Investigation of potential phenotypes of foot osteoarthritis: cross-sectional analysis from the Clinical Assessment Study of the Foot

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ABSTRACT

Objective

To investigate the existence of distinct foot osteoarthritis (OA) phenotypes based on pattern of joint involvement and comparative symptom and risk profiles.

Methods

Participants aged ≥50 years reporting foot pain in the previous year were drawn from a population-based cohort. Radiographs were scored for OA in the 1st metatarsophalangeal (MTPJ), 1st and 2nd cuneometatarsal, navicular first cuneiform and talonavicular joints according to a published atlas. Chi-square tests established clustering, and odds ratios examined symmetry and pairwise associations of radiographic OA in the feet. Distinct underlying classes of foot OA were investigated by latent class analysis (LCA) and their association with symptoms and risk factors was assessed.

Results

In 533 participants (mean age 64.9 years, 55.9% female) radiographic OA clustered across both feet ($p<0.001$), and was highly symmetrical (adjusted odds ratio 3.0, 95% CI: 2.1,4.2). LCA identified three distinct classes of foot OA: 'no or minimal foot OA' (64%); 'isolated 1st MTPJ OA' (22%); 'polyarticular foot OA' (15%). After adjustment for age and gender, polyarticular foot OA was associated with nodal OA, increased BMI, and more pain and functional limitation compared to the other classes.

Conclusion

Patterning of radiographic foot OA has provided insight into the existence of two forms of foot OA: isolated 1st MTPJ OA and polyarticular foot OA. The symptom and risk factor profiles in individuals with polyarticular foot OA indicate a possible distinctive phenotype of foot OA, but further research is needed to explore the characteristics of isolated 1st MTPJ and polyarticular foot OA.

SIGNIFICANCE AND INNOVATIONS

- There is a lack of epidemiological studies investigating the patterning of foot OA.
- First empirical evidence for the separation of 1st MTPJ OA from a form of multi-joint 'polyarticular foot OA' on the basis of patterning of joint involvement on plain radiographs.
- The symptom and risk factor profiles of those with polyarticular foot OA indicate a possible distinct phenotype of foot OA.

The pattern and location of joint involvement have played a fundamental role in shaping the current understanding of osteoarthritis (OA). Whether it is the differing effects of risk alleles and gene expression on hip and knee OA (1), the contrasting risk profiles of tibiofemoral and patellofemoral joint OA (2), or the symmetry and clustering of small joint involvement in hand OA (3), joint-specific perspectives have proved insightful.

The foot joint complex presents a novel challenge in this regard. With few exceptions, population-based epidemiologic studies have focussed on the metatarsophalangeal joints (MTPJs), predominantly the 1st MTPJ, for the purpose of estimating prevalence (4). Using a recently developed radiographic atlas for semi-quantitative scoring of plain radiographs of the feet (5), Menz et al. (6), and Roddy et al. (7), have observed the frequent occurrence of osteophytes or joint space narrowing (JSN) in joints located in the medial column of the midfoot (specifically, second cuneometatarsal (2nd CMJ), talonavicular (TNJ), and navicular first cuneiform (NCJ) joints). While it remains the case that the 1st MTPJ is most commonly implicated in foot OA, these observations could be consistent with two quite different scenarios, both of which carry implications for how foot OA is understood and managed: either there are forms of OA at the foot that occur independently, or 1st MTPJ OA is associated with OA at other proximal joints in the foot as part of a more widespread polyarticular presentation.

Distinctions in the patterning and risk factor profiles of foot OA have the potential to provide new insights into causation. The foot may be similar to the hand in that specific localised risk factors could be associated with limited forms of OA, while systemic risk factors, including age, gender and metabolic factors are more likely to be associated with more widespread polyarticular forms of OA. The accompanying symptoms may also vary in different forms of foot OA. The identification of phenotypes at other sites, such as the thumb base and patellofemoral joint, has led to greater understanding about the aetiology and presentation of OA at these locations (8,9). Early research targeting treatments for these sites has shown some positive outcomes (10,11), and this approach may also be appropriate for different forms of foot OA.

In this study, we sought to analyse cross-sectional data from a population-based survey of foot pain and OA in adults aged ≥50 years to investigate patterns of radiographic foot OA through examination of clustering, symmetry and co-occurrence of joint involvement in the foot. Latent class analysis (LCA) was used to determine whether subgroups of foot OA existed and these were compared with respect to their symptom and risk factor profiles.

PATIENTS AND METHODS

Study design

The Clinical Assessment Study of the Foot (CASF) is a prospective observational cohort study. All adults aged ≥50 years registered with four general practices in North Staffordshire, UK, were mailed a Health Survey questionnaire, irrespective of any foot-related health care consultation. Responders to the Health Survey reporting pain in or around the foot within the last year and who consented to further contact, were invited to attend a research clinic (12). A flowchart showing the recruitment of participants to the CASF study has been published previously (7).

All participants provided written informed consent. Ethical approval for the study was obtained from the Coventry Research Ethics Committee (REC reference number: 10/H1210/5).

Scoring of foot radiographs

At the research clinics, weight-bearing dorso-plantar and lateral radiographs were taken separately of each foot, according to a standardised protocol. A single experienced reader (MM), who had undergone a period of training, scored five joints in each foot (1st MTPJ, 1st and 2nd CMJs, NCJ, and TNJ) for osteophytes and JSN (0-3) according to a published atlas (5). The joints examined were selected based on their inclusion in the published radiographic foot atlas, which had determined that they were the most commonly affected, clearly visible on dorso-plantar and lateral views and could be reliably scored (5). Sixty randomly selected radiographs were rescored after eight weeks (by MM) to assess intra-rater reliability and were scored by a second experienced reader (HBM) to determine inter-rater reliability. As reported previously, reliability for the presence of OA was excellent for intra-rater (mean κ=0.94, mean % exact agreement=99%) and moderate for inter-rater reliability (mean κ=0.46, mean % exact agreement=79%)(7).

Radiographic OA in a foot joint was defined as grade ≥2 for osteophytes or JSN on either dorso-plantar or lateral views.

Individuals were excluded from the current analyses if medical records (primary care or local hospital) or a clinical x-ray report by a consultant musculoskeletal radiologist identified them as having rheumatoid, psoriatic, or non-specific inflammatory arthritis.

Descriptive characteristics and symptoms

The following information was collected in the Health Survey questionnaire: higher education attendance; foot pain location by foot; foot pain in the 1st MTPJ and midfoot regions as indicated on a foot manikin (© The University of Manchester 2000. All rights reserved)(13); foot pain duration; number of days with foot pain, aching or stiffness in the last month (14); foot pain severity by Numerical Rating Scale (NRS) 0-10; satisfaction with foot symptoms; Manchester Foot Pain and Disability Index (MFPDI)(15); Short Form 12 (SF12) physical and mental component scores (16); Hospital Anxiety and Depression Scale (HADS)(17). Further details on the data collection methods and outcome measures can be found in the published study protocol (12).

Risk factor profiles

A number of potential risk factors previously found to be associated with foot OA were examined, including age, gender, obesity and structural characteristics (hallux valgus, footwear, and previous foot/ankle injury)(18). In addition, metabolic factors (hypertension, type 2 diabetes, impaired fasting glucose (IFG), dyslipidaemia, lipid-lowering drugs)and nodal OA, which have been implicated in OA aetiology at other joints, were investigated (19-22). Demographic data (age, gender, occupation) along with the presence of hip pain and knee pain in the last year, wearing of high heeled and narrow toed footwear between the ages of 20 to 49 years (12), and intermittent claudication determined from the Edinburgh Claudication Questionnaire (23), were collected in the Health Survey questionnaire. Self-reported hallux valgus was determined using a validated line-drawing instrument consisting of five drawings for each foot, with each one illustrating a sequential increase in hallux valgus angle of 15 degrees (24). Participants selected the drawing that best depicted the severity of hallux valgus for each foot. Hallux valgus was

classed as present in a foot if any of three most severe drawings were selected (24). At the research clinics, the presence of finger nodes were determined by observation and palpation, and height and weight were measured to calculate body mass index (BMI). Previous foot and ankle injuries were recorded during a standardised clinical interview (12). Posterior-anterior radiographs were also taken of each hand and interphalangeal joints were scored (by MM) for the presence of OA (Kellgren and Lawrence grade≥2). Primary care medical records were reviewed for participants providing consent (95%). Diagnoses or consultations for hypertension, type 2 diabetes or IFG and dyslipidaemia (raised cholesterol or triglycerides) or a prescription of a lipid-regulating drug in the 18-months prior to clinic attendance were identified. A classification of metabolic syndrome was defined as the presence of three or more of the following: BMI>30kg/m^2, hypertension, dyslipidaemia and type 2 diabetes or IFG (based on previous criteria)(25).

Statistical analysis

Clustering of joint involvement within the foot was examined using the chi-square test with the expected frequency calculated from the Poisson distribution. The frequency of OA in a joint occurring in isolation and with other joints in the same foot was calculated. Logistic regression was used to examine the interrelationships of radiographic OA at different pairs of joints within each foot and the presence of symmetrical radiographic OA affecting the same joint in both feet. Generalised estimating equations (GEE) were used to determine overall symmetry across the five foot joints adjusting for age, gender, presence of OA in each foot joint and the number of foot joints affected with radiographic OA within the person. Results are presented as odds ratios (OR) with 95% confidence intervals (CI).

LCA was undertaken to identify classes of radiographic foot OA based on the presence of radiographic OA in the joints of the feet. The optimal number of classes was determined by a combination of:

i) Goodness-of-fit statistics (Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), sample size adjusted BIC, and the Lo-Mendell-Rubin adjusted likelihood ratio test (LRT))(26)

ii) Uncertainty of classification measures (entropy (27) and average posterior probabilities (28))

iii) Class size of at least 10% of the sample

iv) Clinical relevance and interpretability.

Further investigation to compare the descriptive characteristics, symptoms and risk factor profiles of each of the classes of foot OA identified by LCA was undertaken. Analyses were adjusted for age and gender, which were considered potential confounders. For continuous data, multiple linear regression was used, means and their 95% confidence intervals were presented for each latent class with significant differences between the classes being determined using F-tests. For dichotomous and ordinal data, logistic regression was used to obtain probabilities and their 95% confidence intervals; significant differences between the classes was established using Chi-square tests. With regard to the MFPDI, scores have previously been shown to fit the Rasch model and this form was used for both subscales (29).

All analyses were two-tailed and were deemed statistically significant if $p<0.05$. Analysis was performed using STATA v13 (Stata Corporation, Texas, USA) except the LCA, which was performed in MPLUS v7.11(30).

RESULTS

Of the 560 participants who attended research clinics, 24 with inflammatory arthritis were excluded and three did not have foot radiographs, leaving 533 for analysis. Participants had a mean age of 64.9 years (standard deviation (s.d.) 8.4) and 55.9% were female. Radiographic data were missing for 12 1st MTPJs affecting eight participants. Overall, 62.7% had radiographic OA in one or more foot joints with the 1st MTPJ being the most frequently affected (27%, n=287) followed by the 2nd CMJ (17%, n=184), TNJ (15%, n=158), NCJ (8%, n=86), and the 1st CMJ (5%, n=50)(Supplementary Figure 1).

The mean number of joints affected was 1.4 (s.d. 1.6), with 21% participants having OA in one joint and 42% having OA in two or more joints (Table 1). Radiographic OA was found to cluster significantly in individuals across both feet ($p<0.001$), more than was expected by chance, but clustering was not seen separately in the left ($p=0.078$) or right foot ($p=0.575$)(Table 1). The analysis was repeated stratifying by gender and the same findings occurred in both males and females, although females had slightly higher frequencies of joint involvement (data not shown).

Radiographic OA in the 1st MTPJ tended to occur in isolation, whereas OA in the NCJ, 2nd CMJ and 1st CMJ tended to co-occur with other joints (Table 2). When stratified by gender the same findings were seen except for 1st CMJ OA, which occurred slightly more frequently in isolation in males compared to females (data not shown). The possible combinations of joint involvement are presented in a 5-way Venn diagram in Supplementary Figure 2.

Although unilateral OA was more prevalent than bilateral OA, strong associations were seen for symmetry in each of the foot joints, with the strongest association found in the NCJ where the odds of NCJ OA given its presence in the same joint in the other foot increased 20-fold (Table 3). The unadjusted overall symmetry for foot OA was OR=12.9 (95% CI: 9.9,16.8). After adjustment for age, gender, presence of OA in each foot joint and the total number of foot joints with radiographic OA across both feet, OR for overall symmetry remained significant but reduced to 3.0 (2.1,4.2). This indicates the presence of confounding; sensitivity analysis found that the

total number of foot joints with radiographic OA across both feet was the variable that caused the largest reduction in the odds. Stratification by gender produced similar results, but overall adjusted symmetry in the foot was stronger in females (4.3 (2.7,6.8)) compared to males (1.8 (1.1,3.1)).

Bivariate associations between paired combinations of foot joints within the left foot were found to be statistically significant between the 2nd CMJ and NCJ, the NCJ and TNJ, and the 1st MTPJ and 2nd CMJ (Figure 1). In the right foot, statistically significant associations were found between all paired combinations of the midfoot joints (1st CMJ, 2nd CMJ, NCJ and TNJ)(Figure 1).

LCA of radiographic OA in each foot joint was undertaken (Supplementary Table 1). The 3-class solution was considered the best fit as the BIC was at its lowest, the Lo-Mendell-Rubin adjusted LRT indicated that the 4-class solution was not significantly better than the 3-class solution, and entropy was high. The 3-class solution also had average posterior probabilities that were above 0.7 (Table 4), indicating better classification and greater distinction between latent classes compared to the other class solutions, and all classes were at least 10% of the total sample.

In the 3-class solution, class 1 was the largest (n=339, 64%) and was characterised by low probabilities of radiographic OA occurring in all ten foot joints, and was therefore labelled as 'no or minimal foot OA'. Class 2 (n=112, 21%) had high probabilities of radiographic OA in the 1st MTPJ in both the left and right feet, and was labelled as 'isolated 1st MTPJ OA'. Class 3 (n=82, 15%) had medium-to-high probabilities of OA in both 2nd CMJs and NCJs in the midfoot with medium probabilities of OA in the TNJs and 1st MTPJs, hence was labelled as 'polyarticular foot OA' (Table 4).

The isolated 1st MTPJ OA and polyarticular foot subgroups were significantly older than the no or minimal foot OA subgroup, after adjustment for gender (Table 5). Following adjustment for age, the polyarticular foot subgroup had a significantly higher probability of being female in

comparison to the other subgroups. After adjustment for both age and gender, the polyarticular foot OA subgroup had significantly more persistent and severe pain, greater functional limitation, higher BMI and increased presence of nodal hand OA compared with the other subgroups. No statistically significant between-group differences were seen for socioeconomic, recalled footwear at age 20-49 years, previous foot/ankle injury, and selected metabolic factors.

DISCUSSION

Our findings, based on the pattern of joint involvement on plain radiography and comparative symptom and risk profiles, suggest a distinction between isolated 1st MTPJOA and a form of more widespread OA in the foot that involves multiple midfoot joints. This latter group had more severe pain and disability and was associated with female gender and the presence of nodal hand OA. Our study found few other significant differences between these groups after adjusting for age and gender, although the range of information gathered on risk factors was relatively limited.

While patterning of OA in the foot has not been examined before in detail, our findings are consistent with previous observations that foot OA seems to affect multiple joints (6), and co-occurrence is present in certain midfoot joints (31). The involvement of multiple foot joints is akin to the polyarticular and highly symmetrical form of OA that is seen in hands (3,32). Although studies of symmetry in the hands have reported associations between the presence of OA in a joint and its presence in the same joint on the opposite hand (33-35), these studies only adjusted for age. We found comparable estimates for foot OA symmetry when adjusting for age alone, which then attenuated considerably when further adjustment was made for gender, foot joint and total number of affected foot joints. We have previously shown a nearly four-fold increase in odds for hand OA symmetry in a parallel community-based cohort (36). It appears, therefore, that OA in the weight-bearing small joints of the feet demonstrates the same high level of symmetry as hand OA.

The identification of a subgroup with isolated 1st MTPJ involvement frequently occurring in isolation is suggestive that some individuals have a specific predilection for the development of OA in this joint, possibly as a result of altered foot structure or inappropriate footwear. Indeed, cross-sectional studies have reported characteristic variations of skeletal morphology in two conditions commonly associated with 1st MTPJ OA: hallux valgus and hallux rigidus (37,38). Although we found no significant differences in prevalence of hallux valgus between the three subgroups, the role of other structural characteristics (such as variation in metatarsal length)

cannot be discounted. Although non-statistically significant, there was a slight increase in the probability that individuals had worn high or very high-heeled shoes between the ages of 20 to 49 years, which is consistent with a previous study that found high-heeled footwear to be associated specifically with disorders of the forefoot and toes (39). However, while the proportion reporting they had worn narrow toed footwear was higher in the isolated 1st MTPJ OA than the no or minimal foot OA subgroup, it was lowest in the polyarticular foot OA subgroup.

While multiple joint involvement and symmetry were observed in both the isolated 1st MTPJ and polyarticular foot OA subgroups, those in the polyarticular foot OA subgroup had wider joint involvement, which also included the 1st MTPJ. This is suggestive of a stronger influence of systemic risk factors and could be indicative of a generalised form of OA. The significantly greater proportion of females in the polyarticular foot OA subgroup is consistent with the strong patterns of symmetry and multiple joint involvement that has been seen in hand OA (32,33). This has been ascribed to post-menopausal changes, increasing the susceptibility of females to the development of generalised OA (40). The significantly increased frequency of nodal OA in the polyarticular foot OA group would support the possible involvement of OA at other sites.

Metabolic factors have been associated with OA at other weight-bearing (19,41), and non-weight-bearing sites (20,42), through altered lipid metabolism and chronic inflammatory responses (43,44). However, in this analysis only increased BMI was found in those with polyarticular foot OA compared to the other subgroups. Alternatively, the increased BMI in the polyarticular foot OA could be indicative of a mechanical cause. Other research has found both obesity and alterations in midfoot loading to be associated with midfoot OA (45,46).

The polyarticular foot OA subgroup was distinct, cross-sectionally, from the other two classes of foot OA in terms of descriptive characteristics and symptoms, while differentiation between those classed as having no or minimal foot OA and those with isolated 1st MTPJ OA was negligible. However, minor differences included the isolated 1st MTPJ subgroup being slightly older, having more joints affected with radiographic OA and having foot pain for slightly longer

durations. These factors may represent the accumulation of joints affected by OA over time, and it possible that isolated 1st MTPJ OA is a precursor to the development of more widespread foot OA seen in the polyarticular OA subgroup. Such progression might occur due to the modification of local biomechanical factors as a consequence of 1st MTPJ OA (47), altered foot biomechanics related to the presence of OA at the knee (48), or systemic factors as part of a generalised form of OA (40). However, the polyarticular foot OA subgroup were not found to be older than the isolated 1st MTPJ subgroup. Longitudinal data would be required to investigate this further.

While negligible differences in the symptom and risk factor profiles between the 1st MTPJ OA and the no or minimal foot OA subgroups do not confirm a distinct 1st MTPJ OA phenotype, its existence cannot be ruled out. The limited person-level measures included in the analysis may have meant that discrimination was not possible. More comprehensive foot specific data on symptoms and risk factors such as the type and location of foot injuries and objective functional measures might be more informative. In addition, further insight into foot OA phenotypes will be achieved through replication of this work in different study populations, investigation of the clinical presentations, co-occurrence of OA at other joints sites and the course of symptoms over time.

The variation in symptoms along with the potentially different causal mechanisms indicates that separate treatment strategies may be appropriate. To date, a range of treatment options have been investigated for foot OA, including steroid joint injections (49,50), insoles (51), and a range of surgical procedures (52), but the effectiveness of these treatments in general (18), and particularly in relation to different forms of foot OA, is not known.

Several methodological strengths and limitations should be considered when interpreting the findings in this paper. This analysis included participants recruited from the general population who reported having foot pain in the previous year, thus a wide range of foot pain and radiographic severities were present. A standardised radiographic protocol was used to obtain weight–bearing views so JSN was appropriately assessed and multiple planes captured OA features, which have been noted to vary on different views (6). However, in this analysis only five

joints in each foot were examined. It is possible that other foot joints may be affected by OA and contribute to the patterning and subgroups observed. Intra-rater reliability for the presence of OA was found to be excellent. Despite inter-rater reliability being moderate, it was comparable with the original atlas (5). Although the study population had a prevalence of OA in one or more foot joints of 63%, when multiple foot joints were examined the numbers in some of the combinations were quite small. This is likely to have reduced the statistical power, potentially leading to type II error. Additionally, although all individuals in the study had reported having foot pain in the last year, the latent classes of foot OA were based only on radiographic structural changes. As discordance between symptoms and structural changes are often seen, further investigation characterising polyarticular foot OA and 1st MTPJ OA in relation to symptomatic radiographic disease is needed.

In conclusion, this is the first detailed analysis of the pattern of multiple-joint involvement in foot OA. We have demonstrated that, as is the case for OA at other small joint sites, particularly the hands, patterning of individual joint involvement in radiographic foot OA is polyarticular and strongly symmetrical. Patterns of joint involvement in radiographic foot OA have indicated a distinction between individuals with isolated 1st MTPJ OA and those with a more widespread form of OA labelled ‘polyarticular foot OA’ but which also includes one or both 1st MTPJs. Our findings of these different forms of foot OA have provided new insights into possible causes, with a joint specific predilection to OA at the 1st MTPJ and possible systemic risk factors and mechanical mechanisms, which leads to a more generalised presentation of OA that includes the midfoot. While a greater symptomatic burden was seen in those with polyarticular foot OA, further investigation is needed to examine if these subgroups differ in their foot specific symptoms, clinical presentation, and the symptomatic course over time to extend our understanding of foot OA and how it should be best managed.

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520 Table 1. Observed and expected numbers of joints with radiographic OA in the feet of 533 adults aged 50 years

521 and over

Number of joints with radiographic OA	Left foot (0-5) n=533		Right foot (0-5) n=533		Across both feet (0-10) n=533	
	Observed (%)	Expected	Observed (%)	Expected	Observed(%)	Expected
0	280 (52.5%)	269	259 (48.6%)	252	199 (37.3%)	127
1	164 (30.8%)	184	182 (34.2%)	189	113 (21.2%)	182
2	67 (12.6%)	63	65 (12.2%)	71	111 (20.8%)	131
3	21 (3.9%)	14	21 (3.9%)	18	54 (10.1%)	63
4	1 (0.2%)	2	5 (0.9%)	3	29 (5.4%)	22
5	0 (0%)	0	1 (0.2%)	0	14 (2.6%)	6
6	†	†	†	†	9 (1.7%)	2
7	†	†	†	†	4 (0.8%)	0
8	†	†	†	†	0 (0%)	0
9	†	†	†	†	0 (0%)	0
10	†	†	†	†	0 (0%)	0
X^2	6.8		2.9		161.2	
df	3		4		6	
P value	0.078		0.575		<0.001	

522 *X^2, Chi-square test; df, degrees of freedom; † Only five joints in each foot were assessed.*

523

524

525 Table 2. Frequency of radiographic OA occurring in isolation and combined with other joints
526 in the same foot in 1066 feet

Foot joint	Frequency of radiographic OA occurring in isolation from other joints in the same foot % (n)	Frequency of radiographic OA occurring with ≥1 other joint in the same foot % (n)
1st MTPJ	60.6% (174/287)	39.4% (113/287)
1st CMJ	40.0% (20/50)	60.0% (30/50)
2nd CMJ	33.7% (62/184)	66.3% (122/184)
NCJ	17.4% (15/86)	82.6% (71/86)
TNJ	47.5% (75/158)	52.5% (83/158)

527 *MTPJ, metatarsophalangeal joint; CMJ, cuneometatarsal joint; NCJ, navicular first cuneiform joint; TNJ,*
528 *talonavicular joint.*
529

530 Table 3. Symmetry of radiographic OA in the left and right feet of 533 adults aged 50 years and over

Foot joint	Total number of individuals examined	Number (%) with no OA in either foot	Number (%) with OA in left foot only	Number (%) with OA in right foot only	Number (%) with OA in both left and right feet	Odds Ratio* (95% CI)
1st MTPJ	525	329 (62.7)	45 (8.6)	62 (11.8)	89 (17.0)	10.5 (6.7, 16.5)
1st CMJ	533	490 (91.9)	23 (4.3)	13 (2.4)	7 (1.3)	11.5 (4.2, 31.5)
2nd CMJ	533	397 (74.5)	38 (7.1)	50 (9.4)	48 (9.0)	10.0 (6.0, 16.8)
NCJ	533	468 (87.8)	19 (3.6)	25 (4.7)	21 (3.9)	20.7 (9.9, 43.3)
TNJ	533	414 (77.7)	35 (6.6)	45 (8.4)	39 (7.3)	10.3 (5.9, 17.8)

531 *95%CI, 95% confidence interval; MTPJ, metatarsophalangeal joint; CMJ, cuneometatarsal joint; NCJ, navicular first cuneiform*
532 *joint; TNJ, talonavicular joint. * The odds of having OA in a joint given its presence in the same joint in the other foot.*
533

534 Table 4. Latent classes of radiographic foot OA

	Class 1 No or minimal foot OA	Class 2 Isolated 1st MTPJ OA	Class 3 Polyarticular foot OA
Class size (%) based on most likely latent class membership	341 (64.0%)	115 (21.6%)	77 (14.5%)
Average posterior probabilities for most likely latent class membership	0.969	0.937	0.844
Right 1st MTPJ	0.130	0.723	0.348
Right 1st CMJ	0.016	0.013	0.162
Right 2nd CMJ	0.061	0.205	0.665
Right NCJ	0.031	0.000	0.436
Right TNJ	0.118	0.152	0.329
Left 1st MTPJ	0.000	1.000	0.310
Left 1st CMJ	0.049	0.031	0.119
Left 2nd CMJ	0.052	0.152	0.627
Left NCJ	0.013	0.032	0.392
Left TNJ	0.110	0.134	0.265

535 *Figures are probabilities unless otherwise indicated. MTPJ, metatarsophalangeal joint; CMJ, cuneometatarsal joint; NCJ,*
536 *navicular first cuneiform joint; TNJ, talonavicular joint.*
537

538

539 Table 5. Characteristics and risk factors of the three distinct classes of foot OA identified by latent class
540 analysis adjusted for age and gender

	No or minimal foot OA†	Isolated 1st MTPJ OA†	Polyarticular foot OA†	Difference between the three groups (significance) †
Frequency, n (%)	341 (64.0)	115 (21.6)	77 (14.5)	-
Descriptive characteristics and symptoms				
Duration of foot pain, n: *P* (95%CI)				
<12 months	48: 0.14 (0.11,0.17)	15: 0.11 (0.07, 0.15)	6: 0.11 (0.06, 0.15)	
1 – 5 years	120: 0.33 (0.28,0.37)	28: 0.29 (0.23, 0.34)	18: 0.28 (0.22, 0.35)	
5 – 10 years	63: 0.23 (0.19,0.26)	29: 0.23 (0.20,0.27)	30: 0.23 (0.20,0.27)	
>10 years	110: 0.30 (0.26,0.35)	43: 0.37 (0.29,0.45)	23: 0.38 (0.28,0.47)	0.172
Foot pain on most or all days in last month, n: *P* (95%CI)	171: 0.50 (0.45,0.56)	57: 0.51 (0.41,0.60)	51: 0.69 (0.59,0.79)	0.012
Foot pain in both feet, n: *P* (95%CI)	166: 0.50 (0.44,0.55)	55: 0.47 (0.38,0.56)	51: 0.65 (0.54,0.76)	0.046
1st MTPJ foot pain in last month, n: *P* (95%CI)	140: 0.41 (0.36,0.47)	57: 0.51 (0.42,0.60)	52: 0.69 (0.59,0.80)	<0.001
Midfoot pain in last month, n: *P* (95%CI)	175: 0.52 (0.47,0.58)	47: 0.41 (0.32,0.50)	52: 0.69 (0.59,0.80)	0.001
Very or somewhat dissatisfied with foot symptoms, n: *P* (95%CI)	168: 0.49 (0.44,0.54)	47: 0.43 (0.34,0.53)	45: 0.61 (0.50,0.73)	0.054
Number of foot joints ROA grade ≥2 (0-10), mean (95%CI)	0.6 (0.5,0.7)	2.4 (2.2,2.6)	3.8 (3.4,4.1)	<0.001
Foot pain severity (0-10) in the last month, mean (95%CI)	5.2 (5.0,5.5)	4.9 (4.4,5.4)	6.0 (5.4,6.6)	0.020
MFPDI (5 point scale from -2 to 2), mean (95%CI)[a]				
Pain subscale	-0.3 (-0.4,-0.1)	-0.5 (-0.7,-0.2)	0.3 (0.0,0.7)	0.002
Function subscale	-0.7 (-1.0,-0.5)	-0.9 (-1.3,-0.5)	0.0 (-0.4,0.5)	0.007
SF12, mean (95%CI)[b]				
Physical component score	38.0 (36.6,39.3)	40.3 (38.1,42.5)	37.2 (34.2,40.1)	0.146
Mental component score	48.7 (47.5,50.0)	50.2 (48.3,52.1)	48.4 (45.8,51.1)	0.376
HADS, mean (95%CI)[c]				
Anxiety scale	7.3 (6.8,7.8)	6.7 (5.9,7.5)	6.8 (5.8,7.7)	0.306
Depression scale	5.7 (5.2,6.1)	4.8 (4.1,5.5)	5.8 (5.0,6.7)	0.106
Risk factors				
Age, mean (95%CI)	63.9 (63.1,64.8)	66.1 (64.6,67.7)	67.3 (65.4,69.2)	0.002
BMI, mean (95%CI)	29.9 (29.3,30.5)	30.1 (29.1,31.2)	32.5 (31.2,33.8)	0.002
Female gender, n: *P* (95%CI)	177: 0.52 (0.47,0.57)	62: 0.54 (0.45,0.63)	59: 0.77 (0.67,0.86)	0.001
Manual occupational class, n: *P* (95%CI)	173: 0.54 (0.48,0.59)	55: 0.51 (0.41,0.60)	44: 0.61 (0.50,0.72)	0.406
Attended higher education, n: *P* (95%CI)	95: 0.28 (0.23,0.33)	25: 0.24 (0.16,0.32)	17: 0.23 (0.13,0.32)	0.468

Previous ever foot or ankle injury, n: *P* (95%CI)	234: 0.68 (0.64,0.73)	76: 0.66 (0.57,0.75)	53: 0.70 (0.59,0.80)	0.836
High & very high heeled footwear ever worn between ages 20-49 years, n: *P* (95%CI)[d]	124: 0.71 (0.64,0.78)	48: 0.79 (0.68,0.89)	42: 0.71 (0.60,0.83)	0.507
Narrow & very narrow toe box ever worn between ages of 20-49 years, n: *P* (95%CI)[e]	201: 0.62 (0.58,0.66)	76: 0.67 (0.59,0.74)	56: 0.61 (0.51,0.70)	0.493
Hallux valgus present in either foot, n: *P* (95%CI)[f]	133: 0.40 (0.35,0.46)	56: 0.48 (0.40,0.57)	44: 0.52 (0.41,0.63)	0.105
Intermittent claudication, n: *P* (95%CI)[g]	26: 0.09 (0.06,0.12)	6: 0.06 (0.01,0.10)	3: 0.05 (0.00,0.10)	0.388
Diabetes (type 2) or Impaired Fasting Glucose, n: *P* (95%CI)	44: 0.14 (0.10,0.18)	16: 0.14 (0.08,0.20)	17: 0.22 (0.13,0.32)	0.178
Hypertension, n: *P* (95%CI)	101: 0.33 (0.28,0.38)	35: 0.31 (0.22,0.39)	24: 0.29 (0.19,0.38)	0.713
Dyslipidaemia (raised cholesterol or triglycerides), n: *P* (95%CI)	178: 0.56 (0.51,0.61)	67: 0.60 (0.51,0.69)	47: 0.62 (0.51,0.73)	0.565
Metabolic syndrome, n: *P* (95%CI)[h]	60: 0.20 (0.15,0.24)	20: 0.17 (0.11,0.24)	21: 0.26 (0.16,0.36)	0.303
Hip pain in last year, n: *P* (95%CI)	186: 0.56 (0.51,0.61)	64: 0.55 (0.46,0.64)	52: 0.64 (0.53,0.75)	0.434
Knee pain in last year, n: *P* (95%CI)	249: 0.74 (0.69,0.79)	87: 0.76 (0.68,0.84)	69: 0.88 (0.81,0.96)	0.050
Nodal hand OA, n: *P* (95%CI)[i]	68: 0.21 (0.17,0.25)	26: 0.22 (0.15,0.29)	31: 0.34 (0.24,0.44)	0.040

Labels indicating what the numbers represent for each row are specified in the first column. MTPJ, metatarsophalangeal joint; n, number; P, probability; 95%CI, 95% confidence interval; MFPDI, Manchester Foot Pain and Disability Index; ROA, Radiographic OA; SF12, Short Form 12; HADS, Hospital Anxiety and Depression Scale; BMI, Body Mass Index. † Analyses are adjusted for age and gender, [a] Positive scores on the Rasched MFPDI indicate more pain and functional impairment (15), [b] Lower scores on SF12 indicate poorer physical and mental health (16), [c] Higher scores on the HADS indicate more severe anxiety and depression (17), [d] Exposure was restricted to females and defined as previous high or very high footwear worn on most days for at least one ten-year period between the ages 20-49 years, [e] Defined as previous narrow or very narrow toe box footwear worn on most days for at least one ten-year period between the ages 20-49 years, [f] Hallux valgus was determined by self-report from line drawings of each foot that depicted increasing grades in the hallux valgus angle of 15^{o} (18), [g] Intermittent claudication was defined as calf pain when walking at an ordinary pace on level ground or uphill (or when hurried) which disappears in 10 minutes or less by standing still (19), [h] Metabolic syndrome was defined as the presence of three or more of the following: BMI>30kg/m^{2}, hypertension, dyslipidaemia and type 2 diabetes or IFG, [i] Nodal hand OA was defined as Kellgren and Lawrence grade ≥2 in ≥2 interphalangeal joints (rays 2-5) and Heberden or Bouchard nodes (rays 2-5) across either hand (30).

Supplementary Table 1. Latent class characteristics for radiographic OA in different foot joints

Number of classes	AIC	BIC	Sample size adjusted BIC	Lo-Mendell-Rubin adjusted LRT P value	Entropy
1	4125.5	4168.3	4136.5	-	-
2	3915.6	4005.5	3938.8	<0.001	0.73
3	**3804.2**	**3941.1**	**3839.5**	**<0.001**	**0.87**
4	3772.7	3956.7	3820.2	0.076	0.88
5	3759.0	3990.1	3818.6	0.131	0.82
6	3751.0	4029.1	3822.8	0.255	0.87

AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; LRT, likelihood ratio test. The bold text indicates the model that was selected as having the optimal number or classes. Lower AIC and BIC, and higher entropy values indicate the optimal number of classes. The change in p-value for the Lo-Mendell-Rubin adjusted LRT from being significant to non-significant indicates where an additional class does not improve the latent class model.

564 **FIGURE LEGENDS**

565

566 Figure 1. A node and edge diagram showing the frequency of OA and the association of
567 radiographic OA between pairs of joints of the left foot and right foot of 533 adults aged 50 years
568 and over

569

570 *The size of each node is proportional to frequency of OA in that joint and the width of the edge is proportional to the*
571 *odds ratio between each pair of joints. MTPJ, metatarsophalangeal joint; CMJ, cuneometatarsal joint; NCJ, navicular*
572 *first cuneiform joint; TNJ, talonavicular joint.*

573

574

575 Supplementary Figure 1. A diagram illustrating the five foot joints examined and the frequency of
576 radiographic OA in 533 adults aged 50 years and over

577

578 *1st MTPJ, first metatarsophalangeal joint; 1st CMJ, first cuneometatarsal joint; 2nd CMJ, second cuneometatarsal joint;*
579 *NCJ, navicular first cuneiform joint; TNJ, talonavicular joint.*

580

581

582 Supplementary Figure 2. A 5-way Venn diagram showing the different combinations of joint
583 involvement within the foot of all individuals (1066 feet)

584

585 *1st MTPJ, first metatarsophalangeal joint; 1st CMJ, first cuneometatarsal joint; 2nd CMJ, second cuneometatarsal joint;*
586 *NCJ, navicular first cuneiform joint; TNJ, talonavicular joint.*