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Distribution and Correlates of Hip-Knee-Ankle Angle in Early Osteoarthritis and Preoperative Total Knee Arthroplasty Patients

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ABSTRACT

Background: Several studies have investigated the distribution of hip-knee-ankle (HKA) angle in healthy populations; however, few have evaluated this metric in patients undergoing total knee arthroplasty (TKA). The purpose of this study is to compare HKA angle distribution in early and advanced knee osteoarthritis (OA) patients.
Methods: Full limb radiographs were used to measure HKA angle for 983 subjects from the Osteoarthritis Initiative (OAI) cohort and 4,901 pre-TKA patients from an institutional cohort. Measurements were made using a previously validated deep learning algorithm. Linear regression models were used to determine the association of HKA alignment angle with patient characteristics.
Results: The mean ± standard deviation HKA angle was −1.3° ± 3.2° in the OAI cohort and −4.1° ± 6.1° in the pre-TKA cohort. In the OAI cohort, normal alignment (64%) was the most common knee alignment followed by varus (29%), and valgus (7%). In pre-TKA patients, the most common alignment was varus (62%), followed by normal (27%) and valgus (11%). In pre-TKA patients, mean HKA angle in primary knee OA, post-traumatic knee OA, and rheumatoid arthritis patients were −4.3° ± 6.1°, −3.2° ± 6.4°, and −2.9° ± 6.1°, respectively. HKA angle was strongly associated (P < .001) with gender and body mass index.
Conclusion: TKA patients have a wider alignment distribution and more severe varus and valgus alignment than individuals "at risk" for knee OA from the OAI cohort. These epidemiologic findings improve our understanding of HKA angle distribution and its correlation with demographic characteristics in early and late-stage arthritis.

Hip-knee-ankle (HKA) angle is defined as the angle formed by the mechanical axis of the femur and tibia as measured on a full limb radiograph [1]. In a neutrally aligned knee, this line passes from the center of the femoral head, through the midpoint between the tibia intercondylar eminences, and through the center of the talus. HKA angle has an important role in proportional load distribution between medial and lateral compartments of the knee joint. While in a neutrally aligned knee, 60%-70% of knee force passes across the medial compartment during daily activity, in varus and valgus knees the force passes disproportionately through the medial and lateral compartments, respectively [2,3].

HKA angle is an important measure of the lower limb due to its association with knee osteoarthritis (OA) and its application for preoperative planning in knee joint reconstruction surgeries such as osteotomies and knee arthroplasty [4,5]. Severity of lower limb malalignment is associated with progression of knee OA,

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magnitude of cartilage loss as assessed by magnetic resonance imaging, and quantitative joint loss on radiographs [6–8].

There are several studies that investigated the distribution of knee alignment in healthy individuals [9–12]. Yet relatively little is known how knee alignment differs in early and advanced knee OA patients. This is in part due to the need for full-length lower extremity radiographs for HKA angle measurement, which in turn makes large-scale epidemiologic studies cumbersome and expensive. In a small study by Cooke et al [13], investigators showed that knee alignment in 167 patients with knee OA (-3.95 ± 7.75) differed significantly from 119 healthy adults (-0.97 ± 2.68) and overall alignment was more varus by approximately 3°. Furthermore, Brouwer et al [8] investigated the association between knee malalignment and the development and progression of knee OA in 1,501 participants, but the study was limited since it relied on anatomic axis in knee radiographs instead of the mechanical axis in full-limb radiographs.

We therefore aimed to compare HKA angle distribution in 2 large cohorts representing different stages of knee OA. One cohort included individuals from the Osteoarthritis Initiative (OAI) with either established knee OA or significant risk factors for development of knee OA. The other cohort included individuals with advanced symptomatic knee OA who underwent TKA (pre-TKA). We compared the distribution of HKA angles in these cohorts, and examined the association between HKA angle with age, gender, body mass index (BMI), and the etiology of arthritis. We hypothesized that HKA angle distribution would differ in these cohorts and by patient characteristics.

Patients and Methods

The study population included 2 cohorts: 983 subjects from the OAI cohort and 4,901 TKA patients from the institutional joint replacement registry. Mean age of the 983 OAI subjects was 61.5 ± 9.1 years, mean BMI was 27.6 ± 4.3 kg/m^2, mean KL (Kellgren and Lawrence) grade was 1.08 ± 1.14, and 53% were female. Briefly, the OAI is a publicly available, longitudinal, observational cohort study of individuals with either established knee OA or with significant risk factors for development of knee OA [14]. The institutional TKA cohort comprised 4,901 patients with advanced symptomatic knee OA who underwent TKA surgery between 2000 and 2017 and had full-limb presurgery radiographs available. Mean age of the 4,901 pre-TKA patients was 66 ± 10.4 years, mean BMI was 31.7 ± 6 kg/m^2, and 55% were female. Age and BMI were similar between males and females (Table 1). The most common etiology for TKA was primary knee OA (83%), followed by post-traumatic arthritis (14%) and rheumatoid arthritis (RA) (1%).

For measurement of the HKA angles, we used a previously developed and validated deep learning algorithm [15]. Briefly, the deep learning algorithm was developed using radiographs from the OAI cohort and validated using institutional radiographs. The mean difference between human-level and machine-level HKA measurements was $0.44° \pm 0.35°$, and differences of 1.5° or more between human-level and machine-level measurements were observed in less than 0.6% of cases, indicating almost perfect performance. By convention, varus angles were indicated by negative numbers and valgus angles were indicated by positive numbers. Knees were considered as having varus malalignment if the HKA angle was $-3°$ or less, as normal if the HKA angle was between $-3°$ and $+3°$, and as having valgus malalignment if the HKA angle was 3° or more.

Statistical Analysis

Demographic data were presented using means and standard deviations for continuous data and counts and percentages for categorical data, as appropriate. To account for issues of multiple testing, we employed a multivariate analysis of variance test to evaluate relationships among age, gender, BMI, and etiology of arthritis with HKA angles. We explored several alternative models that included transformations of the BMI variable (ie, square root BMI, log BMI, cube root BMI, BMI squared, BMI cubed) to account for curvilinear relationships of BMI with HKA angles as well as interaction terms. The R^2 values for different models were relatively low at 0.05 and 0.09 for both legs. Each BMI transformation resulted in changes to the R^2 of only tenths or hundredths of a percent. Thus, none were deemed to be a significant improvement to the model's ability to explain variation in HKA angles. The untransformed BMI was used for all analyses. Similarly, the R^2 values in models with and without the gender $\times$ BMI interaction term were similar a R^2 differences of about 0.1% in the left leg and 0.3% in the right leg. All statistical analyses were performed using [SAS/STAT] software, Version [9.4] of the SAS System for [Unix], copyright 2016 (SAS Institute Inc, Cary, NC). *P*-values <.05 were considered statistically significant.

Results

Mean HKA angle for the 983 OAI subjects was $-1.3° \pm 3.2°$ (Fig. 1). Mean HKA angle in male and female subjects were $-1.9° \pm 3.2°$ and $-0.8° \pm 3.1°$, respectively. The most common categorical knee alignment was normal (64%) followed by varus (29%) and valgus (7%). The distribution of the HKA angle among the 4,901 pre-TKA patients in the institutional cohort was wider than the OAI cohort with a mean of $-4.1° \pm 6.1°$ and a median of $-4.6°$ (Fig. 1). The most common categorical knee alignment was varus (62%), followed by normal (27%) and valgus (11%). Mean HKA angle in male and female patients was $-5.2° \pm 5.6°$ and $-3.3° \pm 6.4°$, respectively (Fig. 2). Although there was similar male to female ratio in varus malalignment knees (50%), valgus malaligned

Table 1
Characteristics of 4,901 Institutional Pre-TKA Patients.

| Characteristic	Male	Female	Total
Number of patients	2,203	2,698	4,901
Age ± SD (y)	66.5 ± 10.4 (range 17-96)	65.5 ± 10.4 (range 22-96)	66 ± 10.4 (range 17-96)
Height ± SD (cm)	177.4 ± 36.8 (range 153-200)	162.3 ± 13.7 (range 109-89)	169.1 ± 27.7 (range 109-200)
Weight ± SD (kg)	98 ± 18.5 (range 58-174)	84.3 ± 18.6 (range 37-172)	90.4 ± 19.7 (range 37-174)
Body mass index ± SD (kg/m^2)	31.3 ± 5.3 (range 18.1-56.8)	31.9 ± 6.6 (range 15.6-61.2)	31.7 ± 6 (range 15.6-61.2)
Arthritis etiology (% of total)			
Primary osteoarthritis	1,747 (79.3%)	2,323 (86.1%)	4,070 (83.0%)
Post-traumatic osteoarthritis	380 (17.2%)	288 (10.7%)	668 (13.6%)
Rheumatoid arthritis	16 (0.7%)	29 (1.1%)	45 (0.9%)
Other	60 (2.7%)	58 (2.1%)	118 (2.4%)

SD, standard deviation; TKA, total knee arthroplasty.
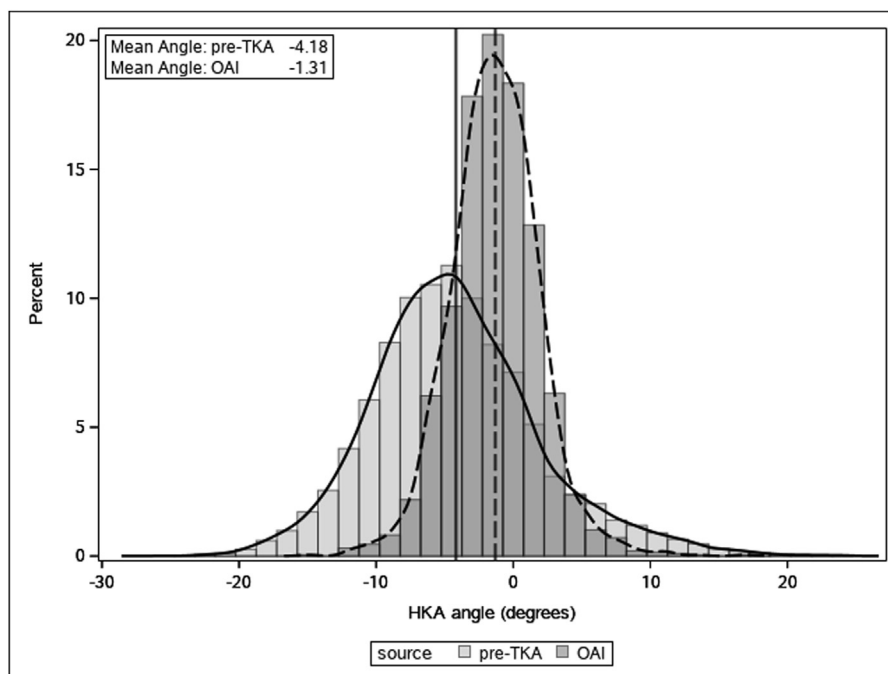
Fig. 1. Distribution of hip-knee-ankle angle and mean HKA in 983 OAI participants and 4,901 institutional pre-TKA patients. HKA, hip-knee-ankle; OAI, Osteoarthritis Initiative.

knees were more common among female compared to male patients (71% vs 29%). Normal knee alignment was more common among females compared to males (60% vs 40%). Mean HKA angle in primary knee OA, post-traumatic knee OA, and RA patients were −4.3° ± 6.1°, −3.2° ± 6.4°, and −2.9° ± 6.1°, respectively (Table 2).

In multivariate analysis of variance (Table 3), we observed strong associations ($P < .001$) between HKA angle with gender and BMI and a significant quantitative interaction between gender and BMI ($P < .001$). The association between BMI and HKA angles was different in females and males (Fig. 3A and B). At lower BMI, HKA angles were more varus in males than in females. However, at
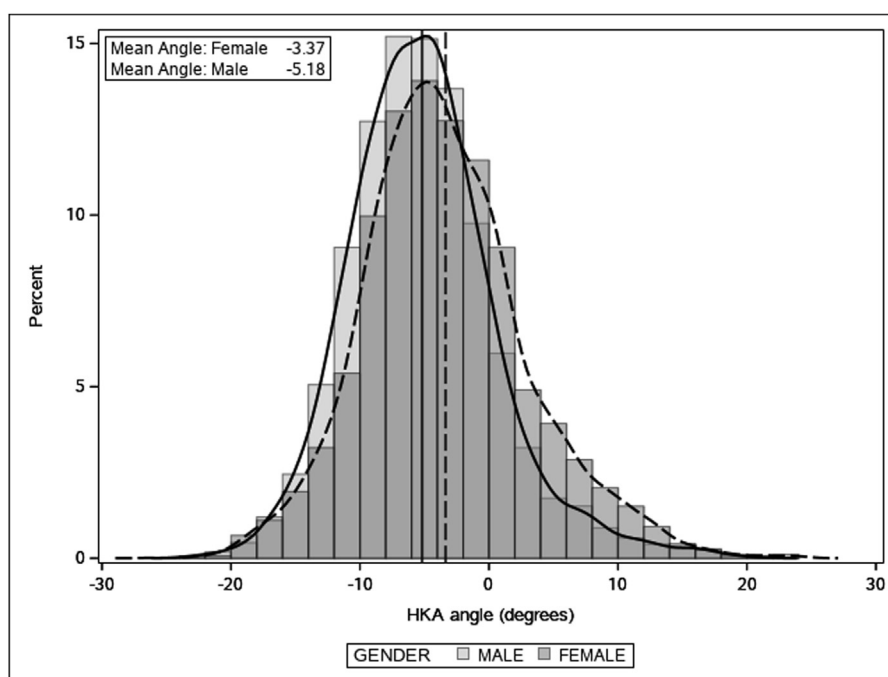
Fig. 2. Distribution of HKA angle and mean HKA of 2,203 male and 2,698 female institutional pre-TKA patients. HKA, hip-knee-ankle; TKA, total knee arthroplasty.

Table 2
HKA Angle Measurements by Arthritis Etiology in 4,901 Institutional Pre-TKA Patients.

Characteristic	Male (N = 2,203)	Female (N = 2,698)	All (N = 4,901)
HKA angle ± range	−5.2° ± 5.6°	−3.3° ± 6.4°	−4.1° ± 6.1°
Primary osteoarthritis	−5.4° ± 5.5°	−3.5° ± 6.4°	−4.3° ± 6.1°
Post-traumatic osteoarthritis	−4.1° ± 6.3°	−2.2° ± 6.4°	−3.2° ± 6.4°
Rheumatoid arthritis	−4.8° ± 4.4°	−1.8° ± 6.7°	−2.9° ± 6.1°

HKA, hip-knee-ankle; TKA, total knee arthroplasty.

higher BMI, HKA angles were more varus in females than in males. For example, mean HKA angle was −1.3° in male patients with a normal BMI (18.5-25 kg/m^2) and −3.8° in female patients with a normal BMI, corresponding to a difference of 2.5°. At a BMI of >40 kg/m^2, mean HKA angle was −5° in both females and males with a difference of only 0.5° (Fig. 3A and B).

Discussion

Lower limb malalignment as measured by the HKA angle is an established risk factor for knee OA. A better understanding of the distribution of HKA angle over time and how it relates to other knee OA risk factors is important to understand the etiology of knee OA, enhance preoperative planning, and potentially enable more patient-specific TKA alignment targets. However, measurement of the HKA angle is a cumbersome task in research settings for large patient cohorts. We used a previously validated deep learning model to automatically measure HKA angle in 2 large cohorts of patients representing both early and advanced knee OA. Our findings indicate that the distribution of knee alignment differ significantly in early and advanced knee OA. In pre-TKA patients, knee alignment is strongly associated with both gender and BMI, and the association between BMI and knee alignment differs in females and males.

The first notable finding of our study is the significant difference in HKA angles in the OAI cohort and the institutional pre-TKA patients. Although the OAI population is a selected group of participants [16] at high risk for knee OA [14], our institutional cohort comprised patients with advanced radiographic and symptomatic knee OA with plans for TKA. Therefore, the most common alignment in the OAI dataset was normal (between −3° and 3°), whereas the most common alignment among the pre-TKA patients was varus. This finding is consistent with previous studies reporting on HKA angle in healthy and low-grade knee OA populations [9,11−13,17].

In pre-TKA patients, we examined the cross-sectional association of HKA angles with 4 patient characteristics: age, gender, BMI, and arthritis etiology. Male patients had more varus knee malalignment compared to female patients overall, but this difference was highly variable between BMI categories. Another important finding is that about 40% of the pre-TKA cohort had either normal or valgus knee alignment. Female to male ratio was 3:2 in the

Table 3
Association of Patient Characteristics With HKA Angles in 4,901 Institutional Pre-TKA Patients.

Characteristic	F-Value	P-Value
Age	0.64	.5268
Gender	17.52	<.0001
Body mass index	38.77	<.0001
Arthritis etiology	6.38	<.0001
Gender × body mass index	6.83	.0011

HKA, hip-knee-ankle; TKA, total knee arthroplasty.

normal knee alignment group and was even higher (about 2.5:1) in the valgus knee malalignment group. High BMI is a well-known risk factor for knee OA and most patients in our preoperative cohort were obese. We found that every 5 kg/m^2 increase in BMI was associated with −0.60° change in HKA angle. Furthermore, we found that HKA angles were more varus in males than in females at lower BMI and the opposite at higher BMI. This finding is in agreement with a previous study of 300 subjects with OA [18] which showed that BMI and malalignment were correlated in varus knees but not in those with valgus knees. In terms of etiology, all 3 arthritis etiologic groups (Primary OA, RA, post-traumatic) had mean varus malalignment with primary OA being the most pronounced.

Although we could not find any studies reporting on HKA angle measurements in preoperative full-limb radiographs of patients who underwent TKA, there are a few studies that investigated HKA angle distribution in full-limb radiographs of individuals with knee OA. Cooke et al [13] measured HKA angles in 167 participants with symptomatic knee OA with a mean age of 66 years. Overall alignment in this group was 3° varus, and HKA angle in male and female patients was −5.9° and −2.3°, respectively and categorically male patients were more likely to have varus whereas female patients were more likely to have valgus knee OA. In a study by Kraus et al [17], HKA angle was measured in 57 participants (40 female and 17 male) with symptomatic knee OA with a mean age of 67 years. They graded severity of knee OA based on the standard KL radiographic system and reported HKA angle for each group. HKA angle in their population ranged from 16° varus to 13° valgus alignment. They did not observe any association between age and HKA angle, but the severity of knee OA and BMI was associated with HKA angle. It is important to note that a few studies reported on knee alignment angle based on knee anteroposterior radiographs instead of full-limb radiographs [8,19,20]. Although there is a correlation between mechanical and anatomical alignment [17,21], this method is not optimal since the anatomical axis has approximately 4°-6° of femoral valgus compared to mechanical axis, and cannot account for extraarticular deformities [17].
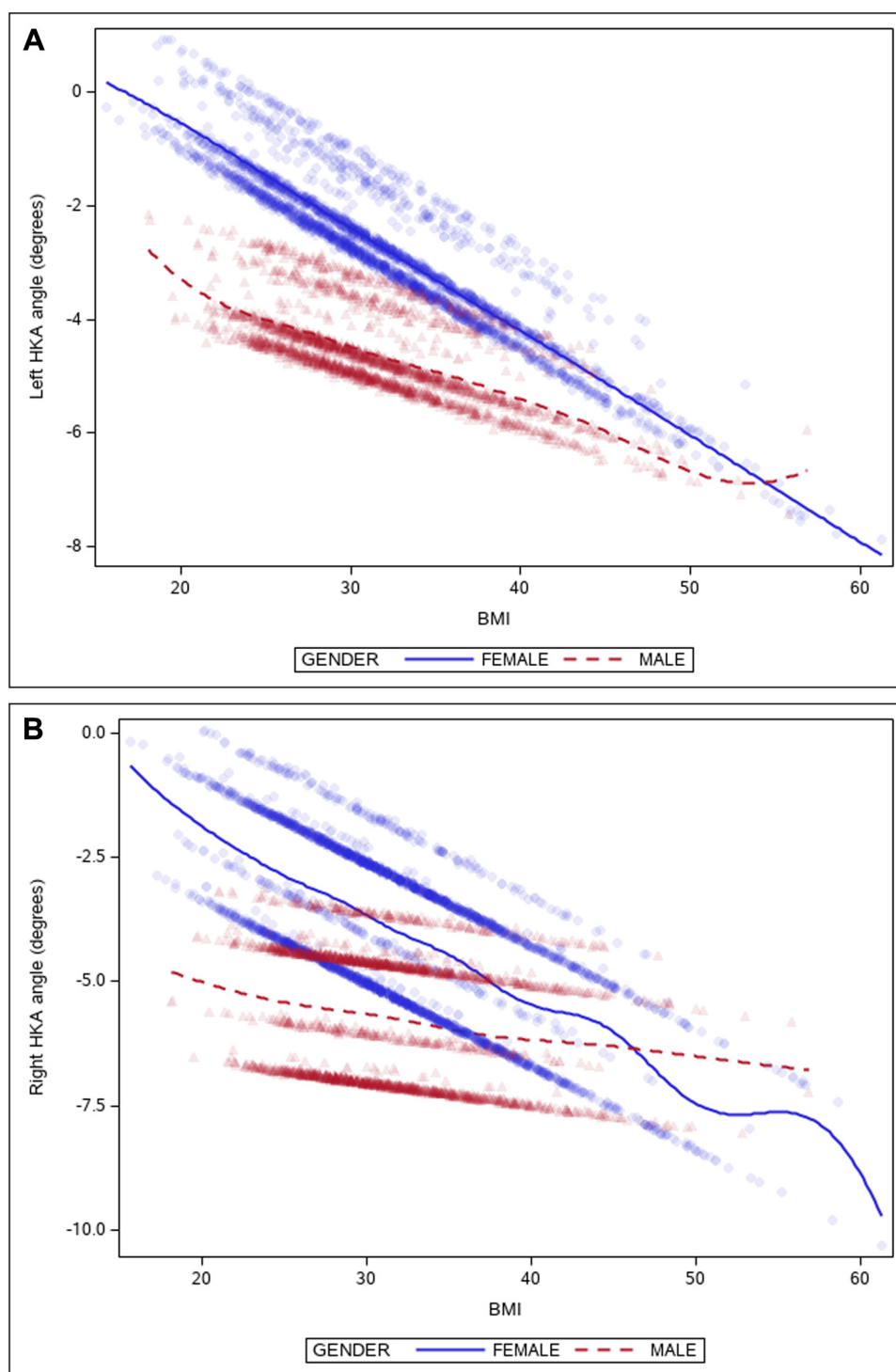
There are several potential limitations of this study. First, although our model had high precision in measuring HKA angles and we randomly annotated and checked images in different alignment ranges which showed acceptable precision (mean error of 1.7°), there is still a chance that errors in our model prediction could affect the distribution of the alignment angle in our cohort. Second, the study reports knee alignment results in only a subset of subjects from the OAI and pre-TKA patients from an academic institution. Selection bias is a concern when only a subset of subjects is included from both cohorts. Importantly, we did not have data on KL grades in pre-TKA patients and therefore are unable to examine alignment distribution by OA grade. However, the large cohort size, inclusion of subjects with discrepant knee OA severity and association with other patient characteristics are the unique strengths of the study. Finally, we did not have computed tomography data for our cohort to use as a ground truth for HKA angle measurement. Therefore, we could not study the effect of the limb rotation on HKA angle measurements. Despite these limitations, this study demonstrates the potential of deep learning tools to measure hard-to-ascertain radiographic features in large-scale research projects with relative ease and speed. It takes 1 second for the algorithm to measure HKA angle in each image. For the future direction of this study, we will use the same approach and a validated algorithm to measure HKA angles in post-TKA images which would make it feasible to correlate post-TKA angle with patient outcome and longevity of the prosthesis.

In conclusion, patients presenting for TKA have a wider alignment distribution and more severe varus and valgus

Fig. 3. (A) Distribution of left HKA angles by BMI in males and females. (B) Distribution of right HKA angles by BMI in males and females. HKA, hip-knee-ankle; BMI, body mass index.

alignment than individuals "at risk" for knee OA from the OAI cohort. Males tend to have more varus alignment than females and females have a higher likelihood to be in categorical valgus. BMI has a strong association with knee alignment and more prominently in females with a trend toward varus alignment as BMI increases. These epidemiologic data can serve as a benchmark for future studies and potentially improve understanding of preoperative to postoperative alignment change in TKA patients and how this influences survivorship, function, and patient satisfaction.

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