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Patterns of Change Over Time in Knee Bone Shape Are Associated with Sex

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Abstract

Background Knee osteoarthritis (OA) is more common in females than in males; however, the biological mechanisms for the difference in sex in patients with knee OA are not well understood. Knee shape is associated with OA and with sex, but the patterns of change in the bone's shape over time and their relation to sex and OA are unknown and may help inform how sex is associated with shape and OA and whether the effect is exerted early or later in life.

Questions/purposes (1) Does knee shape segregate stably into different groups of trajectories of change (groups of knees that share similar patterns of changes in bone shape over time)? (2) Do females and males have different trajectories of bone shape changes? (3) Is radiographic OA at baseline associated with trajectories of bone shape changes?

Methods We used data collected from the NIH-funded Osteoarthritis Initiative (OAI) to evaluate a cohort of

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Each author certifies that his or her institution waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.
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people aged 45 to 79 years at baseline who had either symptomatic knee OA or were at high risk of having it. The OAI cohort included 4796 participants (58% females; n = 2804) at baseline who either had symptomatic knee OA (defined as having radiographic tibiofemoral knee OA and answering positively to the question "have you had pain, aching or stiffness around the knee on most days for at least one month during the past 12 months") or were at high risk of symptomatic knee OA (defined as having knee symptoms during the prior 12 months along with any of the following: overweight; knee injury; knee surgery other than replacement; family history of total knee replacement for OA; presence of Heberden's nodes; daily knee bending activity) or were part of a small nonexposed subcohort. From these participants, we limited the eligible group to those with radiographs available and read at baseline, 2 years, and 4 years, and randomly selected participants from each OAI subcohort in a manner to enrich representation in the study of the progression and nonexposed subcohorts, which were smaller in number than the OA incidence subcohort. From these patients, we randomly sampled 473 knees with radiographs available at baseline, 2 years, and 4 years. We outlined the shape of the distal femur and proximal tibia on radiographs at all three timepoints using statistical shape modelling. Five modes (each mode represents a particular type of knee bone shape variation) were derived for the proximal tibia and distal femur's shape, accounting for 78% of the total variance in shape. Group-based trajectory modelling (a statistical approach to identify the clusters of participants following a similar progression of change of bone shape over time, that is, trajectory group) was used to identify distinctive patterns of change in the bone shape for each mode. We examined the association of sex and radiographic OA at baseline with the trajectories of each bone shape mode using a multivariable polytomous regression model while adjusting for age, BMI, and race.

Results Knee bone shape change trajectories segregated stably into different groups. In all modes, three distinct trajectory groups were derived, with the mean posterior probabilities (a measure of an individual's probability of being in a particular group and often used to characterize how well the trajectory model is working to describe the population) ranging from 84% to 99%, indicating excellent model fitting. For most of the modes of both the femur and tibia, the intercepts for the three trajectory groups were different; however, the rates of change were generally similar in each mode. Females and males had different trajectories of bone shape change. For Mode 1 in the femur, females were more likely to be in trajectory Groups 3 (odds ratio 30.2 [95% CI 12.2 to 75.0]; $p < 0.001$) and 2 than males (OR 4.1 [95% CI 2.3 to 7.1]; $p < 0.001$); thus, females had increased depth of the intercondylar fossa and broader shaft width relative to epicondylar width compared with males. For Mode 1 in the tibia, females were less likely to be in trajectory Group 2 (OR 0.5 [95% CI 0.3 to 0.9]; $p = 0.01$) than males (that is, knees of females were less likely to display superior elevation of tibial plateau or decreased shaft width relative to head width). Radiographic OA at baseline was associated with specific shape-change trajectory groups. For Mode 1 in the femur, knees with OA were less likely to be in trajectory Groups 3 (OR 0.4 [95% CI 0.2 to 0.8]; $p = 0.008$) and 2 (OR 0.6 [95% CI 0.3 to 1.0]; $p = 0.03$) than knees without OA; thus, knees with OA had decreased depth of the intercondylar fossa and narrower shaft width relative to epicondylar width compared with knees without OA. For Mode 1 in the tibia, knees with OA were not associated with trajectory.

Conclusions The shapes of the distal femur and proximal tibia did not change much over time. Sex and baseline knee radiographic OA status are associated with the trajectory of change in the bone's shape, suggesting that both may contribute earlier in life to the associations among trajectories observed in older individuals. Future studies might explore sex-related bone shape change earlier in life to help determine when the sex-specific shapes arise and also the degree to which these sex-related shapes are alterable by injury or other events.

Level of Evidence Level III, prognostic study.

Introduction

Osteoarthritis (OA) is the most frequently occurring form of arthritis and currently affects at least 27 million adults in the United States, almost 6 million more than in 1995 [28]. Females have a higher prevalence of OA than males and greater differences in OA patterns. The reasons for the difference in prevalence by sex remain uncertain. Although the epidemiology of OA is complex, overall, females are at a higher risk of having OA and have more severe knee OA than males [38]. Females have a smaller volume of knee cartilage than males, independent of bone size and body mass, which may predispose them to OA [9]. Multiple studies have found that variations in knee shape are associated with pathologic states such as OA or injury [1, 4, 15, 16]. Relationships between sex and knee bone shape may be related to the causes of OA and may allow us to understand how OA arises in the knee and why we see more OA in females. It is also inviting to consider whether shape-related sex-specific prostheses in knee replacements might result in better outcomes for both females and males. Although studies up to now have largely demonstrated no benefit of sex-specific prostheses [6, 21, 25, 26, 32, 39], the purported sex-related shape differences these prostheses were designed around have not been observed in more recent studies [3, 32], and an improved approach to examining shape differences may be able to identify reproducible sex-related differences that could inform a new generation of sex-specific prosthetic design that might have a better chance of improving clinical outcomes. Furthermore, bone shape may change over time as patients age and this change in shape may be associated with OA. If OA predisposes the knee to architectural alteration and degradation over time, there may be ramifications in terms of functional limitation, and an investigation of bone shape change may ultimately inform research into how OA causes disability.

Recently, bone shape, as characterized using statistical shape modeling, has been demonstrated to be a viable approach to describe shape differences across populations, and statistical shape modeling is useful for investigating associations with patient characteristics such as sex, disease, or injury states [4, 13, 16, 31, 41, 42, 45]. Most statistical shape modeling studies to date have examined cross-sectional associations or evaluated the relationship between the bone shape and incident OA [4, 13, 16, 31, 34, 41, 42, 45]. In a recent study, repeated three-dimensional (3-D) MRI-based statistical shape modeling was used to evaluate change in the knee shape in a small group of people with an acute ACL injury. The authors found an observable shape alteration in the year after their injury [35]. Although that study demonstrated the potential for shape change after injury, it did not address the question of shape change over long periods of time in the absence of an injury, which would be the case for most individuals. It also did not directly address the question of shape change over time and its relation to OA or sex. We wished to evaluate whether knees change shape over time, whether patterns of change are segregated by sex, and whether the presence of OA was associated with the patterns of shape change. We used the Osteoarthritis Initiative (OAI), a large cohort of people with knee OA or at risk of having it who were followed over a long period of time (more information is available online at https://data-archive.nimh.nih.gov/oai).

Specifically, we asked: (1) Does knee shape segregate stably into different groups of trajectories of change (groups of knees that share similar patterns of changes in bone shape over time)? (2) Do females and males have different trajectories of bone shape changes? (3) Is radiographic OA at baseline associated with trajectories of bone shape changes?

Patients and Methods

Study Design

The current study was designed as an observational cohort study following participants during a 4-year period. Participants were drawn from the NIH-funded OAI, which enrolled 4796 participants at baseline who had knee OA or were at a high risk of having the condition and were aged 45 to 79 years, in four university-based clinical centers with a coordinating center at the University of California, San Francisco (https://data-archive.nimh.nih.gov/oai). Approval for the overall OAI project was given by the institutional review boards at each OAI center, and the institutional review board at the University of California, Davis waived approval for this study.

The OAI cohort included 4796 participants (58% females; n = 2804) at baseline who either had symptomatic knee OA ("progression subcohort": defined as having radiographic tibiofemoral knee OA and answering positively to the question "have you had pain, aching or stiffness around the knee on most days for at least 1 month during the past 12 months") or were at high risk of symptomatic knee OA ("incidence subcohort": defined as having knee symptoms during the prior 12 months along with any of the following: overweight; knee injury; knee surgery other than replacement; family history of total knee replacement for OA; presence of Heberden's nodes; daily knee bending activity) or were part of a small non-exposed subcohort. Participants were eligible for participation in the current study if they had no rheumatoid arthritis, osteonecrosis, or amputation and still had a patella present at baseline; had not undergone knee arthroplasty at baseline; had radiographs taken at baseline, 2 years, and 4 years; and had Kellgren-Lawrence grades at baseline, 2 years, and 4 years.

From these participants, we randomly selected participants from each OAI subcohort in a manner to enrich representation in the study of the progression and nonexposed subcohorts, which were smaller in number than the incidence subcohort. The participant sample resulted in 10% of the progression subcohort, 5% of the incidence subcohort, and 60% of the nonexposed control subcohort participants. The selection process resulted in 474 participants (Fig. 1). One participant was excluded due to incomplete radiograph information, leaving 473 participants. For the trajectory analyses, one knee from each participant was used, specifically the right knee unless only the left knee was available.

Among the 473 participants, 54% (254) were females and 84% (397) of participants self-identified as white or Caucasian. The mean ± SD age of the participants was 60 years ± 9 years, and the mean BMI was 28 kg/m^2 ± 5 kg/m^2, with 44% (210) of the patients being overweight (BMI 25 to < 30 kg/m^2) and 33% (155) being obese (BMI ≥ 30 kg/m^2). Among the 473 patients, 44% (206) of knees with a measured bone shape had tibiofemoral radiographic OA at baseline (Table 1).

Statistical Shape Modelling

The statistical shape modeling methods applied in this study have been described previously [41, 42, 45]. Briefly, all radiographs were reviewed for image quality and

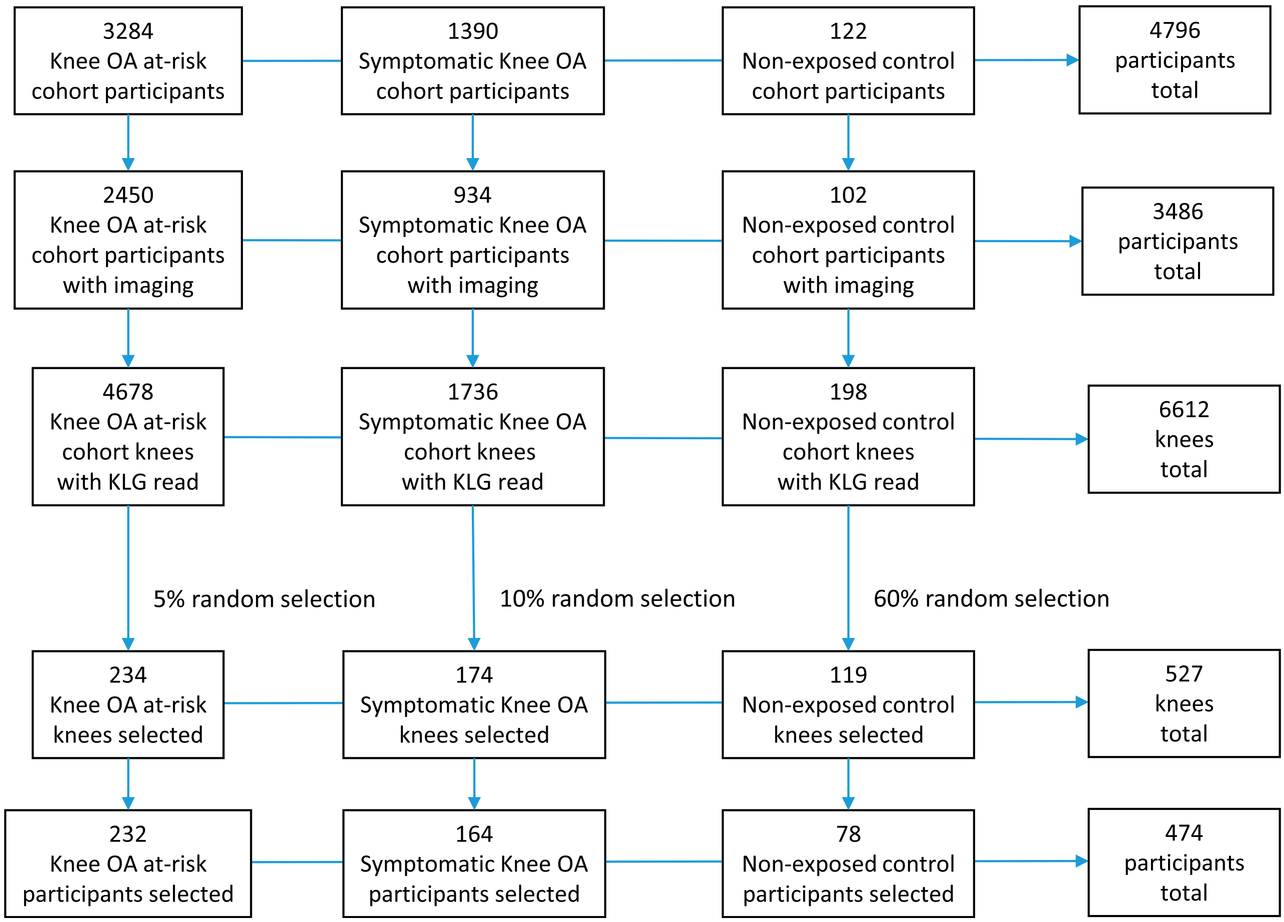

Fig. 1. This flowchart illustrates the study selection approach; KLG = Kellgren-Lawrence grade.

sufficient anatomic coverage, and radiographs were excluded if the edges of bones could not be visualized or completely outlined. A single reader (JP) outlined the distal femoral head and proximal tibia using a standardized semi-automatic algorithm on digitized baseline AP radiographs for all knees. Intrarater reliability for the distal femur and proximal tibia were 97% and 92%, respectively, for point placement within 2 mm and 99% and 97%, respectively, for point placement within 3 mm. Statistical shape models were then derived for the femur (41 points) and tibia (40 points). Composite femoral and tibial shapes were compiled to generate reference models. We then measured modes of variation in shape from the references. The mean shape and modes (variations of bone shape) sufficient to

Table 1. Baseline characteristics by sex and TF ROA (n = 473)

Characteristics	Females (n = 254)	Males (n = 219)	p value	TF ROA (n = 206)	No TF ROA (n = 267)	p value
Age (years), mean ± SD	60 ± 9	60 ± 9	0.89	61 ± 9	58 ± 9	< 0.001
Females				52% (108)	55% (146)	0.63
Self-identified white	81% (205)	88% (192)	0.04	77% (158)	90% (239)	< 0.001
BMI (kg/m^2), mean ± SD	28 ± 6	29 ± 4	0.52	30 ± 5	27 ± 4	< 0.001
Normal weight, BMI < 25	30% (76)	15% (32)	< 0.001	10% (21)	33% (87)	< 0.001
Overweight, BMI 25 to < 30	36% (91)	54% (119)		43% (88)	46% (122)	
Obese, BMI ≥ 30	34% (87)	31% (68)		47% (97)	22% (58)	
TF ROA	43% (108)	45% (98)				

p value from Student's t-test for continuous characteristics.
Chi-square test for categorical characteristics; TF ROA = tibiofemoral radiographic osteoarthritis.

explain 75% of the total variance in shape in this population were derived using a principal components analysis; the five modes of the tibia and femur each accounted for 78% of the total shape variance in that bone (Fig. 2). Mode scores were recorded as the number of SDs of the particular mode that an individual knee differed from the mean value for the bone shape mode, referred to as the standardized score of the bone shape.

Higher values of femoral Mode 1 displayed an increased depth of the intercondylar fossa and broadening of the shaft width relative to epicondylar width. With higher values of femoral Mode 2, we observed primarily a lateral shift of the angulation of the head with respect to the shaft. Femoral Mode 3 depicted mainly a reduction of inferior projection of both condylar heads with respect to the intercondylar fossa with higher values of the mode. Higher values of femoral Mode 4 represented shapes where there was increase of inferior projection of the lateral condylar head and a decrease of inferior projection of the medial head with respect to the patellar groove along with differences in the width and angle of the shaft relative to the epicondylar width. Mode 5 higher values were associated primarily with shape and medial extension of the medial epicondyle.

In tibial Mode 1, positive values represent shapes with increased superior elevation of the tibial plateaus along with decreased shaft width relative to head width. Higher values of tibial Mode 2 demonstrate increased head width with respect to shaft width and concurrent lateral angulation of the head with respect to the shaft and increased concavity of the lateral plateau with decreased concavity of the medial plateau. The higher values of tibial Mode 3 manifest in slightly increased tibial width along with medial plateau depression and lateral plateau elevation. The higher values of Mode 4 represent elevation of the medial lip and slight broadening of the lateral plateau and straightening of the lateral border of the bone at the shaft/head interface. The higher values of tibial Mode 5 mainly represent shapes with elevation of the lateral plateau and depression of the medial plateau.

Baseline radiographs of knees with OA were read centrally in the OAI for Kellgren-Lawrence grade (0-4) of tibiofemoral radiographic OA by two experienced readers (PA, BS) [24]. Disagreements between readers were adjudicated by an expert panel [45]. Cross-sectional Kellgren-Lawrence grade scores had a kappa of 0.7. Tibiofemoral radiographic OA was defined as a Kellgren-Lawrence grade ≥ 2.

Statistical Analysis

We described the baseline characteristics of the participants using the mean ± SD for continuous variables and count (percentage) for categorical variables. Trajectory groups for each bone shape mode were identified using group-based trajectory modelling (Proc Traj, an open source procedure to estimate a discrete mixture model for clustering of longitudinal data series) [22]. Assuming that the population is composed of a finite number of distinct groups, the group-based trajectory model is a statistical approach to identify the clusters of participants following a similar progression of some behavior (such as change of bone shape model) over time, that is, a trajectory [33]. To determine the number of groups, we fitted models up to four groups and selected the optimal number of trajectory groups based on the Bayesian information criteria [33]. In addition, we required the smallest group to include at least 5% of the participants to provide a meaningful description of patterns of change from a clinical perspective: in other words, if any trajectory group included only a small proportion of the participants' knees (< 5%) it is unlikely that group would be clinically significant, so we required that any described group included at least 5% of the knees, and eliminated any groups that included less. To select the shape of each group's trajectory over time, we fitted models with linear or quadratic polynomial terms and selected the shape of the trajectory based on a combination of the Bayesian information criteria and substantive knowledge [33]. We used the posterior probabilities of group membership, a measure of an individual's probability of being in a particular group and often used to characterize how well the trajectory model is working, to describe the population to assess the fit of the model. A high probability of membership in a single group represents a good model fit. Next, we examined the association of sex and knee OA with trajectories of changes in bone shape as a multilevel categorical outcome using polytomous logistic regression, with age, BMI, and race adjusted as potential confounders. Then, we further included baseline tibiofemoral OA in the model to assess its association with the trajectory of changes in the bone shape. All analyses were performed using SAS (V.9.2; SAS Institute, Cary, NC, USA). A significance level with an α of 0.05 was used.

Results

Does the Shape of the Knee Segregate Stably Into Different Groups of Trajectories of Change?

Knee bone shape change trajectories segregated stably into different groups. In all modes, three distinct trajectory groups were derived, with the mean posterior probabilities (a measure of an individual's probability of being in a particular group and often used to characterize how well the trajectory model is working to describe the population) ranging from 84% to 99%, indicating excellent model fitting. For the modes (types of shape difference) of the femur

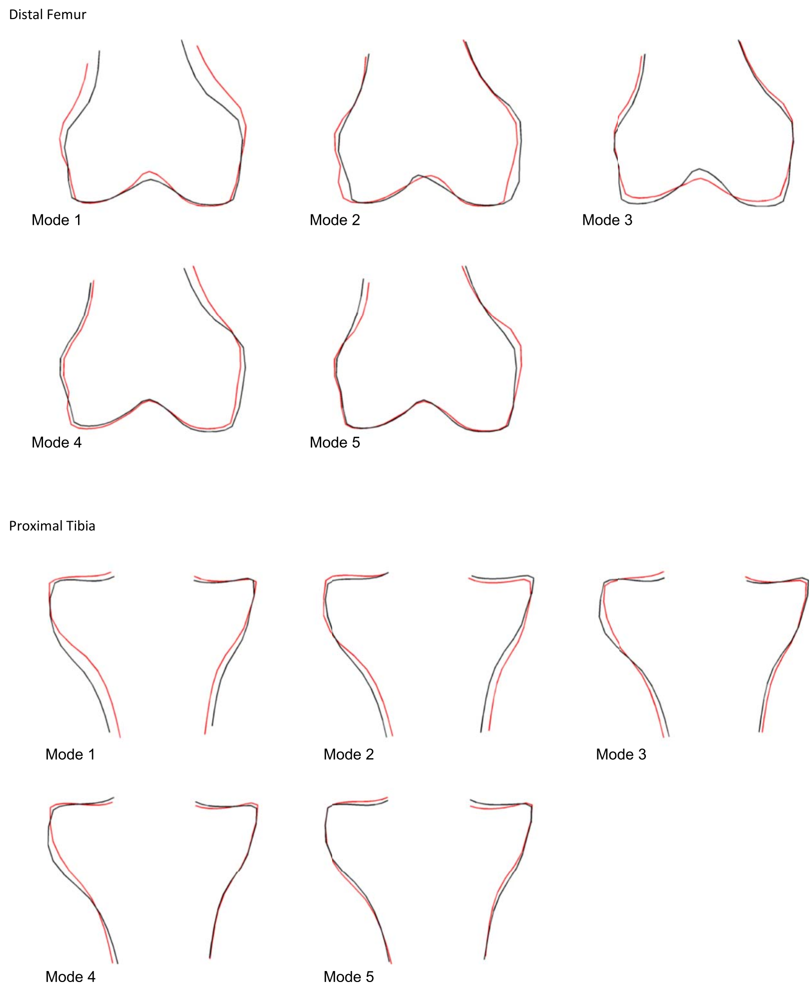

Fig. 2 These images illustrate all modes for the distal femur and proximal tibia. Bone shapes are shown with + 2 SDs (in red outlines) and -2 SDs (in black outlines) for each of the five femur and tibia shape modes. Higher values of femoral Mode 1 display increased depth of the intercondylar fossa and broadening of the shaft width relative to epicondylar width. With higher values of femoral Mode 2, we observe primarily a lateral shift of the angulation of the head with respect to the shaft. Femoral Mode 3 depicts primarily a reduction of inferior projection of both condylar heads with respect to the intercondylar fossa with higher values of the mode. Higher values of femoral Mode 4 represent shapes where there is an increase of the inferior projection of the lateral condylar head and a decrease of the inferior projection of the medial head with respect to the patellar groove along with differences in the width and angle of the shaft relative to the epicondylar width. Mode 5 higher values are associated primarily with shape and medial extension of the medial epicondyle. In tibial Mode 1, positive values represent shapes with increased superior elevation of the tibial plateaus along with decreased shaft width relative to head width. Higher values of tibial Mode 2 demonstrate increased head width with respect to shaft width, concurrent lateral angulation of the head with respect to the shaft, and increased concavity of the lateral plateau with decreased concavity of the medial plateau. The higher values of tibial Mode 3 manifest in slightly increased tibial width along with medial plateau depression and lateral plateau elevation. Higher values of Mode 4 represent elevation of the medial lip and slight broadening of the lateral plateau and straightening of the lateral border of the bone at the shaft/head interface. Higher values of tibial Mode 5 primarily represent shapes with elevation of the lateral plateau and depression of the medial plateau.

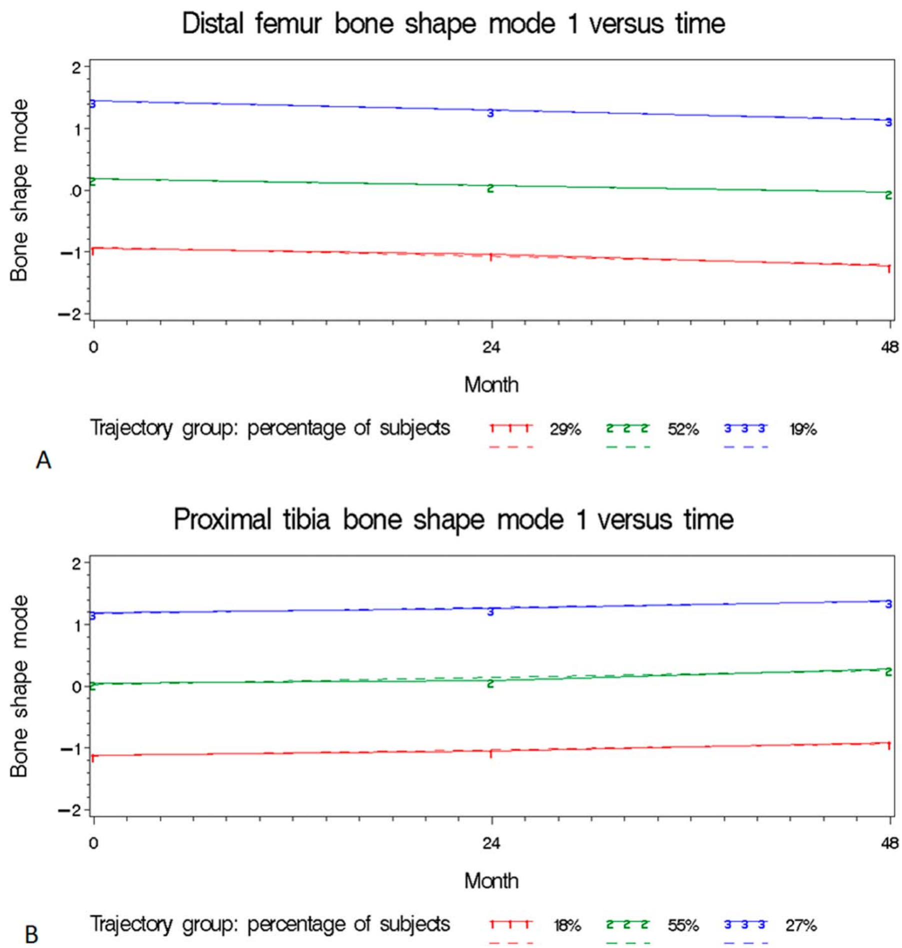

Fig. 3 Trajectory groups during a 4-year period for Mode 1 of the distal femur and Mode 1 of the proximal tibia display little or no change. (**A**) The three trajectory groups of Mode 1 in the femur and their change over 4 years are displayed. (**B**) The three trajectory groups of Mode 1 of the tibia and their change over 4 years are shown here.

and tibia, the average measure of the given mode at baseline for the three trajectory groups for that mode were different; however, the speed of mode change over time was similar in each trajectory group and slopes were shallow or flat (Fig. 3).

Do Females and Males Have Different Trajectories of Bone Shape Changes?

Females and males had different trajectories of bone shape change, and they differed markedly. Mode 1 in the femur and tibia (higher values of femoral Mode 1 display increased the depth of the intercondylar fossa and broadening of the shaft width relative to the epicondylar width; in tibial Mode 1, positive values represented shapes with increased superior elevation of the tibial plateaus along with decreased shaft width relative to head width) explained the greatest amount of variance in shape. In Mode 1 of the femur, females were more likely to be in trajectory Groups 3 (odds ratio 30.2; 95% CI [12.2 to 75.0]; $p < 0.001$) and 2 (OR 4.1; [95% CI 2.3 to 7.1]; $p < 0.001$) than males; thus, females had increased depth of the intercondylar fossa and broader shaft width relative to epicondylar width compared with males (Table 2). Other associations between the trajectory of change in the femur's shape and sex were noted for Mode 2 (females were less likely to be in Groups 2 or 3 than males and thus displayed a medial shift of the angulation of the head with respect to the shaft), Mode 4 (females were more likely to be in Groups 2 or 3 than males and therefore had increased inferior projection of the lateral condylar head and decreased inferior projection of the medial head), and Mode 5 (females were less likely to be in Group 3 than males and thus had less extension of the medial epicondyle). For Mode 1 in the tibia, females were less likely to be in trajectory Group 2 (OR 0.5 [95% CI 0.3

Table 2. Sex, baseline TF ROA, and trajectory of the shape of the distal femur

Mode of bone shape	Characteristics	Trajectory Group 2 versus Group 1[a]		Trajectory Group 3 versus Group 1[a]	
		OR (95% CI)	p value	OR (95% CI)	p value
1	Sex, females versus males	4.1 (2.3 to 7.1)	< 0.001	30.2 (12.2 to 75.0)	< 0.001
	TF ROA, yes versus no	0.6 (0.3 to 1.0)	0.03	0.4 (0.2 to 0.8)	0.008
2	Sex, females versus males	0.5 (0.3 to 0.9)	0.02	0.5 (0.3 to 1.0)	0.05
	TF ROA, yes versus no	1.4 (0.8 to 2.7)	0.26	1.2 (0.6 to 2.4)	0.61
3	Sex, females versus males	0.7 (0.3 to 1.4)	0.27	1.1 (0.5 to 2.4)	0.77
	TF ROA, yes versus no	1.0 (0.5 to 2.1)	0.99	2.9 (1.3 to 6.2)	0.008
4	Sex, females versus males	3.7 (2.1 to 6.6)	< 0.001	5.0 (2.6 to 9.4)	< 0.001
	TF ROA, yes versus no	0.8 (0.5 to 1.5)	0.56	1.7 (0.9 to 3.2)	0.11
5	Sex, females versus males	1.0 (0.6 to 1.9)	0.93	0.2 (0.1 to 0.5)	< 0.001
	TF ROA, yes versus no	0.5 (0.3 to 0.9)	0.03	0.2 (0.1 to 0.5)	< 0.001

[a]Adjusting for age, race, and BMI categories (normal, overweight, and obese); TF ROA = tibiofemoral radiographic osteoarthritis.

to 0.9]; p = 0.01) than males and thus had decreased superior elevation of the tibial plateaus and increased shaft width relative to head width. For Modes 2 and 3 in the tibia, females were also less likely than males to be in trajectory Group 3 of each mode and thus had decreased lateral angulation of the head with respect to the shaft and decreased concavity of the lateral plateau and increased concavity of the medial plateau, along with medial plateau elevation and lateral plateau depression (Table 3). No other associations between sex and trajectory of the femur or tibia's shape were identified. Adjustment for age, BMI and race produced no changes in any odds ratios reported.

Is Radiographic OA at Baseline Associated With Trajectories of Bone Shape Changes?

Radiographic OA at baseline was associated with specific shape change trajectory groups. For Mode 1 in the femur, knees with OA were less likely to be in trajectory Groups 3 (OR 0.4 [95% CI 0.2 to 0.8]; p = 0.008) and 2 (OR 0.6 [95% CI 0.3 to 1.0]; p = 0.03) than knees without OA. Knees with OA were more likely to be in trajectory Group 3 of Mode 3 in the femur than knees without OA (OR 2.9 [95% CI 1.3 to 6.2]; p = 0.008) and thus had reduced inferior projection of both condylar heads. Knees with OA were also less likely to be in trajectory Groups 2 and 3 of Mode 5 in the femur than knees without OA and thus had less medial extension of the medial epicondyle. For Mode 1 in the tibia, knees with OA were not associated with trajectory (OR 1.2 [95% CI 0.7 to 2.4]; p = 0.50) in trajectory Group 3; OR 1.1 [95% CI 0.6 to 1.9]; p = 0.78 in trajectory Group 2). We identified no other associations between tibiofemoral radiographic OA and trajectory of the femoral or tibial shape.

Discussion

Knee OA is more common in females than in males; however, the biological mechanisms for this sex difference in

Table 3. Sex, baseline TF ROA, and trajectory of the shape of the proximal tibia

Mode of bone shape	Characteristics	Trajectory Group 2 versus Group 1[a]		Trajectory Group 3 versus Group 1[a]	
		OR (95% CI)	p value	OR (95% CI)	p value
1	Sex, females versus males	0.5 (0.3 to 0.9)	0.01	0.7 (0.4 to 1.2)	0.17
	TF ROA, yes versus no	1.1 (0.6 to 1.9)	0.78	1.2 (0.7 to 2.4)	0.50
2	Sex, females versus males	0.7 (0.4 to 1.2)	0.17	0.4 (0.2 to 0.8)	0.02
	TF ROA, yes versus no	0.5 (0.3 to 1.0)	0.06	0.5 (0.3 to 1.1)	0.10
3	Sex, females versus males	0.9 (0.5 to 1.6)	0.72	0.4 (0.2 to 0.7)	0.001
	TF ROA, yes versus no	0.8 (0.5 to 1.4)	0.48	1.2 (0.7 to 2.3)	0.51
4	Sex, females versus males	1.6 (0.8 to 3.4)	0.22	1.9 (0.9 to 4.2)	0.10
	TF ROA, yes versus no	0.7 (0.3 to 1.4)	0.31	0.7 (0.3 to 1.6)	0.43
5	Sex, females versus males	1.1 (0.6 to 1.9)	0.78	1.2 (0.6 to 2.5)	0.58
	TF ROA, yes versus no	0.8 (0.5 to 1.5)	0.50	0.7 (0.3 to 1.5)	0.32

[a]Adjusting age, race, BMI categories (normal, overweight, obese); TF ROA = tibiofemoral radiographic osteoarthritis.

knee OA are not well understood. Knee shape is associated with OA and sex, but patterns of change in the bone's shape over time and their relation to sex and OA were previously unknown. We examined whether knee shape changes over time in an older population susceptible to OA and found there is relatively little change, but there are associations of sex and OA with some shape patterns of the femur and tibia. Adjusting for age, race and BMI made little difference in the effect size or significance of association.

This study had a number of limitations. First, although this was to our knowledge the largest radiography-based statistical shape modeling study examining trajectories of change in bone shape over time and their relation to sex and OA, it had a relatively small sample size, and smaller effect sizes may have been missed because of insufficient statistical power; however, smaller effect sizes will also likely represent associations of lesser importance. Second, the 4-year time span is relatively short, and different patterns of changes in bone shape might have emerged if we had used a longer observation period, although given the very small rates of change of shape over time, it is unlikely that observation periods of any reasonable length would have changed the findings of this study. Although radiograph acquisition was standardized and tightly controlled, subject positioning differences may have nonetheless been present, and may have contributed an unknown amount or direction of confounding to the results. It is unlikely that even systemic radiograph positioning problems would be pervasive enough to account for the large effect sizes seen here for segregation by sex of trajectory groups, and random positioning problems would have likely biased towards the null. This statistical shape modeling study was based on 2-D imaging, and 3-D imaging might have identified features not observable on plain radiography; it is unknown whether any such features would have been associated with sex or OA.

Due to the absence of 3-D MRI readings for the current study's knees in OAI, we could not examine the relation of soft tissue elements to bone shape. Although elements such as mechanical axis, the integrity of the cruciate ligaments and the collateral ligaments, as well as meniscal and articular cartilage status could potentially affect bone shape, we believe all these factors are unlikely to have occurred before or at the same time when a participant's sex was determined. Thus, these factors are unlikely to be potential confounders but rather mediators between sex and bone shape trajectory. As a result, adding these covariates in the regression model may bias the association between sex and bone shape trajectory. Specifically, by adding these covariates, the model may not generate the total effect but the direct effect of sex on the trajectory of bone shape. Furthermore, such a direct effect (that is, the effect of sex on trajectory of bone shape not through its effect on these variables) may also be susceptible to potential selection bias. This issue has been discussed by many investigators [8, 40].

Does the Shape of the Knee Segregate Stably Into Different Groups of Trajectories of Change?

The trajectories of changes in the knee's shape during the 4-year period appeared to be stable in an older population. This finding differs in some ways from the findings of prior studies, primarily that of Zhong et al. [50], who reported changes in the knee's shape within 3 years after ACL reconstruction. However, that study differs from the current one in many ways; bone shape remodeling occurred in the context of a joint injury, and the age of the participants was much younger than that in the current study (mean age of approximately 30 years versus a mean age of almost 60 years). Pedoia et al. [35] reported shape change in the knee after anterior cruciate ligament injury in young persons, but this study differed in many ways from the current one, particularly in the injury-related context as well as using 3-D MRI rather than radiography. A study examining shape variations over time in a different joint, the hip, reported changes in the volume and shape of the femoral head and neck during 36 months that were associated with hip pain [20]. However, there are multiple differences from the current study: a different joint, much younger participant age (47 years versus almost 60 years), and MRI was used instead of radiography. In many physiologic parameters (for example, blood pressure), people divide into separate groups early in life and subsequently follow the slope of change in that parameter through the ensuing decades [27, 36]. Bone shape differences and factors that divide knees into different trajectory groups may arise early in life, as observed in the studies above, and then persist into late life without radical change, as observed in the current study.

The current study also sheds new light on the malleability or fixed nature of bone shape at different ages. Recently investigators have reported bone shape changes within a year after ACL tears in young people [35], and the extent of the shape changes reported in that study is striking. This naturally raises the question of whether such bone shape changes are occurring as a normal part of aging or in response to changes over time in life circumstances or habits, and particularly whether shape changes occur in conjunction with OA in the older population who are at greater risk for the disease. The current study clearly shows that although different trajectory groups are associated with OA in older persons, the shape changes vary little over time, suggesting that the rapid shape change noted after trauma early in life does not occur widely in response to age-related OA. When a surgeon must consider delaying surgery due to patient hesitation or other factors, this study may reassure them that at least in the area of bone shape, little is likely to change as a result of the delay.

Do Females and Males Have Different Trajectories of Bone Shape Changes?

Multiple studies using statistical shape modeling have found that there are sex-related differences in knee shape in individuals with and without knee OA [2, 30, 34, 42, 45], but these have all evaluated bone shape at a single timepoint. A few published studies described change in the knee's shape over time [20, 35, 50]; however, none of these trajectory-related statistical shape modeling studies examined the relation of sex to change in bone shape over time. This may be because all of the studies had relatively small numbers of participants and likely did not have power to identify sex-related differences. To our knowledge, the current study is the first to identify sex-related differences in trajectories of bone shape changes over time as measured by statistical shape modeling. A prior cross-sectional study reported that a shape mode was strongly associated with sex, which is very similar in shape to our current study's femoral Mode 1 [42], and this mode in the current study has the largest effect size for association with sex, lending face validity to the findings. The strong association, along with the relative stability of shape in older age, suggests that sex, which is present at birth, contributes to bone shape early in life and that trajectories in shape changes even late in life are influenced by this early determinative factor.

The findings of the current study have both relevance to clinical research on the relation of sex differences and OA with bone shape and have clinical relevance, as well. The magnitude of the associations between sex and bone shape trajectory groups are striking, with ORs of 4.1 to 30.2 for Mode 1 in the femur. This has relevance to the field of OA research, as investigators in the field of OA have struggled to identify the underlying reasons and mediating factors to try to explain why women are substantially more likely to develop OA than men, and why the phenotypes that knee OA takes differs between females and males in its manifestations [17, 23, 28, 29, 43, 44, 48]. We have previously identified associations between knee bone shape and sex among persons without OA [42], and have reported mediation of the relation between sex and OA by bone shape [45], but it has remained unknown until the current study whether differences by sex in bone shape are established early in life and persist or whether sex continues to exert active influence later in life on the shape of the knee bones; the current study demonstrates clearly that sex has an influence on bone shape but that this influence is mostly exerted early in life. This ultimately has clinical relevance because it suggests that interventions late in life that might be based on physiologic and morphologic sex differences may not be as effective for altering the course of OA.

There has been considerable work in the orthopaedic field on the question of whether gender-specific TKA implants confer outcome benefits in function or pain or other measures. Earlier studies identified three primary morphologic differences that were claimed to differ by sex and which were used subsequently in designing and testing gender-specific implants: women were reported to have a less prominent anterior condyle, an increased quadriceps angle (or "Q angle"), and a reduced mediolateral to AP aspect ratio [5, 7, 10-12, 14, 18, 19, 37, 46-49]. However, other cadaveric and systematic review studies have reported "no meaningful anatomic differences between male and female knees" [3, 32], or have found more complicated relationships between sex and anatomy involving other interacting factors [2]. Merchant et al. [32] systematically reviewed the studies on which the reported sex differences were based and stated that two of the proposed sex differences "do not exist" and the "third is so small that it likely has no clinical effect." Gender-specific prostheses are available based on these three purported sex-related shape differences, and studies examining outcomes have found no apparent clinical benefit in terms of pain, patient satisfaction, ROM, and other outcomes [6, 21, 25, 26, 32, 39]. Thus, the design and use of gender-specific prostheses to date has been based on sex shape differences which may not even exist, and this may explain why there has been no apparent clinical benefit.

The current study has taken a very different approach to examining differences in shape by sex among older persons by using statistical shape modeling and has identified bone shape differences with high levels of segregation by sex. Notably, none of the modes where differences by sex were found in the current study (femoral Modes 1, 4, and 5, and tibial Modes 1, 2, and 3) have any definite relation to the three morphologic sex differences that all gender-specific prostheses have to date been designed around. Despite the inability of prior gender-specific prostheses to improve outcomes, the current study supports the potential for consideration of prosthetic designs based around other sex-related shape differences.

Is Radiographic OA at Baseline Associated with Trajectories of Bone Shape Changes?

Studies have reported the cross-sectional association between knee shape modes and OA [4, 16], and bone shape as a predictor of the incidence or progression of knee OA has also been recently studied. Neogi et al. [34] evaluated statistical shape modeling using MRI of the femur, patella, and tibia to determine whether modelling could predict incident knee OA during a 12-month period and identified that a shape mode that combined multiple types of knee shape difference was strongly associated with disease. Wise et al. [45] reported that the bone shape at baseline was associated with incident knee OA and in part mediated the relationship between sex and OA. Investigators have also reported associations between bone shape in two and three dimensions with hip OA [13, 20, 31]. Inamdar et al. [20] performed a longitudinal evaluation of the proximal femur's shape using 3-D MRI in males and females and identified two modes that were associated over time with changes in cartilage composition, self-reported pain, and cartilage lesions. However, the sample size was limited to 46 patients and the longitudinal evaluation was limited to 36 months; therefore, larger studies with longer follow-up will be needed to determine the clinical relevance of these findings in the hip. Thus, although there appears to be some support from published studies that the shape of multiple joints is associated with incident or cross-sectional radiographically defined OA, the current study found an association between trajectories of shape changes and OA in the knee specifically. Bone shape may ultimately be incorporated into predictive models for OA, but once older age is reached, the joint's shape has mostly been determined, and any effect on the incidence of OA is not likely to derive from shape change trajectories.

Without further work, it is not possible to define how elements of mode-shape difference affect the associations with OA or sex, and so discussion of this is by its nature speculative. Nonetheless, it is worth noting that for the femur, adjusted associations for trajectory groups with OA were strongest for Modes 1, 3, and 5, and that both Modes 1 and 5 largely represent differences in the shapes of the epicondyles and their relation to the shaft, which echoes prior studies showing juxtarticular shape changes associated with distant OA [41]; femoral Mode 3 involves differences in the inferior projection of the medial and lateral condyles and their relation to the intertrochanteric groove, areas that are points of contact in the joint and directly involved in cartilage and subchondral bone disease. Shape differences in the tibia were not found to be associated with OA in adjusted analyses.

In summary, using a statistical shape modeling approach, the shapes of the distal femur and proximal tibia did not change much over 4 years in older age. Sex and baseline knee radiographic OA status are associated with the trajectory of bone shape changes, suggesting that both may contribute earlier in life to associations with trajectory group observed in older individuals. Information about the association between sex and specific bone shapes may suggest new avenues for investigation of sex-specific knee replacement prostheses. Future studies might explore sex-related bone shape change earlier in life and over longer periods of time to help determine when the sex-specific shapes arise and also the degree to which these sex-related shapes are alterable by injury or other events.

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