Faber, B. G., Baird, D., Gregson, C. L., Gregory, J. S., Barr, R. J., Aspden, R. M., ... Osteoporotic Fractures in Men (MrOS) Study Research Group (2017). DXA-derived hip shape is related to osteoarthritis: findings from in the MrOS cohort. Osteoarthritis and Cartilage, 25(12), 2031-2038. https://doi.org/10.1016/j.joca.2017.09.006

Publisher's PDF, also known as Version of record
License (if available): CC BY
Link to published version (if available): 10.1016/j.joca.2017.09.006

Link to publication record in Explore Bristol Research
PDF-document

This is the final published version of the article (version of record). It first appeared online via Elsevier at https://www.sciencedirect.com/science/article/pii/S1063458417312037. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research
General rights
This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/pure/about/ebr-terms
DXA-derived hip shape is related to osteoarthritis: findings from in the MrOS cohort

B.G. Faber † *, D. Baird †, C.L. Gregson ‡, J.S. Gregory ¶, R.J. Barr †, R.M. Aspden ‡, J. Lynch ¶, M.C. Nevitt ¶, N.E. Lane ‡, E. Orwoll ¶, J.H. Tobias †, for the Osteoporotic Fractures in Men (MrOS) Study Research Group

SUMMARY

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

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

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

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

© 2017 The Authors. Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

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

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

A limitation of the above approaches towards studying hip shape is their reliance on use of radiographs. Whereas sample sizes based on radiographic collections are large enough for conventional epidemiological studies, they provide limited power for genetic studies. Lindner et al. examined genetic influences on hip shape in 929 cases of unilateral RHOA, observing associations between three studies. Lindner et al. on radiographic collections are large enough for conventional is their reliance on use of radiographs. Whereas sample sizes based old, ambulatory, and without bilateral hip replacements. A full and San Diego, California). To be eligible, men had to be from March 2005 to May 2006, on average 4.6 years later.

Demographic characteristics

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

DXA protocol

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

SSM

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

Methods

Study participants

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

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

SSM

Hip DXA scans were uploaded to SHAPE software (University of Aberdeen). A 58-point model was used that automatically placed points around anatomical landmarks of the upper femur and adjacent acetabulum; all images were reviewed and, where necessary, points were manually re-positioned by a trained operator to ensure they were positioned on the bone edge (Fig. 1). Before marking up MrOS scans, a training set of 100 images was used to ensure accurate point placement. Median point-to-point difference (i.e., distance between a given point placed by the operator and the average point after combining placements by all operators) was derived for each operator, a score of <3 pixels denoting acceptable accuracy. Firstly, Procrustes analysis was performed to transform the points without deformation by scaling, rotation and translation so that they are aligned as closely as possible, this is followed by PCA. SHAPE is based on the algorithm first validated by Cootes et al. when measuring the shape of resistors, heart chambers and hands and more recently validated by Linder et al. against manually derived geometric measures from hip radiographs. SHAPE through SSM produces linearly independent variations in hip shape (HSM). Each mode was normalized to zero mean and unit standard deviation (SD) for the whole cohort so that each image (and therefore participant) is assigned a set of mode scores in units of SDs describing how far they lie from the mean. Images producing HSM scores above or below 4SDs were manually checked by two operators, and point placement corrected where necessary. Mode shapes were subsequently assigned to cam or pincer-type deformities based on consensus visual interpretation.
reader and scored, using a previously published atlas \(23\), for concentric, medial or lateral joint space narrowing (JSN) \((0–4)\), osteophyte formation at the inferior and superior femur and acetabulum \((0–3)\), bone cysts \((0–3)\), subchondral sclerosis \((0–3)\), and femoral head deformity \((0–3)\) \(18\). In addition, binary measures were created for the presence of osteophytes, JSN or subchondral sclerosis, based on mild (grade \(\geq 1\)) used for primary analyses, moderate (grade \(\geq 2\)) or severe (grade \(\geq 3\)) cut-offs. Radiographs with definite osteophytes or JSN were then examined by a second reader to reach a consensus score. Croft scores, based on an aggregate of these scores, were subsequently generated \(14\), with a score \(\geq 2\) (requiring the presence of osteophytes or JSN) taken as the presence of moderate RHOA which was used in primary analyses, and a score \(\geq 3\) denoting severe RHOA \(18\).

### Hip pain

All participants who attended visit two were asked to undergo a hip examination. The participant’s right hip was internally rotated and patient-reported pain was documented generating a binary outcome. Participants completed a questionnaire concerning right hip pain on walking in the last 30 days (scored 0–4), which was converted to a binary measure i.e., presence or absence of right hip pain on walking in the last 30 days. Finally, all patients had a standardized Western Ontario and McMaster Universities Arthritis Index (WOMAC) score calculated out of 20. The WOMAC score, which has been validated as a measure of hip OA \(25\), encompasses pain, stiffness and function to give an overall score of disease, 0 being no limitation and 20 being severe limitation.

### Statistical analysis

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

### Results

#### Population characteristics

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

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

|               | Prevalence \(n\) [%] |
|---------------|------------------|
| **Radiographic OA** |                  |
| Croft < 2     | 3811 [93]        |
| Croft \(\geq 2\) | 289 [7.1]        |
| Any osteophyte (i.e., score \(\geq 1\)) | 100 [2.4]        |
| Lateral acetabular | 788 [19.2]      |
| Lateral femoral | 401 [9.8]        |
| Inferior acetabular | 404 [9.9]    |
| Inferior femoral | 272 [6.6]        |
| Any joint space narrowing (i.e., score \(\geq 1\)) | 107 [5.1]       |
| Lateral       | 207 [5.1]        |
| Medial        | 446 [10.9]       |
| Concentric    | 148 [3.6]        |
| Other bone lesions | 148 [3.6]   |
| Cysts         | 44 [1.1]         |
| Any subchondral sclerosis (i.e., score \(\geq 1\)) | 278 [6.8]       |
| Chondrocalcinosis | 9 [0.02]      |
| Joint deformity | 35 [0.9]        |
| **Symptoms**  |                  |
| Hip pain on examination | 451 [11.4] |
| Hip pain on walking       | 829 [20.2]      |
| WOMAC                | 0.9 [2.3, 0, 20.0] |

Prevalence based on 4100 individuals with right hip X-rays. Results are shown as prevalence [%], apart from the WOMAC score which is presented as mean [SD, Min, Max]. \(N = 4,100\) except for pain on examination \((N = 3,946)\), walking \((N = 4,098)\) and WOMAC score \((N = 4,076)\).
The first ten HSMs in our cohort explained 81.4% of the total variance in hip shape. Five HSMs were found to be associated with RHOA (see below), which together explained 48.3% of the total variance in hip shape. All five HSMs associated with RHOA showed features of FAI on visual inspection, either in the form of pincer- or cam-type deformities (Figs. 2 and 3), whereas the remaining HSMs were unrelated to these deformities. No HSM was related to both deformities, implying these represent statistically independent contributions to hip shape. HSM 1, which accounted for 22.3% of total variance in hip shape, was positively associated with pincer-type deformity (Fig. 2). HSM 8, which accounted for 2.8% of total variance in hip shape, was negatively associated with pincer-type deformity. HSM 3 and HSM 4, which explained 12.1% and 9.2% of total variation in hip shape, respectively, were negatively associated with cam-type deformity. HSM 10, which explained 1.9% of total variation in hip shape, was positively associated with cam-type deformity.

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

**HSMs 1 and 8 (pincer-type deformities) vs radiographic hip OA**

In unadjusted analyses, HSM 1 was positively associated with the presence of RHOA, defined as Croft score $\geq 2$ [OR 1.23 (1.09, 1.39)], whereas HSM 8 was negatively associated [OR 0.79 (0.70, 0.89)] (Table II). Results were unaffected by adjustment for age, weight, height and race. In terms of specific radiographic components, in adjusted analyses, HSM 1 was positively associated with the presence of acetabular [OR 1.13 (1.04, 1.22)] and inferior femoral [OR 1.22 (1.07, 1.38)] osteophytes (Table III), and with medial JSN.

![Fig. 2. HSMs 1 and 8. Pincer-type variations in hip shape demonstrated by HSM 1 and HSM 8. HSM 1 has a positive relationship with a pincer-type variation. HSM 8 has a negative relationship with a pincer-type variation. Dashed line = +2 SDs, solid line = –2SDs.](image)

![Fig. 3. HSMs 3, 4 and 10. Cam-type variation in hip shape demonstrated by HSMs 3, 4 and 10. HSMs 3 and 4 have a negative relationship with a cam-type variation. HSM 10 has a positive relationship with a cam-type variation. Dashed line = +2 SDs, solid line = –2SDs.](image)
Table II

| Osteophyte Score | Lateral acetabulum | Lateral femoral | Inferior acetabulum | Inferior femoral | P value |
|------------------|--------------------|----------------|---------------------|-----------------|---------|
|                   | OR [95% CI]        | Lateral acetabulum | OR [95% CI]        | Lateral femoral | OR [95% CI]        | Inferior acetabulum | OR [95% CI]        | Inferior femoral | OR [95% CI]        | P value |
| HSM 1 ≥2         | 1.13 [1.04, 1.22]  | 1.11 [1.00, 1.24] | 0.047               | 1.13 [1.02, 1.26] | 0.019               | 1.22 [1.07, 1.38]  | 0.0022*           |
| HSM 2 ≥2         | 1.01 [0.90, 1.14]  | 1.06 [0.91, 1.24] | 0.45                | 1.18 [1.10, 1.39] | 0.00044           | 1.41 [1.10, 1.80]  | 0.0068           |
| HSM 3 ≥2         | 0.89 [0.76, 0.96]  | 0.80 [0.73, 0.88] | 0.0040*             | 0.82 [0.76, 0.89] | 0.00017*           | 0.86 [0.76, 0.97]  | 0.016            |
| HSM 4 ≥2         | 0.92 [0.85, 1.00]  | 0.85 [0.78, 0.96] | 0.0058              | 0.83 [0.75, 0.92] | 0.00048*           | 0.86 [0.76, 0.97]  | 0.016            |
| HSM 5 ≥2         | 0.96 [0.85, 1.08]  | 0.83 [0.71, 0.98] | 0.024               | 0.83 [0.70, 0.97] | 0.023               | 0.70 [0.55, 0.90]  | 0.0058           |
| HSM 6 ≥2         | 0.89 [0.76, 0.96]  | 0.81 [0.73, 0.90] | 7.7 × 10⁻⁵           | 0.84 [0.75, 0.93] | 0.0011*             | 0.78 [0.69, 0.89]  | 0.00014*          |
| HSM 7 ≥2         | 0.89 [0.79, 1.00]  | 0.74 [0.63, 0.87] | 0.00025*            | 0.84 [0.71, 0.99] | 0.035               | 0.77 [0.60, 0.99]  | 0.044            |
| HSM 8 ≥2         | 1.12 [1.03, 1.21]  | 1.0063              | 0.082               | 1.12 [1.01, 1.25] | 0.005               | 1.22 [1.07, 1.39]  | 0.00022*         |
| HSM 9 ≥2         | 1.11 [0.98, 1.24]  | 1.11 [1.10, 1.37]  | 0.054               | 1.23 [1.04, 1.45] | 0.017               | 1.40 [1.08, 1.82]  | 0.010            |

Table III

| Table shows results of logistic regression analysis between HSMs and osteoarthritis, dependent on score ≥1 (any osteophyte) and ≥2 (moderate to severe osteophytes only), at different sites in 4,100 individuals. Results show OR of having any osteophyte per SD increase in HSM [95% confidence intervals] and P value, adjusted for age, weight, height and race. *P < 0.005.

Table IV

| Lateral JSN | Medial JSN | Concentric JSN | Subchondral sclerosis | OR [95% CI] | P value |
|-------------|------------|---------------|-----------------------|-------------|---------|
| HSM 1       | 1.01 [0.87, 1.16] | 0.91 | 1.55 [1.40, 1.71] | 4.3 × 10⁻¹⁷ | 1.23 [1.04, 1.45] | 0.013 |
| HSM 2       | 0.73 [0.63, 0.84] | 8.6 × 10⁻⁶ | 1.32 [1.19, 1.46] | 9.2 × 10⁻⁸ | 0.98 [0.83, 1.15] | 0.79 |
| HSM 3       | 0.84 [0.73, 0.97] | 0.020 | 1.32 [1.20, 1.46] | 5.9 × 10⁻⁸ | 1.05 [0.89, 1.25] | 0.54 |
| HSM 4       | 0.71 [0.62, 0.82] | 4.3 × 10⁻⁴ | 0.67 [0.76, 0.98] | 0.0057 | 0.87 [0.74, 1.03] | 0.11 |
| HSM 5       | 1.16 [1.01, 1.35] | 0.039 | 1.11 [1.00, 1.23] | 0.041 | 0.93 [0.79, 1.10] | 0.29 |
| HSM 6       | 1.10 [0.99, 1.22] | 0.11 | 1.17 [1.00, 1.37] | 0.054 | 1.23 [1.04, 1.45] | 0.017 |

Table IV shows results of logistic regression analysis between HSMs and JSN in 4,100 individuals. Results show OR of having any JSN or subchondral sclerosis per SD increase in HSM [95% confidence intervals and P value, adjusted for age, weight, height and race. *P < 0.005.

HSMs 3, 4 and 10 (cam-type deformities) vs radiographic hip OA

In unadjusted analyses, HSM 3 and HSM 4 were inversely associated with prevalent RHOA [OR 0.73 (0.65, 0.83) and 0.82 (0.73, 0.93), respectively], whereas HSM 10 was positively related [OR 1.21 (1.07, 1.37)] (Table II). Equivalent results were seen in analyses adjusted for age, weight, height and race. In terms of specific radiographic components, in adjusted analyses HSM 3 was inversely related to the presence of osteophytes at all sites [OR 0.76–0.89] (Table III), and to lateral JSN [OR 0.73 (0.63, 0.84)] and subchondral sclerosis [OR 0.76 (0.67, 0.85)], whereas there was a positive association with medial JSN [OR 1.32 (1.19, 1.46)] (Table IV).

HSM 4 was inversely related to the presence of inferior acetabular osteophytes [OR 0.83 (0.75, 0.92)], but positively related to medial JSN [OR 1.32 (1.20, 1.46)]. HSM 10 was positively associated with inferior femoral osteophytes [OR 1.22 (1.07, 1.39)] and subchondral sclerosis [OR 1.21 (1.07, 1.38)]. Equivalent observations were seen in unadjusted analyses (data not shown).

Association of hip shape with hip pain

In adjusted analyses, HSM 3 was inversely associated with hip pain on internal rotation [OR 0.84 (0.76, 0.92)] and on walking [OR 0.86 (0.81, 0.95)], and with WOMAC pain score [OR 0.87 (0.80, 0.93)]. Similar results were seen in unadjusted analyses (data not shown). There was weak evidence that HSM 4 was inversely associated with hip pain on examination and on walking with WOMAC score, and that HSM 8 was positively related to these parameters (all P < 0.02); however, for all these P values were >0.05.
Sensitivity analyses

Similar point estimates were observed for associations between HSMs and RHOA using a definition of Croft score $\geq 3$ as opposed to $\geq 2$ (Table II). Equivalent results were also obtained for associations between hip shape and moderate or severe osteophytes (i.e., grade $\geq 2$), compared to those seen for grade $\geq 1$ osteophytes as presented in the main results (Table III).

Discussion

We examined associations between hip shape, as assessed by SSM performed on hip DXA scans, and prevalent RHOA ascertained approximately 5 years later, in a large population based cohort of older men. We found that five out of the top ten HSMs were associated with prevalent RHOA, and one mode was also associated with hip pain. Taken together, these findings suggest that SSM applied to hip DXA scans can be successfully used to identify shape changes associated with hip OA, particularly radiographic features.

Given the substantial number of large population based cohorts with available hip DXA scans, this finding opens up the possibility of identifying novel genetic risk factors for hip OA, based on GWAS studies of DXA-derived hip shape.

All five HSMs associated with RHOA showed features of FAI, reflecting either cam- or pincer-type deformities. Given the cross-sectional nature of this analysis, it was not possible to distinguish shape changes resulting from hip OA, from those causing it. That said, our finding that three HSMs, indicative of cam-type deformity, are related to RHOA is consistent with previous studies suggesting that cam-type deformity is a risk factor for RHOA, based on SSM$^{14}$ and measured geometric parameters.$^{26,27}$ As well as being related to global RHOA as reflected by Croft score, HSM 3, HSM 4, and HSM 10 showed equivalent relationships with osteophytes at different sites, and in the case of HSM 3 with lateral JSN and subchondral sclerosis. HSM 3 also showed the strongest association with hip pain. However, the associations between hip shape and hip pain were generally weaker than that for RHOA. This lack of concordance between radiographic and clinical features of hip OA is well recognized,$^{28,29}$ and was supported by further analyses in which we examined associations between RHOA as defined by Croft score $\geq 2$ and clinical features. Whereas RHOA was positively associated with pain on examination and on walking, these associations were relatively modest (RR 1.67 and 1.51, respectively).

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

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

As well as contributing to cam- and pincer-type deformities, HSMs may have reflected the presence of OA in other ways. For example, HSM 1 and HSM 3 were suggestive of greater supero-medial JSN, and HSM 8 lesser supero-lateral JSN. In addition, alteration in the size of the lesser trochanter associated with HSM 3 may reflect variation in the extent of internal rotation of the hip during image acquisition, which may in turn reflect underlying hip OA given the latter is associated with limited internal rotation. HSMs were also related to differences which may reflect other risk factors for developing OA apart from FAI. For example, HSM 1 was related to size of the femoral head and greater trochanter, and femoral neck width, which have recently been reported to be associated with prevalent radiographic knee OA$^{30}$. That said, HSM 2 and HSM 9, which were also related to femoral head size but showed no relation to pincer- or cam-type deformities, were unrelated to RHOA or hip pain.

Strengths and limitations

This study represents the first report of associations between DXA-derived hip shape and RHOA in a population based sample. The large size of the sample represents a further strength. The fact that this is a male cohort may have further increased power in light of previous findings suggesting the relationships between hip shape and RHOA are stronger in males than in females$^{31,32}$, though to what extent our findings are applicable to females requires further study. Our study also highlights the benefit of using large DXA cohorts for hip shape research, though given the greater resolution of radiographs, the latter are more suitable in smaller studies, and in clinical practice. One limitation of this study was our lack of baseline radiographs. Therefore, the associations which we observed between HSMs, as assessed on baseline DXA scans, and RHOA based on radiographs collected 5 years later, could have reflected relationships with prevalent as opposed to incident OA. This distinction is important, since in examining associations with prevalent OA, it is difficult to infer causality, and the shape changes we observed could have been a result of, rather than a risk factor for, hip OA. A further limitation is the relatively low image resolution of the DXA scanner used in MrOS, making it difficult to determine to what extent associations between DXA-derived hip shape and RHOA reflected characteristics of established OA such as osteophytes, as opposed to shape changes representing possible OA risk factors such as those related to FAI. Newer DXA devices provide sufficient resolution for identifying osteophytes on hip DXA scans$^{33}$. In addition, shape results could conceivably be affected by the degree of hip rotation; although the lower leg is strapped into a fixed position during scanning, the degree of hip rotation achieved might be affected by anatomical features such as pelvic size and shape, and associated hip disease. Another limitation, is that our HSMs cannot be directly applied to other cohorts since SSM using PCA is specific to the images used to make the model. Finally, SSM is not designed specifically to evaluate FAI and based on our findings more analysis, using methods specific to FAI such as alpha-angle, should be done to replicate these findings.

Conclusions

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

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

Conflict of Interest
We have none to declare.

Acknowledgements
BF conducted this research whilst on a clinical research primer fellowship awarded by the Elizabeth Blackwell Institute, University of Bristol, UK. This study was funded by Arthritis Research UK project grant ref 20244. CG is funded by Arthritis Research UK grant ref 20000. The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and NIH Roadmap for Medical Research under the following grant numbers: R01 AR052000, K24 AR048841, U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128.

References
1. Verbrugge LM, Patrick DL. Seven chronic conditions: their impact on US adults’ activity levels and use of medical services. Am J Public Health 1995;85(2):173–82.
2. Agricola R, Heijboer MP, Roze RH, Reijman M, Bierma-Zeinstra SM, Verhaar JA, et al. Pincer deformity does not lead to osteoarthritis of the hip whereas acetabular dysplasia does: acetabular coverage and development of osteoarthritis in a nationwide prospective cohort study (CHECK). Osteoarthritis and Cartilage 2013;21(10):1514–21.
3. Baker-LePain JC, Lane NE. Relationship between joint shape and the development of osteoarthritis. Curr Opin Rheumatol 2010;22(5):538–43.
4. Ganz R, Parvizi J, Beck M, Leunig M, Nötzli H, Siebenrock KA. Femoroacetabular impingement: a cause for osteoarthritis of the hip. Clin Orthop Relat Res 2003;417:112–20.
5. Beck M, Kalhor M, Leunig M, Ganz R. Hip morphology influences the pattern of damage to the acetabular cartilage: femoroacetabular impingement as a cause of early osteoarthritis of the hip. J Bone Joint Surg 2005;87(7):1012–8.
6. Murray RO. The aetiology of primary osteoarthritis of the hip. Br J Radiol 1965;38(455):810–24.
7. Gregory JS, Waarsing JH, Day J, Pols HA, Reijman M, Weinans H, et al. Early identification of radiographic osteoarthritis of the hip using an active shape model to quantify changes in bone morphometric features: can hip shape tell us anything about the progression of osteoarthritis? Arthritis Rheum 2007;56(11):3634–43.
8. Lynch JA, Parimi N, Chaganti RK, Nevitt MC, Lane NE. The association of proximal femoral shape and incident radiographic hip OA in elderly women. Osteoarthritis and Cartilage 2009;17(10):1313–8.
9. Nelson AE, Golightly YM, Renner JB, Schwartz TA, Liu F, Lynch JA, et al. Variations in hip shape are associated with radiographic knee osteoarthritis: cross-sectional and longitudinal analyses of the Johnston County Osteoarthritis Project. J Rheumatol 2016;43(2):405–10.
10. Barr RJ, Gregory JS, Reid DM, Aspden RM, Yoshida K, Hosie G, et al. Predicting OA progression to total hip replacement: can we do better than risk factors alone using active shape modelling as an imaging biomarker? Rheumatology (Oxford) 2012;51(3):562–70.
11. Agricola R, Reijman M, Bierma-Zeinstra SMA, Verhaar JAH, Weinans H, Waarsing JH. Total hip replacement but not clinical osteoarthritis can be predicted by the shape of the hip: a prospective cohort study (CHECK). Osteoarthritis and Cartilage 2013;21(4):599–64.
12. Lindner C, Thigarahaj S, Wilkinson JM, Panoutsopoulou K, Day-Williams AG, OC, et al. Investigation of association between hip osteoarthritis susceptibility loci and radiographic proximal femur shape. Arthritis Rheumatol 2015;67(8):2076–84.
13. Estrada K, Styrkarsdottir U, Evangelou E. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet 2012;15;44(5):491–501.
14. Waarsing JH, Rozendaal RM, Verhaar JA, Bierma-Zeinstra SM, Weinans H. A statistical model of shape and density of the proximal femur in relation to radiological and clinical OA of the hip. Osteoarthritis and Cartilage 2010;18(6):787–94.
15. Kindz MB, Welsing PM, Vignon EP, Bijlsma JW, Viergever MA, Marijnissen AC, et al. A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. Osteoarthritis and Cartilage 2011;19(7):768–78.
16. Blank JB, Cawthon PM, Carreon-Petersen ML, Harper L, Johnson JP, Mitson E, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemp Clin Trials 2005;26(5):557–68.
17. Orwell E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study, Ao:~/N\sqrt{\Delta t}. A large observational study of the determinants of fracture in older men. Contemp Clin Trials 2005;26(5):569–85.
18. Chaganti RK, Parimi N, Lang T, Orwell E, Stefanick ML, Nevitt M, et al. Bone mineral density and prevalent osteoarthritis of the hip in older men for the osteoporotic fractures in men (MrOS) study group. Osteoporos Int 2010;21(8):1307–16.
19. Cooites TF, Taylor CJ, Cooper DH, Graham J. Active shape models – their training and application. Comput Vis Image Understand 1995;61(1):38–59.
20. Lindner C, Thigarahaj S, Wilkinson JM, OC, Gallis WA, Cooites TF. Development of a fully automatic shape model matching (FASMM) system to derive statistical shape models from radiographs: application to the accurate capture and global representation of proximal femur shape. Osteoarthritis and Cartilage 2013;21(10):1537–44.
21. Gregory JS, Aspden RM. Femoral geometry as a risk factor for osteoporotic hip fracture in men and women. Med Eng Phys 2008;30(10):1275–86.
22. Ahedi HG, Aspden RM, Blizard LC, Saunders FR, Cicuttini FM, Aitken DA, et al. Hip shape as a predictor of osteoarthritis
progression in a prospective population cohort. Arthritis Care Res (Hoboken) 2016:1566–73.

23. Lane NE, Nevitt MC, Genant HK, Hochberg MC. Reliability of new indices of radiographic osteoarthritis of the hand and hip and lumbar disc degeneration. J Rheumatol 1993;20(11):1911–8.

24. Croft P, Cooper C, Wickham C, Coggon D. Defining osteoarthritis of the hip for epidemiologic studies. Am J Epidemiol 1990;132(3):514–22.

25. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15(12):1833–40.

26. Agricola R, Heijboer MP, Bierma-Zeinstra SMA, Verhaar JAN, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Ann Rheum Dis 2013;72(6):918–23.

27. Doherty M, Courtney P, Doherty S, Jenkins W, Maciewicz RA, Muir K, et al. Nonspherical femoral head shape (pistol grip deformity), neck shaft angle, and risk of hip osteoarthritis: a case-control study. Arthritis Rheum 2008;58(10):3172–82.

28. Nelson AE, Liu F, Lynch JA, Renner JB, Schwartz TA, Lane NE, et al. Association of incident symptomatic hip osteoarthritis with differences in hip shape by active shape modeling: the Johnston County Osteoarthritis Project. Arthritis Care Res 2014;66(1):74–81.

29. Yoshida K, Barr RJ, Galea-Soler S, Aspden RM, Reid DM, Gregory JS. Reproducibility and diagnostic accuracy of Kellgren-lawrence grading for osteoarthritis using radiographs and dual-energy X-ray absorptiometry images. J Clin Densitom 2015;18(2):239–44.