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Constitutional morphological features and risk of hip osteoarthritis: a case control study using standard radiographs

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Title: Constitutional morphological features and risk of hip osteoarthritis: a case control study using standard radiographs

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Abstract	~~242~~245
Introduction	~~505~~487
Methods	~~728~~723
Results	~~586~~551
Discussion	~~1086~~1229
Total	~~2905~~2990

Key messages

What is already known about this subject?

Several constitutional variants of hip joint shape associate with increased risk of hip osteoarthritis (OA). However, whether these relate to each other, and the overall contribution of morphological variants to risk of hip OA are unknown.

What does this study add?

Fourteen morphological features of the hip and pelvis, ten of which had not been studied ~~adequately~~ before, were shown to ~~independently~~ associate with hip OA after adjusting for age, gender and body mass index (BMI). The strongest association was with more vertical ~~wide~~ sourcil angle (SA). Three clusters of features were identified, and the proportional risk contribution (PRC) to hip OA was 35% for the combined variants, compared to 21% for other recognised risk factors combined.

How might this impact on clinical practice or future developments?

Although prospective studies are required to ~~confirm causality~~provide further support for causality, morphological variation is a strong risk factor for hip OA and may partially explain its heritability. SA measured on standard radiographs may be used as a single surrogate marker to assess morphological risk of hip OA.

ABSTRACT

Objectives To evaluate the risk of association with hip osteoarthritis (OA) of 14 morphological features measured on standard antero-posterior pelvis radiographs.

Methods A case-control study of 566 symptomatic unilateral hip OA cases and 1108 controls without hip OA, using the Genetics of Osteoarthritis and Lifestyle (GOAL) database. Unaffected hips of cases were assumed to reflect pre-OA morphology of the contralateral affected hip. Odds ratios (ORs) with 95% confidence interval (CI) adjusted for confounding factors were calculated using logistic regression. Hierarchical clustering on principal component (HCPC) method was used to identify clusters of morphological features. Proportional risk contribution (PRC) of these morphological features in the context of other risk factors of hip OA was estimated using receiver operating characteristic (ROC) analysis.

Results All morphological features showed right-left symmetry in controls. Each feature was ~~independently~~ associated with hip OA after adjusting for age, gender, and body mass index (BMI). Increased sourcil angle (SA) had the strongest association (OR: 6.93, 95%CI 5.16 to 9.32). Three clusters were identified. The PRC varied between individual features, as well as between clusters. ~~The PRC for combined morphological features~~ It was 35% (95%CI 31 to 40%) for all 14 morphological features, compared to 21% (95%CI 19 to 24%) for all other well-established risk factors.

Conclusions Constitutional morphological variation strongly associates with hip OA development and may explain much of its heritability. Relevant morphological measures can be assessed readily on standard radiographs to help predict risk of

hip OA. Prospective studies are required to provide further support for~~confirm~~ causality.

Keywords Hip osteoarthritis; Morphology; Sourcil angle; Heritability

INTRODUCTION

Osteoarthritis (OA) is a common complex disorder with multiple interactions between genetic, constitutional and environmental risk factors.[1] Strong genetic contribution to hip OA is supported by 60% heritability in a classic twin study in women~~ with radiographic hip OA~~,[2] and a five-fold increased prevalence of radiographic hip OA in siblings of people with hip OA requiring total hip replacement.[3] Morphological variation of the hip and pelvis is also emphasised as a potentially important constitutional risk factor for hip OA.[4-9]

It is recognised that rare monogenic abnormalities of bone shape such as severe acetabular dysplasia can cause young-onset hip OA.[10] However, it is possible that more subtle variations in joint and bone morphology, resulting from multiple common gene polymorphisms, may impose biomechanical insult and partially explain genetic predisposition in common hip OA. This is supported by studies showing that mild hip dysplasia,[5] non-spherical femoral head ("pistol grip" deformity)[4, 11] and high or low neck shaft angle[4, 10] are relatively common and ~~independently~~ associate with increased risk of hip OA. Studies using statistical shape modelling also report associations between variations in proximal femoral shape and risk of hip OA.[12-14] It is also noteworthy that three genetic associations with large joint OA confirmed with genome-wide significance (GDF5,[15, 16] FRZB[17, 18] and MCF2L[19]) are involved in early skeletal growth ~~and may help determine joint morphology~~. Furthermore, hip OA frequently occurs

without OA at other sites,[20, 21] supporting the importance of local factors in its development.

Previously we used the Genetics of OA and Lifestyle (GOAL) database to demonstrate that mild acetabular dysplasia (assessed by acetabular depth (AD), ~~and~~ centre edge angle (CEA)),[5] non-spherical femoral head shape (assessed by femoral head to femoral neck ratio (FHNR))[4] and both high and low neck shaft angle (NSA)[4] ~~independently~~ associate with hip OA. Because morphological features can be secondary to hip OA, we undertook measures of the unaffected hip of people with unilateral hip OA under the assumption that this reflects the constitutional morphology of the affected hip prior to hip OA development. This assumption was supported by right-left symmetry ~~of the studied features~~ in normal controls without hip OA.[4, 5] However, these and other morphological features may relate to, or interact with each other to increase risk of hip OA. In addition, the proportional risk contribution (PRC) of local morphological features in the context of overall risk of developing hip OA is unknown. The objectives of this study were to ~~use the GOAL database to~~: (1) examine 10 additional morphological features of the hip and pelvis that can be measured readily on plain radiographs, for right-left symmetry and age variation; and (2) measure their risk contributions, both individually and in combination with others ~~reported measures~~, and in the context of other recognised risk factors for hip OA. The new features we assessed were: femoral head diameter (FHD);[22] femoral neck length (FNL)[23] and femoral neck width (FNW);[6, 23, 24] femoral head offset (FHO);[25] femoral outer shaft diameter (OSD) and inner shaft diameter (ISD); sourcil angle (SA);[26, 27] mid-centre distance (MCD); and pelvic width (PW) and pelvic height (PH).

METHODS

Cases and controls

All participants (566 unilateral hip OA cases and 1108 non-OA controls) were selected from the Nottingham GOAL database, which was ~~established primarily for a~~ hospital-based case-control ~~studies~~ study to investigate genetic associations and gene-environmental interaction in people with knee or hip OA. 59% of unilateral hip OA individuals had right hip OA and 41% had left hip OA. The laterality of unaffected hips was matched in the same ratio to controls. All participants were Caucasian and aged between 45 and 80 years. Details of recruitment, exclusion criteria, questionnaire, and clinical and radiographic assessments of participants have been published previously.[4, 5, 28, 29]

Radiographic assessment of hips

A standard protocol was used to obtain antero-posterior (AP) non weight-bearing radiographs of the pelvis with the participants supine and feet internally rotated 10°.[4] All radiographs were scored previously by a single observer for radiographic features of hip OA, which included minimum joint space width (JSW).[4, 5] Radiographic hip OA was defined as JSW ≤2.5 mm.[30] Those participants with unilateral hip OA, that is no symptoms and normal radiographic appearance (JSW >2.5 mm and no other OA features) in the contralateral hip, were included for morphological assessment of the unaffected hip. The asymptomatic control group (all with JSW >2.5 mm and no radiographic features of OA in either hip) underwent morphological assessment of both hips. These controls also had no symptoms or radiographic evidence (Kellgren Lawrence grade <2) of knee OA. The anatomical

indices that were measured are described in table 1 and figure 1. Data for four (AD, CEA, FHNR and NSA) of these features had previously been scored by a single observer with good reproducibility,[4, 5] and were re-used in the current study. The ten other new features were measured both in normal controls and participants with unilateral hip OA by a different single trained reader (HA) using HIPAX software (Hipax, Vorstetten, Germany). As in our previous studies, this reader was blind to participant identifiers, demographic and clinical information.

Patient and public involvement

There was no patient and public involvement for this study.

Table 1 Descriptions of the morphological landmarks and measurements of the hip joint and pelvic bones examined in this study

Morphological measurements	Descriptions
Centre of femoral head	The equatorial centre of the head was determined by fitting it's geometry within a concentric circle on the Perspex template of the Lequesne arthrometer.[48]
Femoral shaft axis	Two points in the centre of the femoral shaft were measured to be equidistant from the medial and lateral borders, one at the lowest part of the femoral shaft and the other one below the lesser trochanter. The line connecting these two points described the axis of the femoral shaft.
Femoral neck axis	The midpoint of the shortest segment of the femoral neck was measured to be equidistant from the superior and inferior borders. A line passing through the centre of the femoral head and the midpoint of the femoral neck described this axis.
Acetabular depth (AD)	The distance between the deepest point of the acetabular roof to a line drawn between the edge of the articular surface of the acetabulum and the upper corner of the symphysis pubis on the same side.[7]
Centre edge angle (CEA)	The angle between the line from the femoral head centre to the lateral aspect of the acetabulum, and a vertical line drawn from the centre of the femoral head at right angles to the line joining the two femoral head centres.[49]
Femoral head to femoral neck ratio (FHNR)	The ratio of femoral head diameter divided by femoral neck width.[4]
Neck shaft angle (NSA)	The angle between the femoral shaft axis and femoral neck axis.
Femoral head diameter (FHD)	The maximum diameter was described by drawing a line through the central point of the femoral head and at a right angle to the femoral neck axis line.
Femoral neck width (FNW)	This was the minimum femoral neck diameter, determined by drawing a line at the narrowest point of the femoral neck and at a right angle to the femoral neck axis.
Femoral neck length (FNL)	The distance from the defined centre of the femoral head to the intersection of the femoral neck axis and femoral shaft axis.
Outer shaft diameter of the femur (OSD)	This was defined as the full diameter of the femoral shaft, which was made at the level of half of the femoral head diameter, distal to the lesser trochanter.
Inner shaft diameter of the femur (ISD)	This was measured at the level of half of the head diameter distal to the lesser trochanter. This measurement represents the thickness of the medullary canal of the femoral bone.
Mid-centre distance (MCD)	The distance from the centre of the femoral head to the midline of the pelvic X-ray and perpendicular to this midline point.
Sourcil angle (SA)	The angle formed between a line extending from the medial to the lateral edge of the sourcil and a horizontal line.[27]
Femoral head offset (FHO)	The distance from the centre of the femoral head to the axis of the femoral shaft in a right angle.
Pelvic width (PW)	The widest diameter of the pelvic bone on the radiograph.
Pelvic height (PH)	The greatest height of the pelvic bone at the centre of the pelvis on the radiograph.

Statistical analysis

The intra-observer reproducibility of measuring the 10 new morphological features was assessed using a random sample of 30 pelvis radiographs on three occasions (beginning, middle and end of study). Inter-observer reproducibility was assessed by measuring 30 pelvis radiographs for 2 previously assessed measures (NSA and FHNR) and comparing results to those of the previous readers.[4] Intra-class correlation coefficient (ICC) was used to determine reproducibility.

Symmetry of the morphological measurements was determined using paired t-test and minimal detectable change (MDC) in the control group.[31] ~~To determine the difference, a paired-t test in the same group and an independent t-test between two different groups were used for~~ The difference between groups was determined using t-test (continuous data~~),~~ or ~~whereas~~ χ^2 test ~~was used for~~ (categorical data). Correlations between the measurements ~~and other parameters~~ were examined using Pearson correlation coefficient. The dose-response relationship of individual morphological measurements in tertiles and risk of OA was examined ~~(graded risk)~~. ~~We used multivariable l~~Logistic regression model was used to calculate ~~adjusted~~ odds ratio (OR) and 95% confidence intervals (CI) adjusting for confounding factors such as age, gender and body mass index (BMI).

Cluster analysis was undertaken using the hierarchical clustering on principal component (HCPC) method to examine clusters of morphological measurements. ~~HCPC allows combination of two different statistical methods such as hierarchical clustering (HC) and principal component analysis (PCA) for clustering. PCA is primarily used for dimension reduction, whereas HC clusters the population. Firstly, PCA was performed followed by HC using squared Euclidean distance and the~~

~~Ward linkage method (between the groups).~~ HCPC was done using "factoextra" and "FactoMineR" packages in R.[32] Distribution of clusters was plotted in the factor map.

The PRC was estimated using receiver operating characteristic (ROC) curves where areas under the curve (AUC) were proportionalised according to risk factors.[33] Firstly, we built the full risk model with all risk factors available in a ROC curve (AUC_f). The full risk model included established risk factors such as age, gender, weight, height, BMI, calcaneal bone mineral density (BMD), finger nodes in at least two rays of each hand, type 3 pattern of index to ring finger (2D:4D) ratio, history of hip injury, manual occupation,[4, 29, 34] and all 14 morphological features (i.e. both the newly assessed and previously measured features in GOAL). Secondly, we removed the risk factor(s) of interest to examine the contribution of the risk factor(s) removed through the reduction of the ROC curve, i.e., the partial AUC (AUC_p). Thirdly we calculated the PRC using the following formula: $PRC=(AUC_f - AUC_p) / (AUC_f – 0.5)$, where 0.5 is the AUC under the diagonal line of the ROC curve indicating no discrimination at all by all included risk factors.[33] Data were analysed using STATA V.15 and R v.3.5. A significance level of $p <0.05$ was set for all analyses.

RESULTS

Characteristics of the study participants

Characteristics of study participants are shown in table 2. Of 1674 participants, 566 had unilateral hip OA (cases) and 1108 had no hip OA (normal controls). Gender, height and ~~prevalence of~~ manual occupation were similar ~~in each~~ between groups,

but cases were older and had higher weight, BMI and BMD than controls. Prevalence of nodal hand OA, type 3 pattern 2D:4D finger ratio, and frequency of self-reported hip injury were also higher in the OA group.

Table 2 Characteristics of the study participants

	Unilateral hip OA (n=566)	**Non-OA controls (n=1108)**
Age (years)	67.5 ± 7.2	64.2 ± 8.4**
Women (%)	47.9	46.3
BMI (kg/m^2)	29.3 ± 5.0	27.5 ± 4.6**
Weight (kg)	81.1 ± 16.4	76.9 ± 15.1**
Height (cm)	166.1 ± 9.4	166.9 ± 9.2
Calcaneal BMD	0.9 ± 1.3	0.7 ± 1.2**
Finger nodes (%)	23.1	11.6**
Type 3 2D:4D ratio (%)	41.3	34.2*
History of hip injury (%)	7.1	1.6**
Manual occupation (%)	36.9	33.9

Mean ± SD or prevalence are shown.

*p <0.05, **p <0.01

BMD, bone mineral density; BMI, body mass index; OA, osteoarthritis.

Repeatability of measurements

In addition to the excellent reproducibility of the four features reported previously,[4, 5] the 10 new features had good intra-observer agreement ~~at each of~~ across the three time points, the ICCs ranging from 0.84 to 0.97 for all features (p <0.05). There was also good agreement between the two readers for NSA and FHNR with ICCs of 0.87 and 0.85 respectively (p <0.05).

Symmetry and age association in non-OA controls

In the non-OA control group the paired t-test showed that mean differences between left and right sides for most measurements were not statistically significant except for AD, CEA, ISD and MCD. However, the magnitude of these differences was ~~small, and was~~ less than MDC_{90} (~~see~~ online supplementary ~~table~~ Table S1). While age was associated with most morphological features on the left and right, it was not associated with symmetry, i.e., the difference between left and right (~~see~~ online supplementary ~~table~~ Table S2).

Risk of hip OA

Table 3 represents the ~~odds ratio~~OR of hip OA associated with individual morphological measures. ~~Analysis was~~After adjust~~mented~~ for age, gender and BMI, ~~as the confounders showed that~~ the risk of hip OA ~~was~~ increased as the tertiles for AD, CEA, FHD, FHNR, FNL, ISD, OSD, PW decreased. In contrast, SA showed a positive dose response, the risk of hip OA being 7 times higher for Tertile 3 versus Tertile 1 (OR: 6.93, 95%CI 5.16 to 9.32, p <0.01).

FNW, MCD, FHO, PH and NSA showed a U-shape association with hip OA. Using Tertile 2 as the referent, the results showed that either the smaller or larger of these measures were associated with increased risk of OA. ~~Larger measurements of FNW and MCD but smaller measurements of FHO and PH appear to increase the risk of hip OA. Whereas~~ For example, ~~both~~ either high ~~and~~ or low NSA ~~each~~ associated with greater risk of hip OA, ORs being 1.50 (95% CI 1.15 to 1.96) and 1.36 (95% CI 1.05 to 1.75), respectively. The results ~~of relative risk of hip OA due to individual morphological measures stratified~~ by gender are shown in supplementary table S3 (online supplementary Table S3).

Table 3 Morphological features and association with hip OA

		Frequency (%)		OR (95%CI)	
		Cases	Controls	Crude	Adjusted
Acetabular depth	T1	273 (48.23)	285 (25.75)	1 (referent)	1 (referent)
	T2	164 (28.98)	396 (35.77)	0.43 (0.33-0.56)**	0.45 (0.35-0.59)**
	T3	129 (22.79)	426 (38.48)	0.31 (0.24-0.41)**	0.30 (0.23-0.39)**
	P trend			<0.001	
Centre edge angle	T1	290 (51.24)	277 (25.00)	1 (referent)	1 (referent)
	T2	163 (28.80)	443 (39.98)	0.35 (0.27 to 0.45)**	0.33 (0.26 to 0.43)**
	T3	113 (19.96)	388 (35.02)	0.27 (0.21 to 0.36)**	0.23 (0.17 to 0.30)**
	P trend			<0.001	
Femoral head diameter	T1	210 (37.10)	348 (31.41)	1 (referent)	1 (referent)
	T2	172 (30.39)	386 (34.84)	0.74 (0.58 to 0.95)*	0.58 (0.43 to 0.79)**
	T3	184 (32.51)	374 (33.75)	0.81 (0.64 to 1.04)	0.57 (0.39 to 0.84)**
	P trend			0.100	
Femoral head to femoral neck ratio	T1	239 (42.23)	326 (29.48)	1 (referent)	1 (referent)
	T2	191 (33.75)	380 (34.36)	0.68 (0.54 to 0.87)**	0.65 (0.50 to 0.84)**
	T3	136 (24.03)	400 (36.17)	0.46 (0.35 to 0.60)**	0.41 (0.31 to 0.56)**
	P trend			<0.001	
Femoral neck length	T1	217 (38.75)	321 (30.51)	1 (referent)	1 (referent)
	T2	178 (31.79)	359 (34.13)	0.73 (0.57 to 0.94)*	0.71 (0.55 to 0.93)*
	T3	165 (29.46)	372 (35.36)	0.65 (0.50 to 0.84)**	0.64 (0.48 to 0.83)**
	P trend			0.001	
Inner shaft diameter	T1	214 (39.05)	314 (31.56)	1 (referent)	1 (referent)
	T2	195 (35.58)	318 (31.96)	0.89 (0.70 to 1.15)	0.79 (0.60 to 1.02)
	T3	139 (25.36)	363 (36.48)	0.56 (0.43 to 0.73)**	0.44 (0.33 to 0.58)**
	P trend			<0.001	
Outer shaft diameter	T1	201 (36.68)	313 (32.86)	1 (referent)	1 (referent)
	T2	176 (32.12)	332 (33.37)	0.86 (0.67 to 1.11)	0.68 (0.51 to 0.90)**
	T3	171 (31.20)	336 (33.77)	0.83 (0.64 to 1.07)	0.60 (0.44 to 0.82)**
	P trend			0.143	
Pelvic width	T1	174 (37.26)	346 (31.77)	1 (referent)	1 (referent)
	T2	148 (31.69)	370 (33.98)	0.79 (0.61 to 1.03)	0.70 (0.53 to 0.92)*
	T3	145 (31.05)	373 (34.25)	0.77 (0.59 to 1.00)	0.60 (0.45 to 0.79)**
	P trend			0.054	
Sourcil angle	T1	90 (16.27)	464 (41.95)	1 (referent)	1 (referent)
	T2	158 (28.57)	394 (35.62)	2.06 (1.53 to 2.77)**	2.11 (1.55 to 2.86)**
	T3	305 (55.15)	248 (22.42)	6.34 (4.66 to 8.62)**	6.93 (5.16 to 9.32)**
	P trend			<0.001	
Femoral head offset	T1	217 (38.75)	321 (30.69)	1.57 (1.22 to 2.03)**	1.67 (1.28 to 2.19)**
	T2	160 (28.57)	373 (35.66)	1 (referent)	1 (referent)
	T3	183 (32.68)	352 (33.65)	1.21 (0.93 to 1.56)	1.19 (0.91 to 1.56)
	P trend			NA	
Femoral neck width	T1	184 (32.51)	377 (34.03)	1.04 (0.81 to 1.33)	1.01 (0.73 to 1.37)
	T2	178 (31.45)	378 (34.12)	1 (referent)	1 (referent)
	T3	204 (36.04)	353 (31.86)	1.22 (0.96 to 1.57)	1.34 (1.01 to 1.79)*
	P trend			NA	
Mid-centre distance	T1	172 (30.39)	386 (34.84)	0.99 (0.77 to 1.28)	1.03 (0.79 to 1.34)
	T2	173 (30.57)	385 (34.75)	1 (referent)	1 (referent)
	T3	221 (39.05)	337 (30.42)	1.46 (1.14 to 1.87)**	1.43 (1.11 to 1.85)**
	P trend			NA	
Pelvic height	T1	145 (38.87)	320 (31.34)	1.45 (1.08 to 1.94)	1.51 (1.09 to 2.07)*
	T2	111 (29.76)	355 (34.77)	1 (referent)	1 (referent)
	T3	117 (31.37)	346 (33.89)	1.08 (0.80 to 1.46)	1.05 (0.75 to 1.47)
	P trend			NA	
Neck shaft angle	T1	209 (36.99)	366 (33.18)	1.40 (1.09 to 1.78)**	1.36 (1.05 to 1.75)*
	T2	176 (31.15)	431 (39.08)	1 (referent)	1 (referent)
	T3	180 (31.86)	306 (27.74)	1.44 (1.11 to 1.85)**	1.50 (1.15 to 1.96)**
	P trend			NA	

Logistic regression was adjusted for age, gender and body mass index. For femoral head offset, femoral neck width, mid-centre distance, pelvic height and neck shaft angle, Tertile 2 was used as referent.

*p <0.05, **p <0.01.
NA, not applicable; OA, osteoarthritis; OR, odds ratio; T, tertile.

Clusters of morphological features

The 14 morphological features were associated with each other (online supplementary Table S4). Three clusters were identified within the 14 morphological features (figure 2). Cluster 1 included FHNR (non-spherical femoral head). Cluster 2 included SA, NSA, FNW, and MCD. Cluster 3 included AD and CEA (i.e. mild acetabular dysplasia), FHD, FNL, OSD, ISD, FHO, PW and PH. The contribution of the individual morphological features to each cluster is shown in supplementary table ~~S4~~S5 (online supplementary Table S5).

Proportional risk contribution

~~Table 4 presents the results of AUC and PRC of multivariate models.~~ The AUC for the full model including all risk factors was 0.81 (95%CI 0.79 to 0.83), of which 34.95% (95%CI 30.93 to 39.65) was explained by the 14 morphological features, and 21.36% (95%CI 18.62 to 24.21) was explained by all other established risk factors (Table 4). Of the 14 morphological features, SA had the highest contribution (PRC=7.12%, 95% CI 6.01 to 8.07). The PRC of cluster 1, 2 and 3 was 2.26% (95%CI 1.80 to 2.46), 7.12% (95%CI 6.31 to 8.42) and 7.44% (95%CI 6.61 to 8.42), respectively.

Table 4 AUC and PRC of multivariate models

	AUC	95%CI	PRC (%)	95%CI

Full model	0.809	0.785 to 0.833	100	
Partial model without other risk factors	0.743	0.716 to 0.771	21.359	18.619 to 24.211
Partial model without morphological features	0.701	0.672 to 0.730	34.951	30.931 to 39.649
Partial model without SA	0.787	0.762 to 0.813	7.120	6.006 to 8.070
Partial model without FHNR	0.802	0.778 to 0.827	2.265	1.802 to 2.456
Partial model without ISD	0.803	0.777 to 0.827	1.942	1.802 to 2.807
Partial model without CEA	0.804	0.780 to 0.828	1.618	1.502 to 1.754
Partial model without FHD	0.805	0.780 to 0.829	1.294	1.201 to 1.754
Partial model without FHO	0.806	0.782 to 0.830	0.971	0.901 to 1.053
Partial model without FNW	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without FNL	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without NSA	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without MCD	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without PW	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without AD	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without PH	0.809	0.785 to 0.833	0	0
Partial model without OSD	0.809	0.785 to 0.833	0	0
Partial model without cluster 1	0.802	0.778 to 0.827	2.265	1.802 to 2.456
Partial model without cluster 2	0.787	0.761 to 0.812	7.120	6.306 to 8.421
Partial model without cluster 3	0.786	0.761 to 0.811	7.443	6.606 to 8.421

The ~~Full~~ full model included other risk factors and morphological features.

Other risk factors included age, gender, weight, height, body mass index, calcaneal bone mineral density, finger nodes, type 3 2D:4D finger ratio, history of hip injury, and manual occupation.

Morphological features included AD, CEA, FHNR, NSA, FHD, FNL, FNW, FHO, OSD, ISD, MCD, SA, PW, and PH.

AD, acetabular depth; AUC, areas under the curve; CEA, centre edge angle; FHD, femoral head diameter; FHNR, femoral head to femoral neck ratio; FHO, femoral head offset; FNL, femoral neck length; FNW, femoral neck width; ISD, inner shaft diameter; MCD, mid-centre distance; NSA, neck shaft angle; OSD, outer shaft diameter; PH, pelvic height; PRC, proportional risk contribution; PW, pelvic width; SA, sourcil angle.

DISCUSSION

This is the first large study to assess 14 hip and pelvis morphological features, individually and in composite, and their contribution to the risk of hip OA. The right-left symmetry of all measures demonstrated in the normal controls supports the assumption that the unaffected hip of unilateral hip OA cases represents the pre-OA morphology of the affected hip.[4, 5] Although age associated with some morphological features, it was not associated with the symmetry, i.e., the difference between left and right. The main findings are: (1) all 14 hip morphological features associated with increased risk of hip OA independent of age, gender and BMI, with larger SA being the strongest risk factor; (2) two patterns of associations were ~~identified~~ observed - dose response ~~(single direction for risk)~~ and U-shaped curve response (both higher and lower values associating with increased risk); (3) three clusters were identified (figure 2); and (4) the total contribution of the 14 morphological features to risk of hip OA was greater (35%) than the sum of other recognised risk factors (21%).

Our findings of small FHD, wide FNW, and short FNL as risk factors for hip OA concur with the ~~conclusions of~~ previous ~~less robust~~ studies.[6, 11, 14, 22-24] Biomechanically many of these features have a plausible aetiological mechanism. For example, small FHD and/or wide FNW may both encourage “cam type” impingement of the proximal femur on the acetabulum,[25] as does a non-spherical femoral head.[35] Furthermore, a small femoral head has a smaller surface area for load transmission, thus the force per unit area may be higher and cause increased joint tissue stress. On the other hand, a wide FNW may encourage “pincer-type” impingement of the femoral head-neck junction against the acetabular rim.[25] The explanation for smaller measurements of both OSD and

ISD could relate to the inverse relationship between osteoporosis and OA.[36] Low FHO and wide MCD necessitates a greater abductor muscles force to maintain body balance[37] and the resultant greater stress on the hip may predispose to OA. The association of AD, CEA, FHNR and NSA with hip OA were reported and discussed in our previous studies.[4, 5]

Importantly, our findings indicated that of the 14 features studied, increased SA was the strongest individual risk factor for hip OA and showed the highest PRC. Departure of the acetabular sourcil orientation from the horizontal plane will negatively affect the equilibrium of forces across the hip joint,[26] and with bigger SA the femoral head is less covered by the acetabulum, which is consistent with the negative correlation between SA and CEA, so the unit force per surface area is increased. In previous studies, SA related more than other indices with development of OA[38, 39] and it is considered a more precise measure for mild dysplasia than CEA.[40] Therefore overall, more vertical~~wide~~ SA is a major morphological risk factor and may be used as a single surrogate marker in clinical practice to assess morphological risk of hip OA.

~~By using the HCPC method, t~~The 14 morphological features were assigned into three clusters. Cluster analysis may uncover relationships between measures. For example, in a case with high NSA (coxa valga), the increased inclination of the weight-bearing surface of the acetabulum (assessed by SA) can increase the compressive forces on the joint and lower the threshold for the onset of OA.[41] The coexistence of less acetabular coverage and shorter femoral neck were reported in one hip shape mode (HSM) derived by statistical shape modelling which positively associated with incident hip OA.[14] But in another HSM, more

coverage of the femoral head and wider PW were found to associate with OA,[14] which is inconsistent with our findings. The higher proportion of women and the different definition of PW in that study[14] should be considered when comparing the results with ours. However, the possible explanation for the associations observed for PW and PH are open to speculation. Further prospective study for causality is still required.

The risk contribution of the 14 morphological features (PRC=35%, 95%CI 31% to 40%) was significantly larger than other established risk factors including age, gender, BMI, history of hip injury, physical occupation, nodal OA, and 2D:4D finger ratio (PRC=21%, 95%CI 19% to 24%). This suggests that local morphological risk factors may contribute more than systemic factors to development of hip OA. The results align with the literature for incidence and progression of hip OA[42, 43] and may be explained by shared single nucleotide polymorphisms (SNPs) between OA and hip shape.[44, 45]

There are several caveats to this study. Firstly, this was a cross-sectional case-control study. Whether these morphological features cause hip OA requires a prospective population-based study. Although we used the unaffected hips of people with unilateral hip OA to determine constitutional pre-OA shape, it is possible that the morphology in the unaffected hip had adapted to altered gait pattern and abnormal loading caused by hip OA on the other side[46], in accord with Wolff's law which states that bones adapt their mass and shape in response to loading.[47] In addition, the apparently normal hips could have undergone bone remodelling due to early OA before other features such as cartilage loss were evident.[23] Furthermore, we did not account for presence of symptoms or

structural OA in other lower limb joints (knees, ankles, feet) of cases which may have affected biomechanical stress on the unaffected hip. Also ~~we based absence of structural hip OA on~~ radiographic assessment ~~alone, which~~ is less sensitive to early OA changes than other imaging modalities, such as magnetic resonance imaging (MRI). We also found that some morphological features changed with age in the control group. Although symmetry was unaffected by age, we cannot be certain that the current features measured in unaffected hips of cases would fully reflect the pre-OA morphology on the affected side before ~~if~~ it developed OA many years ago~~before~~. Secondly, although we observed symmetry of morphological features in the non-disease control group, this does not exclude the possibility of asymmetry in the cases before they developed unilateral hip OA, or the presence of additional unidentified risk factors on the affected side, or protective factors on the unaffected side. This again requires a prospective cohort study to confirm whether the pre-disease morphological features are truly symmetrical between the left and right sides, and to determine how many people with the features of interest subsequently go on to develop bilateral hip OA. Thirdly, the GOAL database includes only Caucasian participants so the generalisability of the findings is limited and requires study in other populations. Fourthly~~Thirdly~~, we undertook measurements on a single two-dimensional standard AP pelvis radiograph without other views. Although this is conventional and readily applicable to large-scale population studies, it has major limitations for identifying true morphological variations in 3-dimensions. A further caveat is that measurement of morphological features was not undertaken blind of hip OA status, since pelvic images were saved on software (HIPAX) that prevents image cropping. Furthermore, despite the use of a standardised protocol, variations in positioning may have affected some

assessments, for example due to anteversion or rotation secondary to pain or deformity in the affected hip.

In conclusion, we have confirmed 14 morphological features that associate with increased risk of hip OA. The risk contribution of these features is more than that of other conventional risk factors combined. SA is the strongest risk factor and could be used as a single surrogate measure of morphological risk in large epidemiological studies or in clinical settings. Future prospective studies are required to ~~definitively confirm~~provide further support for causality between these features and OA.

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Contributors Study design: HA, QJ, WZ, MD. Data analysis: HA, QJ, SS, AS, WZ, MD. All authors were responsible for interpretation of the data and for drafting, revising and approving the final submitted manuscript.

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Competing interest MD reports grants from AstraZeneca and Versus Arthritis for this study, and personal fees from Grunenthal, Mallinckrodt outside the submitted work; WZ reports personal fees from Regeneron Inc outside the submitted work.

Patient and public involvement No.

Patient consent for publication Not required.

Ethics approval The GOAL study was conducted with the approval of the Nottingham Research Ethics Committee.

Provenance and peer review Not commissioned, to be externally peer reviewed.

Data availability statement Data are available upon reasonable request by contacting the corresponding author.

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Figure legend~~LEGEND~~

Figure 1 Diagram showing the morphological measurements of the hip and pelvic bones: AD, acetabular depth; CEA, centre edge angle; FHD, femoral head diameter; FHO, femoral head offset; FNL, femoral neck length; FNW, femoral neck width; ISD, inner shaft diameter; MCD, mid-centre distance; NSA, neck shaft angle; OSD, outer shaft diameter; PH, pelvic height; PW, pelvic width; SA, sourcil angle.

Figure 2 Diagram showing the morphological features were assigned into 3 clusters: Cluster 1 includes FHNR; cluster 2 includes SA, NSA, FNW and MCD; and cluster 3 includes AD, CEA, FHD, FNL, OSD, ISD, FHO, PW, PH.

AD, acetabular depth; CEA, centre edge angle; FHD, femoral head diameter; FHNR, femoral head to femoral neck ratio; FHO, femoral head offset; FNL, femoral neck length; FNW, femoral neck width; ISD, inner shaft diameter; MCD, mid-centre distance; NSA, neck shaft angle; OSD, outer shaft diameter; PH, pelvic height; PW, pelvic width; SA, sourcil angle.

Title: Constitutional morphological features and risk of hip osteoarthritis: a case control study using standard radiographs

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Key messages

What is already known about this subject?

Several constitutional variants of hip joint shape associate with increased risk of hip osteoarthritis (OA). However, whether these relate to each other, and the overall contribution of morphological variants to risk of hip OA are unknown.

What does this study add?

Fourteen morphological features of the hip and pelvis, ten of which had not been studied before, were shown to associate with hip OA after adjusting for age, gender and body mass index (BMI). The strongest association was with more vertical sourcil angle (SA). Three clusters of features were identified, and the proportional risk contribution (PRC) to hip OA was 35% for the combined variants, compared to 21% for other recognised risk factors combined.

How might this impact on clinical practice or future developments?

Although prospective studies are required to provide further support for causality, morphological variation is a strong risk factor for hip OA and may partially explain its heritability. SA measured on standard radiographs may be used as a single surrogate marker to assess morphological risk of hip OA.

ABSTRACT

Objectives To evaluate the risk of association with hip osteoarthritis (OA) of 14 morphological features measured on standard antero-posterior pelvis radiographs.

Methods A case-control study of 566 symptomatic unilateral hip OA cases and 1108 controls without hip OA, using the Genetics of Osteoarthritis and Lifestyle (GOAL) database. Unaffected hips of cases were assumed to reflect pre-OA morphology of the contralateral affected hip. Odds ratios (ORs) with 95% confidence interval (CI) adjusted for confounding factors were calculated using logistic regression. Hierarchical clustering on principal component (HCPC) method was used to identify clusters of morphological features. Proportional risk contribution (PRC) of these morphological features in the context of other risk factors of hip OA was estimated using receiver operating characteristic (ROC) analysis.

Results All morphological features showed right-left symmetry in controls. Each feature was associated with hip OA after adjusting for age, gender, and body mass index (BMI). Increased sourcil angle (SA) had the strongest association (OR: 6.93, 95%CI 5.16 to 9.32). Three clusters were identified. The PRC varied between individual features, as well as between clusters. It was 35% (95%CI 31 to 40%) for all 14 morphological features, compared to 21% (95%CI 19 to 24%) for all other well-established risk factors.

Conclusions Constitutional morphological variation strongly associates with hip OA development and may explain much of its heritability. Relevant morphological measures can be assessed readily on standard radiographs to help predict risk of hip OA. Prospective studies are required to provide further support for causality.

Keywords Hip osteoarthritis; Morphology; Sourcil angle; Heritability

INTRODUCTION

Osteoarthritis (OA) is a common complex disorder with multiple interactions between genetic, constitutional and environmental risk factors.[1] Strong genetic contribution to hip OA is supported by 60% heritability in a classic twin study in women,[2] and a five-fold increased prevalence of radiographic hip OA in siblings of people with hip OA requiring total hip replacement.[3] Morphological variation of the hip and pelvis is also emphasised as a potentially important constitutional risk factor for hip OA.[4-9]

It is recognised that rare monogenic abnormalities of bone shape such as severe acetabular dysplasia can cause young-onset hip OA.[10] However, it is possible that more subtle variations in joint and bone morphology, resulting from multiple common gene polymorphisms, may impose biomechanical insult and partially explain genetic predisposition in common hip OA. This is supported by studies showing that mild hip dysplasia,[5] non-spherical femoral head ("pistol grip" deformity)[4, 11] and high or low neck shaft angle[4, 10] are relatively common and associate with increased risk of hip OA. Studies using statistical shape modelling also report associations between variations in proximal femoral shape and risk of hip OA.[12-14] It is also noteworthy that three genetic associations with large joint OA confirmed with genome-wide significance (GDF5,[15, 16] FRZB[17, 18] and MCF2L[19]) are involved in early skeletal growth. Furthermore, hip OA frequently occurs without OA at other sites,[20, 21] supporting the importance of local factors in its development.

Previously we used the Genetics of OA and Lifestyle (GOAL) database to demonstrate that mild acetabular dysplasia (assessed by acetabular depth (AD),

centre edge angle (CEA)),[5] non-spherical femoral head shape (assessed by femoral head to femoral neck ratio (FHNR))[4] and both high and low neck shaft angle (NSA)[4] associate with hip OA. Because morphological features can be secondary to hip OA, we undertook measures of the unaffected hip of people with unilateral hip OA under the assumption that this reflects the constitutional morphology of the affected hip prior to hip OA development. This assumption was supported by right-left symmetry in normal controls without hip OA.[4, 5] However, these and other morphological features may relate to, or interact with each other to increase risk of hip OA. In addition, the proportional risk contribution (PRC) of local morphological features in the context of overall risk of developing hip OA is unknown. The objectives of this study were to: (1) examine 10 additional morphological features of the hip and pelvis that can be measured readily on plain radiographs, for right-left symmetry and age variation; and (2) measure their risk contributions, both individually and in combination with others, and in the context of other recognised risk factors for hip OA. The new features we assessed were: femoral head diameter (FHD);[22] femoral neck length (FNL)[23] and femoral neck width (FNW);[6, 23, 24] femoral head offset (FHO);[25] femoral outer shaft diameter (OSD) and inner shaft diameter (ISD); sourcil angle (SA);[26, 27] mid-centre distance (MCD); and pelvic width (PW) and pelvic height (PH).

METHODS

Cases and controls

All participants (566 unilateral hip OA cases and 1108 non-OA controls) were selected from the Nottingham GOAL database, which was a hospital-based case-

control study to investigate genetic associations and gene-environmental interaction in people with knee or hip OA. 59% of unilateral hip OA individuals had right hip OA and 41% had left hip OA. The laterality of unaffected hips was matched in the same ratio to controls. All participants were Caucasian and aged between 45 and 80 years. Details of recruitment, exclusion criteria, questionnaire, and clinical and radiographic assessments of participants have been published previously.[4, 5, 28, 29]

Radiographic assessment of hips

A standard protocol was used to obtain antero-posterior (AP) non weight-bearing radiographs of the pelvis with the participants supine and feet internally rotated 10°.[4] All radiographs were scored previously by a single observer for radiographic features of hip OA, which included minimum joint space width (JSW).[4, 5] Radiographic hip OA was defined as JSW ≤2.5 mm.[30] Those participants with unilateral hip OA, that is no symptoms and normal radiographic appearance (JSW >2.5 mm and no other OA features) in the contralateral hip, were included for morphological assessment of the unaffected hip. The asymptomatic control group (all with JSW >2.5 mm and no radiographic features of OA in either hip) underwent morphological assessment of both hips. These controls also had no symptoms or radiographic evidence (Kellgren Lawrence grade <2) of knee OA. The anatomical indices that were measured are described in table 1 and figure 1. Data for four (AD, CEA, FHNR and NSA) of these features had previously been scored by a single observer with good reproducibility,[4, 5] and were re-used in the current study. The ten other new features were measured both in normal controls and participants with unilateral hip OA by a different single trained reader (HA) using HIPAX

software (Hipax, Vorstetten, Germany). As in our previous studies, this reader was blind to participant identifiers, demographic and clinical information.

Patient and public involvement

There was no patient and public involvement for this study.

Table 1 Descriptions of the morphological landmarks and measurements of the hip joint and pelvic bones examined in this study

Morphological measurements	Descriptions
Centre of femoral head	The equatorial centre of the head was determined by fitting it's geometry within a concentric circle on the Perspex template of the Lequesne arthrometer.[48]
Femoral shaft axis	Two points in the centre of the femoral shaft were measured to be equidistant from the medial and lateral borders, one at the lowest part of the femoral shaft and the other one below the lesser trochanter. The line connecting these two points described the axis of the femoral shaft.
Femoral neck axis	The midpoint of the shortest segment of the femoral neck was measured to be equidistant from the superior and inferior borders. A line passing through the centre of the femoral head and the midpoint of the femoral neck described this axis.
Acetabular depth (AD)	The distance between the deepest point of the acetabular roof to a line drawn between the edge of the articular surface of the acetabulum and the upper corner of the symphysis pubis on the same side.[7]
Centre edge angle (CEA)	The angle between the line from the femoral head centre to the lateral aspect of the acetabulum, and a vertical line drawn from the centre of the femoral head at right angles to the line joining the two femoral head centres.[49]
Femoral head to femoral neck ratio (FHNR)	The ratio of femoral head diameter divided by femoral neck width.[4]
Neck shaft angle (NSA)	The angle between the femoral shaft axis and femoral neck axis.
Femoral head diameter (FHD)	The maximum diameter was described by drawing a line through the central point of the femoral head and at a right angle to the femoral neck axis line.
Femoral neck width (FNW)	This was the minimum femoral neck diameter, determined by drawing a line at the narrowest point of the femoral neck and at a right angle to the femoral neck axis.
Femoral neck length (FNL)	The distance from the defined centre of the femoral head to the intersection of the femoral neck axis and femoral shaft axis.
Outer shaft diameter of the femur (OSD)	This was defined as the full diameter of the femoral shaft, which was made at the level of half of the femoral head diameter, distal to the lesser trochanter.
Inner shaft diameter of the femur (ISD)	This was measured at the level of half of the head diameter distal to the lesser trochanter. This measurement represents the thickness of the medullary canal of the femoral bone.
Mid-centre distance (MCD)	The distance from the centre of the femoral head to the midline of the pelvic X-ray and perpendicular to this midline point.
Sourcil angle (SA)	The angle formed between a line extending from the medial to the lateral edge of the sourcil and a horizontal line.[27]
Femoral head offset (FHO)	The distance from the centre of the femoral head to the axis of the femoral shaft in a right angle.
Pelvic width (PW)	The widest diameter of the pelvic bone on the radiograph.
Pelvic height (PH)	The greatest height of the pelvic bone at the centre of the pelvis on the radiograph.

Statistical analysis

The intra-observer reproducibility of measuring the 10 new morphological features was assessed using a random sample of 30 pelvis radiographs on three occasions (beginning, middle and end of study). Inter-observer reproducibility was assessed by measuring 30 pelvis radiographs for 2 previously assessed measures (NSA and FHNR) and comparing results to those of the previous readers.[4] Intra-class correlation coefficient (ICC) was used to determine reproducibility.

Symmetry of the morphological measurements was determined using paired t-test and minimal detectable change (MDC) in the control group.[31] The difference between groups was determined using t-test (continuous data) or χ^2 test (categorical data). Correlations between the measurements were examined using Pearson correlation coefficient. The dose-response relationship of individual morphological measurements in tertiles and risk of OA was examined. Logistic regression model was used to calculate odds ratio (OR) and 95% confidence intervals (CI) adjusting for confounding factors such as age, gender and body mass index (BMI).

Cluster analysis was undertaken using the hierarchical clustering on principal component (HCPC) method to examine clusters of morphological measurements. HCPC was done using “factoextra” and “FactoMineR” packages in R.[32] Distribution of clusters was plotted in the factor map.

The PRC was estimated using receiver operating characteristic (ROC) curves where areas under the curve (AUC) were proportionalised according to risk factors.[33] Firstly, we built the full risk model with all risk factors available in a ROC curve (AUC_f). The full risk model included established risk factors such as age,

gender, weight, height, BMI, calcaneal bone mineral density (BMD), finger nodes in at least two rays of each hand, type 3 pattern of index to ring finger (2D:4D) ratio, history of hip injury, manual occupation,[4, 29, 34] and all 14 morphological features (i.e. both the newly assessed and previously measured features in GOAL). Secondly, we removed the risk factor(s) of interest to examine the contribution of the risk factor(s) removed through the reduction of the ROC curve, i.e., the partial AUC (AUC_p). Thirdly we calculated the PRC using the following formula: $PRC=(AUC_f - AUC_p) / (AUC_f – 0.5)$, where 0.5 is the AUC under the diagonal line of the ROC curve indicating no discrimination at all by all included risk factors.[33] Data were analysed using STATA V.15 and R v.3.5. A significance level of $p <0.05$ was set for all analyses.

RESULTS

Characteristics of the study participants

Characteristics of study participants are shown in table 2. Of 1674 participants, 566 had unilateral hip OA (cases) and 1108 had no hip OA (normal controls). Gender, height and manual occupation were similar between groups, but cases were older and had higher weight, BMI and BMD than controls. Prevalence of nodal hand OA, type 3 pattern 2D:4D finger ratio, and frequency of self-reported hip injury were also higher in the OA group.

Table 2 Characteristics of the study participants

	Unilateral hip OA (n=566)	Non-OA controls (n=1108)
Age (years)	67.5 ± 7.2	64.2 ± 8.4**
Women (%)	47.9	46.3
BMI (kg/m^2)	29.3 ± 5.0	27.5 ± 4.6**
Weight (kg)	81.1 ± 16.4	76.9 ± 15.1**
Height (cm)	166.1 ± 9.4	166.9 ± 9.2
Calcaneal BMD	0.9 ± 1.3	0.7 ± 1.2**
Finger nodes (%)	23.1	11.6**
Type 3 2D:4D ratio (%)	41.3	34.2*
History of hip injury (%)	7.1	1.6**
Manual occupation (%)	36.9	33.9

Mean ± SD or prevalence are shown.

*p <0.05, **p <0.01

BMD, bone mineral density; BMI, body mass index; OA, osteoarthritis.

Repeatability of measurements

In addition to the excellent reproducibility of the four features reported previously,[4, 5] the 10 new features had good intra-observer agreement across the three time points, the ICCs ranging from 0.84 to 0.97 for all features (p <0.05). There was also good agreement between the two readers for NSA and FHNR with ICCs of 0.87 and 0.85 respectively (p <0.05).

Symmetry and age association in non-OA controls

In the non-OA control group the paired t-test showed that mean differences between left and right sides for most measurements were not statistically significant except for AD, CEA, ISD and MCD. However, the magnitude of these

differences was less than MDC_{90} (online supplementary Table S1). While age was associated with most morphological features on the left and right, it was not associated with symmetry, i.e., the difference between left and right (online supplementary Table S2).

Risk of hip OA

Table 3 represents the OR of hip OA associated with individual morphological measures. After adjustment for age, gender and BMI, the risk of hip OA increased as the tertiles for AD, CEA, FHD, FHNR, FNL, ISD, OSD, PW decreased. In contrast, SA showed a positive dose response, the risk of hip OA being 7 times higher for Tertile 3 versus Tertile 1 (OR: 6.93, 95%CI 5.16 to 9.32, p <0.01).

FNW, MCD, FHO, PH and NSA showed a U-shape association with hip OA. Using Tertile 2 as the referent, the results showed that either the smaller or larger of these measures were associated with increased risk of OA. For example, either high or low NSA associated with greater risk of hip OA, ORs being 1.50 (95% CI 1.15 to 1.96) and 1.36 (95% CI 1.05 to 1.75), respectively. The results by gender are shown in supplementary table S3 (online supplementary Table S3).

Table 3 Morphological features and association with hip OA

		Frequency (%)		OR (95%CI)	
		Cases	Controls	Crude	Adjusted
Acetabular depth	T1	273 (48.23)	285 (25.75)	1 (referent)	1 (referent)
	T2	164 (28.98)	396 (35.77)	0.43 (0.33-0.56)**	0.45 (0.35-0.59)**
	T3	129 (22.79)	426 (38.48)	0.31 (0.24-0.41)**	0.30 (0.23-0.39)**
	P trend			<0.001	
Centre edge angle	T1	290 (51.24)	277 (25.00)	1 (referent)	1 (referent)
	T2	163 (28.80)	443 (39.98)	0.35 (0.27 to 0.45)**	0.33 (0.26 to 0.43)**
	T3	113 (19.96)	388 (35.02)	0.27 (0.21 to 0.36)**	0.23 (0.17 to 0.30)**
	P trend			<0.001	
Femoral head diameter	T1	210 (37.10)	348 (31.41)	1 (referent)	1 (referent)
	T2	172 (30.39)	386 (34.84)	0.74 (0.58 to 0.95)*	0.58 (0.43 to 0.79)**
	T3	184 (32.51)	374 (33.75)	0.81 (0.64 to 1.04)	0.57 (0.39 to 0.84)**
	P trend			0.100	
Femoral head to femoral neck ratio	T1	239 (42.23)	326 (29.48)	1 (referent)	1 (referent)
	T2	191 (33.75)	380 (34.36)	0.68 (0.54 to 0.87)**	0.65 (0.50 to 0.84)**
	T3	136 (24.03)	400 (36.17)	0.46 (0.35 to 0.60)**	0.41 (0.31 to 0.56)**
	P trend			<0.001	
Femoral neck length	T1	217 (38.75)	321 (30.51)	1 (referent)	1 (referent)
	T2	178 (31.79)	359 (34.13)	0.73 (0.57 to 0.94)*	0.71 (0.55 to 0.93)*
	T3	165 (29.46)	372 (35.36)	0.65 (0.50 to 0.84)**	0.64 (0.48 to 0.83)**
	P trend			0.001	
Inner shaft diameter	T1	214 (39.05)	314 (31.56)	1 (referent)	1 (referent)
	T2	195 (35.58)	318 (31.96)	0.89 (0.70 to 1.15)	0.79 (0.60 to 1.02)
	T3	139 (25.36)	363 (36.48)	0.56 (0.43 to 0.73)**	0.44 (0.33 to 0.58)**
	P trend			<0.001	
Outer shaft diameter	T1	201 (36.68)	313 (32.86)	1 (referent)	1 (referent)
	T2	176 (32.12)	332 (33.37)	0.86 (0.67 to 1.11)	0.68 (0.51 to 0.90)**
	T3	171 (31.20)	336 (33.77)	0.83 (0.64 to 1.07)	0.60 (0.44 to 0.82)**
	P trend			0.143	
Pelvic width	T1	174 (37.26)	346 (31.77)	1 (referent)	1 (referent)
	T2	148 (31.69)	370 (33.98)	0.79 (0.61 to 1.03)	0.70 (0.53 to 0.92)*
	T3	145 (31.05)	373 (34.25)	0.77 (0.59 to 1.00)	0.60 (0.45 to 0.79)**
	P trend			0.054	
Sourcil angle	T1	90 (16.27)	464 (41.95)	1 (referent)	1 (referent)
	T2	158 (28.57)	394 (35.62)	2.06 (1.53 to 2.77)**	2.11 (1.55 to 2.86)**
	T3	305 (55.15)	248 (22.42)	6.34 (4.66 to 8.62)**	6.93 (5.16 to 9.32)**
	P trend			<0.001	
Femoral head offset	T1	217 (38.75)	321 (30.69)	1.57 (1.22 to 2.03)**	1.67 (1.28 to 2.19)**
	T2	160 (28.57)	373 (35.66)	1 (referent)	1 (referent)
	T3	183 (32.68)	352 (33.65)	1.21 (0.93 to 1.56)	1.19 (0.91 to 1.56)
	P trend			NA	
Femoral neck width	T1	184 (32.51)	377 (34.03)	1.04 (0.81 to 1.33)	1.01 (0.73 to 1.37)
	T2	178 (31.45)	378 (34.12)	1 (referent)	1 (referent)
	T3	204 (36.04)	353 (31.86)	1.22 (0.96 to 1.57)	1.34 (1.01 to 1.79)*
	P trend			NA	
Mid-centre distance	T1	172 (30.39)	386 (34.84)	0.99 (0.77 to 1.28)	1.03 (0.79 to 1.34)
	T2	173 (30.57)	385 (34.75)	1 (referent)	1 (referent)
	T3	221 (39.05)	337 (30.42)	1.46 (1.14 to 1.87)**	1.43 (1.11 to 1.85)**
	P trend			NA	
Pelvic height	T1	145 (38.87)	320 (31.34)	1.45 (1.08 to 1.94)	1.51 (1.09 to 2.07)*
	T2	111 (29.76)	355 (34.77)	1 (referent)	1 (referent)
	T3	117 (31.37)	346 (33.89)	1.08 (0.80 to 1.46)	1.05 (0.75 to 1.47)
	P trend			NA	
Neck shaft angle	T1	209 (36.99)	366 (33.18)	1.40 (1.09 to 1.78)**	1.36 (1.05 to 1.75)*
	T2	176 (31.15)	431 (39.08)	1 (referent)	1 (referent)
	T3	180 (31.86)	306 (27.74)	1.44 (1.11 to 1.85)**	1.50 (1.15 to 1.96)**
	P trend			NA	

Logistic regression was adjusted for age, gender and body mass index. For femoral head offset, femoral neck width, mid-centre distance, pelvic height and neck shaft angle, Tertile 2 was used as referent.

*p <0.05, **p <0.01.

NA, not applicable; OA, osteoarthritis; OR, odds ratio; T, tertile.

Clusters of morphological features

The 14 morphological features were associated with each other (online supplementary Table S4). Three clusters were identified within the 14 morphological features (figure 2). Cluster 1 included FHNR (non-spherical femoral head). Cluster 2 included SA, NSA, FNW, and MCD. Cluster 3 included AD and CEA (i.e. mild acetabular dysplasia), FHD, FNL, OSD, ISD, FHO, PW and PH. The contribution of the individual morphological features to each cluster is shown in supplementary table S5 (online supplementary Table S5).

Proportional risk contribution

The AUC for the full model including all risk factors was 0.81 (95%CI 0.79 to 0.83), of which 34.95% (95%CI 30.93 to 39.65) was explained by the 14 morphological features, and 21.36% (95%CI 18.62 to 24.21) was explained by all other established risk factors (Table 4). Of the 14 morphological features, SA had the highest contribution (PRC=7.12%, 95% CI 6.01 to 8.07). The PRC of cluster 1, 2 and 3 was 2.26% (95%CI 1.80 to 2.46), 7.12% (95%CI 6.31 to 8.42) and 7.44% (95%CI 6.61 to 8.42), respectively.

Table 4 AUC and PRC of multivariate models

	AUC	95%CI	PRC (%)	95%CI
Full model	0.809	0.785 to 0.833	100	
Partial model without other risk factors	0.743	0.716 to 0.771	21.359	18.619 to 24.211
Partial model without morphological features	0.701	0.672 to 0.730	34.951	30.931 to 39.649
Partial model without SA	0.787	0.762 to 0.813	7.120	6.006 to 8.070
Partial model without FHNR	0.802	0.778 to 0.827	2.265	1.802 to 2.456
Partial model without ISD	0.803	0.777 to 0.827	1.942	1.802 to 2.807
Partial model without CEA	0.804	0.780 to 0.828	1.618	1.502 to 1.754
Partial model without FHD	0.805	0.780 to 0.829	1.294	1.201 to 1.754
Partial model without FHO	0.806	0.782 to 0.830	0.971	0.901 to 1.053
Partial model without FNW	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without FNL	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without NSA	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without MCD	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without PW	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without AD	0.808	0.784 to 0.832	0.324	0.300 to 0.351
Partial model without PH	0.809	0.785 to 0.833	0	0
Partial model without OSD	0.809	0.785 to 0.833	0	0
Partial model without cluster 1	0.802	0.778 to 0.827	2.265	1.802 to 2.456
Partial model without cluster 2	0.787	0.761 to 0.812	7.120	6.306 to 8.421
Partial model without cluster 3	0.786	0.761 to 0.811	7.443	6.606 to 8.421

The full model included other risk factors and morphological features.

Other risk factors included age, gender, weight, height, body mass index, calcaneal bone mineral density, finger nodes, type 3 2D:4D finger ratio, history of hip injury, and manual occupation.

Morphological features included AD, CEA, FHNR, NSA, FHD, FNL, FNW, FHO, OSD, ISD, MCD, SA, PW, and PH.

AD, acetabular depth; AUC, areas under the curve; CEA, centre edge angle; FHD, femoral head diameter; FHNR, femoral head to femoral neck ratio; FHO, femoral head offset; FNL, femoral neck length; FNW, femoral neck width; ISD, inner shaft diameter; MCD, mid-centre distance; NSA, neck shaft angle; OSD, outer shaft diameter; PH, pelvic height; PRC, proportional risk contribution; PW, pelvic width; SA, sourcil angle.

DISCUSSION

This is the first large study to assess 14 hip and pelvis morphological features, individually and in composite, and their contribution to the risk of hip OA. The right-left symmetry of all measures demonstrated in the normal controls supports the assumption that the unaffected hip of unilateral hip OA cases represents the pre-OA morphology of the affected hip.[4, 5] Although age associated with some morphological features, it was not associated with the symmetry, i.e., the difference between left and right. The main findings are: (1) all 14 hip morphological features associated with increased risk of hip OA independent of age, gender and BMI, with larger SA being the strongest risk factor; (2) two patterns of associations were observed - dose response and U-shaped curve response (both higher and lower values associating with increased risk); (3) three clusters were identified (figure 2); and (4) the total contribution of the 14 morphological features to risk of hip OA was greater (35%) than the sum of other recognised risk factors (21%).

Our findings of small FHD, wide FNW, and short FNL as risk factors for hip OA concur with the previous studies.[6, 11, 14, 22-24] Biomechanically many of these features have a plausible aetiological mechanism. For example, small FHD and/or wide FNW may both encourage “cam type” impingement of the proximal femur on the acetabulum,[25] as does a non-spherical femoral head.[35] Furthermore, a small femoral head has a smaller surface area for load transmission, thus the force per unit area may be higher and cause increased joint tissue stress. On the other hand, a wide FNW may encourage “pincer-type” impingement of the femoral head-neck junction against the acetabular rim.[25] The explanation for smaller measurements of both OSD and ISD could relate to the inverse relationship between osteoporosis and OA.[36] Low FHO and wide MCD necessitates a greater

abductor muscles force to maintain body balance[37] and the resultant greater stress on the hip may predispose to OA. The association of AD, CEA, FHNR and NSA with hip OA were reported and discussed in our previous studies.[4, 5]

Importantly, our findings indicated that of the 14 features studied, increased SA was the strongest individual risk factor for hip OA and showed the highest PRC. Departure of the acetabular sourcil orientation from the horizontal plane will negatively affect the equilibrium of forces across the hip joint,[26] and with bigger SA the femoral head is less covered by the acetabulum, which is consistent with the negative correlation between SA and CEA, so the unit force per surface area is increased. In previous studies, SA related more than other indices with development of OA[38, 39] and it is considered a more precise measure for mild dysplasia than CEA.[40] Therefore overall, more vertical SA is a major morphological risk factor and may be used as a single surrogate marker in clinical practice to assess morphological risk of hip OA.

The 14 morphological features were assigned into three clusters. Cluster analysis may uncover relationships between measures. For example, in a case with high NSA (coxa valga), the increased inclination of the weight-bearing surface of the acetabulum (assessed by SA) can increase the compressive forces on the joint and lower the threshold for the onset of OA.[41] The coexistence of less acetabular coverage and shorter femoral neck were reported in one hip shape mode (HSM) derived by statistical shape modelling which positively associated with incident hip OA.[14] But in another HSM, more coverage of the femoral head and wider PW were found to associate with OA,[14] which is inconsistent with our findings. The higher proportion of women and the different definition of PW in that study[14]

should be considered when comparing the results with ours. However, the possible explanation for the associations observed for PW and PH are open to speculation. Further prospective study for causality is still required.

The risk contribution of the 14 morphological features (PRC=35%, 95%CI 31% to 40%) was significantly larger than other established risk factors including age, gender, BMI, history of hip injury, physical occupation, nodal OA, and 2D:4D finger ratio (PRC=21%, 95%CI 19% to 24%). This suggests that local morphological risk factors may contribute more than systemic factors to development of hip OA. The results align with the literature for incidence and progression of hip OA[42, 43] and may be explained by shared single nucleotide polymorphisms (SNPs) between OA and hip shape.[44, 45]

There are several caveats to this study. Firstly, this was a cross-sectional case-control study. Whether these morphological features cause hip OA requires a prospective population-based study. Although we used the unaffected hips of people with unilateral hip OA to determine constitutional pre-OA shape, it is possible that the morphology in the unaffected hip had adapted to altered gait pattern and abnormal loading caused by hip OA on the other side[46], in accord with Wolff's law which states that bones adapt their mass and shape in response to loading.[47] In addition, the apparently normal hips could have undergone bone remodelling due to early OA before other features such as cartilage loss were evident.[23] Furthermore, we did not account for presence of symptoms or structural OA in other lower limb joints (knees, ankles, feet) of cases which may have affected biomechanical stress on the unaffected hip. Also radiographic assessment is less sensitive to early OA changes than other imaging modalities,

such as magnetic resonance imaging (MRI). We also found that some morphological features changed with age in the control group. Although symmetry was unaffected by age, we cannot be certain that the current features measured in unaffected hips of cases would fully reflect the pre-OA morphology on the affected side before it developed OA many years ago. Secondly, although we observed symmetry of morphological features in the non-disease control group, this does not exclude the possibility of asymmetry in the cases before they developed unilateral hip OA, or the presence of additional unidentified risk factors on the affected side, or protective factors on the unaffected side. This again requires a prospective cohort study to confirm whether the pre-disease morphological features are truly symmetrical between the left and right sides, and to determine how many people with the features of interest subsequently go on to develop bilateral hip OA. Thirdly, the GOAL database includes only Caucasian participants so the generalisability of the findings is limited and requires study in other populations. Fourthly, we undertook measurements on a single two-dimensional standard AP pelvis radiograph without other views. Although this is conventional and readily applicable to large-scale population studies, it has major limitations for identifying true morphological variations in 3-dimensions. A further caveat is that measurement of morphological features was not undertaken blind of hip OA status, since pelvic images were saved on software (HIPAX) that prevents image cropping. Furthermore, despite the use of a standardised protocol, variations in positioning may have affected some assessments, for example due to anteversion or rotation secondary to pain or deformity in the affected hip.

In conclusion, we have confirmed 14 morphological features that associate with increased risk of hip OA. The risk contribution of these features is more than that of other conventional risk factors combined. SA is the strongest risk factor and could be used as a single surrogate measure of morphological risk in large epidemiological studies or in clinical settings. Future prospective studies are required to provide further support for causality between these features and OA.

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Patient and public involvement No.

Patient consent for publication Not required.

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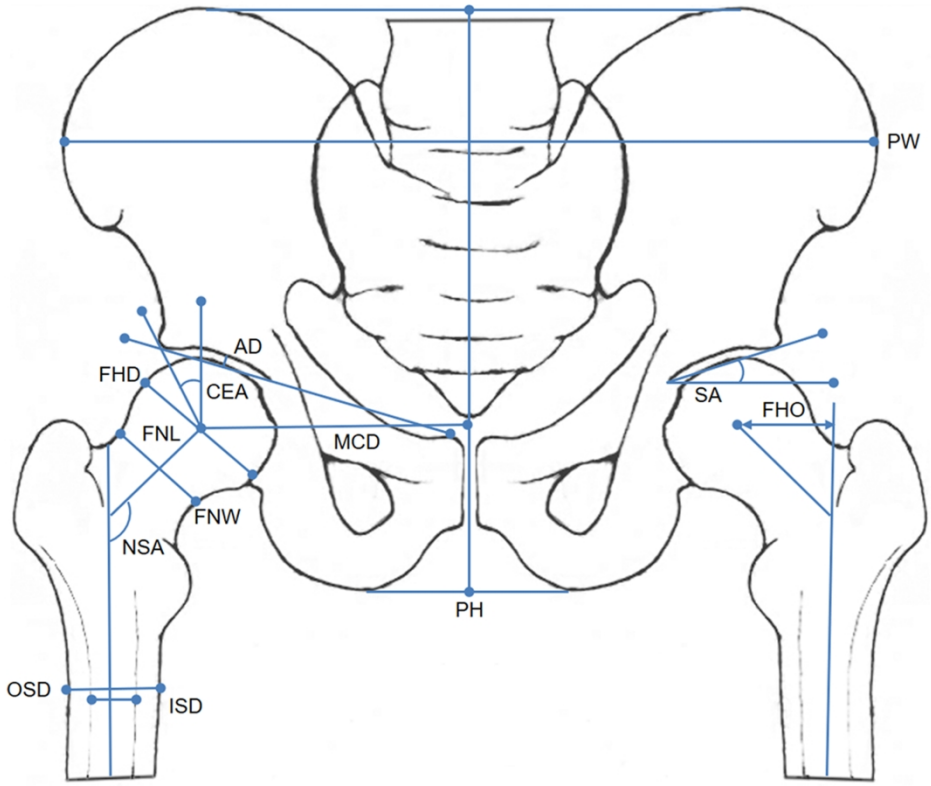
Figure legend

Figure 1 Diagram showing the morphological measurements of the hip and pelvic bones: AD, acetabular depth; CEA, centre edge angle; FHD, femoral head diameter; FHO, femoral head offset; FNL, femoral neck length; FNW, femoral neck width; ISD, inner shaft diameter; MCD, mid-centre distance; NSA, neck shaft angle; OSD, outer shaft diameter; PH, pelvic height; PW, pelvic width; SA, sourcil angle.

Figure 2 Diagram showing the morphological features were assigned into 3 clusters: Cluster 1 includes FHNR; cluster 2 includes SA, NSA, FNW and MCD; and cluster 3 includes AD, CEA, FHD, FNL, OSD, ISD, FHO, PW, PH.

AD, acetabular depth; CEA, centre edge angle; FHD, femoral head diameter; FHNR, femoral head to femoral neck ratio; FHO, femoral head offset; FNL, femoral neck length; FNW, femoral neck width; ISD, inner shaft diameter; MCD, mid-centre distance; NSA, neck shaft angle; OSD, outer shaft diameter; PH, pelvic height; PW, pelvic width; SA, sourcil angle.



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20x16mm (5000 x 5000 DPI)

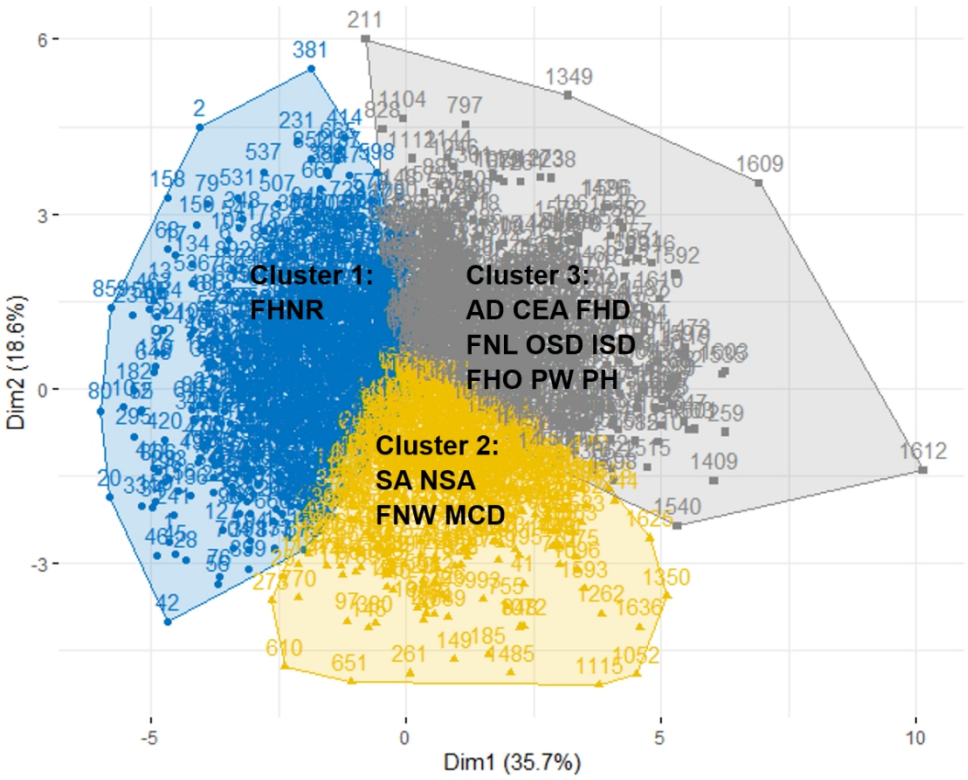

Figure 2 Diagram showing the morphological features were assigned into 3 clusters: Cluster 1 includes FHNR; cluster 2 includes SA, NSA, FNW and MCD; and cluster 3 includes AD, CEA, FHD, FNL, OSD, ISD, FHO, PW, PH.AD, acetabular depth; CEA, centre edge angle; FHD, femoral head diameter; FHNR, femoral head to femoral neck ratio; FHO, femoral head offset; FNL, femoral neck length; FNW, femoral neck width; ISD, inner shaft diameter; MCD, mid-centre distance; NSA, neck shaft angle; OSD, outer shaft diameter; PH, pelvic height; PW, pelvic width; SA, sourcil angle.

89x70mm (350 x 350 DPI)

Supplementary Material:

Supplementary table S1:
Results of paired t-test and MDC (90% level) performed between left and right sides to assess symmetry

	Mean (SD)		Mean difference		
Hip morphology	**Left**	**Right**	**D (95% CI)**	**p-value**	**MDC_{90}**
Acetabular depth	13.79 (3.04)	13.43 (3.03)	0.36 (0.11- 0.62)	<0.01	3.25
Centre edge angle	37.88 (6.21)	37.08 (6.39)	0.80 (0.28- 1.33)	<0.01	7.20
Femoral head diameter	57.23 (4.83)	57.43 (4.89)	-0.20 (-0.61- 0.20)	0.33	2.27
Femoral head to femoral neck ratio	1.43 (0.09)	1.43 (0.09)	0 (-0.01- 0.01)	0.44	0.08
Femoral head offset	48.49 (6.77)	48.34 (6.53)	0.15 (-0.42- 0.72)	0.61	5.38
Femoral neck length	61.88 (6.31)	61.97 (6.22)	-0.09 (-0.63- 0.44)	0.73	5.66
Femoral neck width	40.64 (4.83)	40.77 (4.86)	-0.13 (-0.54- 0.27)	0.52	2.26
Inner shaft diameter	20.70 (3.03)	20.98 (3.01)	-0.28 (-0.55- -0.02)	0.04	1.73
Mid-centre distance	110.51 (6.27)	111.13 (6.34)	-0.62 (-1.14- -0.09)	0.02	5.30
Neck shaft angle	128.45 (5.97)	128.44 (5.99)	0.01 (-0.49- 0.51)	0.98	6.84
Outer shaft diameter	38.03 (3.43)	38.09 (3.43)	-0.06 (-0.36- 0.25)	0.72	1.79
Sourcil angle	5.86 (4.69)	5.77 (5.00)	0.09 (-0.32- 0.49)	0.67	4.08

D, mean difference; MDC, minimal detectable change; SD, standard deviation.

The MDC was calculated by multiplying the standard error of the measurement (SEM) by the z score associated with either 90% or 95% confidence level and the square root of 2. Thus, MDC= z-score x SEM x square root of 2. The SEM measures the amount of error in the measurement. The SEM was calculated using the formula: $SEM=s[(1 - r)^{1/2}]$, where, s is estimated as the pooled standard deviation of left and right assessments (Square root of $[(SD_{left})^2+(SD_{right})^2/2]$ and r is the intra-class correlation coefficient (ICC). The MDC is estimated based on 90% CI (z=1.65). The criteria for symmetry in this study was that the mean difference between the left and right sides should be less than the MDC_{90}.

Supplementary table S2:
Correlations between age and morphological features in control group

	Left	Right	Difference
Hip morphology	**r value**	**r value**	**r value**
Acetabular depth	-0.027	-0.034	-0.008
Centre edge angle	0.091**	0.095**	0.013
Femoral head diameter	0.265**	0.271**	-0.049
Femoral head to femoral neck ratio	-0.138**	-0.156**	0.009
Femoral head offset	0.161**	0.124**	0.025
Femoral neck length	0.123**	0.103**	-0.018
Femoral neck width	0.257**	0.266**	-0.042
Inner shaft diameter	0.268**	0.262**	0.003
Mid-centre distance	0.081*	0.095**	-0.036
Neck shaft angle	-0.132**	-0.082**	-0.035
Outer shaft diameter	0.208**	0.222**	-0.027
Sourcil angle	-0.001	0.003	-0.015

Difference is the difference between left hip and right hip.

*p<0.05, **p<0.01.

r, Pearson correlation.

Supplementary table S3:

Relative risk of hip OA due to individual morphological measures in women and men

Hip morphology		Men					Women				
		Frequency (%)		OR (95%CI)			Frequency (%)		OR (95%CI)		
		Cases	Controls	Crude	Adjusted		Cases	Controls	Crude	Adjusted	
Acetabular depth	T1	138 (46.78)	159 (26.77)	1 (referent)	1 (referent)	T1	138 (50.92)	125 (24.37)	1 (referent)	1 (referent)	
	T2	92 (31.19)	208 (35.02)	0.51 (0.36- 0.71)**	0.53 (0.38- 0.75)**	T2	68 (25.09)	193 (37.62)	0.32 (0.22- 0.47)**	0.33 (0.22- 0.49)**	
	T3	65 (22.03)	227 (38.21)	0.33 (0.23- 0.48)**	0.32 (0.22- 0.47)**	T3	65 (23.99)	195 (38.01)	0.30 (0.20- 0.44)**	0.27 (0.18- 0.40)**	
	P trend			<0.001		P trend			<0.001		
Centre edge angle	T1	161 (54.58)	160 (26.89)	1 (referent)	1 (referent)	T1	140 (51.66)	147 (28.65)	1 (referent)	1 (referent)	
	T2	80 (27.11)	225 (37.82)	0.35 (0.25- 0.50)**	0.35 (0.25- 0.50)**	T2	72 (26.57)	188 (36.65)	0.40 (0.28- 0.58)**	0.34 (0.23- 0.51)**	
	T3	54 (18.31)	210 (35.29)	0.25 (0.17- 0.38)**	0.24 (0.16- 0.35)**	T3	59 (21.77)	178 (34.70)	0.35 (0.23- 0.51)**	0.24 (0.15- 0.37)**	
	P trend			<0.001		P trend			<0.001		
Femoral head diameter	T1	96 (32.54)	201 (33.78)	1 (referent)	1 (referent)	T1	108 (39.85)	154 (30.02)	1 (referent)	1 (referent)	
	T2	100 (33.90)	198 (33.28)	1.05 (0.75- 1.48)	0.94 (0.66- 1.34)	T2	85 (31.37)	177 (34.50)	0.68 (0.47- 0.98)*	0.64 (0.43- 0.95)*	
	T3	99 (33.56)	196 (32.94)	1,06 (0.75- 1.49)	0.93 (0.65- 1.32)	T3	78 (28.78)	182 (35.48)	0.61 (0.42- 0.88)**	0.44 (0.30- 0.67)**	
	P trend			0.75		P trend			0.007		
Femoral head to femoral neck ratio	T1	135 (45.76)	194 (32.61)	1 (referent)	1 (referent)	T1	123 (45.39)	148 (28.96)	1 (referent)	1 (referent)	
	T2	96 (32.54)	197 (33.11)	0.70 (0.50- 0.97)*	0.75 (0.53- 1.05)	T2	92 (33.95)	174 (34.05)	0.63 (0.45- 0.90)*	0.69 (0.47- 1.01)	
	T3	64 (21.69)	204 (34.29)	0.45 (0.31- 0.65)**	0.51 (0.35- 0.73)**	T3	56 (20.66)	189 (36.99)	0.35 (0.24- 0.53)**	0.47 (0.31- 0.71)**	
	P trend			<0.001		P trend			<0.001		
Femoral neck width	T1	83 (28.14)	214 (35.97)	1 (referent)	1 (referent)	T1	80 (29.52)	183 (35.67)	1 (referent)	1 (referent)	
	T2	90 (30.51)	209 (35.13)	1.11 (0.78- 1.58)	1.02 (0.71- 1.46)	T2	92 (33.95)	170 (33.14)	1.23 (0.86- 1.79)	1.02 (0.69- 1.52)	
	T3	122 (41.36)	172 (28.91)	1.83 (1.29- 2.59)**	1.57 (1.10- 2.24)*	T3	99 (36.53)	160 (31.19)	1.41 (0.98- 2.04)	1.03 (0.70- 1.53)	
	P trend			<0.001		P trend			0.061		
Inner shaft diameter	T1	114 (40.28)	157 (30.61)	1 (referent)	1 (referent)	T1	104 (39.25)	145 (30.08)	1 (referent)	1 (referent)	
	T2	95 (33.57)	165 (32.16)	0.79 (0.56- 1.12)	0.72 (0.50- 1.04)	T2	84 (31.70)	167 (34.65)	0.70 (0.48- 1.01)	0.59 (0.39- 0.88)*	
	T3	74 (26.15)	191 (37.23)	0.53 (0.37- 0.77)**	0.47 (0.32- 0.69)**	T3	77 (29.06)	170 (35.27)	0.63 (0.43- 0.91)*	0.38 (0.25- 0.58)**	
	P trend			<0.001		P trend			0.014		
Outer shaft diameter	T1	100 (35.34)	169 (32.94)	1 (referent)	1 (referent)	T1	106 (40.00)	147 (30.50)	1 (referent)	1 (referent)	
	T2	93 (32.86)	169 (32.94)	0.93 (0.65- 1.32)	0.83 (0.58- 1.20)	T2	80 (30.19)	167 (34.65)	0.66 (0.46- 0.96)*	0.55 (0.36- 0.83)**	
	T3	90 (31.80)	175 (34.11)	0.87 (0.61-1.24)	0.70 (0.48- 1.01)	T3	79 (29.81)	168 (34.85)	0.65 (0.45- 0.94)	0.37 (0.25- 0.57)**	
	P trend			0.44		P trend			0.02		
Sourcil angle	T1	41 (14.09)	254 (42.83)	1 (referent)	1 (referent)	T1	48 (18.32)	211 (41.13)	1 (referent)	1 (referent)	

	T2	94 (32.30)	201 (33.90)	2.89 (1.90- 4.41)**	2.91 (1.91- 4.45)**	T2	65 (24.81)	194 (37.82)	1.47 (0.96- 2.24)	1.38 (0.87- 2.17)
	T3	156 (53.61)	138 (23.27)	7.00 (4.50- 10.89)**	7.45 (4.92- 11.25)**	T3	149 (56.87)	108 (21.05)	6.06 (3.91- 9.39)**	6.53 (4.22- 10.11)**
	P trend			<0.001		P trend			<0.001	
Mid-centre distance	T1	82 (27.80)	216 (36.31)	1 (referent)	1 (referent)	T1	92 (33.95)	170 (33.14)	1.14 (0.79- 1.64)	1.09 (0.74- 1.62)
	T2	91 (30.85)	205 (34.45)	1.17 (0.82- 1.67)	1.08 (0.75- 1.56)	T2	84 (31.00)	177 (34.50)	1 (referent)	1 (referent)
	T3	122 (41.36)	174 (29.24)	1.85 (1.30- 2.61)**	1.69 (1.19- 2.41)**	T3	95 (35.06)	166 (32.36)	1.21 (0.84- 1.73)	1.07 (0.73- 1.58)
	P trend			<0.001		P trend			NA	
Femoral head offset	T1	92 (31.62)	189 (34.36)	0.85 (0.60- 1.21)	0.86 (0.60- 1.24)	T1	116 (43.12)	139 (28.02)	1 (referent)	1 (referent)
	T2	102 (35.05)	179 (32.55)	1 (referent)	1 (referent)	T2	79 (29.37)	176 (35.48)	0.54 (0.37- 0.78)**	0.46 (0.31- 0.68)**
	T3	97 (33.33)	182 (23.09)	0.93 (0.66-1.32)	0.99 (0.69-1.41)	T3	74 (27.51)	181 (36.49)	0.49 (0.34- 0.71)**	0.40 (0.27- 0.60)**
	P trend			NA		P trend			<0.001	
Neck shaft angle	T1	137 (46.44)	223 (37.67)	1.66 (1.17- 2.34)**	1.61 (1.13- 2.28)**	T1	84 (31.11)	180 (35.23)	1 (referent)	1 (referent)
	T2	73 (24.75)	197 (33.28)	1 (referent)	1 (referent)	T2	92 (34.07)	199 (38.94)	0.99 (0.69-1.42)	1.01 (0.69- 1.49)
	T3	85 (28.81)	172 (29.05)	1.33 (0.91- 1.94)	1.37 (0.93- 2.01)	T3	94 (34.81)	132 (25.83)	1.52 (1.05- 2.21)*	1.79 (1.19- 2.70)**
	P trend			NA		P trend			0.028	
Pelvic height	T1	65 (36.52)	173 (32.58)	1.32 (0.87- 2.01)	1.44 (0.93- 2.23)	T1	76 (38.97)	153 (31.22)	1 (referent)	1 (referent)
	T2	52 (29.21)	183 (34.46)	1 (referent)	1 (referent)	T2	61 (31.28)	167 (34.08)	0.73 (0.49- 1.10)	0.74 (0.48- 1.15)
	T3	61 (34.27)	175 (32.96)	1.23 (0.80- 1.87)	1.27 (0.82- 1.96)	T3	58 (29.74)	170 (34.69)	0.69 (0.46- 1.03)	0.60 (0.39- 0.94)*
	P trend			NA		P trend			0.066	
Pelvic width	T1	82 (35.19)	189 (32.59)	1.24 (0.85- 1.81)	1.34 (0.91- 1.98)	T1	93 (39.74)	155 (30.45)	1 (referent)	1 (referent)
	T2	70 (30.04)	201 (34.66)	1 (referent)	1 (referent)	T2	78 (33.33)	170 (33.40)	0.76 (0.52- 1.11)	0.53 (0.35-0.81)**
	T3	81 (34.76)	190 (32.76)	1.22 (0.84- 1.78)	1.09 (0.74- 1.60)	T3	63 (26.92)	184 (36.15)	0.57 (0.39- 0.84)**	0.34 (0.22- 0.53)**
	P trend			NA		P trend			0.004	
Femoral neck length	T1	105 (36.08)	177 (31.95)	1.24 (0.88- 1.76)	1.22 (0.85- 1.74)	T1	112 (41.64)	145 (29.12)	1.75 (1.21- 2.53)**	1.79 (1.20- 2.67)**
	T2	91 (31.27)	191 (34.48)	1 (referent)	1 (referent)	T2	78 (29.00)	177 (35.54)	1 (referent)	1 (referent)
	T3	95 (32.65)	186 (33.57)	1.07 (0.75- 1.52)	1.10 (0.77-1.58)	T3	79 (29.37)	176 (35.34)	1.02 (0.69- 1.48)	1.01 (0.67- 1.50)
	P trend			NA		P trend			NA	

Logistic regression was adjusted for age and body mass index. For femoral head offset, neck shaft angle, pelvic height, pelvic width and femoral neck length in men and mid-centre distance, femoral neck length in women, Tertile 2 was used as referent.

*p<0.05, **p<0.01.

NA, not applicable; OA, osteoarthritis; OR, odds ratio; T, tertile.

Supplementary table S4:

Correlations between the 14 hip morphological features

	r value													
Hip morphology	**AD**	**CEA**	**FHD**	**FHNR**	**FHO**	**FNL**	**FNW**	**ISD**	**MCD**	**NSA**	**OSD**	**PH**	**PW**	**SA**
AD	1.000													
CEA	0.737*	1.000												
FHD	0.067*	-0.078*	1.000											
FHNR	0.065*	0.079*	-0.348*	1.000										
FHO	0.068*	0.077*	0.342*	-0.033	1.000									
FNL	0.082*	0.012	0.43*	0.046	0.842*	1.000								
FNW	0.017	-0.094*	0.876*	-0.702*	0.254*	0.271*	1.000							
ISD	0.156*	0.104*	0.377*	-0.193*	0.309*	0.339*	0.365*	1.000						
MCD	-0.118*	-0.278*	0.541*	-0.121*	0.103*	0.259*	0.448*	0.257*	1.000					
NSA	0.002	-0.1*	-0.004	0.099*	-0.625*	-0.188	-0.046	-0.085*	0.156*	1.000				
OSD	0.089*	0.027	0.649*	-0.316*	0.604*	0.588*	0.613*	0.667*	0.382*	-0.274*	1.000			
PH	0.213*	0.017	0.758*	-0.334*	0.346*	0.394*	0.702*	0.419*	0.49*	-0.042	0.643*	1.000		
PW	0.338*	0.261*	0.481*	-0.141*	0.259*	0.295*	0.412*	0.334*	0.535*	-0.031	0.459*	0.534*	1.000	
SA	-0.577*	-0.669*	0.024	-0.164*	-0.093*	-0.053*	0.087*	-0.089*	0.214*	0.078*	-0.011	-0.011	-0.239*	1.000

*p<0.05.

r, Pearson correlation.

AD, acetabular depth; CEA, centre edge angle; FHD, femoral head diameter; FHNR, femoral head to femoral neck ratio; FHO, femoral head offset; FNL, femoral neck length; FNW, femoral neck width; ISD, inner shaft diameter; MCD, mid-centre distance; NSA, neck shaft angle; OSD, outer shaft diameter; PH, pelvic height; PW, pelvic width; SA, sourcil angle.

Supplementary table S5:

Clusters of morphological features according to their highest values

	Cluster 1		Cluster 2		Cluster 3	
Hip morphology	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Acetabular depth	NA	NA	10.70	2.31	**15.01**	**2.89**
Centre edge angle	36.83	6.37	30.08	5.53	**40.08**	**5.74**
Femoral head diameter	52.96	3.03	59.87	3.60	**60.54**	**3.94**
Femoral head to femoral neck ratio	**1.47**	**0.08**	1.37	0.07	1.40	0.07
Femoral head offset	45.02	5.87	47.22	6.19	**53.29**	**6.21**
Femoral neck length	58.50	5.26	61.09	5.72	**66.15**	**5.89**
Femoral neck width	36.59	2.88	**44.14**	**3.70**	43.77	3.96
Inner shaft diameter	19.04	2.45	NA	NA	**22.56**	**2.83**
Mid-centre distance	107.58	5.47	**114.32**	**5.69**	112.93	6.41
Neck shaft angle	129.12	6.36	**129.25**	**6.13**	126.08	5.75
Outer shaft diameter	35.31	2.43	38.88	2.56	**41.03**	**2.79**
Pelvic height	240.08	10.86	258.23	11.38	**264.44**	**13.11**
Pelvic width	345.63	19.76	355.01	18.97	**373.32**	**19.55**
Sourcil angle	6.83	5.41	**11.72**	**4.48**	4.60	4.33

The bold black font were the highest values for the morphological features.

NA, not applicable; SD, standard deviation.