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1 **DXA-derived hip shape is related to osteoarthritis: findings from in the MrOS cohort**

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1 **Abstract**

2 **Objective** Statistical shape modeling (SSM) of radiographs has been used to explore relationships  
3 between altered joint shape and hip osteoarthritis (OA). We aimed to apply SSM to Dual-energy  
4 X-ray Absorptiometry (DXA) hip scans, and examine associations between resultant hip shape  
5 modes (HSMs), radiographic hip OA (RHOA), and hip pain, in a large population based cohort.

6 **Method** SSM was performed on baseline hip DXA scans from the Osteoporotic Fractures in Men  
7 (MrOS) Study. Associations between the top ten HSMs, and prevalent RHOA from pelvic  
8 radiographs obtained 4.6 years later, were analysed in 4100 participants. RHOA was defined as  
9 Croft score  $\geq 2$ . Hip pain was based on pain on walking, hip pain on examination, and Western  
10 Ontario and McMaster Universities Arthritis Index (WOMAC).

11 **Results** The five HSMs associated with RHOA showed features of either pincer- or cam-type  
12 deformities. HSM 1 (increased pincer-type deformity) was positively associated with RHOA  
13 [1.23 (1.09,1.39)] [odds ratio and 95% CI]. HSM 8 (reduced pincer-type deformity) was  
14 inversely associated with RHOA [0.79 (0.70,0.89)]. HSM 10 (increased cam-type deformity)  
15 was positively associated with RHOA [1.21 (1.07,1.37)]. HSM 3 and HSM 4 (reduced cam-type  
16 deformity) were inversely associated with RHOA [0.73 (0.65,0.83) and 0.82 (0.73,0.93)  
17 respectively]. HSM 3 was inversely related to pain on examination [0.84 (0.76,0.92)] and  
18 walking [0.88, (0.81,0.95)], and to WOMAC score [0.87 (0.80,0.93)].

19 **Conclusions** DXA-derived measures of hip shape are associated with RHOA, and to a lesser  
20 extent hip pain, possibly reflecting their role in the pathogenesis of hip OA.

21

## 1 **Introduction**

2 Hip osteoarthritis (OA) is an increasingly important cause of morbidity as the mean age of the  
3 population increases (1). Identification of underlying risk factors may open up new avenues for  
4 preventative strategies. One of the most important is abnormalities of hip development leading to  
5 alterations in hip shape, exemplified by developmental dysplasia of the hip which is screened for  
6 routinely in neonates (2, 3). More subtle alterations in hip shape have also been reported to be  
7 associated with hip OA. For example, cam-type deformities, caused by extra bone growth around  
8 the anterolateral aspect of the femoral head-neck junction resulting in a non-spherical femoral  
9 head, leading to femoro-acetabular impingement (FAI) (4), are associated with premature onset  
10 of OA (5, 6). FAI may also result from a pincer-type deformity where the acetabulum overhangs  
11 and encroaches on the lateral aspect of the femoral head, for which currently there is  
12 contradictory evidence in terms of associations with OA (2, 5).

13 In the above studies, hip shape was defined using geometric parameters measured on radiographs  
14 such as femoral neck or centre-edge angle. An alternative approach, statistical shape modeling  
15 (SSM), has been developed whereby principal component analysis is used to derive a set of  
16 orthogonal hip shape modes (HSMs), which together provide a more complete description of hip  
17 shape (7). Using this method, changes to the lateral curvature of the femoral head (7), and larger  
18 femoral head relative to femoral shaft (8) have been reported to be associated with more rapid  
19 progression of radiographic hip OA (RHOA) and, interestingly, with prevalent knee OA (9).  
20 However, these studies were based on SSM of the femoral head alone, additional information is  
21 provided by models which also include the acetabulum(10). For example, in a recent study by  
22 Agricola et al using a combined femoral head and acetabulum SSM, a retroverted acetabulum  
23 (defined as the posterior acetabular wall located medially with respect to the centre of the  
24 femoral head) was found to be predictive of RHOA (11).

25 A limitation of the above approaches towards studying hip shape is their reliance on use of  
26 radiographs. Whereas sample sizes based on radiographic collections are large enough for

1 conventional epidemiological studies, they provide limited power for genetic studies. Lindner et  
2 al examined genetic influences on hip shape in 929 cases of unilateral RHOA, observing  
3 associations between three loci and hip shape following a look up of 41 candidates (12).  
4 However, considerably larger samples, including unaffected individuals, are required to perform  
5 genome wide association studies (GWAS) intended to identify novel genetic loci. For example,  
6 in the osteoporosis field, the largest GWAS study to date identified 56 loci associated with bone  
7 mineral density (BMD) of which 32 were novel, based on DXA scans from over 90,000  
8 individuals from population based cohorts (13). Widely available hip DXA scans may also prove  
9 useful in evaluating relationships between hip shape and hip OA. For example, Waarsing et al  
10 applied a statistical model combining shape and density from hip DXA scans in 218 patients  
11 with hip OA, following which several modes were found to be associated with features of RHOA  
12 (14). However, to what extent pure shape measures derived from hip DXA scans are also related  
13 to RHOA, and whether similar relationships are observed in population-based cohorts, is  
14 currently unclear.

15 To establish whether DXA-derived hip shape represents a useful phenotype for future GWAS  
16 studies intended to identify novel genetic risk factors for hip OA, in the present study, we aimed  
17 to examine whether hip shape derived from a SSM applied to hip DXA scans is associated with  
18 RHOA in the Osteoporotic Fractures in Men (MrOS) Study; in this population-based cohort, hip  
19 radiographs were performed a mean of 4.6 years following baseline DXA scans. Given the lack  
20 of concordance between radiographic findings and symptoms in hip OA (15), we also aimed to  
21 examine to what extent hip shape shows equivalent associations with hip pain, ascertained at the  
22 same time as hip radiographs using a combination of questionnaires and examination.

## 1 **Methods**

### 2 *Study participants*

3 The MrOS cohort, within which this cross-sectional study is based, is a prospective study of  
4 5,994 men recruited between 2000-2002 at six centers around the United States (Birmingham,  
5 Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near  
6 Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California). To be eligible, men had  
7 to be  $\geq 65$  years old, ambulatory, and without bilateral hip replacements. A full description of the  
8 MrOS cohort has been previously published (16, 17). We used hip shape data derived from DXA  
9 scans performed at the baseline visit, as part of a separate study examining genetic influences on  
10 this phenotype. Pelvic X-rays for assessing RHOA, and hip examination and symptoms  
11 questionnaire, were obtained as part of a second visit conducted from March 2005 to May 2006,  
12 on average 4.6 years later.

13

### 14 *Demographic characteristics*

15 All demographic information is taken from visit one. The participant's age was taken as the age  
16 in years at their last birthday. A Harpenden stadiometer (Holtain Ltd, Crynch, Wales) measured  
17 standing height in centimeters, which was based on an average of two readings, if these differed  
18 by  $\geq 4$  mm, two further readings were taken. Weight was measured to the nearest 0.1 kilograms  
19 using a standard balance-beam scale or digital scales using standard protocols. Race was a self-  
20 identified criterion with the participants asked to select one of the following: white, African  
21 American, Asian, native Hawaiian or other Pacific Islander, American Indian or Alaskan native,  
22 multi-racial and unknown.

### 23 *DXA protocol*

1 Right hip DXA imaging was performed at the baseline visit unless they had a right hip  
2 replacement in which case a left hip scan was performed. A QDR 4500 Hologic machine  
3 (Waltham, MA) was used at all six sites. There was a standardized protocol for positioning  
4 participants and all DXA technicians were certified centrally (18).

5

### 6 *Statistical shape modelling*

7 Hip DXA scans were uploaded to SHAPE software (University of Aberdeen). A 58-point model  
8 was used that automatically placed points around anatomical landmarks of the upper femur and  
9 adjacent acetabulum; all images were reviewed and, where necessary, points were manually re-  
10 positioned by a trained operator to ensure they were positioned on the bone edge (Figure 1).  
11 Before marking up MrOS scans, a training set of 100 images was used to ensure accurate point  
12 placement. Median point-to-point difference (ie distance between a given point placed by the  
13 operator and the average point after combining placements by all operators) was derived for each  
14 operator, a score of  $\leq 3$  pixels denoting acceptable accuracy. Firstly, Procrustes analysis was  
15 performed to transform the points without deformation by scaling, rotation and translation so that  
16 they are aligned as closely as possible, this is followed by Principal Component Analysis (PCA).  
17 SHAPE is based on the algorithm first validated by Cootes et al when measuring the shape of  
18 resistors, heart chambers and hands and more recently validated by Linder et al against manually  
19 derived geometric measures from hip radiographs (19, 20). SHAPE through SSM produces  
20 linearly independent variations in hip shape (hip shape modes (HSM))(21, 22). Each mode was  
21 normalized to zero mean and unit standard deviation for the whole cohort so that each image  
22 (and therefore participant) is assigned a set of mode scores in units of standard deviations (SD)  
23 describing how far they lie from the mean. Images producing HSM scores above or below 4SDs  
24 were manually checked by two operators, and point placement corrected where necessary. Mode  
25 shapes were subsequently assigned to cam or pincer-type deformities based on consensus visual  
26 interpretation.



1

## 2 ***Radiographic hip OA***

3 At visit two, standing pelvic radiographs were performed using a standardized protocol. Each  
4 radiograph was read by a primary reader and scored, using a previously published atlas (23), for  
5 concentric, medial or lateral joint space narrowing (JSN) (0-4), osteophyte formation at the  
6 inferior and superior femur and acetabulum (0-3), bone cysts (0-3), subchondral sclerosis (0-3),  
7 and femoral head deformity (0-3) (18). In addition, binary measures were created for the  
8 presence of osteophytes, JSN or subchondral sclerosis, based on mild (grade  $\geq 1$ ) used for  
9 primary analyses, moderate (grade  $\geq 2$ ) or severe (grade  $\geq 3$ ) cut-offs. Radiographs with definite  
10 osteophytes or JSN were then examined by a second reader to reach a consensus score. Croft  
11 scores, based on an aggregate of these scores, were subsequently generated (24), with a score  $\geq 2$   
12 (requiring the presence of osteophytes or JSN) taken as the presence of moderate RHOA which  
13 was used in primary analyses, and a score  $\geq 3$  denoting severe RHOA (18).

14

## 15 ***Hip pain***

16 All participants who attended visit two were asked to undergo a hip examination. The  
17 participant's right hip was internally rotated and patient-reported pain was documented  
18 generating a binary outcome. Participants completed a questionnaire concerning right hip pain on  
19 walking in the last thirty days (scored 0-4), which was converted to a binary measure i.e.  
20 presence or absence of right hip pain on walking in the last thirty days. Finally, all patients had a  
21 standardized Western Ontario and McMaster Universities Arthritis Index (WOMAC) score  
22 calculated out of 20. The WOMAC score, which has been validated as a measure of hip OA (25),  
23 encompasses pain, stiffness and function to give an overall score of disease, 0 being no limitation  
24 and 20 being severe limitation,

1

## 2 *Statistical analysis*

3 To limit multiple testing, we restricted our analyses to the ten HSMs explaining the greatest  
4 proportion of variance in hip shape. Demographic statistics were summarized as mean (SD) for  
5 continuous variables and counts (percentages) for categorical variables. Logistic regression was  
6 used to analyse associations between each of these HSMs as separate predictors, modelled as  
7 continuous variables, and binary OA outcomes; ordinal logistic regression was used to examine  
8 relationships with WOMAC pain score outcomes, results are given as an odds ratio (OR).  
9 Sensitivity analyses were also performed where we compared the results after applying different  
10 Croft score definitions for OA, and different cut-offs for defining osteophytes. In the adjusted  
11 regression models we adjusted for age, height, weight and race as *a priori* confounders, as  
12 recorded at visit one. In setting P values for the strength of evidence against the null hypothesis,  
13 we considered our top ten HSMs as independent exposures, and a global Croft score of  $\geq 2$   
14 (indicating at least moderate OA) as our primary outcome, based on our fully adjusted model,  
15 giving a Bonferroni-corrected P value of 0.005. All statistical analysis used Stata release 14  
16 statistical software (StataCorp, College Station, TX, USA).

17

## 1 **Results**

### 2 *Population Characteristics*

3 Of the 5994 MrOS participants attending visit one, right DXA scans were available in 5862  
4 (97.8%), having excluded those with incomplete data (N=86), previous joint replacement (N=45)  
5 or poor image quality (N=1), from which hip shape was generated. At this baseline visit,  
6 participants were a mean of 72.8 years of age, 83.6 kg in weight, and 174.4 cm in height, giving  
7 mean BMI of 27.5 kg/m<sup>2</sup>. At visit 2 (a mean of 4.6 years later), right hip radiographs were read  
8 for RHOA, which were available for 4100 (69.9%) of these participants, who formed the basis of  
9 the present study, of whom 90.7% were white, 3.3% Asian, 3.2% African American and 2.8%  
10 multiracial/unknown/other.

11 At visit 2, 7.1% had evidence of RHOA, based on Croft score  $\geq 2$  (Table 1). Lateral acetabular  
12 osteophytes were the most common radiographic feature of hip OA, with any osteophyte at this  
13 site present in 19.2% of participants. Furthermore, at visit 2, 11.4% had hip pain on examination,  
14 and 20.2% reported hip pain on walking.

15

### 16 *Hip shape modes*

17 The first ten HSMs in our cohort explained 81.4% of the total variance in hip shape. Five HSMs  
18 were found to be associated with RHOA (see below), which together explained 48.3% of the  
19 total variance in hip shape. All five HSMs associated with RHOA showed features of FAI on  
20 visual inspection, either in the form of pincer- or cam-type deformities (Figures 2 & 3), whereas  
21 the remaining HSMs were unrelated to these deformities. No HSM was related to both  
22 deformities, implying these represent statistically independent contributions to hip shape. HSM  
23 1, which accounted for 22.3% of total variance in hip shape, was positively associated with  
24 pincer-type deformity (Figure 2). HSM 8, which accounted for 2.8% of total variance in hip

1 shape, was negatively associated with pincer-type deformity. HSM 3 and HSM 4, which  
2 explained 12.1% and 9.2% of total variation in hip shape respectively, were negatively  
3 associated with cam-type deformity (Figure 3). HSM 10, which explained 1.9% of total variation  
4 in hip shape, was positively associated with cam-type deformity.

5 These modes also reflected other shape differences. HSM 1 was associated with a larger femoral  
6 head, larger lesser and greater trochanters, wider femoral neck width, and narrower supero-  
7 medial joint space; HSM 3 was related to a smaller lesser trochanter and narrower supero-medial  
8 joint space; HSM 4 was associated with altered neck shaft angle leading to medial displacement  
9 of the femoral head; and HSM 8 was related to a wider supero-lateral joint space. In contrast, the  
10 HSMs not associated with measures of hip OA were unrelated to pincer- or cam-type  
11 deformities; HSM 2 featured a smaller femoral head with a steeper femoral neck angle and larger  
12 lesser trochanter, HSM 5 a smaller lesser trochanter, HSM 6 a deeper superior curvature to the  
13 femoral neck and larger lesser trochanter, HSM 7 a smaller lesser trochanter and HSM 9 a  
14 smaller femoral head.

15

### 16 *Hip shape modes 1 and 8 (pincer-type deformities) versus radiographic hip osteoarthritis*

17 In unadjusted analyses, HSM 1 was positively associated with the presence of RHOA, defined as  
18 Croft score  $\geq 2$  [OR 1.23 (1.09, 1.39)], whereas HSM 8 was negatively associated [OR 0.79  
19 (0.70, 0.89)] (Table 2). Results were unaffected by adjustment for age, weight, height and race.

20 In terms of specific radiographic components, in adjusted analyses, HSM 1 was positively  
21 associated with the presence of acetabular [OR 1.13 (1.04, 1.22)] and inferior femoral [OR 1.22  
22 (1.07, 1.38)] osteophytes (Table 3), and with medial JSN [OR 1.55 (1.40, 1.71)] and subchondral  
23 sclerosis [OR 1.23 (1.09, 1.39)] (Table 4). Conversely, HSM 8 was inversely associated with  
24 osteophytes at all four locations (OR 0.78 to 0.89) (Table 4), and with lateral JSN [OR 0.71  
25 (0.62, 0.82)] and subchondral sclerosis [OR 0.79 (0.69, 0.89)].

1

## 2 ***Hip shape modes 3, 4 and 10 (cam-type deformities) versus radiographic hip osteoarthritis***

3 In unadjusted analyses, HSM 3 and HSM 4 were inversely associated with prevalent RHOA [OR  
4 0.73 (0.65, 0.83) and 0.82 (0.73, 0.93) respectively], whereas HSM10 was positively related [OR  
5 1.21 (1.07, 1.37)] (Table 2). Equivalent results were seen in analyses adjusted for age, weight,  
6 height and race. In terms of specific radiographic components, in adjusted analyses HSM 3 was  
7 inversely related to the presence of osteophytes at all sites (OR 0.76 to 0.89) (Table 3), and to  
8 lateral JSN [0.73 (0.63, 0.84)] and subchondral sclerosis [OR 0.76 (0.67, 0.85)], whereas there  
9 was a positive association with medial JSN [OR 1.32 (1.19, 1.46)] (Table 4). HSM 4 was  
10 inversely related to the presence of inferior acetabular osteophytes [OR 0.83 (0.75, 0.92)], but  
11 positively related to medial JSN [OR 1.32 (1.20, 1.46)]. HSM 10 was positively associated with  
12 inferior femoral osteophytes [OR 1.22 (1.07, 1.39)] and subchondral sclerosis [OR 1.21 (1.07,  
13 1.38)]. Equivalent observations were seen in unadjusted analyses (data not shown).

14

## 15 ***Association of hip shape with hip pain***

16 In adjusted analyses, HSM 3 was inversely associated with hip pain on internal rotation [OR 0.84  
17 (0.76, 0.92)] and on walking [OR 0.88 (0.81, 0.95)], and with WOMAC pain score [OR 0.87  
18 (0.80, 0.93)]. Similar results were seen in unadjusted analyses (data not shown). There was weak  
19 evidence that HSM 4 was inversely associated with hip pain on examination and on walking and  
20 with WOMAC score, and that HSM 8 was positively related to these parameters (all  $P < 0.02$ );  
21 however, for all these p values were  $> 0.005$ .

## 22 ***Sensitivity analyses***

23 Similar point estimates were observed for associations between HSMs and RHOA using a  
24 definition of Croft score  $\geq 3$  as opposed to  $\geq 2$  (Table 2). Equivalent results were also obtained

- 1 for associations between hip shape and moderate or severe osteophytes (*i.e.* grade  $\geq 2$ ), compared
- 2 to those seen for grade  $\geq 1$  osteophytes as presented in the main results (Table 3).
- 3

## 1 **Discussion**

2 We examined associations between hip shape, as assessed by SSM performed on hip DXA scans,  
3 and prevalent radiographic hip OA ascertained approximately five years later, in a large  
4 population based cohort of older men. We found that five out of the top ten hip shape modes  
5 were associated with prevalent RHOA, and one mode was also associated with hip pain. Taken  
6 together, these findings suggest that SSM applied to hip DXA scans can be successfully used to  
7 identify shape changes associated with hip OA, particularly radiographic features. Given the  
8 substantial number of large population based cohorts with available hip DXA scans, this finding  
9 opens up the possibility of identifying novel genetic risk factors for hip OA, based on GWAS  
10 studies of DXA-derived hip shape.

11 All five hip shape modes associated with RHOA showed features of FAI, reflecting either cam-  
12 or pincer-type deformities. Given the cross-sectional nature of this analysis, it was not possible to  
13 distinguish shape changes resulting from hip OA, from those causing it. That said, our finding  
14 that three hip shape modes, indicative of cam-type deformity, are related to RHOA is consistent  
15 with previous studies suggesting that cam-type deformity is a risk factor for RHOA, based on  
16 SSM (26), and measured geometric parameters (27, 28). As well as being related to global  
17 RHOA as reflected by Croft score, HSM 3, HSM 4, and HSM 10 showed equivalent  
18 relationships with osteophytes at different sites, and in the case of HSM 3 with lateral JSN and  
19 subchondral sclerosis. HSM 3 also showed the strongest association with hip pain. However, the  
20 associations between hip shape and hip pain were generally weaker than that for RHOA. This  
21 lack of concordance between radiographic and clinical features of hip OA is well recognized  
22 (15), and was supported by further analyses in which we examined associations between RHOA  
23 as defined by Croft score  $\geq 2$  and clinical features. Whereas RHOA was positively associated  
24 with pain on examination and on walking, these associations were relatively modest (RR 1.67  
25 and 1.51 respectively).

1 Our observation that two HSMs reflecting pincer-type deformity were positively associated with  
2 RHOA is also consistent with the view that pincer-type deformity contributes to FAI, which is in  
3 turn thought to be an important cause of hip OA (5). That said, there is little evidence that pincer-  
4 type deformity is associated with RHOA in the general population. Indeed, in a recent study of  
5 720 individuals from the CHECK study, pincer-type deformity, as measured on radiographs  
6 based on the centre-edge angle, was found to be protective against incident OA (2). One possible  
7 explanation for these apparently discrepant findings is that the relationship between pincer-type  
8 deformity and RHOA depends upon gender, since our present findings derived from the all-male  
9 MrOS cohort, whereas CHECK was 79% female.

10 Whilst the five HSMs associated with RHOA could be divided into those reflecting cam- and  
11 pincer-type deformities, these appearances may have arisen as a consequence of other OA related  
12 phenotypes. For example, the image resolution of DXA scans used in this study was too low to  
13 clearly visualize osteophytes, and so superior femoral osteophytes and lateral acetabular  
14 osteophytes may have been included inadvertently, leading to the impression of cam-and pincer-  
15 type deformities respectively. Moreover, since we were only able to include the superior  
16 acetabulum in our SSM, we were unable to evaluate medial JSN and to exclude medial  
17 displacement of the femoral head as a cause of acetabular overhang, as opposed to pincer-type  
18 deformity. Our observation that HSM 1, which was positively related to pincer-type deformity,  
19 was also positively related to medial JSN on subsequent radiographs, is consistent with this  
20 alternative explanation.

21 As well as contributing to cam- and pincer-type deformities, hip shape modes may have reflected  
22 the presence of OA in other ways. For example, HSM 1 and HSM 3 were suggestive of greater  
23 supero-medial JSN, and HSM 8 lesser supero-lateral JSN. In addition, alteration in the size of the  
24 lesser trochanter associated with HSM 3 may reflect variation in the extent of internal rotation of  
25 the hip during image acquisition, which may in turn reflect underlying hip OA given the latter is  
26 associated with limited internal rotation. Hip shape modes were also related to differences which<sup>15</sup>



1 may reflect other risk factors for developing OA apart from FAI. For example, HSM 1 was  
2 related to size of the femoral head and greater trochanter, and femoral neck width, which have  
3 recently been reported to be associated with prevalent radiographic knee OA (9). That said, HSM  
4 2 and HSM 9, which were also related to femoral head size but showed no relation to pincer-or  
5 cam-type deformities, were unrelated to RHOA or hip pain.

## 6 *Strengths and limitations*

7 This study represents the first report of associations between DXA-derived hip shape and RHOA  
8 in a population based sample. The large size of the sample represents a further strength. The fact  
9 that this is a male cohort may have further increased power in light of previous findings  
10 suggesting the relationships between hip shape and RHOA are stronger in males than in females  
11 (29), though to what extent our findings are applicable to females requires further study. Our  
12 study also highlights the benefit of using large DXA cohorts for hip shape research, though given  
13 the greater resolution of radiographs, the latter are more suitable in smaller studies, and in  
14 clinical practice. One limitation of this study was our lack of baseline radiographs. Therefore, the  
15 associations which we observed between HSMs, as assessed on baseline DXA scans, and RHOA  
16 based on radiographs collected five years later, could have reflected relationships with prevalent  
17 as opposed to incident OA. This distinction is important, since in examining associations with  
18 prevalent OA, it is difficult to infer causality, and the shape changes we observed could have  
19 been a result of, rather than a risk factor for, hip OA. A further limitation is the relatively low  
20 image resolution of the DXA scanner used in MrOS, making it difficult to determine to what  
21 extent associations between DXA-derived hip shape and RHOA reflected characteristics of  
22 established OA such as osteophytes, as opposed to shape changes representing possible OA risk  
23 factors such as those related to FAI. Newer DXA devices provide sufficient resolution for  
24 identifying osteophytes on hip DXA scans (30). In addition, shape results could conceivably be  
25 affected by the degree of hip rotation; although the lower leg is strapped into a fixed position  
26 during scanning, the degree of hip rotation achieved might be affected by anatomical features<sup>16</sup>

1 such as pelvic size and shape, and associated hip disease. Another limitation, is that our HSMs  
2 cannot be directly applied to other cohorts since SSM using PCA is specific to the images used  
3 to make the model. Finally, SSM is not designed specifically to evaluate FAI and based on our  
4 findings more analysis, using methods specific to FAI such as alpha-angle, should be done to  
5 replicate these findings.

## 6 *Conclusions*

7 Having applied a SSM of the femoral head and superior acetabulum to hip DXA scans from the  
8 MrOS cohort, we found that five out of the top ten hip shape modes were associated with  
9 RHOA, of which one mode was also related to hip pain. That these modes were associated with  
10 either cam- or pincer-type deformities is consistent with previous studies implicating FAI in the  
11 pathogenesis of hip OA. Furthermore, the observation that DXA-derived hip shape is related to  
12 prevalent hip OA suggests this may represent a useful phenotype for future GWAS studies  
13 intended to identify novel genetic risk factors for hip OA.

14

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12

1 **Author Contributions**

2 BF, CG, RA, EO and JT conceptualized the study. BF, DB, JG, RB, JL, MN, NL and EO  
3 collected the data. BF, DB, CG, EO and JT developed the analysis plan and analysed the data.  
4 BF, RA, NL, EO, JT obtained funding. All authors contributed to the interpretation of the results,  
5 wrote the manuscript and have approved the final version of the manuscript. BF had full access  
6 to all the data and takes responsibility for its integrity and accuracy.

1 **Conflict of Interest**

2 We have none to declare.

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- 42

1 **Table 1** Prevalence of radiographic and hip OA and hip pain

	Prevalence n [%]
<b>Radiographic OA</b>	
Croft <2	3811 [93]
Croft ≥2	289 [7.1]
Croft ≥3	100 [2.4]
<i>Any osteophyte (i.e. score ≥ 1)</i>	
Lateral acetabular	788 [19.2]
Lateral femoral	401 [9.8]
Inferior acetabular	404 [9.9]
Inferior femoral	272 [6.6]
<i>Any joint space narrowing (i.e. score ≥ 1)</i>	
Lateral	207 [5.1]
Medial	446 [10.9]
Concentric	148 [3.6]
<i>Other bone lesions</i>	
Cysts	44 [1.1]
Any subchondral sclerosis(i.e. score ≥ 1)	278 [6.8]
Chondrocalcinosis	9 [0.02]
Joint deformity	35 [0.9]
<b>Symptoms</b>	
Hip pain on examination	451 [11.4]
Hip pain on walking	829 [20.2]
WOMAC	0.9 [2.3, 0, 20.0]

2

3 Prevalence based on 4100 individuals with right hip X-rays. Results are shown as prevalence  
 4 [%], apart from the Western Ontario and McMaster Universities Arthritis Index (WOMAC)  
 5 score which is presented as mean [SD, Min, Max]. N = 4,100 except for pain on examination (N  
 6 = 3,946), walking (N = 4,098) and WOMAC score (N = 4,076).



**Table 2** Associations of hip shape modes with the presence of radiographic hip OA based on the Croft score

	Unadjusted Croft $\geq 2$		Adjusted Croft $\geq 2$		Unadjusted Croft $\geq 3$		Adjusted Croft $\geq 3$	
	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P
HSM 1	1.23 [1.09, 1.39]	0.00072*	1.23 [1.09, 1.39]	0.00082*	1.08 [0.89, 1.32]	0.43	1.10 [0.9, 1.35]	0.35
HSM 2	1.04 [0.92, 1.17]	0.56	1.01 [0.89, 1.14]	0.89	0.95 [0.78, 1.16]	0.63	0.93 [0.76, 1.14]	0.51
HSM 3	0.73 [0.65, 0.83]	3.6x10 <sup>-7</sup> *	0.73 [0.65, 0.83]	4.0x10 <sup>-7</sup> *	0.60 [0.50, 0.73]	3.7x10 <sup>-7</sup> *	0.60 [0.50, 0.73]	3.5x10 <sup>-7</sup> *
HSM 4	0.82 [0.73, 0.93]	0.0014*	0.83 [0.73, 0.93]	0.0021*	0.67 [0.55, 0.83]	0.00014*	0.69 [0.56, 0.84]	0.00028*
HSM 5	1.02 [0.91, 1.16]	0.71	1.03 [0.91, 1.17]	0.62	1.02 [0.83, 1.24]	0.88	1.01 [0.82, 1.24]	0.94
HSM 6	0.92 [0.82, 1.03]	0.14	0.92 [0.82, 1.03]	0.16	0.87 [0.72, 1.05]	0.15	0.86 [0.71, 1.05]	0.14
HSM 7	0.95 [0.84, 1.07]	0.40	0.98 [0.87, 1.11]	0.79	0.90 [0.74, 1.1]	0.30	0.96 [0.79, 1.18]	0.72
HSM 8	0.79 [0.70, 0.89]	0.00016*	0.78 [0.69, 0.88]	7.4 x 10 <sup>-5</sup> *	0.64 [0.52, 0.79]	2.6 x 10 <sup>-5</sup> *	0.63 [0.51, 0.78]	1.4 x 10 <sup>-5</sup> *
HSM 9	0.95 [0.84, 1.07]	0.39	0.95 [0.84, 1.07]	0.41	0.93 [0.76, 1.14]	0.48	0.94 [0.77, 1.14]	0.52
HSM 10	1.21 [1.07, 1.37]	0.0020*	1.24 [1.1, 1.41]	0.00061*	1.29 [1.05, 1.59]	0.014	1.35 [1.1, 1.66]	0.0048*

Table shows results of logistic regression analysis between hip shape modes (HSMs) and Croft score in 4,100 individuals. Results show odds ratio of having a Croft score per standard deviation increase in hip shape mode [95% confidence intervals] and *P*-value. Adjusted = adjusted analysis for age, weight, height and race. \**P*<0.005

**Table 3** Associations of hip shape modes with osteophytes at different sites

	Osteophyte Score	Lateral acetabulum		Lateral femoral		Inferior acetabulum		Inferior femoral	
		OR [95% CI]	P value	OR [95% CI]	P value	OR [95% CI]	P value	OR [95% CI]	P value
HSM1	≥ 1	1.13 [1.04, 1.22]	0.0031*	1.11 [1.00, 1.24]	0.047	1.13 [1.02, 1.26]	0.019	1.22 [1.07, 1.38]	0.0022*
	≥ 2	1.01 [0.90, 1.14]	0.81	1.06 [0.91, 1.24]	0.45	1.18 [1.01, 1.39]	0.044	1.41 [1.10, 1.80]	0.0068
HSM3	≥ 1	0.89 [0.82, 0.96]	0.0034*	0.78 [0.70, 0.87]	2.7 x 10 <sup>-6</sup> *	0.76 [0.69, 0.85]	2.9 x 10 <sup>-7</sup> *	0.80 [0.71, 0.90]	0.00035*
	≥ 2	0.79 [0.70, 0.89]	7.5 x 10 <sup>-5</sup> *	0.60 [0.52, 0.71]	1.8 x 10 <sup>-10</sup> *	0.73 [0.62, 0.86]	0.00017*	0.73 [0.57, 0.93]	0.011
HSM4	≥ 1	0.92 [0.85, 1.00]	0.041	0.86 [0.78, 0.96]	0.0058	0.83 [0.75, 0.92]	0.00048*	0.86 [0.76, 0.97]	0.016
	≥ 2	0.96 [0.85, 1.08]	0.48	0.83 [0.71, 0.98]	0.024	0.83 [0.70, 0.97]	0.023	0.70 [0.55, 0.90]	0.0058
HSM8	≥ 1	0.89 [0.82, 0.96]	0.0034*	0.81 [0.73, 0.90]	7.7 x 10 <sup>-5</sup> *	0.84 [0.75, 0.93]	0.0011*	0.78 [0.69, 0.89]	0.00014*
	≥ 2	0.89 [0.79, 1.00]	0.046	0.74 [0.63, 0.87]	0.00025*	0.84 [0.71, 0.99]	0.035	0.77 [0.60, 0.99]	0.044
HSM10	≥ 1	1.12 [1.03, 1.21]	0.0063	1.10 [0.99, 1.22]	0.082	1.12 [1.01, 1.25]	0.035	1.22 [1.07, 1.39]	0.0022*
	≥ 2	1.1 [0.98, 1.24]	0.11	1.17 [1.00, 1.37]	0.054	1.23 [1.04, 1.45]	0.017	1.40 [1.08, 1.82]	0.010

Table shows results of logistic regression analysis between hip shape modes (HSMs) and osteophytes, dependent on score  $\geq 1$  (any osteophyte) and  $\geq 2$  (moderate to severe osteophytes only), at different sites in 4,100 individuals. Results show odds ratio of having any osteophyte per standard deviation increase in hip shape mode [95% confidence intervals] and p value, adjusted for age, weight, height and race. \*P<0.005

**Table 4** Associations of hip shape modes with joint space narrowing and subchondral sclerosis

	Lateral JSN		Medial JSN		Concentric JSN		Subchondral sclerosis	
	OR [95% CI]	P value	OR [95% CI]	P value	OR [95% CI]	P value	OR [95% CI]	P value
HSM1	1.01 [0.87, 1.16]	0.91	1.55 [1.40, 1.71]	4.3 x 10 <sup>-17</sup> *	1.23 [1.04, 1.45]	0.013	1.23 [1.09, 1.39]	0.0011*
HSM3	0.73 [0.63, 0.84]	8.6 x 10 <sup>-6</sup> *	1.32 [1.19, 1.46]	9.2 x 10 <sup>-8</sup> *	0.98 [0.83, 1.15]	0.79	0.76 [0.67, 0.85]	6.8x 10 <sup>-6</sup> *
HSM4	0.84 [0.73, 0.97]	0.020	1.32 [1.20, 1.46]	5.9 x 10 <sup>-8</sup> *	1.05 [0.89, 1.25]	0.54	0.84 [0.74, 0.95]	0.0067
HSM8	0.71 [0.62, 0.82]	4.3 x 10 <sup>-6</sup> *	0.87 [0.78, 0.96]	0.0057	0.87 [0.74, 1.03]	0.11	0.79 [0.69, 0.89]	0.00018*
HSM10	1.16 [1.01, 1.35]	0.039	1.11 [1.00, 1.23]	0.041	0.93 [0.79, 1.10]	0.39	1.21 [1.07, 1.38]	0.0025*

Table shows results of logistic regression analysis between hip shape modes (HSM) and joint space narrowing (JSN) and subchondral sclerosis in 4,100 individuals. Results show odds ratio of having any JSN or subchondral sclerosis per standard deviation increase in hip shape mode [95% confidence intervals] and p value, adjusted analysis for age, weight, height and race. \*P<0.005

## Figure Legends

**Figure 1:** An example DXA image

### Figure 1

This is a DXA image taken from the MrOS cohort. The 58 points used for the SSM are marked on the image. Key points are marked in red and these represent anatomical reference points to ensure accurate marking. There are two key lateral acetabular points placed on the outer edge of the acetabulum and one key medial acetabular point placed at the end of the acetabular eyebrow. The other key points are located around the trochanters, the femoral head and the femoral neck.

**Figure 2:** Hip shape modes 1 and 8

Figure 2

Pincer-type variations in hip shape demonstrated by hip shape mode 1 and hip shape mode 8. Hip shape mode 1 has a positive relationship with a pincer-type variation. Hip shape mode 8 has a negative relationship with a pincer-type variation. Dashed line = +2 SDs, solid line = - 2SDs

**Figure 3:** Hip shape modes 3, 4 and 10

Figure 3

Cam-type variation in hip shape demonstrated by hip shape modes 3, 4 and 10. Hip shape modes 3 and 4 have a negative relationship with a cam-type variation. Hip shape mode 10 has a positive relationship with a cam-type variation. Dashed line = +2 SDs, solid line = - 2SDs.