Tibiofemoral subchondral surface ratio (SSR) is a predictor of osteoarthritis symptoms and radiographic progression: data from the Osteoarthritis Initiative (OAI)

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SUMMARY

Objective: Symptomatic knee osteoarthritis (OA) is poorly correlated with radiographic severity, but subchondral bone measures may be useful for risk assessment as bone shape is grossly unaffected at early radiographic stages. We sought to determine whether compartment-specific size mismatch in the naturally asymmetric tibiofemoral joint, measured as tibiofemoral subchondral surface ratio (SSR): (1) predicts incident symptoms, (2) predicts incident or progressive OA, (3) is reproducible and time invariant.

Design: OA Initiative participants with baseline MRIs and up to 48-month follow-up (n = 1,338) were analyzed. Logistic regression was used to determine the association between SSR and incident symptoms, incident OA, and progression of OA after adjusting for demographic, radiologic, injury-related, and lifestyle-related factors. Reproducibility was assessed as % coefficient of variation (CV) on repeat MRI studies at baseline and 24 months.

Results: Increased medial SSR is protective against incident symptoms at 48 months (per 0.1 increase: OR 0.48 CI 0.30, 0.75; P = 0.001). Increased lateral SSR values are protective against lateral OA incidence (OR 0.23 CI 0.06, 0.77; P = 0.016) or progression (OR 0.66 CI 0.43, 0.99; P = 0.049) at 24 months. Both medial and lateral SSR are stable over time (medial: mean change 0.001 SD 0.016; lateral: mean change 0.000 SD 0.017) and are highly reproducible (3.0% CV medial SSR; 2.7% CV lateral SSR).

Conclusions: A larger medial SSR is protective against developing OA-related symptoms. A larger lateral SSR is protective against lateral OA incidence or progression. Finally, lateral and medial SSR are stable over time and are highly reproducible across MRI studies.

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Introduction

Knee osteoarthritis (OA) is common in the United States, with an estimated 37% prevalence of radiographic OA among adults over age 60. Knee OA is a multifactorial disease process and many risk factors have been identified including obesity, age, genetics, sex, race, tobacco use, comorbid joint diseases, trauma, and knee alignment. Biomechanical factors that lead to excessive joint loading such as obesity, hip-knee-ankle alignment and frequent squatting or kneeling cause mechanical wear of articular cartilage with a corresponding chronic inflammatory response. Obesity is also associated with knee symptoms, with a corresponding decrease in symptom severity after weight loss.

Identification of patients anatomically predisposed to developing symptomatic OA would provide an opportunity for the clinician to counsel patients to minimize lifestyle related OA risk factors and potentially delay or prevent symptom onset. In particular, measurements of based on subchondral contour would be useful for risk assessment as asymptomatic patients often already have significant cartilage loss at the time of evaluation. The tibiofemoral joint is naturally asymmetric, and this results in an intrinsic degree...
of size mismatch between corresponding subchondral bone plates within each compartment. Recent knee morphology research suggests that subchondral bone shape is actually quite variable across individuals. Mahfouz et al. in their principal components analyses of a large sample of computed tomography (CT)-derived knee subchondral surface models found significant individual, sex, and race-specific variation in distal femur and proximal tibial shape and size.\(^{15}\) In contrast with the well-studied relationship between knee alignment and OA, very little is known about the role of subchondral bone shape in OA pathogenesis or progression. Specifically, no research has been conducted to determine the relationship between subchondral size mismatch and radiographic or symptomatic OA. It is also unknown whether more subtle variations in subchondral size mismatch occur over time in knees that are non-arthritic or are at early stages of OA.

This study was designed to address these gaps in knowledge by determining whether degree of compartment-specific asymmetry, measured as the tibiofemoral subchondral surface ratio (SSR): (1) is predictive of incident symptoms; (2) is predictive of incident or progressive OA; (3) covaries with time or OA progression. We hypothesize that tibiofemoral SSR is associated with OA incidence, progression, and symptoms. We also hypothesize that, with the exception of knees with severe radiographic changes including subchondral surface deformation, tibiofemoral SSR is a stable metric, which remains constant over time.

Methods

Data sources and patient selection

The OA Initiative (OAI) is an NIH-funded, multi-center, observational cohort study focused on knee OA. The study protocol, amendments, and informed consent documentation were reviewed and approved by the Institutional Review Boards at all participating sites. A total of 4,796 participants ages 45–79 were recruited to either an incidence or progression subcohort. Participants in the progression subcohort had both frequent knee symptoms and radiographic signs of OA in at least one native knee at baseline. Participants in the incidence subcohort were either asymptomatic and/or did not have radiographic signs of OA in either knee at baseline; however, all participants in the incidence subcohort were required to have at least one OA risk factor (frequent symptoms, overweight, history of knee injury or surgery, history of total knee replacement in parent or sibling, Heberden’s nodes present on hands, frequent repetitive knee bending, or age 70–79). Data used in the preparation of this article were obtained from the OAI database, which is available for public access at [http://www.oai.ucsf.edu](http://www.oai.ucsf.edu). Specific datasets used are the clinical datasets for baseline (version 0.2.2), 24 months (version 3.2.1) and 48 months (version 6.2.1) in addition to magnetic resonance imaging (MRI) datasets (Eckstein group) for baseline (version 0.5), 24 months (version 3.5), and 48 months (version 6.4). This study was conducted without the review of the OAI Publications Committee of its scientific content and data interpretation.

We utilized a convenience sample of all participants in the OA Initiative who had a baseline knee MRI that was quantitatively assessed by a single vendor (Chondrometrics, Gmbh, Airing; Parcelsus University, Salzburg) (n = 1,338 patients; n = 685 progression cohort, n = 653 incidence subcohort). To ensure all observations were independent, we utilized one knee per patient only (1,338 patients, 251 left knees, 1,087 right knees). Of the 96 patients with bilateral knee MRIs, we selected the knee with the most complete follow-up radiologic data or at random when similar data were available. No further inclusion or exclusion criteria were applied. At baseline, the mean age of this sample was 62.4 ± 9.2 years, 40.4% (n = 579) were male, 59.6% (n = 854) were female, 80.0% (n = 1,146) were Caucasian, 17.3% (n = 248) were African-American, and 61.6% (n = 884) were symptomatic. The majority of participants had OA at baseline (n = 987, 68.9% Kellgren and Lawrence (KL) grades 2–3, n = 66, 4.6% KL grade 4), though a substantive minority of patients had no radiographic OA (n = 380, 26.5% KL grades 0–1).

MRI assessment and measurement of SSR

All patients underwent 3.0 T knee MRIs at baseline and a subset of patients also underwent serial MRIs at 2 years (n = 745) and 4 years (n = 86) follow-up. Articular cartilage segmenting of all knee MRIs was performed on either a coronal fast low angle shot (FLASH) water excitation (WE) sequence (1.5 mm slice thickness; echo time (TE) 7.57 ms, repetition time (TR) 20 ms; in-plane resolution 0.31 mm × 0.31 mm; acquisition time 8 min, 30 s) or sagittal double echo steady state (DESS) WE sequence (0.7 mm slice thickness; TE 4.7 ms, TR 16.3 ms, in-plane resolution 0.37 mm × 0.46 mm, acquisition time 10 min 23 s)\(^{16}\). All knee MRIs were quantitatively assessed by a single vendor (Chondrometrics, Gmbh, Airing; Parcelsus University, Salzburg); detailed descriptions of the measurement methods are reported by Eckstein et al.\(^{17,18}\). Articular surface area, subchondral surface area, and average cartilage thickness of the medial and lateral compartments reported by the vendor were utilized in this analysis. Regions of denuded cartilage were included in the subchondral surface area but not the articular surface area or cartilage measurements. Osteophytes and cartilage overlying osteophytes were not included in any of these measurements. All measurements were extracted directly from the OAI database.

The tibiofemoral SSR was defined as the weight-bearing femoral subchondral surface area divided by the tibial subchondral surface area; the study authors utilized the subchondral surface measures from the OAI database to calculate this ratio for both medial and lateral compartments and for the entire tibiofemoral joint. The weight-bearing portion of the femoral condyle was defined in the sagittal DESS sequence as 60% of the surface between the trochlear notch (anteriorly) and the posterior end of the femoral condyles [Fig. 1]\(^{19}\). This was defined in the coronal FLASH sequence as the entire subchondral condylar surface in 60% of slices visualizing the condyle when starting at the trochlear notch (the anteriormost slice with divergence of the trochlea into the femoral condyles) and advancing posteriorly to include the last slice demonstrating the circular structure of the posterior condyle (both bone and cartilage) of the compartment being measured\(^{20}\). The tibial subchondral surface area was determined by segmentation of the entire subchondral and articular surfaces of the respective plateaus; this included portions of the subchondral surface completely denuded of overlying cartilage and did not include osteophytes. The two methods (sagittal DESS or coronal FLASH) were shown by Eckstein et al.\(^{20}\) to be reliably interchangeable\(^{20}\). For sagittal DESS, there is high reported reproducibility of measurements in all tibial and femoral regions for subchondral surface area (RMS coefficient of variation (CV%) range 2.6% for medial tibia to 9.2% for lateral tibia), cartilage surface area (CV 2.9% medial tibia to 9.1% lateral tibia), and cartilage thickness (CV 2.3% medial tibia to 4.5% medial femur)\(^{17}\). High reproducibility has also been reported for coronal FLASH WE for subchondral bone (CV 2.8% for medial tibia to 5.4% for medial femur), cartilage surface area (CV 2.5% medial tibia to 5.9% medial femur), and cartilage thickness (CV 3.0% medial tibia to 3.8% medial femur)\(^{21,22}\).

Clinical assessments

Demographic and medical history data from the baseline study questionnaires and self-reported knee symptom-related data were
process for discrepant scores. OA severity in individual compartment was categorized by OARSI osteophyte grade.\(^2\)

OA was defined by either (1) a KL grade $\geq 2$ at baseline for the entire joint, or (2) OARSI grade $\geq 1$ for individual compartments. Incident OA was defined by either (1) a change from KL grade from $<$2 at baseline to $\geq 2$ at follow-up for the entire joint, or (2) a change in OARSI grade from $<$1 at baseline to $\geq 1$ at follow-up for an individual compartment. Finally, progressive OA was defined as (1) any increase in KL grade for the entire joint, or (2) an increase in Osteoarthritis Research Society International (OARSI) grade or a definite increase in joint space narrowing as determined by the reviewer for an individual compartment. Fixed flexion PA radiographs were also used to quantitatively assess joint space width (JSW) at specific locations along the joint line with a validated protocol described in detail by Neumann et al.\(^2\) Joint widths at the 0.200 and 0.800 coordinates were used to characterize medial and lateral JSW due to high cross-sectional and longitudinal reliability within the OAI study. Finally, as malalignment is a known risk factor for OA progression\(^3\), data on degree of valgus or varus were also utilized; these measures were obtained on full-limb radiographs with a standard protocol\(^2\).

**Statistical analysis**

**Descriptive data and univariate analysis**

All statistical tests were performed with a standard software package (JMP 9.0.3; SAS institute, Cary, NC). No published data regarding SSRs were available at the time of study design to perform an a priori power analysis, and we therefore relied on convenience sampling methods. Descriptive statistics were first generated for demographic, clinical, and radiologic factors after stratifying by baseline symptom status. Baseline differences in SSR by OA and symptom status were determined by two-tailed Student’s t-tests and one-way analysis of variance (ANOVA). As expected, KL-grade 4 knees had gross changes in subchondral contour with a mean SSR that differed significantly from moderately arthritic knees (KL grades 2 and 3; $P < 0.001$) [Fig. 2]; therefore, grade 4 knees at baseline ($n = 66$) were excluded from further

**Radiographic assessments**

All OAI radiographs and radiologic assessments were obtained using a standardized protocol; all measurements were extracted directly from the OAI database. Briefly, serial bilateral knee radiographs were obtained with a standard fixed-flexion posterior-anterior (PA) view and a KL grade\(^2\) for OA severity was assigned by two independent reviewers with an established adjudication

\[\text{Fig. 1. Segmentation of the weight-bearing femoral condyle in a sagittal sequence. The weight-bearing region is defined as 60\% of the subchondral surface between the trochlear notch (anterior white line) and the posterior end of the femoral condyles. Note that the anterior white line is oriented parallel to the femoral shaft and through the trochlear notch in a central slice between the medial and lateral femoral condyles (not in the slice shown here). The posterior ends of the medial and lateral formal condyles are determined by the slice depicting the most posterior aspects of the respective condyles. The SSR is defined as the weight-bearing femoral condylar surface area divided by the subchondral surface area of the corresponding tibial plateau.}\]
analyses. Unadjusted estimates of SSR as a risk factor for incident symptoms, incident OA, and progressive OA were then determined by simple logistic regression analysis (maximum likelihood method for model fitting; P-values reported from likelihood-ratio tests).

**Multivariate analysis**

Several logistic regression models were created to determine the independent association between medial and lateral SSR and incident symptoms, incident radiographic OA, or progression of radiographic OA at 24 and 48 months. Potential covariates in the models included age, BMI, sex, race, knee injury and surgery history, tobacco use, physical activity level (PASE score), KL and OARSI grades, OA-related symptom status, patellofemoral crepitus or positive patellar grind test, medial and lateral joint width, average cartilage thickness, and joint alignment. To control for confounding between SSR and the outcome of interest, all factors were individually assessed for inclusion in each model and added if inclusion resulted in a 10% change or greater in the standardized coefficient for either medial or lateral SSR. This “change in estimate” criterion is a common epidemiologic method to select for important confounders while minimizing variability of the estimated effect of interest by avoiding entry of unnecessary variables into the model.11,14

**Time invariance and precision (reproducibility) of SSR**

The mean change in SSR was determined between MRIs performed at baseline, 24 months and 48 months. Linear regression models were created to determine independent predictors of change in SSR (as a continuous variable only) by 24 and 48 months. Among knees that did not progress to KL grade 4, precision (reproducibility) was assessed between baseline and 24-month MRIs (n = 745) as the root mean square (RMS) coefficient of variation percentage (CV %) and the Pearson correlation coefficient. Knee MRIs performed at 48 months were not utilized for reliability due to small sample size (n = 86).

**Results**

**Descriptive data and univariate analyses**

Participants who were symptomatic at baseline were more likely to have a history of prior injury (39.7% vs 24.8%; P = 0.001) or prior surgery (26.8% vs 10.6%; P < 0.001), had a higher average BMI (30.2 vs 27.8; P < 0.001), and were more likely to have radiographic signs of OA (85.9% KL grade 2 or higher vs 51.1%; P < 0.001) (Table I). Symptomatic patients at baseline also had a 9.6% larger medial SSR (0.534 vs 0.488; P < 0.001). After stratification by OA status, medial SSR was larger among symptomatic participants with OA (KL grades 2 and 3) by 10.6% (5.462 vs 4.937; P = 0.001) but was not significantly larger among symptomatic participants without OA (KL grades 0 and 1) (4.876 vs 4.813; 1.6% difference, P = 0.30).

In the simple (unadjusted) models (Table II), each 0.1 unit increase in medial SSR was associated with a higher risk of medial OA progression (odds ratio (OR) 1.43 CI 1.15, 1.77; P = 0.0015) and lateral OA progression (OR 1.87 CI 1.44, 2.42; P < 0.001) at 48 months but a lower risk of incident symptoms (OR 0.58 CI 0.39, 0.84; P = 0.0035). Conversely, each 0.1 unit increase in lateral SSR was associated with a lower risk of incident lateral OA at 24 months (OR 0.29 CI 0.09, 0.83; P = 0.021) or 48 months (OR 0.43 CI 0.17, 0.98; P = 0.04) but not OA progression or incident symptoms at either time point (P > 0.25).

Multivariate analysis

In the fully adjusted models (Table III), each 0.1 unit increase in medial SSR resulted in a significant reduction in risk of developing symptoms at 24 months (odds ratio (OR) 0.50 confidence interval (CI) 0.31, 0.78; P = 0.002) or 48 months (OR 0.48 CI 0.30, 0.75; P = 0.001). Increased medial SSR was also associated with a reduction in medial OA incidence at 48 months (OR 0.51 CI 0.24, 0.98; P = 0.042) with a trend toward significance at 24 months (OR 0.54 CI 0.23, 1.15; P = 0.11). Conversely, each 0.1 unit increase in lateral SSR was associated with lower risk of lateral OA incidence and lateral OA progression; this relationship was statistically significant at 24 months (incidence: OR 0.23 CI 0.06, 0.77 P = 0.016;
relationship between SSR and frequent OA symptoms and no adjustment for either patellofemoral crepitus on patellar grind was required in any model.13,34

Table II
Unadjusted odds of radiographic OA incidence & progression and OA-related symptom incidence at 24 and 48 months due to SSR

<table>
<thead>
<tr>
<th></th>
<th>Medial SSR (continuous value)</th>
<th>Lateral SSR (continuous value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted odds ratio</td>
<td>P-value</td>
</tr>
<tr>
<td>24 Months</td>
<td>OA incidence</td>
<td>1.11 (0.54, 2.15)</td>
</tr>
<tr>
<td></td>
<td>Medial OA incidence</td>
<td>0.74 (0.34, 1.48)</td>
</tr>
<tr>
<td></td>
<td>Lateral OA incidence</td>
<td>1.11 (0.45, 2.42)</td>
</tr>
<tr>
<td></td>
<td>OA progression</td>
<td>1.18 (0.94, 1.47)</td>
</tr>
<tr>
<td></td>
<td>Medial OA progression</td>
<td>1.43 (1.15, 1.77)</td>
</tr>
<tr>
<td></td>
<td>Lateral OA progression</td>
<td>11.76 (3.3, 3.22)</td>
</tr>
<tr>
<td></td>
<td>Incident symptoms</td>
<td>0.69 (0.47, 1.00)</td>
</tr>
<tr>
<td>48 Months</td>
<td>OA incidence</td>
<td>1.28 (0.71, 2.23)</td>
</tr>
<tr>
<td></td>
<td>Medial OA incidence</td>
<td>0.62 (0.31, 1.13)</td>
</tr>
<tr>
<td></td>
<td>Lateral OA incidence</td>
<td>0.85 (0.38, 1.74)</td>
</tr>
<tr>
<td></td>
<td>OA progression</td>
<td>1.27 (1.04, 1.54)</td>
</tr>
<tr>
<td></td>
<td>Medial OA progression</td>
<td>1.43 (1.17, 1.75)</td>
</tr>
<tr>
<td></td>
<td>Lateral OA progression</td>
<td>1.14 (1.44, 2.42)</td>
</tr>
<tr>
<td></td>
<td>Incident symptoms</td>
<td>0.58 (0.39, 0.84)</td>
</tr>
</tbody>
</table>

* Reported as odds per 0.1 unit increase in SSR.
† KL grade 4 knees were excluded as a significant difference in surface area ratios were observed between moderately arthritic (grades 2 and 3) and severely arthritic (grade 4) knees [Fig. 2] which we believe is due to deformity of bone contour (an explicit criterion for grade 4 designation)11.

Table III
Adjusted odds of radiographic OA incidence & progression and OA-related symptom incidence at 24 and 48 months due to SSR

<table>
<thead>
<tr>
<th></th>
<th>Medial SSR (continuous value)</th>
<th>Lateral SSR (continuous value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted odds ratio</td>
<td>P-value</td>
</tr>
<tr>
<td>24 Months</td>
<td>OA incidence</td>
<td>1.75 (0.80, 3.70)</td>
</tr>
<tr>
<td></td>
<td>Medial OA incidence</td>
<td>0.54 (0.23, 1.15)</td>
</tr>
<tr>
<td></td>
<td>Lateral OA incidence</td>
<td>1.85 (0.65, 4.71)</td>
</tr>
<tr>
<td></td>
<td>OA progression</td>
<td>0.79 (0.59, 1.06)</td>
</tr>
<tr>
<td></td>
<td>Medial OA progression</td>
<td>1.01 (0.74, 1.37)</td>
</tr>
<tr>
<td></td>
<td>Lateral OA progression</td>
<td>1.25 (0.84, 1.86)</td>
</tr>
<tr>
<td></td>
<td>Incident symptoms</td>
<td>0.50 (0.31, 0.78)</td>
</tr>
<tr>
<td>48 Months</td>
<td>OA incidence</td>
<td>1.66 (0.79, 3.36)</td>
</tr>
<tr>
<td></td>
<td>Medial OA incidence</td>
<td>0.51 (0.24, 0.98)</td>
</tr>
<tr>
<td></td>
<td>Lateral OA incidence</td>
<td>1.14 (0.45, 2.71)</td>
</tr>
<tr>
<td></td>
<td>OA progression</td>
<td>0.91 (0.55, 1.24)</td>
</tr>
<tr>
<td></td>
<td>Medial OA progression</td>
<td>1.04 (0.78, 1.40)</td>
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<tr>
<td></td>
<td>Lateral OA progression</td>
<td>1.34 (0.88, 2.03)</td>
</tr>
<tr>
<td></td>
<td>Incident symptoms</td>
<td>0.48 (0.30, 0.75)</td>
</tr>
</tbody>
</table>

* Bold represents statistically significant result.
† Reported as odds per 0.1 unit increase in SSR.
‡ KL grade 4 knees were excluded as a significant difference in surface area ratios were observed between moderately arthritic (grades 2 and 3) and severely arthritic (grade 4) knees [Fig. 2] which we believe is due to deformity of bone contour (an explicit criterion for grade 4 designation)11.
§ After adjusting for sex, race, age, BMI, tobacco use, activity level, knee coronal alignment, baseline symptoms, injury history, surgery history, KL grade, and JSW.

Time invariance and precision (reproducibility) of SSR

There is very little variability in medial or lateral SSR over time among subjects with KL grade 0–3 knees. At 24 months, the mean changes in SSR were close to zero for both medial (mean change 0.001 ± 0.016 standard error of measurement (SEM) 0.001) and lateral compartments (mean change 0.000 ± 0.019 SEM 0.001) (Table V) a similarly small mean change was observed between SSR at baseline and 48 months for both medial (mean change 0.002 ± 0.017 SEM 0.002) and lateral compartments (mean change 0.001 ± 0.015 SEM 0.002). Other than progression to KL grade 4 (P < 0.001), there were no significant predictors of change in SSR at 24 months or 48 months (P > 0.25 for all factors). Finally, among participants who did not progress to KL grade 4, there was very high reproducibility between SSR measurements obtained from MRIs performed at baseline and 24 months; there was an estimated 3.0% CV (root mean squared error (RMSE) 0.0155; Pearson’s r = 0.978) for medial SSR and 2.7% CV (RMSE 0.0167; Pearson’s r = 0.970) for lateral SSR.

Discussion

Symptomatic knee OA is a major cause of morbidity in the elderly. A large body of research is devoted to prediction and prevention of radiographic OA; however, far fewer studies have been published that focus on predicting symptoms, and the relationship between symptom status and radiographic severity is poor.17,18. The motivation for this investigation was our hypothesis that SSR, a measure of size mismatch between subchondral surfaces in the naturally asymmetric tibiofemoral joint, would be predictive of radiographic or symptomatic OA and be time-invariant. Our findings confirm this hypothesis and address a critical gap in knowledge by demonstrating that a relatively large weight-bearing medial condylar surface relative to the medial plateau is an independent predictor of future symptoms. This important finding allows for more effective risk assessment for future symptoms, even if early radiographic changes are present.

The findings from this study directly support utilization of medial SSR as a clinical screening tool for future knee OA-related symptoms in select patients. In particular, an increased medial SSR is protective against development of future knee symptoms among currently asymptomatic Caucasian and African American patients over age 45 who do not have existing KL grade 4 OA. Given recent advances in cartilage-based MRI biomarkers of disease activity such as T2 or T1rho mapping,35–38 a screening MRI in patients at high risk for OA may provide an opportunity to assess both current disease activity and risk of developing knee symptoms. Patients with modifiable OA risk factors such as frequent stair climbing or obesity are particularly well-suited for a screening MRI, as the clinician can counsel patients with a low medial SSR value and high disease activity that lifestyle modification to minimize arthritis risk factors will be especially important to avoid future knee symptoms. However, in order to facilitate use of SSR in a clinical setting it will be necessary to determine an efficient means of approximating subchondral surface area. The technique utilized to determine medial SSR values relies on manual segmentation methods that are reproducible but could not be performed in a basic image viewing software program,21 whereas an approximating measure for condylar surface such as coronal width multiplied by 60% of sagittal length could be performed in any image viewer.

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The results of this study also demonstrate that race-specific differences in SSR may account for some of the differences in symptom prevalence and severity observed between Caucasians and African-Americans. However, even after adjustment in the logistic regression model, African-American race remained a significant independent predictor of baseline symptom status relative to Caucasians (OR 2.57 CI 1.68–4.00, P < 0.001). This may be related to race-specific differences observed in the expression of several genes implicated in OA pathophysiology. Another possible explanation for this persistent association is presented in a recent study by Allen et al. in which the authors conclude that race-specific differences in symptom status are largely attributable to factors such as arthritis self-efficacy and coping strategies.

The association between lateral SSR and lateral compartment OA progression is interesting, though this study is not appropriately designed to establish a causal mechanism. However, these findings do provide a context to guide future studies to further define the relationship between lateral SSR and lateral OA. Similar to previous studies demonstrating the relationship between knee valgus and joint loading, the effect of lateral SSR on knee loading could be tested in an animal model by directly measuring compressive contact stress or in vivo by correlating lateral SSR with lateral compartment tracer uptake and distribution pattern in bone.

The time-invariance and high reproducibility of SSR across multiple MRI studies in knees that remain below KL grade 4 is an important finding, particularly in the context of utilizing SSR to predict incident knee symptoms or KOA progression. As radiographic severity is poorly correlated with symptom status, it is important to identify prognostic factors for future symptoms that are insensitive to early radiologic changes. This was a major part of our rationale for investigating subchondral size mismatch instead of cartilage surface area mismatch as asymptomatic patients may already have significant cartilage loss at the time of evaluation. Similarly, radiologic measures are more useful as predictive tools if they are independent of disease severity; while cartilage-based measures are important biomarkers of disease activity, subchondral measures such as lateral SSR may predict risk of future OA progression regardless of current severity. Finally, the stability of medial SSR values over time suggests that utilization of previously acquired knee MRIs for unrelated complaints is an acceptable cost-saving alternative to acquiring a new MRI for screening purposes.

Use of secondary data from the OAIF allowed us to account for many relevant confounders in this investigation. In particular, the association between medial SSR and baseline or incident symptoms was much stronger after adjustment for confounders than in the unadjusted analysis. However, use of secondary data was also a major limitation as the findings from this study may not be generalizable to populations that are underrepresented in this sample such as patients younger than 45 years and or who are not Caucasian or African-American. Finally, though the methods for obtaining the measures used to calculate SSR are validated and reproducible with conventional MRI sequences, the clinical applicability of SSR screening to assess risk of future symptoms may be limited by the time burden of manual segmentation until a more efficient surrogate MRI or radiographic measure is established for routine clinical use.

In conclusion, MRI-based screening for medial SSR in asymptomatic Caucasian or African-American patients over 45 with KL grade 0–3 knees is a valid assessment of future symptom risk. Lateral SSR is an independent predictor of lateral OA progression, and both lateral and medial SSR are time-invariant in KL grade 0–3 knees. Further research is recommended to identify and validate simplified versions of SSR for clinical use and to determine the causal mechanisms between medial SSR and knee symptoms or lateral SSR and lateral OA progression.

### Table IV

Sensitivity analysis of medial compartment SSR as a risk factor for incident symptoms at 24 or 48 months

<table>
<thead>
<tr>
<th>Incident symptoms</th>
<th>Adjusted odds ratio</th>
<th>P-value</th>
<th>Adjusted odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 months</td>
<td>1.37 (0.38, 8.79)</td>
<td>0.067</td>
<td>0.71 (0.24, 3.41)</td>
<td>0.402</td>
</tr>
<tr>
<td>48 months</td>
<td>0.42 (0.23, 0.790)</td>
<td>0.0008</td>
<td>0.40 (0.23, 0.73)</td>
<td>0.0025</td>
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<tr>
<td></td>
<td>0.39 (0.22, 0.67)</td>
<td>0.00475</td>
<td>0.47 (0.29, 0.78)</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>0.59 (0.34, 0.99)</td>
<td>0.0019</td>
<td>0.59 (0.36, 0.98)</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>0.54 (0.30, 0.95)</td>
<td>0.0019</td>
<td>0.33 (0.17, 0.60)</td>
<td>0.0266</td>
</tr>
<tr>
<td></td>
<td>0.47 (0.23, 0.89)</td>
<td>0.0002</td>
<td>0.48 (0.23, 0.92)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>0.40 (0.12, 1.05)</td>
<td>0.065</td>
<td>0.55 (0.19, 1.36)</td>
<td></td>
</tr>
</tbody>
</table>

### Table V

CV RMSE, mean difference (SD) and correlation for lateral SSR and medial SSR, between MRI studies at baseline and 24 months

<table>
<thead>
<tr>
<th></th>
<th>Medial SSR</th>
<th>Lateral SSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SSR — baseline</td>
<td>0.54263</td>
<td>0.6161</td>
</tr>
<tr>
<td>Mean SSR — 24 months</td>
<td>0.54403</td>
<td>0.6161</td>
</tr>
<tr>
<td>Mean difference (SD)</td>
<td>0.0012 (0.0157)</td>
<td>0.0000 (0.0168)</td>
</tr>
<tr>
<td>Minimum difference</td>
<td>−0.0639</td>
<td>−0.0819</td>
</tr>
<tr>
<td>Maximum difference</td>
<td>0.0634</td>
<td>0.0571</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.0155</td>
<td>0.0167</td>
</tr>
<tr>
<td>RMSE CV%</td>
<td>2.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.978</td>
<td>0.970</td>
</tr>
</tbody>
</table>

### Competing interests

Dr. Flanigan is a consultant for Sanofi and Smith & Nephew. The authors declare no conflicts of interest.

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References


