Running Head: Predicted medial knee contact force and cartilage loss in osteoarthritis

Title: Association of machine learning based predictions of medial knee contact force with cartilage loss over 2.5 years in knee osteoarthritis

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Abstract

Objective: The relationship between in vivo knee load predictions and longitudinal cartilage changes has not been investigated. This study aimed to develop an equation to predict the medial tibiofemoral contact force (MCF) peak during walking in persons with instrumented knee implants, and to apply this equation to determine the relationship between the predicted MCF peak and cartilage loss in persons with knee osteoarthritis.

Methods: In adults with knee osteoarthritis [39 women, 8 men; age 61.1 ± 6.8 years], baseline biomechanical gait analyses were performed and annualized change in medial tibial cartilage volume (mm$^3$/year) over 2.5 years was determined using magnetic resonance imaging. In a separate sample of patients with force-measuring tibial prostheses [3 women, 6 men; age 70.3 ± 5.2 years], gait data plus in vivo knee loads were used to develop an equation to predict the MCF peak using machine learning. This equation was then applied to the knee osteoarthritis sample, and the relationship between the predicted MCF peak and annualized cartilage volume change was determined.

Results: The MCF peak was best predicted using gait speed, the knee adduction moment peak and the vertical knee reaction force peak (root mean square error=132.88 N, $R^2=0.81$, $p<0.001$). In participants with knee osteoarthritis, the predicted MCF peak was related to cartilage volume change ($R^2=0.35$, $\beta=-0.119$, $p<0.001$).

Conclusion: Machine learning was used to develop a novel equation for predicting the MCF peak from external biomechanical parameters. Predicted MCF peak was positively related to medial tibial cartilage volume loss in persons with knee osteoarthritis.
Introduction

Mechanical loading is implicated in the onset and progression of cartilage loss, a hallmark of knee osteoarthritis (OA) (1–7). Mechanical loads are theorized to be related to cartilage loss through their role in increasing compressive forces across joint surfaces (8). However, such a relationship has not yet been verified in persons with knee OA since non-invasive, in vivo force measurement is not possible; direct measurement of knee contact forces is only possible using instrumented knee implants (9). Therefore, loads acting within native knees are estimated using musculoskeletal modeling from motion analysis data; or surrogate measures reflecting knee joint loading are calculated using inverse dynamics.

Key external biomechanical parameters used to describe loading across knee joint surfaces include the knee adduction moment (KAM), the knee flexion moment (KFM), the vertical knee reaction force (vKRF), gait speed, and measures of body size (height, body mass and body mass index (BMI)). The KAM reflects the distribution of load between medial and lateral knee compartments (10). The KFM provides insight into net muscle contraction across the knee (11). During stance, the quadriceps produce an internal knee extension moment to counterbalance the external KFM, increasing compressive forces within the joint (1). The vKRF represents an equal and opposite vertical force acting between the tibia and femur, without accounting for muscle forces (12). Finally, although gait speed and measures of body size do not directly reflect joint loading, these are main effectors of the vertical ground reaction force (13) – a primary determinant of the KAM, KFM and vKRF (12,14,15).

Due to the theoretical relationship between mechanical loads and cartilage degeneration, and to the high prevalence of tibiofemoral OA in the medial compartment (16), measurement and prediction of medial knee contact forces (MCFs) are of particular interest. Direct measurements in patients with instrumented tibial prostheses and estimates from tibiofemoral contact force models confirm correlations between external biomechanical parameters and MCFs during gait (9,10,17–22). In patients with instrumented knee implants, the KAM (9,17–19), vKRF (10) and gait speed (17) were independently positively associated with the MCF. Interestingly, combining the KFM with the KAM enabled more useful predictions of the MCF than when either variable was analyzed separately (9,18), supporting the notion that these variables collectively describe the knee loading environment (1,3,18).
Furthermore, higher body mass and higher BMI were each associated with greater peak knee compressive forces in persons with knee OA (20–22).

Ample evidence links external gait measures to medial cartilage loss in knee OA. For instance, a higher KAM peak (3,4) and KAM impulse (4,6) at baseline predicted greater loss of medial knee cartilage over 1–5 years. A greater KFM peak at baseline was associated with reduced medial knee cartilage over 5 years (3). Furthermore, a higher BMI at baseline predicted greater medial knee cartilage loss over 2 years (23). Interestingly, the impact of a higher KAM peak and KAM impulse at baseline on medial knee cartilage loss over 2.5 years was amplified with increasing BMI (7).

Conversely, no known work has examined the relationship between the vKRF or gait speed with morphological cartilage changes in knee OA, though their relationship with cartilage loss seems logical seeing as these parameters directly influence knee load magnitudes. Since instrumented knee prostheses lack cartilage, MCF measurements acquired with such technology cannot be used to directly predict cartilage loss. Instead, biomechanical and/or statistical predictions of MCF can be developed in persons with instrumented prostheses and then validated in the population of interest (i.e., knee OA).

A primary goal of the field is to confirm whether knee contact forces are in fact related to cartilage loss. Thus far, studies have examined the relationship between external knee loading variables as surrogates of contact forces, and medial knee cartilage loss. To our knowledge, the relationship between the MCF (what the surrogate measures are said to represent) and cartilage loss has not yet been modelled directly. The purpose of this study was to confirm the relationship between the predicted MCF peak during walking and changes in medial tibial cartilage volume over 2.5 years in participants with clinical and radiographic knee OA. To accomplish this, we developed an equation to predict the MCF peak from external knee loading parameters using data from patients with instrumented tibial prostheses, which was then used to predict the MCF peak for a separate sample of participants with knee OA. It was hypothesized that a higher predicted MCF peak at baseline would be associated with greater cartilage volume loss in persons with knee OA.

**Patients and Methods**

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This analysis was performed using two datasets: one from participants with knee OA and another from patients with instrumented tibial prostheses. First, gait biomechanics and knee cartilage volume change were documented in a subset of participants with knee OA enrolled in a longitudinal, observational study. This study was approved by the Hamilton Integrated Research Ethics Board (10-475). Second, gait biomechanics data from a sample who received instrumented knee implants were used to derive a statistical model predicting the MCF peak. This study was approved by the ethics board of the “Charité Universitätsmedizin Berlin” (EA4/069/06) and registered at the German Clinical Trials Register (DRKS00000606) (www.orthoload.com). This research was completed in compliance with the Helsinki Declaration. All participants provided written, informed consent.

Participants with Knee Osteoarthritis

The knee OA cohort comprised a convenience sample of 64 adults 40 to 70 years of age with clinical knee OA, who were recruited from local rheumatology and orthopaedic clinics. Clinical knee OA was diagnosed according to the American College of Rheumatology criteria (24). Potential participants were excluded if they had other types of arthritis; past lower-extremity joint injury and/or surgery; ipsilateral hip or ankle conditions (including OA); regular need for an adaptive walking aid; lower-extremity trauma or intra-articular therapies within 3 months prior to commencing the study. If participants had bilateral OA, the most symptomatic knee was studied.

At baseline, Kellgren-Lawrence scores (25) were determined by an experienced radiologist from anteroposterior weight-bearing knee radiographs acquired in a standardized fixed-flexion position (26). These measurements have demonstrated moderate to very good interobserver reliability with intraclass correlation coefficients (ICCs) ranging between 0.51 and 0.89 (27). In addition, descriptive statistics were recorded, including sex, age, height, body mass, BMI and anatomical knee alignment (28). In the current analysis, only participants with radiographic knee OA (i.e., Kellgren-Lawrence score ≥2) at baseline, and who had baseline and follow-up cartilage measurements were included [n=47; 39 women, 8 men; age 61.1 ± 6.8 years; Kellgren-Lawrence scores: grade 2=18, grade 3=18 grade 4=11].

Cartilage Morphology

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At baseline and approximately 2.5 years follow-up, participants with knee OA underwent magnetic resonance imaging (MRI) of the study knee using the same 1T peripheral scanner (OrthOne, ONI Medical Systems). Participants were scanned in the morning and asked to minimize weight-bearing prior to MRI acquisition. For analysis of cartilage morphometry, MRI scans were acquired using a coronal, T1-weighted, fat-saturated, spoiled gradient recalled acquisition in the steady-state sequence with 0.3125 x 0.3125 mm in-plane resolution and 1.5 mm slice thickness (60 ms repetition time; 12.4 ms echo time; 40° flip angle).

Medial tibial cartilage volume was determined from automated, atlas-based, segmentations of MRI scans (Qmetrics) (29). Test-retest precision error for medial tibial cartilage volume using the same 1T scanner was 3.6% (30). Baseline and follow-up cartilage values were used to calculate annualized cartilage volume change (mm³/year) for each participant using the following equation:

$$\Delta \text{Cartilage/year} = \frac{\text{Cartilage volume at follow-up} - \text{cartilage volume at baseline}}{\# \text{years between time points}}.$$

**Biomechanical Assessment**

Within one week of baseline MRI, participants with knee OA underwent gait analyses to calculate three-dimensional knee kinematics and kinetics during self-paced barefoot walking. Active infrared markers, mounted in triads on rigid plates, were fixated to the sacrum, and lateral aspects of the mid-thigh, mid-shank and foot of the study leg. Standard bony anatomical landmarks were digitized to create participant-specific rigid link-segment models of the pelvis and leg, as described previously (31). Marker trajectories were collected at 100 Hz with a nine-camera motion capture system (Optotrak Certus, Northern Digital). Kinetics were recorded synchronously at 1000 Hz with a floor-embedded force platform (OR6-7-1000, AMTI). Five self-paced barefoot gait trials, where the foot of the study leg landed fully on the force platform, were collected.

Gait data were processed with commercial software (Visual 3D, C-Motion). Marker trajectory and force plate data were filtered with a second order, low-pass (6 Hz cut-off), bidirectional Butterworth filter (32). External knee moments and reaction forces were resolved in a three-dimensional floating axis coordinate system (33) using inverse dynamics (12). The following external biomechanical parameters – representing theoretically-relevant potential predictors of MCF (9,10,17–22) – were computed and extracted for five gait cycles, and then averaged: gait speed; external KAM
peak; external KAM impulse; external KFM peak; and vKRF peak. Given the importance of the first KAM and KFM peaks to the progression of cartilage loss in knee OA (3,6), and to ensure analysis of temporally-matching outcomes between participants, the peak values for the kinetic outcomes (i.e., KAM, KFM, vKRF) were extracted from the first 50% of stance. The KAM impulse, which captures both the magnitude and duration of load (34), was computed for the entire stance phase using trapezoidal integration of only positive values.

Patients with Instrumented Knee Implants – In Vivo Knee Loads
To allow predictions of the in vivo MCF peak, gait data were also acquired in a separate sample of patients with force-measuring tibial prostheses as a result of total knee arthroplasty to treat advanced OA [n=9; 3 women, 6 men; age 70.3 ± 5.2 years] (9,17,35) (www.orthoload.com). Details of the design, calibration and accuracy of the instrumented tibial tray have been reported elsewhere (36,37). Gait data were collected over 8 years (1–3 time points per participant); the earliest time point was 11.2 months after implantation. Marker trajectories (100 Hz or 120 Hz, Vicon), ground reaction forces (1000 Hz or 960 Hz, AMTI), and internal knee implant kinetics (~100 Hz, Innex FIXUC, Zimmer) were collected synchronously during barefoot walking at self-determined slow, natural, and fast walking speeds. A range of walking speeds was included to capture greater variability in MCF peaks, and to allow broader generalizability of the model. Marker trajectory and force plate data were processed using the same rigid link-segment model and processing parameters (i.e., filter, joint coordinate system, inverse dynamics) as described for the knee OA sample (Visual 3D, C-Motion), and the same descriptive statistics and external biomechanical parameters were computed. To enable prediction of the MCF peak from external parameters, and to ensure temporal consistency with the extracted kinetic outcomes (i.e., KAM peak, KFM peak, vKRF peak), the first peak of the MCF was extracted from the measured in vivo loads for each trial. In total, 218 gait trials were analyzed, representing an average of 24.2 trials per participant (minimum=7; maximum=40).

Predictions of Medial Knee Contact Force Peak
The best combination of predictors of the measured MCF peak was determined in patients with instrumented knee implants using the machine learning method Least Absolute Shrinkage and
Selection Operator (LASSO) regression (38,39). LASSO is a regularized form of least squares regression that uses a tunable parameter ($\lambda$). When $\lambda$ is set to 0, LASSO is equivalent to least squares regression; as $\lambda$ is increased, unimportant beta coefficients are reduced to zero. Model selection was therefore simplified to identify the $\lambda$ between 0 and 100 with the smallest out-of-sample root mean square error (RMSE) using leave-one-out cross-validation (38,39). In other words, the RMSE was assessed on the samples of data left out during each cross-validation step and represents prediction error on data not used to fit the model. To prevent data leakage, cross-validation was performed at the participant level instead of at the trial level. Potential predictors included: height (m); body mass (kg); BMI (kg/m$^2$); gait speed (m/s); KAM peak (Nm); KAM impulse (Nm•s); KFM peak (Nm); vKRF peak (N); as well as the squared versions of each term and all possible two-way interactions. To create the final model, predictors with non-zero beta coefficients at the optimal $\lambda$ were fitted to the data from all 218 trials using least squares regression. To account for non-independence of repeated measurements, a cluster-robust variance matrix was used (40).

Predicted MCF model fit parameters, including the fitted beta coefficients, model R$^2$ and RMSE, as well as the out-of-sample cross-validation RMSE were calculated. In addition, simple linear regressions were run for each of the identified predictors to determine how well they individually predicted the MCF peak.

**Statistical Analysis**

Descriptive statistics were calculated as means and standard deviations for continuous data and counts for categorical data. Demographic, anthropometric and overground, self-paced gait data were compared between the two samples (knee OA and instrumented knee implant) using independent samples t-tests; if assumptions of normality or homogeneity of variance were not met, two-sample Mann-Whitney U tests were used. To determine whether cartilage volume changed from baseline to follow-up in participants with knee OA, a one-sample t-test was used.

To determine the relationship between the predicted MCF peak and the change in medial tibial cartilage volume, a two-step approach was used. First, predictions of the MCF peak were calculated for all knee OA participants using the aforementioned equation generated in patients with
instrumented knee implants. Second, the relationship between the predicted MCF peak and the annualized cartilage volume change was fitted using ordinary least squares regression.

To assess the fidelity of the MCF peak predictions in the knee OA sample, and their relationship with cartilage change, additional analyses were performed. Reliability of the MCF peak predictions was determined using data from a subsample of knee OA participants (n=40) for whom gait data were available from a second occasion ~6 months following the baseline assessment. Relative and absolute test-retest reliabilities were estimated using a Shrout and Fleiss type 2,1 ICC and the standard error of measurement (SEM), respectively. Furthermore, the predictive model of cartilage change was assessed for assumptions of linear regression, including linearity, normality of residuals and homoscedasticity. Finally, a multivariate linear regression model between the identified predictors of the MCF peak and cartilage volume change was created. The goodness-of-fit of this multivariate model was compared to that of the MCF peak model using the likelihood ratio test. All data and statistical analyses were performed with StatsModels for Python 3.7 (41).

Results
At baseline, the knee OA group had a higher proportion of women (p=0.001) and was younger (p<0.001) than the instrumented knee implant group. Participants with knee OA were also shorter (p=0.002) and weighed less (p=0.010) (likely attributable to the sex discrepancy between groups); however, they did not differ in BMI (p=0.326). Demographic and anthropometric data as well as all tested biomechanical parameters for the knee OA group and the instrumented knee implant group are given in Table 1. The KAM peak (∆=-12.79 Nm; p=0.017) and KAM impulse (∆=-6.57 Nm•s; p=0.016) were lower in the knee OA group compared to the instrumented knee implant group; no between-group differences were observed for gait speed, KFM peak, vKRF peak and measured/predicted MCF peak (p>0.05).

In patients with instrumented knee implants, the identified parameters that best predicted the MCF peak using LASSO regression were: gait speed, KAM peak and vKRF peak. The optimal lambda of the LASSO regression was 10.5. The linear model fit using the predictors identified from the LASSO analysis and all data had an $R^2=0.81$ (p<0.001) and RMSE=132.88 N (Table 2). Leave-one-out cross-validation showed that the model had an out-of-sample RMSE=196.58 N. Figure 1
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displays visual assessment of model fit for the predicted MCF peak model, including a quantile-quantile (QQ) plot, probability-probability (PP) plot, histogram of residuals, and a plot of measured versus predicted MCF peaks. Simple linear regression of the identified predictors showed that they were each related to the MCF peak (gait speed $R^2=0.19$, $p=0.018$; KAM peak $R^2=0.55$, $p=0.006$; vKRF peak $R^2=0.49$, $p=0.025$) (Table 3).

For the knee OA group, the mean follow-up time was 2.57 ± 0.53 years. Between baseline and follow-up assessments, medial tibial cartilage volume was reduced by 47.95 ± 65.72 mm$^3$/year ($p<0.001$), which is equivalent to 2.63 ± 3.88%/year. The total change in cartilage volume over the duration of the study was 6.39 ± 9.41%, which was greater than the measurement error of 3.6%. No evidence of a ceiling effect on cartilage change was observed in participants with Kellgren-Lawrence grade 4 knees, as this subgroup experienced significant cartilage loss over the duration of the study ($p=0.005$). Test-retest reliability estimates for the predicted MCF peak were as follows: ICC=0.908 (95% confidence interval: 0.833–0.950) and SEM=102.48 N, which is equivalent to 7.6% of the group mean. The predicted MCF peak was a significant predictor ($R^2=0.35$, $\beta=-0.119$, $p<0.001$, RMSE=52.60 mm$^3$/year) of annualized change in medial tibial cartilage volume over 2.5 years (Figure 2). An $R^2$ of 0.35 renders a Cohen’s $f^2$ of 0.54, signifying a large effect of the MCF peak on cartilage loss (42). The multivariate model of cartilage volume change containing the three predictors of the MCF peak (gait speed, KAM peak, vKRF peak) produced an $R^2$ of 0.41 ($p<0.001$); however, the goodness-of-fit was not different between the multivariate model and the single predictor (MCF peak) model ($p=0.094$).

Discussion
This work is the first to provide direct evidence that the MCF is positively related to loss of medial tibial cartilage volume in people with knee OA, supporting the notion that mechanical loading is a key contributor to structural disease progression. While direct measurement of knee contact forces in patients with instrumented tibial prostheses represents the gold standard for determining internal joint loads, such measurements are not possible in native knees. Accurate and reliable predictions of the MCF peak can be statistically modelled based on specific external biomechanical gait parameters obtained with motion analysis and inverse dynamics. The implication of a higher gait speed, KAM
peak and vKRF peak in increasing the compressive forces across the joint surfaces and ultimately contributing to cartilage breakdown make these biomechanical parameters ideal targets for intervention. Strategies to reduce the magnitude of these parameters may curb the deleterious effects of knee biomechanics on the progression of cartilage loss in knee OA.

The predicted MCF peak explained 35% (p<0.001) of the variance in 2.5-year changes in medial tibial cartilage volume. Prior studies have modelled the relationship between biomechanical outcomes (e.g., KAM) and medial tibial cartilage volume change; however, direct comparisons with the current model are not possible because either the R² was not reported (6) or the model included multiple covariates (7). Instead, our multivariate analysis may provide insight around this point. The multiple linear regression model of cartilage change that included the three predictors of the MCF peak (gait speed, KAM peak, vKRF peak) as individual variables yielded an R² of 0.41 (p<0.001). It was expected that this multivariate model would yield a higher R² than that of the single predictor MCF peak model because it is based on the same core predictors but has more degrees of freedom (3 versus 1). The greater degrees of freedom with the same inputs necessarily improve model flexibility and fit, thereby decreasing the RMSE and increasing the R². Nonetheless, the goodness-of-fit between the two models was not different. Therefore, the MCF peak model predicted cartilage loss in a way that was comparable to that of the best possible linear combination of the same core predictors, demonstrating good generalizability of the MCF peak prediction equation in the OA sample.

Ultimately, the fact that the measurement of interest (MCF peak) had the ability to predict the future outcome (cartilage loss) to which it is theorized to be related (8) provides predictive validity (43) – a form of criterion validity – for the MCF peak equation.

In the current analysis, the MCF prediction model showed a positive relationship between all predictors and the MCF peak, explaining 81% of the variance. These results, and those from the univariate regression analyses, corroborate findings from prior works in patients with instrumented knee implants. For instance, single-subject analyses that included different gait patterns (e.g., normal, medial thrust, walking poles) showed that the first KAM peak was independently associated with the first MCF peak (R²=0.57) (18); the current study showed nearly the same strength of association (R²=0.55). In a different analysis, the first vKRF peak predicted the first MCF peak (R²=0.38) (10); a stronger association (R²=0.49) between these variables was observed in the present work, which may
be attributed to its larger sample size (n=9 versus n=1). The only known study examining the link between gait speed and the MCF was performed on baseline data from the same patients with instrumented knee implants included in the current analysis. In that study, gait speed explained 49% of the variance in the MCF peak during early stance (17). The current study noted a weaker univariate association (R²=0.19), likely because the MCF was analyzed as a discrete peak rather than continuous data (17). Ultimately, it seems intuitive that the MCF is best predicted by a combination of measures that reflect axial loading (vKRF), mediolateral force distribution (KAM), and a general mediator of knee loads (gait speed).

Joint contact forces have been predicted using two primary modelling methods: statistical and musculoskeletal. Statistical models predict measured contact forces from extracted biomechanical measurements, such as from patients with instrumented knee implants (9,10,17–19). For single-subject analyses of different gait patterns, the lowest reported RMSEs were 15% (10) and 32% body weight (18) for the first MCF peak. Alternatively, musculoskeletal models estimate the muscle forces necessary to generate the measured joint mechanics, resolving for physiologic joint loads (44–47). For example, using the common approach of minimizing the sum of muscle activations squared, an error of 40% body weight was obtained for the predicted first peak of the compressive joint reaction force (cJRF: compressive tibiofemoral load along the long axis of the tibia) during gait (47). By tuning muscle parameters of the same general model to match the peak cJRF‡, lower errors were achieved (e.g., RMSE of 28% body weight over the entire gait cycle waveform) (44). More complex approaches have incorporated subject-specific musculoskeletal geometry, joint kinematics determined from fluoroscopy, and different electromyography-informed optimization methods to resolve muscle forces (45). These approaches, depending on the model and optimization used, yielded RMSEs from ~22% to 105% bodyweight (~150 N to >700 N) when predicting the MCF for the stance phase waveform. The current analysis yielded a cross-validation RMSE of 196.58 N (22.0% body weight) and a RMSE of 132.88 N (14.9% body weight) when tested on all participants used to fit the model. These errors are comparable to those from the aforementioned “best” statistical models (10,17) and the most complex musculoskeletal models (45).

‡ The authors tuned a set of muscle synergies which penalized individual muscles or groups of muscles using weighting constants. All possible weighting constants were tested, and the combination that produced the smallest compressive force with an error less than 20% was selected.
However, when comparing the ability of models to predict their respective outcomes, factors other than reported errors must be considered. First, predictions from most statistical models and all musculoskeletal models referenced above were fitted and then tested on data from a single participant, likely resulting in overfit models. Given the rarity of the data and complexity involved in modelling, the analysis of a single participant is not surprising and represents unique, important data to advance the field. Second, while muscle parameter tuning can reduce model errors, this approach is only possible with data from instrumented prostheses (44,45). Without muscle tuning, RMSEs were relatively high at ~100% body weight for predictions of the entire MCF stance phase waveform (45). Third, the resources and competencies required for scaling musculoskeletal models, as well as collecting and analyzing medical imaging, fluoroscopy and electromyography data are immense. Finally, no known comparable work has performed any form of model validation. The comparable errors obtained in the present analysis using only motion capture data; model validation using both cross-validation and predictions of cartilage loss in persons with knee OA; excellent reliability of the MCF predictions in the knee OA sample; and the considerably lower barrier to implementation make using such a statistical equation to predict the MCF appealing.

This study had limitations. Most patients with knee implants were men, whereas most knee OA participants were women. Further, the equation to predict the MCF peak was derived using gait data from nine patients with total knee replacements. Yet, the observed relationship between the predicted MCF peak and cartilage volume loss in persons with knee OA provides criterion validity of the generated equation. In addition, the MCF prediction equation was based on barefoot gait data only, thereby limiting its generalizability to shod conditions. Finally, the knee OA sample comprised mostly older, overweight women with radiographic disease. Thus, the extent to which the association between the predicted MCF peak and cartilage loss can be extended to other populations is uncertain.

In conclusion, results from this work provide robust evidence supporting the role of higher MCFs in cartilage volume loss in persons with clinical and radiographic knee OA. Using “gold standard” measurements from patients with instrumented tibial prostheses, reliable, accurate and generalizable predictions of the MCF peak were statistically modelled based on key external biomechanical gait parameters obtained with motion analysis and inverse dynamics. This work acts as a stepping-stone toward confirming the theoretical relationship between the MCF and cartilage loss;
with technological and analytical advancements, future studies can improve upon our predictions. Nonetheless, these findings underscore the notion that accurate knee load predictions can be obtained without the need for far more resource-intensive approaches. Strategies to reduce the MCF magnitude may aid in curbing structural disease progression associated with mechanical loading in knee OA.

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Figure Legends

Figure 1. Visual assessment of model fit for the medial knee contact force (MCF) peak predicted from external biomechanical gait outcomes. Included are a quantile-quantile (QQ) plot of residuals (A), probability-probability (PP) plot of residuals (B), histogram of residuals (C), and a scatter plot of measured versus predicted MCF peaks (D). For the QQ plot, PP plot and histogram, the solid orange line represents a theoretical normal distribution. For the QQ plot and PP plot, limited deviation of the blue scatter points from the orange line indicates that the residuals follow a normal distribution. In the scatter plot of measured versus predicted MCF peaks, the orange line represents a 1:1 relationship between measured and predicted values: tighter fit of the scatter points indicates smaller error in the predicted MCF peak.

Figure 2. Predicted medial knee contact force (MCF) peak versus annualized change in medial tibial cartilage volume over 2.5 years in participants with knee osteoarthritis. The fitted model (orange line) and its 95% confidence band (grey) are overlaid on a scatter plot of individual observations (n=47).
Table 1. Demographic, anthropometric and gait data at baseline for the knee osteoarthritis (OA) group and the instrumented knee implant group. Gait data are for overground barefoot walking trials performed at a self-selected, natural speed. Values are given as counts for sex and as mean ± standard deviation for all other measurements. Values in bold are statistically significant (p<0.05).

|                         | Knee OA (n=47) | Knee Implant (n=9) | P-value |
|-------------------------|----------------|-------------------|---------|
| Sex (n)                 | 39 women, 8 men | 3 women, 6 men    | 0.001   |
| Age (years)             | 61.1 ± 6.8     | 70.3 ± 5.2        | <0.001  |
| Height (m)              | 1.63 ± 0.08    | 1.72 ± 0.04       | 0.002   |
| Body mass (kg)          | 76.1 ± 16.1    | 91.1 ± 12.5       | 0.010   |
| BMI (kg/m\(^2\))       | 28.8 ± 5.8     | 30.8 ± 4.5        | 0.326   |
| Coronal knee alignment (°) | -2.3 ± 3.5†  | 2.4 ± 4.2‡        | N/A*    |
| Gait speed (m/s)        | 1.17 ± 0.22    | 1.16 ± 0.11       | 0.350   |
| KAM peak (Nm)           | 25.03 ± 14.35  | 37.82 ± 13.53     | 0.017   |
| KAM impulse (Nm•s)      | 9.15 ± 6.58    | 15.72 ± 7.23      | 0.016   |
| KFM peak (Nm)           | 43.33 ± 18.09  | 30.78 ± 11.86     | 0.051   |
| vKRF peak (N)           | 749.64 ± 136.64| 803.21 ± 113.79   | 0.275   |
| Measured MCF peak (N)   | 1355.25 ± 326.02| 1578.75 ± 264.21 | 0.058   |
| Predicted MCF peak (N)  | 1355.25 ± 326.02| 1578.75 ± 264.21 | 0.058   |

Note: BMI = body mass index; KAM = knee adduction moment; KFM = knee flexion moment; vKRF = vertical knee reaction force; MCF = medial knee contact force; N/A = not applicable.

† Anatomical tibiofemoral angle determined from weight-bearing anteroposterior knee radiographs acquired in a fixed-flexion position (28). A negative value indicates valgus alignment.

‡ Mechanical tibiofemoral angle (hip-knee-ankle angle) determined from standing anteroposterior full-leg radiographs (28). A positive value indicates varus alignment.

* Knee alignment measurements were not compared statistically because anatomical (knee OA sample) and mechanical (knee implant sample) alignments are inconsistent with one another (28).
Table 2. Final linear regression model used to predict the measured medial knee contact force peak from external biomechanical gait outcomes in patients with instrumented knee implants. Values in bold are statistically significant (p<0.05).

| Final Model |  |  |  |
|-------------|------------------|------------------|------------------|
| R²=0.81 (p<0.001) | RMSE=132.88 N | Cross-validation RMSE=196.58 N |  |  |
| Intercept | -446.21 | 303.75 | 0.142 |
| Gait speed (m/s) | 398.06 | 67.90 | <0.001 |
| KAM peak (Nm) | 15.27 | 3.35 | <0.001 |
| vKRF peak (N) | 1.27 | 0.32 | <0.001 |

Note: RMSE = root mean square error; KAM = knee adduction moment; vKRF = vertical knee reaction force.
Table 3. Univariate linear regression models between each predictor of the MCF peak identified from the LASSO regression (gait speed, KAM peak, vKRF peak) and the measured MCF peak in patients with instrumented knee implants. Values in bold are statistically significant (p<0.05).

| Model          | $R^2$  | RMSE  | Cross-validation RMSE | $\beta$ Coefficient | Standard Error | P-value |
|----------------|--------|-------|-----------------------|----------------------|----------------|---------|
| Gait Speed Model | 0.19  | 275.86 | 330.97               | 894.57               | 174.58         | <0.001  |
| KAM Peak Model  | 0.55  | 206.60 | 268.33               | 743.19               | 200.67         | <0.001  |
| vKRF Peak Model | 0.49  | 218.29 | 311.14               | 74.82                | 548.80         | 0.892   |

Note: MCF = medial knee contact force; LASSO = Least Absolute Shrinkage and Selection Operator; KAM = knee adduction moment; vKRF = vertical knee reaction force; RMSE = root mean square error.
$R^2 = 0.35$, $p < 0.001$

Root Mean Square Error = 52.60 mm$^3$/year

$\Delta$ Cartilage Volume = $112.645 - 0.119$ (MCF Peak)