

Osteoarthritis and Cartilage



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

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SUMMARY

Objective: To evaluate the accuracy and sensitivity of a *fully automatic shape model matching (FASMM)* system to derive statistical shape models (SSMs) of the proximal femur from non-standardised anteroposterior (AP) pelvic radiographs.

Design: AP pelvic radiographs obtained with informed consent and appropriate ethical approval were available for 1105 subjects with unilateral hip osteoarthritis (OA) who had been recruited previously for The arcOGEN Study. The *FASMM* system was applied to capture the shape of the unaffected (i.e., without signs of radiographic OA) proximal femur from these radiographs. The accuracy and sensitivity of the *FASMM* system in calculating geometric measurements of the proximal femur and in shape representation were evaluated relative to validated manual methods.

Results: *De novo* application of the *FASMM* system had a mean point-to-curve error of less than 0.9 mm in 99% of images ($n = 266$). Geometric measurements generated by the *FASMM* system were as accurate as those obtained manually. The analysis of the SSMs generated by the *FASMM* system for male and female subject groups identified more significant differences (in five of 17 SSM modes after Bonferroni adjustment) in their global proximal femur shape than those obtained from the analysis of conventional geometric measurements. Multivariate gender-classification accuracy was higher when using SSM mode values (76.3%) than when using conventional hip geometric measurements (71.8%).

Conclusions: The *FASMM* system rapidly and accurately generates a global SSM of the proximal femur from radiographs of varying quality and resolution. This system will facilitate complex morphometric analysis of global shape variation across large datasets. The *FASMM* system could be adapted to generate SSMs from the radiographs of other skeletal structures such as the hand, knee or pelvis.

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Introduction

The analysis of geometric measurements made of skeletal elements from standard two-dimensional radiographs is an established and routine clinical tool used in the diagnosis, prognosis and

management of many skeletal disorders. Recently, detailed morphometric analyses have been conducted to identify key features of bone shape that contribute to disease incidence and progression and that may serve as biomarkers for pre-symptomatic diagnosis and treatment evaluation. Such studies have also been extended to identify potential genetic regulators of bone shape that may thereby contribute to disease susceptibility^{1,2}. Specifically, with regards to the relationship between geometric measurements of proximal femur shape and hip osteoarthritis (OA), analyses have established, for example, that the radiographic shape of the femoral neck is associated with the onset and progression of hip OA³, and that femoral neck width (FNW) and the ratio of femoral head diameter (FHD) to FNW can be used to identify individuals at risk of OA⁴.

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We have previously generated a semi-automatic system that digitally captures the shape of skeletal elements through the use of Active Shape Models (ASMs) and represents shape as a statistical shape model (SSM)⁵. An SSM describes every shape by the sum of a mean shape and a linear combination of a number of shape modes where the shape mode values vary between subjects. Hence, SSMs provide a *global* representation of shape rather than reducing shape to a series of linear measurements which enables the description and analysis of shape variation across datasets. Gregory *et al.* first described the application of ASMs to generate an SSM of proximal femur shape in their analysis of osteoporotic hip fracture⁶. Thereafter, this approach has been used in a number of studies to investigate the relationship between features of proximal femur shape and the onset, incidence and progression of hip OA^{1,7–10}. More recently, Agricola *et al.* have shown that SSM variation can be used as a biomarker to predict the risk of total hip replacement in OA cases¹¹. In the above studies the standard, semi-automatic ASM methodology has been applied which requires the initial manual placement of landmark points to define the approximate shape and position of the skeletal element (the initialisation phase) followed by an automated search to outline the contour of the bone. The accuracy of the resultant SSM therefore depends on the precision and consistency of the manual initialisation phase.

As the current *semi-automatic* ASM methodology is time-consuming and vulnerable to intra- and inter-operator error, its application to large-scale morphometric analyses is limited. We have therefore developed a *fully automatic shape model matching* (FASMM) system that uses an SSM to capture and represent the shape of skeletal element/s within standard radiographs¹². In this paper, we demonstrate the use of the FASMM system for segmentation of the proximal femur from anteroposterior (AP) radiographs via its rapid and accurate placement of 65 reference points along the contour of the proximal femur without any manual intervention. We show that these automatically placed reference points and the SSM derived from these points can reliably predict a number of standard hip geometric measurements. Further, we demonstrate the utility of this system in identifying differences in shape variation between large datasets through its application to an analysis of proximal femur shape variation between males and females.

Methods

Dataset

AP pelvic radiographs were available from hip OA subjects recruited in Stage 2 of The arcOGEN Consortium Study¹³. Inclusion criteria and ethical approval for Stage 2 subject recruitment were as previously described¹³. For this study, radiographs were selected from hip OA subjects who had no evidence of radiographic OA in one of their hip joints (with the presence of OA being defined as Kellgren–Lawrence score ≥ 2). Demographic data for each subject included body mass index (BMI) and date of birth but the date of X-ray was not consistently available. Geometric measurements (derived using a previously validated open-access software tool for measuring hip morphological characteristics (SHIPs)¹⁴, which comprised the *manual measurements* for this study) were available for the unaffected hip joint from radiographs of 786 of the above 1105 subjects. These manual measurements included FHD, FNW, femoral neck axis length (FNAL), femoral neck shaft angle (FNSA), and alpha angle (AA). From these measurements the FHD–FNW ratio, FNAL–FHD ratio, and FNAL–FNW ratio were calculated. The FHD, FNW and FNAL measurements were all given in pixels. Pixel size information was not however available for any of the radiographs. Measurements made by two independent observers for a subset of 25 radiographs were available for estimates of inter-

observer variability¹⁴. The formula for calculating the coefficient of variation (CV%) for each measurement was: $CV\% = 100 \times ((\delta/\sqrt{2})/\mu)$ where δ represents the standard deviation (SD) of the differences between the paired measurements, and μ is the mean of all the values for that measurement.

The FASMM system

We have previously described a methodology for automatic femur segmentation in pelvic radiographs using regression voting¹², which improves and extends the standard ASM approach⁵, and is the basis of the FASMM system. Here, we focused on finding and segmenting the left proximal femur in AP radiographs where the left hip was OA-free. For cases where the right hip was OA-free we mirrored the image so that it appeared on the left. The FASMM system was trained to segment the proximal femur by first detecting it in the radiograph and then outlining its contour using 65 points (see Fig. 1). All points were placed in consistent positions across images through using nine anchor points that defined specific anatomical features with remaining points being evenly spaced relative to these points. As in Fig. 1, the system uses a front-view femur model that excludes both the lesser and greater trochanters. The system was designed to accommodate radiographs of differing quality, femur position/orientation and area of the pelvis. This allowed inclusion of radiographs obtained retrospectively from several recruitment centres that varied in resolution (555–4723 pixels wide), exposure contrast, focus to film distance, and position of beam centre relative to the hip joint.

The FASMM system was developed using 839 of the 1105 images. For this study to avoid training and testing on the same dataset, we split the 839 images into two subsets of 419 and 420 images respectively, and trained a system on each subset. We trained a further system using all 839 images for *de novo* application to the remaining 266 images. The refined FASMM system now trained on all 1105 images is freely available for non-commercial research purposes from <http://personalpages.manchester.ac.uk/postgrad/claudia.lindner/>.

Calculation of geometric measurements from the points placed by the FASMM system

Manual measurements were available for 786 images. For comparison, these measurements (see Fig. 2) were automatically calculated from a subset of the 65 points generated by the FASMM system for each of the 786 images and application of custom code developed in Matlab R2010a. As with the manual measurements, FHD, FNW and FNAL were pixel-based. Due to the extent of variation in image-size across our dataset, these measurements were utilised for the subject-specific comparison of manual vs automatic measurements and to derive ratios that were independent of image-size.

Based on the 65 points as generated by the FASMM system (see Fig. 1), the geometric measurements were calculated on a subset of these points as follows. To obtain the diameter and centre of the femoral head a circle was fitted to points [20–35] so as to minimise the average distance between the circle and these points. The femoral neck axis was derived by firstly identifying the minimum path between the contours through point sets [10–17] and [36–44], and then fitting a line through the midpoint of this path (femoral neck centre) and the centre of the femoral head. The FNAL was given by the distance between the centre of the femoral head and the intersection point of the femoral neck axis and the contour through points [56–62]. The FNW was calculated by firstly fitting a line through the centre of the femoral neck that is perpendicular to the femoral neck axis, and then secondly calculating the distance

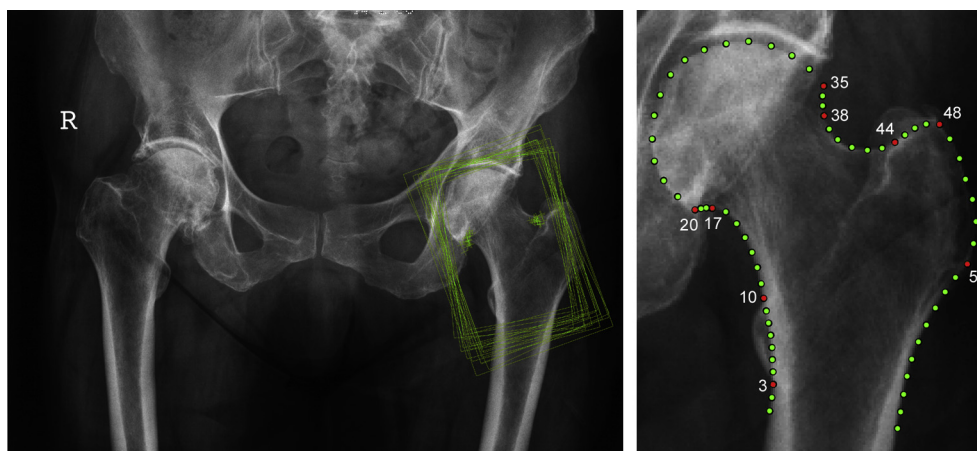


Fig. 1. Fully automatic segmentation of the proximal femur: Detecting the proximal femur in the image (left) and outlining its contour using 65 points (right). All anchor points are highlighted in red and were chosen to mark the following features: the beginning (point 3) and the end (point 10) of the lesser trochanter projected to the nearby femoral shaft contour, inflexion points at the inferior (point 17) and superior (point 38) femoral head–neck junction, the inferior (point 20) and superior (point 35) end of the hemispheric femoral head shape, the projected beginning of the trochanteric fossa (point 44) as well as local maxima at the superior contour of the greater trochanter (point 48) and at the inferior end of the greater trochanter (point 55). Note that these features are based on the visual appearance of the proximal femur in AP pelvic radiographs; this does not necessarily correspond with three-dimensional anatomical features.

between the intersection points of this line with the contours through point sets [10–17] and [36–44]. To obtain the AA we calculated the angle between the femoral neck axis and a line fitted to the centre of the femoral head as well as the intersection point of the femoral head circle and the contour through points [36–44]. The femoral shaft axis was obtained by calculating the midpoints of point pairs [1,63], [2,63], [1,64], [2,64], [1,65] and [2,65] and then fitting a line through these midpoints. We calculated the FNSA by

defining the angle between this shaft axis and the femoral neck axis.

The automatically and manually calculated measurements were compared using the Bland and Altman method¹⁵. We also calculated the Pearson's correlation coefficient for each measurement. All plots and calculations were made using Matlab R2010a. As the FASMM system is a deterministic algorithm (i.e., for the same radiograph it always produces the same measurements), the CV% was calculated between the automatic measurements and the average of the manual measurements made by two observers. This was then compared to the inter-observer variability of the manual measurements.

Prediction of geometric measurements from the SSM generated by the FASMM system

The SSM mode values were calculated by building an SSM based on the 65 points generated for each subject by the FASMM system. We then used linear regression to predict the morphometric measurements based on the SSM mode values. As our SSM did not include any absolute scales (as most images were not calibrated), we excluded FHD, FNW and FNAL from this analysis. The automatically predicted SSM based measurements and the manual measurements were compared using the Bland and Altman method¹⁵. We also calculated the Pearson's correlation coefficient for each measurement. All plots and calculations were made using Matlab R2010a.

Male vs female proximal femur shape

We used the SSM mode values to investigate whether there was a significant difference in radiographic proximal femur shape between the 662 females and 443 males within the 1105 case cohort. The SSM mode values were calculated by building an SSM based on the 65 points for every image obtained by applying the FASMM system. The mean shape variation was calculated across all images and then individually for males and females. A univariate independent two-sample Welch's *t*-test on the SSM mode values was used to compare the two groups.

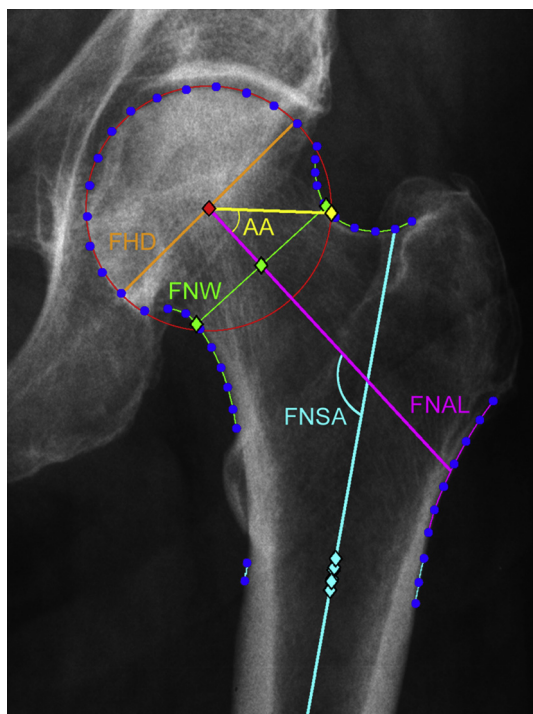


Fig. 2. Geometric measurements based on output of the FASMM system: FHD, FNAL, FNW, FNSA, AA. Note that the fully automatic calculation of these measurements is based on the blue contour points only whereas the fully automatic prediction uses an SSM that includes all 65 contour points.

We then investigated the accuracy of the SSM and the conventional geometric measurements to gender-classify the data using Gaussian probability density functions (PDFs). Out of the 786 images for which manual measurements were available we used 598 images to train the system used for classification. We tested the classification system on the remaining 188 images (108 females and 80 males) for which manual measurements were available. These 188 images were a subset of the 266 images that were not involved in developing the FASMM system. We analysed the gender-classification performance of (1) a combination of SSM mode values that explain 98% of shape variation using male and female multivariate PDFs; (2) a combination of all five non-pixel-based geometric measurements (FHD–FNW ratio, FNAL–FHD ratio, FNAL–FNW ratio, FNSA, and AA) using male and female multivariate PDFs; (3) individual non-pixel-based geometric measurements (FHD–FNW ratio, FNAL–FHD ratio, FNAL–FNW ratio, FNSA, and AA) using male and female univariate PDFs.

As the male and female groups did not differ significantly in terms of year of birth (YOB) or BMI [108 females (YOB: 1939.3 \pm SD: 9.1; BMI: 29.5 \pm SD: 5.3) and 80 males (YOB: 1940.2 \pm SD: 9.5; BMI: 28.9 \pm SD: 5.9)], findings were not adjusted according to these criteria.

Results

Application of the FASMM system

The FASMM system was applied to the dataset of 1105 images in three stages: (1) we trained the system on 419 images and applied it to 420 different images; (2) we switched the datasets and trained the system on the set of 420 images before applying it to the set of 419 images; (3) we trained the system on all 839 images from the first two stages and tested it on the remaining 266 images. These 266 images had therefore not been included in any of the training or testing phases of the development of the system¹². *De novo* testing of the system against these images, using previously described methods¹², demonstrated a mean point-to-curve error of less than 0.9 mm on 99% of images and of less than 3.3 mm on 100% of the images. This accuracy is consistent with our previous findings¹². The latest version of the system can process one image on average in 10 s (on a 3.3 GHz Intel Core Duo PC using 3.5 GB RAM and running Windows XP SP3). An analysis of the resultant SSM demonstrated that 17 shape modes accounted for 98% of the overall shape variation given by the whole dataset.

Comparison of manual vs automatically generated measurements

To determine whether conventional geometric measurements could be automatically calculated from the 65 points placed by the FASMM system and whether these measurements were as accurate as those generated manually, we compared the two sets of measurements obtained from 786 images. Fig. 3 shows the Bland and Altman plots for the automatically generated points based measurements against the manual measurements¹⁴, for each of the 786 images. As is evident from Fig. 3, the automatic and manual measurements were similar across a broad range of values. The limits of agreement between the two sets of measurements were less than 10% across the range of measurements, and with a bias approaching 0%. The only exception to this was the AA which had poor limits of agreement with up to 50% difference in measurement over ± 2 SD.

We calculated the CV% between the manual measurements obtained by two independent observers on 25 images. As shown in Table I, the inter-observer CV% was between 0.7% and 1.5% for all measurements, with the exception of the AA which was 3.2%. For comparison, we then calculated the CV% between the mean values

for the manually obtained measurements and those obtained automatically for the same set of images. The automatic-manual CV% was between 1.0% and 1.9% for all measurements, with the exception of the AA which was 19.2% (see Table I).

Comparison of manual measurements vs those predicted from the SSM

To determine whether geometric measurements could be accurately predicted from the SSM mode values generated by the FASMM system, we compared the SSM based measurements with those obtained manually. Fig. 4 shows the Bland and Altman plots for the manual measurements against measurements predicted by applying linear regression to the SSM mode values. The plots indicate that the SSM mode values can predict the manual measurements. As above, the automatically predicted SSM based measurements and those obtained manually were in very good agreement across a broad range of values. The limits of the agreement between the methods were less than 10% across the range of measurements, and with a bias approaching 0%. Again, the only exception was the AA which had poor limits of agreement with up to 30% difference in measurement over ± 2 SD.

Comparison of male vs female proximal femur shape

SSM mode values for the 662 females and 443 males within the 1105 case cohort were calculated and the mean SSM values for each mode and each of the groups compared using a univariate independent two-sample Welch's *t*-test. We used the Kolmogorov–Smirnow test to verify that the data for each mode and every subject group were normally distributed. Eleven of the 17 modes had male vs female mean values that were significantly different ($P < 0.05$). After Bonferroni adjustment, five of the 17 modes had male vs female mean values that were significantly different ($P < 0.003$). Fig. 5 provides a pictorial representation of the difference between male and female radiographic proximal femur shape showing the overall mean shape as well as indicating the mean male and female shapes.

We then investigated the accuracy of the subject-specific SSM mode values generated by the FASMM system to predict whether a radiograph had been obtained from a male or a female subject. We found that gender-classification based on a multivariate PDF using all 17 shape modes had a 76.3% success rate. In contrast, when using a multivariate PDF based on the five non-pixel-based conventional geometric measurements (combined ratios of FHD–FNW, FNAL–FHD, FNAL–FNW, FNSA and AA) to gender-classify the same data, the success rate was 71.8%. Further, when using a univariate PDF based on the individual ratios for gender-classification the success rates were: FHD–FNW ratio: 68.7%, FNAL–FHD ratio: 62.7%, FNAL–FNW ratio: 69.1%, FNSA: 63.6%, and AA: 67.9%.

Discussion

We have demonstrated that the newly developed FASMM system can automatically, rapidly and accurately capture the shape of the proximal femur from non-standardised AP pelvic radiographs. Conventional hip morphologic measurements (with the exception of the AA) can also be accurately and automatically calculated from the FASMM generated contour as well as from the FASMM generated SSM, despite it being an abstract representation of radiographic shape. Hence, the FASMM system will facilitate detailed analysis of global shape variation across large (either retrospective or prospective) datasets.

The FASMM system can be applied to the analysis of shape variation between subject groups, as demonstrated by our

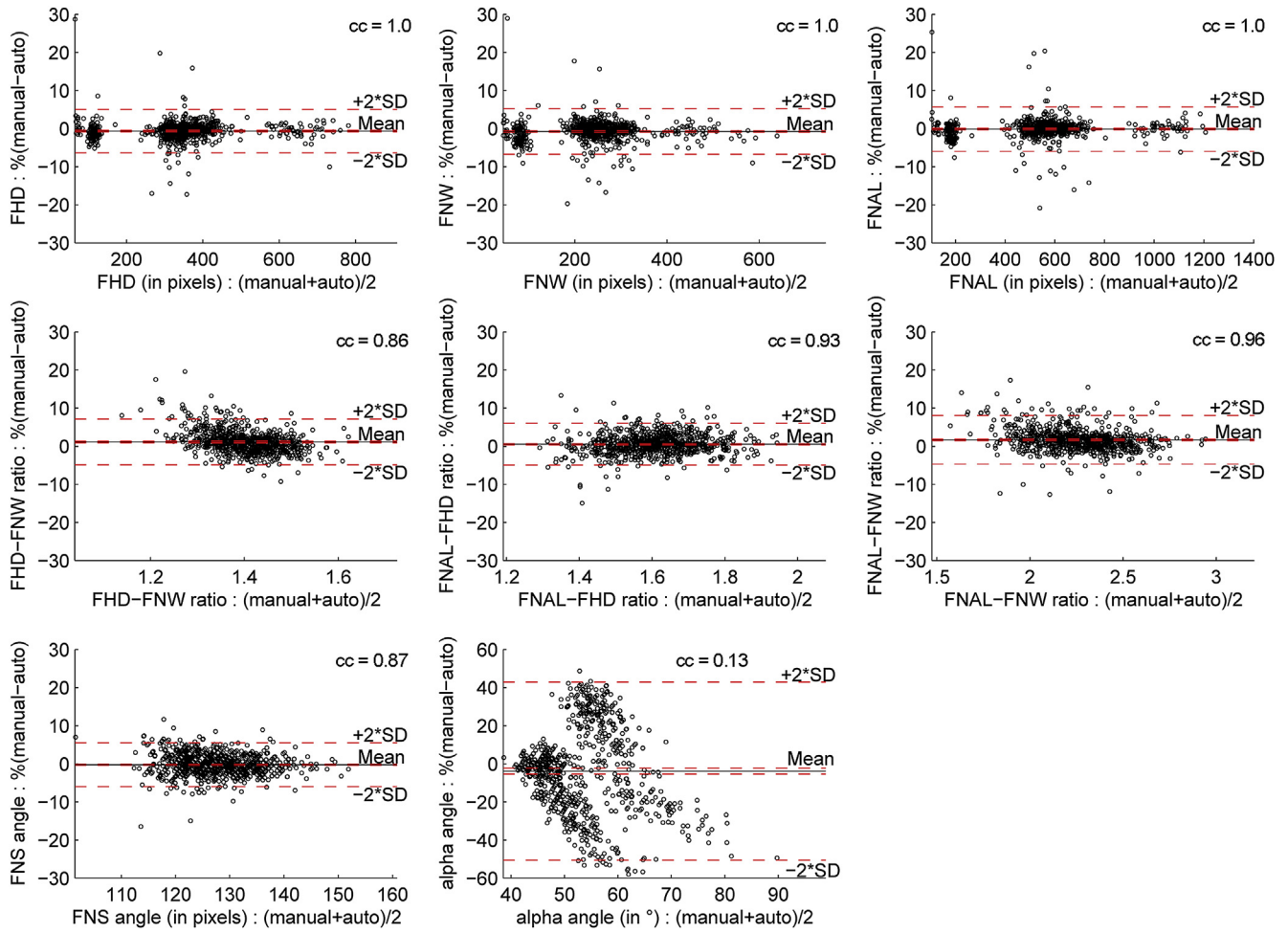


Fig. 3. Bland–Altman plots for manual measurements vs fully automatic measurements (cc = Pearson’s correlation coefficient): These data show high correlation and less than 10% difference between the methods (red dotted line labelled ± 2 SD, indicating limits of agreement between methods), and minimal bias (red dotted lines indicating 95% confidence interval (CI) of mean) for all but the alpha angle.

identification of significant differences between male and female proximal femur shape using the system. Further, we found that applying a multivariate approach to gender-classify images using combinations of geometric measurements increased classification accuracy in comparison to that of single measurements. Gender-classification accuracy was increased still further by incorporating global shape information (via using SSM mode values generated by the FASMM system). These findings suggest that using SSM mode values increases the power to detect shape differences between subject groups. The shape difference identified between males and

females (Fig. 5) is consistent with findings that the pistol-grip deformity is more prevalent in men¹⁹. In our analysis, only relative shape differences between males and females were analysed and not differences in size. Future extension of the FASMM system will explore inclusion of both specification and quantification of shape variation across subject groups.

The AA is a measurement used to quantify cam-type deformity which is a risk factor highly associated with hip OA that might be modifiable via early surgical intervention^{10,16}. In our analyses, the AA estimated using the FASMM system did not correlate well with

Table I

Manual inter-observer and fully automatic vs manual repeatability. The automatic measurements were calculated from the 65 points for each image generated using the FASMM system.

	FHD	FNW	FNAL	FNSA	AA	FHD–FNW ratio	FNAL–FHD ratio	FNAL–FNW ratio
Inter-observer variation based on two independent sets of manual measurements								
Mean	376.5	262.6	602.4	128.5	49.4	1.44	1.60	2.31
SD	6.5	4.7	6.5	1.2	2.2	0.03	0.03	0.04
95% CI	373.9–379.0	260.8–264.4	599.8–604.9	128.0–129.0	48.6–50.3	1.43–1.45	1.59–1.62	2.30–2.33
CV%	1.2	1.3	0.8	0.7	3.2	1.5	1.5	1.3
Automatic–manual variation based on automatic search results and averaged manual measurements								
Mean	373.9	265.2	601.1	128.4	49.9	1.41	1.60	2.27
SD	5.2	6.4	10.1	3.2	13.6	0.03	0.04	0.05
95% CI	371.8–375.9	262.7–267.7	597.1–605.1	127.1–129.7	44.5–55.2	1.40–1.42	1.59–1.62	2.26–2.30
CV%	1.0	1.7	1.2	1.8	19.2	1.6	1.9	1.6

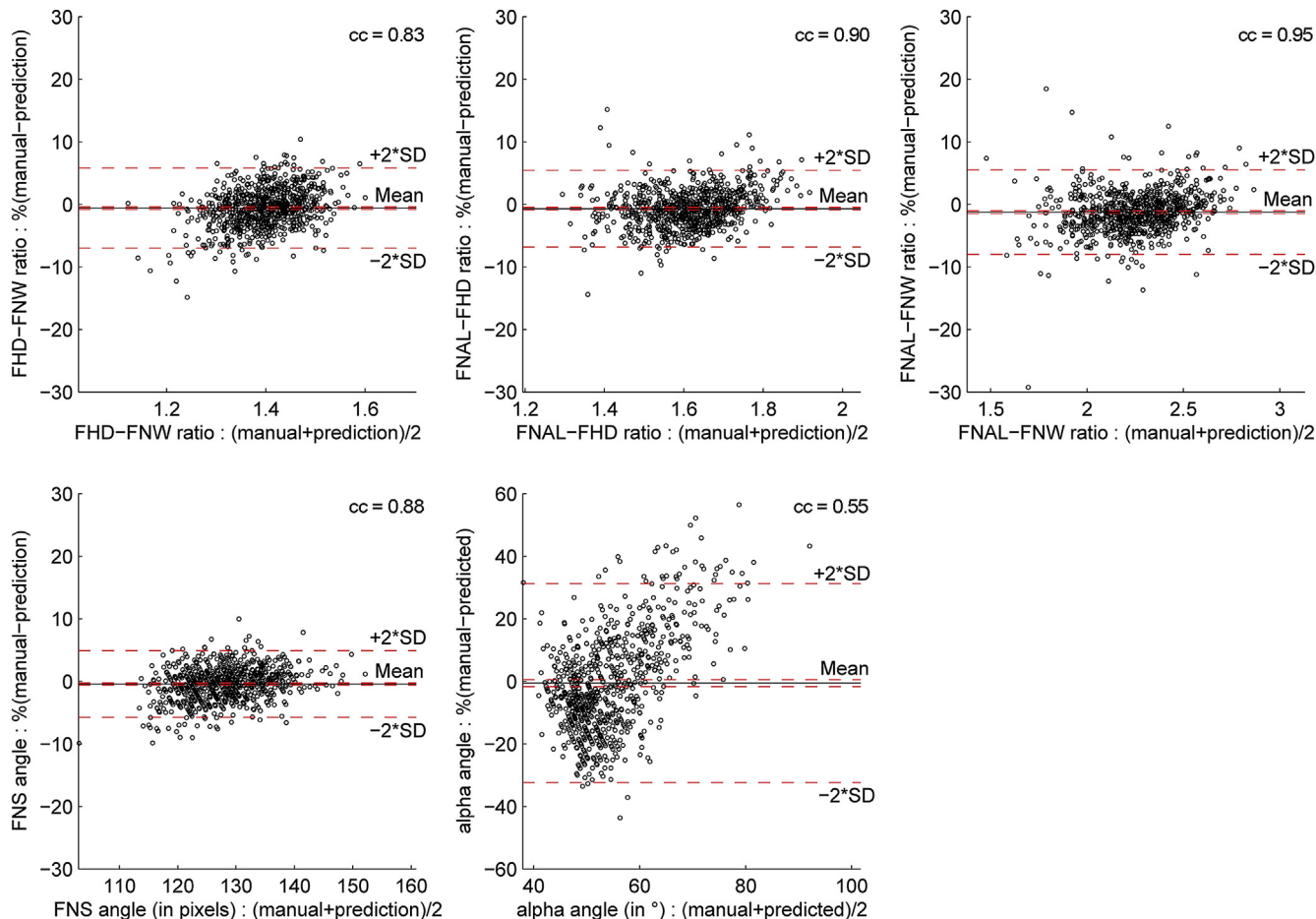


Fig. 4. Bland–Altman plots for manual measurements vs prediction using linear regression based on shape model mode values (cc = Pearson’s correlation coefficient): These data show high correlation and less than 10% difference between the methods (red dotted line labelled ± 2 SD, indicating limits of agreement between methods), and minimal bias (red dotted lines indicating 95% CI of mean) for all but the alpha angle.

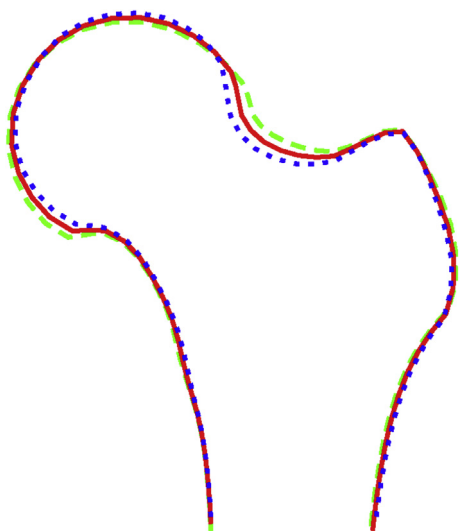


Fig. 5. Shape differences between male (---) and female (—) proximal femur shape based on fully automatic search results for 1105 images, where differences from the mean (—) have been exaggerated by a factor of 3 to aid visualisation.

the manual measurements. We assume the reason for this to be that there is no objective and reproducible way of measuring the AA on AP pelvic radiographs but that its measurement includes the subjective positioning and fitting of a circle to the contour of the femoral head. When we attempted to implement an automatic (and hence objective) calculation of the AA, we were not able to define a method of calculation that could be applied consistently across the range of femoral head shapes and that also reflected cam-type deformity correctly. In particular, using the intersection point of the femoral head circle and the superior femoral neck contour given by points [35–44] (see Fig. 1) to define the AA resulted in a large number of cases where the AA did not accurately reflect the presence/absence of cam-type deformity. The two main reasons for this are likely to be the range of skeletal shape variation in the area of the superior femoral head–neck junction, and because point 35 (which defines the superior end of the hemispheric femoral head shape) does not always lie inside the circle that best fits to points [20–35]. However, as the automatic fitting of a circle to the femoral head using points [20–35] as described above led to high agreement between manual and fully automatic values for all other geometric measurements, we did not change our approach to fitting the femoral head circle but excluded point 35 from the superior femoral neck contour for the calculation of the AA. This appeared to improve the agreement between the calculated AA and the observed presence/absence of cam-type deformity but showed

poor AA estimation when compared to manual measurements. In addition to inherent problems in its measurement, the use of the AA obtained from AP pelvic radiographs to predict the presence/absence of cam-type deformity has been questioned because AA measurements based on AP pelvic radiographs do not correlate very well with measurements derived from three-dimensional magnetic resonance imaging (MRI) data^{17,18}. Doherty *et al.* have, however, suggested that cam-type deformity can be identified by the presence of a pistol-grip deformity which in turn can be defined by the FHD–FNW ratio¹⁹. We have shown accurate prediction of the FHD–FNW ratio using the FASMM system. In addition, as SSMs provide a global representation of shape, information about cam-type deformity will be contained in the SSM mode values and thereby provide a more accurate method for its detection.

A limitation of this study is that it relies on single two-dimensional radiographic views to quantify proximal femur shape. The two-dimensional radiographic shape of the proximal femur may vary due to the inclination of the pelvis and rotation of the legs during image acquisition. In previous work, we have however shown that the degree of position-related shape variation is small compared to the overall shape variation of the proximal femur as derived from AP pelvic radiographs²⁰, and hence will not significantly hamper analysis of global shape variation across large datasets.

In the specific application of the FASMM system presented here, we have trained the system to capture the shape of the unaffected proximal femur from AP pelvic radiographs of subjects with unilateral OA. This provides a mechanism for the analysis of proximal femur shape variation that may increase susceptibility to OA and disease progression. Our preliminary experiments (unpublished) have also shown that the system as currently configured performs well on joints with mild OA where there is only minor deviation from the *unaffected* shape. In order to capture and analyse the range of shape variation of joints affected by OA related pathology, the FASMM system will be extended by including OA-affected images in the training phase of the system to capture features such as osteophytes, atrophic bone patterns and cysts. Thereby the system will fulfil a recognised need for better joint-specific phenotypic definition of OA as well as for fast and reliable methods to standardise radiographic scoring²¹. Further, we are currently extending the FASSM system to incorporate the lesser and greater trochanters into the model and we are applying the FASMM system to the segmentation of the pelvis, the knee joint and the joints of the hand. Application of the FASSM system will therefore benefit morphological studies aimed at understanding the aetiology and progression of diseases of the major joint sites.

Author contributions

All authors have made substantial contributions to data acquisition or study execution, manuscript preparation, and final approval of the submitted article. CL takes responsibility for the integrity of the work as a whole.

Conflict of interest

The authors declare not to have any conflict of interest.

Role of funding source

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