Gait Risk Factors for Disease Progression Differ Between Non-traumatic and Post-traumatic Knee Osteoarthritis

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Abstract

Objective: To examine if relationships between knee osteoarthritis (OA) progression with knee moments and muscle activation during gait vary between patients with non-traumatic and post-traumatic knee OA.

Design: This longitudinal study included participants with non-traumatic (n=17) and post-traumatic (n=18) knee OA; the latter group had a previous anterior cruciate ligament rupture. Motion capture cameras, force plates, and surface electromyography measured knee moments and lower extremity muscle activation during gait. Cartilage volume change were determined over 2 years using magnetic resonance imaging in four regions: medial and lateral plateau and condyle. Linear regression analysis examined relationships between cartilage change with gait metrics (moments, muscle activation), group, and their interaction.

Results: Measures from knee adduction and rotation moments were related to lateral condyle cartilage loss in both groups, and knee adduction moment to lateral plateau cartilage loss in the non-traumatic group only [β=-1.336, 95% confidence intervals (CI)=-2.653 to -0.019]. Generally, lower levels of stance phase muscle activation were related to greater cartilage loss. The relationship between cartilage loss in some regions with muscle activation characteristics varied between non-traumatic and post-traumatic groups including for: lateral hamstring (lateral condyle β=0.128, 95%CI=0.003 to 0.253; medial plateau β=0.199, 95%CI=0.059 to 0.339), rectus femoris (medial condyle β=-0.267, 95%CI=-0.460 to -0.073), and medial hamstrings (medial plateau; β=-0.146, 95%CI=-0.244 to -0.048).

Conclusion: Findings indicate that gait risk factors for OA progression may vary between patients with non-traumatic and post-traumatic knee OA. These OA subtypes should be considered in studies that investigate gait metrics as risk factors for OA progression.

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Key Words: knee osteoarthritis, anterior cruciate ligament, trauma, gait, magnetic resonance imaging, cartilage

Introduction

Trauma is a risk factor for osteoarthritis (OA) and people are 3.8 times more likely to develop knee OA if they sustained a traumatic injury[1]. Knee OA can be classified as non-traumatic (patients with no history of knee trauma but developed OA) and post-traumatic (patients having a knee trauma and subsequently developed OA).

Knee moments during gait are associated with OA progression in patients with non-traumatic knee OA[2-5]. These include knee adduction (KAM), flexion (KFM) and rotation (KRM) moments. KAM is a surrogate measure for the ratio of medial to lateral knee compartment loading[6]. Studies reported that higher KAM values were related to cartilage loss in the medial femur and medial tibia, as measured by magnetic resonance imaging (MRI)[2-5]. These findings are supported by studies in which OA progression was determined with other means (e.g. radiographs)[7-9]. The relationship between KFM and OA progression is less clear. In one study, higher KFM values during gait were associated with changes in tibia medial-lateral cartilage thickness ratios over 5 years[4], whereas in other studies there were no relationships between KFM and medial tibia or medial femur cartilage loss[3,5]. Finally, features of the KRM were reported to be different in both asymptomatic and knee OA participants that demonstrated radiographic medial joint space narrowing over 3 to 7 years compared to those having no progression[7,10].

Less studied is the impact of muscle activation on OA progression, which should be considered since muscle forces influence joint loading[11]. Hodges et al[12] demonstrated that prolonged medial knee muscle (vastus medialis/semimembranosus) activation during gait was associated with medial tibia cartilage volume loss over 12 months; however, prolonged lateral knee muscle (vastus lateralis/biceps femoris) activation was protective against cartilage loss. In contrast, Davis et al[7] found greater lateral hamstring activation during gait in patients that demonstrated medial compartment joint space narrowing over 3 years measured using radiographs compared to patients without narrowing. Patients that underwent knee arthroplasty 5-8 years after baseline gait assessments had higher or prolonged hamstring and quadriceps activation during gait compared to patients that did not undergo knee arthroplasty[10,13]. Although these data are interesting, additional work is required to examine relationships between muscle activation magnitude or timing and OA progression.

Previous studies investigating the role of gait metrics on OA progression have only included patients with non-traumatic knee OA[4,5,8] or have not indicated if patients were classified as non-traumatic or post-traumatic[2,3,7]. Considering these OA subtypes demonstrate differences in moments and muscle activation during gait[14,15], then the impact of gait metrics on disease progression may vary. However, there is a paucity of studies comparing progression risk factors between non-traumatic and post-traumatic knee OA.

We aimed to determine if knee moments and muscle activation during gait were associated with knee OA structural progression over 2 years, and to examine if this relationship varies between non-traumatic and post-traumatic knee OA. We hypothesized that the KAM and

prolonged quadriceps/hamstring activation would be related to OA cartilage volume loss in the non-traumatic OA group in both the medial and lateral knee compartments, but not in the post-traumatic OA group.

Method

Participants

This was a longitudinal, cohort study. Participants diagnosed with symptomatic knee OA, according to clinical criteria from the American College of Rheumatology[16], and between 35 to 75 years of age were enrolled. Participants were recruited from January 2015 to March 2017 from three tertiary hospitals in Montreal, Canada and the local community using convenience sampling. Exclusion criteria included: trauma or surgery within one year, previous joint arthroplasty, inflammatory arthritis, or neurological conditions. Each participant provided written, informed consent. The project was approved by the local research ethics board and procedures were in accordance with this ethics board and with the Helsinki Declaration of 1975, as revised in 2000.

Participants that sustained a previous traumatic anterior cruciate ligament (ACL) rupture were classified as post-traumatic knee OA. Participants gave an estimate of when this injury occurred. Participants that reported no previous ACL rupture were classified as non-traumatic knee OA. A musculoskeletal radiologist with 8 years of experience (MB) confirmed ACL status

(injured, normal, and/or reconstructed) on MRIs. The side with the most severe symptoms was selected when participants reported bilateral knee OA.

A sample size calculation determined 22 participants per group (44 total) would be required for a linear regression analysis examining the relationship between cartilage volume change and KAM parameters (PS Power and Sample Size Calculations Version 3.0)[17]. The sample size estimation was based on a previous study that found KAM impulse was associated with cartilage volume loss in patients with knee OA over one year[2]. Lower 95% confidence intervals (CI) of the regression coefficients (i.e. regression line slope) ranged between 6.0 and 10.6, and an average of this range (8.3) was used. Standard deviation estimates for medial compartment cartilage volume change over two years (8% cartilage loss) and KAM impulse (0.4 Nm*s/%body weight*height) were determined from previous studies[2,18]. Alpha and power values were set at 0.05 and 0.80, respectively, with a dropout rate of 20%. We were unable to estimate the sample size based on the relationship between cartilage loss with the interaction between gait parameters and knee OA subtype since this data were not available.

Demographic variables [e.g. body mass index (BMI)] were collected. The Intermittent and Constant Osteoarthritis Pain Scale (ICOAP) measured constant and intermittent pain[19]. Higher scores indicating greater pain intensity and frequency. The International Physical Activity Questionnaire Short Form (IPAQ) measured physical activity and total metabolic equivalents per week were reported[20]. Gait testing and MRI were completed at baseline and 2-year follow-up visits. Radiographs were collected at baseline only. Baseline data have been previously reported including descriptions of collection and processing procedures[15,21].

Radiographs

Radiographic measures were taken from standing hip to ankle, anterior-posterior radiographs[22]. Kellgren-Lawrence disease severity scores (KL-scores; 0=no OA to 4=severe) quantified disease severity for medial and lateral knee compartments[23]. Knee alignment was determined using the mechanical axis angle (MAA; positive values=valgus), as previously described[22].

Gait Data Collection

Motion and force data were collected with an eight-camera motion capture system (OQUS 300+, Qualisys) sampled at 100 Hz, and two force plates (BP400600, AMTI) sampled at 2000 Hz. Forty reflective markers (12.7 mm diameter) were attached to participants according to a cluster based system[24]. Muscle activation was measured with a 16-channel electromyography (EMG) system (Trigno, Delsys) sampled at 2000 Hz. Surface electrodes were placed on muscles according to previous guidelines[25]: medial and lateral gastrocnemius, vastus lateralis and medialis, rectus femoris, and medial and lateral hamstrings. Prior to electrode placement, the skin was shaved and cleaned with alcohol. Qualisys Track Manager (version 2.16) software was used for data collection.

Firstly, participants stood on a force plate to measure body mass and identify knee and ankle joint centres. Next, participants were required to flex/extend and abduct/adduct each hip in

order to identify functional hip joint centers[26]. Gait testing were performed with participants ambulating barefoot over 8 m at self-selected speeds. Participants completed at least four practice gait trials. Seven successful gait trials were collected; however, only five trials were processed. Additional trials were collected to account for potential errors. Finally, participants completed a series of maximum voluntary isometric contractions (MVIC) using a previously described protocol[15] including 1) knee extension in sitting with the knee in 45^{o}, 2) knee flexion in sitting with the knee 55^{o} of flexion, 3) knee extension in supine with the knee in 15^{o} of flexion, 4) knee flexion in prone with the knee in 55^{o}, 5) ankle plantarflexion in long sitting with the ankle in neutral, and 6) unilateral heel raise. Participants performed exercises 1-5 on a dynamometer (Cybex Norm). MVIC exercises were used to normalize gait EMG waveforms.

Gait Data Processing

Gait data processing and was performed using Visual3D (version 5.02, C-motion). Marker and force plate data were filtered with recursive, low-pass, 4th order Butterworth filters with frequency cuts offs of 8 Hz and 20 Hz, respectively. The speed of posterior superior iliac spine makers was used to define gait speed. Three-dimensional net external knee moments, in Newtons*meters (Nm), were calculated about the joint coordinate system using inverse dynamics. Flexion (sagittal), adduction (frontal), and lateral rotation (transverse) represented positive values. Discrete parameters were extracted from knee moments: maximum KAM value (KAM peak); area under the stance phase KAM using the trapezoidal method (KAM impulse); maximum KFM value during stance (KFM peak); and the difference in the maximum KRM

value during early/mid-stance and minimum KRM value during late stance (KRM range). These parameters have demonstrated relationships to OA progression[2-4,7].

Gait EMG processing included band-pass (20-500 Hz) filtering with a 4th order recursive Butterworth filter, wave rectification, creating a linear envelope (low-pass, 4th order recursive Butterworth filter at 6 Hz), and amplitude normalizing to the peak EMG from MVIC exercises. EMG gait waveforms were time normalized to 100% of the gait cycle and ensemble averages were created from five trials for each participant. To identify important EMG waveforms characteristics, principal component analysis (PCA) was utilized[27]. Ensemble EMG waveforms for each muscle group (gastrocnemius, quadriceps, hamstrings) from the baseline data collection were entered into data matrices (**X**). Separate PCAs were conducted for each muscle group. To increase the robustness of the PCA, data from healthy participants (n=22) were included to increase sample size (Table 1). Covariance matrices were determined from (**X**) and an eigenvector decomposition of covariance matrices produced eigenvectors (**U**). Eigenvectors are also called principal components (*PC*), and they represent unique waveform characteristics (e.g. shape). Only the first three *PCs* were retained for each muscle group because they account for at least 80% of the EMG waveforms variance[25]. Principal component scores (*PC-scores*; also known as z-scores) were calculated for each participant ensemble EMG waveform (*PC-scores*=(X-$\bar{X}$)*U), and they represent how closely a waveform matches the waveform characteristic[27].

Magnetic Resonance Imaging

MRI procedures were previously described[21,28]. The MRI (GE Discovery MR750) was conducted with a 3.0T high-resolution system with an eight-channel knee coil. Sequence acquisition was a T1-weighted, 3D sagittal gradient echo sequence with fat suppression (flip angle 20^{o}, repetition time 42 ms, echo time 7 ms, slice thickness 1.5 mm). An automatic knee cartilage segmentation process was used to determine cartilage volume for four separate regions: 1) lateral condyle, 2) lateral plateau, 3) medial condyle, and 4) lateral plateau. Percentage of cartilage volume change between the 2-year follow-up and baseline was determined for each region. Negative values represented cartilage loss. A previous study demonstrated that this procedure has low error between repeated images (0.14 to 1.20%)[28].

Statistical Analysis

Descriptive statistics were determined for demographic variables, ICOAP, IPAQ, KL-scores, MAA, and gait speed. Hypothesis-driven, linear regression analyses examined relationships between percentage of cartilage volume change with group (non-traumatic vs. post-traumatic) and gait parameters. Dependent variables were cartilage volume change in each region. Firstly, baseline cartilage volume for the region of interest was entered as a confounder to account for variations in baseline volume. Next, group (non-traumatic/post-traumatic) was entered and then a gait variable (i.e. knee moment discrete parameters or EMG *PC-scores*). Finally, the interaction between the group and the gait variable was entered; however, this was only retained in the final model if the interaction coefficient improved the model. Additionally, BMI was entered as confounder for knee moment analyses only since moments are greatly impacted by body mass. Variables were continuous except for group (0=non-traumatic, 1=post-

traumatic). Regression coefficients with 95% CI were reported. Separate analyses were performed for each cartilage volume region with each gait variable. Unadjusted Pearson correlation coefficients with 95% CI were calculated between cartilage volume change and gait variables to assist in interpretation. Normality (P-P plots), linearity/homoscedasticity (predicted values vs. standardized residuals), independent errors (Durbin-Watson test), multicollinearity (tolerance), and influential cases (Cook's distance, leverage) were examined to ensure statistical assumptions were met. Participants that did not have MRI data from both baseline and 2-year follow-up visits were excluded. Analyses were performed with SPSS version 24.0 (IBM).

Results

The final sample included 17 participants in the non-traumatic (12 female) and 18 participants in the post-traumatic (7 female) OA groups (Table 1). A diagram demonstrating exclusions is provided in Figure 1. Participants lost to follow-up were not included in analyses; the majority were female (5 out of 6) and had a high BMI (mean 34.0 kg/m^2). In those included, 9 of the 18 participants in the post-traumatic OA group had an ACL reconstruction. Mean time from self-report injury to data collection was 21 years (standard deviation 10 years) in the post-traumatic OA group. Twenty-four participants had higher KL-scores in the medial compartment, five participants had higher KL-scores in the lateral compartment, and five had equal KL-scores between compartments. Regression analysis assumptions were met unless otherwise noted below. Interpretations of significant regression coefficients are described below.

Knee Moments-Lateral Condyle

KAM peak was related to lateral condyle cartilage loss (Table 2), with lower KAM peak values associated with greater cartilage loss in both groups (Figure 2). A KAM peak decrease by 10 Nm would result in an additional cartilage volume loss of 2.38% in the lateral condyle over two years. Similarly, lower KAM impulse was associated with greater lateral condyle cartilage loss in both groups (Table 2, Figure 2).

KRM range was related to lateral condyle cartilage loss (Table 2), with lower KRM range associated with greater cartilage loss in both groups (Figure 2). A KRM range decrease by 5 Nm would result in an additional cartilage volume loss of 3.01% in the lateral condyle over two years.

Knee Moments-Lateral Plateau

KAM impulse, group and their interaction were related to lateral plateau cartilage loss (Table 2), with lower KAM impulse values associated with greater cartilage loss in the non-traumatic group (Figure 2). In this group, a KAM impulse decrease by 5 Nm*s would result in an additional cartilage volume loss of 4.30% in the lateral plateau over two years. The relationship was weaker in the post-traumatic group.

Knee Moments- Medial Condyle and Medial Plateau

There were no substantial relationships between medial condyle and medial plateau cartilage loss with discrete knee moments, group, or their interaction (Table 3). There were no relationships between KFM peak and cartilage loss in any region (Table 2 and 3).

Muscle Activation-Lateral Condyle

EMG waveform characteristics captured by the *PCs* and explained variance are provided in Table 4. Vastus medialis *PC3-scores* were related to lateral condyle cartilage loss (Supplemental Table 1). Vasus medialis *PC3* represented the amplitude of mid-stance activation. Lower *PC3-scores*, indicating lower mid-stance activation, were associated with greater lateral condyle cartilage loss in both groups (Supplemental Figure 1).

The interaction between lateral hamstring *PC2-scores* and group was related to lateral condyle cartilage loss (Supplemental Table 1). Lateral hamstring *PC2* represented the difference in activation between swing phase and mid-stance. Lower *PC2-scores*, representing greater swing phase activation and reduced mid-stance activation, were associated with greater lateral condyle cartilage loss in the post-traumatic group (Figure 3). There was no relationship in the non-traumatic group. However, there were influential cases and a sensitivity analysis is provided in the Supplemental.

Muscle Activation-Lateral Plateau

Vastus lateralis *PC2-scores* were related to lateral plateau cartilage loss (Supplemental Table 2). Vastus lateralis *PC2* represented the difference in late swing/early stance activation compared to late stance activation. Lower *PC2-scores*, indicating lower late stance activation, were associated with greater lateral plateau cartilage loss in both groups (Supplemental Figure 1).

Vastus lateralis *PC3-scores* were related to lateral plateau cartilage loss (Supplemental Table 2). Vasus lateralis *PC3* represented the amplitude of mid-stance activation. Lower *PC3-scores*, indicating lower mid-stance activation, were associated with greater lateral plateau cartilage loss in both groups (Supplemental Figure 1).

Muscle Activation-Medial Condyle

Rectus femoris *PC2-scores*, group, and their interaction were related to medial condyle cartilage loss (Supplemental Table 3). Rectus femoris *PC2* represented the difference in late swing/early stance activation compared to late stance activation. Lower *PC2-scores*, indicating lower activation during late stance, were associated with greater medial condyle cartilage loss in the non-traumatic group (Figure 3). This relationship was weaker in the post-traumatic group.

Rectus femoris *PC3-scores* were related to medial condyle cartilage loss (Supplemental Table 3). Rectus femoris *PC3* represented the amplitude of mid-stance activation. Lower *PC3-scores*, indicating lower mid-stance activation, were associated with greater medial condyle cartilage loss in both groups (Supplemental Figure 2).

Muscle Activation-Medial Plateau

Examining the assumptions, one participant did not fit medial tibial plateau regression models (standardized residuals=-4.34 to -3.55) and was an influential case (leverage=0.19 to 0.45). Removal of the participant diminished most regression coefficients and improved the distribution of the residuals. Thus, the participant was excluded from these analyses. The participant was from the non-traumatic group and had the lowest baseline medial tibia cartilage volume (182 mm^3; group mean=1716 mm^3). A moderate cartilage loss (-138 mm^3) resulted in a large percent change (-76.03%) compared to the group mean (-5.57%).

Vastus medial *PC2-scores* were related to medial plateau cartilage loss (Supplemental Table 4). Vastus medialis *PC2* represented the difference in late swing/early stance activation compared to late stance activation. Lower *PC2-scores*, indicating lower late stance activation, were associated with greater medial plateau cartilage loss in both groups (Supplemental Figure 2). However, there were influential cases and a sensitivity analysis is provided in the Supplemental.

The interaction between lateral hamstring *PC2-scores* and group was related to medial plateau cartilage loss (Supplemental Table 4). Lateral hamstring *PC2* represented the difference in activation between swing phase and mid-stance. Lower *PC2-scores*, representing greater swing phase activation and reduced mid-stance activation, were associated with greater medial

plateau cartilage loss in the post-traumatic group (Figure 3). This relationship was weaker in the non-traumatic group.

The interaction between medial hamstring *PC1-scores* and group was related to medial plateau cartilage loss (Supplemental Table 4). Medial hamstring *PC1* represented the overall shape and amplitude of activation. Lower *PC1-scores*, indicating lower activation levels, were associated with greater medial plateau cartilage loss in the non-traumatic group (Figure 3). This relationship was in the opposite direction for the post-traumatic group.

Discussion

KAM and KRM were associated with lateral condyle cartilage volume loss in both non-traumatic and post-traumatic groups, while the relationship between KAM and lateral plateau cartilage loss only existed in the non-traumatic group. Lower levels of muscle activation during stance phase were generally related to greater cartilage volume loss, which did not support the study hypothesis; however, the relationship depended on the OA subtype in some instances. Findings demonstrate that gait risk factors for OA progression vary between patients with non-traumatic and post-traumatic knee OA. Hence, these OA subtypes should be considered in OA progression studies and when evaluating disease-modifying interventions that aim to slow OA progression (e.g. osteotomy). However, given the small sample size, caution should be used when interpreting the findings.

KAM and KRM, but not KFM, were related to cartilage loss. Firstly, both lower KAM peak and impulse were related to lateral condyle cartilage loss in non-traumatic and post-traumatic groups. This relationship was present in the lateral plateau for the non-traumatic group but not the post-traumatic group, which partially supports the study hypothesis. Lower KAM values would suggest a shift of dynamic knee loads to the lateral compartment. This increased lateral loading may have contributed to OA progression within this compartment. There were no relationships between KAM with medial condyle or plateau cartilage loss which does not concur with previous studies or our hypothesis[2,4,5,7,8]. Differences in study samples and regions of cartilage measurement could explain this disparity. In previous studies[2,5,7,8], participants had primarily medial compartment OA and OA progression was only evaluated in the medial compartment. The current study included participants with lateral compartment OA and cartilage measurements from this region were performed. Alternatively, findings in the medial compartment could be due to type II error. Secondly, lower KRM range was associated with lateral condyle cartilage loss, which is similar to a previous study examining radiographic OA progression[10]. Thus, knee moments are related to OA progression, although the relationship might vary between OA subtypes.

EMG waveform shape characteristics (*PC2-scores*, *PC3-scores*) were most frequently related to cartilage loss. Lower muscle activation during mid-stance and late stance was generally associated with greater cartilage loss in both groups. However, the relationship between some EMG characteristics and cartilage loss depended on the OA group. Lower lateral hamstring mid-stance activation (*PC2-scores*) was related to greater lateral condyle and medial plateau cartilage loss in the post-traumatic group only, although influential cases might partially

account for this finding. In the non-traumatic group, lower rectus femoris late stance activation (*PC2-scores*) and lower medial hamstring activation throughout gait (*PC1-scores*) were related to medial condyle and plateau cartilage loss, respectively. However, lower medial hamstring activation was protective against medial plateau cartilage loss in the post-traumatic group. These findings partially conflict with previous studies[7,12] in which elevated and prolonged activation is related to medial compartment OA progression; although previous studies disagree with each other if prolonged lateral knee muscle activation are protective or promote OA progression. As stated above, disparities in the results could be due to differences in study samples and regions in which progression were measured. Our findings imply that increased and prolonged muscle activation during stance was protective against cartilage volume loss. This contradicts the hypothesis that elevated and prolonged muscle activation increases knee contact forces, leading to faster progression. Alternatively, perhaps higher and prolonged muscle activation during stance stiffened the knee and provided more effective control over OA-related abnormal knee arthrokinematics[11,29]. Abnormal arthrokinematics have been postulated to cause OA, particularly in patients following knee trauma[30]. Patients with knee OA that have greater passive (i.e. stress tests) and dynamic (i.e. varus thrust) frontal plane instability demonstrate greater muscle co-activation during gait[29,31]. This suggests that increased and prolonged muscle activation might attempt to normalize knee arthrokinematics, which could slow OA progression. Further work is needed to determine the role of muscle activation in OA initiation and progression, and the optimal amount of knee loading required to maintain joint health.

Risk factors for OA progression differed between non-traumatic and post-traumatic groups. KAM impulse was associated with lateral plateau cartilage loss only in the non-traumatic

group. This could be due to the fact that initial lateral plateau tissue damage from trauma might have been the strongest factor in OA initiation/progression in participants with post-traumatic OA and KAM during gait played a less decisive role. In support, the interaction between KAM and group was only found at the lateral plateau, which is the most common site of bone marrow lesion and fractures with cortical discontinuity following ACL injury[32,33]. Loading distribution during gait, which KAM serves as a proxy, maybe more important in OA progression at the lateral plateau in patients with non-traumatic knee OA. In regard to muscle activation, the strength and direction of the relationships between muscle activation and cartilage loss depended on the OA subtype. Differences in joint stability and arthrokinematics between groups might have altered the relationship between muscle force and subsequent joint loads, thereby impacting progression.

The small sample size was a limitation. This prevented the inclusion of other confounders (e.g. sex) in analyses and the study might have been underpowered to detect interactions. Since we examined medial and lateral compartment OA, our sample was heterogeneous. Including lateral compartment OA was more representative of the population since lateral compartment OA changes are common in patients with post-traumatic knee OA[34]. We did not control for physical activity prior to the MRI, which might impact cartilage measurements. Previous rehabilitation or the type of physical activity participants completed were not recorded. The graft type was not recorded for participants that had an ACL reconstruction and graft location could impact muscle function. Finally, only ACL ruptures were considered and findings cannot be generalized to other injuries.

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In conclusion, knee moments and muscle activation during gait were associated with cartilage volume loss in participants with non-traumatic and post-traumatic knee OA. The strength and direction of these relationships depended on the OA subtypes, demonstrating that risk factors for OA progression vary between these groups. Hence, the effectiveness of disease modifying interventions might vary between these OA subtypes. For muscle activation, while we showed that lower levels of muscle activation were generally related to cartilage loss, additional work is required to determine the role of muscle function in knee OA progression.

Author Contributions

All authors made substantial contributions. Shawn Robbins was responsible for conception and design, obtaining funding, collection and assembly of data, analysis and interpretation of the data, drafting and revision of the article, and final approval of the article. Mathieu Boily was responsible for analysis and interpretation of the data, critical revision of the article for important intellectual content, and final approval of the article. Moreno Morelli, Paul Martineau, and John Antoniou were responsible for providing the OA patients, critical revision of the article for important intellectual content, and final approval of the article. François Abram was responsible for setting the MRI sequences, MRI data processing, interpretation of the MRI data, critical revision of the article for important intellectual content, and final approval of the article. Jean-Pierre Pelletier was responsible for study design, data analysis and interpretation, article revision, and final approval of the article. Johanne Martel-Pelletier was responsible for study design, data analysis and interpretation, drafting, and revision and final approval of the

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article. Shawn Robbins (shawn.robbins@mcgill) takes responsibility for the integrity of the work as a whole, from inception to finished article.

Acknowledgements- Other Contributors

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The funding sources had no role in this research.

Conflict of Interest

Jean-Pierre Pelletier and Johanne Martel-Pelletier are shareholders in ArthroLab Inc., Montreal, Canada. François Abram is an employee of ArthroLab Inc., Montreal, Canada. ArthroLab Inc. was responsible for setting the MRI data acquisition as well as processing and analysing the images. The other authors have no conflicts of interest related to this study.

Data Statement

Data are confidential and are not available through an online database.

References

1. Richmond SA, Fukuchi RK, Ezzat A, Schneider K, Schneider G, Emery CA. Are joint injury, sport activity, physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. J Orthop Sports Phys Ther 2013;43:515-24. doi:10.2519/jospt.2013.4796
2. Bennell KL, Bowles KA, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis 2011;70:1770-4. doi:10.1136/ard.2010.147082
3. Chang AH, Moisio KC, Chmiel JS, Eckstein F, Guermazi A, Prasad PV, et al. External knee adduction and flexion moments during gait and medial tibiofemoral disease

progression in knee osteoarthritis. Osteoarthritis Cartilage 2015;23:1099-106. doi:10.1016/j.joca.2015.02.005

4. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. Osteoarthritis Cartilage 2014;22:1833-9. doi:10.1016/j.joca.2014.08.009

5. Brisson NM, Wiebenga EG, Stratford PW, Beattie KA, Totterman S, Tamez-Pena JG, et al. Baseline knee adduction moment interacts with body mass index to predict loss of medial tibial cartilage volume over 2.5 years in knee osteoarthritis. J Orthop Res 2017;35:2476-83. doi:10.1002/jor.23564

6. Zhao D, Banks SA, Mitchell KH, D'Lima DD, Colwell CW Jr., Fregly BJ. Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. J Orth Res 2007;25:789-97.

7. Davis EM, Hubley-Kozey CL, Landry SC, Ikeda DM, Stanish WD, Astephen Wilson JL. Longitudinal evidence links joint level mechanics and muscle activation patterns to 3-year medial joint space narrowing. Clin Biomech 2019;61:233-9. doi:10.1016/j.clinbiomech.2018.12.016

8. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis 2002;61:617-22.

9. Hatfield GL, Stanish WD, Hubley-Kozey CL. Three-dimensional biomechanical gait characteristics at baseline are associated with progression to total knee arthroplasty. Arthritis Care Res 2015;67:1004-14. doi:10.1002/acr.22564

10. Costello KE, Astephen Wilson JL, Stanish WD, Urquhart N, Hubley-Kozey CL. Differences in baseline joint moments and muscle activation patterns associated with knee osteoarthritis progression when defined using a clinical versus a structural outcome. J Appl Biomech 2020:1-13. doi:10.1123/jab.2019-0127

11. Brandon SC, Miller RH, Thelen DG, Deluzio KJ. Selective lateral muscle activation in moderate medial knee osteoarthritis subjects does not unload medial knee condyle. J Biomech 2014;47:1409-15. doi:10.1016/j.jbiomech.2014.01.038

12. Hodges PW, van den Hoorn W, Wrigley TV, Hinman RS, Bowles KA, Cicuttini F, et al. Increased duration of co-contraction of medial knee muscles is associated with greater progression of knee osteoarthritis. Man Ther 2016;21:151-8. doi:10.1016/j.math.2015.07.004

13. Hatfield GL, Costello KE, Astephen Wilson JL, Stanish WD, Hubley-Kozey CL. Baseline gait muscle activation patterns differ for osteoarthritis patients who undergo total knee arthroplasty 5-8 years later from those who do not. Arthritis Care Res 2021;73:549-58. doi:10.1002/acr.24143

14. Robbins SM, Birmingham TB, Jones IC, Sischek EL, Dietzsch M, Giffin JR. Comparison of gait characteristics between patients with nontraumatic and posttraumatic medial knee osteoarthritis. Arthritis Care Res 2016;68:1215-23. doi:10.1002/acr.22822

15. Robbins SM, Morelli M, Martineau PA, St-Onge N, Boily M, Dimentberg R, et al. A comparison of muscle activation and knee mechanics during gait between patients with non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis Cartilage 2019;27:1033-42. doi:10.1016/j.joca.2019.02.798

16. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.

17. Dupont WD, Plummer WD Jr. Power and sample size calculations for studies involving linear regression. Controlled clinical trials 1998;19:589-601.

18. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Labonte F, Beaudoin G, de Guise JA, et al. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. Arthritis Rheum 2004;50:476-87. doi:10.1002/art.20000

19. Robbins SM, Rastogi R, Howard J, Rosedale R. Comparison of measurement properties of the P4 pain scale and disease specific pain measures in patients with knee osteoarthritis. Osteoarthritis Cartilage 2014;22:805-12. doi:10.1016/j.joca.2014.03.018

20. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International Physical Activity Questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381-96. doi: 10.1249/01.MSS.0000078924.61453.FB

21. Robbins SM, Abram F, Boily M, Pelletier JP, Martel-Pelletier J. Relationship between alignment and cartilage thickness in patients with non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis Cartilage 2019;27:630-7. doi:10.1016/j.joca.2019.01.002

22. Specogna AV, Birmingham TB, DaSilva JJ, Milner JS, Kerr J, Hunt MA, et al. Reliability of lower limb frontal plane alignment measurements using plain radiographs and digitized images. J Knee Surg 2004;17:203-10.

23. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.

24. Collins TD, Ghoussayni SN, Ewins DJ, Kent JA. A six degrees-of-freedom marker set for gait analysis: repeatability and comparison with a modified Helen Hayes set. Gait Posture 2009;30:173-80. doi:10.1016/j.gaitpost.2009.04.004

25. Hubley-Kozey CL, Robbins SM, Rutherford DJ, Stanish WD. Reliability of surface electromyographic recordings during walking in individuals with knee osteoarthritis. J Electromyogr Kinesiol 2013;23:334-41. doi:10.1016/j.jelekin.2012.12.002

26. Schwartz MH, Rozumalski A. A new method for estimating joint parameters from motion data. J Biomech 2005;38:107-16. doi:10.1016/j.jbiomech.2004.03.009

27. Deluzio KJ, Astephen JL. Biomechanical features of gait waveform data associated with knee osteoarthritis: an application of principal component analysis. Gait Posture 2007;25:86-93. doi:10.1016/j.gaitpost.2006.01.007

28. Dodin P, Pelletier JP, Martel-Pelletier J, Abram F. Automatic human knee cartilage segmentation from 3D magnetic resonance images. IEEE Trans Biomed Eng 2010;57:2699-711. doi:10.1109/TBME.2010.2058112

29. Lewek MD, Rudolph KS, Snyder-Mackler L. Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. Osteoarthritis Cartilage 2004;12:745-51. doi:10.1016/j.joca.2004.05.005

30. Andriacchi TP, Koo S, Scanlan SF. Gait mechanics influence healthy cartilage morphology and osteoarthritis of the knee. J Bone Joint Surg Am 2009;91:95-101. doi:10.2106/JBJS.H.01408

31. Dixon PC, Gomes S, Preuss RA, Robbins SM. Muscular co-contraction is related to varus thrust in patients with knee osteoarthritis. Clin Biomech 2018;60:164-9. doi:10.1016/j.clinbiomech.2018.10.021

32. Frobell RB, Roos HP, Roos EM, Hellio Le Graverand MP, Buck R, Tamez-Pena J, et al. The acutely ACL injured knee assessed by MRI: are large volume traumatic bone marrow lesions a sign of severe compression injury? Osteoarthritis Cartilage 2008;16:829-36. doi:10.1016/j.joca.2007.11.003

33. Driban JB, Lohmander S, Frobell RB. Posttraumatic bone marrow lesion volume and knee pain within 4 weeks after anterior cruciate ligament injury. J Athl Train 2017;52:575-80. doi:10.4085/1062-6050-52.1.09

34. Sward P, Kostogiannis I, Neuman P, Von Porat A, Boegard T, Roos H. Differences in the radiological characteristics between post-traumatic and non-traumatic knee osteoarthritis. Scand J Med Sci Sports 2010;20:731-9. doi:10.1111/j.1600-0838.2009.01000.x

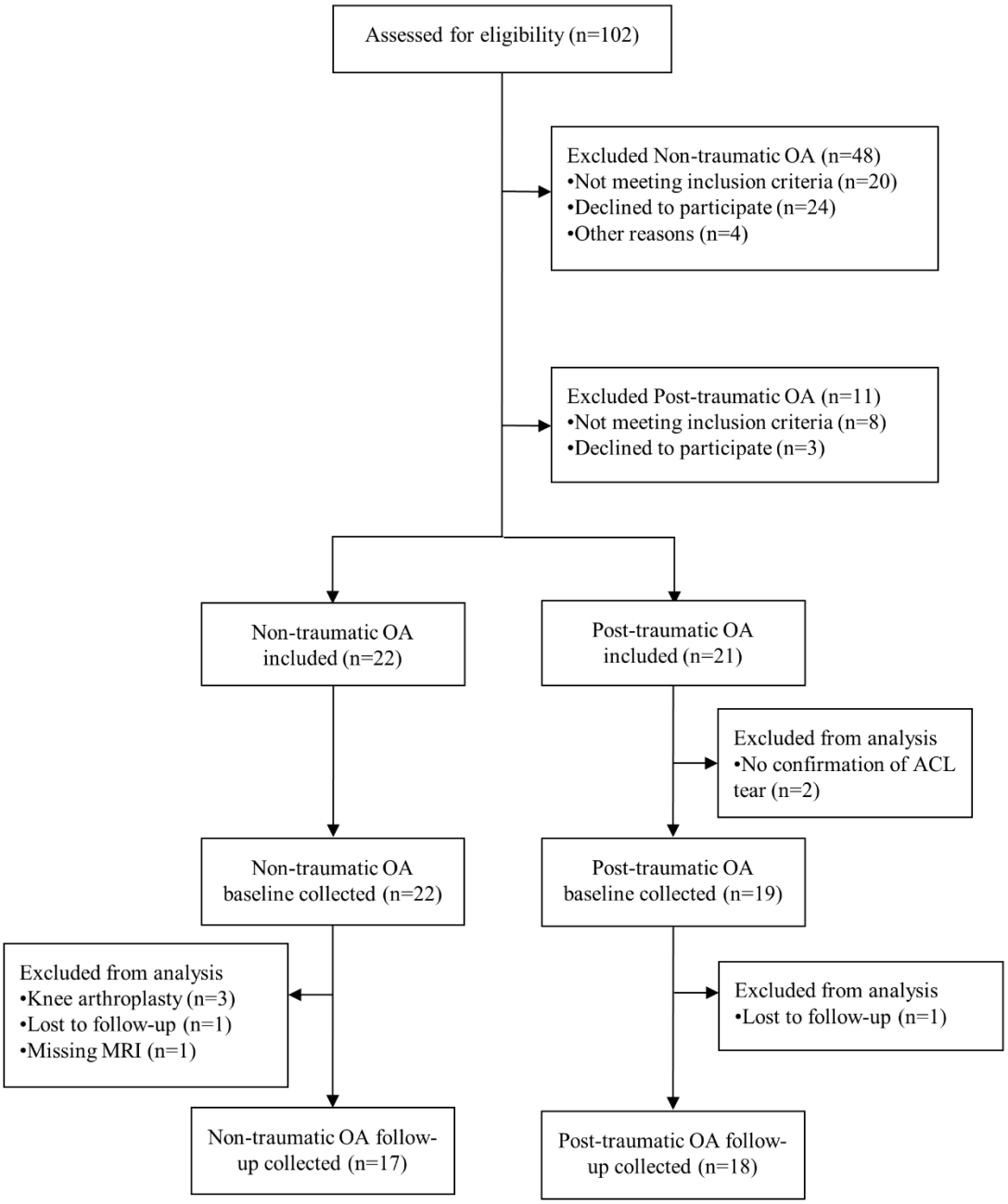

Figure 1: Flow diagram of the participants. OA, osteoarthritis; ACL, anterior cruciate ligament.

Robbins SM, Pelletier JP, Abram F, Boily M, Antoniou J, Martineau PA, Morelli M, Martel-Pelletier J (2021). Gait risk factors for disease progression differ between non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis and Cartilage. 29(11):1487-1497. doi: 10.1016/j.joca.2021.07.014

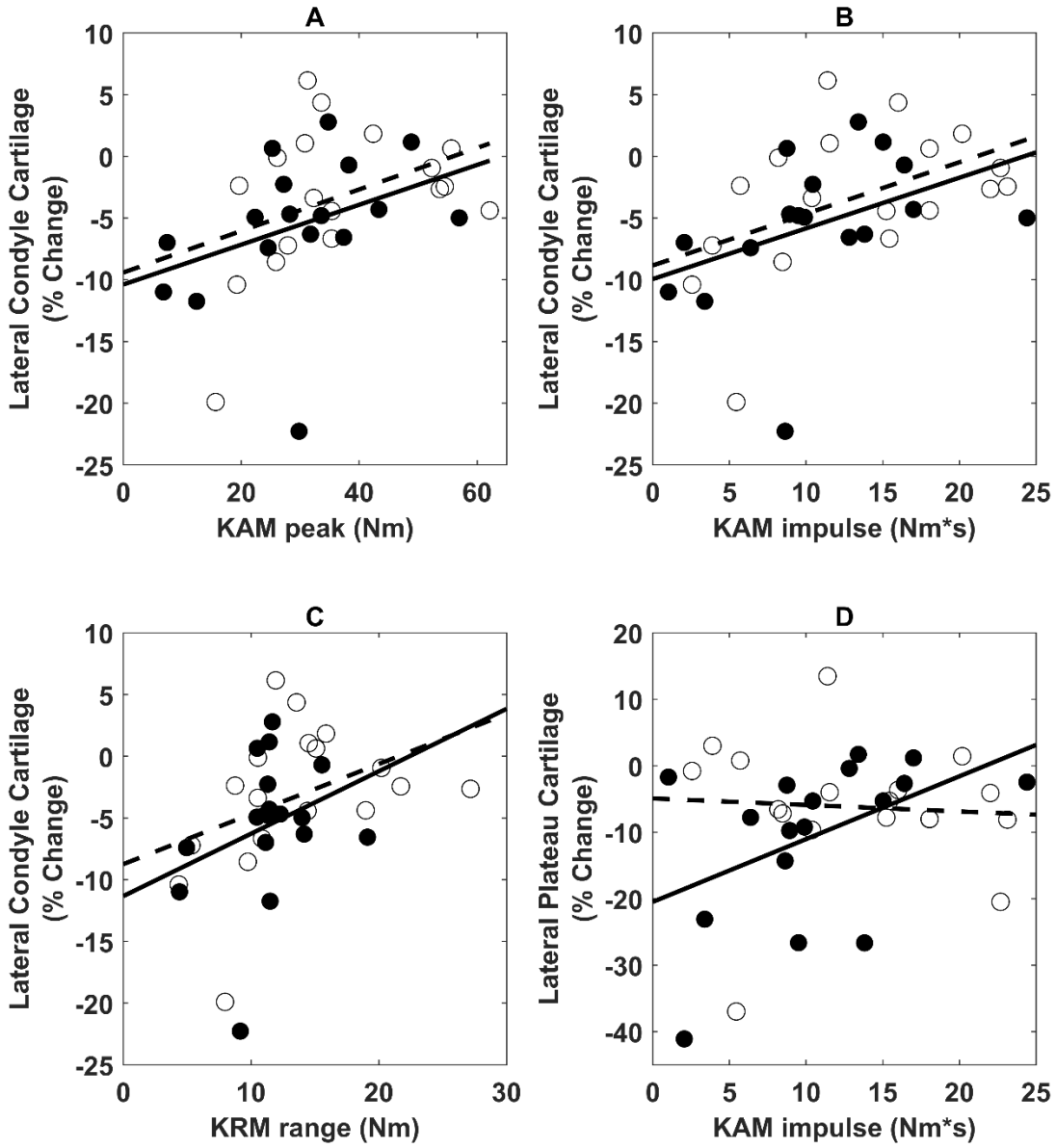

Figure 2. Relationships between A) knee adduction moment (KAM) peak with lateral condyle cartilage volume change (non-traumatic r=0.467, 95CI%=-0.018 to 0.774; post-traumatic r=0.328, 95%CI=-0.164 to 0.690), B) KAM impulse with lateral condyle cartilage volume change (non-traumatic r=0.500, 95%CI=0.025 to 0.791; post-traumatic r=0.476, 95%CI=0.012 to 0.772), C) knee rotation moment (KRM) range with lateral condyle cartilage volume change (non-traumatic r=0.356, 95%CI=-0.150 to 0.715; post-traumatic r=0.391, 95%CI=-0.93 to 0.725), and D) KAM impulse with lateral plateau cartilage volume change (non-traumatic r=0.387, 95%CI=-0.115 to 0.732; post-traumatic r=-0.020, 95%CI=-0.483 to 0.451). The non-traumatic group are represented by filled dots and post-traumatic by unfilled dots. The lines of best fit are shown for the non-traumatic (solid line) and post-traumatic (dashed line) groups.

Robbins SM, Pelletier JP, Abram F, Boily M, Antoniou J, Martineau PA, Morelli M, Martel-Pelletier J (2021). Gait risk factors for disease progression differ between non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis and Cartilage. 29(11):1487-1497. doi: 10.1016/j.joca.2021.07.014

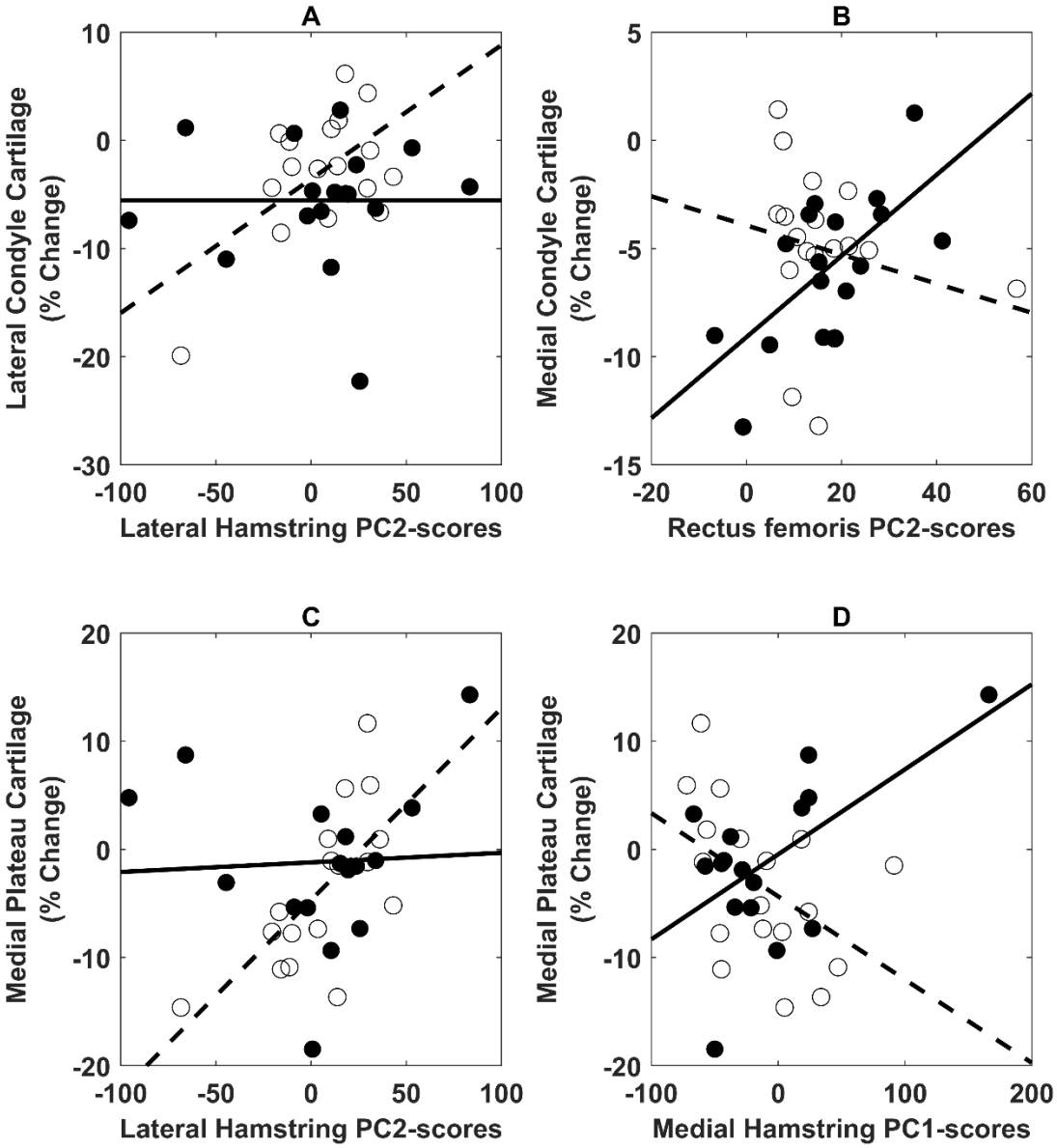

Figure 3. Relationships between A) lateral hamstring principal component (*PC*) 2-scores with lateral condyle cartilage volume change (non-traumatic r=0.000, 95%CI=-0.481 to 0.481; post-traumatic r=0.578, 95%CI=0.135 to 0.829), B) rectus femoris *PC2-scores* with medial condyle cartilage volume change (non-traumatic r=0.662, 95%CI=0.266 to 0.867; post-traumatic r=-0.214, 95%CI=-0.619 to 0.281), C) lateral hamstring *PC2-scores* with medial plateau cartilage volume change (non-traumatic r=0.051, 95%CI=-0.456 to 0.533; post-traumatic r=0.668, 95%CI=0.276 to 0.869), and D) medial hamstring *PC1-scores* with medial plateau cartilage volume change (non-traumatic r=0.578, 95%CI=0.115 to 0.835; post-traumatic r=-0.470, 95%CI=-0.768 to -0.004). The non-traumatic group are represented by filled dots and post-traumatic by unfilled dots. The lines of best fit are shown for the non-traumatic (solid line) and post-traumatic (dashed line) groups.

Robbins SM, Pelletier JP, Abram F, Boily M, Antoniou J, Martineau PA, Morelli M, Martel-Pelletier J (2021). Gait risk factors for disease progression differ between non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis and Cartilage. 29(11):1487-1497. doi: 10.1016/j.joca.2021.07.014

Table 1: Participant characteristics.

Variables		Non-traumatic OA Group (n=17)		Post-traumatic OA Group (n=18)		Healthy Group (n=22)
Age, years		59 (7)		57 (9)		59 (7)
Female, % (n)		71% (12)		39% (7)		73% (16)
Height, m		1.67 (0.07)		1.70 (0.10)		1.65 (0.09)
Mass, kg		77.61 (17.12)		75.81 (16.35)		72.7 (12.1)
Body mass index, kg/m^2		28.05 (6.93)		25.83 (3.22)		27.0 (4.6)
ICOAP-Constant pain (/100)		17 (25)		16 (19)		0 (0)
ICOAP- Intermittent pain (/100)		29 (23)		27 (21)		3 (8)
IPAQ- Total (METS/week)		4205 (2986)		4670 (2439)		4119 (3118)
Gait speed, m/s		1.20 (0.14)		1.22 (0.13)		1.25 (0.17)
MAA*, ^{o}		-0.28 (5.71)		-2.84 (4.55)		-
KL-scores*, frequency	Score	Medial	Lateral	Medial	Lateral	
	0	0	8	0	7	-
	1	2	1	1	3	-
	2	10	2	11	6	-
	3	3	4	4	1	-
	4	1	1	2	1	-

Results are shown as mean (standard deviation) unless otherwise indicated.
OA, osteoarthritis; ICOAP, Intermittent and Constant Osteoarthritis Pain Scale; IPAQ, International Physical Activity Questionnaire Short Form; METS, metabolic equivalents; MAA, mechanical axis angle (varus alignment is negative, valgus alignment is positive); KL-scores, Kellgren-Lawrence radiographic disease severity scores.
* One participant from the non-traumatic OA group was missing MAA and KL-scores.
Radiographic measures were not available for the healthy group.

Robbins SM, Pelletier JP, Abram F, Boily M, Antoniou J, Martineau PA, Morelli M, Martel-Pelletier J (2021). Gait risk factors for disease progression differ between non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis and Cartilage. 29(11):1487-1497. doi: 10.1016/j.joca.2021.07.014

Table 2: Unstandardized regression coefficients with 95% confidence intervals with lateral condyle and plateau cartilage volume change as the dependent variables and external knee moment discrete parameters as the independent variables.

Region	Gait Parameter	Unstandardized Regression Coefficients (95% Confidence Interval)		
		Gait Parameter	Group*	Interaction†
Lateral Condyle	KAM peak	0.238 (0.066, 0.411)	1.297 (-2.889, 5.483)	-
	KAM impulse	0.596 (0.240, 0.953)	1.389 (-2.567, 5.345)	-
	KFM flexion	0.16 (-0.148, 0.179)	2.757 (-1.909, 7.423)	-
	KRM range	0.603 (0.119, 1.086)	1.864 (-2.334, 6.062)	-
Lateral Plateau	KAM peak	0.128 (-0.216, 0.471)	3.556 (-4.929, 12.040)	
	KAM impulse	0.861 (-0.136, 1.858)	19.620 (2.324, 36.916)	-1.336 (-2.653, -0.019)
	KFM flexion	-0.074 (-0.389, 0.241)	4.274 (-3.899, 12.447)	-
	KRM range	-0.599 (-1.600, 0.402)	5.872 (-2.315, 14.060)	-

KAM, knee adduction moment; KFM, knee flexion moment; KRM, knee rotation moment.
* Group is coded as 0=non-traumatic and 1=post-traumatic.
† Interactions only remained in the final model if they were significant.

Robbins SM, Pelletier JP, Abram F, Boily M, Antoniou J, Martineau PA, Morelli M, Martel-Pelletier J (2021). Gait risk factors for disease progression differ between non-traumatic and post-traumatic knee osteoarthritis. Osteoarthritis and Cartilage. 29(11):1487-1497. doi: 10.1016/j.joca.2021.07.014

Table 3: Unstandardized regression coefficients with 95% confidence intervals with medial condyle and plateau cartilage volume change as the dependent variables and external knee moment discrete parameters as the independent variables.

Region	Gait Parameter	Unstandardized Regression Coefficients (95% Confidence Interval)		
		Gait Parameter	Group*	Interaction†
Medial Condyle	KAM peak	0.037 (-0.064, 0.137)	0.916 (-1.697, 3.529)	-
	KAM impulse	0.156 (-0.057, 0.369)	0.674 (-1.840, 3.188)	-
	KFM flexion	0.029 (-0.060, 0.117)	1.330 (-1.147, 3.808)	-
	KRM range	0.149 (-0.132, 0.430)	0.851 (-1.691, 3.392)	-
Medial Plateau	KAM Peak	0.003 (-0.409, 0.415)	2.830 (-8.021, 13.681)	-
	KAM impulse	0.212 (-0.671, 1.094)	2.088 (-8.548, 12.725)	-
	KFM flexion	-0.102 (-0.462, 0.258)	2.539 (-7.651, 12.730)	-
	KRM range	-0.372 (-1.496, 0.752)	3.732 (-6.719, 14.182)	-

KAM, knee adduction moment; KFM, knee flexion moment; KRM, knee rotation moment.
* Group is coded as 0=non-traumatic and 1=post-traumatic.
† Interactions only remained in the final model if they were significant.

Table 4: Interpretations and explained variance for each principal component (*PC*) derived from electromyography waveforms during gait.

Muscle group	*PC*	Description	Explained Variance (%)
Gastrocs	1	Overall amplitude and general shape (higher scores = greater activation)	55.96
	2	Timing shift in gastrocnemius activation (higher scores = later onset)	18.76
	3	Difference in gastrocnemius activation between early and mid-/ late stance (higher score = greater difference)	10.90
Quadriceps	1	Overall amplitude and general shape (higher scores = greater activation)	77.61
	2	Difference in quadriceps activation between late swing/early stance and late stance (higher scores = greater late stance activation)	6.52
	3	Amplitude of quadriceps activation during mid-stance (higher scores = greater mid-stance activation)	4.43
Hamstrings	1	Overall amplitude and general shape (higher scores = greater activation)	57.79
	2	Difference in hamstring activation between mid-stance and swing (higher scores = greater mid-stance activation and lower swing activation)	15.10
	3	Difference in hamstring activation between mid/late stance and early stance/late swing (higher scores = lower mid/late stance activation and higher early stance/late swing activation)	8.94