Title

The natural history of radiographic first metatarsophalangeal joint osteoarthritis: a nineteen-year population based cohort study

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Abstract

Objective: To assess the long-term prevalence, natural history, progression and incidence of radiographic first metatarsophalangeal joint (1st MTPJ) osteoarthritis (OA).

Methods: A longitudinal, cohort design was used in which radiographic OA at the 1st MTPJ was investigated in participants at year 6 (1995) and year 23 (2013-2015) from the Chingford 1000 Women study. Radiographic features of osteophytes (OPs) and/or joint space narrowing (JSN) at the 1st MTPJ were scored according to a validated foot atlas. Natural history was determined by the change in prevalence, incidence, progression and worsening of OA in the 1st MTPJ.

Results: Complete case matched foot radiographic data were available for 193 of the women currently enrolled in the study, mean age: 75.7 years (SD: 5.2; range 69-90). At the level of the 1st MTPJ, prevalence of OA at year 6 was 21.76% in the left and 24.35% in the right and at year 23 was 23.83% in the left and 32.64% in the right. Over the 19-year period, 13.5% of women developed incident OA in the right 1st MTPJ and 8.3% in the left. Both progression and worsening of OA were more evident for OPs and in the right 1st MTPJs.

Conclusion: In this longest study of the natural history of radiographic 1st MTPJ OA to date, the prevalence and incidence of 1st MTPJ OA increased over a 19-year period. Progression and/or worsening of 1st MTPJ OA over time appears to be driven by OP development rather than JSN suggestive of a biomechanical cause.

Keywords

Foot, Feet, Joints, Osteoarthritis, Natural history

Significance and Innovations

- Investigation of osteoarthritis over time is a major evidence gap in the field of foot and ankle osteoarthritis. This study is the first to do so over a nineteen-year period, confirming that the prevalence of radiographic osteoarthritis within the first metatarsophalangeal joint (1st MTPJ) in older women increases over time.
- Although previously observed in hand osteoarthritis, the discordance in right-left findings for osteophyte development and joint space narrowing observed in the 1st MTPJ over time has not been described previously.
- Findings from this study implicate biomechanical factors as a cause in the development of 1st MTPJ osteoarthritis. Further work is required to investigate potential biomechanical risk factors for the development and progression of 1st MTPJ osteophytes and osteoarthritis.

Introduction

There is increasing evidence from a growing number of population cohort studies that foot osteoarthritis (OA) is common, especially in older adults with foot pain (1-4). The UK population prevalence of symptomatic radiographic foot OA overall has been estimated at 17% and, for the individual joint level, at 8% for the first metatarsophalangeal joints (1st MTPJ) in adults aged over 50 years (2). Foot pain has been reported to affect between 7-13% in adults in the US (30-100 years) (5) and in the UK 10% report disabling foot pain (6). Structural foot OA has also been linked to outcomes such as foot pain, restricted activity, lower quality of life (2, 7-10) and increased General Practitioner encounters (11, 12).

Studies reporting on the incidence of OA of the knee and hip are becoming more evident (13-15). Slow development of radiographic knee OA, stable progression and improvement over long periods has also been reported (16, 17). In contrast to knee and hip OA, there are very few studies on the epidemiology of foot and ankle OA or their management. Evidence relating to foot OA is often reported from cross-sectional study designs and comparatively little is known about potential changes in foot joints over time (9, 10). A recent study investigating self-reported foot pain over 18 months, reported little symptomatic changes in three different foot OA phenotypes determined at baseline (18).

The lack of foot specific longitudinal data, notably lack of valid measurement criteria of foot OA progression over time, has been highlighted as a limitation in the current body of knowledge on radiographic foot OA which makes investigations evaluating clinical interventions challenging (2, 9). Thus, further longitudinal investigation of incidence, progression and natural history of foot OA is warranted in order to target preventive therapies and reduce known modifiable risk factors for both the incidence and progression of foot OA (9, 10). One US cohort study, reporting on findings from the Clearwater Osteoarthritis community based cohort has presented foot OA incidence data (19). Over a period of seven years, 364 (25%) and 404 (27%) participants developed structural left and right 1st MTPJ OA, respectively (19). Unfortunately, a key limiting factor for the generalisability of those findings is that the sample was selected according to the presence of hindfoot valgus and thus the data are not representative of the general population.

The UK Chingford 1000 women study is a 25-year longitudinal population cohort, which provides a unique opportunity to investigate foot OA over time. The aim of this study was to assess the long-term natural history of 1st MTPJ OA by observing prevalence, incidence, progression and worsening

of radiographic foot OA in this well described UK population-based cohort of older women over a nineteen-year period.

Patients and Methods

Participant selection

The Chingford 1000 Women study was established in 1989 to study the health of women in mid-life. It is a prospective cohort that originally comprised 1003 women aged 45-64 from a general practice in Chingford, North-East London, UK. Participants have been followed annually since 1989 and are described in detail elsewhere (20-23).

All participants retained within the Chingford 1000 Women's study that had complete foot radiographs at year 6 (1995) and also at year 23 (2013-2015) were included in this study. Participants with foot radiographs that were damaged and/or unreadable from either year or were missing from year 6 were excluded (n=25). All included participants provided informed written consent. (Research Ethics Committee approval reference number: LREC R&WF 96 and REC: 84131).

Data Collection

Assessments for year 23 took place during a single appointment at the Silverthorne Medical Centre, Chingford, UK. On each occasion, the same consultation rooms and facilities were utilised. Foot radiographs were obtained in 1995 at the 'InHealth' NHS Stratford site, UK. Due to a change in contract, all follow-up radiographs in 2013-2015 were undertaken at Holly House Private Hospital in Chigwell, UK. A standard operating procedure for foot radiographs had been drawn up *a priori* and for both radiography sites consensus meetings with the radiographers were held to ensure consistency between sites. Data collection for year 6 had been carried out by the previous study investigators at the Stratford site. All foot radiographs were performed at both time points after the demographic assessments on the same day or as close as possible.

Assessment of participant characteristics

General characteristic data including age, weight and height, were recorded by an experienced registered nurse (MDan) at both data collection points.

Assessment of radiographic foot osteoarthritis

All foot radiographs obtained at year 23 were a single dorsoplantar view of both feet and separate lateral views of both feet according to a standardised protocol (24, 25). Foot radiographs were taken

barefoot and partially weight-bearing and were available in electronic format. The radiographic films were reviewed by a Consultant Radiologist at the 'InHealth' Stratford NHS radiology unit or at the Holly House Hospital department of radiology for any radiographic 'red flags' or clinically significant abnormality.

Radiographic features of osteophytes (OPs) and/or joint space narrowing (JSN) at each 1st MTPJ were scored according to the La Trobe Foot Atlas (24). The atlas uses a four-point scale of 0, 1, 2 and 3 to score OPs (0=absent; 1=small; 2=moderate; 3=severe) and JSN (0=none; 1=definite; 2=severe; 3=bone-on-bone at least one point) in both feet in 2 views (dorsoplantar and lateral). Although the scale description proposed in the La Trobe Foot Atlas publication describes JSN grade 3 as "joint fusion" we have interpreted this more precisely as "bone-on-bone" (26).

For year 23, the presence of radiographic OA was defined as one radiographic feature graded as '2' or higher (24). This was limited to the dorsoplantar view to match those at year 6 where all foot x-rays had been taken of both feet together as dorsoplantar views and only available as plain film. The advice given in the La Trobe Foot Atlas indicates that use of both dorsoplantar and lateral views is 'gold standard' and should be applied where possible to ensure an appropriate level of sensitivity to OA (24). However, further evaluation of the La Trobe Foot Atlas has shown that good sensitivity (94.6%) can be obtained in the 1st MTPJ when only a dorsoplantar view is available (27). For these reasons the 1st MTPJ alone was selected as the focus of investigation in this study.

All radiographs were scored by a single trained reader (PMc). Reliability results for OP and JSN scoring at five foot joints have been detailed previously (26). Intra-rater agreement was also established for the presence or absence of OA at the 1st MTPJ using Cohens Kappa statistic, cross referenced to the values criteria by Landis and Koch (28). Reliability was moderate (K= 0.51) for the left 1st MTPJ and substantial (K= 0.61) for the right 1st MTPJ (26).

Statistical Analysis

Data from the 'Chingford Women's Study' are maintained in an 'Access' database (Access 2000, Microsoft Office). Study data for year 23 were collected and managed using REDCap (Research Electronic Data Capture) software (29) hosted at the University of Oxford. The data were exported and all data evaluation and statistical analyses were conducted using Stata version 14.1 (Stata Corp, College Station, Texas, USA).

Complete case analysis was performed based on those participants who had radiographic foot data at both year 6 and 23 time points. Natural history was determined by observing the change in prevalence of OA in the 1st MTPJ of case matched participants from year 6 to year 23, and by defining incidence, progression and worsening of OA in the 1st MTPJ during the study time period.

Prevalence was calculated at both the subject level (using either foot) and at the 1st MTPJ level (with each subject supplying two feet to the analysis) and was defined using the La Trobe Foot Atlas grade of ≥2 for either OP or JSN (24). Incidence of 1st MTPJ OA was calculated at the subject level and was defined by having a La Trobe Foot Atlas grade of 0 or 1 of both OP and JSN at year 6 and a grade ≥2 for OP or JSN at year 23. Incident unilateral and bilateral 1st MTPJ OA was defined as having a La Trobe Foot Atlas grade of 0 or 1 of both OP and JSN in both 1st MTPJs at year 6 and having a grade of ≥2 for OP or JSN in one or both first MTPJs at year 23, respectively.

Progression was calculated at the 1st MTPJ level and was defined as having a La Trobe Foot Atlas grade score of 2 for OP and/or JSN in the 1st MTPJ at year 6 with an increase to a score 3 for the corresponding OP and/or JSN by year 23 in the left and right 1st MTPJs. At the subject level, we also determined the number of participants who had unilateral 1st MTPJ OA at the first period of observation (grade $\underline{\geq}$2 for OP or JSN) but bilateral disease at the second period of observation.

Worsening was calculated at the 1st MTPJ level and was defined as an increase of La Trobe Foot Atlas grade from any grade (including grades 0, 1 and 2). The group with worsening essentially includes incident cases, participants with disease progression as well as participants with mild progression who moved from a La Trobe Foot Atlas grade of 0 to 1.

Results

Of the original 1003 participants at baseline (year 0), 846 (84.34%) attended year 6 and 332 (33.3%) attended the year 23 clinical appointments. Reasons for loss to follow-up from baseline included death (n=223), withdrawal (n=311), moved (n=67), uncontactable (n=61) and did not attend year 23 (n=9) (see Figure 1 recruitment flow chart). There were no significant differences in terms of age, height, weight or BMI between responders and non-responders from the previous visit.

At year 23, 218 attended for foot radiographs. Of these 193 had foot radiographs taken at year 6. Data from 193 participants who had complete radiographic foot data at both year 6 and year 23

were therefore included in the analyses. The mean age of included participants at year 23 was 75.7 years (SD: 5.2), range 68-90 years and mean BMI was 27.9 (SD: 4.5).

Natural history of radiographic 1st MTPJ OA

In participants (n=193) at year 6 the prevalence of 1st MTPJ OA in either foot was 33.2% (n=64), being present in 21.8% (n=42) of left feet and 24.4% (n=47) of right feet, and being bilateral in 13.0% (n=25). At year 23 the prevalence of 1st MTPJ OA in either foot had increased to 40.9% (n= 79), with 23.8% (n=46) having involvement of the left foot, 32.6% (n=63) the right foot, and 15.5% (n=30) having bilateral involvement.

Incidence of radiographic 1st MTPJ OA

Of 129 participants with no OA in either 1st MTPJ at year 6, 7.0% (n=9) participants developed incident 1st MTPJ radiographic OA in the left foot and 17.1% (n=22) in the right foot over a period of 19 years. At the subject level, 21.7% (n=28) developed 1st MTPJ OA in either foot, and 2.3% (n=3) developed bilateral 1st MTPJ OA.

Progression of radiographic 1st MTPJ OA

For participants who had 1st MTPJ OA defined as a score of 2 at year 6 (n=35 left; n=43 right) progression to a score of 3 at year 23 in the corresponding feature (OP or JSN) was seen in 28.6% (n=10) left 1st MTPJs and 34.9% (n=15) right 1st MTPJs at year 23.

For participants who had bilateral 1st MTPJ OA, defined by a score of 2 in either JSN or OP in both 1st MTPJs at year 6 (excluding those with a score of 3 in the alternate feature), progression to a score of 3 in both 1st MTPJs at year 23 was seen in 22.2% (n=4) at year 23.

For participants who had unilateral 1st MTPJ OA, defined by a score of 2 for OP or JSN at year 6, progression to a score of 3 in both 1st MTPJs (bilateral OA) at year 23 was seen in 28.2% (n=11). Individual OP and JSN progression can be seen in Table 1.

Worsening of radiographic 1st MTPJ OA

From year 6 to year 23, for those participants who had 1st MTPJ JSN scores of 0, 1 or 2 (i.e. excluding any participants who had a score of 3) changes were noted towards a corresponding higher score of 1, 2 or 3 (i.e. worsening) in 28.6% (n=54) right 1st MTPJs and 33.9% (n=63) left 1st MTPJs at year 23.

From year 6 to year 23, for those participants who had 1st MTPJ OP scores of 0, 1 or 2 (i.e. excluding any participants who had a score of 3) changes were noted towards a corresponding higher score of 1, 2 or 3 (i.e. worsening) in 30.5% (n=58) right 1st MTPJs and 23.0% (n=43) left 1st MTPJs at year 23. A breakdown of worsening score changes is shown in Table 2.

Discussion

The results from this study provide new longitudinal evidence for the natural history of radiographic 1st MTPJ OA in a sample of older women from a UK population-based cohort. Over half of women (59%) remained free of radiographic 1st MTPJ OA over the period of this study. The prevalence of 1st MTPJ OA increased and 22% of those free of radiographic OA at baseline (year 6) developed it by year 23. Both progression (defined as a score of 2 at year 6 and 3 at year 23) and worsening (defined as a score of 0, 1 or 2 at year 6, increasing to higher score 1, 2 or 3 at year 23) of OA were more evident in the right 1st MTPJs.

Very few studies have reported on the epidemiology of foot OA making comparison of cohort data that does exist in this field challenging (30). Figures for radiographic foot OA prevalence estimates vary considerably depending on the population, the radiographic views taken, which foot joints are examined, the grading systems applied and whether symptomatic or asymptomatic foot OA is studied (9, 26). As such, longitudinal investigation of foot OA is rare. A recent cohort study investigation reported little change in foot pain severity over an 18 month period, but used radiographic foot OA phenotypes as the baseline stratification criteria and did not perform follow up foot x-rays (18).

The prevalence of radiographic 1st MTPJ OA in our cross-sectional analysis of year 6 (33.1%) and year 23 (40.9%) data is higher than that of women in the Clearwater Osteoarthritis Study (17.7%) with a mean age of 62 years (19). This may in part be due to the differences in grading radiographic OA. The current study utilised the La Trobe foot atlas (24) unlike the Clearwater Osteoarthritis Study which used Kellgren and Lawrence criteria (19, 31). Other studies using the La Trobe Foot Atlas have determined the cross sectional prevalence of 1st MTPJ OA based on the presence of corresponding

symptoms, and therefore report lower prevalence (7.8%) than that of radiographic change (2).

The Kellgren and Lawrence system that is a widely used to grade radiographic OA at a range of joints (31) has been criticised as having inherent difficulties at all joint sites including the small joints of the foot, due to inconsistent interpretation and application of the grades between studies (9). To overcome these issues in inconsistent interpretation of radiographic foot OA between studies the La Trobe foot specific radiographic atlas and grading system was developed (24, 27). As subsequent investigations have adopted this grading system (2, 26, 32), comparison of prevalence figures for OA with older investigations, such as the Clearwater study (19), become difficult.

Whilst just over half of our participants remained free of radiographic 1st MTPJ OA over the course of the study, 21.7% developed 1st MTPJ OA in either foot and 2.3% developed bilateral 1st MTPJ OA. As an indirect comparison in the same cohort, 39.5% of participants developed incident knee radiographic OA in at least one knee over a 14 year period and the annual cumulative incidence of radiographic knee OA was similar at 2.3% at the knee level and 2.8% at the subject level (17).This is supported by the findings of other investigators who reported that 2% of participants in the Framingham study had incident knee OA over a mean interval of 8.1 years (33). Incidence of hip OA is slightly higher than that reported in the knee. In the Johnston County Osteoarthritis Project (US) radiographic OA developed in 7.4% of the hips with no OA at baseline and 3.6% of the hips with mild or moderate OA progressed over the follow-up period (34). Franklin et al. (2011) found 2.5% to have radiographic OA of the hips with follow-up at 11 and 28 years after the original diagnosis (35). For hand OA among women in the Framingham study incidence is also comparable to the knee at 1% which increased with age and 'levelled off' at the age of 80 (36, 37).

Among our participants who scored 2 on the La Trobe Foot Atlas Scale for 1st MTPJ OA at baseline, progression was found to be greater in the right foot and approximately one-third of women with unilateral 1st MTPJ OA at baseline developed bilateral 1st MTPJ OA by the end of the study. Interestingly, there was a notable difference between worsening of scores for joint space narrowing and scores for osteophytes in left and right feet, with right sided worsening being driven largely by osteophytes and left side worsening by joint space narrowing. To our knowledge, these findings have not been previously reported. Discordance in symmetry of OA has been reported for the hands, with the suggestion that biomechanical factors acting primarily through osteophyte development may predispose to the asymmetric development of OA (38). In the same study, joint space narrowing was found to be more symmetrical and thus consistent with being driven more by constitutional and genetic factors. It is possible that this is also true for the foot joints. If our

findings are confirmed, further work should involve exploration of risk factors such as physical and occupational activity that may contribute to increased forces and damage being transmitted through the 1st MTPJ. Such analysis could potentially uncover opportunities for earlier intervention and prevention of the development of 1st MTPJ OA.

Limitations

The main limitation of our study relates to the high attrition rate of participants, which is a caveat in many longitudinal studies. There is potential for deaths and withdrawal due to disability and illness to bias towards a healthier cohort who attended the follow up visits. Also the study population was limited to women, predominately Caucasian and older, and from a single geographic region in the UK, which limits the generalisability of the findings. Other important caveats are that only one x-ray view (non-weight-bearing dorsoplantar) was examined, our assessor was not blinded to the time point of the study at which the image was taken and that clinical data (symptoms) and possible risk factors for progression (e.g. BMI, footwear, constitutional alignment, age at onset of OA, presence of nodal hand OA etc.) were not examined. Investigation of such possible risk factors for progression merit investigation in future studies.

Conclusion

This is the longest study to date to examine the natural history of radiographic 1st MTPJ OA. The findings demonstrate that the prevalence of radiographic OA within the 1st MTPJ in older women increases over a 19-year period. Whilst, just over half of participants remained free of radiographic 1st MTPJ OA during that time, incident cases, progression and/or worsening of the 1st MTPJ OA over time was observed in the remaining participants. The discordance in right-left findings for osteophyte development and joint space narrowing observed over time has not been described previously. Findings from this study implicate biomechanical factors in the development of 1st MTPJ OA, and investigation of potential biomechanical risk factors for the development and progression of 1st MTPJ OA seems warranted.

Declarations

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Authors' contributions

PM, CB, NA, LG, WD, DS and MDoh conceived and designed the study.

PM & MDan acquired all foot radiographs; PMc read all foot radiographs.

PM and MDan completed all recruitment and clinical assessments.

PM, CB, LG, AD completed all data management, data entry and data analyses

LG completed statistical analysis

PM, CB, LG, WD, DS, NA, MDoh helped to draft the manuscript.

All authors read and approved the final manuscript.

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CB is currently being supported to undertake Fellowship from the National Institute for Health Research (CDF-2015—08—032). The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the National Institute for Health Research, NHS or the Department of Health.

Ethics approval and consent to participate

Full ethical approval was granted by Waltham Forest and Redbridge local research ethic committee (reference number: LREC R&WF 96); the study was sponsored by Whipps Cross Hospital Research and Development Unit. Approval for the year 23 foot study was granted by NRES Committee South Central – Oxford A which was received in May 2013 (REC number: 84131).

Competing interests

There were no benefits received nor will there be from commercial or business based organisations either directly or indirectly relating to this article to any persons involved in this research. The authors declare that they have no competing interests.

List of abbreviations

AFA: Australian Foot Atlas

OA: Osteoarthritis

MTPJ: Metatarsophalangeal joint

CMJ: Cuneometatarsal joint

N1stCNJ: Navicular first cuneiform joint

TNJ: Talonavicular joint

DP: Dorsoplantar

OPs: osteophytes

JSN: Joint space narrowing

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Figures

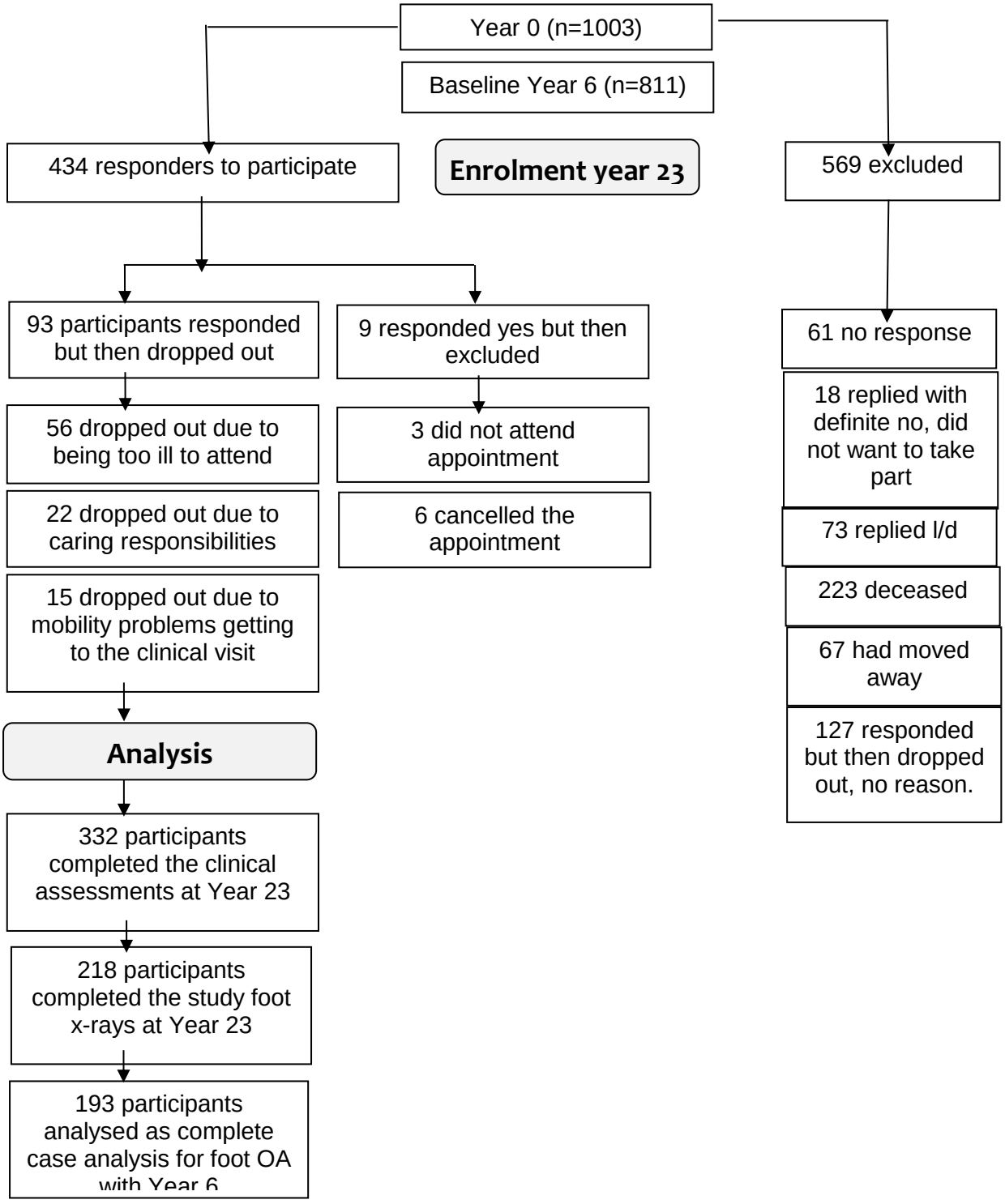
Figure 1. Participant recruitment flow diagram for the year 23 Chingford 1000 women's foot study.

Tables

Table 1. Progression of first metatarsal phalangeal joint osteoarthritis over a 19 year period at the joint, foot and subject level

Table 2. Worsening change in first metatarsal phalangeal joint osteophyte (OP) and joint space narrowing (JSN) scores between year 6 and 23

Figure 1. Participant recruitment flow diagram for the year 23 Chingford 1000 women's study.



Key: l/d = long distance (the participant moved out of the area and found it too far to travel for subsequent visits).

589 **Table 1.** Progression of first metatarsophalangeal joint (MTPJ) osteoarthritis over a 19 year period at
590 the joint, foot and subject level
591

Grade 2 OA at year 6	Progression at year 23 % (n)
Left JSN (*n=8)	12.5 (1)
Left OP (*n=32)	31.3 (10)
Right JSN (*n=11)	36.4 (4)
Right OP (*n=40)	35.0 (14)
Left first MTPJ (*n= 35)	28.6 (10)
Right first MTPJ (*n=43)	34.9 (15)
Bilateral to bilateral first MTPJ progression (*n=18)	22.2 (4)
Unilateral to bilateral first MTPJ progression (*n=39)	28.2 (11)

592 **Key:** * = number of participants with grade 2 at year 6; JSN=joint space narrowing; OP=osteophyte
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594
595 **Table 2.** Worsening change in first metatarsal phalangeal joint osteophyte (OP) and joint space
596 narrowing (JSN) scores between year 6 and 23
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	Right		Left	
Change in score from year 6 to 23	JSN n (%)	OP n (%)	JSN n (%)	OP n (%)
0-1	38 (70.4)	17 (29.3)	29 (46.0)	15 (34.9)
0-2	1 (1.9)	4 (6.9)	10 (15.9)	3 (7.0)
0-3	0 (0.0)	1 (1.7)	2 (3.2)	1 (2.3)
1-2	8 (14.8)	18 (31.0)	13 (20.6)	13 (30.2)
1-3	3 (5.6)	4 (6.9)	8 (12.7)	1 (2.3)
2-3	4 (7.4)	14 (24.1)	1 (1.6)	10 (23.3)
Total cases	54 (100.0)	58 (100.0)	63 (100.0)	43 (100.0)

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