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Risk factor heterogeneity for medial and lateral compartment knee osteoarthritis: analysis of two prospective cohorts

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SUMMARY

Objective: To evaluate the etiologic heterogeneity between medial and lateral tibiofemoral radiographic osteoarthritis (ROA).
Methods: Knees without medial or lateral tibiofemoral ROA at baseline were followed for 60-month in Multicenter Osteoarthritis Study (MOST) and for 48-month in Osteoarthritis Initiative (OAI). We examined the relation of previously reported risk factors to incident medial and lateral tibiofemoral ROA separately and determined the etiology heterogeneity with a ratio of rate ratios (RRs) (i.e., the RR for medial tibiofemoral ROA divided by the RR for lateral tibiofemoral ROA) using a duplication method for Cox proportional hazard regression.
Results: Of 2,016 participants in MOST, 436 and 162 knees developed medial or lateral tibiofemoral ROA, respectively. Obesity and varus malalignment were 95% and 466% more strongly associated with incident medial tibiofemoral ROA than with lateral tibiofemoral ROA, respectively (ratios of RRs, 1.95 [95% confidence interval (CI):1.05–3.62] and 5.66 [95% CI:3.20–10.0]). In contrast, the associations of female sex and valgus malalignment with incident medial tibiofemoral ROA were weaker or in an opposite direction compared with lateral tibiofemoral Osteoarthritis (OA) (ratios of RRs, 0.40 [95% CI:0.26–0.63] and 0.20 [95% CI:0.12–0.34], respectively). Older age tended to show a weaker association with incident medial tibiofemoral ROA than with incident lateral tibiofemoral ROA. No heterogeneity was observed for the relation of race, knee injury, or contralateral knee ROA. These findings were closely replicated in OAI.
Conclusion: Risk factor profiles for medial and lateral tibiofemoral ROA are different. These results can provide a framework for the development of targeted prevention and potential treatment strategies for specific knee OA subtypes.

Introduction

Osteoarthritis (OA) is the most common joint disorder and a leading cause of disability among older adults. Although numerous studies have been undertaken to identify risk factors for OA and to develop prevention and treatment measures, few effective and safe interventions are available to date[1].

For many years, knee OA was considered a single disease entity, characterized by the loss of articular cartilage. However, as evidence has accumulated, it has become apparent that knee OA is composed of several distinct subtypes[2–7]. Furthermore, where subtypes exist, there may also be differences in the profile of risk factors that contribute specifically to each disease subtype, a characteristic known as “etiologic heterogeneity”.

Our understanding of etiologic heterogeneity between subtypes of knee OA would help guide prevention and treatment strategies

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by targeting risk factors that specifically contribute to the risk of each sub-population (i.e., personalized medicine). For example, tibiofemoral joint is one of the most commonly affected joints by OA; however, the loss of cartilage can occur in either medial or lateral compartment. Some risk factors for medial tibiofemoral OA have been found to be different from those for lateral tibiofemoral OA[8–13]; however, no study to date has formally assessed the etiologic heterogeneity between the two subtypes. Therefore, the purpose of this study was to analyze two large prospective cohort studies of knee OA by applying a method specifically designed to identify and quantify etiologic heterogeneity.

Methods

Study population

The study population was derived from two National Institutes of Health (NIH)-funded prospective cohorts for knee OA, the Multicenter Osteoarthritis Study (MOST) and the Osteoarthritis Initiative (OAI). Beginning in 2003, MOST enrolled 3,026 individuals aged 50–79 years (60% females) who had or were at risk of knee OA and were recruited from two communities (Birmingham, AL, and Iowa City, IA) (http://most.ucsf.edu/studyoverview.asp). Similarly, starting from 2002, OAI enrolled 4,976 individuals aged 45–79 years (59% females) who had or were at risk of knee OA or its progression at four study sites (Baltimore, MD, Pittsburgh, PA, Pawtucket, RI, and Columbus, OH). (https://data-archive.nimh.nih.gov/oai/about-oai).

Within these two cohorts, our study population consisted of subjects who had at least one knee without medial or lateral tibiofemoral radiographic OA (ROA) at baseline (i.e., Kellgren and Lawrence [KL] grade < 2 or joint space narrowing [JSN] score $= 0$ in both the medial and lateral tibiofemoral compartments) (Fig. 1). After excluding knees without JSN or KL assessment conducted at baseline or any follow-up visit to allow ascertainment of incident knee radiographic osteoarthritis (ROA), there were 3,411 eligible knees from 2,016 participants in the MOST cohort and 5,860 eligible knees from 3,476 participants in the OAI for follow-up (Fig. 1).

Assessment of risk factors

In MOST and OAI, information about socio-demographic factors (i.e., age, sex and race). and history of knee injury (defined as a knee injured badly enough to limit one's ability to walk for at least 2 days) was collected at baseline and each subsequent follow-up visit. We specifically examined the association of race with incidence of medial and lateral ROA among White and African America population. Participants were weighed (using a balance beam scale) without shoes or heavy clothes, and had their height measured (using a stadiometer) without shoes. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in square meters (m^2) and categorized as follows: normal (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥ 30 mg/m^2). Knee alignment in MOST was measured from full-limb standing posterior-anterior radiographs using software (OAISYS Inc.) applied to the digitized image[14–16]. Malalignment was defined as a hip-knee-ankle angle of 2° or more in either the varus (negative) or valgus (positive) direction. Neutral alignment was defined as anything less than 2° varus or valgus[17,18]. In the OAI, no full-limb standing posterior-anterior radiographs were available for all participants at baseline; thus, knee alignment was assessed using the femorotibial angle, a proxy for the hip-knee-ankle angle, on a short-knee fixed flexion radiograph[19,20]. Neutral alignment was defined as a femorotibial angle of -5.9 to $-1.9°$ in men and -6.8 to $-2.8°$ in women, respectively. Malalignment was defined in either the varus (femorotibial angle $< -5.9°$ for men and $< -6.8°$ for women) or valgus (femorotibial angle $> -1.9°$ for men and $> -2.8°$ for women) directions[21,22]. KL grade of the contralateral knee assessed at baseline was also considered a potential risk factor for incident medial/lateral tibiofemoral ROA.

Assessment of endpoints: medial vs lateral tibiofemoral ROA

Bilateral knee radiographs were taken at the baseline, 30-, and 60-month visits in the MOST, and at the baseline, 12-, 24-, 36-, and 48-month visits in the OAI. KL and JSN grades at the tibiofemoral joint were assessed at a centeralized reading center. Incident medial or lateral tibiofemoral ROA was defined as the first development of KL grade ≥ 2 and JSN ≥ 1 in the respective compartment[9]. If a knee had JSN ≥ 1 in both compartments at the same study visit, the compartment with the higher JSN score was regarded as the one that developed ROA first. If JSN scores were the same for both compartments, the compartment with the higher osteophyte score was regarded as the one that developed ROA first.

Statistical analysis

Our cohort follow-up began at baseline and ended at the visit of incident medial or lateral tibiofemoral ROA diagnosis, loss to

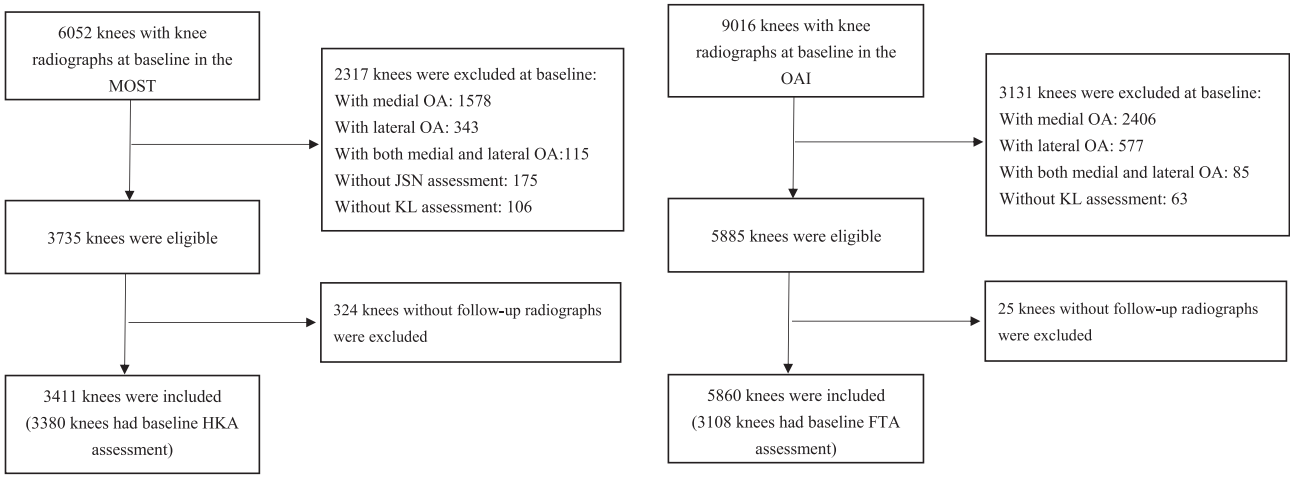

Fig. 1. Flow Chart of Study Population Definition. MOST, Multicenter Osteoarthritis Study; OAI, Osteoarthritis Initiative; OA, osteoarthritis; KL, Kellgren and Lawrence; JSN, joint space narrowing; HKA, hip-knee-ankle angle; FTA, femorotibial angle.

follow-up, or the end of the study period (i.e., the 60-month visit in the MOST or the 48-month visit in the OAI), whichever came first. We calculated the incidence rate by dividing the number of incident medial and lateral tibiofemoral ROA cases by the total follow-up years[23]. We assumed that only one subtype (i.e., either medial or lateral tibiofemoral incident ROA) could occur within a single knee. To account for competing risks (i.e., the occurrence of one subtype of tibiofemoral ROA would preclude the occurrence of another subtype of tibiofemoral ROA), we performed a cause-specific proportional hazard model when examining the relation of each risk factor to the hazard of one specific subtype of tibiofemoral ROA. We did this among knees that had not yet developed either subtype of tibiofemoral ROA[24,25]. Since subjects may contribute data on an outcome (i.e., incident medial/lateral ROA) from each of their two knees, we accounted for intra-subject correlation of the outcome using a marginal approach that estimated the effect of each risk factor while accounting for between-knee correlation by means of "sandwich estimation" of the covariance matrix accomplished in Statistical Analysis System (SAS)[26]. In this analysis, we assumed that the association of each risk factor with either medial or lateral ROA incidence was the same between left and right knee. Finally, we tested whether the risk factor–disease association differed for medial vs lateral tibiofemoral ROA using a ratio of rate ratios (RRs). The ratio of rate ratio was calculated as the RR for medial tibiofemoral ROA divided by the RR for lateral tibiofemoral ROA[25].

For each specific risk factor, we adjusted for potential confounders according to our understanding of the causal structure among the risk factor, potential confounders, and endpoints, guided by a causal diagram (see Appendix). For example, when assessing the effect of sex, we adjusted only for age and race, as other covariates cannot confound the relation. However, when examining the effect of contralateral knee's KL, we adjusted for age, sex, BMI, race, knee malalignment, and knee injury history.

Initially, we conducted the analyses for MOST and OAI separately. Since the relation of each risk factor to the risk of either medial or lateral tibiofemoral ROA from two cohorts was similar, we combined the results from the two cohorts using the inverse-variance weighted meta-analysis method[27].

Finally, we conducted two sensitivity analyses to assess the robustness of our study findings. First, to avoid potential confounding bias from baseline KL grade when assessing the relation of malalignment to the risk of incident medial and lateral tibiofemoral ROA, we adjusted for baseline KL grade in the multivariable regression model. Second, to minimize potential misclassification bias of outcome assessment, we excluded the knees where incident lateral and medial tibiofemoral ROA occurred at the same visit. All analyses were performed using SAS V9.4 and STATA 11.0 software. A two-sided P-value < 0.05 was considered statistically significant.

Results

The baseline characteristics of the two study populations are shown in Table I. For participants in MOST, 58.9% were female with a mean age of 61.5 years and 86.2% were White. The mean BMI of participants was 29.7 kg/m^2, with 40.1% being overweight and 42.1% being obese. Nearly one third of the participants had a history of knee injury, 48.4% of them had varus malalignment, and 24.7% had valgus malalignment. Among eligible knees, 5.2% had KL grade 2 but JSN = 0. There were 12.5%, 6.9%, 1.9% of contralateral knees at baseline that had KL grade of two, three and four, respectively. Similar demographic features were observed among participants in OAI cohort. However, mean BMI was slightly lower (28.0 kg/m^2), less participants were obese (32.6%), the prevalence of knee malalignment tended to be lower (varus knees: 26.8%; valgus knees: 8.4%), and slightly high percentage (14.2%) of eligible knees with KL grade 2 at baseline. Furthermore, the percentage of ROA at baseline in the contralateral knees were also higher in OAI than their counterparts in MOST.

Table I
Characteristics of the study populations from the MOST and OAI cohorts

Characteristics	MOST (N = 2,016)	OAI (N = 3,476)
Age, years (Mean ± SD)	61.5 ± 7.9	60.3 ± 9.1
Female, N (%)	1,187 (58.9)	2,016 (58.0)
Race		
Whites, N (%)	1,738 (86.2)	2,875 (82.7)
Black, N (%)	250 (12.4)	517 (14.9)
Asian, N (%)	–	29 (0.8)
Other Non-white, (%)	28 (1.4)	55 (1.6)
BMI, kg/m^2 (Mean ± SD)	29.7 ± 5.2	28.0 ± 4.6
Overweight, N (%)	809 (40.1)	1,388 (39.9)
Obese, N (%)	849 (42.1)	1,134 (32.6)
History of knee injury, N (%)	671 (33.4)	1,282 (36.9)
Varus alignment, N (%)*	966 (48.4)	582 (26.8)
Valgus alignment, N (%)*	493 (24.7)	183 (8.4)
Baseline KL grade in eligible knees†		
0, (%)	2558 (69.1)	3440 (58.7)
1, (%)	877 (25.7)	1587 (27.1)
2, (%)‡	176 (5.2)	833 (14.2)
Baseline KL grade in Contralateral knees†		
0, (%)	2075 (61.3)	3024 (51.9)
1, (%)	591 (17.5)	1127 (19.3)
2, (%)	422 (12.5)	1202 (20.6)
3, (%)	232 (6.9)	359 (6.2)
4, (%)	65 (1.9)	120 (2.1)

MOST, Multicenter Osteoarthritis Study; OAI, Osteoarthritis Initiative; N, number of subjects; SD, standard deviation; BMI, body mass index.
* The total number of subjects for alignment assessment was 1,996 in the MOST and 2,169 in the OAI.
† Number represents number of knees.
‡ JSN = 0.

Of the 3,411 knees without medial and lateral tibiofemoral ROA at baseline in MOST, 436 (7.23/100 knee-years) developed medial tibiofemoral ROA and 162 (1.13/100 knee-years) developed lateral tibiofemoral ROA during 60-month follow-up period. The association with older age tended to be weaker with the risk of medial tibiofemoral ROA than that of lateral tibiofemoral ROA (RR per 5-year increase in age = 1.04 vs 1.13, respectively) (Table II). Female sex was not statistically significant associated with the risk of medial tibiofemoral ROA (RR = 1.05) but with a statistically significant higher risk of lateral tibiofemoral ROA (RR = 2.59), resulting in a ratio of RRs of 0.40 (95% confidence interval [CI]: 0.26 to 0.63; P < 0.001). In contrast, obesity was more strongly associated with the risk of medial tibiofemoral ROA (RR = 2.97) than with lateral tibiofemoral ROA (RR = 1.52), with a ratio of RRs of 1.95 (95% CI: 1.05 to 3.62; P = 0.03). Varus malalignment at baseline was positively associated with the risk of medial tibiofemoral ROA (RR = 1.59) and inversely with the risk of lateral tibiofemoral ROA (RR = 0.28), with ratio of RRs of 5.66 (95% CI: 3.20 to 10.00; P < 0.001). In contrast, valgus malalignment at baseline was inversely associated with the risk of medial tibiofemoral ROA (RR = 0.40) and positively with lateral tibiofemoral ROA (RR = 1.97), with ratio of RRs of 0.20 (95% CI: 0.12 to 0.34; P < 0.001). Sensitivity analysis of adjusting for baseline KL grade did not change the result materially. No apparent heterogeneity was observed for the relation of race, knee injury, or contralateral knee's KL grade to the risk of medial vs lateral tibiofemoral ROA. The results did not change when we excluded the knees (n = 22) in which incident medial and lateral tibiofemoral ROA occurred at the same visit.

Of the 5,860 knees with no medial or lateral tibiofemoral ROA at baseline in OAI, 308 (1.47/100 knee-years) developed medial tibiofemoral ROA and 83 (0.40/100 knee-years) developed lateral tibiofemoral ROA during the 48-month follow-up period. The

Table II
Risk factor heterogeneity for incident medial vs lateral tibiofemoral OA in the MOST cohort

Risk factors	No. of knees	Medial tibiofemoral OA			Lateral tibiofemoral OA			Ratio of RRs (95% CI)	*P*-value for etiologic heterogeneity
		Number (Rate, per 100 knee-years)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)	Number (Rate, per 100 knee-years)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)		
Age (years)	3,411	436 (7.23)	1.04* (0.98, 1.11)	1.04* (0.98, 1.11)	162 (2.69)	1.12* (1.01, 1.23)	1.13* (1.03, 1.25)	0.92 (0.82, 1.04)	0.19
Sex								0.40 (0.26, 0.63)	<0.001
Men	1,392	173 (7.05)	1.00 (reference)	1.00 (reference)	34 (1.39)	1.00 (reference)	1.00 (reference)		
Women	2,019	263 (7.36)	1.05 (0.86, 1.29)	1.05 (0.86, 1.28)	128 (3.58)	2.6 (1.77, 3.83)	2.59 (1.77, 3.81)		
Race								0.65 (0.39, 1.09)	0.11
White	2,941	373 (7.16)	1.00 (reference)	1.00 (reference)	133 (2.55)	1.00 (reference)	1.00 (reference)		
Black	421	56 (7.69)	1.09 (0.80, 1.49)	1.12 (0.82, 1.54)	29 (3.98)	1.59 (1.06, 2.37)	1.73 (1.15, 2.58)		
BMI									0.04
Normal	634	42 (3.72)	1.00 (reference)	1.00 (reference)	23 (2.04)	1.00 (reference)	1.00 (reference)		
Overweight	1,377	146 (5.94)	1.6 (1.1, 2.34)	1.75 (1.19, 2.57)	69 (2.81)	1.38 (0.85, 2.24)	1.39 (0.86, 2.27)	1.25 (0.67, 2.33)	
Obese	1,400	248 (10.16)	2.75 (1.92, 3.94)	2.97 (2.07, 4.28)	70 (2.87)	1.42 (0.87, 2.31)	1.52 (0.93, 2.50)	1.95 (1.05, 3.62)	
Knee injury								1.09 (0.74, 1.61)	0.66
No	2,591	298 (6.48)	1.00 (reference)	1.00 (reference)	114 (2.48)	1.00 (reference)	1.00 (reference)		
Yes	809	137 (9.77)	1.60 (1.31, 1.95)	1.71 (1.41, 2.09)	47 (3.35)	1.43 (1.02, 2.00)	1.57 (1.13, 2.19)		
Alignment									<0.001
Neutral	1,403	163 (6.54)	1.00 (reference)	1.00 (reference)	70 (2.81)	1.00 (reference)	1.00 (reference)		
Varus	1,337	233 (10.00)	1.53 (1.25, 1.87)	1.59 (1.30, 1.95)	17 (0.73)	0.26 (0.15, 0.44)	0.28 (0.16, 0.48)	5.66 (3.20, 10.00)	
Valgus	640	32 (2.79)	0.43 (0.29, 0.64)	0.40 (0.27, 0.60)	73 (6.35)	2.27 (1.63, 3.16)	1.97 (1.41, 2.76)	0.20 (0.12, 0.34)	
Contralateral knee's KL	3,385	429 (7.18)	1.58 (1.49, 1.69)	1.54 (1.45, 1.65)	162 (2.71)	1.61 (1.44, 1.79)	1.68 (1.49, 1.89)	0.92 (0.80, 1.05)	0.24

OA, osteoarthritis; MOST, Multicenter Osteoarthritis Study; RR, rate ratio; CI, confidence interval; BMI, body mass index; KL, Kellgren–Lawrence grade.
* RR for 5 years increase in age.
† RRs for age, sex, and race were mutually adjusted for age, sex, and race; RRs for BMI, knee injury, and malalignment were mutually adjusted for all factors except contralateral knee's KL in this table; RRs for contralateral knee's KL were mutually adjusted for all factors in the table.

etiologic heterogeneity was similar to that observed in MOST cohort across the purported risk factors: the ratios of RRs for age, female sex, obesity, varus alignment, valgus alignment, and contralateral knee's KL grade at baseline were 0.89 (95% CI: 0.77 to 1.02), 0.29 (95% CI: 0.15 to 0.57), 1.54 (95% CI: 0.70 to 3.39), 3.85 (95% CI: 1.45 to 10.27), and 0.95 (95% CI: 0.76, 1.20), respectively (Table III). All sensitivity analysis did not change the results materially.

When the results from MOST and OAI were combined, the associations of older age, female sex, and valgus malalignment with the incident lateral tibiofemoral ROA were stronger than that with the incident medial tibiofemoral ROA (all P values < 0.05). In contrast, the relation of obesity and varus malalignment to the incident medial tibiofemoral ROA were more pronounced than with the incident lateral tibiofemoral ROA (all $P < 0.05$). No etiologic heterogeneity was observed for race, a history of knee injury, or contralateral knee KL grade at baseline (Fig. 2).

Discussion

In two large prospective cohort studies of knee OA, we found that the risk factor profile for incident medial tibiofemoral ROA

Table III
Risk factor heterogeneity for incident medial vs lateral tibiofemoral OA in the OAI cohort

Risk factors	No. of Knees	Medial tibiofemoral OA			Lateral tibiofemoral OA			Ratio of adjusted RRs (95% CI)	*P*-value for etiologic heterogeneity
		Number (Rate, per 100 knee-years)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)	Number (Rate, per 100 knee-years)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)		
Age (years)	5,860	308 (1.47)	1.06* (1.00, 1.13)	1.07* (1.00, 1.13)	83 (0.40)	1.20* (1.06, 1.35)	1.21* (1.06, 1.37)	0.89 (0.77, 1.02)	0.08
Sex								0.29 (0.15, 0.57)	<0.001
Men	2,404	128 (1.47)	1.00 (reference)	1.00 (reference)	14 (0.16)	1.00 (reference)	1.00 (reference)		
Women	3,456	180 (1.47)	1.01 (0.79, 1.29)	0.99 (0.77, 1.26)	69 (0.56)	3.55 (1.92, 6.56)	3.37 (1.83, 6.22)		
Race								0.74 (0.39, 1.42)	0.37
White	4,846	250 (1.43)	1.00 (reference)	1.00 (reference)	64 (0.37)	1.00 (reference)	1.00 (reference)		
Black	870	51 (1.73)	1.29 (0.93, 1.80)	1.34 (0.96, 1.86)	18 (0.61)	1.78 (1.00, 3.16)	1.80 (1.03, 3.14)		
BMI									0.29
Normal	1,704	46 (0.74)	1.00 (reference)	1.00 (reference)	15 (0.24)	1.00 (reference)	1.00 (reference)		
Overweight	2,336	118 (1.40)	1.9 (1.32, 2.74)	1.59 (1.09, 2.30)	36 (0.43)	1.78 (0.91, 3.49)	1.60 (0.81, 3.14)	0.99 (0.46, 2.15)	
Obese	1,820	144 (2. 27)	3.08 (2.16, 4.41)	2.38 (1.66, 3.41)	32 (0.50)	2.1 (1.07, 4.11)	1.54 (0.76, 3.10)	1.54 (0.70, 3.39)	
Knee injury								0.90 (0.53, 1.52)	0.70
No	4,309	188 (1.22)	1.00 (reference)	1.00 (reference)	50 (0.32)	1.00 (reference)	1.00 (reference)		
Yes	1,551	120 (2.17)	1.96 (1.55, 2.48)	1.87 (1.47, 2.38)	33 (0.60)	2.03 (1.3, 3.16)	2.08 (1.30, 3.31)		
Alignment									<0.001
Neutral	2,189	202 (2.59)	1.00 (reference)	1.00 (reference)	56 (0.72)	1.00 (reference)	1.00 (reference)		
Varus	714	89 (3.49)	1.35 (1.06, 1.73)	1.43 (1.10, 1.85)	5 (0.20)	0.27 (0.11, 0.69)	0.37 (0.14, 0.95)	3.85 (1.45, 10.27)	
Valgus	205	14 (1.97)	0.79 (0.46, 1.36)	0.71 (0.41, 1.21)	20 (2.82)	4.09 (2.45, 6.82)	3.24 (1.92, 5.47)	0.22 (0.10, 0.46)	
Contralateral knee's KL	5,832	303 (1.45)	1.66 (1.52, 1.81)	1.30 (1.17, 1.43)	82 (0.39)	1.66 (1.41, 1.95)	1.36 (1.11, 1.67)	0.95 (0.76, 1.2)	0.69

OA, osteoarthritis; OAI, Osteoarthritis Initiative; RR, rate ratio; CI, confidence interval; BMI, body mass index.
* RR for 5 years increase in age.
† RRs for age, sex, and race were mutually adjusted for age, sex, and race; RRs for BMI, knee injury, and malalignment were mutually adjusted for all factors in this table.

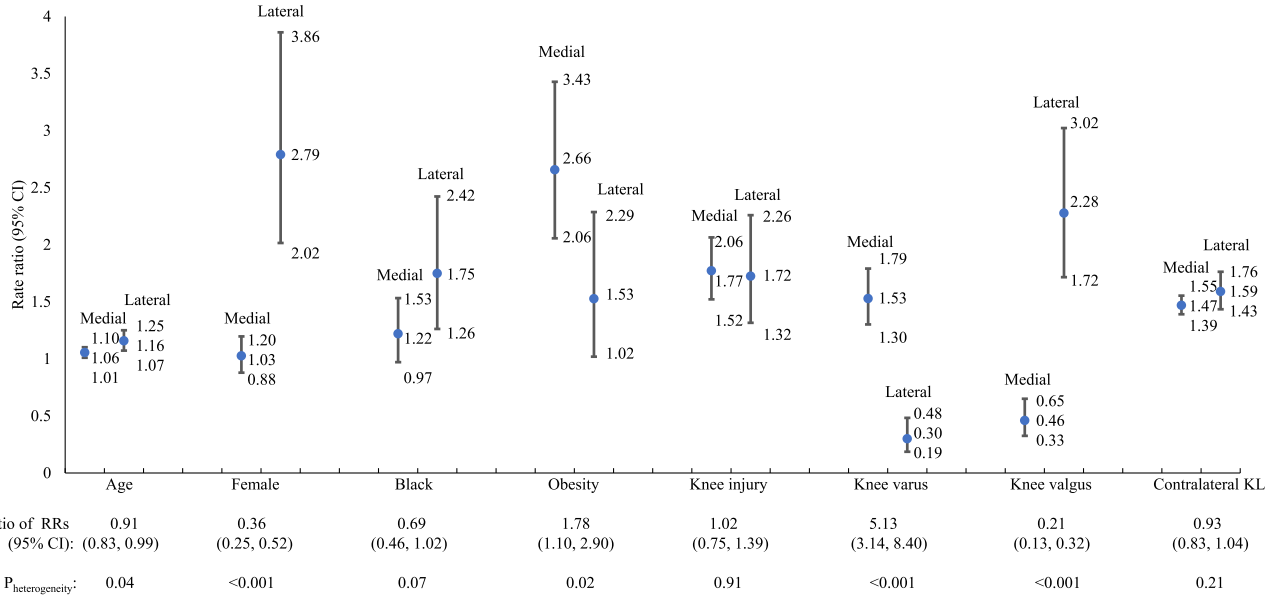

Fig. 2. Risk Factor Heterogeneity for Incident Medial vs Lateral Tibiofemoral OA Combining the Findings from the MOST and OAI. MOST, Multicenter Osteoarthritis Study; OAI, Osteoarthritis Initiative; OA, osteoarthritis; Lateral, lateral tibiofemoral osteoarthritis; Medial, medial tibiofemoral osteoarthritis BMI, body mass index; CI, confidence interval; KL, Kellgren and Lawrence.

significantly differed from that for incident lateral tibiofemoral ROA. Specifically, obesity and varus knee malalignment were more strongly associated with incident medial tibiofemoral ROA, whereas older age, female sex, and valgus knee malalignment were more strongly associated with incident lateral tibiofemoral ROA. These findings were consistent between the two cohorts, underscoring the strength of the observation.

In our study, female sex was associated with a nearly three-fold higher incident lateral tibiofemoral ROA than men, but not with the incident medial tibiofemoral ROA. Our findings are also consistent with previous prevalent endpoint analyses of knee ROA among White[9,13]. The exclusive association between women and risk of lateral tibiofemoral ROA could be explained by a wider pelvis[28,29], an increased Q-angle[30,31], and greater knee valgus among women[32,33], contributing to increased loading of the lateral knee compartment during weight-bearing activities.

Obesity was 78% more strongly associated with incident medial tibiofemoral ROA than with incident lateral tibiofemoral ROA. A previous study using prevalent cases of knee ROA reported similar findings[10]. Furthermore, the effect of weight gain on cartilage volume loss was found to be greater in the medial tibiofemoral compartment[34], and weight loss in obese persons has structure-modifying effect on medial but not lateral tibiofemoral articular cartilage[34,35]. These findings are consistent with our understanding of biomechanical loading of the tibiofemoral joint. During weight-bearing activities, such as walking, the body's center of gravity is medial of the knee, resulting in greater compressive load exerted on the medial compartment of the knee than on the lateral compartment[36]. Therefore, any increase in knee load due to greater BMI would likely be more consequential for medial compartment joint damage, contributing to the risk of medial tibiofemoral ROA.

Knee alignment is a key determinant of load distribution. Any shift away from a neutral or collinear alignment of the hip, knee, and ankle can affect load distribution at the knee[12,37]. An earlier study of the progression of knee ROA found that knees with varus mechanical axes were at a high risk for progression of medial tibiofemoral ROA, whereas valgus alignment was associated with increased risk of lateral tibiofemoral ROA progression[12]. However, epidemiologic studies of knee alignment in relation to the risk of incident knee ROA have been challenging, and one reason may be that there are few subjects with significant malalignment at baseline among individuals without tibiofemoral ROA[38]. A previous analysis using MOST and OAI data reported that valgus malalignment (hip-knee-ankle angle (HKA) > 3.0°) significantly increased the risk of incident lateral tibiofemoral ROA in MOST, however this observation was not confirmed in OAI[39]. Another study also found that self-reported history of varus malalignment in early adulthood (20–29 years) was strongly associated with prevalent medial tibiofemoral ROA and valgus malalignment with prevalent lateral tibiofemoral ROA[11]. Our study expanded on these findings and found that varus malalignment was 409% more strongly associated with incident medial than with incident lateral tibiofemoral ROA, and valgus malalignment was 376% more strongly associated with incident lateral than with incident medial tibiofemoral ROA.

Older age was associated with both medial and lateral tibiofemoral ROA and the association was stronger with lateral than medial tibiofemoral ROA. The underlying mechanisms to explain this discrepancy are unclear, although a previous study found that knee alignment became increasingly valgus with increasing age[40], and this may contribute to the risk of lateral tibiofemoral ROA. Also, our findings are consistent with other reports that the prevalence of lateral tibiofemoral ROA was greater among African Americans than among Whites[8]. We also found that African Americans tended to have a relatively higher risk of lateral tibiofemoral ROA than medial tibiofemoral ROA when compared with Whites although the test for etiologic heterogeneity was not statistically significant owing to a small number of incident cases of lateral tibiofemoral ROA in African Americans. It is possible that the differences observed in knee alignment between races may underlie the reported associations[9]. Finally, although knee injury and contralateral knee OA were both highly associated with tibiofemoral OA[41–43], none of these factors indicated apparent etiologic heterogeneity for medial and lateral tibiofemoral ROA in the current study.

Implications for practice and research

The etiologic heterogeneity observed in our study can potentially allow investigators to develop personalized preventive and treatment strategies targeting a specific subtype of knee OA. For example, several previous clinical trials of patients regardless of their obesity status have failed to observe the expected benefit of such realigning approaches[44–48], and it should be recognized that almost all these trials were conducted among overweight and obese patients. However, our findings suggest that laterally wedged shoe insoles or lateral valgus realigning braces for the treatment of medial tibiofemoral OA may be more effective when targeting patients with a normal BMI instead of those with overweight or obesity. Similarly, our findings also imply that weight loss interventions for knee OA would be more effective for OA patients with neutral rather than with varus malalignment. Conceptually, these approaches are consistent with the rationale for selecting a more homogenous population with unique risk factor for an intervention trial, as it would provide more precise information about a causal relation[49,50].

The strengths and limitations of our study deserve comment. First, we used data collected from two large well-executed cohort studies that were specifically designed to assess risk factors for the incidence and progression of knee OA. We were able to replicate the results from MOST in OAI study, assuring the robustness of our findings. Second, our study that applied a statistical method specifically to assess etiologic heterogeneity in knee OA. The statistical methods used in our study require large sample sizes to obtain robust estimates; thus, even the MOST and OAI cohorts are both large we were unable to detect a statistically significant heterogeneity of some risk factors, such as race, on risk of medial vs lateral tibiofemoral ROA because the number of subtype of participants was not sufficiently large enough. Fourth, two different measures (i.e., the hip-knee-ankle angle from the long-leg films in MOST and the femorotibial angle from knee radiographs in OAI) were used to assess knee alignment; nevertheless, previous studies have demonstrated a strong correlation between femorotibial angle and hip-knee-ankle (R^2 values around 0.53)[21] and the associations were also comparable in our study. Finally, we were unable to assess whether OA at other sites could affect the occurrence of tibiofemoral medial or lateral ROA due to lack of the information from either study.

Conclusions

The profile of risk factors for medial tibiofemoral ROA differs substantially from that for lateral tibiofemoral ROA using two large prospective cohorts. These findings increase our understanding of OA etiology and may provide a useful guide for the development of targeted preventive and treatment strategies for specific knee OA subtypes.

Contributors

HKC and YZ are joint senior authors.

JW, HKC, and YZ had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JW, HKC, TY, and YZ were responsible for conception of the study and drafted the manuscript. HKC, and YZ were responsible for the design of the study. JW, NL, and MW contributed to data analysis. DG, NEL, CZ, TY, GL, HKC, and YZ contributed to revisions of the manuscript. All the authors contributed to the interpretation of the data and critically reviewed the manuscript for publication. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Ethical Approval

This study received approval from the medical ethical committee, and participants gave written informed consent.

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Appendix

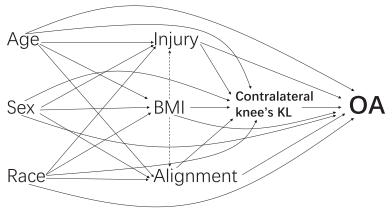

Figure. Causal Diagram of Potential Interrelationship of Risk Factors and Outcome Variable. BMI, body mass index; KL, Kellgren and Lawrence; OA, osteoarthritis.

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