Arthritis Care & Research
Vol. 69, No. 10, October 2017, pp 1566–1573
DOI 10.1002/acr.23166

ORIGINAL ARTICLE

Hip Shape as a Predictor of Osteoarthritis Progression in a Prospective Population Cohort

HARBEER G. AHEDI,[1] RICHARD M. ASPDEN,[2] LEIGH C. BLIZZARD,[1] FIONA R. SAUNDERS,[2] FLAVIA M. CICUTTINI,[3] DAWN A. AITKEN,[1] GRAEME JONES,[1] AND JENNIFER S. GREGORY[2]

Objective. **Hip morphology plays a significant role in the incidence and progression of hip osteoarthritis (OA). We hypothesized that hip shape would also be associated with other key factors and tested this in a longitudinal community-based cohort combining radiographic, magnetic resonance imaging (MRI), dual-energy x-ray absorptiometry (DXA), and clinical data.**

Methods. **Baseline DXA images of the left hip of 831 subjects from the Tasmanian Older Adult Cohort were analyzed using an 85-point statistical shape model. Hip pain was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index, and muscle strength was measured using a dynamometer. Hip structural changes were assessed using MRI and radiographic OA using plain radiographs.**

Results. **Six shape modes accounted for 68% of shape variation. At baseline, modes 1, 2, 4, and 6 were associated with radiographic hip OA; modes 1, 3, 4, and 6 were correlated with hip cartilage volume; and all except mode 2 were correlated with muscle strength. Higher mode 1 and lower mode 3 and mode 6 scores at baseline predicted hip pain at followup and higher mode 1 and mode 2 scores were associated with hip effusion-synovitis. Higher scores for mode 2 (decreasing acetabular coverage) and lower scores for mode 4 (nonspherical femoral head) at baseline predicted 10-year total hip replacement (THR), while mode 4 alone was correlated with bone marrow lesions (BMLs), effusion-synovitis, and increased cartilage signal.**

Conclusion. **Hip shape is associated with radiographic OA, THR, hip pain, effusion-synovitis, BMLs, muscle strength, and hip structural changes. These data suggest that different shape modes reflect multiple facets of hip OA.**

INTRODUCTION

Osteoarthritis (OA) is a musculoskeletal disorder that affects older adults worldwide and imposes a considerable economic burden on society (1). Although OA is a disease of the whole joint, bone and cartilage remain the focus of its clinical manifestation (2). Structural changes such as bone marrow lesions (BMLs) and cartilage defects are linked with the progression of hip OA (3–7). In addition to these, the morphology of the hip can predict the development of hip OA (8), but most current assessments are semiquantitative and focus on changes in the cartilage and the presence of bony outgrowths (9,10). However, subtle morphologic changes are difficult to detect with predefined geometric measures, which do not capture the total morphology of the hip.

Statistical shape modeling (SSM) (11) is a sophisticated technique that yields a quantitative measure of hip morphology from 2-dimensional images of the joint, such as radiographs (8), and can identify subtle shape variation within a population. An SSM generates a set of linearly independent "modes of variation," each of which describes a coordinated pattern of variation in hip shape within a study group. Each mode has a mean of 0 and unit SD. Every image is then assigned a score for each mode describing how many SDs it lies from the mean. For instance, in a longitudinal study using radiographs from the Rotterdam study, subjects who had low scores for mode 6 (describing the upper femoral neck with a sharper transition from the femoral head into the lower femoral

The Tasmanian Older Adult Cohort study was supported by the National Health and Medical Research Council of Australia, the Tasmanian Community Fund, the Masonic Centenary Medical Research Foundation, the Royal Hobart Hospital Research Foundation, and the Arthritis Foundation of Australia. Dr. Ahedi's work was supported by an Australian Government Postgraduate Award and by an Osteoarthritis Research Society International collaborative scholarship.

[1]Harbeer G. Ahedi, PhD, Leigh C. Blizzard, PhD, Dawn A. Aitken, PhD, Graeme Jones, MD: Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia; [2]Richard M. Aspden, DSc, Fiona R. Saunders, PhD, Jennifer S. Gregory, PhD: Aberdeen Centre for Arthritis and Musculoskeletal Health, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK; [3]Flavia M. Cicuttini, PhD: Monash University, Melbourne, Victoria, Australia.

Address correspondence to Harbeer G. Ahedi, PhD, Menzies Institute for Medical Research, University of Tasmania, Private Bag 23, Hobart, Tasmania 7001, Australia. E-mail: harbeer.ahedi@utas.edu.au.

Submitted for publication June 9, 2016; accepted in revised form December 6, 2016.

Significance & Innovations

- Scores from statistical shape models from baseline dual-energy x-ray absorptiometry images of the hip in a longitudinal population cohort are strongly associated with total hip replacement 10 years later.
- Baseline measures of hip shape were strongly associated with hip pain, hip bone marrow lesions (BMLs), hip cartilage volume, larger hip effusion-synovitis, increased cartilage signal, and radiographic hip osteoarthritis (OA) over a 5-year period.
- Early pistol-grip deformity is correlated with hip BMLs, hip effusion-synovitis size, lower cartilage volume, and lower leg strength.
- Hip morphologic features are associated with key clinical, radiographic, and structural factors relevant for the incidence and progression of OA and provide a basis for identifying and monitoring early hip OA. This will enable early modifications to diet and exercise to benefit the patient, as well as assist clinicians and companies seeking to reduce the time taken to test new therapeutics.

neck) at baseline were at higher risk of developing severe hip OA and total hip replacement (THR) (8). Subsequently, we have shown that SSM can be used to model dual-energy x-ray absorptiometry (DXA) images (12,13) and that Kellgren-Lawrence grading can be applied to these images with as much precision as to radiographs (14). In another longitudinal, nested, case–control study of elderly women, hip shape modes specifically reflecting sizes of the femoral head, femoral neck, or greater trochanter modestly predicted hip OA (15). Moreover, hip shape modes could also predict THR independently of clinical, geometric, and radiologic factors (16). However, shape modes describing radiographic OA may not necessarily be associated with clinical descriptors such as pain or crepitus (17,18). Hence, different shape modes might better predict either clinical or radiologic progression of hip OA and may differ between men and women, as hip and pelvic shape differs by sex (19).

OA is a multifactorial disease, and it is unknown to what extent morphologic aspects of the hip relate to disease progression. Studies to date have shown that SSM is a powerful quantitative tool and is sensitive to changes in bone shape (8,15–17,20,21), but it has not been used to study hip OA in a large community-based cohort and has not previously been tested for associations with BMLs or effusion-synovitis. Thus, the aim of this study was to describe the association between hip shape measured at baseline and clinical, demographic, structural, and radiologic features of hip OA both at baseline and over time in an older adult Australian cohort using a combination of radiographic, magnetic resonance imaging (MRI), DXA, and patient questionnaire data.

SUBJECTS AND METHODS

Subjects. The Tasmanian Older Adult Cohort (TASOAC) study is an ongoing prospective, population-based study that was initiated in 2002. A total of 1,100 subjects were enrolled in the study between March 2002 and September 2004 (phase I). Followup data for 3 clinic visits (phases II, III, and IV) were collected for 875, 769, and 568 participants, respectively. These visits were conducted approximately 3 years, 5 years, and 10 years from baseline.

A total of 1,099 subjects attended a clinic for baseline measurements. Of these, 264 subjects did not have a DXA image, and images for 4 subjects were corrupted, leaving 831 subjects with complete baseline data. The hip joint shape was measured using baseline DXA scans. All other measures were collected from clinical visits or questionnaires between baseline and the 5-year (phase III) followup, aside from THR, which was recorded up to 10 years after the baseline visit (phase IV) (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23166/abstract).

Written informed consent was obtained from all participants and the Southern Tasmanian Health and Medical Human Research Ethics Committee approved this study. Demographic characteristics, medical history, and lifestyle factors were assessed using self-administered questionnaires. Height and weight were measured and body mass index (BMI) calculated using standard protocols (22). At each followup assessment, participants were asked if they had undergone THR surgery and, if so, in which hip.

Hip pain. At baseline, self-reported hip pain was recorded as yes/no using a standardized questionnaire. The presence and severity of hip pain for all of the subjects at the followup visits for phases II and III was determined using a hip-specific Western Ontario and McMaster Universities Osteoarthritis pain score (23).

Muscle strength and MRI. Muscle strength (leg strength) was measured at each visit to the nearest kilogram-force in both legs simultaneously, using a dynamometer (TTM Muscular Metre), as described previously (24). The right hip was imaged in the sagittal plane during visits at phases II and III using a 1.5 Tesla GE Signa whole-body magnetic resonance scanner with a phased-array flex-coil using 2 sequences. Sagittal plane imaging was chosen to facilitate the quantitative analysis.

Sagittal images were obtained at a partition thickness of 1.5 mm with an in-plane resolution of 0.39 x 0.39 mm (512 x 512 pixels) (25) using a T1-weighted, fat-suppressed, 3-dimensional gradient-recalled acquisition in the steady state. The parameters for this were as follows: flip angle 55 degrees, repetition time 58 msec, echo time 12 msec, inversion time 130 msec, field of view 16 cm, 60 partitions, 512 x 512–pixel matrix, acquisition time 11 minutes 56 seconds, and 1 acquisition. The second set of sagittal images was obtained with a slice thickness of 3.5 mm and an interslice gap of 1.5 mm (4) using a short T1 inversion recovery (STIR)–weighted, fat saturation, 2-dimensional fast spin-echo sequence. This sequence used a repetition time of 4,340 msec, echo time of 28.4 msec, field of view of 20 cm, 15 partitions (16 slices), and a 512 x 512–pixel matrix.

Hip cartilage volume. Baseline femoral head cartilage volume was measured for each individual from the T1-weighted images using the software program Osiris (Windows version 3.5, Geneva University Hospital). The volume of the femoral head cartilage was calculated by manually drawing contours around the cartilage boundaries on each image section. These data were then resampled using bilinear and cubic interpolation for the final 3-dimensional rendering. Intraobserver reliability was assessed, and the coefficient of variation was 2.5% (25).

BMLs. Quantitative assessment of subchondral hip BMLs in STIR MRI images was done using OsiriX software (Mac version, University of Geneva). BMLs were identified as areas of increased signal intensity adjacent to the subchondral bone on the femoral head and/or the acetabulum (3,4).

High cartilage signal. High cartilage signal was identified as an increase in the signal intensity of the articular cartilage due to increased water content that appears as a bright band in the cartilage either adjacent to a hip BML or at any location on the STIR MRI slice if no BML was present (26,27). High cartilage signal was graded as 0 for absent and 1 for present (3,4).

Hip effusion-synovitis. Hip effusion-synovitis was identified and assessed in STIR images from phases II and III. The observer (HGA) manually selected the MR slice with the largest effusion-synovitis and determined the maximum cross-sectional area of the bright region by manually drawing contours around the outer edges. In a reliability study of 40 subjects with repeated measurements after 4 weeks, the intrarater agreement (kappa) for the presence of hip effusion-synovitis was 0.84, and the intraclass correlation coefficient for hip effusion-synovitis cross-sectional area was 0.97.

Radiologic assessment. Anteroposterior radiographs of the pelvis were obtained at the first visit with the individual weight-bearing and with both feet internally rotated by 10 degrees. Radiographs were read by 2 trained readers using the Osteoarthritis Research Society International grading system. Radiographic features of joint space narrowing (JSN; axial and superior) and osteophytes (superior acetabular and femoral) of both hips were graded separately on a 4-point scale (range 0–3, where 0 = no disease and 3 = most severe disease). Any score other than 0 for either JSN or osteophytes was regarded as evidence of radiographic hip OA. Thus, after combining the JSN and osteophytes scores, the presence of radiographic hip OA was defined as a total score of 1 or greater in the left hip for comparison with the DXA images.

DXA imaging and SSM. At phase I, DXA images were taken of the left hip using a Hologic Delphi scanner. Images were extracted from the Hologic data files using custom-made Matlab software (Math Works Inc.) and saved as 8-bit bitmap image files. An 85-point SSM was built to assess the shape of the femoral head, acetabulum, and femoral neck using the Active Shape Modelling toolkit (University of Manchester). This model included not only the femoral head but also osteophytes and the acetabulum and extended down the upper femoral diaphysis to include cortical thickness. The SSM template is a set of landmark points that define the shape to be identified. For comparison between images, each point is always placed on the same anatomic feature on the outline of the bone (see Supplementary Figure 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23166/abstract).

The coordinates of the points were collected and transferred to custom-written SHAPE software (University of Aberdeen). Using SHAPE, the data underwent Procrustes transformation, to remove size and orientation effects, and were subjected to principal components analysis to generate an independent set of orthogonal mode scores for each image (17). The distribution of each mode was normalized to 0 mean and unit SD so that the scores assigned to each image are in units of SDs. References to a lower score, therefore, implies a position toward the more negative end of the distribution rather than smaller in absolute terms. A scree plot was generated to visualize the variance described by each mode. A set of 10 images was selected at random from the data set, and the points were placed on the images by 2 independent observers (HGA and FRS). Point-to-point variability (the distance between equivalent points placed by each observer) was calculated. The distribution was not normal and the median was 1.6 pixels.

Statistical analysis. Characteristics of the population were summarized as means and SDs or as frequencies and percentages. At baseline, the associations of hip shape mode scores with the presence of hip pain and radiographic features were assessed using log-binominal regression analyses. Pairwise Pearson's correlations were used to calculate the correlations of hip shape mode scores with age, BMI, hip cartilage volume, and leg strength, while a generalized linear model was applied to calculate the link between hip shape mode scores and sex. Followup data from all phases were combined for analysis to identify any OA-related changes at any subsequent stage following recruitment, and longitudinal associations of baseline hip shape with the presence of hip pain, MRI-based structural findings, and THR were explored using log-binomial regression. Linear regression analyses were used to investigate longitudinal associations of baseline mode scores with hip pain severity. Pairwise correlation coefficients were calculated between hip shape, hip BMLs, and effusion-synovitis size. All models were adjusted for age, sex, and BMI. Correlations between repeated measurements on individuals were taken into account by adjusting standard errors using the sandwich (robust) estimator of variance (28–30). All statistical analyses were performed using Intercooled Stata, version 12.

RESULTS

Characteristics of the sample population are shown in Table 1. From the shape of the scree plot, the first 6 shape modes were selected. The shape variations described by each mode of the 6 modes of variation are shown in Supplementary Table 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23166/abstract), and variations in the modes with the most frequent associations (modes 1, 2, 4, and 6) are shown in Figure 1. These 6 modes accounted for 68% of the total variation in the population, and all were >3.5%. Mode scores for men and women are shown separately in Supplementary Table 2 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23166/abstract), and mode 2 was the only mode not associated with sex. The prevalence ratio (PR) for men to women was 0.84 for mode 1 ($P < 0.001$); men had, on average, higher mode 1 scores than women, while higher scores for modes 3–6 were more common among women (PR range 1.16–1.35; $P < 0.001$).

Self-reported hip pain at baseline was not associated with hip shape (Table 2) but modes 2 and 6 were associated with the presence of radiographic hip OA. Further analysis of the components of radiographic hip OA showed that lower scores in modes 1 and 2 were weakly associated with the presence of JSN, and lower mode 4 scores were associated with an increased prevalence of osteophytes. Mode 6 was positively associated with the major features of radiographic OA, with each SD increase in score corresponding to a 23%, 15%, and 13% greater prevalence of JSN, osteophytes, and radiographic hip OA, respectively.

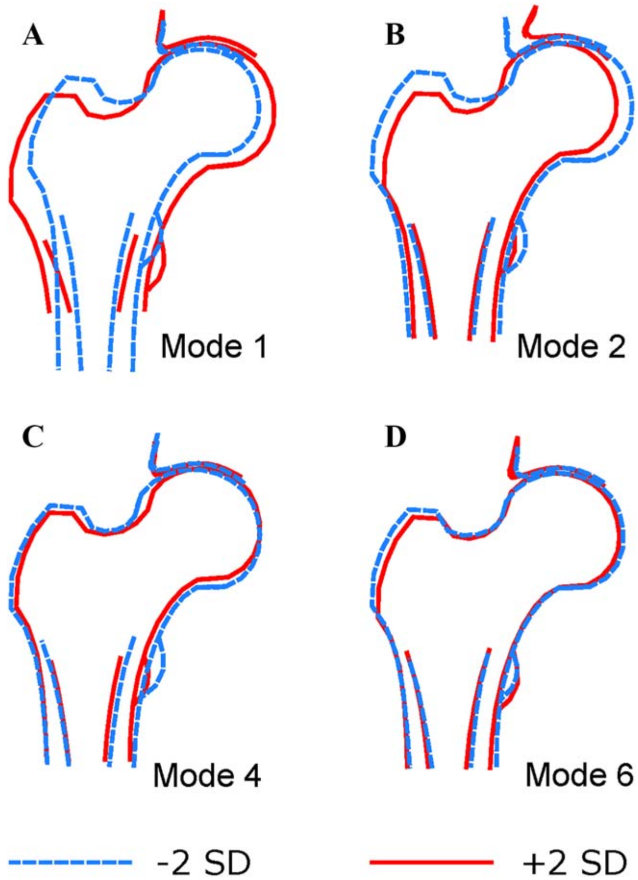

Figure 1. Variations in shape for +2 (red) and −2 (blue) SDs in mode score from the mean of 0 for modes 1, 2, 4, and 6. Descriptions of the key features identified by each mode are given in Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23166/abstract).

Table 1. Characteristics of the TASOAC cohort at baseline and followup (n = 831)*

Characteristic	Value
Baseline	
Age, mean ± SD years	63.2 ± 7.45
Male	49
Body mass index, mean ± SD	27.7 ± 4.63
Hip cartilage volume, mean ± SD mm^3	5,340 ± 1,100
Presence of hip pain	42
Radiologic hip osteoarthritis	41
Followup	
Presence of hip pain (WOMAC; yes/no)	47
WOMAC hip pain score, mean ± SD	2.60 ± 5.24
Leg strength, mean ± SD kg	93.1 ± 48.5
Presence of hip bone marrow lesions	18
Hip bone marrow lesion area, mean ± SD cm^2	0.20 ± 0.52
Presence of hip cartilage defects	72
Presence of high cartilage signal	74
Presence of hip effusion synovitis	95
Hip effusion synovitis area, mean ± SD cm^2	1.96 ± 1.60
Total hip replacement†	2.64

* Values are percentages unless indicated otherwise. Data from all followup visits were combined to identify features of osteoarthritis at any stage subsequent to recruitment. TASOAC = Tasmanian Older Adult Cohort; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Includes all hip replacements (left or right) from all followup assessments.

Correlations of hip shape modes with age, BMI, leg strength, and baseline MRI-based structural findings are shown in Table 3. Age at baseline was significantly associated with lower mode 2 scores, describing a wider neck, loss of joint space, and greater femoral head coverage. Lower scores for modes 1–4 were modestly correlated with greater BMI. Higher mode 1 scores, along with lower scores for modes 3–6, were associated with greater leg strength and greater hip cartilage volume. Although not associated with the presence of hip pain at baseline, hip shape was associated with the presence and severity of hip pain at followup (Table 4). Higher mode 1 scores and lower scores for modes 3 and 6 predicted an increase in the prevalence of hip pain at followup. Mode 3 score was also negatively associated with the severity of hip pain. Modes 2 and 4 at baseline were also correlated with MRI-

Table 2. The associations of hip shape with hip pain, JSN, and radiographic hip OA at baseline*

Mode	Hip pain	JSN	Osteophytes	Radiographic hip OA
1	1.03 (0.92, 1.14)	0.88 (0.78, 0.99)†	0.94 (0.82, 1.09)	0.94 (0.84, 1.05)
2	0.99 (0.90, 1.11)	0.76 (0.70, 0.85)†	1.05 (0.91, 1.22)	0.85 (0.76, 0.95)†
3	0.97 (0.90, 1.08)	0.96 (0.85, 1.09)	1.09 (0.94, 1.26)	0.98 (0.90, 1.11)
4	0.97 (0.90, 1.08)	1.03 (0.91, 1.17)	0.79 (0.70, 0.92)†	1.07 (0.95, 1.20)
5	1.04 (0.93, 1.17)	0.93 (0.83, 106)	0.94 (0.81, 1.09)	0.93 (0.82, 1.04)
6	0.96 (0.90, 1.07)	1.23 (1.09, 1.40)†	1.15 (1.00, 1.33)†	1.13 (1.01, 1.27)†

* Values are prevalence ratios (95% confidence intervals), adjusted for age, sex, and body mass index at baseline. JSN = joint space narrowing; OA = osteoarthritis.
† $P < 0.05$.

based hip structural changes at followup and with subsequent THR (Table 5). Mode 2 was strongly and positively associated with increased prevalence of THR, with a single SD increase in score indicating a 60% increase in prevalence. Mode 4 was strongly and negatively associated with the presence of both BMLs and high cartilage signal, and a reduction of 1 SD in mode 4 score indicated a 40% increase in both the prevalence of THR and the presence of BMLs. A diagrammatic summary of the significant associations between mode scores and prevalence can be found in Supplementary Figure 3 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23166/abstract).

DISCUSSION

This study links the predictive power of SSM, for quantifying the shape of the hip, with radiographic OA, THR, BMLs, effusion-synovitis, pain, and anthropometric data. A particular strength is the application of SSM to a population-based cohort to compare a quantitative description of joint shape at baseline with comprehensive participant data from MRI, radiographs, and DXA images, as well as questionnaire data, at baseline and over the following 10 years. In this way, we have identified features of hip shape that are associated with both the incidence and the progression of hip OA.

In this cohort, whose average age was 63 years at enrollment, nearly 40% of participants already reported hip pain. At followup, the proportion with hip pain increased slightly, and over 10 years, 29 subjects underwent THR. Morphologic variation was found between men and women, with higher scores for mode 1 and lower scores for modes 3–6 being more common in men. Mode 1 represents the largest variation in shape, and higher scores are associated with increasing head size and femoral neck length and width (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23166/abstract). During followup, MRI showed that approximately one-fifth of the cohort had a hip BML, approximately three-quarters had a high cartilage signal, and most showed signs of hip effusion-synovitis.

Interestingly, these modes had similar associations with greater hip cartilage volume and leg strength, even after adjustment for sex. Associations with radiographic hip OA were largely negative, and no association was found with hip pain. Lower mode 1 scores, for instance, indicating a shorter, narrower femoral neck, were associated with greater JSN. Surprisingly, although osteophytes could be included in the SSM, none of these 6 modes showed any variation in the location of the points marking the positions of osteophytes, although modes 4 and 6 were both associated with the presence of osteophytes as seen in the radiographic scoring.

Table 3. Correlations of hip shape mode scores with age, BMI, leg strength, and hip cartilage volume at baseline*

Mode	Age, years	BMI, kg/m^2	Leg strength, kg	Hip cv, cm^3
1	−0.04	−0.12†	0.20†	0.40†
2	−0.13†	−0.07‡	0.00	−0.03
3	−0.03	−0.11†	−0.15†	−0.20‡
4	−0.04	−0.10†	−0.13†	−0.25†
5	−0.04	−0.04	−0.22†	−0.13
6	−0.04	−0.02	−0.13†	−0.21‡

* Correlations with leg strength and hip cartilage volume were adjusted for age, sex, and body mass index (BMI). cv = cartilage volume.
† $P < 0.001$.
‡ $P < 0.05$

Table 4. Associations of hip shape modes at baseline with the presence and severity of hip pain at followup*

Mode	Presence PR (95% CI)	Severity β (95% CI)
1	1.09 (1.00, 1.20)†	0.17 (−0.20, 0.55)
2	0.99 (0.91, 1.09)	−0.13 (−0.50, 0.21)
3	0.91 (0.82, 0.99)†	−0.43 (−0.84, −0.02)†
4	0.99 (0.90, 1.09)	−0.12 (−0.55, 0.30)
5	1.03 (0.94, 1.14)	0.10 (−0.24, 0.45)
6	0.91 (0.84, 0.99)†	−0.05 (−0.40, 0.30)

* PRs and beta coefficients were all adjusted for age, sex, and body mass index, with clustering of observation on subjects at phases II and III taken into account. PR = prevalence ratio; 95% CI = 95% confidence interval.
† Statistically significant.

Table 5. Associations of hip shape modes at baseline with MRI-based structural findings and THR at followup*

Mode	Any hip BMLs PR (95% CI)	High cartilage signal PR (95% CI)	Hip effusion-synovitis, ≥2 sites PR (95% CI)	THR PR (95% CI)	BML, cm^2 *r*	Effusion-synovitis, cm^2 *r*
1	1.30 (0.92, 1.81)	1.03 (0.92, 1.20)	1.12 (0.91, 1.40)	0.84 (0.63, 1.12)	0.06	0.20†
2	1.22 (0.89, 1.70)	1.06 (0.96, 1.20)	1.22 (1.00, 1.50)‡	1.60 (1.20, 2.15)‡	0.08	0.21†
3	1.12 (0.82, 1.52)	1.04 (0.93, 1.15)	0.95 (0.77, 1.20)	0.75 (0.60, 1.00)	−0.00	−0.10
4	0.60 (0.42, 0.82)‡	0.89 (0.80, 0.99)‡	1.13 (0.92, 1.41)	0.63 (0.50, 0.84)‡	−0.13§	−0.11§
5	0.82 (0.60, 1.14)	1.02 (0.91, 1.15)	0.88 (0.72, 1.08)	1.34 (0.99, 1.80)	−0.09	0.07
6	0.90 (0.62, 1.30)	0.97 (0.87, 1.08)	0.91 (0.71, 1.20)	0.96 (0.72, 1.30)	−0.07	0.00

* PRs and correlation coefficients (*r*) were all adjusted for age, sex, and body mass index, with clustering of observation on subjects at phases II and III taken into account. MRI = magnetic resonance imaging; THR = total hip replacement; BMLs = bone marrow lesions; PR = prevalence ratio; 95% CI = 95% confidence interval.
† $P < 0.001$.
‡ Statistically significant.
§ $P < 0.05$.

Decreasing scores for mode 2 indicated characteristics such as increasing acetabular coverage, a smoother transition of the upper femoral head into the femoral neck, and an increasingly nonspherical femoral head, which may indicate a pistol grip–like deformity and femoroacetabular impingement (9). At baseline, a lower score for this mode was associated with more prevalent JSN and radiographic OA. Lower mode 4 scores, indicating prominent features of pistol-grip deformity, along with higher mode 6 scores, indicating a flatter femoral head, shorter femoral neck, and sharp transition of the femoral head into the neck were associated with a greater prevalence of osteophytes. Associations of shape modes with radiographic hip OA have been previously published, and variations in the shape of the femoral head, its transition into the superior aspect of the neck, and the length of the femoral neck have been reported to be associated with the risk of radiographic hip OA (8,15–19).

Higher baseline mode 1 scores and lower mode 6 scores were associated with incident hip pain at followup. Lower mode 3 scores were associated with a greater prevalence and severity of hip pain. Lower mode 3 scores indicate a shorter femoral neck and sharp transition of the lower femoral head into the femoral neck. Previous studies have shown that morphologic variations in the femoral neck are predictive of hip pain (17,31). Modes 1 and 6 were associated not only with radiographic features (at baseline), but mode 1 also correlated with hip effusion-synovitis cross-sectional area at followup. These factors might explain the associations of these modes with hip pain. Overall, our results are consistent with previous studies that have found associations between shape modes and hip pain (17,19).

Modes 2 and 4 appear to be strongly associated with structural changes in the subchondral bone of the hip, which are risk factors for the progression of OA (3,4). For instance, at baseline, lower scores of these modes were associated with greater JSN and prevalence of osteophytes, respectively. Similarly, at followup, a low mode 4 score predicted OA-related features, such as a higher probability of the presence of BMLs, high cartilage signal, and larger BML and hip effusion-synovitis size. In contrast, higher mode 2 scores were found to be associated with effusion-synovitis. Features highlighted by both these modes correspond to cam deformity and pistol-grip deformity, which are well-known risk factors for the development of hip OA (9,32). As this is the first study to identify the link between hip shape and structural changes such as BMLs, there are no previous data exploring the association; these morphologic features could encourage structural changes in the subchondral bone and cartilage (8,15,16,19).

Higher scores of both mode 1 and mode 2 modestly correlated with larger effusion-synovitis cross-sectional area, and a +1 SD higher mode 2 score predicted a 22% greater prevalence of the presence of hip effusion-synovitis. In further analyses, longitudinal associations were found between baseline shape and change in hip effusion-synovitis (from phase II to phase III). Over this period, a 1 SD lower baseline mode 1 score was associated with greater hip effusion-synovitis cross-sectional area (β −0.20 [95% confidence interval (95% CI) −0.30, −0.06]), whereas no association was found with mode 2. Mode 1 thus appears to be predictive not only of hip pain but also hip effusion-synovitis, and future studies will explore whether this is an early indicator of later radiographic OA, as suggested by other studies (33).

The same 2 modes that were most strongly associated with MRI structural features, modes 2 and 4, also showed the strongest associations with hip replacement. Increasing mode 2 and decreasing mode 4 scores were strongly associated with THR. Every 1 SD increase in mode 2 score increased the risk of THR by approximately 60%, and a −1 SD change in mode 4 increased the risk of THR by approximately 40%. Both of these modes identified shape patterns related to OA, such as the transition of the femoral head into the femoral neck, the size of the greater trochanter, and a flattening of the femoral head itself, and mode 2 captured coverage of the femoral head by the acetabulum (17). Overall, excessive coverage of femoral head by the acetabulum, also known as femoral-acetabular impingement, along with features related to pistol-grip deformity, are known to be associated with a greater risk of hip OA (9,32,34).

A number of limitations need to be noted. This study uses DXA images of the left hip, while MRI-detected anomalies were measured in the right hip, so the joint appearances may not be directly comparable. Nevertheless, it has been shown that OA in the ipsilateral joint strongly predicts and is associated with OA in the contralateral joint, and studies using SSM have reported similar results (35). The effect of the internal/external rotation of the femur, arising from variations in patient positioning, cannot be ruled out, and even when using standardized protocols, in which the position of the feet is carefully controlled, this might influence the DXA images. Nevertheless, SSM has the potential to pick up the effects of rotation from the variation in shape during the development of the model (8,17,21). Point placement on identifiable landmarks is important to define the model and is a potential source of error. After initial manual placement on a small number of images, the SSM is a semiautomated program that uses points at defined locations to measure the global shape of the hip joint. Each image is checked by the user and points are adjusted if visually incorrect. The small point-to-point error is an indicator of the placement of points by different observers to within a few pixels.

In summary, in this population-based study, 2-dimensional hip shape measured on entry to the study is shown to be associated with radiographic OA and muscle strength at baseline. More interestingly, shape is also strongly predictive of THR, as well as indicators of OA, such as hip pain, BMLs, effusion-synovitis, and hip structural changes occurring up to 10 years later. These data suggest that different morphologic features identified by shape modes have relevance for multiple facets of hip OA, both radiographic and clinical. It adds further evidence for the use of SSM as an imaging biomarker for the incidence and progression of OA. Where standardized radiographs or DXA images are available, we believe that in due course it may be possible to include a measure of shape into clinical imaging practice for the early detection and staging of OA.

ACKNOWLEDGMENTS

The authors thank the participants in the TASOAC study, as well as Catrina Boon and Pip Boon for their contributions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ahedi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ahedi, Aspden, Saunders, Aitken, Jones, Gregory.

Acquisition of data. Ahedi, Aspden, Gregory.

Analysis and interpretation of data. Ahedi, Blizzard, Saunders, Cicuttini, Aitken, Jones, Gregory.

REFERENCES

1. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014;73:1323–30.
2. Aspden RM. Osteoarthritis: a problem of growth, not decay? Rheumatology (Oxford) 2008;47:1452–60.
3. Ahedi H, Aitken D, Blizzard L, Cicuttini F, Jones G. The association between hip bone marrow lesions and bone mineral density: a cross-sectional and longitudinal population-based study. Osteoarthritis Cartilage 2013;19:838–48.
4. Ahedi H, Aitken D, Blizzard L, Cicuttini F, Jones G. A population-based study of the association between hip bone marrow lesions, high cartilage signal, and hip and knee pain. J Clin Rheumatol 2013;33:369–76.
5. Neumann G, Mendicuti AD, Zou KH, Minas T, Coblyn J, Winalski CS, et al. Prevalence of labral tears and cartilage loss in patients with mechanical symptoms of the hip: evaluation using MR arthrography. Osteoarthritis Cartilage 2007; 15:909–17.
6. Teichtahl AJ, Wang Y, Smith S, Wluka AE, Giles GG, Bennell KL, et al. Structural changes of hip osteoarthritis using magnetic resonance imaging. Arthritis Res Ther 2014; 16:466.
7. Ahedi HG, Aitken DA, Blizzard LC, Ding CH, Cicuttini FM, Jones G. Correlates of hip cartilage defects: a cross-sectional study in older adults. J Rheumatol 2016; 43:1406–12.
8. 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;56:3634–43.
9. Doherty M, Courtney P, Doherty S, Jenkins W, Maciewicz RA, Muri 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;58:3172–82.
10. Kasper K, Goving SJ, Sonne-Holm S. Prevalence of malformations of the hip joint and their relationship to sex, groin pain and risk of osteoarthritis: a population-based survey. J Bone Joint Surg 2010;92:1162–9.
11. Cootes TF. Active shape models. Hogg DB, ed. Berlin: Springer-Verlag; 1992.
12. Yoshida K, Barr RJ, Gregory JS, Aspden RM, Alesci S, Macfarlane GJ, et al. Link between the severity of osteoarthritis and the shape of the hip joint using DXA images [abstract]. Rheumatology (Oxford) 2009;48:I99.
13. Yoshida K, Gregory JS, Barr JR, Alesci S, Aspden RM, Reid DM. Temporal structural changes in hip OA detected using shape and appearance modelling of DXA images: a one-year prospective cohort study [abstract]. Osteoarthritis Cartilage 2009;17 Suppl 1:S24.
14. 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;18:239–44.
15. Lynch JA, Parimi N, Chaganti RK, Nevitt MC, Lane NE, and the Study of Osteoporotic Fractures Research Group. The association of proximal femoral shape and incident radiographic hip OA in elderly women. Osteoarthritis Cartilage 2009;17:1313–8.
16. 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;51:562–70.
17. Waarsing JH, Rozendaal RM, Verhaar JN, Bierma-Zeinstra SA, Weinans H. A statistical model of shape and density of the proximal femur in relation to radiological and clinical OA of the hip. Osteoarthritis Cartilage 2010;18:787–94.
18. Agricola R, Reijman M, Bierma-Zeinstra SM, Verhaar JA, 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 Cartilage 2013;21:559–64.
19. 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 (Hoboken) 2014;66:74–81.
20. Goodyear SR, Barr RJ, McCloskey E, Alesci S, Aspden RM, Reid DM, et al. Can we improve the prediction of hip fracture by assessing bone structure using shape and appearance modelling? Bone 2013;53:188–93.
21. Gregory JS, Testi D, Stewart A, Undrill PE, Reid DM, Aspden RM. A method for assessment of the shape of the proximal femur and its relationship to osteoporotic hip fracture. Osteoporos Int 2004;15:5–11.
22. Ding C, Cicuttini F, Boon C, Boon P, Srikanth V, Cooley H, Jones G. Knee and hip radiographic osteoarthritis predict total hip bone loss in older adults: a prospective study. J Bone Miner Res 2010;25:858–65.
23. Bellamy B, Buchanan W, Goldsmith C, Camplbell J, Stitt L. 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;15:1833–40.
24. Scott D, Blizzard L, Fell J, Jones G. Prospective associations between ambulatory activity, body composition and muscle function in older adults. Scand J Med Sci Sports 2011;21: 1600–8.
25. Zhai G, Cicuttini F, Srikanth V, Cooley H, Ding C, Jones G. Factors associated with hip cartilage volume measured by magnetic resonance imaging: the Tasmanian Older Adult Cohort Study. Arthritis Rheum 2005;52:1069–76.
26. Totterman S, Tamez-Pena J, Schreyer E, Gonzalez P, Hunter DJ. Cartilage-bone contrast behavior in OAI progression subcohort: correlation to WOMAC scores [abstract]. Osteoarthritis Cartilage 2009;17 Suppl 1:S74–5.
27. King L, Higgs J, Aisen A, Buckwalter K, Martel W, McCune J. MRI in osteoarthritis of the hip: gradations of severity. Magn Reson Imaging 1988;6:229–36.
28. Huber P, ed. The behavior of maximum likelihood estimates under nonstandard conditions. Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability; 1967; Berkeley (CA): University of California Press.
29. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica 1980;48:817–38.
30. Rogers W. Regression standard errors in clustered samples. Stata Tech Bull 1993;13:19–23.
31. Nelson AE, Golightly YM, Liu F, Lynch J, Gregory JS, Aspden RM, 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;43:405–10.
32. Agricola R, Heijboer MP, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Ann Rheum Dis 2013;72:918–23.
33. Bierma-Zeinstra SM, Bohnen AM, Verhaar JA, Prins A, Ginai-Karamat AZ, Lameris JS. Sonography for hip joint effusion in adults with hip pain. Ann Rheum Dis 2000;59:178–82.
34. Gosvig KK, Jacobsen S, Sonne-Holm S, Gebuhr P. The prevalence of cam-type deformity of the hip joint: a survey of 4,151 subjects of the Copenhagen Osteoarthritis Study. Acta Radiol 2008;49:436–41.
35. Sayre EC, Jordan JM, Cibere J, Murphy L, Schwartz TA, Helmick CG, et al. Quantifying the association of radiographic osteoarthritis in knee or hip joints with other knees or hips: the Johnston County Osteoarthritis Project. J Rheumatol 2010;37:1260–5.