbidity were also examined if there was a significant association in univariate analysis, in which case the lowest level of exposure was used as the comparator, e.g., injuries, career duration, matched played and position played (categorised into outfielder with goal-keeper as the comparator).

3.7 Outcome

The main outcomes of the current study were self-reported incident knee pain and multimorbidity.

3.7.1 Knee Pain

In both baseline and follow-up questionnaires, self-reported knee pain was defined as anterior knee pain, either right and/or left using the body pain mannequin. Anterior knee pain was considered because knee OA pain

(tibiofemoral or patellofemoral) is felt anteriorly (Abhishek and Doherty, 2013). A body pain mannequin that enquired about such pain anywhere in the body was used to indicate anterior knee pain that had lasted for most days of the previous month (Figure 38) excluding those with total knee replacement. Incident cases of knee pain were defined as people without knee pain at baseline who reported knee pain at the follow-up survey.

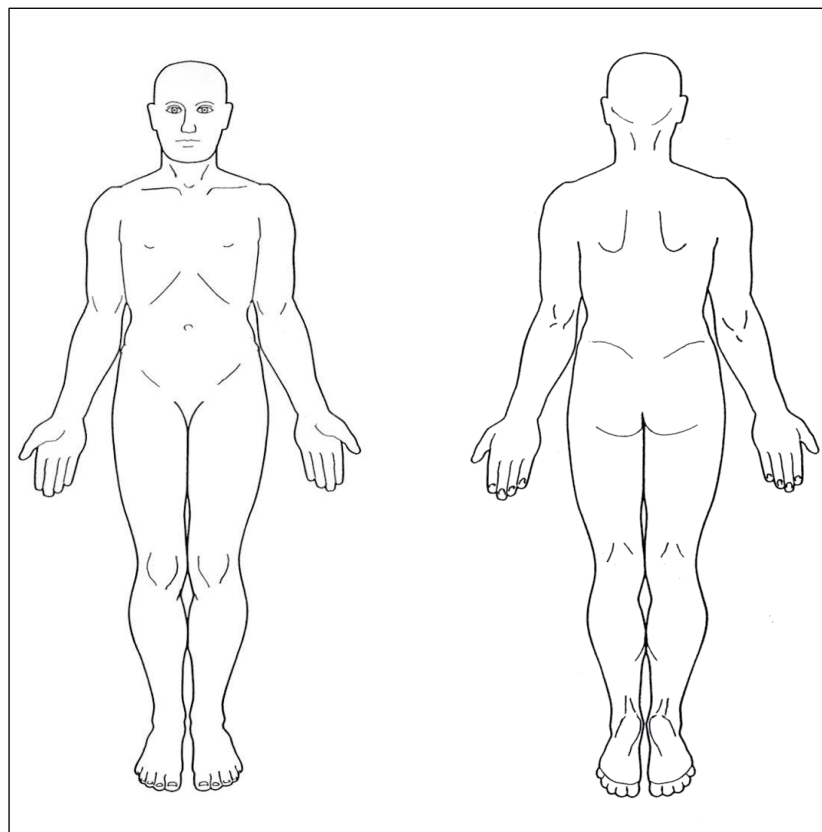


Figure 38. Body mannequin to determine self-reported anterior knee pain and pain for most days in the past month at any other region

3.7.2 Multimorbidity

Multimorbidity, defined as the occurrence of at least two long-term conditions in an individual simultaneously (van den Akker et al., 1996), was determined by adding the numbers of long-term conditions present in each participant in both groups. A list of specific long-term conditions, derived to suit UK adults, was included, each with a tick box, within the question “Have you ever been diagnosed by your doctor as having had any of the following? Please tick all that apply” (Table 14). If they had been given a diagnosis that was not on the list, they could write this into an additional blank space that was provided. Both follow-up questionnaire sent to footballers and controls were similar in these respects. The number of specific long-term conditions listed were subsequently grouped as shown in Table 14.

Table 14. Long-term conditions included in assessment of multimorbidity in footballers and controls

n.		Long-term conditions
1.	Cardiovascular disease	Hypertension
2.		Heart attack- myocardial infarction
3.		Heart failure- enlarged heart
4.		Cardiac arrhythmia- atrial fibrillation
5.		Coronary artery disease
6.		Valve-related conditions (stenosis, incompetence, replacement)
7.		Peripheral vascular diseases (deep vein thrombosis, claudication, pulmonary embolism)
8.	Endocrine, metabolic	Hypercholesterolaemia, hyperlipidaemia

9.		Diabetes mellitus
10.		Thyroid disorder (hypo/hyper)
11.	Neurological	Parkinson's disease
12.		Alzheimer's disease
13.		Dementia
14.		Stroke
15.		Transient Ischaemic Attack
16.		Epilepsy, seizure
17.		Migraine
18.		Multiple sclerosis
19.	Psychological/affective disorders	Depression
20.		Anxiety
21.		Schizophrenia
22.		Psychosis
23.	Cancer	Cancer of specific organs including leukaemia
24.	Lung disease	Asthma
25.		Chronic obstructive pulmonary disease/chronic bronchitis/chronic lung conditions
26.	Musculoskeletal	Rheumatoid arthritis
27.		Gout
28.		Fibromyalgia
29.		Chronic fatigue syndrome, myalgic encephalomyelitis (chronic fatigue syndrome)
30.		Osteoarthritis
31.		Psoriasis (psoriatic arthropathy)
32.		Ankylosing spondylitis
33.		Back pain
34.		Lupus
35.		Sjogren's syndrome
36.	Infection	Human immunodeficiency virus
37.		Hepatitis C, B
38.		Tuberculosis
39.	Hearing	Hearing loss

40.	Vision	Iritis, retinal vein occlusion, glaucoma, blurred vision
41.	Renal	Chronic kidney disease
42.	Liver	Chronic liver disease Gall bladder stone
43.	Gastrointestinal	Irritable bowel syndrome
44.		Ulcerative colitis
45.		Peptic ulcer

Data cleaning and management

Baseline questionnaires from footballers and controls were not directly comparable in terms of medical conditions listed. Seven conditions were listed in the footballers version and 14 conditions were listed in the general population version with a blank space presented in both to be completed if they had been given a diagnosis that was not on the list (Table 15). All the conditions written in the blank space were coded so that they would be comparable when the two databases were merged. All irrelevant information in the blank space was eliminated. For example, high cholesterol was not listed as a condition in the questionnaire sent to footballers, thus a new variable named “high cholesterol” was generated in the footballers database. In terms of the long-term conditions count, OA was counted once even if the participant had OA in other joints.

Footballers and controls who had zero or one condition at baseline were eligible for the analysis to determine the subsequent incidence of multimorbidity. For both groups, the following conditions in those who had one condition at baseline were included for analysis: cardiovascular, musculoskeletal, endocrine,

psychological, liver, neurological, respiratory, hearing loss or vision problems, cancer and gastrointestinal.

Table 15. Specific long-term conditions listed in the baseline questionnaire in footballers versus controls

	Footballers	Controls
1. Diabetes	✓	✓
2. Hypertension	✓	✓
3. Heart attack	✓	✓
4. Depression	✓	
5. Rheumatoid arthritis	✓	
6. Gout	✓	
7. Cancer	✓	✓
8. High cholesterol		✓
9. Stroke		✓
10. Knee osteoarthritis		✓
11. Hip osteoarthritis		✓
12. Irritable Bowel Syndrome		✓
13. Fibromyalgia		✓
14. Chronic Fatigue Syndrome		✓

For each of the 13 specific groups of conditions in footballers and controls (musculoskeletal, cardiovascular, neurological, cancer, respiratory, endocrine, psychological, gastrointestinal, hearing, liver, renal, vision and infection), a new variable was determined for each of the 13 specific group of conditions by

recording the baseline, coded 0 for free of specific group of conditions, 1 for presence of the specific group of conditions, and '999' for missing variables. At the follow-up, a new variable for each of the 13 specific groups of conditions was determined and included any of the conditions listed in Table 22.

3.8 Covariates

Covariates for both knee pain and multimorbidity were selected based on the literature from the data collected in the baseline questionnaire, including age, BMI, pattern 3 2D:4D finger ratio, oral analgesic use and socioeconomic status. Specific covariates for each outcome are shown in Table 16.

Table 16. Covariates for knee pain and multimorbidity

	Knee pain	Multimorbidity
Age	✓	✓
BMI	✓	✓
Knee injury	✓	
Nodal OA	✓	
Pattern 3 2D:4D finger ratio	✓	
Having one condition at baseline		✓
Oral analgesic use	✓	✓
Socioeconomic status	✓	✓

BMI – body mass index; OA – osteoarthritis

Current oral analgesics included paracetamol, non-steroidal anti-inflammatory drugs (NSAID), opioids, and over the counter paracetamol or NSAID.

Pattern 3 2D:4D finger ratio: index finger is shorter than the ring finger.

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to10, determined by post-code.

3.9 Sample Size Calculation

Based on an annual incidence rate of knee pain in the general population of 3% for knee pain in 6 years (2014 to 2020) (Ingham et al., 2011b), the sample size needed was calculated using the z test and a logistic regression model.

Assuming that our data would include multiple confounding factors with a multiple correlation co-efficient $R = 0.30$, two tail and a relative risk of 2.0

between footballers and control men, the minimum sample size needed for this

study was 194 per group, with 85% power and 5% type I error. We had 468 footballers and 619 controls at the follow-up, of whom 50% of footballers and 25% of controls would have had knee pain already according to the previous study (Fernandes et al 2018), which would give 234 footballers and 464 controls at risk of knee pain. We included all available participants to ensure sufficient power for this outcome.

For multimorbidity, based on a cumulative incidence rate of 23% in men in the general population (Shang et al., 2020), the sample size needed was calculated using the z test and a logistic regression model with a multiple correlation coefficient of $R=0.30$, two tail and a relative risk of 0.5. The minimum sample size needed for this study was 237 per group, with 95% power and 5% type I error. We had 468 footballers and 619 controls at the follow-up, of whom 20% of footballers (Lister-Roberts, 2020) and 30% of control men in the general population (Shang et al., 2020) were expected to have had multimorbidity at baseline. This would give 374 footballers and 434 controls at risk of incident multimorbidity. We included all these participants to ensure sufficient power for this outcome. The power calculations were obtained using GPower V.3.1.

3.10 Statistical Analysis

3.10.1 Descriptive analysis

Continuous variables were reported as means and SD and categorical variables as frequencies or percentages. To determine whether there was any difference

between footballers and controls, the t-test (for continuous variables) or χ^2 test (for categorical variables) were used. Statistical significance was defined as $p < 0.05$. For non-normally distributed variables such as age and BMI descriptive data were presented as mean and SD in accordance with the central limit theorem, that is, as sample size increases, the data for these measures tend to be normally distributed (McDonald, 2009). Comparison of two categorical variables was determined using the Chi-square (χ^2) test assuming that groups were independent and that the expected value of the cell was ≥ 5 in at least 80% of the cells. If the expected value of the cell was < 5 in at least 80% of the cells Fisher's exact test was used (McHugh, 2013, Armitage et al., 2008). All statistical analyses were conducted using IBM SPSS Statistics (version 28).

3.10.2 Incidence of knee pain and multimorbidity

This was an inception cohort study, therefore the incidence of knee pain and multimorbidity were calculated by dividing the number of newly developed (incident) cases by the number of people at risk for each condition at baseline for both footballers and controls over 6 years. Our derived study population for incident knee pain were those without knee pain at baseline, whereas for incident multimorbidity it was those with ≤ 1 condition at baseline, and the rest of the study population were removed. Incidence (%) of knee pain and multimorbidity were examined according to age at baseline as follows: 40-49, 50-59, 60-69, 70-79 and 80-89 years. However, the last two categories (70-79 and 80-89) were combined due to the small number of participants.

OR and 95% CI was calculated using logistic regression. The logistic regression model was used for binary outcome variables for the study outcomes of either knee pain or multimorbidity (1=yes, 0=no). This type of regression can be used for analysis of any study designs including case-control studies, cross-sectional and cohort studies with a binary outcome (Campbell, 2006). It is a flexible method for estimating OR and their 95% CI, which can cope with many exposures/confounders and incorporate binary, categorical or continuous exposure variables, and examine interaction terms/effect modification (Kirkwood and Sterne, 2010). The odds of developing incident knee pain or multimorbidity in footballers compared to general population controls was then calculated using logistic regression model after adjustment for age, BMI, socioeconomic status and analgesic use because these factors are the potential confounding factors based on the literature or whether they were significant in the univariate analysis. They were then included in multivariable logistic regression.

Details of missing data for incident knee pain and multimorbidity in the participants are shown in Tables 17-18. Imputation was used for missing data (e.g., socioeconomic status) at random in footballers. This was obtained using Little's missing completely at random (MCAR) test to examine if there is a pattern of missingness in the variables are at random or not (Li, 2013). All variables including categorical and continuous were included and the result revealed a $p=0.246$, indicating that all missing variables were at random for knee pain outcome. A sensitivity analysis was undertaken to compare the results

between the imputed and non-imputed data. Within footballers, mean (SD) socioeconomic status for the knee pain outcome was 7.63 (2.3) before imputation. After imputation with series mean, the mean (SD) for socioeconomic status was 7.61 (2.2).

Little's MCAR test was also used to examine the pattern of missingness for multimorbidity outcome, and the result revealed a $p=0.060$, indicating that all missing variables were at random. Within footballers, mean (SD) socioeconomic status for the multimorbidity outcome was 7.65 (2.2). After imputation with series mean, the mean (SD) for socioeconomic status was 7.63 (2.1).

Table 17. Questionnaire missing data for incident knee pain in footballers and controls

Missing data, n (%)		
	Footballers (n=222)	Controls (n=402)
General questions		
Age	1 (0.5)	0
BMI	5 (2.3)	11 (2.7)
Knee injury	4 (1.8)	3 (0.7)
Physician-diagnosed knee OA	133 (59.9)	0
Nodal OA	1 (0.5)	14 (3.5)
Pattern 3 2D:4D finger ratio	4 (1.8)	11 (2.7)
Current use of analgesics	0	0
Socioeconomic status	27 (12.2)	1 (0.2)
Self-reported outcomes		
Knee pain	0	0
Footballers (n=222)		
Footballers related questions		
Career duration	3 (1.4)	
Matches played	2 (0.9)	
Career training dose (hours)		
< 1000	0	
1000-3999	0	
4000-6999	0	
7000-9999	0	
>10,000	0	
Position played		
Goalkeeper	1 (0.5)	
Outfielder	1 (0.5)	

BMI – body mass index; OA – osteoarthritis

Outfielder included the positions played as defender or midfielder or forward

Table 18. Questionnaire missing data for incident multimorbidity in footballers and controls

Missing data, n (%)		
	Footballers (n=317)	Controls (n=362)
General questions		
Age	0	1 (0.3)
BMI	5 (1.6)	14 (3.9)
Having one condition	0	0
Current use of analgesics	1 (0.3)	0
Socioeconomic status	37 (11.7)	1 (0.3)
Self-reported outcomes		
Multimorbidity	0	0
Footballers (n=317)		
Footballers related questions		
Career duration	5 (1.6)	
Matches played	3 (0.9)	
Career training dose (hours)		
< 1000	0	
1000-3999	0	
4000-6999	0	
7000-9999	0	
>10,000	0	
Position played		
Goalkeeper	0	
Outfielder	0	

BMI – body mass index

Outfielder included the positions played as defender or midfielder or forward

3.10.3 Incidence of specific groups of conditions

The incidence of 13 specific groups of conditions (musculoskeletal, cardiovascular, neurological, cancer, respiratory, endocrine, psychological, gastrointestinal, hearing, liver, renal, vision and infection) were estimated for footballers and controls. The incidence (%) was calculated by the number of people with a newly developed specific-group of condition divided by the total number of participants without the specific conditions at baseline. For example, to calculate the incidence of musculoskeletal conditions, all participants without a musculoskeletal condition at baseline were included. A multivariable logistic regression model was used to examine the multiple risk factors associated with a specific group of conditions (%) where being a footballer (yes/no), age, BMI, socioeconomic status, analgesic use and having one condition at baseline were included in the model. To address Type 1 error due to multiple testing for multiple outcomes, a Bonferroni correction was used (Julien, 2015), correcting the alpha through the Bonferroni method, thus, $\alpha_{\text{Bonferroni-corrected}} \leq 0.0038$, according to the following calculation:

$$\text{Bonferroni corrected alpha} = \frac{\alpha}{n} = \frac{0.05}{13} \leq 0.0038$$

where, α is the original p value and n is number of tests

3.10.4 Risk factors associated with incident knee pain and multimorbidity

A nested case-control study was undertaken within the footballers and the controls. Stratified analysis was done per group (footballers and controls) for risk

factors for knee pain and multimorbidity outcomes in 6 years. A case was defined as an individual with the outcome of interest (knee pain or multimorbidity), whereas a control was defined as an individual without the outcome of interest. Crude OR and 95% CI were calculated using the logistic regression model per risk factor. A multivariable logistic regression model was then used to adjust for potential confounding factors based on the literature or the significance from the univariate analysis. In addition, a backward-stepwise regression approach was also applied to validate the results. To address multiple testing for multiple risk factors, a Bonferroni correction was used for each outcome.

3.10.5 Association between baseline knee pain and incident multimorbidity

The incidence of multimorbidity in those with baseline knee pain and those without baseline knee pain was compared using multivariable logistic regression in footballers, controls and a combined group analysis (adjusted for being footballers). Knee pain was the primary exposure adjusted for age, BMI, socioeconomic status, analgesics and having one condition at baseline. ORs and 95% CIs were used to estimate the association between baseline knee pain and incident multimorbidity. Statistical significance was defined as $p < 0.05$.

Chapter 4 Results and discussion of the longitudinal cohort study

examining the incidence of knee pain and related risk factors among retired male professional footballers compared to men in the general population

4.1 Introduction

This chapter presents the results and discussion for two objectives: (1) to examine the incidence of knee pain; and (2) to examine the association between knee pain at baseline and incident multimorbidity. The prevalence of knee pain was examined in the previous cross-sectional study using a validated question and was found to be higher in footballers than in controls. Two cross-sectional studies undertaken in the same population (footballers and controls) at two time points made it possible to examine the incidence of new knee pain over 6 years using a body mannequin, as well as the associated risk factors.

Hypothesis

Footballers are more likely to develop knee pain than the general population.

4.1 Results

4.1.1 Eligible population for knee pain

Of 486 footballers, and 619 controls returned and completed the questionnaire (see Figure 34, page 155). A total of 222 (45.6%) footballers and 402 (64.9%) controls without knee pain at baseline were eligible for the study of incident knee pain.

4.1.2 Study population for incident knee pain

Table 19 shows the characteristics of the study population. At baseline, the mean age of footballers was younger (58.2 ± 10.7 years) than the controls (62.3 ± 9.3 years) ($p < 0.001$), and the mean BMI was higher in footballers (27.0 ± 2.7 kg/m²) than controls (26.3 ± 3.6 kg/m²) ($p = 0.006$). Footballers had a higher prevalence of knee injury compared to controls (56.0% versus 24.3%, respectively) ($p < 0.001$), consumed more analgesics than controls (21.2% versus 11.9%, respectively) ($p = 0.002$) and had a higher prevalence of physician-diagnosed knee OA than controls (25.8% versus 5.0%, respectively) ($p < 0.001$). There was no difference between groups in prevalence of nodal OA or pattern 3 2D:4D finger ratio. Socioeconomic status was higher (more affluent) in the footballers (7.6 ± 2.2) than the controls (6.7 ± 2.9) ($p < 0.001$).

Table 19. Characteristics of the study populations at baseline for the incident knee pain study

	Footballers	Controls	p-value
Number of participants	222	402	
Age (years), mean (SD)	58.2 (10.7)	62.3 (9.3)	<0.001
BMI (kg/m ²), mean (SD)	27.0 (2.7)	26.3 (3.6)	0.006
Knee injury, n (%)	122 (56.0)	97 (24.3)	<0.001
Physician-diagnosed knee OA, n (%) #	23 (25.8)	20 (5.0)	<0.001
Nodal OA, n (%)	11 (5.0)	21 (5.4)	0.817
Pattern 3 2D:4D finger ratio, n (%)	137 (62.8)	245 (62.7)	0.964
Current use of analgesics, n (%)	47 (21.2)	48 (11.9)	0.002
Socioeconomic status, mean (SD)	7.6 (2.2)	6.8 (2.9)	<0.001

t-test was used for mean (SD), Chi² test used for frequency

Bold indicates a value of p<0.001 or p <0.05

BMI – body mass index; OA – osteoarthritis.

Current oral analgesics included non-steroidal anti-inflammatory drugs, opioids and over the counter painkillers.

Nodal OA was defined as present in those reporting nodes on at a least two rays of both hands.

Pattern 3 2D:4D finger ratio - index finger is shorter than the ring finger.

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to10, determined by post-code.

the percentage is after excluding the missing-value.

4.1.2.1 Incidence of knee pain

The incidence of knee pain in the 6 years was 24% (53/222) in footballers, and 28.8% (116/404) in the controls (p=0.180) (Table 20). Both groups had a similar

incidence of knee pain at the age 40-49 years at baseline. The incidence did not increase with age in footballers and controls (p for trend=0.449).

Table 20. Incidence of knee pain by age between 2014 and 2020

Age, years	Footballers			Controls			p-value
	Total	Incident cases	Incidence (%)	Total	Incident cases	Incidence (%)	
40-49	59	13	22.0%	45	10	22.2%	0.982
50-59	61	13	21.3%	92	33	36.0%	0.055
60-69	65	16	25.0%	171	45	26.3%	0.790
70-89	37	11	29.7%	94	28	29.8%	0.995
Total	222	53	24.0%	402	116	28.8%	0.180

*p <0.05

Multivariable logistic regression

The goodness of fit in the regression model for overall was non-significant indicating a good fit, and variance inflation factor (VIF) was around 1 indicating no multicollinearity between predictors (Appendix E). There was no significant difference in the risk of developing knee pain in footballers compared to controls (aOR 0.77, 95% CI 0.52 – 1.16; p=0.220) after adjustment for age, BMI, socioeconomic status and analgesic use (Table 21).

Table 21. Odds ratio of incident knee pain in footballers compared to controls

	OR (95% CI), p-value
Crude	0.77 (0.53 – 1.12), p=0.181
Adjusted for age	0.78 (0.53 – 1.15), p=0.227
Adjusted for age, BMI, socioeconomic status and analgesic use	0.77 (0.52 – 1.16), p=0.220

OR - odds ratio; CI - confidence interval; BMI - body mass index;

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to10, determined by post-code.

4.1.3 Risk factors for incident knee pain within groups

4.1.3.1 Characteristics between footballers with versus those without incident knee pain

During the 6 year follow-up period 53 footballers developed knee pain (cases), and 169 footballers did not develop knee pain (controls). This permitted a case control study to be undertaken within the footballers. Table 22 shows the characteristics of the study population. At baseline, both groups had similar mean age but the mean BMI was higher in cases (28.0 ± 3.0) than controls (26.7 ± 2.6) ($p=0.007$). There were no differences between the groups in terms of analgesic used, socioeconomic status, nodal OA, or pattern 3 2D:4D finger ratio, and no differences with respect to football-related factors including career duration, number of matches played, career training dose or position played. However, football-related knee injury was higher in cases (70.0%) than controls (51.5%) ($p=0.020$).

Table 22. Comparison between footballers with (cases) and without (controls) incident knee pain

	Cases	Controls	p-value
Number of participants	53	169	
Age (years), mean (SD)	59.0 (10.8)	57.9 (10.6)	0.509
BMI (kg/m ²), mean (SD)	27.8 (3.0)	26.7 (2.6)	0.007
Current use of analgesics, n (%)	11 (20.8)	36 (21.3)	0.932
Socioeconomic status, mean (SD)	7.6 (2.3)	7.6 (2.1)	0.820
Career duration, mean (SD)	14.2 (5.7)	14.2 (5.1)	0.971
Knee injury, n (%)	37 (69.8)	85 (51.5)	0.020
Nodal OA, n (%)	3 (23.1)	8 (19.5)	0.764
Pattern 3 2D:4D finger ratio, n (%)	30 (58.8)	107 (64.1)	0.497
Matches played, mean (SD)	483.15 (263.0)	474.91 (219.9)	
Career training dose (hours), n (%)			
< 1000	4 (7.8)	10 (5.9)	
1000-3999	7 (13.7)	15 (8.9)	
4000-6999	13 (25.5)	51 (30.2)	0.725
7000-9999	14 (26.4)	53 (31.4)	
>10,000	15 (28.3)	40 (23.7)	
Position played, n (%)			
Goalkeeper	7 (13.5)	12 (7.1)	
Outfielder	45 (86.5)	157 (92.9)	0.152

Bold indicates a value of p<0.001 or p <0.05. BMI – body mass index; OA – osteoarthritis.

Oral analgesics include non-steroidal anti-inflammatory drugs, over the counter painkillers and opioids.

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to10, determined by post-code

Career training dose was calculated by multiplying the number of hours played per week by 40 weeks (average season) by career duration.

4.1.3.2 Characteristics between controls with versus those without incident knee pain

During the 6 year follow-up period, 116 men in the general population developed knee pain (cases), and 286 men in the general population did not develop knee pain (controls). This permitted a case control study to be undertaken within the controls. Table 23 shows the characteristics of the study population. At baseline, both groups had similar mean age but the mean BMI was higher in cases (27.21 ± 4.0) than controls (25.93 ± 3.4) ($p < 0.001$). Cases reported higher knee injury compared to controls (31.0% versus 21.6%) ($p = 0.045$) and also had higher physician-diagnosed knee OA than controls ($p < 0.001$). There were no differences between the groups in terms of analgesic used, nodal OA and pattern 3 2D:4D finger ratio. However, cases had lower mean socioeconomic status compared to controls (6.02 versus 7.11) ($p < 0.001$).

Table 23. Characteristics of the study population for incident knee pain in the general population

	Cases	Controls	p-value
Number of participants	116	286	
Age (years), mean (SD)	62.46 (8.7)	62.28 (9.6)	0.430
BMI (kg/m ²), mean (SD)	27.21 (4.0)	25.93 (3.4)	<0.001
Knee injury, n (%)	36.0 (31.0)	61 (21.6)	0.045
Physician-diagnosed knee OA, n (%)	13 (11.2)	7 (2.4)	<0.001
Nodal OA, n (%)	8 (7.4)	13 (4.6)	0.281
Pattern 3 2D:4D finger ratio, n (%)	70 (62.5)	175 (62.7)	0.967
Current use of analgesics, n (%)	18 (15.5)	30 (10.5)	0.159
Socioeconomic status, mean (SD)	6.02 (2.9)	7.11 (2.8)	<0.001

Bold indicates a value of $p < 0.001$ or $p < 0.05$

BMI – body mass index; OA – osteoarthritis.

Current oral analgesics included non-steroidal anti-inflammatory drugs, opioids and over the counter painkillers.

Nodal OA was defined as present in those reporting nodes on at a least two rays of both hands.

2D:4D (pattern 3): index finger is shorter than the ring finger.

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to 10, determined by post-code.

4.1.3.3 Risk factors related to incident knee pain

Table 24 shows incident knee pain related risk factors per group over 6 years using multivariable logistic regression. The goodness of fit in the regression model for footballers and controls were non-significant indicating a good fit, and

VIF was around 1 indicating no multicollinearity between predictors (Appendix E). Within footballers, BMI was significantly associated with increased odds of incident knee pain (multivariable OR 1.17; 95% CI 1.04 – 1.31; $p=0.007$). Footballers who reported having football related-knee injury had significantly greater odds of incident knee pain compared to those without (multivariable OR 2.42, 95% CI 1.22 – 4.79; $p=0.011$). As there were no significant differences in the crude analysis for football related risk-factors (matches played, career length, position played and training dose) in those who developed knee pain compared to those who did not, no multivariable logistic regression was undertaken. Within the general population, BMI was also significantly associated with increased odds of incident knee pain (multivariable OR 1.08, 95% CI 1.01 – 1.14; $p=0.012$), whereas higher socioeconomic status reduced the risk of incident knee pain (multivariable OR 0.88, 95% CI 0.81 – 0.95; $p=0.002$). Validation of the result was examined using backward-stepwise regression showing similar result (Appendix E).

Table 24. Risk factors related to incident knee pain in footballers versus the general population

Exposures	Adjusted odds ratio (95% confidence interval)	
	Footballers	General population
Age, years	1.01 (0.98 – 1.04), p=0.469	1.01 (0.98 – 1.03), p=0.425
BMI, kg/m ²	1.17 (1.04 – 1.31), p=0.007	1.08 (1.01 – 1.14), p=0.012
Knee Injury, y/n	2.42 (1.22 – 4.79), p=0.011	1.74 (1.05 – 2.87), p=0.030
Socioeconomic status (1-10), decile	1.05 (0.90 – 1.23), p=0.465	0.88 (0.81 – 0.95), p=0.002

BMI – body mass index.

Bold indicates a value of Bonferroni adjusted p-value ≤ 0.012

Multivariable odds ratio, all variables are adjusted for each other.

y/n – yes/no

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to10, determined by post-code.

4.1.4 Knee pain and its association with incident multimorbidity

Table 25 shows the association between baseline knee pain and incident multimorbidity in footballers, in controls and overall in both groups combined.

The goodness of fit in the regression model for footballers and controls were non-significant indicating a good fit, and VIF was around 1 indicating no multicollinearity between predictors (Appendix E). The incidence of multimorbidity was higher in footballers with current knee pain at baseline compared to those without knee pain at baseline (44.3% versus 31.5%).

However, after adjusting for age, BMI, socioeconomic status, analgesic use and

having one condition at baseline, there was no significant association between baseline knee pain and multimorbidity incidence in footballers (aOR 1.34, 95% CI 0.78 – 2.30). Similarly, in the controls the incidence of multimorbidity was very similar in those with baseline knee pain compared to those without baseline knee pain (52.6% versus 53.1%), and there was no statistically significant difference after adjusting for the same confounding factors (aOR 0.86; 95% CI 0.49 – 1.50). Overall in both groups combined, the incidence of multimorbidity was 47.1% in individuals with baseline knee pain versus 44.6% in those without baseline knee pain and after adjusting for the confounding factors, there was no statistically significant difference (aOR 1.13, 95% CI 0.78 – 1.65; $p=0.506$) (Table 25).

Table 25. The association between baseline knee pain and incident multimorbidity between 2014-2020

	Footballers		Controls		Overall	
	n	multimorbidity (%)	n	multimorbidity (%)	n	multimorbidity (%)
Knee pain	149	66 (44.3)	76	40 (52.6)	225	106 (47.1)
No knee pain	168	53 (31.5)	256	136 (53.1)	424	189 (44.6)
Crude OR (95%CI)	1.72 (1.09 – 2.73), p=0.020		0.98 (0.58 – 1.64), p=0.940		1.34 (0.95 – 1.89), p=0.090	
aOR (95% CI)						
Model 1	1.68 (1.02 – 2.79), p=0.042		0.90 (0.52 – 1.55), p=0.717		1.31 (0.91 – 1.88), p=0.139	
Model 2	1.57 (0.94 – 2.65), p=0.085		0.91 (0.52 – 1.57), p=0.733		1.24 (0.86 – 1.78), p=0.250	
Model 3	1.34 (0.78 – 2.30), p=0.286		0.86 (0.49 – 1.50), p=0.595		1.13 (0.78 – 1.65), p=0.506	

OR - odd ratio; CI - 95% confidence interval. Bold indicates a value of p<0.001 or p <0.05

Model 1: adjusted for age, body mass index and socioeconomic status.

Model 2: adjusted for age, body mass index, socioeconomic status and analgesic use.

Model 3: adjusted for age, body mass index, socioeconomic status, analgesic use and having one condition at baseline.

Overall group analysis was adjusted for being a footballer in addition to the adjustments for model 1, 2 and 3.

4.2 Discussion

This study determined the incidence of knee pain and its related risk factors in male footballers compared to control men in the general population. The main findings were: (1) the incidence of knee pain was similar between footballers and controls; (2) whilst football-related knee injury and BMI were the major risk factors for incident knee pain in footballers, BMI was a major risk factor and higher socioeconomic status was a protective factor for incident knee pain in the controls; and (3) there was no association between knee pain and incidence of multimorbidity in footballers or controls.

4.2.1 Incidence of knee pain

The incidence of self-reported knee pain over 6 years was similar in footballers and controls (24.0% versus 28.8%, respectively). At baseline the male retired footballers were more likely than the general population to have knee pain (52.2% versus 26.9%) and knee OA (28.3% versus 12.2%), as fully reported by Fernandes et al. (2018). Similarly, the prevalence of knee pain at the “follow-up” using a body pain mannequin was calculated for the whole study population (468 footballers and 619 controls) and was found to be significantly higher in footballers compared to controls (52.6% versus 29.7%; $p < 0.001$). This might indicate that at age 40-60 muscle strength could mitigate knee pain in both footballers and controls, which might explain the large increase at age 70+ in both groups (see Table 20). Age-related sarcopenia commonly occurs at the

age of 45 years, with a large increase at an older age (Shafiee et al., 2017, Cruz-Jentoft and Sayer, 2019). Sarcopenia is age-related decline of skeletal muscle that involves progressive loss of muscle mass, strength and function (Cruz-Jentoft and Sayer, 2019). A recent systematic review and meta-analysis used pooled estimate and reported a higher prevalence of sarcopenia in those with knee OA than in control (OR 1.88, 95% CI 1.53 – 2.30; $I^2= 20\%$), with no association with demographic data (i.e., age, BMI and percentage of females) (Pegreffi et al., 2023). Other studies found a prevalence of knee pain in male retired footballers in Finland of 45% but without a comparison group (Kujala et al., 1995), while one study in Tunisia found that the prevalence of knee pain was lower in male retired footballers (15%) than controls (50%) using VAS to examine the knee pain and found this to range from 15-32 mm in retired footballers and from 25-55 mm in controls (Elleuch et al., 2008). However, all these studies were cross-sectional and not cohort studies so could only report prevalence of knee pain. The current study is the first cohort study to report incident knee pain in male retired footballers.

The incidence of knee pain in the controls (29.0%) differs from the findings of two previous general population studies in the Midlands region of England (Ingham et al., 2011a, Jinks et al., 2008). Ingham et al. (2011) reported a cumulative incidence of knee pain over 12 years of 34.4% in the general population ($n=2,156$) aged 40 years or more (32% in men and 35% in women). However, their follow-up was twice as long as in this study, included both men

and women, and knee pain was defined differently by a question asking about pain experienced around the knee for most days for at least a month during the 12 years follow-up (Ingham et al., 2011a). Jinks et al. (2008) found that the incidence of severe knee pain over 3 years was 7% in the general population (n=2,059, men and women) aged 50 years and older (Jinks et al., 2008). They defined severe knee pain as “presence of any pain or physical functioning limitation on the WOMAC recorded as severe or extreme, either severity of the pain or the presence of some related severe restriction in function or both”, and their follow-up period was half that of the present study (Jinks et al., 2008).

However, Miranda et al. (2002) reported a lower one year incidence rate for knee pain of 10% when men and women were combined in Finland, but they were relatively younger (< 35 to ≥ 55 years) compared to this study (Miranda et al., 2002). They defined knee pain differently using a modified version of the Nordic Questionnaire as “estimate the total number of days you have had knee pain during the preceding 12 months?”. In the questionnaire, knee pain was categorised into five groups as 0 days, 1-7 days, 8-30 days, >30 days but not daily, and daily. The first two categories were combined because some days with pain do not necessarily indicate a significant underlying disorder, and the last two categories were combined due to small number of subject experiencing daily pain (Miranda et al., 2002). The last two categories were used to represent people experiencing daily pain as the knee pain outcome. Moreover, another study reported an incidence of knee pain of 20% in 950 Australian older men

aged 70 years and older over a 2-years period (Fransen et al., 2014). They defined knee pain as “pain in or around wither knee on most days for at least one month in the past 12 months” (Fransen et al., 2014). This variation in incidence of knee pain was due to differences in study population, in the definition used to examine knee pain, and in the follow-up duration.

4.2.2 Risk factors related to incident knee pain

Football related-knee injury (aOR 2.42, 95% CI 1.22 – 4.79) and BMI (aOR 1.17, 95% CI 1.04 – 1.31) were significantly associated with incident knee pain over 6 years in footballers. This is not surprising, as injury is an established risk factor for knee OA and knee pain. Previous studies have found that prior knee injury is a risk factors for knee pain, knee OA and total knee replacement in male retired footballers (Parekh et al., 2021, Gouttebarga et al., 2018a, Merčun et al., 2023). The number of knee injuries were independent risk factors for the increase in risk for each of these outcomes in the study by Parekh et al. (2021). However, all these studies were cross-sectional and not cohort studies. This is the only study to examine risk factors for incident knee pain in male retired footballers. Several physiological, molecular and anatomical factors contribute to post-traumatic joint injury (Kramer et al., 2011). The impacts of joint trauma include structural damage to joint tissues, suppression of collagen and proteoglycan synthesis in articular cartilage, haemarthrosis (bleeding into the joint cavity) and death of articular chondrocytes (Szczodry et al., 2009). All these may contribute

to metabolic changes in articular cartilage and may slowly progress and result in a symptomatic phase as joint pain or dysfunction (Kramer et al., 2011).

BMI is also recognised as a significant risk factor for knee pain in the general population (Cooper et al., 2000, Jinks et al., 2008, Sarmanova et al., 2018).

Another KPIC study conducted by Sarmanova and colleagues found that BMI was a risk for both incident knee pain (aOR 1.06, 95% CI 1.03 – 1.09) and knee pain worsening (aOR 1.05, 95% CI 1.04 – 1.07) in people aged ≥ 40 years after adjustment for age and gender over one year follow-up using a questionnaire (Sarmanova et al., 2018). A 12-years retrospective cohort study in 2,156 people found that BMI was significantly associated with incident knee pain, and being overweight increased the risk to 1.33 (aHR 1.33, 95% CI 1.12 – 1.57) after adjustment for age, gender and other confounding factors, and being obese almost doubled the risk (aHR 1.80, 95% CI 1.37 – 2.38) compared to those with normal BMI (Ingham, 2010). Moreover, the previous prospective studies involving questionnaires or interviews in people aged 50 years or older have all demonstrated that higher BMI was significantly associated with incident knee pain with follow-up ranging from one to three years (Cooper et al., 2000, Jinks et al., 2008, Miranda et al., 2002). All studies that involved the general population have highlighted that BMI is a significant risk factor for incident knee pain despite the variation in participant characteristics, duration of follow-up and the assessments used.

This study found that higher socioeconomic status was a protective factor for incident knee pain, but only in controls. Healthier lifestyle choices such as nutrition and exercise are often assumed to be easier to access with higher income levels (Haws et al., 2017, Estabrooks et al., 2003). Previous studies have reported that lower socioeconomic status was associated with the painful knee OA and total knee replacement not incident knee pain (Kiadaliri et al., 2017, Feldman et al., 2015). Among these studies, one cross-sectional study in Swedish men and women aged between 44 and 74 years determined the association of frequent knee pain and knee OA with the participants occupation and level of education as socioeconomic measures (Kiadaliri et al., 2017). Frequent knee pain was defined as pain with duration $\geq$ one month in one or both knees in the past 12 months. Knee OA was defined radiographically using K-L criteria grade 2 and clinically using the ACR criteria. It was found that relative index of inequality (RII) for education and occupation after adjustment for smoking and BMI were associated with frequent knee pain and knee OA when men and women were combined. Results involving men only showed that the RII for both education 0.67 (95% CI 0.50 – 0.89) and occupation 0.75 (95% CI 0.57 – 0.99) showed significant association with frequent knee pain, after adjustment for BMI and smoking, which means that higher socioeconomic status is protective (Kiadaliri et al., 2017). Another cohort study between 2010 and 2013 in the US focused on TKR in participants with a mean age of 66 years, of whom 59% were female (Feldman et al., 2015). Pain and function were assessed using the WOMAC. After adjustment for age, gender and BMI, the

study found that people with higher educational attainment and higher socioeconomic status had lower pain and better function at the time of TKR than those with low educational attainment and lower socioeconomic status ($p < 0.05$) (Feldman et al., 2015).

4.2.3 Knee pain and its association with incident multimorbidity

This study found no association between baseline knee pain and incidence of multimorbidity in footballers or in controls. No previous studies have examined this association in footballers or in the general population. Knee pain alone is common in middle-aged to older adults as are other long-term conditions (Kuan et al., 2019). Previous cross-sectional studies have suggested that knee pain is a common component of multimorbidity (Swain et al., 2022, McQueenie et al., 2021, Milani et al., 2022). Among these studies, only one examined the association between people with knee pain (including men and women) aged ≥ 40 years in the UK, and found that people with knee pain were more likely to have multimorbidity (aOR 1.35, 95% CI 1.17 – 1.56) (Swain et al., 2022). Other studies have focused on the prevalence of multimorbidity and the risk for knee pain, for example, the odds of reporting knee pain while walking or standing increased two-fold in people with multimorbidity compared to those without (Milani et al., 2022). Moreover, another study examined the relationship between the presence of chronic pain including knee pain, and the number of long-term conditions experienced. It was found that as the number of long-term conditions increased so did the risk of chronic pain, after adjustment for

covariates (McQueenie et al., 2021). Although the current study found no association between knee pain and incident multimorbidity, this may have resulted from the definition of knee pain, a type 2 error due to the small sample size, and the relatively short follow-up period of 6 years as knee pain and multimorbidity have a positive relationship with increasing age. Further larger and longer studies are warranted.

4.2.4 Limitations

There are several limitations to the current study. First, because of the recall bias inherent in a self-reported questionnaire, the responses to questions on health conditions and medication use might have been misreported. Second, the sample size is relatively small. Although an 85% power was considered for incident knee pain with multiple correlation co-efficients, a larger study with higher power is still warranted to confirm the findings. Third, knee pain was self-reported and defined as pain for most days in the past month using a body mannequin. Although having self-reported anterior knee pain using a body mannequin in people of middle-to-older age is most likely to result from knee OA (Ingham et al., 2011a), a more robust definition, including a full clinical assessment and radiographic examination would help to identify the cause of knee pain. Fourth, the follow-up period was only 6 years which may not be sufficient to identify any difference between groups in the incidence of knee pain. Furthermore, post-retirement occupations of the footballers were unknown,

which could have an impact on the incident of knee pain and associated risk factors.

4.2.5 Conclusion

In conclusion, the incidence of knee pain over 6 years did not differ significantly between footballers and controls. Baseline knee pain did not predict the incidence of multimorbidity but higher BMI was a risk factor in both groups. However, football-related injury was a risk factor in footballers and higher socioeconomic status was a protective factor in controls. Although the findings have certain caveats, they support the need for strategies to improve injury prevention and to maintain normal BMI to reduce the onset of knee pain in footballers. Future larger and longer studies involving male and female footballers using a validated assessment for knee pain are still required to confirm and to extend these findings.

Chapter 5 Results and discussion of the longitudinal cohort study

examining incident multimorbidity and its related risk factors in male retired professional footballers compared to men in the general population

5.1 Introduction

This chapter presents the results and discussion for the fourth objective for this thesis, which was to examine the incidence of multimorbidity and associated risk factors within each group. The initial systematic review (Chapter 2) confirmed that no previous study had examined multimorbidity in professional footballers. Therefore, this study aimed to fill that gap.

Hypothesis

The hypothesis being tested was that footballers may be less likely to have multimorbidity than the general population.

5.2 Results

5.2.1 Eligible population for multimorbidity

Among 486 footballers and 619 controls who returned the follow-up questionnaire (see Figure 34, page 155), 317 (65.2%) footballers and 362 (58.5%) controls were at risk for multimorbidity (i.e., with ≤ 1 condition at baseline) who were eligible for this study.

5.2.2 Study population for incident multimorbidity

Table 26 shows the characteristics of the study population. At baseline, the footballers were younger (mean 56.6±10.3 years) than the controls (mean 60.1±9.4 years) ($p<0.001$) and had higher BMI than controls ($p=0.002$).

Consumption of analgesics was more common in footballers than controls (19.0% versus 12.2%, respectively) ($p=0.014$). Footballers had higher socioeconomic status than the controls ($p<0.001$).

Table 26. Characteristics of study population having no or just one condition at baseline

	Footballers	Controls	p-value
Number of participants	317	362	
Age (years), mean (SD)	56.6 (10.3)	60.1 (9.4)	<0.001
BMI (kg/m ²), mean (SD)	26.8 (2.6)	26.1 (3.3)	0.002
Having one condition at baseline, n (%)	135 (42.6)	176 (48.6)	0.116
Current use of analgesics, n (%)	60 (19.0)	44 (12.2)	0.014
Socioeconomic status, mean (SD)	7.6 (2.1)	6.6 (2.9)	<0.001

Bold indicates a value of $p<0.001$ or $p<0.05$

BMI – body mass index

Current use of oral analgesics included non-steroidal anti-inflammatory drugs, over the counter painkillers and opioids.

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to 10, determined by post-code.

5.2.2.1 Incidence of Multimorbidity

Overall, 119 (37.5%) of footballers and 188 (52.0%) of controls developed multimorbidity during the 6 year follow-up period ($p < 0.001$) (Table 27). The incidence increased with age in both groups. The difference between footballers and controls was most notable in the 50-59 age band at baseline ($p = 0.040$) (Table 27). The incidence tended to increase with age both in footballers and controls (p for trend < 0.001).

Table 27. Incidence of multimorbidity by age between 2014 and 2020

Age, years	Footballers			Controls			p-value
	Total	Incident cases	Incidence (%)	Total	Incident cases	Incidence (%)	
40-49	90	24	26.7%	56	17	30.4%	0.629
50-59	110	36	32.7%	108	50	46.3%	0.040
60-69	75	32	42.7%	141	80	56.7%	0.049
70-89	42	27	64.3%	57	41	71.9%	0.418
Total	317	119	37.5%	362	188	52.0%	<0.001

Bold indicates a value of $p < 0.001$ or $p < 0.05$

Chi² test was used

Multivariable logistic regression

The goodness of fit in the regression model when combined was non-significant indicating a good fit, and the VIF was around 1 indicating no multicollinearity

between predictors (Appendix F). The odds of developing multimorbidity was significantly lower in the footballers compared to the controls (OR 0.55, 95% CI 0.41 – 0.75; $p<0.001$) (Table 28). The odds remained significant after the adjustment for age, BMI and other confounding factors (aOR 0.64, 95% CI 0.45 - 0.89; $p=0.009$) (Table 28).

Table 28. Odds ratio of multimorbidity in footballers compared to controls

	OR (95% CI), p-value
Crude OR	0.55 (0.41 - 0.75), $p<0.001$
OR adjusted for age	0.65 (0.47 - 0.89), $p=0.008$
Adjusted for age, BMI, socioeconomic status and analgesic use	0.64 (0.45 - 0.89), $p=0.009$

Bold indicates a value of $p<0.001$ or $p<0.05$

OR - odds ratio; CI - confidence interval; BMI: body mass index.

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to 10, determined by post-code.

5.2.2.2 Incidence of specific groups of conditions

Musculoskeletal conditions and cardiovascular diseases were the two most common conditions to develop during 2014 to 2020 in both footballers and controls, whereas renal diseases and infection were the least common conditions to develop in both groups (Figure 39). Two groups of conditions studied showed a significantly lower incidence in footballers compared to controls, specifically hearing loss (8.0% versus 17.0%, $p<0.001$; aOR 0.43, 95% CI 0.25 – 0.73, $p=0.002$) and anxiety/depression (6.4% versus 14.0%, $p=0.002$;

aOR 0.39, 95% CI 0.22 – 0.70, p=0.002). Details of the incidence of specific conditions are shown in Appendix G. The goodness of fit in the regression model when combined was non-significant indicating a good fit except for incidence of kidney and cancer conditions, and VIF for all 13 long-term conditions was around 1 indicating no multicollinearity between predictors (Appendix F).

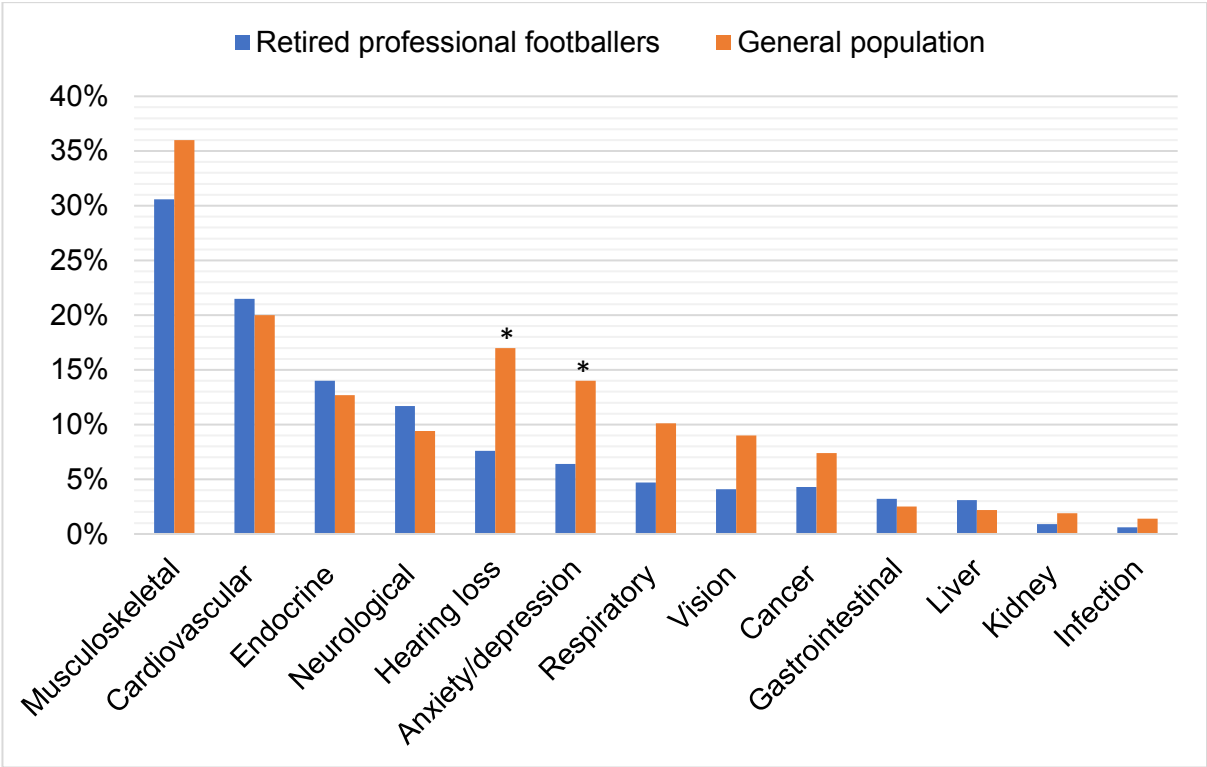


Figure 39. Incidence of specific groups of conditions in footballers and controls between 2014-2020. * Bonferroni adjusted p-value ≤ 0.0038

5.2.3 Risk factors for incident multimorbidity within group

5.2.3.1 Characteristics of footballers with versus those without incident multimorbidity

During 2014-2020, a total of 119 footballers developed multimorbidity (cases), and 198 footballers did not develop this outcome (controls). Table 29 shows the characteristics of the study population. At baseline, the mean age of the cases was older (60.3 ± 10.9 years) than the controls (54.4 ± 9.2 years) ($p < 0.001$), but there was no difference in their BMI. Footballers with multimorbidity (cases) had a higher prevalence of one self-reported condition at baseline than controls (63.9% versus 29.8%) ($p < 0.001$). Similarly, cases more commonly used oral analgesics compared to controls (31.4% versus 11.6%) ($p < 0.001$).

Table 29. Comparison between footballers with and without incident multimorbidity

	Cases	Controls	p-value
Number of participants	119	198	
Age (years), mean (SD)	60.3 (10.9)	54.4 (9.2)	<0.001
BMI (kg/m ²), mean (SD)	27.0 (2.5)	26.6 (2.6)	0.240
Having one condition at baseline, n (%)	76 (63.9)	59 (29.8)	<0.001
Current use of analgesics, n (%)	37 (31.4)	23 (11.6)	<0.001
Socioeconomic status, mean (SD)	7.4 (2.2)	7.7 (2.1)	0.226
Career duration, mean (SD)	13.4 (5.6)	13.5 (5.7)	0.916
Matches played, mean (SD)	464.9 (272.4)	456.3 (238.2)	0.776
Career training dose (hours), n (%)			
< 1000	8 (6.7)	11 (5.6)	
1000-3999	16 (13.4)	35 (17.7)	
4000-6999	30 (25.2)	59 (29.8)	0.294
7000-9999	43 (36.1)	50 (25.3)	
>10,000	22 (18.5)	43 (21.7)	
Position, n (%)			
Goalkeeper	12 (10.1)	18 (9.1)	0.770
Outfielder	107 (89.9)	180 (90.9)	

Bold indicates a value of p<0.001 or p <0.05

Oral analgesics include non-steroidal anti-inflammatory drugs, over the counter painkillers and opioids.

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to10, determined by post-code.

Career training dose was calculated by multiplying the number of hours played per week by 40 weeks (average season) by career duration.

5.2.3.2 Characteristics of controls with versus those without incident multimorbidity

During the 6 year follow-up period, 188 men in the general population developed multimorbidity (cases), and 174 men in the general population did not develop multimorbidity (controls). Table 30 shows the characteristics of the study population. At baseline, the mean age in cases (62.31 ± 8.8) was higher than controls (57.66 ± 9.4) ($p < 0.001$) but the mean BMI was similar. Cases had a higher prevalence of one condition at baseline than controls (61.7% versus 34.5%) ($p < 0.001$). Socioeconomic status was lower in cases than controls (6.30 versus 7.02) ($p < 0.019$).

Table 30. Comparison between the general population with and those without incident multimorbidity

	Cases	Controls	p-value
n	188	174	
Age (years), mean (SD)	62.31 (8.8)	57.66 (9.4)	<0.001
BMI (kg/m ²), mean (SD)	26.28 (3.4)	25.88 (3.2)	0.262
Having one condition at baseline, n (%)	116 (61.7)	60 (34.5)	<0.001
Current use of analgesics, n (%)	25 (13.3)	19 (10.9)	0.489
Socioeconomic status, mean (SD)	6.30 (2.9)	7.02 (2.8)	<0.019

Bold indicates a value of p<0.001 or p <0.05

BMI – body mass index

Current oral analgesics included non-steroidal anti-inflammatory drugs, over the counter painkillers and opioids.

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to10, determined by post-code.

5.2.3.3 Risk factors related to incident multimorbidity

Table 31 shows the risk factors for incident multimorbidity in footballers versus the general population using multivariable logistic regression. The goodness of fit in the regression model for footballers and controls were non-significant indicating a good fit, and the VIF was around 1 indicating no multicollinearity between predictors (Appendix F). Within footballers, age was significantly associated with incident multimorbidity (aOR 1.04, 95% CI 1.01 – 1.07;

$p < 0.001$). The odds increased to three-times greater for those who reported having one condition at baseline compared to those without (aOR 2.98, 95% CI 1.78 – 4.99; $p < 0.001$). Analgesic use also significantly increased the odds of incident multimorbidity to almost three times greater (aOR 2.88, 95% CI 1.53 – 5.40; $p = 0.001$). As there were no significant differences in football related risk-factors (matches played, career length, position played, training dose) in those who developed multimorbidity compared to those who did not in the univariate analysis no multivariable logistic regression was undertaken. Within the general population, using multivariable logistic regression, age was significantly associated with multimorbidity incidence (aOR 1.05, 95% CI 1.03 – 1.08; $p < 0.001$). The odds increased to almost three-times greater for those who reported having one condition at baseline compared to those without (aOR 2.73, 95% CI 1.73 – 4.31; $p < 0.001$). Higher socioeconomic status was a protective factor against the risk of incident multimorbidity (aOR 0.88, 95% CI 0.81 – 0.95; $p = 0.003$). Validation of the result was examined using backward-stepwise regression showing similar result (Appendix F).

Table 31. Risk factors related to incident multimorbidity in the footballers and the general population

Exposures	Adjusted odds ratio (95% confidence interval)	
	Footballers	General population
Age, years	1.04 (1.01 – 1.07), p<0.001	1.05 (1.03 – 1.08), p<0.001
BMI, kg/m ²	1.07 (0.97 – 1.18), p=0.170	1.04 (0.97 – 1.11), p=0.260
Current use of analgesics, y/n	2.88 (1.53 – 5.40), p<0.001	0.69 (0.33 – 1.43), p=0.328
Having one condition at baseline, y/n	2.98 (1.78 – 4.99), p<0.001	2.73 (1.73 – 4.31), p<0.001
Socioeconomic status, (1-10)	0.93 (0.83 – 1.05), p=0.277	0.88 (0.81 – 0.95), p=0.003

BMI - body mass index.

Bold indicates a value of Bonferroni adjusted p-value $\leq 0.05/4 = 0.012$

Multivariable logistic regression where all variables are adjusted for each other.

y/n – yes/no

5.3 Discussion

To the best of our knowledge, this is the first cohort study to compare the incidence of multimorbidity between footballers and the general population. The main findings were: (1) the incidence of multimorbidity was lower in footballers than controls in the 6 year follow-up; (2) the incidence of anxiety/depression and hearing loss were both lower in footballers than in the controls; (3) within footballers, age, having one condition at baseline, and analgesic use were independent risk factors for incident multimorbidity, whereas within the general population group, age and having one condition at baseline independently associated with development of incident multimorbidity, whereas higher socioeconomic status was a protective factor against incident multimorbidity.

5.3.1 Incidence of multimorbidity

The incidence of multimorbidity was lower in footballers (37.5%) than in controls (52.0%) ($p < 0.001$). No previous study has determined the incidence of multimorbidity in retired footballers or in other professional athletes. A previous systematic review reported that the incidence of multimorbidity in the general population ranged from 1.3% to 61.0% for those with ≤ 1 condition at baseline (Kudesia et al., 2021). This wide variation is likely to be due to involvement of different study populations with varying demographic characteristics including males and/or females, ethnicity, aged >45 years, number of conditions examined, and length of follow-up (2 to 22 years). However, our incidence in general population control men was higher (52%) than the findings of a previous

Australian general population study which reported an incidence of 23.7% over 9 years in a total of 53,867 people aged 45-64 years, of whom 56.5% were females (Shang et al., 2020). This may be because that study included people who were free of 10 conditions at baseline including diabetes, asthma, hypertension, cancer (excluded non-melanoma skin cancer), mental disorders (depression and anxiety), cardiovascular diseases (heart disease, stroke), neurodegenerative disorders (dementia and Parkinson's disease), hip replacement and OA and dyslipidaemia. As these conditions were more likely to be clustered with other conditions, the current study, in contrast, included only those with ≤ 1 condition at baseline presenting in both study populations (footballers and controls).

The findings of this study showed that being a footballer reduced the likelihood of developing multimorbidity over 6 years (aOR 0.64, 95% CI 0.45 – 0.89). This difference might be associated with the beneficial effects of regular exercise and socioeconomic wellbeing on both physical and mental health (Runacres et al., 2021), leading to footballers being generally fitter and healthier.

5.3.2 Incidence of specific groups of medical conditions

This study found that footballers had a similar distribution of incident long-term conditions as the general population controls, with musculoskeletal (31.0% versus 36.0%) and cardiovascular (21.4% versus 20.0%), respectively, being the most common in both groups. This differs from a previous Australian study

that included adults aged 45-64 years, of whom 56.5% were females, over 9-years follow-up (Shang et al., 2020). It was found that having cardiometabolic conditions accounts 30.4% and musculoskeletal was 15.2% were common out of six groups of conditions included (Shang et al., 2020). This may be because the authors included just two conditions (OA and hip replacement) for musculoskeletal conditions, and four conditions (cardiovascular diseases, diabetes, hypertension and dyslipidemia) for cardiometabolic disorders in men and women. However, the current study included ten conditions within the for musculoskeletal group and seven conditions within the cardiovascular group and the study involved only men. Although there were differences in the findings of Shang et al and the current study, both cardiovascular and musculoskeletal conditions were the most common chronic conditions observed.

The incidence of anxiety/depression was significantly lower in footballers (6.4%) than in the controls (14.0%) ($p= 0.002$). This may be explained by the generally better health status (i.e., less multimorbidity) and socioeconomic wellbeing in footballers than controls. Earlier studies in retired footballers have reported variation in the prevalence, but not incidence, of depression and anxiety (Fernandes et al., 2019, Sanders and Stevinson, 2017, Gouttebarga et al., 2015a). Among these studies, there was no difference in the prevalence of anxiety and depression between UK male retired footballers and controls using the Hospital Anxiety and Depression Scale (Fernandes et al., 2019). Gouttebarga et al. (2015) reported on the prevalence of mental health problems

descriptively in current and former professional footballers without a comparison group and found it to be high. They included current and retired footballers from six countries, specifically Australia, Ireland, the Netherlands, New Zealand, Scotland and the USA. The definitions of mental health complaints included burnout, anxiety/depression, low self-esteem and adverse nutrition behavior (Gouttebarga et al., 2015a). Sanders and Stevinson (2017) determined depression symptoms using the Short Depression-Happiness Scale and its association with chronic pain and career-ending injury and found that career-ending injury was strongly correlated with an increased likelihood of depression symptoms after retirement (Sanders and Stevinson, 2017). However, variations in the prevalence obtained by these previously published studies in terms of demographic features, presence of comparison group(s) and assessment used means that it is difficult to draw clear conclusions.

One Swedish cohort study with a median follow-up period of 18.5 years involving 1,548 male footballers and 11,674 controls reported that footballers had a lower incidence of diagnosis of depression and anxiety compared to controls (11.4% versus 20.6%, respectively) with an aHR of 0.72 (95% CI 0.61 – 0.84) after adjustment for age, BMI, cognitive ability score, stress resilience, muscle strength score and cardiorespiratory exercise capacity score (Kader et al., 2024). This protective association was reduced with increasing age, and above approximately 70 years of age the risk was similar in footballers and controls (Kader et al., 2024). However, the study included footballers who

played at least one game in the Swedish top division, and whether the number of matches played had an impact is not clear. It is also not clear whether the footballers' work status (active versus retired) had an impact on the outcome.

In the current study, the general population controls had a 14.0% incidence of anxiety/depression over 6 years. Previous studies have reported an incidence of depression ranging from 6.6% – 8.4% with a follow-up period from two to four years (Harris et al., 2006, Meng et al., 2017). These studies included both genders and used different criteria to assess depression such as the 15-item Geriatric Depression Scale and The World Mental Health-Composite International Diagnostic Interview (Harris et al., 2006, Meng et al., 2017). Previous studies reported an incidence of anxiety ranging from 4.95% - 51.3% with a follow-up period ranging from three to fourteen years (de Graaf et al., 2013, Welzel et al., 2021). However, these studies were either retrospective, which is prone to recall bias, or reported results only for older age groups in both genders (de Graaf et al., 2013, Welzel et al., 2021). Nevertheless, differences in the demographics of the population, the diagnostic criteria and length of follow-up probably play an important role in the marked variation of each outcome compared to the current study.

The incidence of hearing loss was lower in footballers (8.0%) than in controls (17.0%) ($p=0.002$). This is the only study to examine the incidence of hearing loss in male retired footballers. With ageing, deterioration in hearing commonly

occurs as a result of systemic inflammation that damages capillaries and cells in the auditory system (Kociszewska and Vlajkovic, 2022). Numerous studies have suggested that hearing impairment independently associates with greater disability and limitations in activities of daily living in adults aged 70 years and older (Chen et al., 2014, Gispén et al., 2014, Mikkola et al., 2015). The incidence of hearing loss of 17% in the controls over 6 years is almost identical to the 17.9% incidence in Australia over 5 years reported by Mitchell et al. (2011). They used a questionnaire, physical examination and audiological examination and found hearing loss to be more common in those aged > 60 years and similar in both sexes (Mitchell et al., 2011). In contrast, the incidence of hearing loss in controls was lower than previous studies in the UK, Northern Finland and US, which reported an incidence ranging from 21.0% to 61.0% with follow-up periods from 7 to 13 years (Lassale et al., 2020, Lohi et al., 2021, Cruickshanks et al., 2003). These studies highlighted that the incidence of hearing loss was associated with age and was more common in males than females.

5.3.3 Risk factors related to incident multimorbidity

This is the only study to determine the risk factors related to incident multimorbidity in male retired footballers. Age was a risk factor for incident multimorbidity in both groups. This could be explained by the ageing process as most chronic conditions are age related. This has an impact on reducing functional and physical health, which later results in greater complications such

as immobility, falls and disability (Fried et al., 2004, Barnett et al., 2012). The current study supports previously reported studies on the association between age and incident multimorbidity in the general population. According to Van den Akker et al. (1998) in the Netherlands, those aged 40 years and older were more likely to develop multimorbidity incidence over one year. It was also highlighted that the risk of multimorbidity increased to 8-fold in people aged ≥ 80 years compared to those aged 25-39 years (Van den Akker et al., 1998). Another Australian cohort study demonstrated the relationship between different age bands and different degrees of multimorbidity with a follow-up of 9 years (Shang et al., 2020). It was found that men in the 55-65 year age band were twice as likely to develop incident multimorbidity (having 2 conditions), tertiary comorbidity and quaternary comorbidity compared to younger men in the 45-54 year age band (Shang et al., 2020). Furthermore, another retrospective cohort in the UK using a primary care database reported that age is significantly associated with increased the risk of having multimorbidity (aOR 1.78, 95% CI 1.76 – 1.81) after adjustment for sex and deprivation (Salisbury et al., 2011). Although there were differences in these studies of the general population in terms of participant demographic features, length of follow-up and assessments used, all have confirmed that age is an established strong risk factor for multimorbidity.

Having one condition at baseline was significantly associated with incident multimorbidity in both footballer and control groups. Although this study did not

categorise the baseline condition as a physical or mental health condition, some diseases can magnify the risk of others (Prince et al., 2007). This could be explained by the type of multimorbidity being associative or random.

“Associative” defines conditions that share a similar pathophysiology or risk factor, whereas “random” is used when there are no known shared pathophysiology or risk factors (Lappenschaar et al., 2012). The results of this study agreed with previous studies of the general population. For example, one study in Sweden reported that the risk of developing multimorbidity was significantly higher in men and women who had one disease and being older (OR 1.09, 95% CI 1.01 – 1.17; $p < 0.05$) over 3 years follow-up (Melis et al., 2014). Other cohort studies in the Netherlands and Australia have found that having two conditions at baseline increased the risk of developing subsequent conditions compared to those with ≤ 1 condition at baseline in people aged 40 years and older with follow-up periods ranging from one to nine years (Van den Akker et al., 1998, Shang et al., 2020).

Current analgesic use, including prescribed NSAIDs and opioids and over the counter paracetamol or NSAIDs, was significantly associated with incident multimorbidity only in footballers (aOR 2.88, 95% CI 1.53 – 5.40). This might suggest that footballers consumed more analgesics because of musculoskeletal pain (Leyk et al., 2023, Fernandes et al., 2019). Oral NSAIDs reduce prostaglandin synthesis through inhibition of cyclo-oxygenase 1 and 2 and this may increase the risk of cardiovascular, renal, central nervous system,

gastrointestinal and other conditions (Varga et al., 2017). Paracetamol also has cyclo-oxygenase inhibitory effects and associates with a similar profile of side-effects, though with a lower incidence, as NSAIDs, including cardiovascular, gastrointestinal, renal and hepatic side-effects (Hinz and Brune, 2012, Sharma and Mehta, 2014, Hyllested et al., 2002). Opioids mediate both the ascending and descending pain pathways (Shenoy and Lui, 2023). Their long-term side effects might include significant impact on cardiovascular, gastrointestinal, respiratory and endocrine systems (Kotlińska-Lemieszek and Żylicz, 2022, Chou et al., 2015). A community-based study in the UK reported a significant association in people with knee pain between prescription of analgesics (i.e., paracetamol, opioids and NSAIDs) and occurrence of comorbidities including musculoskeletal, neurological, psychological, respiratory, chronic widespread pain, and cardiovascular, and the use of paracetamol and opioids interacted positively for the association with multimorbidity (Swain et al., 2022).

Higher socioeconomic status was only a protective factor for incident multimorbidity in the general population. It is commonly believed that lifestyle factors mediate the relationship between socioeconomic status and health, and that healthy lifestyle might reduce the health inequities caused by socioeconomic deprivation (Phelan and Link, 2005). The finding of the current study aligns with the previously reported associations between socioeconomic deprivation and incident multimorbidity in the general population (Bisquera et al., 2022, Head et al., 2021). For example, in the UK retrospective cohort included

including men and women aged 18 to over 80 years (n=826,936) with follow-up of 4.2 years, found that the lower index of multiple deprivation was significantly associated with increased the risk for incident multimorbidity compared to people with higher index of multiple deprivation (aHR 1.46, 95% CI 1.30 – 1.64) after adjustment for age (Bisquera et al., 2022). Another British cohort study reported that having the highest deprivation was significantly associated with an increased incidence of multimorbidity compared to having the least deprivation (aRR 1.22, 1.19 – 1.24) after adjustment for age group, gender and region over 7.3 years (Head et al., 2021). According to a UK CPRD study involving 141,535 men and 141,352 women aged 30 years and older, those with one condition were at risk for multimorbidity but this risk was increased especially in those who were most deprived compared to those least deprived (aRR 1.57, 95% CI 1.51 – 1.63) after adjustment for age and gender (Charlton et al., 2013).

5.3.4 Limitations

There are several limitations to this study. First, it was based on self-reported questionnaires, therefore it is prone to inherent recall bias and might result in under- or over-estimation of exposures, health conditions and analgesic use. Second, the sample size is relatively small. Although a 95% power was considered for incident multimorbidity with multiple correlation co-efficients, a sufficiently powered study with a larger sample size is still warranted to confirm the findings. Third, although there is no universally accepted list of conditions to be included to define multimorbidity, we derived all conditions that are

appropriate to UK adults. An accepted standardised definition would be helpful to allow comparisons between studies despite the regional and demographic characteristics of the population. Fourth, the follow-up period of 6 years was relatively short, which might affect the incidence of multimorbidity which strongly associates with ageing, and longer studies of retired footballers are warranted. Fifth, other risk factors related to multimorbidity such as smoking or alcohol consumption were not possible to include in the analysis because they were not available in the baseline questionnaire (they were only available in the follow-up survey). Sixth, because of the small sample size it was not possible to classify the risk for specific multimorbidity patterns. Future larger and longer studies involving male and female footballers in other countries, both during and following their career period, and including more detailed in-depth assessments, are still required. Seventh, selection for controls were from 12 Nottinghamshire general practices, and having a broader randomly selected community population could be more representative of the UK general population. Furthermore, genetic risk profiles for long-term conditions might have an impact on the results of the incidence of multimorbidity and associated risk factors, and future studies that contain genetic information on participants would be of interest. Finally, it was unclear which job retired footballers may have had after their retirement from football, which could have had an impact on the incidence of knee pain and associated risk factors and the association between knee pain and incident multimorbidity.

5.3.5 Conclusion

In conclusion, the incidence of multimorbidity was lower in male retired footballers compared to men in the general population. Age and having one condition at baseline were risk factors for incident multimorbidity in both groups. However, current analgesic use was a risk factor only in retired footballers, and socioeconomic status was a protective factor only in controls. Future larger and longer studies including both male and female players and general population controls are still required to confirm the findings.

Chapter 6 Association between radiographic knee and foot/ankle osteoarthritis in male retired professional footballers and men in the general population: an observational study

6.1 Introduction

This chapter presents the methods, results and discussion of the final objective for the thesis concerning the possible association between radiographic OA at the knee and the foot/ankle joints. I had the opportunity of studying this in participants who had taken part in two sequential cross-sectional studies that showed an increased risk of OA of the knee and foot/ankle in footballers compared to controls, based on radiographic assessment at both sites.

Hypothesis

The hypothesis being tested was that people with one knee OA are more likely to develop foot/ankle OA (genetic risk), and being footballer (environmental risk) may alter the association.

6.2 Methods

6.2.1 Study design

This study was conducted in the same study populations of male footballers and general population controls and those who had been assessed by questionnaire and radiographs at both baseline and follow-up were eligible for inclusion in this sub-study.

Knee radiographs, which were scored for OA, were undertaken in 2015/16 in a sample of the footballers and controls who had completed the knee study questionnaire. Foot and ankle radiographs which were scored for OA were undertaken in 2021/23 in a sample of the footballers and controls who had completed the FOCUS questionnaire.

The current study aimed to utilise data obtained in the footballers and controls who had undergone both knee and ankle/foot radiographs at different time points in the two previous studies to examine: [1] the association of radiographic OA at the knee and foot/ankle in footballers compared to controls; [2] the interaction between being a footballer and knee OA for the risk of developing foot/ankle OA; and [3] the association between summated scores of OP and JSN in knee OA and summated scores of OP and JSN in foot/ankle OA in footballers compared to controls.

6.2.2 Participants

Knee radiographs were undertaken in Spire Healthcare centres for footballers who lived outside of Nottinghamshire, whereas for footballers living locally in Nottingham and for all controls knee radiographs were undertaken in the City Hospital (Nottingham University Hospital National Health Service (NHS) Trust). For foot/ankle radiographs all controls and footballers who lived locally in Nottinghamshire again underwent foot and ankle radiographs at the City Hospital. However, Spire Healthcare could no longer provide support for this

second study, so footballers who lived outside of Nottinghamshire underwent foot and ankle radiographs at one of four other collaborating NHS sites, specifically the Northern Care Alliance NHS Foundation Trust (Salford Royal Hospital), Leeds Teaching Hospital NHS Trust (Chapel Allerton Hospital), Imperial College Healthcare NHS Trust (Hammersmith Hospital) and University Hospital Southampton NHS Foundation Trust (Southampton General Hospital). This is because of the distance between the NHS sites and the widespread residence of footballers across the UK. Travel expenses were reimbursed for all participants who underwent knee and foot and ankle radiographs.

The eligibility criteria for the radiographic assessment of the ankle/foot was similar for the footballers and controls, other than the requirement for footballers to live within 40 to 50 miles from the five nearest collaborating NHS Trusts, and included the following:

1. Participants who had never had a bilateral ankle joint replacements.
2. Participants without contraindications to having foot and ankle radiographs (they were asked this in the questionnaire).

6.2.3 Questionnaires

For the current study, relevant data contained in the baseline and follow-up questionnaires which were related to radiographic OA at the knee and the foot and/or ankle were extracted from the two retired footballers and KPIC

databases. These data were then combined into a single database using SPSS software. Data related to radiographic OA at the knee were assessed by Gwen Fernandes (GF) and Sanjay Parekh (SP) following training by Sally Doherty – a very experienced scorer for previous large research knee OA studies in Academic Rheumatology. There was agreement with a kappa co-efficient of 66.60 (considered as good) between the two observers (GF and SP). Data on the foot and/or ankle were assessed by Ahmed Thanoon (AT) and me (MS) after training by Professor Catherine Bowen, Professor of Podiatry in the University of Southampton. There was substantial agreement with a kappa co-efficient of 90 (considered as excellent) between the two observers (AT and MS).

General questions

The exposures/variables that were determined to describe the study population (footballers and controls) included age, BMI, index of multiple deprivation, self-reported current use of oral analgesics, nodal OA, 2D:4D finger ratio, physician-diagnosed knee OA and knee injury (already described in section 3.3.2). Other exposures/variables are described as follows:

- Constitutional knee alignment was determined by *“Which picture do you think best shows the angle of each of your legs in your 20s?”* using line drawing tool shows variations of leg alignment (Ingham et al., 2010).

Participants were asked to indicate whether the alignment of their legs was

best represented by a varus (A or B), a straight (C) or a valgus (D or E) diagram (refer to Figure 16, page 37).

- Foot/ankle injury was defined differently in the two study groups as *“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)”* in footballers or (*“all work and other duties during this time”*) in controls.

6.2.4 Recruitment

Among footballers and controls who completed and returned the baseline questionnaire, 470 footballers and 491 controls subsequently underwent bilateral knee radiographs. From footballers and controls who returned completed follow-up questionnaire, 113 footballers and 319 controls subsequently underwent foot/ankle radiographs. A total of 72 (63.7%) footballers and 147 (46.1%) controls had both knee and foot/ankle radiographs and were then included for analysis. Details of recruitment in the 5 NHS sites involved is shown in Appendix H.

6.2.5 Radiographic assessment

6.2.5.1 Knee osteoarthritis

Radiographs for each knee were a single weight-bearing semi-flexed posterior-anterior view of the tibiofemoral compartments of both knees, and a single lying supine 30 degree flexion skyline view of each patellofemoral joint. Radiographic knee OA was assessed using the ordinal K-L composite grade (1-4) which gives a single grade for the combined two tibiofemoral compartments (medial and lateral), and an additional single grade for the patellofemoral joint using verbal descriptions for the features of OA (Table 32) as opposed to a photographic atlas (Kellgren and Lawrence, 1957). As part of the radiographic assessment, radiographic chondrocalcinosis was defined as the presence of chondrocalcinosis (cartilage calcification) in the hyaline or fibrocartilage of any compartment.

Table 32. The Kellgren and Lawrence radiographic scoring system

Grade	Description
0	No radiographic findings of osteoarthritis – normal
1	Doubtful narrowing of joint space, possible osteophyte
2	Definite osteophyte, possible narrowing
3	Moderate multiple osteophyte, definite narrowing, some sclerosis, possible deformity of bone ends
4	Large osteophyte, marked narrowing, severe sclerosis, definite deformity of bone ends.

6.2.5.2 Foot/ankle osteoarthritis

Radiographic assessments were conducted on the study population from November 2021 until March 2023. All participants who indicated willingness to participate in foot and ankle assessment and lived reasonably near one of the collaborating hospitals were invited for a single visit for the radiographs.

Communication with participants was conducted via telephone or email to resolve any queries, to book them in and to remind them of their appointment.

Upon arriving at the hospital, the participants received a folder with all documents required for reimbursement for travel expenses and a copy of the consent document. Prior to the radiographic assessment, each participant was informed of the detailed procedure using the participant information sheet (by Ahmed Thanoon (AT) or Monirah Shuaib (MS)) and any queries were discussed and addressed, prior to written consent being obtained. After that the participants were taken to the Radiology Department.

All radiographic images for foot and ankle were sent from the five NHS sites to the Academic Rheumatology department on encrypted CDs. Upon receiving the radiographic CDs, the main assessor (AT) reviewed them and notified each NHS site if any images were missing or damaged.

Bilateral radiographs for each ankle and foot were taken separately using fully weight-bearing standing positions. Dorso-plantar, medial-oblique and lateral

views were taken for the foot, while antero-posterior and lateral views were taken for the ankle.

For the dorsoplantar view of the feet, the participant was asked to stand in a relaxed position with the participant's body weight distributed equally on the detector with their feet flat. A relaxed position was achieved by asking the participant to walk on the spot for a few steps and then stand relaxed. The x-ray tube was inclined at an angle of 15° upward, with a vertical ray centered at the base of the third metatarsal (Figure 40).



Figure 40. Participant position for bilateral foot radiograph in the dorsoplantar view

From the dorsoplantar view, the limb of interest was tilted medially on the image receptor at an angle of 30-45° and a non-opaque angled pad was placed beneath the foot. This was used to maintain the position while the limb of interest was supported by the contralateral limb (Figure 41). Each foot was imaged separately.

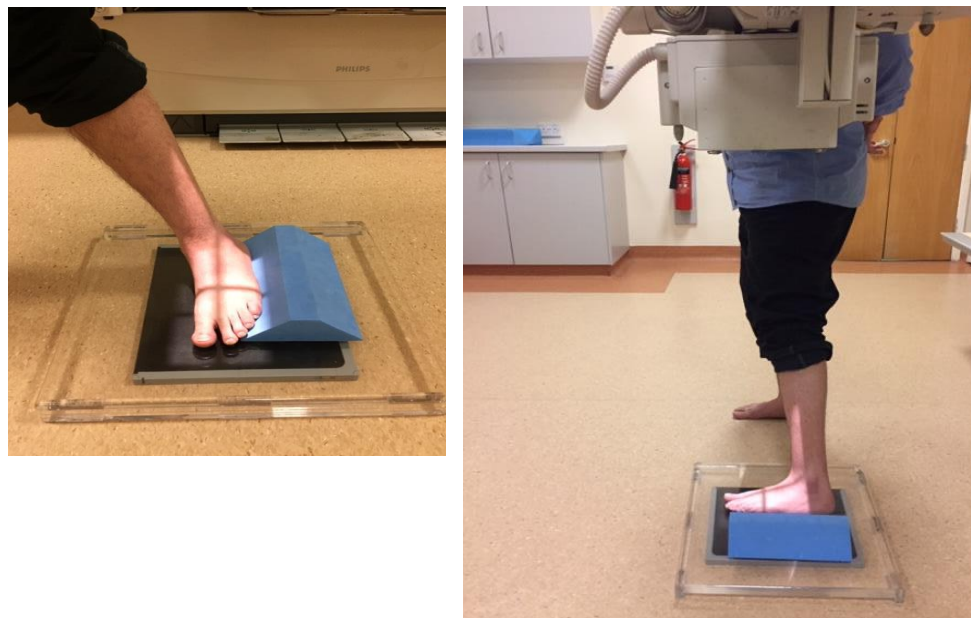


Figure 41. Participant position for unilateral foot radiograph in the medial-oblique view

For lateral views of the foot joints, the participant had to stand on a low platform with the image receptor directed at the lateral aspect of the foot. This position was maintained using a vertical support to so that the participant would be able to rest their forearms, and with a foot stool placed behind for the contralateral foot to rest on (Figure 42). Each foot was assessed separately.

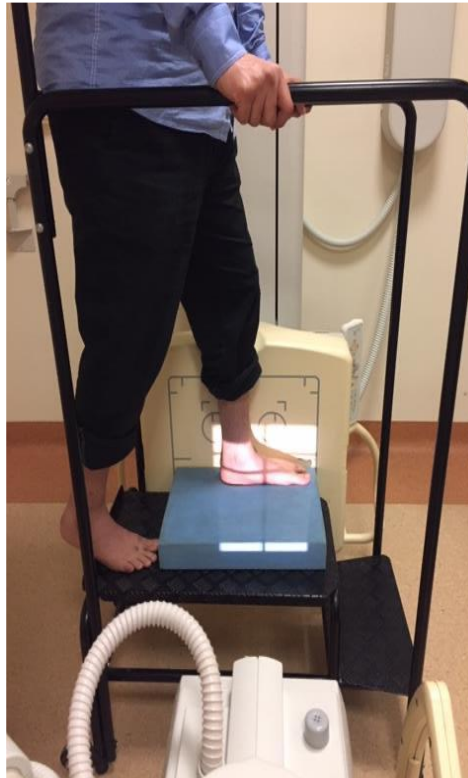


Figure 42. Participant position for unilateral foot and ankle radiographs in the lateral view

For antero-posterior views of each ankle joint, the participant had to stand on a platform raised to the height required by the receptor, distributing the weight equally across the limbs. The ankle was dorsiflexed to 90° and the limb was medially rotated to 20° until both medial and lateral malleoli were equidistant from the image receptor (Figure 43). Each ankle joint was imaged separately.



Figure 43. Participant position for unilateral ankle radiograph in the antero-posterior view

Radiographic foot and ankle OA was assessed using the La Trobe Foot Atlas, and the presence of OA at these joints was defined as grade ≥ 2 for osteophytes (OP) or joint space narrowing (JSN) (Menz et al., 2007, Kraus et al., 2015) (Table 33). The following five foot joints and ankle joint on each side were scored for OA:

- forefoot - the 1st MTPJ
- mid-foot - the 1st CMJ, the 2nd CMJ and the N1st CJ
- hind foot - the TNJ
- ankle - talocrural joint

Table 33. The radiographic scoring for foot and ankle osteoarthritis using the La Trobe Atlas

OP		JSN	
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

OP – osteophytes; JSN – joint space narrowing

A single observer, (AT) in Academic Rheumatology, scored all the foot/ankle radiographs of the footballers and controls for OA to ensure standardisation across both groups using HIPAX Dicom software.

To examine the reproducibility of the results, intra-rater reliability (AT) and inter-rater reliability (AT and MS) were assessed at three time points, specifically at the beginning, middle and end of the study. For each of these assessments, a different random sample of 20 participants (i.e., 40 feet and 40 ankles) were selected and scored (i.e., overall 120 different feet and ankles). For the intra-rater reliability, the single observer (AT) scored a random sample of 20 participants at three time points (the beginning, middle and end of the study) after two weeks of scoring the 20 samples for the inter-rater reliability assessment.

It was impossible to maintain blinding between footballers and controls during the radiographic scoring. This is because the ID system used for radiographic images distinguished footballers as 'FF' and controls as 'FC' and these labels on the films were apparent to the researchers, thus compromising the blinding procedure and introducing potential bias.

A kappa (κ) statistic was calculated to test the agreement within the single scorer and between the two scorers (AT and MS). Fleiss classified the κ -statistic as follows: <0.40 poor agreement, 0.40 - 0.75 fair to good agreement and >0.75 excellent agreement (Fleiss et al., 1981).

6.2.5.3 Scoring techniques

The main assessor (AT) and (MS) both received training from Prof. Catherine Bowen from the University of Southampton online and in-class courses on how to score ankle/foot OA. Then, they both practiced the scoring for about 6 months using Keele ankle/foot x-ray radiographs until they obtained an inter-rater reliability between 70-80% prior to scoring the study films.

When there were difficulties in the interpretation and scoring of radiographs, OP and JSN scores were determined based on a conservative estimate. For example, in case of ambiguity in scoring of an osteophyte or JSN between grade 2 and grade 3 in a joint, the lowest grade of 2 was selected (McQueen et

al., 2017). This approach is widely accepted as it ensures confidence and does not exhibit any bias and uncertainty (McQueen et al., 2017).

If there were issues that prevented the scoring of a particular joint, such as image quality or overlapping of the joints (particularly metatarsals joints), this was coded as '888' indicating unreadability or difficulty to score.

6.2.6 Data management and cleaning

Coding for the outcome of foot/ankle OA was determined as follows:

1. For each of the five joints in the foot, in addition to the ankle joint, a new binary (1=yes, 0= no) variable was obtained for the OP score and another new binary variable was obtained for the JSN score. Presence of OP or JSN in the new variable coded as 1 was defined as grade ≥ 2 "OA cases" and the lower grade 0-1 coded as 0 "non-OA cases" with the missing values recorded as "999" (this was done by AT and validated by MS).
2. The new OP variable for each of the five joints in the foot and the ankle joint included presence of OP in any x-ray view (dorso-plantar or lateral views for the foot joints and anterior-posterior or lateral views for the ankle) of each side. Similarly, the definition for the new JSN for the foot and ankle joints also included presence of JSN in any x-ray view on each side.
3. Then, one final variable for the five foot joints and the ankle joint was defined as the presence of both OP and JSN combined by 'AND'.

4. All the new six variables for the foot and ankle joints were validated by AT.
Details for all data management and cleaning is shown in Appendix I.

6.2.7 Statistical analysis

6.2.7.1 Descriptive analysis

For this sub-study, a similar method of reporting continuous and categorical variables between footballers and controls was as before (see section 3.10.1, pages 174-175). Missing values for footballers and controls are shown in Table 34. No data imputation was used.

Table 34. Missing data for variables in the questionnaire and radiographic assessment for the study population

	Missing data, n (%)	
	Footballers (n=72)	Controls (n=147)
General questions		
Age	0	0
BMI	1 (1.4)	0
Knee injury	1 (1.4)	1 (0.7)
Foot/ankle injury	4 (5.6)	6 (4.1)
Physician-diagnosed knee OA	31 (43.1)	0
Nodal OA	2 (2.8)	3 (2.0)
Pattern 3 2D:4D finger ratio	0	3 (2.0)
Current use of analgesics	0	0
Socioeconomic status	1 (1.4)	0
Radiographic chondrocalcinosis	0	0
Constitutional alignment in their early 20's		
Varus	1 (1.4)	6 (4.1)
Valgus	1 (1.4)	5 (3.4)
Radiographic outcomes		
Knee OA grade ≥ 2	0	0
Knee OA grade ≥ 3	1 (1.4)	3 (2.0)
Foot/ankle OA	0	3 (2.0)
Foot OA	0	2 (1.4)
Ankle OA	0	3 (2.0)

BMI – body mass index; OA – osteoarthritis

6.2.7.2 Association between OA at the knee and foot and/or ankle

The association between knee OA (1= yes, 0= no) and outcomes of either foot OA, ankle OA or foot/ankle OA (1=yes, 0=no) were determined using logistic regression. Stratified analysis was undertaken per group (footballers and controls) and overall to increase the sample size for association between radiographic knee OA and foot/ankle OA using logistic regression. Radiographic knee OA, defined using both K-L grade ≥ 2 (i.e., definite OP and possible JSN) which is used commonly in many studies, and a more stringent definition of K-L grade ≥ 3 (i.e., definite OP plus definite JSN) in any compartments of either knee. Radiographic foot/ankle OA was defined using the La Trobe atlas as grade ≥ 2 (i.e., definite OP or definite JSN) (Menz et al., 2007, Kraus et al., 2015). However, we used a second more stringent definition for foot/ankle OA using the La Trobe atlas which required presence of grade ≥ 2 for both measures (i.e., definite OP plus definite JSN). These two definitions were analogous to the K-L grade definitions used for the knee. The primary comparator was sex matched general population controls.

We also used logistic regression to examine the association between radiographic knee OA defined as K-L (e.g., grade ≥ 2 and ≥ 3) with foot OA and with ankle OA separately defined as (i.e., definite OP plus definite JSN) after adjustment for confounding factors, which were significant in univariate analysis. Interaction analysis between knee OA (K-L grade ≥ 2) and being a footballer for the risk of developing foot/ankle OA was also examined using logistic regression

after adjustment for confounding factors. Goodness of fit was obtained using The Hosmer and Lemeshow test, and multicollinearity was identified by VIF. All multivariable logistic regression model was then used to include variables which were significant in the univariate model. ORs and 95% CI were used to estimate the association between radiographic knee OA and foot/ankle OA. Statistical significance was defined as $p < 0.05$.

6.2.7.3 Association between summated scores of OP and JSN at the knee and foot and/or ankle

The association between summated scores for OP and JSN for knee OA and summated scores for OP and JSN for foot/ankle OA, foot OA and ankle OA were determined using linear regression, which describes the relationship between variables when the outcome is continuous (Martin, 2022). It estimates the best fit straight line through the data, producing the regression coefficient β and estimated 95% CI. It can also cope with more than one predictor variable including continuous, binary or categorical variables (Martin, 2022).

Association between summated scores including OP and JSN at the knee and summated scores including OP and JSN at the foot/ankle was compared using linear regression in footballers, controls and overall. The primary comparator was sex matched general population controls. A multivariable linear regression model was then used to include variables which were significant in the univariate model. Fitness of the linear regression was estimated by ANOVA with

p-value. Multicollinearity between independent variables was identified by VIF. Coefficient β and 95% CI was estimated the association between summated scores of the knee OA and foot/ankle OA. Statistical significance was defined as $p < 0.05$.

6.3 Results

6.3.1 Inter/intra rater reliability

A single observer (GSF) in the Academic Rheumatology Unit scored all the study knee radiographs to ensure standardisation across both groups using HIPAX Dicom software. The inter-rater reliability was moderate to strong overall (Table 35) (Parekh, 2016). For the feet and ankle radiographs, Kappa co-efficient for intra-rater observer (AT) agreement for the 60 random participants (120 feet and ankles) at three time points was 85, which is considered as excellent (Table 36). Similarly, there was substantial agreement with a kappa co-efficient of 90 (considered as excellent) between the two observers (AT and MS) in the overall inter-rater reliability of the 60 random participants (120 feet and ankles) in the dorso-plantar and lateral views (Table 37).

Table 35. Inter-rater reliability between two observers for radiographic assessment of knee osteoarthritis

	Pre-study		Mid-study		End-study	
	K-statics	95% CI	K-statics	95% CI	K-statics	95% CI
<u>NLDA Score (OP)</u>						
TF Joint	0.65	0.56-0.75	0.71	0.63-0.79	0.58	0.42-0.72
PF Joint	0.65	0.57-0.73	0.64	0.56-0.71	0.68	0.59-0.76
Whole Knee	0.66	0.60-0.72	0.68	0.63-0.73	0.65	0.58-0.72
<u>NLDA Score (JSN)</u>						
TF Joint	0.71	0.58-0.81	0.66	0.52-0.77	0.72	0.57-0.85
PF Joint	0.38	0.20-0.57	0.72	0.61-0.82	0.60	0.26-0.81
Whole Knee	0.59	0.48-0.69	0.69	0.60-0.76	0.70	0.57-0.81
<u>K-L Grading</u>						
TF Joint	0.68	0.53-0.80	0.77	0.60-0.89	0.57	0.38-0.74
PF Joint	0.58	0.43-0.77	0.74	0.57-0.86	0.66	0.49-0.83
Whole Knee	0.64	0.53-0.75	0.76	0.65-0.84	0.63	0.51-0.75

NLDA – the Nottingham Line Drawing Atlas; OP – osteophytes; JSN – joint space narrowing; K-L – the Kellgren and Lawrence

This table is from Sanjay Parekh's thesis (Parekh, 2016).

Table 36. Intra-rater reliability of radiographic foot/ankle osteoarthritis

View and feature	Kappa (κ) (95% CI)		
	Start of -study (n=20)	Mid-study (n=20)	End-study (n=20)
Foot (dorso-plantar view)			
1 st MTPJ – OP	0.69 (0.52 - 0.86)	0.92 (0.81 - 1.02)	0.94 (0.87 - 1.02)
1 st MTPJ – JSN	0.76 (0.60 - 0.92)	0.88 (0.75 - 1.00)	0.91 (0.78 - 1.04)
1 st CMJ – OP	0.64 (0.41 - 0.87)	0.86 (0.71 - 1.00)	0.91 (0.78 - 1.03)
1 st CMJ – JSN	0.74 (0.54 - 0.94)	0.92 (0.82 - 1.02)	0.96 (0.90 - 1.03)
2 nd CMJ – OP	0.69 (0.46 - 0.91)	0.90 (0.77 - 1.02)	0.95 (0.85 - 1.05)
2 nd CMJ – JSN	0.81 (0.66 - 0.96)	0.89 (0.77 - 1.00)	0.96 (0.90 - 1.03)
N1 st CJ – OP	0.60 (0.36 - 0.84)	0.89 (0.74 - 1.03)	0.95 (0.86 - 1.04)
N1 st CJ – 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	0.61 (0.54 - 0.68)	0.91 (0.87 - 0.94)	0.94 (0.91 - 0.98)
Foot (lateral view)			
1 st MTPJ – OP	0.58 (0.38 - 0.77)	0.84 (0.66 - 1.02)	0.95 (0.87 - 1.04)
1 st MTPJ – JSN	0.75 (0.56 - 0.93)	0.88 (0.74 - 1.01)	0.96 (0.88 - 1.04)
1 st CMJ – OP	0.72 (0.49 - 0.94)	0.87 (0.72 - 1.02)	0.95 (0.86 - 1.05)
1 st CMJ – JSN	0.76 (0.57 - 0.95)	0.88 (0.71 - 1.05)	0.94 (0.82 - 1.05)
2 nd CMJ – OP	0.46 (0.20 - 0.71)	0.80 (0.62 - 0.98)	0.94 (0.84 - 1.05)
2 nd CMJ – JSN	0.69 (0.50 - 0.87)	0.80 (0.64 - 0.96)	0.93 (0.85 - 1.02)
N1 st CJ – OP	0.76 (0.57 - 0.95)	0.85 (0.69 - 1.00)	0.93 (0.80 - 1.06)
N1 st CJ – 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	0.70 (0.63 - 0.76)	0.87 (0.82 - 0.91)	0.95 (0.93 - 0.98)
Ankle (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	0.72 (0.58 - 0.85)	0.90 (0.81 - 0.98)	0.96 (0.91 - 1.01)
Ankle (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	0.77 (0.65 - 0.89)	0.90 (0.80 - 1.00)	0.95 (0.90 - 1.02)

OP – osteophytes; JSN - joint space narrowing; CI - confidence interval

Foot includes 5 joints: 1st MTPJ, 1st CMJ; 2nd CMJ, N1stCJ and TNJ; 1stMTPJ - 1st Metatarsal-phalangeal joint; 1stCMJ - 1st Cuneo-metatarsal joint; 2ndCMJ - 2nd Cuneo-metatarsal joint; N1stCJ - Navicular-1st cuneiform joint; TNJ - Talonavicular joint; Ankle includes talocrural joint.

Overall include all the joints with both features OP and JSN according to the foot or ankle in specific view.

Table 37. Inter-rater reliability of radiographic foot/ankle osteoarthritis

View and feature	Kappa (κ) (95% CI)		
	Start of -study (n=20)	Mid-study (n=20)	End-study (n=20)
Foot (dorso-plantar view)			
1 st MTPJ - OP	0.93 (0.86 - 1.00)	0.96 (0.90 - 1.03)	0.97 (0.91 - 1.02)
1 st MTPJ - JSN	0.95 (0.90 - 1.00)	0.97 (0.91 - 1.02)	0.95 (0.85 - 1.04)
1 st CMJ - OP	0.88 (0.75 - 0.99)	0.92 (0.88 - 1.02)	0.97 (0.91 - 1.02)
1 st CMJ - JSN	1.00 (1.00 - 1.00)	0.92 (0.83 - 1.00)	0.96 (0.90 - 1.03)
2 nd CMJ - OP	0.88 (0.72 - 1.00)	0.90 (0.78 - 1.02)	0.94 (0.84 - 1.05)
2 nd CMJ - JSN	0.84 (0.72 - 0.97)	0.94 (0.87 - 1.01)	0.96 (0.90 - 1.03)
N1 st CJ - OP	0.90 (0.79 - 1.03)	0.94 (0.83 - 1.05)	0.95 (0.86 - 1.04)
N1 st CJ - 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	0.92 (0.88 - 0.95)	0.94 (0.92 - 0.97)	0.95 (0.92 - 0.98)
Foot (lateral view)			
1 st MTPJ – OP	0.85 (0.73 - 0.96)	0.90 (0.76 - 1.04)	0.91 (0.79 - 1.03)
1 st MTPJ – JSN	0.79 (0.63 - 0.94)	0.88 (0.74 - 1.01)	0.91 (0.80 - 1.03)
1 st CMJ – OP	0.89 (0.76 - 1.00)	0.91 (0.79 - 1.02)	0.90 (0.77 - 1.03)
1 st CMJ – JSN	0.92 (0.81 - 1.00)	0.94 (0.82 - 1.05)	0.94 (0.82 - 1.05)
2 nd CMJ – OP	0.77 (0.58 - 0.96)	0.85 (0.69 - 1.01)	0.89 (0.73 - 1.04)
2 nd CMJ – JSN	0.96 (0.89 - 1.00)	0.92 (0.81 - 1.02)	0.93 (0.84 - 1.02)
N1 st CJ – OP	0.86 (0.72 - 1.01)	0.90 (0.77 - 1.02)	0.93 (0.80 - 1.06)
N1 st CJ – 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	0.83 (0.78 - 0.88)	0.90 (0.86 - 0.94)	0.93 (0.90 - 0.96)
Ankle (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	0.79 (0.67 - 0.91)	0.89 (0.81 - 0.97)	0.92 (0.85 - 0.99)
Ankle (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	0.87 (0.77 - 0.98)	0.93 (0.84 - 1.01)	0.96 (0.90 - 1.02)

OP – osteophytes; JSN - joint space narrowing; CI - confidence interval

Foot includes 5 joints: 1st MTPJ, 1st CMJ; 2nd CMJ, N1stCJ and TNJ; 1stMTPJ - 1st Metatarsal-phalangeal joint; 1stCMJ - 1st Cuneo-metatarsal joint; 2ndCMJ - 2nd Cuneo-metatarsal joint; N1stCJ - Navicular-1st cuneiform joint; TNJ - Talonavicular joint; Ankle includes talocrural joint.

Overall include all the joints with both features OP and JSN according to the foot or ankle in specific view.

6.3.2 Characteristics of the study population

A total of 72 footballers and 147 controls underwent radiographs of their knees (in 2015/16) and foot/ankle joints (in 2021/23) (Table 38). The mean age of footballers was younger (56.5 ± 8.3 years) than the controls (63.5 ± 8.2 years) ($p < 0.001$), but there was no difference in the mean BMI between the two groups at the time of their knee radiographs. Footballers had a higher prevalence of physician-diagnosed knee OA (34.1%) than controls (15.0%) ($p = 0.006$). Both knee injury and foot/ankle injury were significantly higher in footballers than in controls, specifically 62.0% versus 33.0% and 48.5% versus 22.7%, respectively ($p < 0.001$). Radiographic chondrocalcinosis was more common in footballers than controls (18.1% versus 4.8%) ($p = 0.001$). Footballers had higher socioeconomic status than controls ($p = 0.008$) but there were no differences between footballers and controls in current analgesic use, nodal OA, pattern 3 2D:4D finger ratio and constitutional knee malalignment in their 20s. Table 38 shows the characteristics of the study population.

Table 38. Characteristics of the study population at baseline

	Footballers	Controls	p-value
Total number, n	72	147	
Age (years), mean (SD)	56.5 (8.3)	63.5 (8.2)	<0.001
BMI (kg/m ²), mean (SD)	27.0 (2.6)	26.6 (3.4)	0.527
Current use of analgesics, n (%)	15 (20.8)	19 (12.9)	0.129
Physician diagnosis of Knee OA, n (%) #	14 (34.1)	22 (15.0)	0.006
Knee injury, n (%)	44 (62.0)	48 (33.0)	<0.001
Foot/ankle injury, n (%)	33 (48.5)	32 (22.7)	<0.001
Nodal OA, n (%)	3 (4.3)	17 (11.8)	0.076
Pattern 3 2D:4D finger ratio, n (%)	51 (70.8)	86 (59.7)	0.110
Radiographic chondrocalcinosis, n (%)	13 (18.1)	7 (4.8)	0.001
Constitutional knee alignment in their early 20's, n (%)			
Varus, n (%)	11 (15.5)	12 (8.5)	0.123
Valgus, n (%)	0	4 (2.8)	0.153
Socioeconomic status, mean (SD)	7.7 (2.2)	6.7 (3.1)	0.008

Bold indicates a value of p<0.001 or p <0.05

Current oral analgesics included non-steroidal anti-inflammatory drugs, opioids and over the counter painkillers.

Nodal OA was defined as present in those reporting nodes on at a least two rays of both hands.

Pattern 3 2D:4D finger ratio: index finger is shorter than the ring finger.

Socioeconomic status (decile) was measured using the index of multiple deprivation, ranging from 1 to10, determined by post-code.

the percentage is after excluding the missing-data.

6.3.3 Association between radiographic knee OA and foot/ankle OA

Tables 39-40 show the association between radiographic OA of at the knee and foot/ankle using logistic regression. The goodness of fit in the regression model for footballers, controls and overall were non-significant indicating a good fit, and VIF was around 1 indicating no multicollinearity between predictors (Appendix J).

When knee OA was defined by K-L grade ≥ 2 , its association with foot/ankle OA was not significant in footballers (aOR 4.13, 95% CI 0.72 – 23.66; $p=0.111$) but it was significant in controls (aOR 2.57, 95% CI 1.01 – 6.53; $p=0.046$) after adjustment for age and socioeconomic status, knee injury and foot/ankle injury per group. It was also significant when both groups were combined (aOR 2.56, 95% CI 1.15 – 5.71; $p=0.021$) after adjustment for being footballer, age and socioeconomic status, knee injury and foot/ankle injury (Table 39).

When knee OA was defined by K-L grade ≥ 3 , the association was not significant across footballers (aOR 3.55, 95% CI 0.34 – 37.02; $p=0.289$), controls (aOR 2.22, 95% CI 0.56 – 8.70; $p=0.252$) and when both groups were combined (aOR 2.47, 95% CI 0.77 – 7.87; $p=0.126$) after adjustment for age and socioeconomic status, knee injury and foot/ankle injury per group, and for being a footballer in the combined group analysis (Table 40).

Tables 41 shows the for interaction between being a footballer and knee OA for the risk of foot/ankle OA using logistic regression. The goodness of fit in the regression model for interaction between being a footballer and knee OA for the risk of foot/ankle OA was non-significant indicating a good fit, and VIF was around 1 indicating no multicollinearity between predictors (Appendix J). There was no interaction between being a footballer and knee OA (K-L grade ≥ 2) for the outcome risk of foot/ankle OA (aOR 0.80, 95% CI 0.14 – 4.50; $p=0.802$) after adjustment for age, knee injury, foot/ankle injuries, being footballer, knee OA (K-L grade ≥ 2) and socioeconomic status (Table 41).

Table 39. Association between radiographic knee osteoarthritis and foot/ankle osteoarthritis

	Footballers		Controls		Overall	
	n	Foot/ankle OA (%)	n	Foot/ankle OA (%)	n	Foot/ankle OA (%)
K-L knee (grade ≥ 2)						
Knee OA	31	28 (90.3)	43	32 (78.0)	74	60 (83.3)
No knee OA	41	31 (75.6)	104	57 (55.3)	145	88 (61.1)
OR (95% CI)						
Crude	3.01 (0.75 – 12.06), p=0.120		2.87 (1.24 – 6.61), p=0.013		2.90 (1.42 – 5.94), p=0.003	
Model 1	2.58 (0.62 – 10.69), p=0.189		2.37 (1.006 – 5.60), p=0.048		2.42 (1.16 – 5.04), p=0.018	
Model 2	2.41 (0.51 – 11.47), p=0.266		2.36 (0.95 – 5.84), p=0.063		2.25 (1.03 – 4.89), p=0.040	
Model 3	4.13 (0.72 – 23.66), p=0.111		2.57 (1.01 – 6.53), p=0.046		2.56 (1.15 – 5.71), p=0.021	

Bold indicates a value of $p < 0.001$ or $p < 0.05$

OR - odds ratio, CI - confidence interval; OA - osteoarthritis, K-L - Kellgren and Lawrence.

Foot/ankle OA defined as grade ≥ 2 for osteophytes and joint space narrowing.

Model 1 is adjusted for age

Model 2 is adjusted for age, knee injury and foot/ankle injuries

Model 3 is including model 1 and 3 and socioeconomic status

Overall group analysis was adjusted for being a footballer in addition to the adjustments for model 1, 2 and 3.

Table 40. Association between radiographic knee osteoarthritis and foot/ankle osteoarthritis

	Footballers		Controls		Overall	
	n	Foot/ankle OA (%)	n	Foot/ankle OA (%)	n	Foot/ankle OA (%)
K-L knee (grade ≥ 3)						
Knee OA	16	15 (93.8)	18	12 (75.0)	34	27 (84.4)
No knee OA	55	43 (78.2)	126	74 (59.2)	181	117 (65.0)
OR (95% CI)						
Crude OR	4.18 (0.50 – 34.97), p=0.186		2.06 (0.63 – 6.77), p=0.230		2.51 (0.90 – 6.98), p=0.076	
Model 1	3.49 (0.40 – 30.03), p=0.255		1.61 (0.47 – 5.48), p=0.439		2.01 (0.71 – 5.72), p=0.187	
Model 2	3.04 (0.32 – 28.45), p=0.328		2.09 (0.54 – 8.10), p=0.282		2.28 (0.72 – 7.18), p=0.158	
Model 3	3.55 (0.34 – 37.02), p=0.289		2.22 (0.56 – 8.70), p=0.252		2.47 (0.77 – 7.87), p=0.126	

Bold indicates a value of $p < 0.001$ or $p < 0.05$

OR - odds ratio, CI - confidence interval; OA - osteoarthritis, K-L - Kellgren and Lawrence.

Foot/ankle OA defined as grade ≥ 2 for osteophytes and joint space narrowing.

Model 1 is adjusted for age

Model 2 is adjusted for age, knee injury and foot/ankle injuries

Model 3 is including model 1 and 3 and socioeconomic status

Overall group analysis was adjusted for being a footballer in addition to the adjustments for model 1, 2 and 3.

Table 41. Interaction between being a footballer and knee OA for the risk of foot/ankle OA

	OR (95% CI)
Adjusted for age	1.14 (0.22 – 5.88), p=0.874
Adjusted for age, knee injury, foot/ankle injuries	0.86 (0.15 – 4.78), p=0.868
Adjusted for age, knee injury, foot/ankle injuries, being footballer, knee OA and SES	0.80 (0.14 – 4.50), p=0.802

OR – odd ratio; CI – confidence interval; SES – socioeconomic status

6.3.4 Association between radiographic knee OA and foot OA and ankle OA

Table 42 shows the association between radiographic OA at the knee and the foot using logistic regression. The goodness of fit in the regression model for footballers, controls and overall were non-significant indicating a good fit, and VIF was around 1 indicating no multicollinearity between predictors (Appendix J). When knee OA was defined by K-L grade ≥ 2 , its association with foot OA was not significant in footballers (aOR 1.57, 95% CI 0.48 – 5.15; p=0.453), but was significant in controls (aOR 3.86, 95% CI 1.60 – 9.32; p=0.003) and when both groups were combined (aOR 2.73, 95% CI 1.37 – 5.43; p=0.004) after adjustment for age, socioeconomic status, knee injury and foot/ankle injury per group, and for being a footballer for the combined analysis. When knee OA was defined by K-L grade ≥ 3 , its association with foot OA was not significant in footballers (aOR 0.66, 95% CI 0.17 – 2.48; p=0.540) or in controls (aOR 3.26,

95% CI 0.92 – 11.54; $p=0.066$) or when both groups were combined (aOR 1.60, 95% CI 0.67 – 3.83; $p=0.288$) (Table 42).

Table 43 shows the association between radiographic OA at the knee and the ankle. The goodness of fit in the regression model for footballers, controls and overall were non-significant indicating a good fit, and VIF is around 1 indicating no multicollinearity between predictors (Appendix J). When knee OA was defined by K-L grade ≥ 2 , its association with ankle OA was not significant in footballers (aOR 2.74, 95% CI 0.77 – 9.73; $p=0.118$) or in controls (aOR 0.91, 95% CI 0.37 – 2.23; $p=0.848$) or when both groups were combined (aOR 1.32, 95% CI 0.66 – 2.64; $p=0.421$) after adjustment for age, socioeconomic status, knee injury and foot/ankle injury per group, and the same additional adjustment for being a footballer for the combined analysis. Similarly, when knee OA was defined by K-L grade ≥ 3 , its association with ankle OA was not significant in footballers (aOR 1.59, 95% CI 0.36 – 7.02; $p=0.538$) or in controls (aOR 0.30, 95% CI 0.06 – 1.49; $p=0.143$) or when both groups were combined (aOR 0.76, 95% CI 0.31 – 1.88; $p=0.563$) (Table 43).

Table 42. Association between radiographic knee osteoarthritis and foot osteoarthritis

	Footballers		Controls		Overall	
	n	Foot OA (%)	n	Foot OA (%)	n	Foot OA (%)
K-L knee (grade ≥ 2)						
Knee OA	31	22 (71.0)	43	29 (70.7)	74	51 (70.8)
No knee OA	41	23 (56.1)	104	40 (38.5)	145	63 (43.4)
Crude OR (95%CI)	1.91 (0.71 – 5.15), p=0.199		3.86 (1.77 – 8.43), p<0.001		2.98 (1.62 – 5.50), p<0.001	
aOR (95% CI)	1.57 (0.48 – 5.15), p=0.453		3.86 (1.60 – 9.32), p=0.003		2.73 (1.37 – 5.43), p=0.004	
K-L knee (grade ≥ 3)						
Knee OA	16	10 (62.5)	18	11 (68.8)	34	21 (65.6)
No knee OA	55	34 (61.8)	126	55 (43.7)	181	89 (49.2)
Crude OR (95% CI)	1.03 (0.32 – 3.24), p=0.961		2.84 (0.93 – 8.65), p=0.066		1.78 (0.80 – 3.96), p=0.155	
aOR (95% CI)	0.66 (0.17 – 2.48), p=0.540		3.26 (0.92 – 11.54), p=0.066		1.60 (0.67 – 3.83), p=0.288	

Bold indicates a value of p<0.001 or p <0.05

OA – osteoarthritis; OR – odd ratio; CI – confidence interval

Foot OA was defined using La Trobe atlas grade ≥ 2 definite osteophytes and definite joint space narrowing in any of 1st metatarsophalangeal joint, 1st cuneo-metatarsal joint, the 2nd cuneo-metatarsal joint and the navicular-first cuneiform joint.

aOR - OR adjusted for age and socioeconomic status, knee injury and foot/ankle injury per group, and similar covariates in addition to stratum (i.e., being footballer yes=1, no=0) for overall.

Table 43. Association between radiographic knee osteoarthritis and ankle osteoarthritis

	Footballers		Controls		Overall	
	n	Ankle OA (%)	n	Ankle OA (%)	n	Ankle OA (%)
K-L knee (grade ≥ 2)						
Knee OA	31	25 (80.6)	43	11 (26.2)	74	36 (49.3)
No knee OA	41	23 (56.1)	104	25 (24.5)	145	48 (33.6)
Crude OR (95%CI)	3.26 (1.10 – 9.63), p=0.033		1.09 (0.48 – 2.48), p=0.832		1.65 (0.88 – 3.08), p=0.118	
aOR (95% CI)	2.74 (0.77 – 9.73), p=0.118		0.91 (0.37 – 2.23), p=0.848		1.32 (0.66 – 2.64), p=0.421	
K-L knee (grade ≥ 3)						
Knee OA	16	13 (81.3)	18	2 (11.8)	34	15 (45.5)
No knee OA	55	35 (63.6)	126	32 (25.8)	181	67 (37.4)
Crude OR (95% CI)	2.47 (0.62 – 9.74), p=0.195		0.38 (0.08 – 1.76), p=0.219		1.01 (0.43 – 2.35), p=0.971	
aOR (95% CI)	1.59 (0.36 – 7.02), p=0.538		0.30 (0.06 – 1.49), p=0.143		0.76 (0.31 – 1.88), p=0.563	

Bold indicates a value of $p < 0.001$ or $p < 0.05$

OA – osteoarthritis; OR – odd ratio; CI – confidence interval

Ankle OA was defined using La Trobe atlas ≥ 2 definite osteophytes and definite joint space narrowing in talonavicular joint

aOR - OR adjusted for age and socioeconomic status, knee injury and foot/ankle injury per group, and similar covariates in addition to stratum (i.e., being footballer yes=1, no=0) for overall.

6.3.5 Association between summated score of structural changes between knee OA and foot/ankle OA

Multiple linear regression was used to explore how summated scores of OP and JSN in knee OA contributed to summated scores of OP and JSN in foot and/or ankle OA (Table 44). All linear regression model was significant in footballers, in controls and in overall indicating that there is statistically significant linear relationship obtained from ANOVA test (Table 44). VIF was around 1 indicating no multicollinearity between predictors (Appendix K).

After adjustment of covariates, linear regression analysis showed that summated scores of JSN in the knee OA were not significantly associated with summated scores of JSN in the foot/ankle joints in footballers (β 0.12, 95% CI -0.36 to 1.09; $p=0.327$), with an adjusted- R^2 of 0.157 showing that this model accounted for 15.7% of the variance. However, it was significantly associated in controls (β 0.33, 95% CI 0.32 – 1.00; $p<0.001$), with an adjusted- R^2 of 0.118 showing that this model accounted for 11.8% of the variance. It was also significant in the overall when both groups were combined (β 0.25, 95% CI 0.25 – 0.92; $p<0.001$), with an adjusted- R^2 of 0.093 indicating that this model accounted for 9.3% of the variance (Tables 44).

After adjustment of covariates, linear regression analysis showed that summated scores of OP in the knee were not associated significantly with summated scores of OP in the foot/ankle joints in footballers (β 0.23, 95% CI

-0.03 – 0.54; $p=0.078$), with an adjusted- R^2 of 0.099 showing that this model accounted for 9.9% of the variance. However, it was significantly associated in controls (β 0.38, 95% CI 0.19 – 0.47; $p<0.001$), with an adjusted- R^2 of 0.188 showing that this model accounted for 18.8% of the variance, and in the overall when both groups were combined (β 0.30, 95% CI 0.18 – 0.44; $p<0.001$), with an adjusted- R^2 of 0.272 showing that this model accounted for 27.2% of the variance, with summated scores of OP in the foot/ankle joints (Tables 44).

Table 44. Linear regression between summated knee radiographic scores and summated foot/ankle radiographic scores

		β (95% CI), p-value					
		Footballers		Controls		Overall	
Summated JSN scores		Sig.		Sig.		Sig.	
Crude		0.27 (0.11 – 1.36), p=0.021		0.34 (0.36 – 0.96), p<0.001		0.31 (0.40 - 0.98), p<0.001	
Adjusted		0.12 (-0.36 – 1.09), p=0.327	0.008	0.33 (0.32 – 1.00), p<0.001	<0.001	0.25 (0.25 – 0.92), p<0.001	<0.001
Summated OP scores							
Crude		0.30 (0.08 – 0.58), p=0.009		0.42 (0.23 – 0.48), p<0.001		0.34 (0.23 – 0.47), p<0.001	
Adjusted		0.23 (-0.03 – 0.54), p=0.078	0.043	0.38 (0.19 – 0.47), p<0.001	<0.001	0.30 (0.18 – 0.44), p<0.001	<0.001

Bold indicates a value of $p<0.001$ or $p<0.05$

Sig. – referred to significant fit to data in the whole model.

OA – osteoarthritis; JSN - joint space narrowing; OP – osteophytes; CI - confidence interval

Adjusted for age and socioeconomic status, knee injury and foot/ankle injury per group, and similar covariates in addition to stratum (i.e., being footballer yes=1, no=0) for overall.

6.4 Discussion

This study determined the association between radiographic knee OA and foot/ankle OA in male footballers compared to control men in the general population. The main findings were: (1) there was no association between knee OA (K-L grade ≥ 2) and foot/ankle OA in footballers but there was an association in controls; (2) a significant association was only observed for foot OA but not ankle OA in controls; (3) no interaction analysis between being footballer and knee OA for the risk of foot/ankle OA; and (4) a significant association was found in summated scores of OP or JSN between knee and foot/ankle joints in controls only.

This is the only study to date that has examined radiographic OA of the knee and foot/ankle in male footballers and in control men. One study conducted in the US found that the percentage of co-occurrence of radiographic foot OA and OA at the knee (grade ≥ 2 using the K-L) was 9% in men aged ≥ 40 years with an aOR of 3.4 (95% CI 2.4 – 4.7) after adjustment for age, BMI and occupation (Wilder et al., 2005). Previous studies have focused on whether foot and/or ankle symptoms in the general population are potential risks factor for knee OA. For example, Perry et al. (2021) reported that in a community-based 7-year cohort study in the UK, that included men and women aged from 50 to 79 years, having ankle pain either with (aOR 2.30, 95% CI 1.13 – 4.66) or without (aOR 2.53, 95% CI 1.34 – 4.80) foot pain (after adjustment for age, gender, BMI and Charlson Comorbidity score) was significantly associated with incident

symptomatic radiographic knee OA and frequent knee pain over a 7-year follow-up period (Perry et al., 2021).

Similarly, Paterson et al. (2017) found that foot/ankle symptoms in either one or both feet were associated with the development of incident symptomatic radiographic knee OA (K-L grade ≥ 2) (aOR 3.28, 95% CI 1.69 – 6.37) and incident knee pain (aOR 1.55, 95% CI 1.10 – 2.19), after adjustment for age, sex, BMI and other covariates, over a 4-year period in the US community-based men and women aged between 45-79 years (Paterson et al., 2017b).

Furthermore, foot pain has been reported to be prevalent in people with symptomatic and radiographic knee OA (K-L grade >3) compared to those without foot pain (51% versus 41%, respectively) ($p < 0.007$) in Australian men and women aged between 45 to 79 years (Paterson et al., 2015). It has been reported also that the presence of unilateral or bilateral foot pain in people with knee OA can negatively impact health (WOMAC) and function (20-metre walk test and repeated chair stand test) of knee-specific measures (Paterson et al., 2015). All these studies suggest that there is a relationship between foot and/or ankle symptoms and incident symptomatic radiographic knee OA. However, in the Perry et al. (2021) study it was highlighted that the association with incident symptomatic radiographic knee OA and knee pain was driven mostly by ankle pain rather than radiographic OA. These OAI studies conducted by Paterson et al. (2017) and Paterson et al. (2015) enrolled people with evidence of knee OA

or at high risk of developing knee OA, so there is some inherent bias towards developing knee OA.

There was no interaction between being a footballer and knee OA for risk of foot/ankle OA. In addition, when the more stringent definition of knee OA (K-L grade ≥ 3) was used we could not identify any association between radiographic knee OA and foot/ankle OA in footballers, or in controls or when both groups were combined. This might be due to the relatively small sample sizes or because more severe/definite structural changes of foot or/and ankle OA require a longer period to develop. However, we observed a relationship between summated scores of OP and JSN in knee OA and summated scores of OP and JSN in foot/ankle OA in controls and when both groups were combined, but not in the footballers alone.

The association between structural changes in the knee and foot and/or ankle may be explained in part by kinematic alterations. Although little is known about foot/ankle characteristics associated with patellofemoral knee OA, one study has reported that people with patellofemoral knee OA had decreased ankle dorsiflexion range and greater midfoot height mobility compared to controls (Wyndow et al., 2018). On the other hand, some kinematic alterations and manifestations in the foot structures during gait are common in people with medial tibiofemoral knee OA, including the presence of greater subtalar pronation (Levinger et al., 2010), which potentially allows the foot to be

plantigrade in order to compensate for knee varus alignment. As a result, foot pronation leads to greater tibial internal rotation (Resende et al., 2015, Souza et al., 2010), which might increase rotational stress on the tibiofemoral joint and peri-articular structures. Greater rearfoot valgus was also seen as changes in foot kinematics in those with knee OA with varus alignment (Cho et al., 2017). With flat feet, there is an increased risk of knee joint cartilage degradation and pain (Gross et al., 2011). All these indicate a decrease in foot mobility, which can be attributed to reduce the compensatory capacity of the foot/ankle complex (Levinger et al., 2012, Ohi et al., 2017, Norton et al., 2015). As previously mentioned, these studies have investigated the effect of either patellofemoral or tibiofemoral knee OA on foot and/or ankle characteristics. However, the current study included OA at both the tibiofemoral or patellofemoral compartments within the definition of knee OA.

The development of OA at the knee and foot/ankle joints may also be affected by other risk factors, which include constitutional, genetic and environmental factors (Allen et al., 2022). Ageing is a well-established risk factor associated with OA, and results in the reduction of cartilage volume, cartilage vascularisation, reduction of proteoglycan content and cartilage perfusion leading to initiation of the OA process (Anderson and Loeser, 2010). Footballers were younger than controls and were very fit in their early life, which might have delayed the development of OA at foot and/or ankle joints compared to controls. Genetic risk factors might also have an influence on the development of

radiographic OA in these two joints and might explain the presence of this association in controls (Allen et al., 2022). Joint trauma might be another risk factor for these associations, since footballers had higher knee and foot/ankle injuries than controls in the univariate analysis. People with unilateral knee OA and knee injury may exhibit an alteration in their walking pattern, known as an antalgic gait, which involves increasing the weight on the unaffected side of the lower limb in order to reduce pain (Duffell et al., 2014, Van Rossom et al., 2023). These changes could contribute to the development of radiographic OA at the foot and/or ankle joints in the contralateral side. However, this potential hypothesis for this association (knee OA and injury and contralateral foot/ankle OA) has not been examined.

6.4.1 Limitations

There are several limitations to the current study. First, self-reported questionnaires are prone to recall bias, so some information relating to medications, medical diagnoses and injuries might have been mis-reported. Second, the sample sizes are relatively small and this may have contributed to inability to demonstrate some of the associations. The sample size was particularly small in footballers and future larger studies are still required to explore the association of OA at the knee and foot/ankle as these joints are particularly susceptible to joint injuries during the career of professional footballers. Third, the analysis was based on the two cross-sectional studies one for knee OA and the other for foot/ankle OA, 6 years apart. Although features of

OA typically develop and change slowly over time, the relatively short period between radiographic assessment of knee (2015/2016) and foot/ankle (2021/2023) may affect the association. Fourth, the La Trobe Atlas definition of OA (definite OP or definite JSN) was very sensitive and we used a more stringent definition that required the presence of definite OP plus definite JSN, which has not been used before. Thus, there is a need to develop more specific criteria or to use alternative scoring systems such as K-L for foot/ankle OA. Furthermore, the La Trobe Atlas includes only the talocrural joint for the hindfoot, and the other hindfoot subtalar joint is commonly injured in footballers and may also develop OA but was not assessed in this study.

6.4.2 Conclusion

This study found a significant association between radiographic knee OA and foot/ankle OA in controls and when both groups were combined, but no association was apparent in footballers alone. A significant association was also found between summated radiographic scores of individual OA features at the knee and the foot/ankle in controls and when both groups were combined, but not in footballers alone. This suggests that knee OA is associated with foot/ankle OA in the general population. Whether playing football would affect the association remains to be investigated. Further larger observational studies, including women, are needed to advance understanding of the biomechanical pathophysiology of knee OA and foot and/or ankle OA.

Chapter 7 Patient and public involvement and engagement

7.1 Introduction

This chapter presents the Public and Patient Involvement and Engagement (PPIE) inputs undertaken for the PhD project. PPIE was reported following the GRIPP 2 (Guidance for Reporting Involvement of Patients and the Public) reporting guideline for PPIE (Staniszewska et al., 2017).

7.2 Aims

The current study utilised secondary data-analysis, and had two aims for undertaking PPIE:

1. The first PPIE focused on the importance of research questions, justifications and study design.
2. The second PPIE involved feedback on newsletters specifically regarding language, clarity and format.

7.3 Methods

PPIE took place at various time-points from its first establishment. The baseline questionnaire in 2014 and the follow-up questionnaire in 2020 were supported by an advisory group involving people from the Pain Centre and footballers from professional footballers. This group provided input to support research design, question formulation, participant information, and considerations regarding the questionnaire's design, length and burden from their perspectives. Furthermore,

for this PhD project, an advisory group comprising individuals from the Pain Centre PPIE group and footballers were involved in the two PPIEs as outlined below:

The first PPIE

The first PPIE was undertaken via email in June to July 2022. A letter was sent to individuals who were unable to use email for this PPIE. Nine retired male professional footballers selected from the FOCUS participants and 9 people from the Pain Centre PPIE group were sent an email with a lay summary of the project. The PPIE questions focused on the participants views on the study's outcomes (knee pain and multimorbidity), the importance of these, and their future participation as follows:

1. Have you had multiple (more than two) long-term conditions?
(Please type yes or no).
2. If yes, how much do they bother you?
3. Do you think it is important to find out how many people have multiple long-term conditions and the risk factors for having this?
4. What is your view on this project comparing ex-professional football players and men in the general population for knee pain and multiple long-term conditions?
5. Are you happy for us to approach you again to see our progress early in 2023 and to help us to implement the results early in 2024? (Please type yes or no).

The second PPIE

The second PPIE focused on feedback from the Pain Centre people and footballers to obtain their inputs about the FOCUS newsletter in terms of clarity, language and format. An email was sent to all individuals in May-June 2024 with support from the Pain Centre team and the FOCUS administrative team. Two retired male professional footballers randomly selected from the FOCUS participants and 4 people from the Pain Centre PPIE group who indicated willingness in the first PPIE to participate in the next PPIE were sent an email with the FOCUS newsletter (Appendix A) with activated track-changes and a brief text.

Because this study is part of FOCUS, it was agreed to produce an overall newsletter for FOCUS. This would permit a single collection of the PPIE inputs for the whole project rather than multiple requests to our PPIE groups. The original FOCUS newsletter was created by Dr Bonnie Miller (without the PPIE inputs and without the results of the other studies). I contributed to the overall FOCUS newsletter before circulating it for PPI inputs.

7.4 Results

Results for first PPIE

From a total of 9 PPI volunteers (all female) from the Pain Centre, 5 (55.5%) completed the questionnaire. All of them had long-term conditions based on Question 1, and 3 participants suffered from multiple conditions. All of them said

“it is important to examine the occurrence and associated risk factors for multiple long-term conditions”. However, only 2 individuals said “it is a good project”. The majority (4 out of 5) indicated that they would like to participate in a subsequent PPIE of the study (Table 45).

Of 9 questionnaires sent to footballers (all male), 5 responses (55.5%) were received. Although only 2 of the 5 participants had multiple long-term conditions, all of them answered that it was a good project and that it was important to examine how many people have multiple long-term conditions and related risk factors. Also, all of them wished to volunteer to participate in subsequent PPIE for the study (Table 45). Details of the responses of volunteers from the Pain Centre and footballers are shown in Appendix L.

Table 45. Summary of the responses from the footballers and Pain Centre volunteers

	Footballers	Pain center people
Overall	9	9
Response rate, n (%)	5 (55.5%)	5 (55.5%)
Male, n	5	0
Female, n	0	5
Q 1: Have you had multiple (more than two) long-term conditions? (Please type yes or no)	2 yes	5 yes
Q 2: If yes, how much they bother you?	2 yes	3 yes
Q 3: Do you think it is important to find out how many people have multiple long-term conditions and related risk factors?	5 yes	5 yes
Q 4: What is your view on this project comparing ex-professional football players and general population for knee pain and multiple long-term conditions?	5 yes	2 yes
Q5: Are you happy for us to approach you again to see our progress early 2023 and to help us implement the results early 2024? (Please type yes or no).	5 yes	4 yes

Results for second PPIE

From a total of 4 volunteers from the Pain Center, 2 (50%) female individuals responded to the email. Of the 3 randomly selected footballers, 2 (66.6%) replied to the email. All feedback was positive and no further amendments were done (Table 46).

Table 46. Summary of the responses from the footballers and Pain Centre volunteers to the newsletter email

	Footballers	Pain center people
Overall	3	4
Response rate, n (%)	2, (66.6%)	2, (50%)
Male, n	2	0
Female, n	0	2
Responses	I can confirm that I have read the newsletter and am happy to go public with it. Very impressive newsletter. It looks good to me and I don't have any issues with the newsletter. The Newsletter looks very good with great use of photos and drawings. It is easy to read and does give some startling facts and figures. It's not too long winded and does get to the point and quite easy on the eye. Perhaps the next step could be to design some headgear that would help stop injuries or even looking at the ball itself. Although I am sure this is already being done.	

7.5 Discussion

In the first PPIE all the footballers but not the general PPIE participants agreed that it was important to compare multiple long-term conditions and associated risk factors between footballers and general population controls. Although the female PPIE volunteers from the Pain Centre seemed to have more multiple long-term conditions compared to the male footballers, only 2 participants from the Pain Centre said “it is a good project” compared to five out of the five footballers. This may reflect the current concern from footballers about the increased risk of certain diseases such as knee OA and dementia in professional footballers. Also it may be because of the gender difference between the two groups where all PPIE participants from the Pain Centre were women who may have less interest in football.

In the second PPIE, a total of 4 participants including 2 footballers and 2 people from the Pain Centre were happy about the newsletter with no further amendments. This might indicate that no additional participants were needed to provide feedback or the method of obtaining the PPI input limits the discussions between researcher and PPI individuals. One of the women from the Pain Centre suggested a need for future studies, which might indicate that football is popular among both sexes. Providing an overall summary for those who participated in FOCUS and disseminating the newsletter might have a good influence on participants to show them what has been discovered and encourage people to participate in research.

7.5.1 Challenges

As secondary data exists already, people cannot involve, suggest or change how data was originally collected. People may have some difficulties in understating complex data (what information/variables were already available), which could result in a lack of meaningful engagement.

7.5.2 Limitations

There are several limitations relating to the involvement of PPIE individuals. First, there were two PPIE groups: footballers and a general population control. However, all the footballers were male, and all the controls were female, which might have caused a gender bias because females are more likely to develop multimorbidity than males. Secondly, the use of a self-reported questionnaire via email, with no opportunity for interpersonal interaction, might have involved misunderstanding of the questions in the first and second PPIE. Thirdly, there was no regular personal involvement with PPIEs throughout my PhD project. Future research projects involving PPIE which I undertake will include more personal involvement.

7.5.3 Conclusion

PPIE is important in research from establishment of any study. In addition, illustrating the potential for individuals that some further studies could use existing data to examine importance research questions and their involvement in

providing their views on the study outcomes is substantial to make the study's results meaningful for people.

Chapter 8 General discussion and conclusion

8.1 Introduction

This chapter presents a summary of the main findings of the thesis and their interpretation with respect to previous literature, discusses the strengths and limitations of the studies undertaken, and suggests future research questions and potential clinical implications.

8.2 Main findings and interpretation

This PhD thesis focused on OA and multimorbidity in retired professional footballers versus general population controls. In the first part of this thesis, a systematic review and meta-analysis was conducted to capture existing evidence of multimorbidity and long-term conditions and their associated risk factors in professional footballers. In the second part of the thesis, a cohort study was formed to determine the incidence of knee pain (the major complaint of knee OA) and multimorbidity in male professional footballers and their related risk factors in both groups, and the association between baseline knee pain and incident multimorbidity. The comparison was made between retired professional footballers and the general population controls. Finally, the association between radiographic knee OA and radiographic foot/ankle OA was examined. A GANTT chart for delivery of each of the studies undertaken in this PhD is shown in (Appendix M). The following are summary of the findings and general discussion points relating to the key findings of this thesis:

1. In the systematic, most of the retrieved studies focused on a single long-term condition such as OA, knee pain or other specific conditions, and some studies reported on more than one long-term condition but did not report on multimorbidity in professional footballers.
2. The incidence of knee pain was similar between retired male professional footballers and controls (24.0% versus 28.8%, respectively) (aOR 0.77, 95% CI 0.52 – 1.16; $p=0.220$). BMI (aOR 1.17, 95% CI 1.04 – 1.31) and football-related knee injury (aOR 2.42, 95% CI 1.22 – 4.79) were risk factors for incident knee pain in footballers, whereas BMI (aOR 1.08, 95% CI 1.01 – 1.14) and higher socioeconomic status (aOR 0.88, 95% CI 0.81 – 0.95) were associated with incident knee pain in controls.
3. There was no association between knee pain and incidence of multimorbidity both in footballers (aOR 1.34, 95% CI 0.78 – 2.30) or in controls (aOR 0.86; 95% CI 0.49 – 1.50).
4. The incidence of multimorbidity was lower in footballers than controls (37.5% versus 52.0%, respectively) ($p<0.001$) (aOR 0.64, 95% CI 0.45 – 0.89). Increasing age (aOR 1.04, 95% CI 1.01 – 1.07), the presence of one condition at baseline (aOR 2.98, 95% CI 1.78 – 4.99) and analgesic use (aOR 2.88, 95% CI 1.53 – 5.40) were risk factors for incidence of multimorbidity in footballers. Age (aOR 1.05, 95% CI 1.03 – 1.08), the presence of one condition at baseline (aOR 2.73, 95% CI 1.73 – 4.31)

and higher socioeconomic status (aOR 0.88, 95% CI 0.81 – 0.95) were associated with the incidence of multimorbidity in controls.

5. The association between radiographic knee OA and foot/ankle OA was significant in controls (aOR 2.57, 95% CI 1.01 – 6.53; $p=0.046$), especially for foot OA (aOR 3.86, 95% CI 1.60 – 9.32; $p=0.003$), but not in footballers (aOR 4.13, 95% CI 0.72 – 23.66; $p=0.111$).

To date, this is first study incident knee pain in retired footballers and there are relatively few published studies about incidence of knee pain in controls. Knee OA is a common condition in middle age (Guerhazi et al., 2012, Adamson et al., 2006), and it can be diagnosed by clinical examination or plain radiographs (see section 1.1.5.2). We planned to use a validated question in the baseline questionnaire, which was “Have you ever had significant pain in and around your knees for most days of a one month period?” but this was not available at the follow-up questionnaire. Therefore, this study used a line drawing body pain mannequin in both baseline and follow-up questionnaires to allow participants to show the location of any knee pain at each time-point. The method of data collection (e.g., body pain mannequin versus written questions) appears to influence the prevalence of symptom-related outcomes or exposures and written questions are reported to be the most accurate form of assessment (van den Hoven et al., 2010). As stated by Hadler in 1992, “Knee pain is the malady – not OA” (Hadler, 1992). However, having anterior current knee pain for most days of a month in middle-aged and older people is most likely to result from knee OA

(Ingham et al., 2011a, Doherty et al., 2016). Clinical assessment would have been a more accurate method of defining knee OA as it can rule out any other conditions that might have similar manifestations (Abhishek and Doherty, 2013).

Following a systematic search of the available evidence, we found no studies that have examined the incidence of multimorbidity in male retired professional footballers. The current study aimed to fill this gap and found that footballers had a lower incidence of multimorbidity than controls. This might indicate the beneficial effect of physical activity in early life in attenuating the risk of multimorbidity. The beneficial impact of physical activity for both mental and physical health is well-evidenced (Warburton et al., 2006). Analgesic use was only a risk factor for incident multimorbidity in footballers. No study has examined the association between the use of analgesics and the incidence of multimorbidity, but potential adverse effects of using analgesics including paracetamol, NSAIDs and opioids can be explained from a physiological perspective (see section 5.3.3), and further studies are needed to confirm the findings.

Association between radiographic knee OA and foot/ankle OA varied between footballers and controls. The association was more pronounced in controls than in footballers, especially between knee OA and foot OA and this might be due to constitutional risk factors (i.e., age and genetics), whereas in footballers joint injury might affect the association as it was frequently reported at both the knee

and foot/ankle joints. Structural changes in the joints (i.e., knee or foot/ankle) is an common consequences of the ageing process (Guo et al., 2022). Although radiographic assessment is considered a gold-standard in diagnosing OA, some limitations are known with the assessments used in the La Trobe Atlas. The La Trobe Atlas defines foot/ankle OA as the presence of either OP or JSN documented as at least grade ≥ 2 in any of the five foot joints and ankle joint assessed irrespective of the radiographic views (dorsoplantar or lateral view for foot, and anterior-posterior or lateral view for ankle) or the limb side (unilateral or bilateral). This definition results in a very high prevalence of foot/ankle OA, so we defined foot/ankle OA as the presence of both OP plus JSN of at least grade ≥ 2 in any of the six joints including five joints in the foot and one joint in the ankle. This method of defining radiographic foot/ankle OA is very certain as it contains the two cardinal features of OA and aligns with the pathological definition of OA. Other general issues in the La Trobe Atlas are discussed and summarised as follows:

1. *Radiographic images and definition of each grade.* The images of each score do not clearly indicate the variation in the development of OP or JSN. Having scores from 0-4 rather than 0-3 may improve the ability to more accurately assess and score OP and JSN. A limited score for OP or JSN indicating grade 2 OA development is definite for both OP and JSN, and grade 3, which is “severe”, represents “large size” of OP and represents “bone on bone” for JSN. Thus, there is a need for at least one additional grade in

between definite and severe to help with variation in the development of OP or JSN and to help with sensitivity analysis of any outcome used.

2. *No definition for foot deformity or joint subluxation.* Atlas radiographic images for foot/ankle OA in the protocol and the radiographic images of the participants do not always look identical. Also, foot deformities such as hallux valgus and joint subluxation of any metatarsophalangeal joints were not considered in the protocol.
3. *Limited number of joints assessed and views.* There are 32 joints in the foot, of which only 5 (1st MTPJ, 1st CMJ, 2nd CMJ, N1stCJ and TNJ) are included for OA scoring using the La Trobe Atlas. As with the 1stMTPJ , the big toe interphalangeal joint is commonly affected by OA, but is not scored in this system. Similarly, the subtalar joint, which is not a rare site for OA, is omitted from the hindfoot score which is based solely on the talocrural joint. Also, only two views are included for foot OA (i.e., dorsoplantar and lateral), and the medial-oblique view which scores the 2ndCMJ more clearly than other views (Figure 44) is not considered.



Figure 44. The medial-oblique view for the foot providing a clearer view to score the 2nd cuneo-metatarsal joint

We used another method, “summated score of OP and JSN”, to examine the association of OA at the knee and foot/ankle joints. This was used to align better with a pathological definition of OA, but mainly because the atlas system is far too sensitive (almost everyone had foot OA) and this could affect the results of this study.

Neither method of examining the association between knee OA with foot and/or ankle found any significant association in footballers. 113 Footballers consenting to undergo foot/ankle radiographs were recruited from 5 NHS sites. It was difficult to recruit more footballers due to the limited number of appointments per

researcher visit offered by some NHS sites, the footballers' busy schedules, restrictions due to the COVID-19 pandemic, and sometimes train strikes. On the other hand, controls were assessed at just one NHS site. There is a further potential for bias in that agreement to a radiographic assessment might have been influenced by the interest of some participants in discovering whether their injuries had resulted in underlying conditions of the foot and/or ankle. Additionally, some participants may have wanted to contribute to science and give something back.

8.3 Novel findings

This is the first study to examine incident multimorbidity in retired male professional footballers compared to men in the general population. This study is also the first to examine a specific association between radiographic OA at the knee and foot/ankle joints in male retired professional footballers compared to men in the general population.

8.4 Strengths and Limitations

A strength of this thesis was that the initial systematic review was undertaken to confirm that no previous study had examined the incidence of multimorbidity in footballers. Another strength is that it had a cohort study design using data from two existing cross-sectional studies to determine the incidence of knee pain and multimorbidity. This study adds additional benefits to the two cross-sectional studies by showing the risk of developing knee pain and multimorbidity over a 6-

year period in retired male professional footballers compared to men in the general population, and found their related risk factors within groups. Finally, this work informs future research in terms of incident knee pain, multimorbidity and OA of the knee and foot/ankle joints in retired professional footballers.

There were several limitations to this study:

Attrition bias. Loss to subsequent follow-up is a common problem with any cohort study and occurred in both the footballers and the controls. Systematic differences between those who did and those who did not respond to the questionnaires might be apparent due to presence or absence of knee or foot/ankle pain or injuries, or because of a change in their address, or due to death. However, as with recall bias, such factors might be expected to be similar in both groups.

Sex-specific. The study involved male retired professional footballers only. Women professional football players are a relatively new phenomenon and a similar study in retired women players would not have been possible at this point in time.

Generalisability. This study was conducted in a relatively small sample of male professional retired footballers in the top four tiers of the English Football League in the UK and in control men living in the East Midlands general

population. As a result, the generalisability of the results is open to question. Future larger studies with longer follow-up and including female players are needed to confirm our findings. Additionally, our findings may not apply to amateurs or footballers in the lower league due to factors such as differences in level of football training and matches injuries incurred during training or matches, medical support (i.e., access to doctors, physiotherapists, and nutritionists), available resources and facilities, and financial and career support. Further studies are needed for other players of different levels, genders, and countries to enable meaningful comparisons.

Selection bias. The control group might have been subject to selection bias because they were all recruited via the 12 general practices for the original baseline study. On the other hand, selection of footballers was not subject to bias as no single organisation holds a complete record of every retired professional footballer, and the only source for recruitment was multiple professional football bodies. Therefore, professional football clubs and their former players associations, the Professional Footballers Association and the League Managers Association were approached to maximise the recruitment.

8.5 Clinical Implications

The findings of this thesis highlighted several implications for clinical practice, policy makers and stakeholders. This might have no direct economic benefits but potentially can reduce long-term conditions, medication use and health-care

burden. Another implication is the management of musculoskeletal pain in footballers, which can be made easier by taking measures to minimise joint injuries during matches or training and considering non-pharmacological treatment for footballers after retirement. This might contribute to reducing the incidence of multimorbidity by limiting the use of oral analgesics such as paracetamol, opioids and NSAIDs, which might lead to the development of long-term conditions and eventually multimorbidity. Although further studies are still needed to confirm the findings from this study and previous studies regarding the association between knee OA with foot and/or ankle OA or pain (see section 1.2.7, pages 77-78). While the foot is included in the assessment of people with knee OA, it is recommended to consider also including the foot in the rehabilitation program. This might help to provide effective preventative strategies against the development of OA at other joint sites and improve patient care. All these considerations might help to mitigate the burden on the person and healthcare services, and maintain better health status, physical ability and quality of life.

8.6 Future research recommendations

To build on this work and the two previous cross-sectional studies, it is suggested that large prospective studies with regular uniform assessments should be conducted among footballers over a longer period of time to provide a surveillance analysis for any outcomes later in life including knee pain/knee OA or foot/ankle OA or multimorbidity. This would allow us to have a better

understanding about the consequences of joint(s) injuries incurred during football career, and to examine the trajectories of multimorbidity, especially in older age in footballers over a longer follow-up period. As mentioned, OA and neurodegenerative conditions were more common in retired footballers. It may be possible to examine the association of each of these with other comorbidities, enabling patterns of development of “multimorbidity” to be determined over a set period of time. When conducting future prospective studies, it would be worth repeating some uniform questions from the previous cross-sectional studies concerning significant pain (i.e., hip, knee or foot and/or ankle) as these joints were commonly injured in footballers. This would provide better understanding about the nature of the pain and its association with OA later in life.

Some diagnostic assessment could be used to assess specific factors related to multimorbidity, such as cardiopulmonary exercise testing in footballers.

Cardiopulmonary fitness refers to the capacity of the circulatory and respiratory systems to deliver oxygen to skeletal muscle mitochondria to produce energy needed during exercise (Balady et al., 2010). The criterion measure of cardiopulmonary fitness is peak oxygen consumption (VO_{2max}), which declines with increasing age (Balady et al., 2010). Peak oxygen consumption is a crucial indicator of physical function and it is considered a strong predictor of risk for morbidity such as diabetes, hyperlipidemia and hypertension and a predictor for mortality rate (Ross et al., 2016).

Another diagnostic method, such as ultrasound or MRI, for foot/ankle OA could be used in future studies. Although MRI is very expensive and not easily available, ultrasound can be used as it provides reliable assessment of OA related characteristics including inflammation and structural changes in multiplanar images at a relatively low cost (Hayashi et al., 2016). When used alone ultrasound is limited by its inability to assess deep articular structures and the subchondral bone (Hayashi et al., 2016). Therefore, it is suggested that radiographs plus ultrasound are probably the optimal option at present. All these assessment methods are more reliable and accurate, and their use in future studies might help in developing tailored management or prevention.

As discussed, there is a need to establish a better radiographic assessment for foot and ankle OA to allow accurate scoring for the mid-foot as these joints are very small and close to each other. The subtalar joint also should be included because it is an important joint to score for ankle OA. A more stringent definition for foot/ankle OA should be developed and tested using the presence of two OA features (i.e., presence of OP plus presence of JSN).

Female football has become more popular in the last couple of years in the UK. Future research could examine sex-specific prevalence/incidence of knee pain or knee OA or multimorbidity, compared with those previously reported for male footballers in the UK.

Finally, collaborations with other universities across the UK or across different countries to implement similar study designs would provide comparisons across different regions/countries. Conducting multi-regional studies would help identify specific regional risk-factors for such outcomes and could confirm whether the decreased risk for multimorbidity in footballers is generalisable, or specific, to UK footballers.

8.7 Conclusion

Footballers are at higher risk of developing OA and neurodegenerative diseases, which might be explained by the repetitive physical nature of football and the required intensive training, as well as the obvious risk from overt direct injury to the head or joint(s). However, they might be at lower risk of developing diabetes, cardiovascular and multimorbidity, and exercise training in early life might be the reason for this reduced risk. Although the findings have certain limitations, they suggest strategies to improve injury prevention and to maintain normal BMI to reduce onset of knee pain in footballers. The findings also support strategies to limit analgesic used in footballers and to effectively manage musculoskeletal pain during their professional career, which could have consequences after retirement in terms of developing multimorbidity. Further larger and longer studies, involving male and female footballers and in different countries, are still warranted to explore other risk factors and to confirm the findings for incident knee pain and multimorbidity. Further studies are needed also to better understand the biomechanical pathophysiology of knee OA and

foot and/or ankle OA, and to examine the impact of joint injuries particularly in footballers.

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Appendices

Appendix A: FOCUS newsletter



University of
Nottingham
UK | CHINA | MALAYSIA



PAIN CENTRE
VERSUS
ARTHRITIS
at the University of Nottingham



NIHR | Nottingham Biomedical
Research Centre



Professional
Footballers'
Association

Foot or ankle Osteoarthritis and Cognitive impairment in the UK Soccer players (FOCUS) study



Cognitive impairment and self-reported dementia in UK retired professional soccer players: a cross-sectional comparative study

Tara-MeiPvall-Macnab et al
Sports Medicine Open 2023;9:43

UK male retired soccer players had a higher risk of performing below established cut-off scores of dementia screening tests and were more likely to self-report medically diagnosed dementia and neurodegenerative diseases, despite having better overall physical health and fewer dementia risk factors. Further study is needed to determine specific soccer-related risk factors. Read more [here](#)

Heading frequency and risk of cognitive impairment in retired male professional soccer players

Shima Espahbodi et al
JAMA Network Open 2023;6:e2323822

Is repetitive heading of the ball during a professional soccer career associated with an increased risk of cognitive impairment in male soccer players in their later lives? In this cross-sectional study, players with heading frequency more than 15 times per match or training session had more than a 3-fold risk of cognitive impairment compared to those with a heading frequency 0 to 5 times per match or training session. Similar results were observed across different cognitive tests noted with dementia and Alzheimer disease. The findings of the study suggest that heading the ball in soccer is associated with an increased risk of cognitive impairment; the upper-frequency threshold for heading remains to be determined to mitigate this risk. Read more [here](#)

The FOCUS Study

"Football is a game that inspires millions of people, but on a personal level professional footballers often suffer from diseases due to sports-related injuries after their careers on the pitch are over..."

Professor Weiya Zhang, Chief Investigator for the FOCUS study

Thank you to all those who gave their time to help with this research.



".... playing-related injuries are still very much a concern. I'm pleased to be involved in this research as a way of continuing to contribute to football."

Les Bradd, Notts County Club Ambassador

Knee pain, multiple long-term conditions and osteoarthritis of the knee, foot or ankle

Monirah Shuaib, PhD student



This study aimed to answer three questions: (1) Whether professional footballers are more likely to develop knee pain and multimorbidity than the general population in 6 years; (2) What are the risk factors related to the development of these two conditions; (3) Whether osteoarthritis at knee is associated with osteoarthritis at foot or ankle joints.

468 male professional footballers and 619 men of a similar age in the general population were followed up from 2014 to 2020 for newly developed knee pain and multiple long-term conditions. No difference was found for knee pain between professional footballers and general population, but lower rate of multiple long-term conditions in professional footballers (38% vs. 52%). Regular physical activity, younger age and better welfare may explain the difference. The study also found that people with knee osteoarthritis are more likely to have foot or ankle osteoarthritis.

Foot or ankle pain and osteoarthritis in retired professional footballers



Ahmed Thanoon, PhD student

This study aimed to answer two questions: Whether professional footballers are more likely to have foot or ankle pain and osteoarthritis than the general population? If so, what are the specific risk factors associated with the increased risk?

468 professional footballers and 619 general population men completed the questionnaires, of whom 113 footballers and 319 general population men underwent x-rays of both feet and ankles. Professional footballers in their later life were more likely to have foot or ankle pain (35% vs. 26%), osteoarthritis (13% vs. 8%), and surgery due to osteoarthritis (24% vs. 8%) than the same age band of general population control men. The ankle appeared to be the most affected joint. Injury and local steroid injection were the two major risk factors associated with the increased risk of foot or ankle osteoarthritis in the professional footballers.

"This is an extremely complex area of our games, but we are committed to working collectively with our stakeholders to help grow our knowledge in this area through further medical and expert analysis"

Dr Charlotte Cowie,
Head of Medicine, The FA

Acknowledgement:

We would like to thank all footballers and general population control men from the East Midlands in England for participating this study. We would also like to thank Nottingham University Hospitals NHS Trust, Northern Care Alliance, University Hospital Southampton NHS Foundation Trust, Leeds Teaching Hospital NHS Trust and Imperial College Healthcare NHS Trust for their collaborations in completing foot and ankle radiographic examinations of the project.

Contact us:

*If you would like to know more about FOCUS and our current research studies, please get in touch: Telephone: 0115 8231676
Email: msk-recruitment@nottingham.ac.uk*



Appendix B: Data request for baseline data of the questionnaire

KNEE PAIN IN THE COMMUNITY

Data Access Request Form

Rheumatology, Orthopaedics and Dermatology, University of Nottingham

Instructions:

Applicants and collaborators requesting use of existing KPIC data are expected to provide information within each of the sections of this form. **Please submit fully completed form and signed agreement via email to Weiya Zhang (weiya.zhang@nottingham.ac.uk) and annotate "Data Access Request" in the subject line. Incomplete and/or UNSIGNED forms will delay the request process.**

Section 1 - Data Applicant Details & Institutional Information

1.1	Applicant Details	Name: Monirah Ali Shuaib PhD student, School of Medicine, Academic Rheumatology, The University of Nottingham Email: monirah.shuaib@nottingham.ac.uk Telephone Number: 07510975322
1.2	Co Applicant/ Supervisor Details	Professor Weiya Zhang Academic Rheumatology, The University of Nottingham Email: weiya.zhang@nottingham.ac.uk Professor Michael Doherty Academic Rheumatology, The University of Nottingham Email: michael.doherty@nottingham.ac.uk Dr. Michelle Hall Division of Physiotherapy Education, The University of Nottingham Email: michelle.hall@nottingham.ac.uk Dr. Subhashisa Swain Email: subhashisa.swain@phc.ox.ac.uk Nuffield Department of Primary Health Care Sciences, Medical Sciences Division, University of Oxford, Oxford, UK Ahmed Thanoon PhD student, Academic Rheumatology, The University of Nottingham Email: ahmed.thanoon@nottingham.ac.uk

KNEE PAIN IN THE COMMUNITY**Data Access Request Form***Rheumatology, Orthopaedics and Dermatology, University of Nottingham*

1.3	Institution Details	Academic Rheumatology School of Medicine The University of Nottingham Clinical Science Building City Hospital Nottingham NG5 1PB
1.4	Date of Request	3 October 2022
1.5	Have you requested data from the KPIC database before?	☒ No

Section 2 - Project Details

2.1	Project Title	The incidence of knee pain and multimorbidity in retired male professional footballers in the United Kingdom
2.2	Proposed Start Date	1 November 2022
2.3	Proposed End Date	1 November 2023

Section 3 - Ethical Approval

3.1	Does the study supporting your project have ethical approval from an Ethics Committee or an Institutional Review Board?	☐ Yes (Please append a copy of the approval) ☐ In Process (Please go to 3.2) ☒ Not Applicable (You may tick this box if you intend to carry out analysis of existing data where the KPIC ethics approval will operate)

Rheumatology, Orthopaedics and Dermatology, University of Nottingham

3.2	Please specify arrangements for obtaining appropriate ethical approval	

Section 4 - Scientific Project Details

Questionnaire Data

	Please indicate details on the traits/data required	This data access application requests the complete questionnaire data for the subset of the KPIC men at baseline selected for the previous football study by Dr Gwen Fernandes. This will form the control population to examine the incidence knee pain and multimorbidity during the follow-up, and associated risk factors. In addition, we will also use the participants of this subset who participated knee radiographic examination and their knee x-rays scores at baseline to examine the association between knee OA at baseline and foot/ankle/OA at follow-up.
	Please indicate participants required	☐ All participants ☒ Subset (Please provide full description in the scientific outline)

Section 5- Scientific Outline

Please provide a 1-2 page outline of your proposal highlighting the specific project requirements for the KPIC data specified above stating the rationale for using this data, including other study methods considered. Please be as precise as possible with regards to trait data required listing the questionnaire areas of interest and inclusion/exclusion criteria of any participants to be studied or approached for possible recruitment into a new study.

Title: The incidence of knee pain and multimorbidity in male retired professional footballers compared to men in the general population

Background Information

Professional footballers (PFs) have a high injury rate and the knee is involved in 17% of all injuries (1). They are constantly exposed to sport-related musculoskeletal injuries, resulting in short and long-term outcomes such as chronic knee pain (KP) and knee osteoarthritis, but because of their physical fitness they may be less likely to have other chronic conditions such as diabetes (2). However, whether PFs are more likely to have long-term conditions) than the general population remains unknown.

Only a few studies have reported on whether current and retired PFs had long-term conditions and comorbidities (3, 4). Multimorbidity, however, is still evolving and has not been evaluated in PFs. The conditions that may affect current and retired PFs include the following:

- ☐ Musculoskeletal problems such as OA of the hip, knee and ankle joints, being especially linked to serious traumatic injuries and operations throughout their career (2, 5).
- ☐ Mental, psychosocial and neurological health issues, such as anxiety/depression, alcohol abuse, concussion and repetitive head trauma, (6, 7).
- ☐ Cardiovascular conditions, such as increased atrial fibrillation and slow cardiac conduction compared to controls (8), and higher mortality rate caused by myocardial infarction (9).

Conversely, PFs may be much fitter and less obese than population controls, so may be at less risk of other long-term conditions such as diabetes and cancer (7).

Rheumatology, Orthopaedics and Dermatology, University of Nottingham

The association of footballers with possible short- and long-term health consequences, including OA and multimorbidity after retirement, is an important concern due to its impact on their health, wellbeing and quality of life. Accordingly, injury prevention and management in PFs is often debated. However, to develop preventive strategies, to update policies of treatment and management, and to reduce the burden of such chronic conditions, a better understanding of epidemiology in footballers is required, since the incidence of KP and multimorbidity remains substantially unknown. Therefore, the aim of this study is to compare the incidence of KP and multimorbidity in retired male PFs with the general population control men in the UK. In addition, we also would like to investigate two specific associations: [1] association between KP and multimorbidity, and [2] association between knee osteoarthritis (KOA) and foot/ankle osteoarthritis, as KP and KOA are more common in footballers, but their associations with multimorbidity and foot/ankle OA remains unknown.

Objectives:

1. To compare the incidence of KP and multimorbidity in professional footballers and general population male controls between 2014 and 2021.
2. To examine the temporal association between KP and multimorbidity (and specific comorbidity), and to examine the proportional risk contribution of the collected risk factors to multimorbidity.
3. To examine the association between Knee OA and ankle/foot OA.

Methods**1. Study Design**

This is a longitudinal cohort study with two sub-cohorts, footballers and age and sex matched general population. Baseline visit was undertaken in 2016 (10). The cohorts were followed up in 2020/21.

2. Participants

A sample of 878 ex-PFs and 1060 control men who have been identified from the previous footballer's study have agreed to participate in a further study. Ex-PFs were recruited initially by the former players' association and the Professional Footballer's Association (n= 21 professional clubs). They were men aged 40 years and older who had played professionally in the top four tiers of the English Football League.

The comparison group was recruited from KPIC through 12 general practitioner/family medicine (GP) practices in the UK Midlands region. All individuals were male, aged 40 years and older, who were not terminally ill.

3. Questionnaire

All information about KP and multimorbidity were obtained by a postal questionnaire survey from ex-PFs and a sample of men from the general population.

The main outcomes of this study include incidence of KP and multimorbidity. KP will be defined as pain in the knee for most days of the past 1 month? (11). A manikin drawing to locate any other body region pain will also be utilised. The incidence of KP will be calculated by dividing number of new cases with KP developed during the follow-up by the total number of people who do not have KP at baseline. Similarly the incidence of multimorbidity will be calculated by dividing number of new cases developed during the follow-up by the total number of people who do not have KP at baseline (2 long-term conditions).

Radiographic assessment

All radiographs for the knee were in weight-bearing semi flexed posterior-anterior and 30 flexion skyline views. Radiographic knee OA was assessed using Kellgren and Lawrence (K-L) composite grade (0-4) for the combined tibiofemoral compartments (medical and lateral) and separately for combined patellofemoral compartments (medical and lateral) using verbal descriptions for features of OA (JSN and/or osteophyte presence) as opposed to a photographic atlas.

The K-L score was defined as follows: grade 0 (no osteophytes, no narrowing), grade 1 (small osteophytes, possible narrowing), grade 2 (definite osteophytes and possible narrowing) in any compartment. Additionally, The Nottingham Line Drawing Atlas (NLDA) was used to score individual compartment and composite joint space narrowing (JSN), individual compartment and subsequent composite osteophyte and combined (global JSN and osteophyte) scores for each knee. The NLDA provides gender (men and women) specific illustrations for JSN to account for the normally wider joint space width in men and gives 0-5 interval scores for osteophyte at eight sites in the three compartments with consideration for natural variations in osteophyte shape (10).

Radiographic foot/ankle OA are in full weight-bearing standing positions (dorsal and lateral views).

Radiographic features of five foot joints for scoring are 1st metatarsophalangeal joint, the 1st cuneo-metatarsal joint, the 2nd cuneo-metatarsal joint, the navicular-first cuneiform joint and the talonavicular joint. The scoring of the radiographic will use both Menz system for the foot and K-L for the ankle (Tables 1

Rheumatology, Orthopaedics and Dermatology, University of Nottingham

and 2): (12, 13).

Table 1: The radiographic scoring for the foot using Menz system

Osteophytes (OS)		Joint space narrowing (JSN)	
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

Table 2: The radiographic scoring for ankle using Kellgren and Lawrence

Grade	Description
0	No radiographic findings of the osteoarthritis – Normal
1	Doubtful narrowing of joint space, possible osteophyte
2	Definite osteophyte, possible narrowing
3	Moderate multiple osteophyte, definite narrowing, some sclerosis, possible deformity of bone ends
4	Large osteophyte, marked narrowing, severe sclerosis, definite deformity of bone ends.

Confounding/covariates

The following are covariates: age, body mass index, injury, surgery, playing position, polypharmacy, nodal OA, 2d4d finger ratio, social class by post code and comorbidities such as diabetes, hypertension and osteoporosis, psychological conditions and gout.

6. Statistical methods:

The incidence of knee pain and multimorbidity will be calculated for both groups. Categorical variables will be reported as frequencies and percentages, and continuous variables as means and standard deviation (SD). A X^2 test (categorical variables) or a t-test (continuous variables) will be used to determine whether distribution of variables are statistically significantly different between both groups, $P < 0.05$ being considered as statistically significant.

The incidence of both KP and multimorbidity will be calculated across age groups in the ex-footballers and the general population and will be displayed graphically. Prevalence of multimorbidity between people with and without KP at baseline will be compared overall and in subgroup between ex-footballers and the general population.

Logistic regression model will be used to examine the association between KP and risk of multimorbidity during the follow-up (2014 to 2021). Age, body mass index, injury, polypharmacy, being professional footballer and social class according to the post codes will be part of the covariates in the logistic regression model. The logistic regression model will be used to calculate the odds ratio (OR) and 95% confidence interval (CI), adjusted for confounding factors. The association between knee OA at baseline and foot/ankle OA at follow-up will also be analysed. Age, body mass index, injury, polypharmacy, being professional footballer, social class, nodal OA, 2d4d finger ratio and comorbidity (e.g., Charlson comorbidity score) will be adjusted for this association (14). The ROC analysis will be undertaken to estimate the proportional risk contribution as appropriate (15). The statistical analysis will be performed using SPSS statistics, version 27.

7. Data Requested:

The full questionnaire data of the subset of the KPIC control men selected at baseline for the football study, and their knee x-ray scores for osteoarthritis. As both data have already been obtained by Dr Fernandes previously, there are no data extraction required, but approval to use the data for the follow-up outcomes.

Section 6 - Agreement

By signing this form, I confirm that I understand and agree to comply with the conditions stipulated below.

The team at Academic Rheumatology in accordance with University of Nottingham's policy will not be permitted to release new and /or identifiable data until a Material Transfer Agreement (MTA) has been finalized for identifiable material or a Data Transfer Agreement (DTA) has been finalized for new (non-identifiable) data.

- I. The data may only be used for non-commercial academic research. The data and the results of the research may not be used for commercial purposes unless a revenue-sharing agreement or commercial license is drafted and processed by the University of Nottingham contracts team.
- II. No data will be passed to third parties or journals without written permission from the KPIC management team
- III. The data remains the property of the University of Nottingham and if any new variables are derived from the data and /or any changes are made to the data, these will be returned to the KPIC management team upon acceptance for publication by a Journal or at the latest within six months from the end of the project, and any new variables derived from the data and/or changes made to the data shall be the property of the University of Nottingham
- IV. No attempt should be made to link or combine the data provided under this agreement to other information or archived data available for the data sets provided, even if access to that data has been formally granted to you, or it is freely available without restriction, unless specific permission to do so has been received from the relevant access committee(s).
- V. The KPIC team who generated the data will be included as a co-authors and its funder's contribution to this project will be acknowledged in any resulting publications or dissemination material.
- VI. All manuscripts and drafts of oral presentations will be submitted to the KPIC management team for review and approval at least 15 days before submission or presentation. A final version of the manuscript and summary of any oral presentations will be sent to the department on final submission.
- VII. Authorship will be agreed by mutual consent. All publications will have to acknowledge the KPIC resource, its provenance within the ARUK Pain Centre and funding by Arthritis Research UK.
- VIII. The identity of the study participants should be protected at all times and no contact or tracing attempts will be made without the specific consent of the KPIC management team.

Main Applicant's/Supervisor's signature and position: (electronic signature acceptable)

Date: [Click here to enter a date.](#)

Co-Applicant/ Student:

Date: [Click here to enter a date.](#)

Please note that for students' applications, main supervisor must countersign

Rheumatology, Orthopaedics and Dermatology, University of Nottingham

KPIC management group:

Professor Weiya Zhang (Chief investigator)

Professor Michael Doherty

Professor Ana Valdes

Professor David Walsh

Dr Michelle Hall

Professor Eamonn Ferguson

Rheumatology, Orthopaedics and Dermatology, University of Nottingham

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Appendix C: Baseline questionnaire for footballers (C-1) and controls (C-2)

Appendix (C-1): baseline questionnaire for footballers

Supporting Partners:



Osteoarthritis Risk in Professional Footballers

The risk of injury in football is increased due to key risk factors. We want to find out about these risk factors for arthritis in the knees of ex-professional footballers.

We would be very grateful if you could take the time to complete this questionnaire. **Your responses are valued and are vitally important to this project.** It should take approximately 20 minutes to complete.

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

Please ring Gwen Fernandes on (0115) 823-1679 if you have any questions.

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

Funded by:



centre for
sport, exercise
& osteoarthritis



SECTION 1 – About Yourself

1. Date of birth:

		/			/				
Day			Month			Year			

2. Height: *Please complete one box only*

	feet			inches	OR				centimetres

3. Weight: *Please complete one box only*

		stones			pounds	OR				kilograms

4. How much did you approximately weigh **in your 20's**?

		stones			pounds	OR				kilograms

5. Nationality: _____

6. Which ethnic group best describes you?

☐ White Caucasian	☐ Black-Caribbean
☐ White-Hispanic	☐ Black-Africa
☐ Indian	☐ Chinese
☐ Other, <i>please specify</i> : _____	

SECTION 2 – About Your Career

7. At what **age** did you start playing competitive team football?
_____ years old
8. At what **age** did you start playing football professionally?
_____ years old
9. For how long did you or have you played professional football (e.g. 1986 – 1999)
From _____ to _____
10. At what standard did you compete for the **majority** of your professional career?
- | | |
|---|---|
| ☐ Premier League | ☐ Old Division 1 (pre-1992) |
| ☐ Championship | ☐ First Division (1992-2004) |
| ☐ League One | ☐ Old Division 2 (pre-1992) |
| ☐ League Two | ☐ Other, <i>please specify</i> : _____ |
11. Approximately how many matches (playing for at least half the match) did you take part in during your professional career (please include first team, reserve and international games)? (e.g. 100 matches)
_____ matches
12. On average, during your professional career, how many hours per day and how many days per week did you spend training?
_____ hours per day _____ days per week
13. What position did you **mainly** play during your professional career?
Please tick one box only
- | | | | |
|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|
| ☐ Goalkeeper | ☐ Defender | ☐ Midfielder | ☐ Forward |
|-------------------------------------|-----------------------------------|-------------------------------------|----------------------------------|

14. When playing football, are you generally:

☐

Right-footed

☐

Left-footed

☐

Equally proficient

15. If you are a retired professional footballer, please indicate your reasons for retiring.
Please tick all that apply.

☐

Football-related Injury, *please specify:* _____

☐

Age

☐

Chronic Knee Pain

☐

Contract no renewed

☐

Other, *please specify:* _____

16. Please list all your occupations since retirement from playing football professionally.
Please indicate whether the occupation was part time (P) or full time (F)* and how long you had each job for.

List of Occupations	Part time (P) or Full time (F)	Date from: (mm/yy)	Date to: (mm/yy)
1)			
2)			
3)			
4)			
5)			
6)			
7)			

***Part time:** 20 hours or less per week

Full time: More than 20 hours per week

SECTION 3 – About Your Current Health

We would now like to ask you some questions about your current health.

17. Have you **ever** been diagnosed by your doctor as having had any of the following?

- ☐ Diabetes ☐ High Blood Pressure ☐ Heart Attack ☐ Gout
- ☐ Depression ☐ Rheumatoid Arthritis ☐ Cancer
- ☐ Other, *please specify*: _____ ☐ Not Applicable

18. Please list **all your current medication** including those prescribed by your doctor and those bought yourself over the counter (include any hormonal medication, vitamin supplements and alternative medicines).

Please indicate the date you started taking the medication for.

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 _____

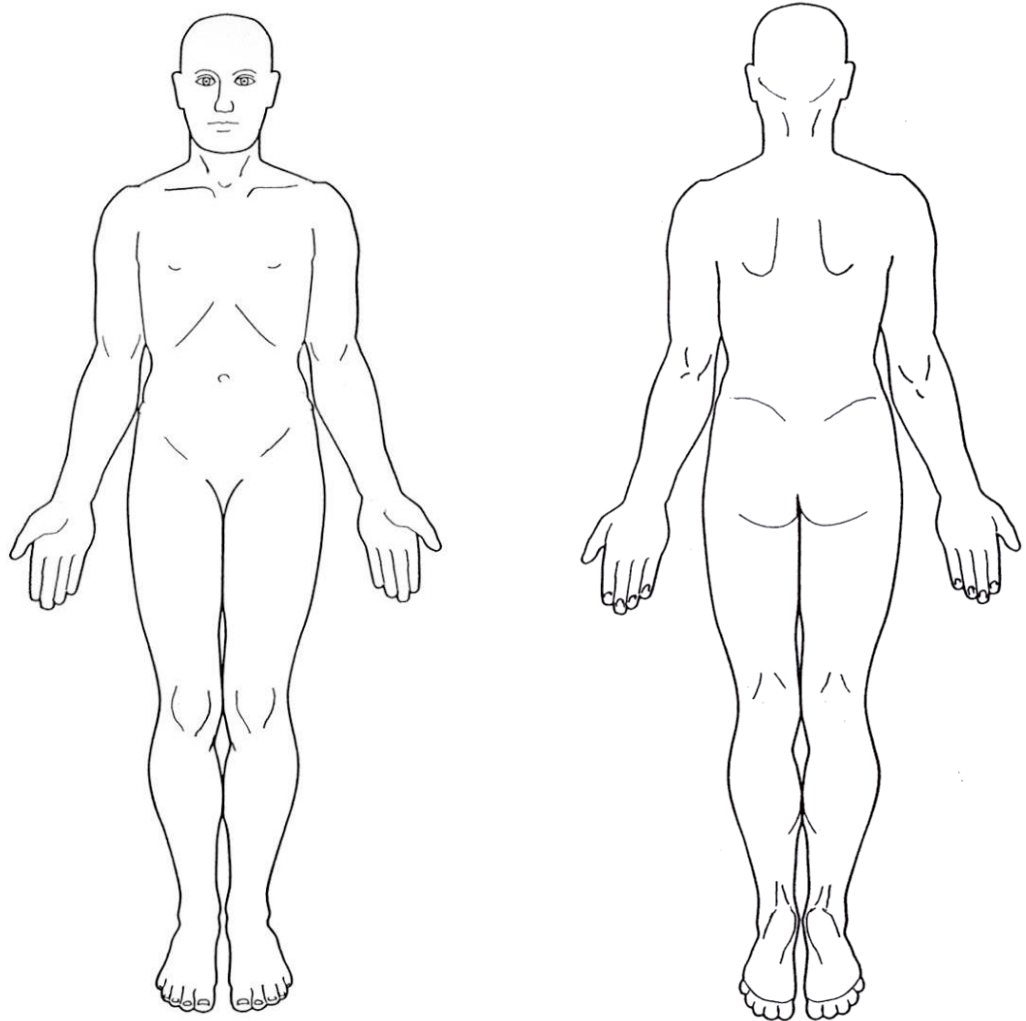
Name of medicine Date started _____

(Please turn over for the next question)

SECTION 4 – About Your Knees

19. 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 that has lasted for most days in the previous month, please tick this box.

☐

20. Have you **ever** had significant pain in and around your knees for **most days of a one month period**?

☐ Yes

☐ No (*Please go to **Question 22***)

21. At what age did you first notice this type of knee pain?

_____ years old

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

☐ Yes

☐ No (*Please go to **Question 26**, page 8*)

23. At what age did you first notice this type of knee pain?

_____ years old

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

☐ Yes, _____ years old

☐ No

(Please turn over for the next question)

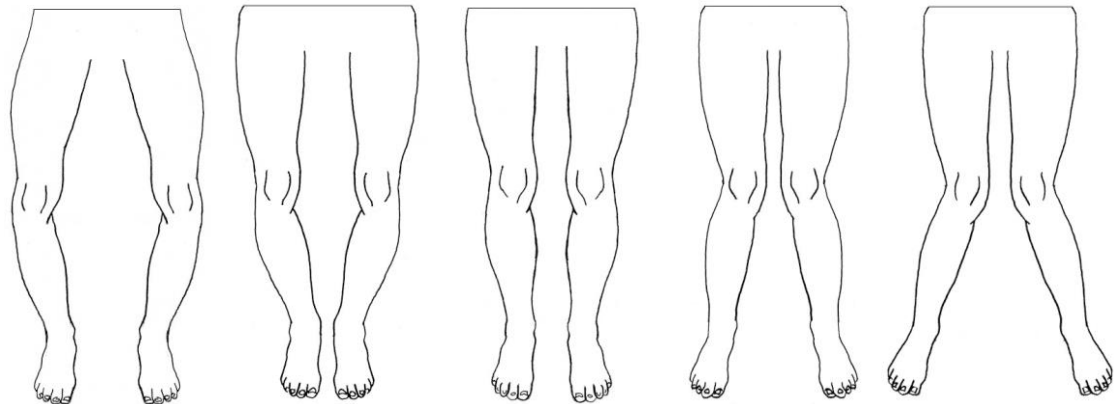
25. Please could you indicate the knee in which you experienced **significant pain** and approximately the age group which it affected you.
*By significant pain, we mean pain you have had for most days for **at least a three month period.***

Age	Left Knee Pain	Right Knee Pain
10 – 15	☐	☐
16 – 20	☐	☐
21 – 30	☐	☐
31 – 40	☐	☐
41 – 50	☐	☐
51 – 60	☐	☐
61 – 70	☐	☐
71 – 80	☐	☐
81 – 90	☐	☐

(Please turn over for the next question)

We are interested in the angle at your knees (that is, straight legs, bow-legged or knock knees) as this may have relevance to the development of osteoarthritis.

Please look at your knees **whilst standing** (preferably in front of a mirror) and tick the appropriate box, in the questions below, to indicate the angle of your knees.



A Very bow legged	B Bow legged	C Straight	D Knocked-knee	E Very knocked-knee

26. Which picture best shows the **current** angle of **each** of your legs?

Right Knee ☐ ☐ **A** ☐ **B** ☐ **C** ☐ **D** ☐ **E**

Left Knee ☐ ☐ **A** ☐ **B** ☐ **C** ☐ **D** ☐ **E**

27. Which picture do **you think** best shows the angle of **each** of your legs **in your 20s**?

Right Knee ☐ ☐ **A** ☐ **B** ☐ **C** ☐ **D** ☐ **E**

Left Knee ☐ ☐ **A** ☐ **B** ☐ **C** ☐ **D** ☐ **E**

(Please turn over for the next question)

SECTION 5 – About Injuries and Surgeries to your Knees

28. Have you ever had a **significant** football-related **injury** to your knees? *We describe a significant injury as one which caused you pain for **most days during a three month period** and resulted in an absence from all training and matches during this time.*

☐ Yes

☐ No (Please go to **Question 31**)

29. Please can you specify the number of significant football related **injuries** you have had through your professional football career in your left knee and right knee.

_____ in your left knee

_____ in your right knee

30. If you **have** suffered with a significant football related injury (*e.g. cruciate ligament rupture (ACL), cartilage injury, fracture on impact*), please could you provide further details on the type of injury , which knee was affected and how old you were when the injury occurred.

Type of Injury	Left Knee	Right Knee	Age when Occurred
1)	☐	☐	
2)	☐	☐	
3)	☐	☐	
4)	☐	☐	
5)	☐	☐	
6)	☐	☐	

31. Similarly, if you **have** suffered with a significant **NON-football** related injury, please could you provide further details on the type of injury, which knee was affected and how old you were when the injury occurred.

Type of Injury	Left Knee	Right Knee	Age when Occurred
1)	☐	☐	
2)	☐	☐	
3)	☐	☐	
4)	☐	☐	

32. Have you ever had any injections into your knees?

☐

Yes

☐

No (Please go to **Question 36**)

33. If you **have had injections** into your knees, please could you state which knee it was and the type of injection you had.

Type of Injection	Left Knee Pain	Right Knee Pain
Steroid / Cortisone	☐	☐
Analgesic / Pain Relief	☐	☐
Hyaluronic Acid	☐	☐
Not Sure	☐	☐
Other, please specify _____	☐	☐

34. Approximately, how many injections **in total** have you had into **each** of your knees over the course of your career (e.g. 1 injection, 5 injection, etc.)

Right Knee _____ injections

Left Knee _____ injections

35. What was the **greatest number** of injections into either of your knees that you ever received **in any one** season?
Please indicate the total number of injections, the knee these were in and the season this occurred.

Knee	Number of Injections	Season (Year)

36. Have you ever had surgery to your knees?

☐ Yes

☐ No (Please go to **Section 6**, page 12)

37. If you **have had any surgery** (e.g. knee joint replacement, cruciate repair or key hole surgery), please could you describe what type of procedure you had, which knee was affected and how old you were when the surgery occurred.

Type of Surgery	Left Knee	Right Knee	Age when Occurred
1)	☐	☐	
2)	☐	☐	
3)	☐	☐	
4)	☐	☐	
5)	☐	☐	
6)	☐	☐	

SECTION 6 – About Your Hands

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

☐

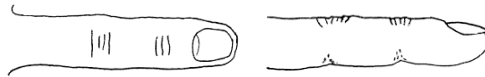
Left-handed

☐

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?

☐

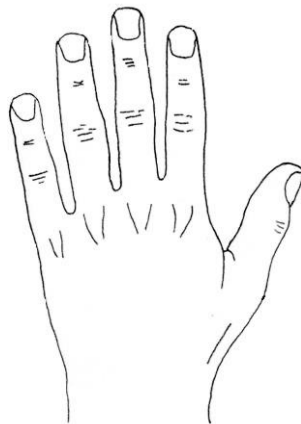
Yes

☐

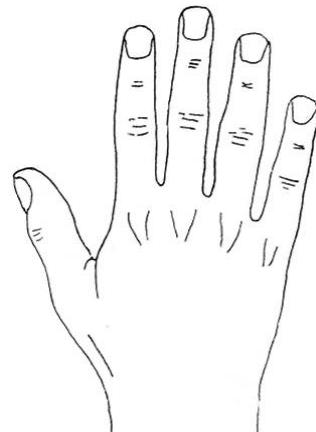
No (Please go to **Question 41**)

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



41. Please could you indicate if any member of your immediate family (parents and/or siblings) has been diagnosed with **osteoarthritis** by a medical professional.

Family Member	Hip	Knee	Hands (Finger Nodes)
1) Mother	☐	☐	☐
2) Father	☐	☐	☐
3) Sibling	☐	☐	☐
4) Sibling	☐	☐	☐
5) Sibling	☐	☐	☐

42. Please could you also indicate whether any member of your immediate family (parents and/or siblings) have had knee or hip replacement surgery?

Family Member	Hip Joint replacement	Knee Joint Replacement
1) Mother	☐	☐
2) Father	☐	☐
3) Sibling	☐	☐
4) Sibling	☐	☐
5) Sibling	☐	☐

41. Please could you indicate if any member of your immediate family (parents and/or siblings) has been diagnosed with **osteoarthritis** by a medical professional.

Family Member	Hip	Knee	Hands (Finger Nodes)
1) Mother	☐	☐	☐
2) Father	☐	☐	☐
3) Sibling	☐	☐	☐
4) Sibling	☐	☐	☐
5) Sibling	☐	☐	☐

42. Please could you also indicate whether any member of your immediate family (parents and/or siblings) have had knee or hip replacement surgery?

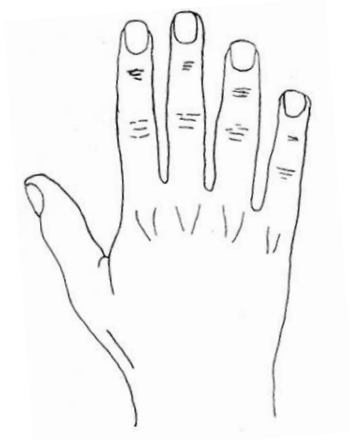
Family Member	Hip Joint replacement	Knee Joint Replacement
1) Mother	☐	☐
2) Father	☐	☐
3) Sibling	☐	☐
4) Sibling	☐	☐
5) Sibling	☐	☐

The 2D:4D ratio is the ratio between the index and ring finger. The length of these two fingers has been associated with competitiveness, athleticism and more recently knee arthritis. Therefore, please could you tell us about your 2D:4D ratio:

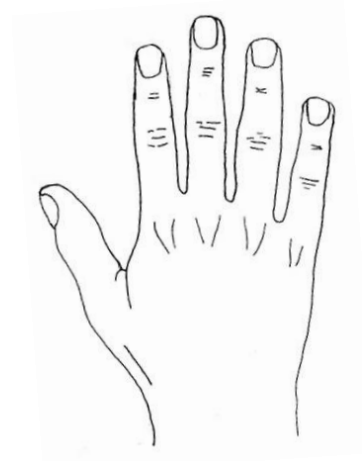
Please look at your right hand with your fingers straight in line with your forearm. Ignore your middle fingers and focus only on your right index and ring fingers.

43. Please select from the pictures below the one that **best** shows the length of your *right index finger in comparison to your right ring finger*.

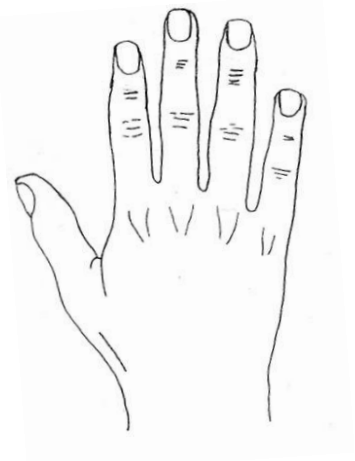
**Index finger is longer
than ring finger**



**Both fingers are of
equal length**



**Ring finger is longer
than index finger**



(Please turn over for the next question)

SECTION 7 – About Your Quality of Life

The following questions are regarding your health-related quality of life. We are able to see the impact any long-term conditions 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

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

☐ Excellent
 ☐ Very Good
 ☐ Good
 ☐ Fair
 ☐ Poor

45. **Compared to one year ago**, how would you rate your general health **now**?

Much better now than one year ago ☐	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 ☐

46. The following questions are about activities you may do during a typical day. **Would your health limit you** in these activities? If so, how much?

	<i>Not, limited at all</i>	<i>Yes, Limited <u>a little</u></i>	<i>Yes, Limited <u>a lot</u></i>
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	☐	☐	☐
	<i><u>Not</u> limited</i>	<i>Yes Limited</i>	<i>Yes Limited</i>

	<i>at all</i>	<i>a little</i>	<i>a lot</i>
Walking half a mile	☐	☐	☐
Walking 100 yards (approx 100 metres)	☐	☐	☐
Bathing and dressing yourself	☐	☐	☐

47. 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)	☐	☐

48. During the **past month**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (e.g. feeling depressed or anxious)?

	Yes	No
Cut down on the amount of time you spent on work or other activities	☐	☐
Accomplished less than you would like	☐	☐
Didn't do work or other activities as carefully as usual	☐	☐

49. 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
☐	☐	☐	☐	☐

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

None	Very mild	Mild	Moderate	Severe	Very Severe
☐	☐	☐	☐	☐	☐

51. 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
☐	☐	☐	☐	☐

52. 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...**

	<i>None of the time</i>	<i>A little of the time</i>	<i>Some of the time</i>	<i>A good bit of the time</i>	<i>Most of the time</i>	<i>All of the time</i>
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?	☐	☐	☐	☐	☐	☐

53. During the **past month**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives etc).

None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
☐	☐	☐	☐	☐	☐

54. How **TRUE** or **FALSE** is **each** of the following statements for you?

	<i>Definitely True</i>	<i>Mostly True</i>	<i>Don't know</i>	<i>Mostly False</i>	<i>Definitely False</i>
I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
I am as healthy as anybody I know	☐	☐	☐	☐	☐
I expect my health to get worse	☐	☐	☐	☐	☐
My health is excellent	☐	☐	☐	☐	☐

(Please turn over)

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. You will be **anonymised** in all further analysis.

We would like to invite a sample of respondents to participate in the second stage of this study. This stage will take place at a location convenient to you and will involve x-rays of your knee joint so that we can study any structural changes.

Please tick this box if you would like more information on this ☐

If you do tick this box, you will receive an information sheet which gives you further details about this stage of the research. You will be given the opportunity to read all the information and then decide whether you would like to take part in the second stage.

Please complete your details below, in order for us to be able to contact you:

Full Name: _____

Address: _____

Best Daytime Phone Number: _____

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

Email address: _____ @ _____

Thank you again for your time

Appendix (C-2) baseline questionnaire for controls

Knee Pain and Related Health

Knee pain, often due to osteoarthritis, is a very common problem affecting 1 in 4 people over the age of 40. We want to understand why some people are more affected than others and the risk factors and health problems associated with knee pain. We would therefore be very grateful if you would take the time to complete this questionnaire, **regardless of whether or not you have knee pain**. We hope you find it interesting. It takes approximately 30 minutes to complete. Most of the questions just require a tick in a box, but for others, clear instructions are given.

We would also be grateful if you could confirm, on the last page of the questionnaire, whether you would be willing to complete a follow-up questionnaire in approximately one year's time and also whether you would like to receive information about further research which will involve a single visit to the Nottingham City Hospital, clinical assessments and an x-ray.

Please return this questionnaire, in the pre-paid envelope (**no stamp required**) to Academic Rheumatology at the Nottingham City Hospital as soon as possible.

Your answers are strictly confidential

If you have any questions or require any assistance completing the questionnaire please telephone: Nadia Frowd on 0115-8231676

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

Chief Investigator – Professor Michael Doherty

Approved by: Nottingham 2 Research Ethics Committee

Funded by:



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Version 2.2, Date 04/12/14

SECTION 1 – About Yourself

1. What is your Date of Birth?

Day
 Month
 Year

2. What Sex are you?

☐ Male
 ☐ Female

3. What is your Height? *Please complete one box only*

Feet
 inches
 OR
 centimetres

4. What is your Weight? *Please complete one box only*

stones
 pounds
 OR
 kilograms

5. Please can you list all **main occupations** you have had, state whether the occupation was full time (F) or part time (P)* and the number of years spent in each occupation.

List of Occupations	Full time (F) or Part time (P)	Time Period (e.g. 3 years)
1)		
2)		
3)		
4)		
5)		
6)		
7)		

***Full time:** More than 20 hours per week
Part time: 20 hours or less per week

SECTION 2: About Your Medical History and Medication

6. Have you **ever** been diagnosed by your doctor as having any of the following?

☐ High Cholesterol

☐ Diabetes

☐ Heart Attack / Angina

☐ Stroke

☐ Hypertension / High Blood Pressure

☐ Irritable Bowel Syndrome

☐ Osteoarthritis of the Hip

☐ Fibromyalgia

☐ Osteoarthritis of the Knee

☐ Chronic Fatigue Syndrome

☐ Cancer *Type:* _____

Other medical conditions not listed above: _____

7. Have you broken either of your legs **in the last 10 years**?

☐ Yes

☐ No

If yes, at what age did this break occur? _____ *years old*

If yes, which bone did you break? _____

8. Have you **ever** suffered significant injury to either of your knees?

☐ Yes, *please specify:* _____

☐ No

If yes, at what age did you suffer the knee injury? _____ *years old*

Did this knee injury require that you see a doctor or go to a hospital for treatment?

☐ Yes

☐ No

9. Please list **all** your **current medication** including those **prescribed by your doctor** and those you **bought yourself** over the counter (*please include any hormonal medication such as oestrogen supplements, vitamin supplements and alternative medicines*). Please indicate the approximate number of months or years you have taken each of these.

Name of Medication	Duration	
	Years	Months
1)		
2)		
3)		
4)		
5)		
6)		
7)		
8)		
9)		
10)		

10. Have you ever taken any “**statins**” medications for lowering your cholesterol and lipids? Examples of statins are Atorvastatin (also known as Lipitor), Simvastatin (also known as Zocor), and Rosuvastatin (also known as Crestor)

☐ Yes ☐ No

Are you still taking a statin?

☐ Yes ☐ No

For approximately how many years have you taken a statin? _____ years

SECTION 3: About Your Knee Pain

11. Have you **ever** had pain in or around a knee on most days for **at least a month**?

☐ Yes

☐ No (*if No, please go to Section 4*)

If yes, at what age did you first notice this type of knee pain? _____ *years old*

12. Have you had knee pain on most days of **this past month**?

☐ Yes

☐ No

13. Has your current knee pain lasted **more than 3 months**?

☐ Yes

☐ No

14. Since it has started, do you think the severity of your knee pain has overall...

☐ Greatly Improved

☐ Slightly Improved

☐ Remained the Same

☐ Worsened

15. Which knee(s) do you / did you experience the pain in?

☐ Right

☐ Left

☐ Both

If both, which overall is the worst knee?

☐ Right

☐ Left

☐ Equal

16. Have you ever had any injections into your knee?

☐ Yes

☐ No

17. If you answered "**yes**", was it:

☐ Steroid Injection

☐ Hyaluronic Acid Injection

☐ Don't Know

18. Have you **ever** had an operation on either of your knees?

☐ Yes

☐ No

If **yes**, what type of operation did you undergo? (If you did not undergo one of the specific operations then please leave the related boxes blank)

Type of Operation	Which Knee? (Right, Left, Both?)	Age at Time of Operation (years)
Arthroscopy / Telescope / Keyhole		
Ligament Repair		
Meniscus or Cartilage Removal		
Joint Replacement		
Other, please specify _____		

19. Have you **ever** consulted a healthcare professional (eg your GP, a hospital specialist, a physiotherapist etc) about your knee pain?

☐ Yes

☐ No

20. Approximately how many different things have you tried for your knee pain (including things like drugs, exercise, changes to diet, footwear modifications etc)? Please include everything you have tried, regardless of whether or not it was recommended by a healthcare professional.

21. Which of the various things you have tried has helped your knee pain the most?

22. **The following questions are to be answered by people who have knee pain.**

We want you to tell us about the knee **where you have the greatest pain**. To get a better sense of the different types of knee pain you may experience, we would like to ask you about any “constant pain” (pain you have all the time) separately from any pain that you may experience less often, that is “intermittent” (pain that comes and goes).

We appreciate that some of these questions may seem a bit repetitive but they have been shown to provide important information about knee pain. **Please answer ALL the questions.**

For each of the following questions please select the answer that best describes **on average your constant knee pain in the PAST WEEK.**

	Not at all	Mildly	Moderately	Severely	Extremely
a. In the past week, how intense has your CONSTANT KNEE PAIN been?	☐	☐	☐	☐	☐
b. In the past week, how much has your CONSTANT KNEE PAIN affected your sleep?	☐	☐	☐	☐	☐
c. In the past week, how much has your CONSTANT KNEE PAIN affected your overall quality of life?	☐	☐	☐	☐	☐
d. In the past week, how frustrated or annoyed have you been by your CONSTANT KNEE PAIN?	☐	☐	☐	☐	☐
e. In the past week, how upset or worried have you been by your CONSTANT KNEE PAIN?	☐	☐	☐	☐	☐

23. Now please select the response that best describes **on average your knee pain that comes and goes** in the **PAST WEEK**

	Not at all	Mildly	Moderately	Severely	Extremely
a. In the past week, how intense has your knee pain that comes and goes been?	☐	☐	☐	☐	☐
b. In the past week, how much has your knee pain that comes and goes affected your sleep?	☐	☐	☐	☐	☐
c. In the past week, how much has your knee pain that comes and goes affected your overall quality of life?	☐	☐	☐	☐	☐
d. In the past week, how frustrated or annoyed have you been by your knee pain that comes and goes ?	☐	☐	☐	☐	☐
e. In the past week, how upset or worried have you been by your knee pain that comes and goes ?	☐	☐	☐	☐	☐
f. In the past week, how frequently has this knee pain that comes and goes occurred?	☐	☐	☐	☐	☐

We now want to ask you about **any kind of knee pain** that you may be currently experiencing

24. **Over the past month**, in your most painful knee, does pain **run up or down** your leg?

☐ Yes

☐ No

Please tell us about the **intensity of discomfort** you experience in or around your **most painful knee**.

25. How would you rate your most painful knee pain on a 0-10 scale at the present time, that is **right now**, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (Please circle only ONE number)

No Pain

Pain as bad as it could be

0	1	2	3	4	5	6	7	8	9	10

26. In the **past month**, how intense was your '**worst knee pain**' rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (Circle only ONE number)

No Pain

Pain as bad as it could be

0	1	2	3	4	5	6	7	8	9	10

27. In the **past month**, on **average**, how **intense** was the pain in your **most painful knee** rated on a 0-10 scale, where 0 is 'no pain' and 10 is 'pain as bad as could be'? (That is, your usual pain at times you were experiencing pain.) (Circle only ONE number)

No Pain

Pain as bad as it could be

0	1	2	3	4	5	6	7	8	9	10

28. This next question is on the pattern of your pain in your **most painful knee**. Which of the 4 different options below is the one that best describes the pattern of your worst knee pain over the past month? (Tick one box)

☐		Persistent pain with slight fluctuations
☐		Persistent pain with pain attacks
☐		Pain attacks without pain between them
☐		Pain attacks with pain between them

29. Please select the response that best describes the **type of pain in your most painful knee** over the **past month**. Please do not leave any questions blank and tick one box.

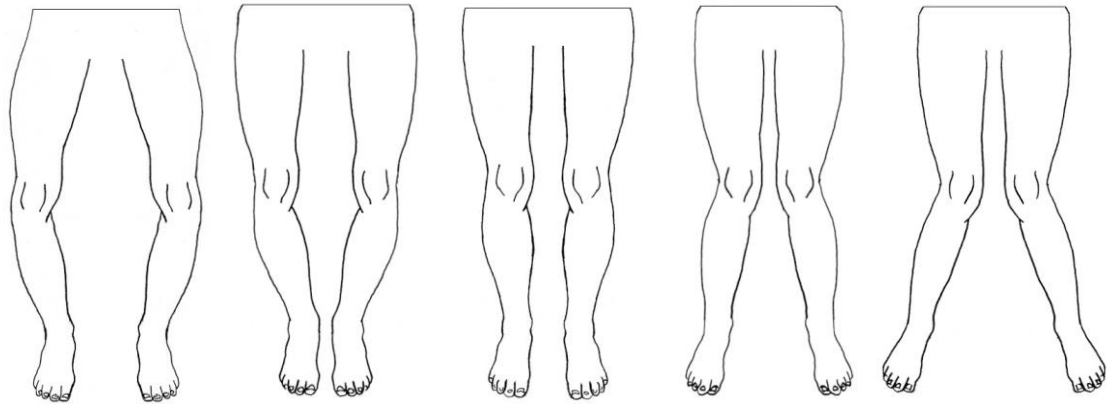
	Never	Hardly Noticed	Slightly	Moderate	Strongly	Very Strongly
a. Do you suffer from a <u>burning</u> sensation (eg stinging nettles) in or around your most painful knee?	☐	☐	☐	☐	☐	☐
b. Do you have a <u>tingling or prickling</u> sensation in the area of your most painful knee 'pain' (eg like crawling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

SECTION 4: About the Angle of your Legs

30. We are interested in the angle of your legs (that is, straight legs, bow-legged or knock knees) as this may have relevance to the development of osteoarthritis.

Please look at your legs **whilst standing** (preferably in front of a mirror) and then indicate the angle of your legs based on the diagrams below.

Most people will have similar angulations in their left and right knees, but in a few people these angulations may differ. We therefore would like you to score your knees separately.



A	B	C	D	E
Very bow legged	Bow legged	Straight	Knocked-knee	Very knocked-knee

a) Which diagram best shows the **current** angle of **each** of your legs?

Right Leg	☐	A	☐	B	☐	C	☐	D	☐	E
Left Leg	☐	A	☐	B	☐	C	☐	D	☐	E

b) Which diagram do **you think** best shows the angle of **each** of your legs **in your 20s**?

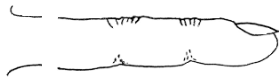
Right Leg	☐	A	☐	B	☐	C	☐	D	☐	E
Left Leg	☐	A	☐	B	☐	C	☐	D	☐	E

SECTION 5: About Your Hands

We are interested in knowing whether you have any finger nodes. These sometimes relate to arthritis in the hand and other joints.

A finger **node** is a firm, bobby swelling on the back of the finger joint. They look like the examples below:

A finger **without** nodes:



A finger **with** nodes:



Please look at your hands and then answer the following questions

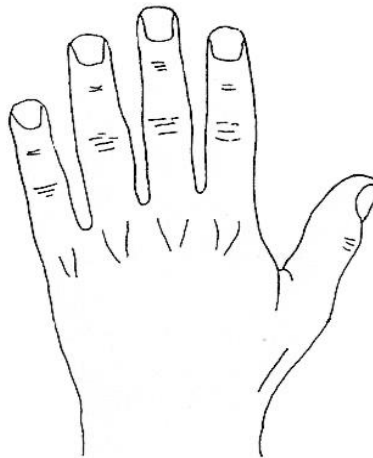
31. Do you think you have any **nodes/swellings** on your hands?

☐ Yes

☐ No (*if No, please go to Question 32*)

If yes, for each hand please circle the finger joint(s) where you have these nodes. *Please circle ALL the joints that are affected*

LEFT



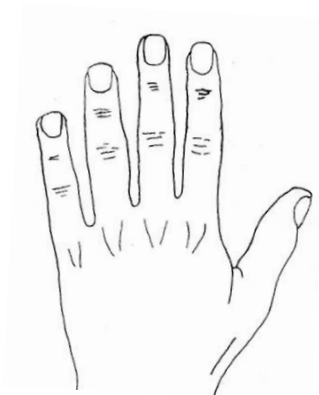
RIGHT



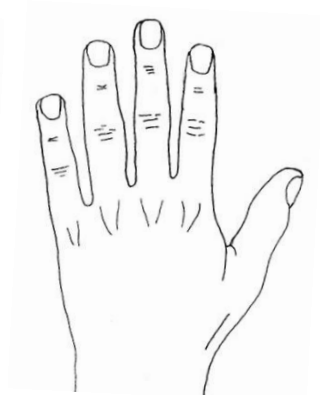
32. We are now interested in which of your **index** and **ring** fingers is longer. **First**, please look at one of your hands with your **fingers straight in line with your forearm**. If you have arthritis in the hands please look at the hand with less arthritis.

Ignore your middle finger and try to **focus only on your index and ring fingers**. Select from the pictures below the one that best shows the length of your **index finger** in comparison to your **ring finger** and tick the appropriate box.

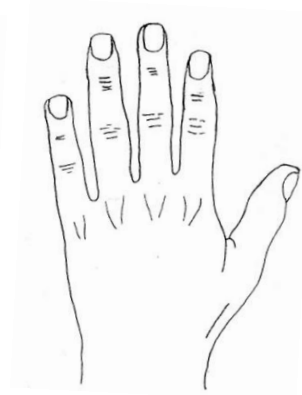
Index finger longer than
ring finger



Both fingers are of
equal length



Ring finger is longer
than index finger



33. Which **hand do you use more often** for writing and brushing your teeth?

☐

Right-Handed

☐

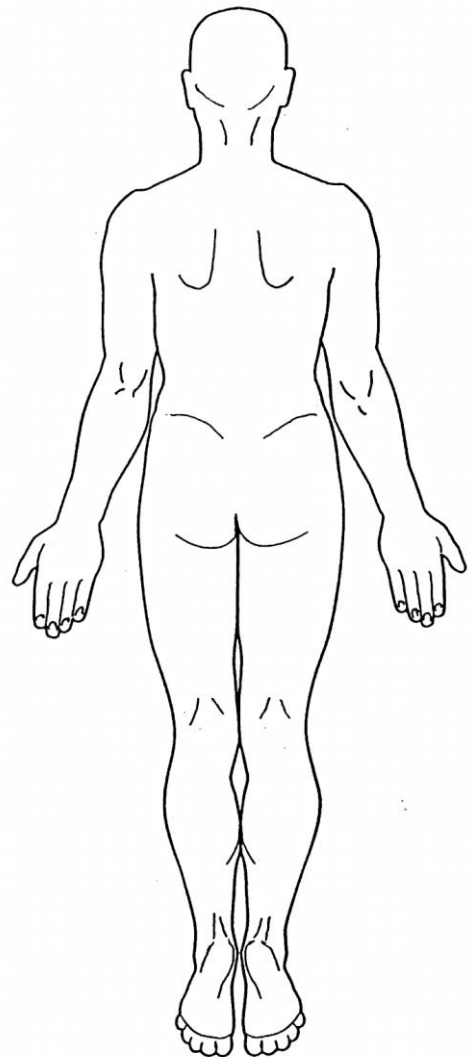
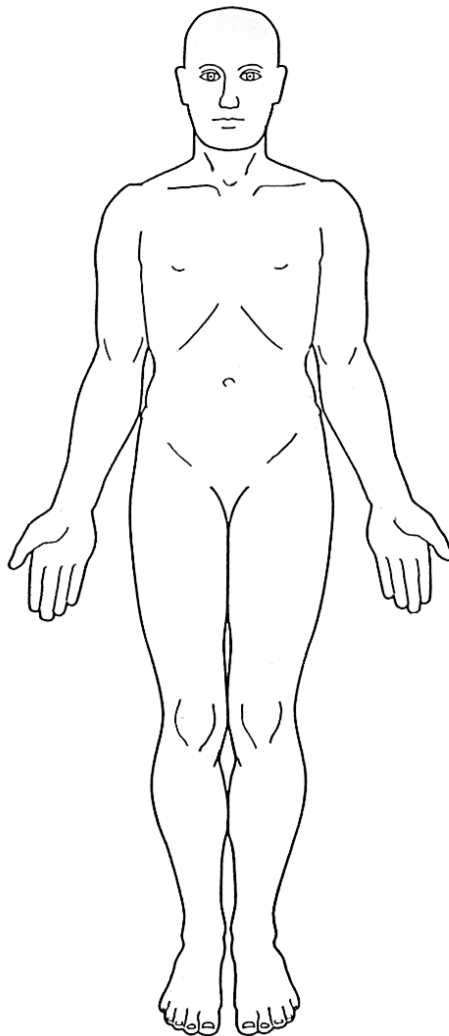
Left-Handed

☐

Equally Proficient

SECTION 6: About Pain Anywhere in your Body

34. This question is about **recent pain** you may have had in **any part of your body**. Please shade in the diagram below to indicate where you have suffered **any pain for most days in the previous month**. By pain we also mean aching, discomfort and/or stiffness. Please **do not include** pain due to feverish illness such as flu. If you **do not have any body pain** that has lasted one day or longer in the last 4 weeks, please tick this box and move ☐ SECTION 7.



35. How much physical pain have you had during the **past 4 weeks**? (*please tick one*)

None	Very mild	Mild	Moderate	Severe	Very Severe
☐	☐	☐	☐	☐	☐

36. If you answered “moderate” or “severe” or “very severe”, has this pain lasted **more than 3 months**?

☐ Yes ☐ No

37. Of the areas highlighted on the previous page, where do you have the strongest pain or the one that disturbs you the most?

38. Have you **ever** consulted a doctor (GP or hospital) about this pain in your body?

☐ Yes ☐ No

SECTION 7: The Way You Feel

39. The following questions are designed to help us to know how you feel. Read each item below and place tick ✓ the box next to the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies. Your immediate reaction to each item will probably be more accurate than a long, thought-out response.

a. I feel tense or 'wound up'

- ☐ most of the time
☐ a lot of the time
☐ from time to time, occasionally
☐ not at all

b. I still enjoy the things I used to enjoy

- ☐ definitely as much
☐ not quite so much
☐ only a little
☐ hardly at all

c. I get a sort of frightened feeling as if something awful is about to happen

- ☐ very definitely and quite badly
☐ yes, but not too badly
☐ a little, but it doesn't worry me
☐ not at all

d. I can laugh and see the funny side of things

- ☐ as much as I always could
☐ not quite so much now
☐ definitely not so much now
☐ not at all

e. Worrying thoughts go through my mind

- ☐ a great deal of the time
☐ a lot of the time
☐ not too often
☐ very little

f. I feel cheerful

- ☐ never
☐ not often
☐ sometimes
☐ most of the time

g. I can sit at ease and feel relaxed

- ☐ definitely
☐ usually
☐ not often
☐ not at all

h. I feel as if I am slowed down

- ☐ nearly all the time
☐ very often
☐ sometimes
☐ not at all

i. I get a sort of frightened feeling like 'butterflies' in the stomach

- ☐ not at all
☐ occasionally
☐ quite often
☐ very often

j. I have lost interest in my appearance

- ☐ definitely
☐ I don't take as much care as I should
☐ I may not take quite as much care
☐ I take just as much care as ever

k. I feel restless as if I have to be on the move

- ☐ very much indeed
☐ quite a lot
☐ not very much
☐ not at all

l. I look forward with enjoyment to things

- ☐ as much as I ever did
☐ rather less than I used to
☐ definitely less than I used to
☐ hardly at all

m. I get sudden feelings of panic

- ☐ very often indeed
☐ quite often
☐ not very often
☐ not at all

n. I can enjoy a good book or radio or television programme

- ☐ often
☐ sometimes
☐ not often
☐ very seldom

SECTION 8: About your Quality of Life

We want to know how you react to illness or pain. Please answer all questions below. Tick one answer even if you cannot answer accurately. Answer the other few questions with a few words or sentences.

40. How often do you see a doctor?

☐

Almost
never

☐

Only very
rarely

☐

About 4
times a year

☐

About once
a month

☐

About once
a week

41. How many different doctors, chiropractors or other health specialists have you seen in the past year?

☐

None

☐

1

☐

2 or 3

☐

4 or 5

☐

6 or more

42. How many times have you had treatment during the past year? (For example, drugs, change of drugs, surgery, etc.)

☐

None

☐

1

☐

2 or 3

☐

4 or 5

☐

6 or more

If yes, what were the treatments?

The next three questions concern your bodily symptoms (for example, pain, aches, pressure in your body, breathing difficulties, tiredness, etc.).

43. Does your pain or other bodily symptoms stop you from working (including both work outside the home and your housework)?

☐

No

☐

Rarely

☐

Sometimes

☐

Often

☐

Most of the time

44. Does your pain or other bodily symptoms stop you from concentrating on what you are doing?

☐

No

☐

Rarely

☐

Sometimes

☐

Often

☐

Most of the time

45. Does your pain or other bodily symptoms stop you from enjoying yourself?

☐

No

☐

Rarely

☐

Sometimes

☐

Often

☐

Most of the time

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

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

47. The following questions are about activities you may do during a typical day. **Would your health limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	Not, limited at all
Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐

48. During the **past month**, have you had any of the following problems with work or other regular daily activities **as a result of your physical health**?

	Yes	No
Accomplished less than you would like	☐	☐
Were limited in the kind of work or other activities	☐	☐

49. During the **past month**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (e.g. feeling depressed or anxious)?

	Yes	No
Accomplished less than you would like	☐	☐
Didn't do work or other activities as carefully as usual	☐	☐

50. During the **past month** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

51. These next questions are about how you feel and how things have been with you **during the past month**. Please give the **one** answer that is closest to the way you have been feeling for **each** item.

How much time **during the last month...**

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

52. During the **past month**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives etc).

None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
☐	☐	☐	☐	☐	☐

53. Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, knee pain, hip pain, back pain or muscle pain. We are interested in the types of thoughts and feeling that you have **when you are in pain**. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. **Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.**

	Not At All	Slight Degree	Moderate Degree	Great Degree	All the time
a. I worry all the time about whether the pain will end	☐	☐	☐	☐	☐
b. I feel I can't go on	☐	☐	☐	☐	☐
c. It's terrible and I think it's never going to get any better	☐	☐	☐	☐	☐
d. It's awful and I feel that it overwhelms me	☐	☐	☐	☐	☐
e. I feel I can't stand it anymore	☐	☐	☐	☐	☐
f. I become afraid that the pain will get worse	☐	☐	☐	☐	☐
g. I keep thinking of other painful events	☐	☐	☐	☐	☐
h. I anxiously want the pain to go away	☐	☐	☐	☐	☐
i. I can't seem to keep it out of my mind	☐	☐	☐	☐	☐
j. I keep thinking about how much it hurts	☐	☐	☐	☐	☐
k. I keep thinking about how badly I want the pain to stop	☐	☐	☐	☐	☐
l. There's nothing I can do to reduce the intensity of the pain	☐	☐	☐	☐	☐
m. I wonder whether something serious may happen	☐	☐	☐	☐	☐

54. How often during the **past 4 weeks** did you:

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. get enough sleep to feel rested in the morning?	☐	☐	☐	☐	☐	☐
b. awaken short of breath or with a headache?	☐	☐	☐	☐	☐	☐
c. have trouble falling asleep?	☐	☐	☐	☐	☐	☐
d. have trouble staying awake during the day	☐	☐	☐	☐	☐	☐

55. **In the past month**, did you feel tired on most days?

☐ Never	☐ Seldom	☐ Sometimes	☐ Often	☐ Always

Thank you very much for taking the time to complete this questionnaire.
We would like to emphasise that your contact details and responses will be kept
completely confidential

We would be grateful if you could now answer the following questions regarding your willingness to participate further in our research.

- 1] **To enable us to evaluate the development and progression of knee pain, we would like to send you a follow-up questionnaire in approximately one years' time. We would therefore be grateful if you could confirm below whether you are happy to receive a follow up questionnaire and also whether you give your permission for us to contact your GP, the Health and Social Care Information service or other central UK NHS body to confirm your contact details, at the time of mailing the follow up questionnaire:**

No, I do not want to receive a follow up questionnaire ☐

Yes, I would be willing to receive a follow up questionnaire and give my permission for the research team to contact my GP, the Health Social Care Information Service or other central UK NHS body to confirm my contact details ☐

If you have answered 'Yes' above, please sign and date:

Signature

Date

- 2] **Depending on your responses in this questionnaire, you may be eligible to participate in a more detailed assessment which involves a clinical assessment and knee x-rays at Nottingham City Hospital. If you are eligible, would you be interested in receiving information that explains this part of the study in detail? Receiving information would not commit you to being in this study.**

Yes, I would like to receive written information ☐

No, I would not like to receive written information ☐

- 3] **Finally, your responses to this questionnaire may make you eligible to participate in future research studies on osteoarthritis at the University of Nottingham. If you are interested, please could you indicate this by ticking the relevant box below? Again, receiving further information would not commit you to being in further studies.**

Yes, I would like to receive written information ☐

No, I would not like to receive written information ☐

If you have answered yes to the questions on page 21, please confirm your contact details below:

Full Name: _____

Address: _____

Best Daytime Phone Number: _____

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

Email address: _____ @ _____

Thank you for your time.

Please return this questionnaire in the pre-paid envelope provided.

Appendix D: Follow-up questionnaire for footballers (D-1) and controls (D-2)

Appendix (D-1) follow-up questionnaire for footballers



University of
Nottingham
UK | CHINA | MALAYSIA



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**

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SECTION 1 – You and Your Current Health

1. Date of Birth:

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

☐ 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, <i>please specify</i> :	☒ 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

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 _____

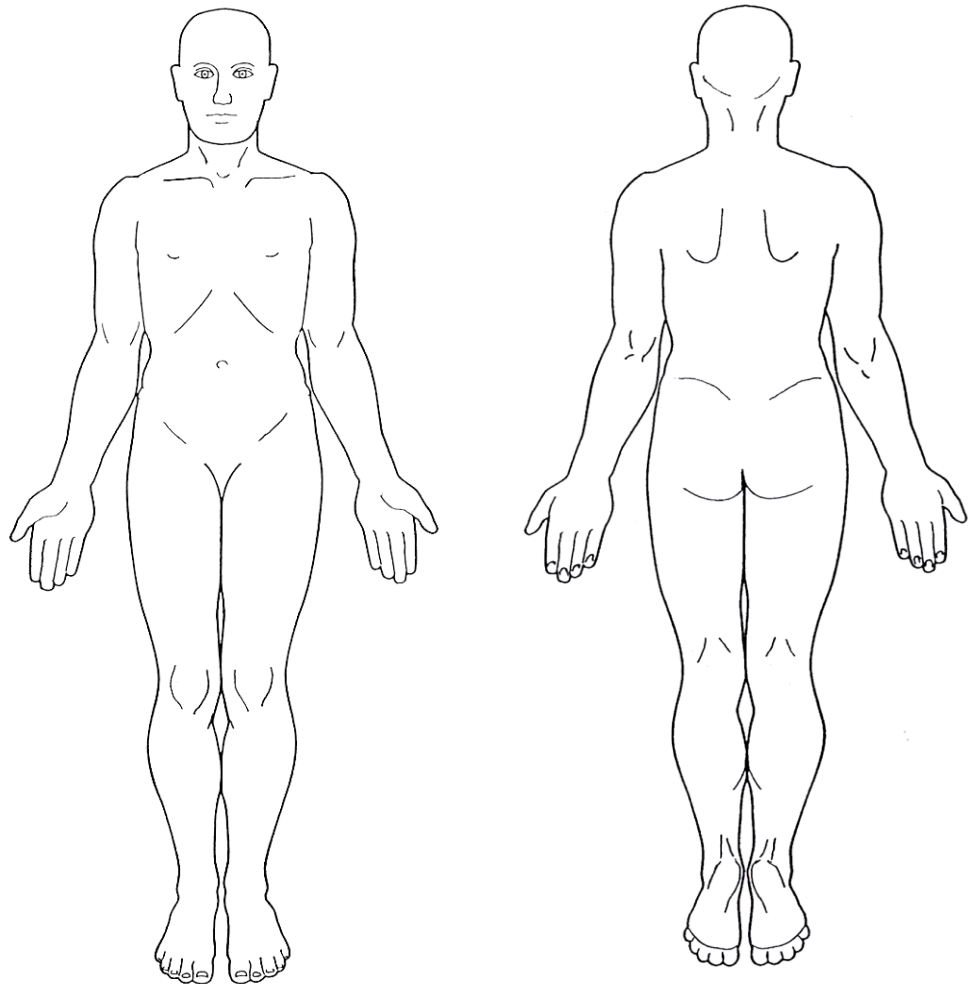
Name of Medicine Date Started _____

Name of Medicine Date Started _____

SECTION 2 – Pain anywhere in your Body

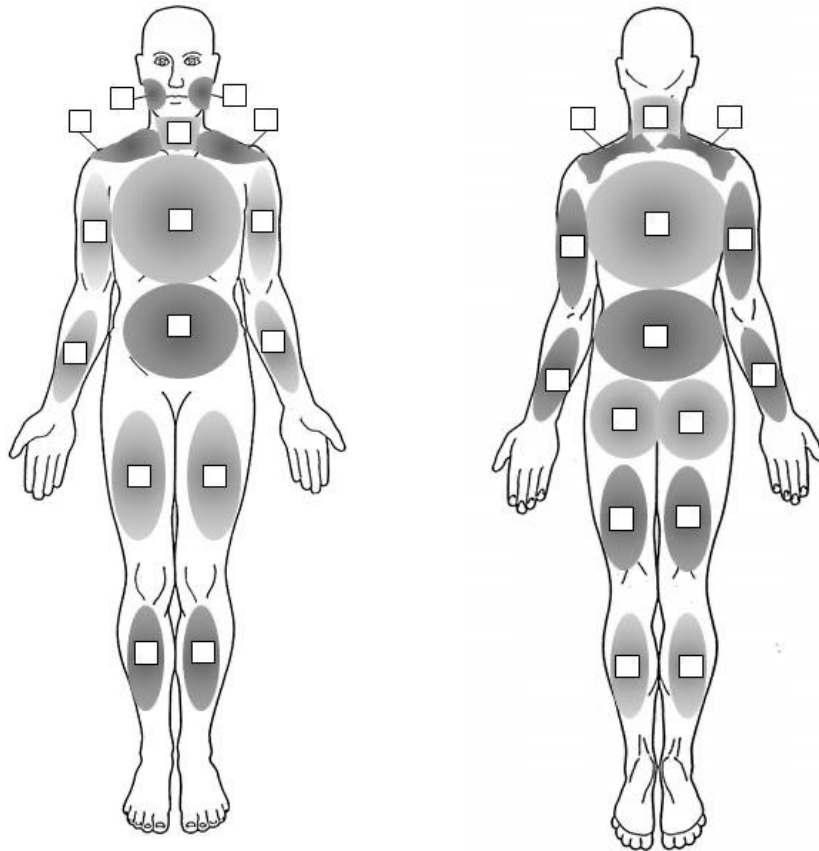
8. Please *shade* in the diagram below to indicate where you have suffered **any pain for most days in the previous month**. By pain we also mean aching, discomfort, and/or stiffness. Please do not include pain due to feverish illness such as the flu.

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



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).



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.

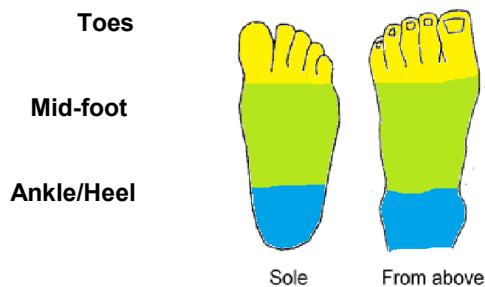
☐ Muscle Pain	☐ Diarrhoea	☐ Headache	☐ Itching
☐ Muscle weakness	☐ Dry mouth	☐ Dizziness	☐ Raynaud's*
☐ Numbness/tingling	☐ Vomiting	☐ Depression	☐ Hives**
☐ Fever	☐ Heartburn	☐ Nervousness	☐ Rash
☐ Irritable bowel Syndrome	☐ Oral ulcers	☐ Blurred vision	☐ Sun sensitivity
☐ Pain/cramps in abdomen	☐ Loss/change 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

SECTION 3 – Your Feet

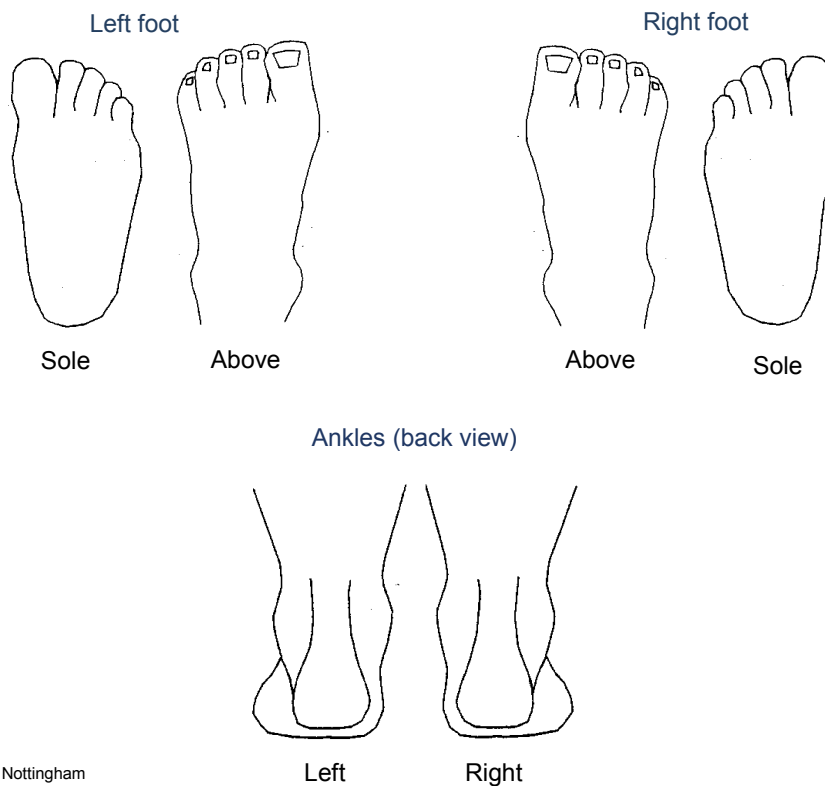
The following questions are about pain you may have in one or both of your feet. Please see the diagram below which shows three **different regions of the foot** i.e. toes, mid-foot, and ankle/heel which have been colour coded here for clarity and reference when completing the questions.



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



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.

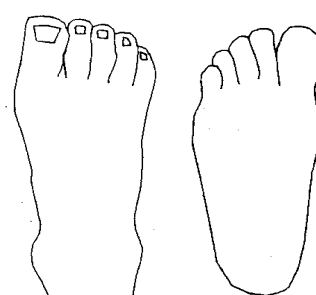
Left foot



Sole

Above

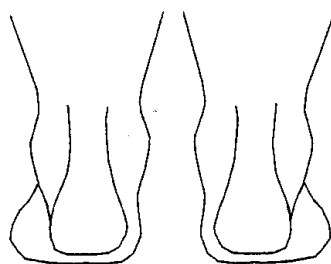
Right foot



Above

Sole

Ankles (back view)



Left

Right

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

Yes ☐

No ☐

If **yes**, please state the foot region and your age when diagnosed:

Ankle years old

Mid-foot 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	☐	☐	☐	☐	☐	☐	☐	☐

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 <u>burning</u> sensation (e.g. stinging nettles) in or around your most painful foot?	☐	☐	☐	☐	☐	☐
b. Do you have a <u>tingling or prickling</u> sensation in the area of your most painful ankle/foot ' (e.g. like crawling ants or electrical tingling)?	☐	☐	☐	☐	☐	☐
c. Is <u>light touching</u> (clothing, a blanket) in this area painful?	☐	☐	☐	☐	☐	☐
d. Do you have <u>sudden</u> pain attacks in the area of your most painful foot, like electrical shocks?	☐	☐	☐	☐	☐	☐
e. Is <u>cold or heat</u> (bath water) in this area occasionally painful?	☐	☐	☐	☐	☐	☐
f. Do you suffer from a sensation of <u>numbness</u> in or around your most painful foot?	☐	☐	☐	☐	☐	☐
g. Does slight <u>pressure</u> in this area, (e.g. with a finger), trigger pain?	☐	☐	☐	☐	☐	☐

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	☐	☐	☐	☐	☐

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

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

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

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, <i>please specify</i>		

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*)

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.

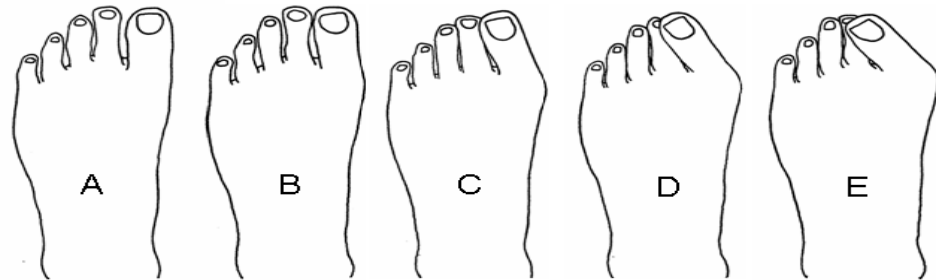
Type of surgery	Right side		Left side		Age
	Ankle	Toes	Ankle	Toes	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	

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

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**.



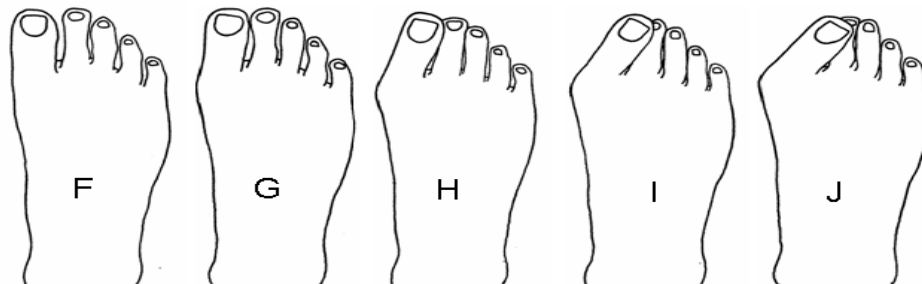
31. Which picture best shows the angle of your left big toe **currently**?

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 ☐

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

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**?

<i>Much better now than one year ago</i>	<i>Somewhat better now than one year ago</i>	<i>About the same as one year ago</i>	<i>Somewhat worse now than one year ago</i>	<i>Much worse now than one year ago</i>
☐	☐	☐	☐	☐

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?

	<i>Yes, Limited <u>a lot</u></i>	<i>Yes, Limited <u>a little</u></i>	<i>Not limited at all</i>
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	☐	☐	☐

	<i>Yes, Limited a lot</i>	<i>Yes, Limited a little</i>	<i>Not, limited at all</i>
Walking half a mile	☐	☐	☐
Walking 100 yards (<i>approximately 100 metres</i>)	☐	☐	☐
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**?

	<i>Yes</i>	<i>No</i>
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)?

	<i>Yes</i>	<i>No</i>
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	☐	☐

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**.....

	<i>All of the time</i>	<i>Most of the time</i>	<i>A good bit of the time</i>	<i>Some of the time</i>	<i>A little of the time</i>	<i>None of the time</i>
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?	☐	☐	☐	☐	☐	☐

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?

	<i>Definitely True</i>	<i>Mostly True</i>	<i>Don't know</i>	<i>Mostly False</i>	<i>Definitely False</i>
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	☐	☐	☐	☐	☐

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

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)

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 ☐

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 ☐

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.**

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.....

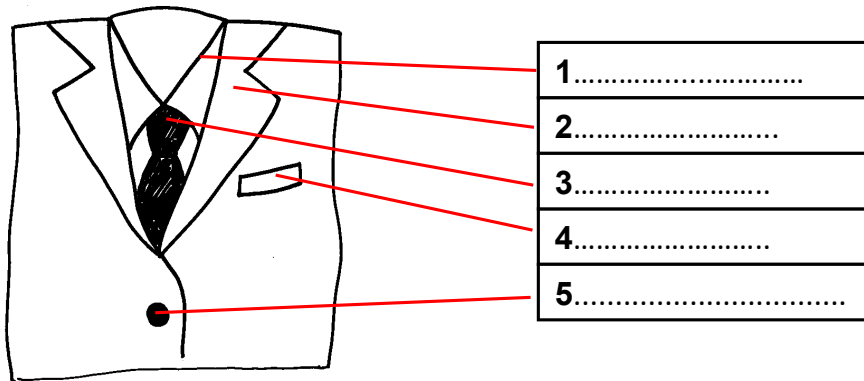
WHY IS A CARROT LIKE A POTATO?.....

WHY IS A LION LIKE A WOLF ?

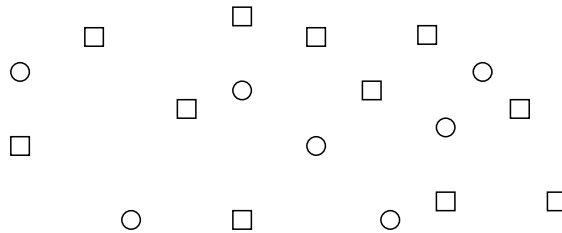
REMEMBER: GOOD CITIZENS ALWAYS WEAR STOUT SHOES

Please Turn Over

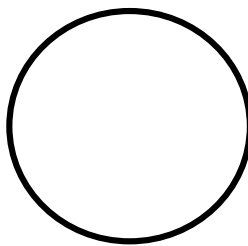
PLEASE NAME THESE ITEMS



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:**

.....

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28

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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29

Appendix (D-2) follow-up questionnaire for controls



University of
Nottingham
UK | CHINA | MALAYSIA



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**

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Final Version 1.0 8.11.19

SECTION 1 – You and Your Current Health

1. Date of Birth:

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

☐ HIV/AIDS	☐ 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, <i>please specify</i> : _____	☒ 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

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 _____

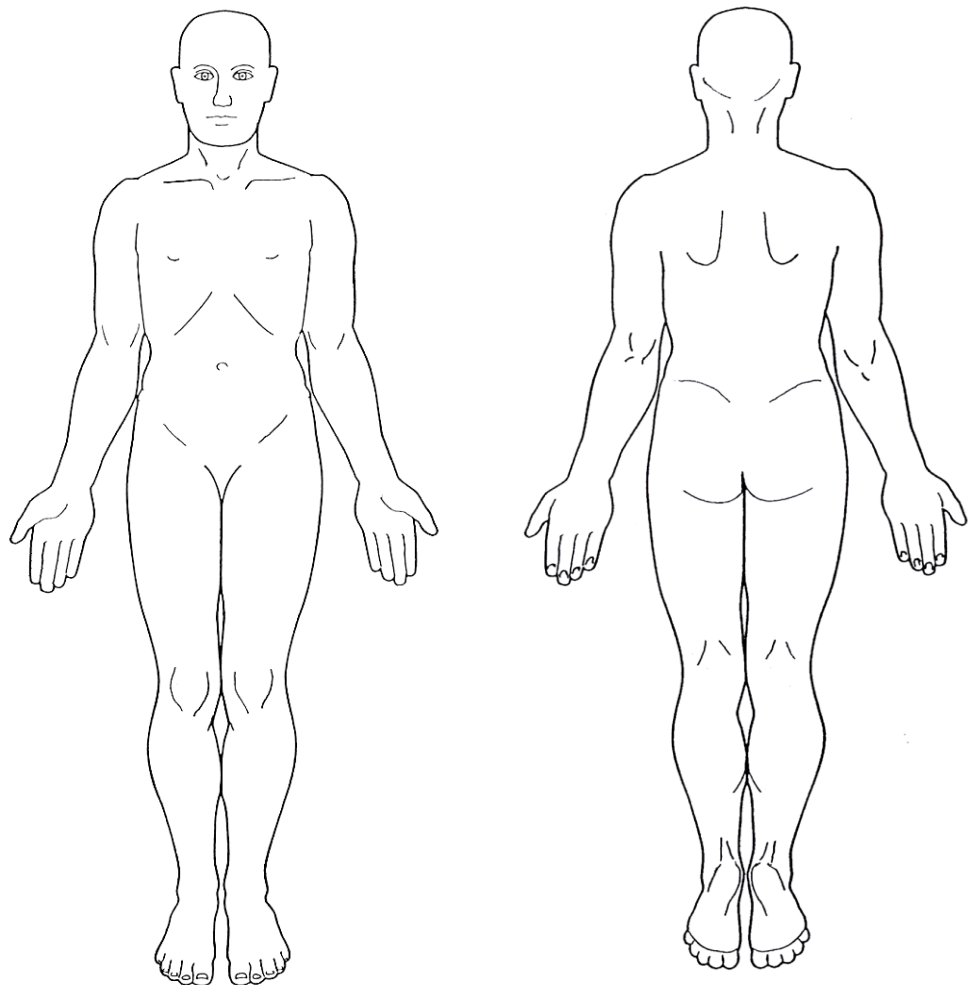
Name of Medicine Date Started _____

Name of Medicine Date Started _____

SECTION 2 – Pain anywhere in your Body

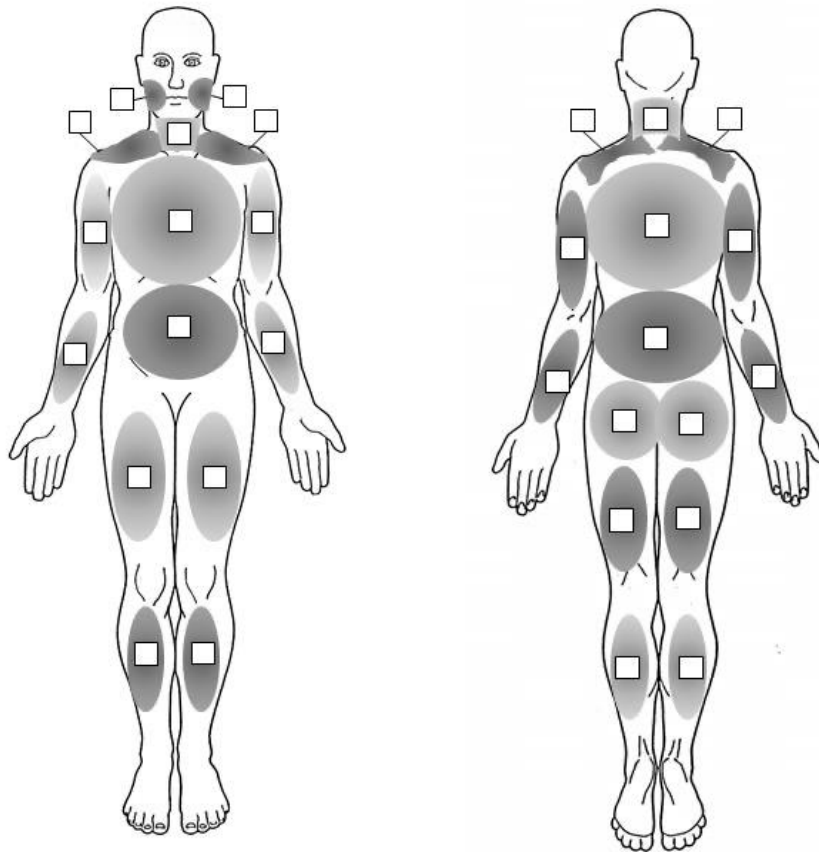
8. Please *shade* in the diagram below to indicate where you have suffered **any pain for most days in the previous month**. By pain we also mean aching, discomfort, and/or stiffness. Please do not include pain due to feverish illness such as the flu.

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



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).



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.

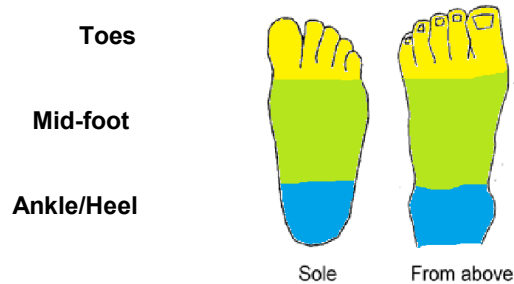
☐ Muscle Pain	☐ Diarrhoea	☐ Headache	☐ Itching
☐ Muscle weakness	☐ Dry mouth	☐ Dizziness	☐ Raynaud's*
☐ Numbness/tingling	☐ Vomiting	☐ Depression	☐ Hives**
☐ Fever	☐ Heartburn	☐ Nervousness	☐ Rash
☐ Irritable bowel Syndrome	☐ Oral ulcers	☐ Blurred vision	☐ Sun sensitivity
☐ Pain/cramps in abdomen	☐ Loss/change 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

SECTION 3 – Your Feet

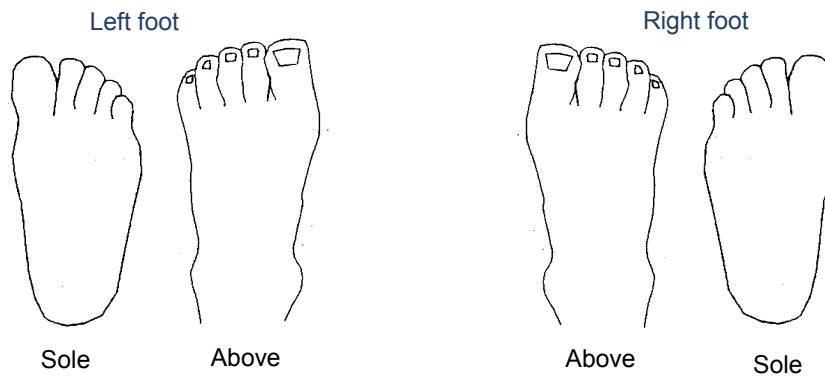
The following questions are about pain you may have in one or both of your feet. Please see the diagram below which shows three **different regions of the foot** i.e. toes, mid-foot, and ankle/heel which have been colour coded for clarity and reference when completing the questions.



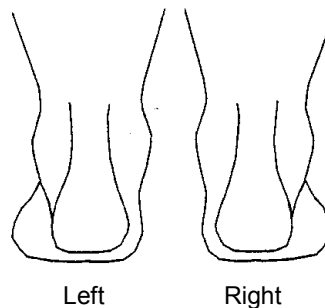
12. Have you had significant pain in or around your feet for **most days in the past month**?

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

No ☐ Please continue to Question 14



Ankles (back view)



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

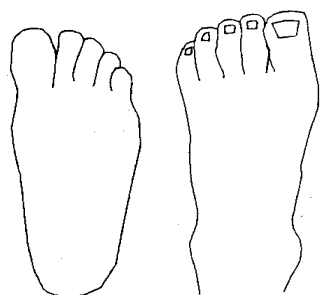
Other Toe(s): years old

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.

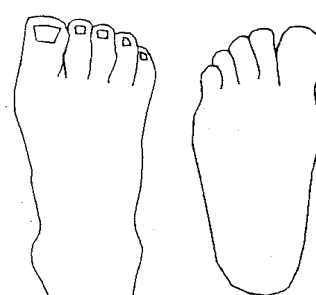
Left foot



Sole

Above

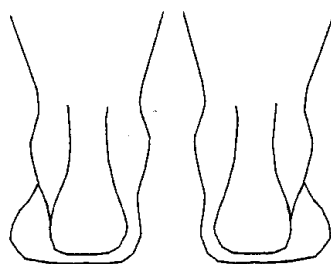
Right foot



Above

Sole

Ankles (back view)



Left

Right

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

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

Ankle ☐ years old Mid-foot ☐ 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	☐	☐	☐	☐	☐	☐	☐	☐

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 <u>burning</u> sensation (e.g. stinging nettles) in or around your most painful foot?	☐	☐	☐	☐	☐	☐
b. Do you have a <u>tingling or prickling</u> sensation in the area of your most painful ankle/foot (e.g. like crawling ants or electrical tingling)?	☐	☐	☐	☐	☐	☐
c. Is <u>light touching</u> (clothing, a blanket) in this area painful?	☐	☐	☐	☐	☐	☐
d. Do you have <u>sudden</u> pain attacks in the area of your most painful foot, like electrical shocks?	☐	☐	☐	☐	☐	☐
e. Is <u>cold or heat</u> (bath water) in this area occasionally painful?	☐	☐	☐	☐	☐	☐
f. Do you suffer from a sensation of <u>numbness</u> in or around your most painful foot?	☐	☐	☐	☐	☐	☐
g. Does slight <u>pressure</u> in this area, (e.g. with a finger), trigger pain?	☐	☐	☐	☐	☐	☐

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	☐	☐	☐	☐	☐

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 all 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 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 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)?

☐ 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.

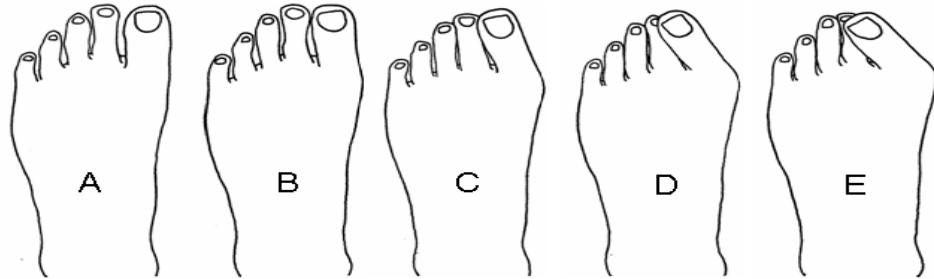
Type of surgery	Right side		Left side		Age
	Ankle	Toes	Ankle	Toes	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	

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 ☐

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

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**?

<i>Much better now than one year ago</i>	<i>Somewhat better now than one year ago</i>	<i>About the same as one year ago</i>	<i>Somewhat worse now than one year ago</i>	<i>Much worse now than one year ago</i>
☐	☐	☐	☐	☐

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, <i>Limited a lot</i>	Yes, <i>Limited a little</i>	Not <i>limited at all</i>
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	☐	☐	☐

	Yes, <i>Limited a lot</i>	Yes, <i>Limited a little</i>	Not, <i>limited at all</i>
Walking half a mile	☐	☐	☐
Walking 100 yards (<i>approximately 100 metres</i>)	☐	☐	☐
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

☐	☐	☐	☐	☐

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

<i>None</i>	<i>Very Mild</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>	<i>Very Severe</i>
☐	☐	☐	☐	☐	☐

42. During the **past month** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

<i>Not at all</i>	<i>Slightly</i>	<i>Moderately</i>	<i>Quite a bit</i>	<i>Extremely</i>
☐	☐	☐	☐	☐

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**.....

	<i>All of the time</i>	<i>Most of the time</i>	<i>A good bit of the time</i>	<i>Some of the time</i>	<i>A little of the time</i>	<i>None of the time</i>
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?	☐	☐	☐	☐	☐	☐

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?

	<i>Definitely True</i>	<i>Mostly True</i>	<i>Don't know</i>	<i>Mostly False</i>	<i>Definitely False</i>
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	☐	☐	☐	☐	☐

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

.....

.....

.....

.....

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 ☐

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.**

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

$20 - 4 = \dots\dots\dots$

$16 + 17 = \dots\dots\dots$

$8 \times 6 = \dots\dots\dots$

$4 + 15 - 17 = \dots\dots\dots$

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

1 S.....

2 S.....

3 S.....

4 S.....

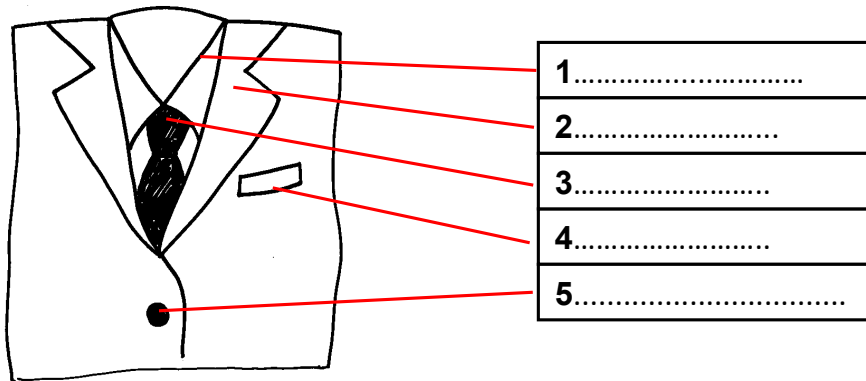
WHY IS A CARROT LIKE A POTATO?.....

WHY IS A LION LIKE A WOLF ?

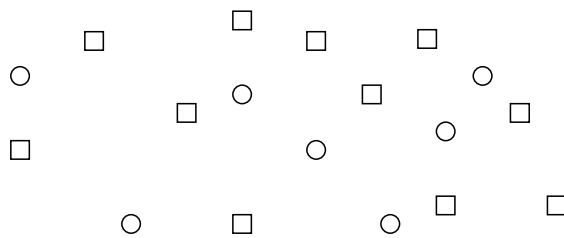
REMEMBER: GOOD CITIZENS ALWAYS WEAR STOUT SHOES

Please Turn Over

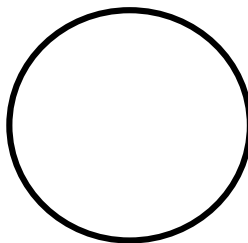
PLEASE NAME THESE ITEMS



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 :**

.....

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The University of Nottingham
© Copyright 2019

25

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 your email address below:

Email address: _____@_____

Thank you for your time

Office use only GMP

Appendix E: Goodness of fit of the model and variance inflation factor for logistic regression of incident knee pain; validation of the results using “backward-stepwise regression”

Goodness of fit and variance inflation factor for logistic regression of risk factors for incident knee pain per group and when combined and

	Footballers	Controls	Overall
Hosmer and Lemeshow test	p=0.207	p=0.475	p=0.481
VIF			
Age	1.054	1.020	1.060
BMI	1.022	1.023	1.031
Knee injury	1.010	1.011	-
Socioeconomic status	1.064	1.045	1.046
Being footballer	-	-	1.102
Analgesics			1.041

VIF - variance inflation factor; BMI - body mass index

Validation for risk factors for incidence of knee pain within groups using backward-stepwise regression

	Odd ratio (95% CI)	p-value
Footballers		
BMI	1.15 (1.02 – 1.29)	0.017
Football related injury	2.33 (1.16 – 4.65)	0.016
Controls		
BMI	1.08 (1.02 – 1.15)	0.013
Socioeconomic status	0.90 (0.83 – 0.97)	0.009
Knee injury	1.70 (1.02 – 2.85)	0.043

CI – confidence interval; BMI – body mass index

Goodness of fit and variance inflation factor for logistic regression of the association between baseline knee pain and incident multimorbidity

	Footballers	Controls	Overall
Hosmer and Lemeshow test	p=0.995	p=0.512	p=0.916
VIF			
Baseline knee pain	1.033	1.036	1.099
Age	1.126	1.073	1.117
BMI	1.027	1.072	1.052
Socioeconomic status	1.008	1.073	1.061
analgesics	1.046	1.098	1.065
Having one condition at baseline	1.144	1.074	1.107
Being footballer	-	-	1.163

VIF - variance inflation factor; BMI – body mass index

Appendix F: Goodness of fit of the model and variance inflation factor for logistic regression of incident multimorbidity and specific long-term condition; validation of the results using “backward-stepwise regression”

Goodness of fit and variance inflation factor for logistic regression of risk factors for incident multimorbidity per group and when combined

	Footballers	Controls	Overall
Hosmer and Lemeshow test	p=0.619	p=0.082	p=0.755
VIF			
Age	1.124	1.087	1.062
BMI	1.027	1.061	1.046
Analgesics use	1.037	1.080	1.033
Having one condition at baseline	1.124	1.070	-
Socioeconomic status	1.006	1.076	1.056
Being footballer	-	-	1.098

VIF - variance inflation factor; CI – confidence interval; BMI -body mass index;

Validation for risk factors related to incidence of multimorbidity within groups using backward-stepwise regression

	Odd ratio (95% CI)	p-value
Footballers		
Age	1.04 (1.01 – 1.06)	0.003
Having one condition at baseline	3.03 (1.80 – 5.10)	<0.001
Analgesics used	2.96 (1.57 – 5.58)	<0.001
Controls		
Age	1.05 (1.03 – 1.08)	<0.001
Socioeconomic status	0.88 (0.82 – 0.95)	0.002
Having one condition at baseline	2.67 (1.71 – 4.18)	<0.001

CI – confidence interval

Goodness of fit and variance inflation factor for logistic regression for each of incident of 13 long-term conditions

Musculoskeletal		
Hosmer and Lemeshow test	p=0.723	
VIF		
Age	1.143	
BMI	1.064	
Socioeconomic status	1.066	
Analgesics used	1.034	
Having one condition at baseline	1.141	
Being footballer	1.138	
Cardiovascular		
Hosmer and Lemeshow test	p=0.784	
VIF		
Age	1.108	
BMI	1.056	
Analgesics used	1.061	
Socioeconomic status	1.059	
Having one condition at baseline	1.079	

Being footballer	1.100
Respiratory	
Hosmer and Lemeshow test	p=0.664
VIF	
Age	1.140
BMI	1.055
Socioeconomic status	1.054
Analgesic used	1.055
Having one condition at baseline	1.105
Being footballer	1.102
Gastrointestinal	
Hosmer and Lemeshow test	p=0.894
VIF	
Age	1.131
BMI	1.057
Socioeconomic status	1.060
Analgesic used	1.055
Having one condition at baseline	1.102
Being footballer	1.102
Liver	
Hosmer and Lemeshow test	p=0.520
VIF	
Age	1.123
BMI	1.051
Socioeconomic status	1.057
Analgesic used	1.055
Having one condition at baseline	1.097
Being footballer	1.100
Kidney	
Hosmer and Lemeshow test	p=0.011
VIF	
Age	1.126
BMI	1.053
Socioeconomic status	1.057
Analgesic used	1.055
Having one condition at baseline	1.098
Being footballer	1.101
Endocrine	
Hosmer and Lemeshow test	p=0.593
VIF	
Age	1.115
BMI	1.048
Socioeconomic status	1.046
Analgesic used	1.050
Having one condition at baseline	1.091

Being footballer	1.091
Neurological	
Hosmer and Lemeshow test	0.579
VIF	
Age	1.143
BMI	1.056
Socioeconomic status	1.054
Analgesic used	1.056
Having one condition at baseline	1.105
Being footballer	1.104
Anxiety/depression	
Hosmer and Lemeshow test	p=0.682
VIF	
Age	1.130
BMI	1.053
Socioeconomic status	1.055
Analgesic used	1.057
Having one condition at baseline	1.101
Being footballer	1.099
Vision	
Hosmer and Lemeshow test	p=0.962
VIF	
Age	1.121
BMI	1.051
Socioeconomic status	1.058
Analgesic used	1.053
Having one condition at baseline	1.096
Being footballer	1.099
Hearing	
Hosmer and Lemeshow test	p=0.901
VIF	
Age	1.121
BMI	1.052
Socioeconomic status	1.060
Analgesic used	1.056
Having one condition at baseline	1.096
Being footballer	1.102
Cancer	
Hosmer and Lemeshow test	p=0.039
VIF	
Age	1.124
BMI	1.051
Socioeconomic status	1.061
Analgesic used	1.063
Having one condition at baseline	1.094
Being footballer	1.111

Infection	
Hosmer and Lemeshow test	p=0.727
VIF	
Age	1.126
BMI	1.053
Socioeconomic status	1.057
Analgesic used	1.055
Having one condition at baseline	1.098
Being footballer	1.101
VIF - variance inflation factor; BMI – body mass index	

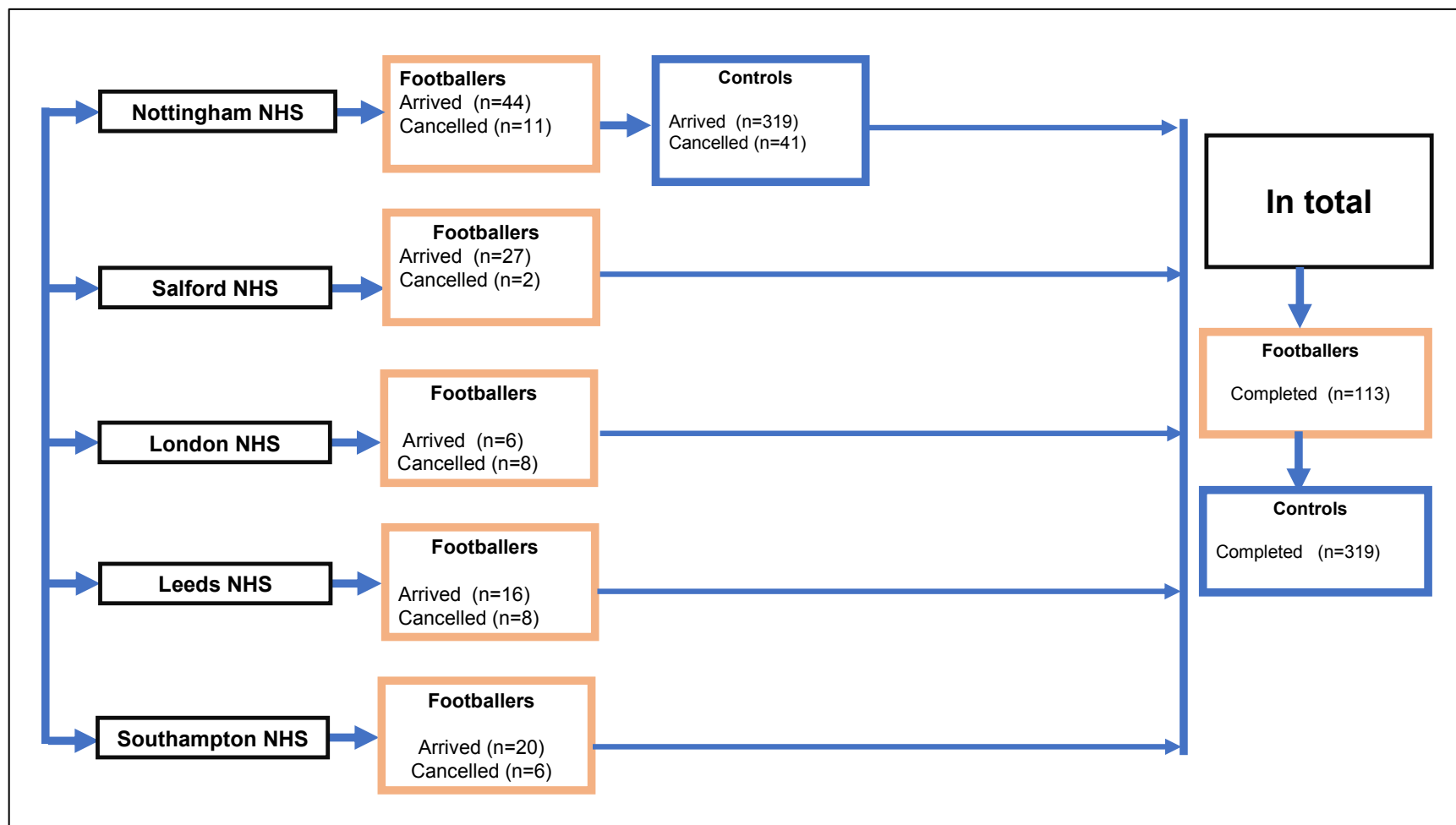
Appendix G: Incidence of specific conditions in the study population during 2014-2020.

	Footballers	Controls	Crude OR (95%CI), p-value	aOR (95%CI), p-value
Musculoskeletal, n (%)	74/239= 31.0%	116/323= 36.0%	0.80 (0.56 – 1.14), p= 0.220	0.81 (0.55 – 1.20), p= 0.307
Cardiovascular, n (%)	62/289= 21.4%	63/317= 20.0%	1.10 (0.74 – 1.63), p= 0.631	1.30 (0.85 – 1.99), p= 0.220
Respiratory, n (%)	15/315= 4.7%	36/355= 10.1%	0.44 (0.23 – 0.82), p= 0.010	0.47 (0.24 – 0.91), p= 0.026
Gastrointestinal, n (%)	10/316= 3.2%	9/353= 2.5%	1.25 (0.50 – 3.11), p= 0.633	1.30 (0.49 – 3.40), p= 0.590
Liver, n (%)	10/317= 3.1%	8/361= 2.2%	1.43 (0.56 – 3.68), p= 0.450	1.49 (0.55 – 3.97), p= 0.424
Kidney, n (%)	3/317= 0.94%	7/362= 1.9%	0.48 (0.12 – 1.89), p= 0.297	0.76 (0.18 – 3.11), p= 0.711
Endocrine, n (%)	44/313= 14.05%	41/323= 12.7%	1.12 (0.71 – 1.77), p= 0.613	1.26 (0.78 – 2.04), p= 0.336
Neurological, n (%)	37/316= 11.7%	33/351= 9.4%	1.27 (0.77 – 2.09), p= 0.333	1.30 (0.77 – 2.19), p= 0.320
Anxiety/depression, n (%)	20/312= 6.4%	50/359= 14.0%	0.42 (0.24 – 0.72), p= 0.002*	0.39 (0.22 – 0.70), p= 0.002*
Vision , n (%)	14/316= 4.4%	32/356= 9.0%	0.46 (0.24 – 0.89), p= 0.022	0.50 (0.25 – 1.01), p=0.054
Hearing loss, n (%)	25/316= 7.9%	61/359= 17.0%	0.40 (0.24 – 0.66), p < 0.001*	0.43 (0.25 – 0.73), p= 0.002*
Cancer, n (%)	13/304= 4.3%	26/352= 7.4%	0.56 (0.28 – 1.11), p= 0.099	0.66 (0.32 – 1.36), p= 0.265
Infection, n (%)	2/317= 0.63%	5/362= 1.4%	0.45 (0.08 – 2.35), p= 0.346	0.77 (0.14 – 4.29), p= 0.770

Adjusted odds ratio for being footballers, age, body mass index, socioeconomic status, analgesics use and having one conditions at baseline.

*p≤ 0.0038

Appendix H: Study population recruited for foot/ankle radiographic assessment in 5 NHS sites



Appendix I: Details for all data management and cleaning of foot and/or ankle OA

Foot rOA					Ankle rOA				
Original Variable	Original Codes	New Variable After Recoding	Recoded Values	Foot OA	Original Variable	Original Codes	New Variable After Recoding	Recoded Values	Ankle OA
L_DP_1stMTPJ_OP	0, 1, 2, 3	L_DP_1stMTPJ_OP_r	0 No OA 1 Present OA		L_AnkleAP_OP	0, 1, 2, 3	L_Ankle_LAT_OP_01	0 No OA 1 Present OA	
L_DP_1stMTPJ_JSN	0, 1, 2, 3	L_DP_1stMTPJ_JSN_r	0 No OA 1 Present OA		L_AnkleAP_JSN	0, 1, 2, 3	L_Ankle_LAT_JSN_01	0 No OA 1 Present OA	
L_DP_1stCMJ_OP	0, 1, 2, 3	L_DP_1stCMJ_OP_r	0 No OA 1 Present OA		R_AnkleAP_OP	0, 1, 2, 3	R_Ankle_LAT_OP_01	0 No OA 1 Present OA	
L_DP_1stCMJ_JSN	0, 1, 2, 3	L_DP_1stCMJ_JSN_r	0 No OA 1 Present OA		R_AnkleAP_JSN	0, 1, 2, 3	R_Ankle_LAT_JSN_01	0 No OA 1 Present OA	
L_DP_2ndCMJ_OP	0, 1, 2, 3	L_DP_2ndCMJ_OP_r	0 No OA 1 Present OA		L_Ankle_LAT_OP	0, 1, 2, 3	L_AnkleAP_OP_01	0 No OA 1 Present OA	
L_DP_2ndCMJ_JSN	0, 1, 2, 3	L_DP_2ndCMJ_JSN_r	0 No OA 1 Present OA		L_Ankle_LAT_JSN	0, 1, 2, 3	L_AnkleAP_JSN_01	0 No OA 1 Present OA	
L_DP_N1stCJ_OP	0, 1, 2, 3	L_DP_N1stCJ_OP_r	0 No OA 1 Present OA		R_Ankle_LAT_OP	0, 1, 2, 3	R_AnkleAP_OP_01	0 No OA 1 Present OA	
L_DP_N1stCJ_JSN	0, 1, 2, 3	L_DP_N1stCJ_JSN_r	0 No OA 1 Present OA		R_Ankle_LAT_JSN	0, 1, 2, 3	R_AnkleAP_JSN_01	0 No OA 1 Present OA	
L_DP_TNJ_JSN	0, 1, 2, 3	L_DP_TNJ_JSN_r	0 No OA 1 Present OA						
R_DP_1stMTPJ_OP	0, 1, 2, 3	R_DP_1stMTPJ_OP_r	0 No OA 1 Present OA						
R_DP_1stMTPJ_JSN	0, 1, 2, 3	R_DP_1stMTPJ_JSN_r	0 No OA 1 Present OA						
R_DP_1stCMJ_OP	0, 1, 2, 3	R_DP_1stCMJ_OP_r	0 No OA 1 Present OA						
R_DP_1stCMJ_JSN	0, 1, 2, 3	R_DP_1stCMJ_JSN_r	0 No OA 1 Present OA						
R_DP_2ndCMJ_OP	0, 1, 2, 3	R_DP_2ndCMJ_OP_r	0 No OA 1 Present OA						
R_DP_2ndCMJ_JSN	0, 1, 2, 3	R_DP_2ndCMJ_JSN_r	0 No OA 1 Present OA						
R_DP_N1stCJ_OP	0, 1, 2, 3	R_DP_N1stCJ_OP_r	0 No OA 1 Present OA						
R_DP_N1stCJ_JSN	0, 1, 2, 3	R_DP_N1stCJ_JSN_r	0 No OA 1 Present OA						
R_DP_TNJ_JSN	0, 1, 2, 3	R_DP_TNJ_JSN_r	0 No OA 1 Present OA						
L_LAT_1stMTPJ_OP	0, 1, 2, 3	L_LAT_1stMTPJ_OP_r	0 No OA 1 Present OA						
L_LAT_1stMTPJ_JSN	0, 1, 2, 3	L_LAT_1stMTPJ_JSN_r	0 No OA 1 Present OA						
L_LAT_1stCMJ_OP	0, 1, 2, 3	L_LAT_1stCMJ_OP_r	0 No OA 1 Present OA						
L_LAT_1stCMJ_JSN	0, 1, 2, 3	L_LAT_1stCMJ_JSN_r	0 No OA 1 Present OA						
L_LAT_2ndCMJ_OP	0, 1, 2, 3	L_LAT_2ndCMJ_OP_r	0 No OA 1 Present OA						
L_LAT_2ndCMJ_JSN	0, 1, 2, 3	L_LAT_2ndCMJ_JSN_r	0 No OA 1 Present OA						
L_LAT_N1stCJ_OP	0, 1, 2, 3	L_LAT_N1stCJ_OP_r	0 No OA 1 Present OA						
L_LAT_N1stCJ_JSN	0, 1, 2, 3	L_LAT_N1stCJ_JSN_r	0 No OA 1 Present OA						
L_LAT_TNJ_OP	0, 1, 2, 3	L_LAT_TNJ_OP_r	0 No OA 1 Present OA						
L_LAT_TNJ_JSN	0, 1, 2, 3	L_LAT_TNJ_JSN_r	0 No OA 1 Present OA						
R_LAT_1stMTPJ_OP	0, 1, 2, 3	R_LAT_1stMTPJ_OP_r	0 No OA 1 Present OA						
R_LAT_1stMTPJ_JSN	0, 1, 2, 3	R_LAT_1stMTPJ_JSN_r	0 No OA 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.

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 format: 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 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 format: 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 2nd 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 2ndCMJ_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 format: 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 AND R_LAT_2ndCMJ_JSN_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 format: 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 format: 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	
	1	Present OA	
	1	Present OA	
	1	Present OA	
	1	Present OA	
Ankle Joints			Prevalence of Ankle rOA 01
New Variable After Recoding	Recoded Values	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 format: 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	

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 Controls=0	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 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 Controls=0	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 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 Controls=0	First_MTPJ_rOA_OP_overall = 1 AND First_MTPJ_rOA_JSN_overall = 1 First_MTPJ_rOA_OP_overall = 0 OR First_MTPJ_rOA_JSN_overall = 0
First_CMJ_rOA_OP_overall	Cases =1 Controls=0	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 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 Controls=0	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 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 Controls=0	First_CMJ_rOA_OP_overall = 1 AND First_CMJ_rOA_JSN_overall = 1 First_CMJ_rOA_OP_overall = 0 OR First_CMJ_rOA_JSN_overall = 0
Second_CMJ_rOA_OP_overall	Cases =1 Controls=0	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 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 Controls=0	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 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 Controls=0	Second_CMJ_rOA_OP_overall = 1 AND Second_CMJ_rOA_JSN_overall = 1 Second_CMJ_rOA_OP_overall = 0 OR Second_CMJ_rOA_JSN_overall = 0
N1stCJ_rOA_OP_overall	Cases =1 Controls=0	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 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 Controls=0	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 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 Controls=0	N1stCJ_rOA_OP_overall = 1 AND N1stCJ_rOA_JSN_overall = 1 N1stCJ_rOA_OP_overall = 0 OR N1stCJ_rOA_JSN_overall = 0
TNJ_rOA_JSN_overall	Cases =1 Controls=0	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 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 Controls=0	L_LAT_TNJ_OP_r = 1 OR R_LAT_TNJ_OP_r = 1 L_LAT_TNJ_OP_r = 0 AND R_LAT_TNJ_OP_r = 0
TNJ_rOA_mMenz	Cases =1 Controls=0	TNJ_rOA_JSN_overall = 1 AND TNJ_rOA_OP_overall = 1 TNJ_rOA_JSN_overall = 0 OR TNJ_rOA_OP_overall = 0
Ankle_rOA_OP_overall	Cases =1 Controls=0	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 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 Controls=0	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 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 Controls=0	Ankle_rOA_OP_overall = 1 AND Ankle_rOA_JSN_overall = 1 Ankle_rOA_OP_overall = 0 OR Ankle_rOA_JSN_overall = 0
Foot_rOA	Cases =1 Controls=0	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 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 Controls=0	Ankle_rOA_mMenz = 1 OR Foot_mMenz = 1 Ankle_rOA_mMenz = 0 AND Foot_mMenz = 0

Appendix J: Goodness of fit of the model and variance inflation factor for logistic regression of association between knee OA and foot and/or ankle OA

	Footballers	Controls	Overall
Knee OA and foot/ankle OA (grade ≥ 2)			
Hosmer and Lemeshow test	p=0.459	p=0.176	p=0.114
VIF			
Knee OA grade ≥ 2	1.272	1.122	1.175
Age	1.143	1.068	1.243
Socioeconomic status	1.033	1.060	1.066
Knee injury	1.327	1.043	1.201
Foot/ankle injuries	1.019	1.026	1.090
Being footballer	-	-	1.385
Knee OA and foot/ankle OA (grade ≥ 3)			
Hosmer and Lemeshow test	p=0.109	p=0.076	p=0.419
VIF			
Knee OA grade ≥ 3	1.129	1.060	1.077
Age	1.091	1.027	1.202
Socioeconomic status	1.065	1.053	1.045
Knee injury	1.097	1.024	1.140
Foot/ankle injuries	1.049	1.031	1.097
Being footballer	-	-	1.392
Knee OA and foot OA (grade ≥ 2)			
Hosmer and Lemeshow test	p=0.756	p=0.188	p=0.720
VIF			
Knee OA grade ≥ 2	1.272	1.122	1.175
Age	1.143	1.068	1.243
Socioeconomic status	1.033	1.060	1.066
Knee injury	1.327	1.043	1.201
Foot/ankle injuries	1.019	1.026	1.090
Being footballer	-	-	1.385

Knee OA and foot OA (grade ≥ 3)			
Hosmer and Lemeshow test	p=0.368	p=0.081	p=0.395
VIF			
Knee OA grade ≥ 3	1.129	1.060	1.077
Age	1.091	1.027	1.202
Socioeconomic status	1.065	1.053	1.045
Knee injury	1.097	1.024	1.140
Foot/ankle injuries	1.049	1.031	1.097
Being footballer	-	-	1.392
Knee OA and ankle OA (grade ≥ 2)			
Hosmer and Lemeshow test	p=0.102	p=0.588	p=0.530
VIF			
Knee OA grade ≥ 2	1.272	1.117	1.166
Age	1.143	1.074	1.248
Socioeconomic status	1.033	1.053	1.062
Knee injury	1.327	1.040	1.196
Foot/ankle injuries	1.019	1.027	1.090
Being footballer	-	-	1.383
Knee OA and ankle OA (grade ≥ 3)			
Hosmer and Lemeshow test	p=0.290	p=0.794	p=0.579
VIF			
Knee OA grade ≥ 3	1.129	1.053	1.071
Age	1.091	1.033	1.207
Socioeconomic status	1.065	1.045	1.044
Knee injury	1.097	1.021	1.138
Foot/ankle injuries	1.049	1.031	1.096
Being footballer	-	-	1.390

VIF - variance inflation factor

Goodness of fit of the model and variance inflation factor for logistic regression of interaction between being a footballer and knee OA for the risk of foot/ankle OA

Hosmer and Lemeshow test	p=0.370
VIF	
Being footballer and knee OA grade ≥ 2	2.584
Knee OA grade ≥ 2	1.800
Age	1.244
Socioeconomic status	1.077
Knee injury	1.214
Foot/ankle injuries	1.090
Being footballer	1.975
VIF - variance inflation factor; OA – osteoarthritis	

Appendix K: Variance inflation factors in linear regression between summated scores of OP and JSN in knee OA and summated scores of OP and JSN in foot/ankle OA

	Footballers	Controls	Overall
Summated scores of OP in knee OA			
VIF			
Summated scores for knee	1.215	1.145	1.222
Age	1.174	1.071	1.262
Socioeconomic status	1.038	1.062	1.068
Knee injury	1.229	1.063	1.200
Foot/ankle injury	1.021	1.026	1.094
Being footballer	-	-	1.425
Summated scores of JSN in knee OA			
VIF			
Summated scores for knee	1.336	1.169	1.259
Age	1.279	1.113	1.328
Socioeconomic status	1.035	1.028	1.047
Knee injury	1.259	1.079	1.216
Foot/ankle injury	1.049	1.026	1.099
Being footballer	-	-	1.409

OP – osteophytes; JSN – joint space narrowing; OA – osteoarthritis; VIF - variance inflation factor

Appendix L: Responses of footballers and Pain Centre people to the first patient public involvement questions

Responses of five footballers to the first patient public involvement questions

	Q 1: Have you had multiple (more than two) long-term conditions? (Please type yes or no)	Q 2: If yes, how much they bother you?	Q 3: Do you think it is important to find out how many people have multiple long-term conditions and related risk factors?	Q 4: What is your view on this project comparing ex-professional football players and general population for knee pain and multiple long-term conditions?	Q5: Are you happy for us to approach you again to see our progress early 2023 and to help us implement the results early 2024? (Please type yes or no).
LB	yes	I have had knee replacement surgery in my left knee and I am awaiting knee surgery in my right knee. In both cases I have had pain for approximately 12 months prior to operation	yes	I am sure the study will show that chances of knee pain in later life will increase dramatically if you were a professional footballer. If I had this knowledge in my younger life I would still have taken the opportunity to become a professional footballer	yes
CB	Had slight problem with cartilage in left knee which has sorted out with 3 week visit to national football centre (exercise & treatment)	Not anymore, have more problem with aching ankles in both legs daily	yes	A good idea, but question are too vague	yes

ST	No	N/A	Yes, as this will hopefully give an insight into possibly addressing any potential risk factors going forward.	I think it's a worthwhile project in comparing the different knee conditions and impacts of sports personnel against the general public, especially if this has potential benefits for future treatments and looking at preventing causes of such conditions going forward	yes
NH	No	N/A	yes	I think it is a useful project to learn how chronic knee pain can impact on individuals and their future health, particularly as someone who has suffered with osteoarthritis in recent years (albeit not in my knees). Better awareness may help individuals mitigate these risks at an earlier stage.	yes
GP	No	N/A	yes	It is important to establish any connections to allow best advice to be given to professional footballers about their future health	yes
Summary	2 said yes	2 said yes	5/5 said yes	5/5 said is good project	5/5 said yes

Responses of five people from Pain Centre to the first patient public involvement questions

Initials	Q 1: Have you had multiple (more than two) long-term conditions? (Please type yes or no)	Q 2: If yes, how much they bother you?	Q 3: Do you think it is important to find out how many people have multiple long-term conditions and related risk factors?	Q 4: What is your view on this project comparing ex-professional football players and general population for knee pain and multiple long-term conditions?	Q5: Are you happy for us to approach you again to see our progress early 2023 and to help us implement the results early 2024? (Please type yes or no).
LSP	Yes	A Lot	Yes	I don't think it is comparable . considering the amount of people with knee pain and long term conditions – doubt a large percentage played football! i was a teenage ballroom dancer. might be worth finding out what people living with these conditions did in their youth?	Yes
RD	Yes	Not that much	Yes I do	There might be some comparisons but for many people who have not played sport there is no comparison	Yes
SS	yes	Some days quite substantially.	Yes I think this is extremely important not just how many people but the likely cost and pressure it will have on relevant services.	It is a really good project and to develop preventative strategies will be good for both footballers and the general public.	Yes

DD	Yes	They impact each other, one makes the other worse and what could make one feel better effects my other condition, so I feel that I am forever compromising in one way or another.	I think that a patient needs to give a full history, including all long-term conditions and needs to be told any related risk factors.	I think that a patient needs to give a full history, including all long-term conditions and needs to be told any related risk factors.	Yes
SV	Yes	(Not sure why the 'do' is emphasized!)Not sure how to answer 'how much' – they flare up and die down – each is different	YES ... do you want to know why I think that?	Is your project about analyzing data that already exists? It's not totally clear. I thought that footballers and knee damage/OA was well researched. The title (research question) is a good one and it summarises the project well. I don't think it comes across clearly enough in what you have written though.	No
Summary	all have multiple conditions!	3 of 5 bothered	all think important	2 of 5	4 of 5

Appendix M: GANTT chart for delivery of each of the studies undertaken in this PhD

