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The longitudinal relationship between tibiofemoral contact stress at baseline and worsening of knee pain over 84-months in The Multicenter Osteoarthritis Study

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Abstract

Objective: Determine whether tibiofemoral contact stress predicts risk for worsening knee pain over 84-months in adults aged 50–79 years with or at elevated risk for knee osteoarthritis.

Design: Baseline tibiofemoral contact stress was estimated using discrete element analysis. Other baseline measures included weight, height, hip-knee-ankle (HKA) alignment, Kellgren-Lawrence grade (KLG) and Western Ontario and McMaster Universities Osteoarthritis Index pain subscale (WOMAC-pain). Logistic regression models assessed the association between baseline contact stress and 84-month worsening of WOMAC-pain.

Results: Data from the dominant knee (72.6% KLG 0/1 and 27.4% KLG≥2) of 208 participants (64.4% female, mean±SD body mass index 29.6±5.1 kg/m^2) were analyzed. Baseline mean and peak contact stress were 3.3±0.9 MPa and 9.4±4.3 MPa, respectively. 47 knees met the criterion for worsening pain. The highest tertiles in comparison to the lowest tertiles of mean {Odds Ratio (95% Confidence Interval) 2.47 (1.03, 5.95); p=0.04} and peak {2.49 (1.03, 5.98); p=0.04} contact stress were associated with worsening pain at 84-months, after adjustment for age, sex, race, clinic site and baseline pain. *Post hoc* sensitivity analyses including adjustment for BMI and HKA alignment attenuated the effect.

Conclusions: These findings suggest that elevated tibiofemoral contact stress can predict the development of worsening of knee pain.

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Keywords

Biomechanics; Joint Loading; Knee Osteoarthritis; Knee Pain

Introduction

Osteoarthritis (OA) is one of the most common musculoskeletal disorders in older adults and the knee is the most commonly affected weight-bearing joint. Knee pain is the most significant symptom associated with knee OA and is the primary reason that patients seek care. Individuals with knee pain experience functional limitations, depressive symptoms and are at greater risk of disability. It has been suggested that knee pain is a better predictor of functional status in patients with knee OA than radiographic disease severity.[1] Therefore, prevention of painful knee OA requires knowledge of risk factors for worsening pain. The ability to predict worsening knee pain could inform the design of therapies to delay or prevent disablement.

From a functional perspective, the initiation of knee OA has been associated with kinematic changes that shift load bearing to infrequently loaded regions of the cartilage that are less able to accommodate these loads.[2] Furthermore, *in vivo* contact stresses are typically related to joint motion and the preservation of normal cartilage.[3] Miyazaki et al. reported that higher loads at the knee during walking result in a more rapid rate of cartilage breakdown in patients with knee OA and can help predict progression of pain.[4] In contrast to the measurement of joint contact force, which describes the overall force transferred between articulating surfaces in the joint, joint contact stresses are inherently more individualized by describing the force transmitted per unit of joint contact area. Personalized estimates of joint contact stress may help to predict patients who are at a greater risk for worsening of knee pain and development of symptomatic knee OA, which could lead to patient-specific analysis and preventative treatment from readily available clinical imaging data.[5] For example, non-surgical treatment options can be targeted to reduce load in the more affected compartment in the knee and relieve pain, e.g. include laterally wedged insoles for medial knee OA, knee sleeves and corrective bracing that target specific joint compartments.[6,7]

An efficient method for estimating articular contact stress, discrete element analysis (DEA),[8,9] may be a feasible means of predicting worsening of knee pain in order to inform preventative therapies. Specifically, DEA estimates of articular contact stress could be used to personalize unloading braces and other orthoses to target unloading of compartments with high contact stress, thereby decreasing the load on the knee, preventing structural deterioration and relieving pain. DEA based estimates of articular contact stress have been found to be predictive of risk for incident symptomatic knee OA,[8] bone marrow lesions (BMLs) and cartilage structural pathology.[10] An increase in BMLs may be associated with increased knee pain.[11] However, multiple studies have reported that there may be discordance between structural changes and symptoms.[12–15] Therefore, the objective of this study was to evaluate DEA-based estimates of mean and peak tibiofemoral articular contact stress as a predictor of longitudinal worsening of knee pain. We tested the hypothesis that a

biomechanical predictor, articular contact stress, predicts clinically meaningful worsening of knee pain over 84-months follow-up.

Methods

Participants

The Multicenter Osteoarthritis (MOST) Study is an NIH-funded longitudinal observational study of 3026 community-dwelling men and women age 50–79 with knee OA or known risk factors for knee OA including age, female sex, overweight, and history of knee symptoms, injury and/or surgery.[16,17] Exclusion criteria included bilateral knee replacement, cancer, or rheumatologic disease; additional details of participant enrollment have been previously described.[8,18] Enrollment was offered to every fourth participant at the University of Iowa (UI) site and every third participant at the University of Alabama (UAB) site (due to enrollment in this study beginning at the UAB site later in the baseline MOST visit). Of 275 knees selected for collection of quantitative (1.5 Tesla) MRI in the MOST cohort, 13 had insufficient cartilage to segment and there were 42 knees for which no satisfactory radiographs were available for registration to the MR data. Institutional Review Boards at the participating institutions approved the data collection for this ancillary study and all participants completed an institutionally approved written informed consent process prior to participation (ClinicalTrials.gov Identifier: NCT03033238). This study conforms to all STROBE guidelines and reports the required information accordingly (see Supplementary Checklist).

Baseline Measures

Participant characteristics, including age, weight and height were collected at baseline and described previously.[18] Body mass index (BMI, kg/m^2) was calculated from mass in kilograms divided by the square of the height in meters (Stadiometer, Holtain, Wales, UK), as measured by trained and certified staff.[18] A long-limb radiograph, including the hip and tibio-talar joints, was acquired for measurement of hip-knee-ankle (HKA) alignment at baseline as described previously by Sharma et al.[19] Varus alignment was defined as 178° or less, valgus as 182° or greater and neutral as 179–181°. Weight-bearing posteroanterior fixed-flexion radiographs were assessed for Kellgren-Lawrence (KL) grades by expert readers from MOST.

Knee Imaging and Contact Stress Estimation

Participants underwent 1.5 Tesla magnetic resonance imaging (MRI) of both knees at baseline using a coronal 3D FLASH VIBE water-excitation sequence. Image resolution was 0.3125×0.3125×3 mm and the imaging parameters were as follows TE, 4.2–9.3 ms and TR 17/18.6 ms. For this study, one knee was included per participant— the dominant knee if acquired and readable, the non-dominant knee if the dominant knee was either not imaged or if the images were unreadable, and the right knee when dominance could not be determined. The dominant knee was defined as the leg with which one would kick a ball.

The bone (The University of Iowa, Iowa City, IA) and cartilage (Chondrometrics GmbH, Ainring, Germany) boundaries were segmented to generate knee-specific 3D clouds of

points. The smoothed 3D bone surface models were then registered to corresponding bone edges on weight bearing, fixed-flexion knee radiographs, using a semi-automated algorithm to rotate the segmented articular surfaces into the weight-bearing configuration of each participant. The 3D cartilage surface models were then integrated into each bone surface model and a previously validated DEA algorithm was used to estimate articular contact stress distributions for each surface (Figure 1).[9,20] The DEA algorithm computes nearest neighbors between facets of two apposed surfaces and applies a spring deformation model to calculate contact stress. The contact stress computation was based on total cartilage thickness, the approximated cartilage elastic modulus (12 MPa),[21] Poisson's ratio (0.42)[22] and the calculated spring deformations associated with the applied bone displacements. Previous work evaluating the reliability of the registration and segmentation methods for DEA revealed excellent day-to-day (intraclass correlation coefficients of 0.93–0.99) and good inter-rater reliability (0.84–0.97).[20]

Knee-Specific Pain

At baseline and 84-month follow-up, participants completed the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (Likert format 3.0) pain sub-scale for the knee that underwent MRI. The WOMAC pain scale is a validated disease-specific questionnaire with well-known clinometric properties for measurement of pain during usual functional activities and therefore provides more context than a numeric rating scale for monitoring OA-related knee pain.[23–27] Participants were asked to "fill in the circle that best describes the amount of pain you have experienced during the past 30 days" for walking on a flat surface, going up stairs, at night while in bed, sitting or lying and standing upright. For each of the five activities, answers included none, mild, moderate, severe, or extreme (0–4 points respectively). Total scores could range from 0 to 20, with higher scores indicating more severe pain. Because small differences in mean scores might be statistically significant simply due to large sample sizes and may not necessarily translate to meaningful changes in pain due to knee OA, we used the minimum clinically important difference (MCID), or the smallest change in an outcome that would be meaningful to the patient, to define worsening of pain at the 84-month follow-up visit as described below.

Statistical Analyses

A sample size was estimated based on an effect size provided by Angst et al. of 0.29.[28] Assuming a type I error of $\alpha = 0.05$ and a type II error of $1\text{-}\beta = 0.80$, a sample size of 188 participants would be adequate to detect worsening of WOMAC-pain at an effect size of at least this level. Participant characteristics were summarized with frequencies and means. The predictor variables were tertiles of 1) mean and 2) peak tibiofemoral articular contact stress in the more severely affected compartment (by radiographic KL grade) in one knee per participant. The outcome variable was the MCID for worsening of WOMAC knee pain score, which was rounded up to 2 points from the 1.32 points calculated by Angst et al.[28] The WOMAC pain scale is an ordinal scoring system, therefore rounding to the next full point ensures no underestimation of worsening pain. The outcome, worsening knee pain, was defined as present if the increase in knee-specific WOMAC pain met or exceeded this MCID threshold between baseline and 84-month follow-up, or if the participant underwent a total knee replacement (TKR) between baseline and follow-up. 84-month follow-up was

evaluated to allow for a sufficient sample size of participants to develop worsening pain. Rates of incident worsening knee pain were summarized as frequencies, percents and differences overall and by strata of baseline KL grade were assessed by ANOVA using Tukey's test for pairwise comparisons.

A Spearman correlation analysis was used to evaluate the correlation between baseline WOMAC pain scores with mean and peak contact stress, as well as worsening of pain by 84-month follow-up. Multiple logistic regression was used to test whether tertiles of mean or peak baseline articular contact stress were associated with worsening knee pain by 84-month follow-up in separate models. We chose to assess tertiles of worsening rather than a continuous assessment in accordance with previous work assessing various predictors for worsening of knee pain.[29,30] Additionally, a continuous model for worsening of knee pain based on contact stress would yield a risk per unit stress, which is less clinically meaningful than evaluating thresholds (i.e. low/middle/high) for increased risk.

Analyses were adjusted for baseline WOMAC knee pain, as well as age, sex, race, and clinic site to assess whether these additional anthropometric factors were predictive of knee pain status. Due to the collinearity of both BMI and HKA alignment with contact stress, these variables were not entered as covariates in the primary analyses. An additional sensitivity analysis was completed with adjustments for BMI and HKA alignment added into the model. Results were reported as odds ratios (ORs) with associated 95% confidence intervals (CI).

Results

A total of 208 knees were available for analyses due to loss at 84-month follow-up (9 deaths, 3 WOMAC knee pain missing; Figure 2). After removal of the 12 knees unavailable for follow-up analyses, there was negligible change in baseline characteristics (Table 1). Median baseline WOMAC pain score was 2 points (interquartile range 0–4). Baseline mean contact stress (mean ± SD) was 3.3 ± 0.9 MPa and baseline peak contact stress (mean ± SD) was 9.4 ± 4.3 MPa. There were no associations between the baseline WOMAC pain score and mean contact stress (r=−0.005; p=0.94), peak contact stress (r=0.05; p=0.48) or worsening of pain by 84-month follow-up (r_s= −0.04; p=0.48). Overall, there was no significant association between baseline KL grade and incident pain worsening. Specifically, pain worsening occurred in 16.2% of KL grade 0, 25% of KL1, 25% of KL2 and 47.8% of KL3. There were no significant differences in rate of incident pain worsening comparing KL0 with KL1, KL2 or KL4, nor in comparing KL1, KL2 or KL4 with any other KL grade. However, KL3 worsened at a significantly higher rate than KL0 (p=0.02 by ANOVA using Tukey's test for pairwise comparisons).

Forty-seven knees (23%) met the MCID criterion for worsening at 84-month follow-up, 9 of which underwent TKR. Between baseline and follow-up, 8 underwent TKA, 13 worsened by 2 points, 10 by 3 points, 6 by 4 points, 3 by 5 points, 5 by 6 points, 1 by 9 points and 1 by 12 points. Compared with participants in the lowest tertile of baseline mean contact stress, the adjusted OR and 95% CIs for worsening knee pain for those in the middle and highest tertiles of mean baseline contact stress were 1.23 (0.49, 3.11) and 2.47 (1.03, 5.95),

respectively, with a p-for-trend across tertiles of 0.03. Compared with participants in the lowest tertile of baseline peak contact stress, the adjusted OR and 95% CIs for worsening knee pain for those in the middle and highest tertiles of peak baseline contact stress were 1.69 (0.69, 4.15) and 2.49 (1.03, 5.96), respectively, with a p-for-trend across tertiles of 0.05 (Table 2). The adjusted OR and 95% CIs for subjects in the middle and highest tertiles of baseline mean and peak contact stress, as well as OR and 95% CIs for all covariates including BMI and HKA alignment, as a predictor for worsening knee pain are given in Figure 3. When BMI and HKA alignment were added into the models for the sensitivity analysis, the results did not achieve statistical significance, with p-for-trend across tertiles of mean and peak contact stress predicting worsening pain of 0.08 and 0.11, respectively.

Discussion

The purpose of this study was to evaluate the relationship between tibiofemoral articular contact stress and longitudinal worsening of knee pain. These results build upon previous work that revealed DEA-based estimates of articular contact stress were predictive of risk for incident symptomatic knee OA at 15-month follow-up[8] and structural pathology, including worsening of bone marrow lesions (BMLs) and cartilage morphology at 30-month follow-up.[10] The current results indicate that participants in the highest tertile of baseline mean or peak tibiofemoral articular contract stress were at elevated risk for clinically meaningful worsening of knee pain at 84-month follow-up. However, there remains a question whether contact stress estimates provide additional information after accounting for BMI and HKA alignment.

The present results suggest that HKA alignment is a greater contributor to worsening of knee pain in comparison with BMI (Figure 3). While HKA alignment can provide insight into preventative non-surgical treatment options for the mediation of knee OA and associated knee pain, these values give a whole limb assessment that could miss some of the local joint biomechanics elucidated by contact stress measurements. Perhaps varus or valgus HKA alignment could be used as an indicator for the subsequent contact stress analysis in patient populations. A longitudinal study by Sharma *et al.* indicated varus and valgus alignment were associated with structural progression of medial and lateral tibiofemoral OA, respectively.[31] When looking into the mediating role of pain, Sharma *et al.* found that pain severity was significantly associated with malalignment severity and that each 5° of greater malalignment was associated with an average of 10/100 mm greater knee pain on a visual analog scale. This finding of a cross-sectional association between malalignment and greater pain severity in the prior study may offer insight into the causality for the association between contact stress estimates, which implicitly include alignment, and worsening of knee pain in our study.

From a clinical perspective, known risk factors for knee OA exist, including age, female sex, overweight BMI, and history of knee symptoms, injury and/or surgery.[16,17] Of these, age, BMI and history of knee symptoms, injury and/or surgery are concurrent risk factors for knee pain. [32,33] While these well-established epidemiological risk factors for worsening pain and knee OA on a population basis are useful for clinicians identifying patients at risk for worsening, a key barrier exists for the prevention and treatment due to the inability to

predict, and mitigate, worsening on a knee-specific basis. Imaging techniques can be utilized for assessing knee-specific parameters for osteoarthritis. On radiographs, KL grade is commonly used as a marker of disease severity and progression. However, the evaluation of two large cohort studies of knee OA suggested that presence of joint damage (as described by KL grade) alone is not indicative of the evolution of pain, but rather worsening of joint damage. Furthermore, individuals with early symptomatic OA whose KL grade changes are only one point did not have an association with worsening of pain.[34] On MRI, multiple features used to characterize knee OA, including the presence of osteophytes, BMLs, cartilage morphology, and meniscal damage among others, are evaluated for associations with incidence and progression of knee pain. However, these findings are often inconsistent. A recent study aiming to clarify both the cross-sectional and longitudinal associations of MR-based markers of knee OA with knee pain indicated only osteophytes and cartilage defects were consistently associated with pain longitudinally.[15]

The present study indicates that articular contact stress, which accounts for both bone structure and cartilage morphology, is associated with 84-month worsening of knee pain. Additionally, contact stress estimates can provide clinicians with evidence to select appropriate treatments for reducing articular contact stress in the knee joint,[35–37] as well as improving knee symptoms, physical function and potentially delaying or preventing the progression of knee OA. Laterally wedged insoles are commonly prescribed to shift loading from the medial to lateral compartments in patients with medial knee OA. However, there has been a reported lack of consistency in the clinical efficacy of this treatment, possibly due to improper patient selection.[7] The addition of contact stress information could inform not only the prescription of laterally wedged insoles, but also be used as a biomechanical marker for efficacy of this treatment strategy, as demonstrated by a finite element analysis-based study completed by Liu *et al.*[38] Results from multiple clinical trials indicate realigning braces are effective in improving knee pain and physical function,[39,40] as well as reducing adverse biomechanics.[6,41] Contact stress estimates could help both to identify patients with early knee OA most likely to benefit from these conservative treatments as well as to evaluate the biomechanical effects. Segal *et al.* used DEA-based contact stress estimates to assess the biomechanical effect of a single-upright brace for the realignment of the tibiofemoral joint in participants with unicompartmental tibiofemoral OA.[37]

A limitation of any study of biomechanics as a predictor of pain, a subjective experience, is the relatively weak relationship between structural changes and patient-reported outcomes, specifically symptoms. In this case, potential for discordance between contact stress and structure as well as an additional discordance between structure and pain could attenuate associations. Furthermore, pain is a subjective experience with great interindividual variability and can depend on many factors not limited to the presence of disease, such as psychosocial factors and central sensitization. Additional methods for identifying and evaluating severity of pain that account for some of these factors could beyond the WOMAC pain score could provide greater insight into the relationship between contact stress and knee pain. Furthermore, a limitation of any observational study is that participants are free to receive treatments over the follow-up period, so the variability between participants in the effects of usual care received cannot be completely standardized.

An additional limitation of the present study is a reduction in sample size (n=55; 20%) due to difficulties with either the radiograph or MRI acquisition, or cartilage segmentation. For example, the DEA algorithm used in this study relies on the presence of cartilage, therefore participants with full thickness cartilage lesions or holes at baseline could not be included in the current analysis and would require a different computational approach. Additionally, we were unable to register some 3D models to radiographs for a variety of reasons, including inferior quality of the radiographs, the distance from the beam generator to the knee, or the different degrees of knee flexion on the lateral and posterior-anterior radiographs (i.e. images not acquired with simultaneous biplanar imaging). Furthermore, the contact stress estimates were based on total cartilage thickness, with constant estimated values for the elastic modulus and Poisson's ratio, however cartilage is a biphasic tissue. Therefore, accuracy of the contact stress estimates was decreased by simplifying cartilage to a linear elastic material in the DEA methods. The cartilage segmentations were limited to the weight-bearing region of the tibiofemoral joint that is customarily studied for cartilage thickness measurements, potentially resulting in edge loading at the boundaries in the biomechanical models used in this study. Furthermore, the meniscus, which is responsible for the distribution and mediation of the tibiofemoral contact stress, was not explicitly included in the DEA model used in this study. Explicit inclusion of menisci and complete, biphasic cartilage models could yield more accurate contact stress estimates.

Recently, the introduction of standing CT has presented the ability to acquire 3D images of the knees under weight-bearing conditions.[42,43] Future studies involving this technology, rather than MRI and radiographs, for generation of the 3D models used in the DEA algorithm has the potential to provide more accurate bony segmentations, resulting in improved contact stress estimates from this DEA model as well as a reduction in computational cost. Automation of DEA techniques would allow for time-efficient computation of this potentially clinically meaningful outcome, enabling personalization of preventative therapies for patients at elevated risk for worsening of symptomatic knee OA.

Advances in 3D joint imaging and computing power have enabled this study evaluating the association between knee-specific tibiofemoral contact stress and worsening of knee pain. Identification of adults at elevated risk for worsening knee pain is important for participant selection for clinical trials, as well as to guide prognosis, preventative therapies and allocation of healthcare resources. Our findings suggest that knees with greater articular contact stress at baseline are at increased risk for knee pain worsening. These longitudinal results, in addition to prior findings,[8,10] provide support for the hypotheses that elevated contact stress is associated with an increased risk for worsening of knee pain and OA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is Known/What is New:

- What is Known: Epidemiological risk factors for worsening knee osteoarthritis (OA) and knee pain on a population basis are well-established; however, one key barrier to prevention and treatment has been the inability to predict knee-specific worsening. Patient-specific models of the knee joint can bridge epidemiology and biomechanics to personalize strategies for mitigating the burden of knee OA and pain.
- What is New: These longitudinal findings suggest that knees with greater articular contact stress at baseline have increased risk for knee pain worsening, supporting the use of personalized estimates of contact stress to guide treatment for mitigating worsening knee pain.

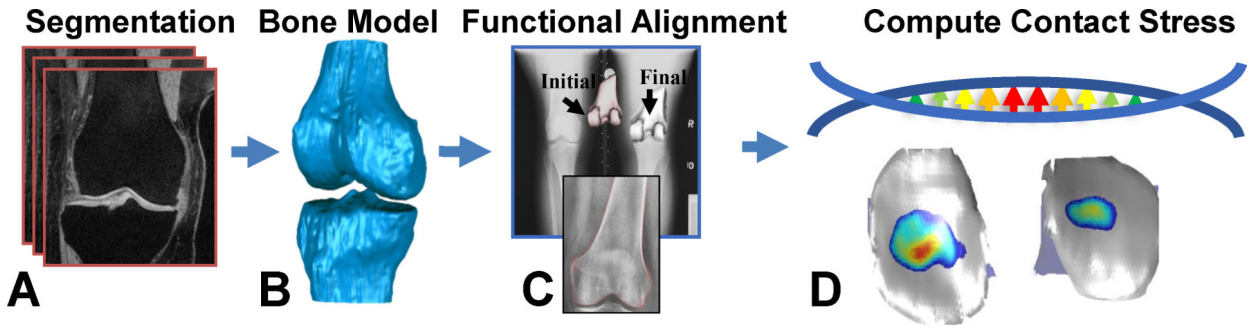


Figure 1:

Process for Tibiofemoral Articular Contact Stress Estimation.[20] **(A)** Segmentation of magnetic resonance (MR) images of tibiofemoral joint. **(B)** Bone models generated from segmentation of MR images. **(C)** Alignment of bone models to standing radiograph. **(D)** Computation of contact stress via discrete element analysis.

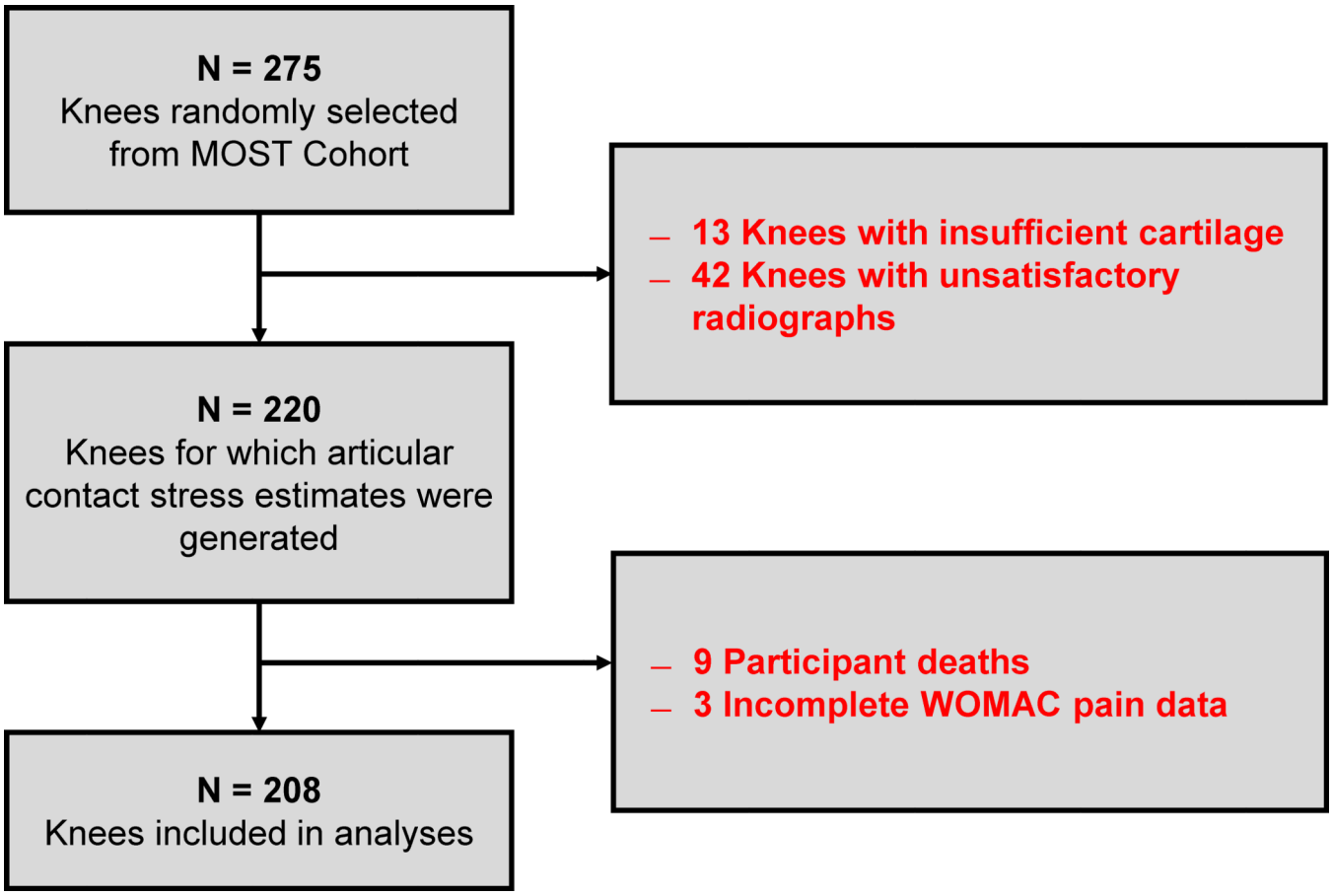
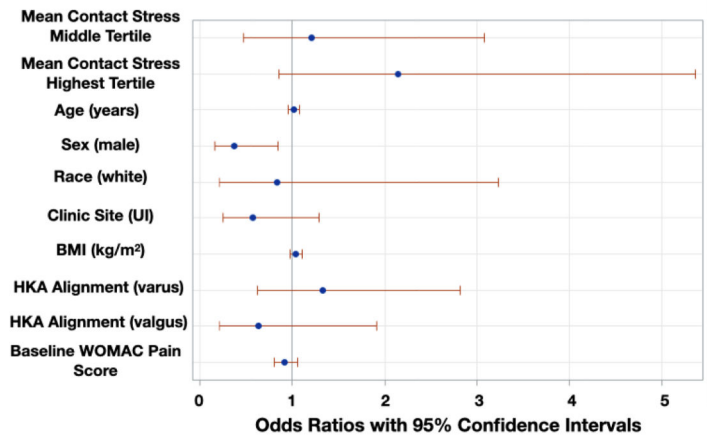


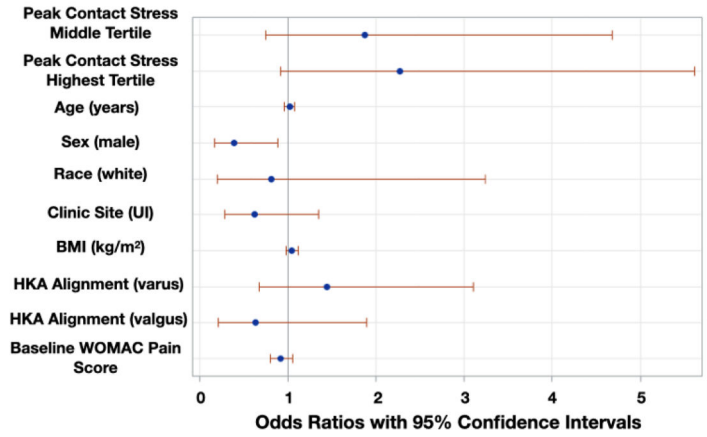
Figure 2:
Participant Inclusion Diagram

A



Parameter	Odds Ratio (95% CI)
Mean Contact Stress - Middle Tertile	1.21 (0.48 – 3.09)
Mean Contact Stress - Highest Tertile	2.15 (0.86 – 5.37)
Age (years)	1.02 (0.96 – 1.07)
Sex (male)	0.37 (0.17 – 0.84)
Race (white)	0.83 (0.22 – 3.23)
Clinic Site (UI)	0.57 (0.26 – 1.29)
BMI (kg/m^2)	1.04 (0.97 – 1.11)
Varus HKA Alignment	1.33 (0.62 – 2.82)
Valgus HKA Alignment	0.64 (0.21 – 1.92)
Baseline WOMAC Pain Score	0.92 (0.80 – 1.06)

B



Parameter	Odds Ratio (95% CI)
Peak Contact Stress - Middle Tertile	1.87 (0.75 – 4.68)
Peak Contact Stress - Highest Tertile	2.27 (0.92 – 5.62)
Age (years)	1.02 (0.96 – 1.07)
Sex (male)	0.37 (0.17 – 0.84)
Race (white)	0.83 (0.22 – 3.23)
Clinic Site (UI)	0.57 (0.26 – 1.29)
BMI (kg/m^2)	1.04 (0.97 – 1.11)
Varus HKA Alignment	1.33 (0.62 – 2.82)
Valgus HKA Alignment	0.64 (0.21 – 1.92)
Baseline WOMAC Pain Score	0.92 (0.80 – 1.06)

Figure 3:

(A) Odds Ratios with 95% Confidence Intervals (CI) for Mean Contact Stress and all Covariates as Predictors for Worsening Knee Pain. **(B)** Odds Ratios with 95% Confidence Intervals for Peak Contact Stress and all Covariates as Predictors for Worsening Knee Pain. All analyses were completed with the lowest tertile of baseline contact stress as the referent group.

Table 1:

Baseline characteristics of participants (N=208)

Baseline Characteristic	Mean ± SD and Frequency (%)
Age [years]	60.1 ± 6.4
BMI [kg/m^2]	29.6 ± 5.1
Baseline WOMAC knee pain	2.6 ± 2.9
N (%) Female	134 (64.4)
N (%) Clinic Site UI	95 (45.7)
N (%) KL grade	
0	111 (53.4)
1	40 (19.2)
2	32 (15.4)
3	23 (11.1)
4	2 (1.0)
N (%) HKA Alignment Angle	
Varus < 179°	97 (46.6)
Neutral 179° – 181°	76 (36.5)
Valgus > 181°	35 (16.8)
Peak Contact Stress [MPa]	9.4 ± 4.3
Mean Contact Stress [MPa]	3.3 ± 0.9

Abbreviations: BMI, body mass index; WOMAC, Western Ontario McMaster Universities Index of Osteoarthritis; UI, University of Iowa; KL, Kellgren-Lawrence; HKA, hip-knee-ankle

Table 2:

The relationship between tertile of baseline tibiofemoral contact stress and worsening of Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index knee pain.

Variable	Tertile	Range of Contact Stress (MPa)	N (%) with worsening	Adjusted[a] OR (95% CI)	*p* value
Mean Contact Stress	Low	<=2.78	12 (17.4)	1 (referent)	
	Middle	2.78–3.59	13 (18.6)	1.23 (0.49, 3.11)	0.66
	High	>=3.59	22 (31.9)	2.47 (1.03, 5.95)	0.04
	p-for-trend			*0.030*	
Peak Contact Stress	Low	<=7.16	10 (14.5)	1 (referent)	
	Middle	7.16–9.47	16 (22.9)	1.69 (0.69, 4.15)	0.25
	High	>=9.47	21 (30.4)	2.49 (1.03, 5.98)	0.04
	p-for-trend			*0.048*	

Abbreviations: OR, odds ratio; CI, confidence interval

a: Adjusted for age, sex, race, clinic site and baseline WOMAC pain score