The effect of alignment on knee osteoarthritis initiation and progression differs based on anterior cruciate ligament status: data from the Osteoarthritis Initiative

Shawn M Robbins, BScPT, PhD[1]; Nicolas Raymond, BSc[2]; François Abram, PhD[3]; Jean-Pierre Pelletier, MD[4]; Johanne Martel-Pelletier, PhD[4]

[1]Centre for Interdisciplinary Research in Rehabilitation, Lethbridge-Layton-MacKay Rehabilitation Centre, and School of Physical and Occupational Therapy, McGill University, Montreal, Canada
[2]School of Physical and Occupational Therapy, McGill University, Montreal, Canada
[3]Medical Imaging, ArthroLab Inc., Montreal, Canada
[4]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, Canada

ORCID ID: Robbins (0000-0002-8108-0561); Pelletier (0000-0001-9930-6453); Martel-Pelletier (0000-0003-2618-383X)

Please address correspondence to:
Shawn Robbins
School of Physical and Occupational Therapy
Davis House, McGill University, 3654 Promenade Sir-William-Osler
Montreal, QC, Canada, H3G 1Y5
Phone: (514) 398-4400 extension 00720
Email: shawn.robbins@mcgill.ca

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ABSTRACT

Introduction/Objective: Knee alignment and anterior cruciate ligament (ACL) injury are risk factors for knee osteoarthritis (OA). The objective was to examine interactions between knee alignment and ACL status on cartilage volume loss in participants with or at risk of knee OA.

Method: Participants were from the Osteoarthritis Initiative, a longitudinal cohort study. Data were from baseline, and 24 and 72 month follow-up visits. Participants with knee OA (progression subcohort) or at risk of knee OA (incidence subcohort) that had partial or full ACL tears (OA-ACL group; n=66) or an intact ACL (OA-only group, n=367) were selected. Femur-tibia angles from radiographs quantified knee alignment. Changes in tibial and femoral cartilage volume were measured using magnetic resonance imaging. Hierarchical linear models examined if knee alignment, presence of ACL, and their interaction were related to cartilage volume loss after accounting for other variables.

Results: Interactions between alignment and ACL status were significantly related to cartilage volume loss in the lateral plateau [β=-20.19, 95% confidence interval (CI)=-34.65 to -5.73] and lateral condyle (β=-23.64, 95%CI=-43.06 to -4.23). Valgus alignment was related to lateral compartment cartilage loss in the OA-ACL group, but not in the OA-only group. Varus alignment was related to cartilage loss in the medial plateau (β=7.49, 95%CI=0.17 to 14.80) and medial condyle (β=19.70, 95%CI=5.96 to 33.44) in both groups.

Conclusion: The impact of knee alignment on knee OA initiation and progression varies based on ACL status. Initial lateral compartment damage or changes in joint kinematics after ACL rupture might account for these findings.

Key Words: knee osteoarthritis, magnetic resonance imaging, articular cartilage, anterior cruciate ligament, varus, valgus

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Key Points

- The relationship between knee alignment and lateral compartment cartilage loss depended on the status of the anterior cruciate ligament in participants with knee osteoarthritis or at risk for knee osteoarthritis.
- Valgus alignment was related to lateral compartment cartilage loss in participants with a deficient anterior cruciate ligament.
- Varus alignment was related to medial compartment cartilage loss regardless of the status of the anterior cruciate ligament.

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INTRODUCTION

Knee osteoarthritis (OA) is one of the most prevalent chronic conditions affecting 16% of adults over the age of 45 years [1]. Knee alignment is a known risk factor in knee OA incidence and progression. For example, varus alignment was related to the incidence of tibiofemoral OA [odds ratio (OR)=1.49)] and the progression of medial compartment knee OA (OR=3.59) over 30 months [2]. Valgus alignment, measured with long limb radiographs, greater than 3° beyond neutral was associated with knee OA incidence (OR=2.5) and lateral compartment knee OA progression (OR=3.9) over 30 months [3]. Knee alignment impacts load distribution with varus alignment shifting load to the medial compartment and valgus alignment shifting load to the lateral compartment [4]. Loading is thought to be a key factor in knee OA disease progression and proxies of dynamic knee loading have been shown to predict knee OA progression [5].

Knee trauma is another risk factor for knee OA initiation. A meta-analysis indicated that a history of knee injury was a strong risk factor in knee OA development across studies (pooled OR=4.20) [6]. Specific to anterior cruciate ligament (ACL) injury, radiographic knee OA was diagnosed in 51% of women soccer players 12 years after ACL injury [7]. It is hypothesized that after knee trauma, there is alteration in knee kinematics [8]. This would load tissue unconditioned to such loads leading to breakdown [8]. Alternatively, damaged tissue is likely more susceptible to further breakdown and this damage results in an imbalance of catabolic and anabolic factors [9].

The development of knee OA is not solely due to a single risk factor, but is multifactorial involving the interaction of multiple elements [10]. Although knee alignment and history of ACL injury are risk factors in knee OA initiation and progression, the interaction between these factors has not yet been explored. Considering that an injured ACL affects joint kinematics, it is

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conceivable that knee alignment may have a different impact on an ACL intact or ACL deficient knee [11]. Therefore, the objective was to examine the interaction between knee alignment and ACL status on indicators of knee OA progression, specifically cartilage volume loss measured using magnetic resonance imaging (MRI), in participants from the Osteoarthritis Initiative (OAI) with knee OA or at risk of knee OA.

MATERIALS AND METHODS

Study Participants

Participants were from the OAI which is a longitudinal, prospective observational study of participants with knee OA or at risk for developing knee OA [12]. The OAI database is publically available online [12]. Exclusion criteria for the OAI, which were assessed during screening interviews and visits, include inflammatory arthritis, severe joint narrowing in both knees, current or planned (within 24 months) knee replacement in the study knee, pregnancy, and unable to undergo MRI [12]. In the current analysis, additional exclusion criteria included previous ACL reconstruction, missing all follow-up MRI data, and missing radiographic knee alignment measures. Participants with severe knee OA [Kellgren Lawrence scores (KL-scores)=4] were also excluded since additional progression would be limited. In participants that had data for bilateral knees, only 1 knee was selected based on MRI availability or the knee with the highest KL-score.

Knees (n=1756) that had the status of their ACL assessed using the MRI Osteoarthritis Knee Score (MOAKS) were identified from OAI progression and incidence subcohorts. Participants were from 4 OAI projects that had completed MOAKS scoring (projects #22, 30, 63, 65), which included the Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium and the Pivotal OAI MR Imaging Analyses [13-15]. Only the MOAKS ACL and meniscal scoring were utilized from this data set; the cartilage volume measurements were done using an automated method (see below). The progression subcohort included

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participants that had frequent knee symptoms over the last year and had radiographic evidence of knee OA. The incidence subcohort included participants that did not have symptomatic knee OA, but have characteristics that put them at risk for developing symptomatic knee OA (e.g. infrequent symptoms) [12]. Both subcohorts were included to examine the impact of risk factors on early (i.e. prior to radiographic evidence) to moderate stages of the disease. Data were downloaded from the OAI in April/May 2018.

Readings that had confirmed partial ACL tear or full ACL tear (n=157) assessed using MRI (OAI central reading) were selected. After excluding knees based on the above criteria (Fig. 1), 66 participants that had knee OA or were at risk of knee OA and had sustained an ACL rupture were included (OA-ACL group; 27 women, 39 men; 40 from progression subcohort, 26 from incidence subcohort). This included 46 participants with a partial ACL tear and 20 participants with a full ACL tear. For the OA-only group, there were initially 1599 readings with an intact ACL with no evidence of ACL reconstruction. An additional exclusion criterion for this group was a self-reported history of trauma. Including participants with a history of trauma in the OA-only group would have been a confounder since this group is being compared to participants that had an ACL rupture, with trauma being the mostly likely cause. This criterion ensured the OA-only group likely developed knee OA without a history of serious trauma. After applying exclusion criteria (Fig. 1), 367 participants that had knee OA or were at risk of knee OA and had an intact ACL were included (OA-only group; 256 women, 111 men; 137 from progression subcohort, 230 from incidence subcohort). Demographic variables (e.g. age) were downloaded from the OAI database.

MRI Measures

MRI data from the baseline data collection visit, and 24 month and 72 month follow-ups were utilized. OAI protocol for MRI collection was previously described [12,16]. Briefly, 3T scanners (Siemens Trio) with a knee coil (USA Instruments) acquired the images. Relevant

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sequences for the current study included coronal intermediate-weighted 2D turbo spin echo, sagittal 3D dual-echo in steady state with selective water excitation, and axial and coronal multiplanar reformation of the dual-echo in steady state sequence [16,17].

Cartilage Volume-Dependent Variable. From sagittal 3D dual-echo in steady state sequences, cartilage volume was determined using automatic knee cartilage segmentation (ArthroLab Inc.). Procedures have been described with evidence of reliability and validity [18,19]. Cartilage volumes were determined for 4 regions: medial and lateral tibial plateau; medial and lateral femoral condyles. Changes in cartilage volume from baseline to both 24 and 72 month follow-ups were determined for each region. Negative scores indicated cartilage volume loss.

Anterior Cruciate Ligament Status. ACL status at baseline was downloaded from the OAI database [12,17] and used to determine group allocation. Images were blinded and assessed by 2 radiologists at the Boston Imaging Core Lab [12,14]. Coronal and sagittal views were used to score ACL tear on a scale of 0-2, where 0=normal, 1=partial tear, and 2=complete tear. Presence of ACL reconstruction was also scored and used as an exclusion criterion.

Meniscus Status. Similar to the ACL, meniscal status was downloaded from the OAI database. Medial and lateral menisci were assessed by 2 radiologists using the MOAKS [12,17]. Three subregions were scored for both medial and lateral menisci and the presence of a tear was assessed using 9 categories. Categories 0 (normal) and 1 (signal abnormality) were considered as intact meniscus subregions. Categories 2 to 8 were different types of tears (e.g. radial, complete maceration). Participants with a tear in any subregion were coded as 1, while participants with completely intact medial and lateral menisci were coded as 0.

Radiographic Assessment

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Knee alignment and disease severity were downloaded from the OAI. They were measured from bilateral posterior-anterior fixed flexion knee radiographs. Participants were standing on a plexiglass frame that ensured consistent positioning and knees were flexed 20 to 30° [20].

Femur-tibia angle (FTA) quantified knee alignment as previously described [21]. The femur axis was centred between outer margins of the lateral and medial femoral epicondyles and perpendicular to a line tangent to the base of the femoral condyles. The tibia axis was centred between points on the tibia outer edges taken 1 cm and 10 cm inferior to the tibial plateau. FTA was the angle between tibia and femur axes. An angle of approximately -4.7° represents neutral alignment [21]. More negative values represent varus alignment and higher values represent valgus. FTA has demonstrated excellent intra- and inter-rater reliability (intraclass correlation coefficient>0.97), and is correlated with the hip-knee-ankle (HKA) alignment angle (r=0.72) [21]. Also, FTA and HKA angle had similar relationships to longitudinal cartilage loss [22]. HKA angle was not utilized because OAI did not consistently collect it at baseline and it was missing from 253 participants from the included sample. However, a conversion from FTA to HKA angle using sex-specific regression equations has been previously published and HKA angles were determined using this method (see Table IV, reader 2 from this previous study) [21].

Disease severity was determined using KL-scores. This is a 5 point scale which classifies OA disease severity from 0 (none) to 4 (severe) [23]. Two expert readers independently completed KL-scores and a consensus was reached.

Statistical analysis

Descriptive statistics were calculated for study variables. Welch t-tests, which adjust for unequal sample sizes, compared demographic variables and baseline cartilage volume between OA-only and OA-ACL groups [24]. A contingency table with a chi-squared test compared the

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proportion of sex and meniscal tears within each group. Mann-Whitney U tests compared KL-scores since this data were not normally distributed. To address the study objective, hierarchical linear models were constructed and dependent variables were changes in cartilage over 24 or 72 months in each knee region. Separate models were constructed for each knee region in order to determine the impact of FTA and ACL status on each region separately. The initial model included confounder variables to account for group differences (age, sex, body mass index, KL-scores, meniscal status, and OAI subcohort), time (24 or 72 months), and baseline cartilage volume for the region of interest. Group (OA-ACL vs OA-only) and FTA variables were then entered separately. The final model added the interaction between group and FTA. These steps were completed regardless of whether they produced significant changes in the model. Time, sex, meniscal status, OAI subcohort, and group were entered as categorical variables. Age, body mass index, KL-scores, baseline cartilage volume, and FTA were entered as continuous variables. The intercept was entered as a random effect and other variables were fixed effects. Wald statistic and associated p values were examined for the slope parameters of the variables. A p value of 0.05 determined statistical significance. Different stages of model development were compared by examining change in -2 log-likelihood (-2LL) and critical values for the chi-squared statistic. Full maximum-likelihood was chosen, Kenward-Roger method was used to calculate degrees of freedom, and the covariance structure was unstructured [25,26]. Unadjusted Pearson correlations between FTA and cartilage volume change were also completed to assist in interpreting any significant model interactions. Diagnostics were examined including examining normality, multicollinearity, linearity, homoscedasticity, and influential cases. In addition, a sensitivity analysis was conducted where HKA angle (converted from FTA using published equations) was entered into the models instead of FTA [21]. Hierarchical linear models were constructed using SAS Enterprise Guide (version 7.13) and remaining analyses were performed in SPSS (version 20).

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RESULTS

Table 1 provides participants' characteristics at baseline. There were statistically significant differences between groups, with the OA-ACL group having greater height (p=0.008) and weight (p=0.003). This was likely due to a greater proportion (p<0.001) of men in the OA-ACL group and a greater proportion of women in the OA-only group. There was a greater proportion (p<0.001) of participants with a meniscal tear in the OA-ACL group (83%) than the OA-only group (46%). The OA-ACL group (mean FTA=-6.46^{o}) had statistically significant lower FTA values (greater varus; p=0.006) than the OA-only group (mean FTA=-5.40^{o}). The OA-ACL group also had higher mean ranks for KL-scores indicating greater radiographic severity (p<0.001). The OA-only group had statistically significant lower baseline cartilage volume measures in the lateral tibial plateau (p=0.002), lateral femoral condyle (p<0.001), and medial femoral condyle (p=0.028). Twenty-five participants in the OA-ACL group did not have MRI scans at 72 months.

Hierarchical Linear Models (Table 2)

Medial Tibial Plateau. For medial tibial plateau cartilage volume change, adding group did not significantly improve the model (-2LL change=0.9, p=0.343) after accounting for confounders, time, and baseline cartilage volume. However, adding FTA significantly improved the model (-2LL change=6.4, p=0.011). Finally, adding group by FTA interaction did not significantly change the model (-2LL change=0.2, p=0.655). For the final model, the FTA slope parameter was statistically significant (p=0.045). A greater decrease in medial tibial plateau cartilage volume was associated more pronounced varus alignment. Specifically, each degree of varus alignment (lower FTA values) was associated with a decrease in medial tibial plateau volume over time of 7.49 mm^3 after accounting for the other variables.

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Medial Femoral Condyle. For medial femoral condyle cartilage volume change, adding group did not significantly improve the model (-2LL change=0.2, p=0.655). Adding FTA did significantly improve the model (-2LL change=5.0, p=0.025). Adding group by FTA interaction did not significantly change the model (-2LL change=3.1, p=0.078). For the final model, the FTA slope parameter was statistically significant (p=0.005). A greater decrease in medial femoral condyle cartilage volume was associated greater varus alignment. Each degree of varus alignment (lower FTA values) was associated with a decrease in medial femoral condyle volume over time of 19.70 mm^3 after accounting for the other variables.

Lateral Tibial Plateau. For lateral tibial plateau cartilage volume change, adding group (-2LL change=1.0, p=0.317) and FTA (-2LL change=0.8, p=0.371) did not significantly improve the model. However, adding group by FTA interaction did significantly improve the model (-2LL change=7.3, p=0.007). For the final model, slope parameters for group (p=0.004) and group by FTA interaction (p=0.006) were statistically significant. The significant interaction indicated that greater valgus alignment (higher FTA values) was associated with greater lateral tibial plateau cartilage loss in the OA-ACL group at 24 months (unadjusted r=-0.25) and 72 months (unadjusted r=-0.22) (Fig. 2). There was no relationship between FTA and lateral tibial plateau cartilage loss in the OA-only group (24 month unadjusted r=0.06; 72 month unadjusted r=0.06) (Fig. 2).

Lateral Femoral Condyle. For lateral femoral condyle cartilage volume change, adding group (-2LL change=0.2, p=0.655) and FTA (-2LL change=0.9, p=0.343) did not significantly improve the model. Adding group by FTA interaction did significantly improve the model (-2LL change=5.7, p=0.017). For the final model, slope parameters for group (p=0.046) and group by FTA interaction (p=0.017) were statistically significant. The significant interaction indicated that greater valgus alignment (higher FTA values) was associated with greater lateral femoral

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condyle cartilage loss in the OA-ACL group at 24 months (unadjusted r=-0.16), although the relationship was non-existent at 72 months (unadjusted r=-0.04) (Fig. 3). There was no relationship between FTA and lateral femoral condyle cartilage loss in the OA-only group (24 month unadjusted r=0.06; 72 month unadjusted r=0.04) (Fig. 3).

Diagnostics. Assumptions of normality, no multicollinearity, linearity, and homoscedasticity were all confirmed through diagnostic analyses (e.g. residual plots). However, 1 or 2 participants had substantially higher Cook's distance than the other participants for each region and were considered influential cases. These participants had large decreases in cartilage volume. Removing these participants from hierarchical linear models did not change the statistical significance of the slope parameters for medial tibial plateau, lateral tibial plateau, and lateral femoral condyle analyses. However, removing 2 outliers from the medial femoral condyle analysis resulted in a significant slope parameter for the group by FTA interaction (β=-25.36, 95% confidence interval=-49.07, -1.65; p=0.036). When this analysis included the entire sample (Table 2), this interaction was trending to significance (p=0.081). The significant interaction indicated that higher varus alignment was associated with greater medial femoral condyle cartilage loss in the OA-only group (24 month unadjusted r=0.20; 72 month unadjusted r=0.20). This relationship was weaker in the OA-ACL group (24 month unadjusted r=0.11; 72 month unadjusted r=-0.08).

Sensitivity Analysis. In addition, HKA angle (converted from FTA) was entered into the models instead of FTA. There were no changes in statistical significance of the slope parameters for alignment (HKA), group, and alignment by group interaction for most knee regions (Table 3). The only exception was the lateral femoral condyle region. The interaction parameter remained statistically significant, but the group parameter was no longer statistically significant (Table 3).

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DISCUSSION

The impact of knee alignment, assessed with the FTA, on cartilage volume loss varied between participants with knee OA or participants at risk of developing knee OA depending on the status of the ACL. Greater valgus alignment was related to cartilage volume loss in the lateral compartment over 24 to 72 months in the OA-ACL group. This relationship was not present in the OA-only group. Varus alignment was related to cartilage volume loss in the medial compartment in both groups; however, a subanalysis that removed 2 influential cases found that this relationship was stronger in the OA-only group in the medial femoral condyle region. Thus, the role of knee alignment in knee OA initiation and progression likely varies between patients that have an intact or deficient ACL.

The current finding that knee alignment relates to cartilage volume loss in the medial compartment or disease progression in patients with knee OA is consistent with other studies [27,28,2]. Varus alignment results in a medial shift of the load-bearing axis, thereby increasing forces within the medial compartment [2,29]. The cartilage and surrounding tissue are unable to absorb these forces adequately and this leads to tissue damage long term including cartilage thinning. Similarly, valgus alignment increases lateral compartment load. However, the relationship between cartilage loss in the lateral compartment and alignment only existed in the OA-ACL group. One possible explanation is some participants in the OA-ACL group sustained a traumatic injury that resulted in the ACL rupture. Tissue damage occurs more frequently in the lateral compartment following traumatic ACL rupture, including cortical depression fractures, meniscal tears, and bone marrow lesions [30]. Valgus alignment would place a greater load on this damaged tissue which would be unable to absorb the normal loading that occurs with daily activities leading to further tissue degeneration. Alternatively, changes in knee mechanics, including arthrokinematics, exist after ACL disruption [31-33]. Negative consequences of these mechanical changes may be accentuated by malalignment. Regardless, it appears the role of knee alignment on OA progression varies between patients with and without an intact ACL.

Although relationships between FTA and cartilage loss were significant, correlations were generally low. For instance, correlations between FTA with lateral tibial plateau and lateral femoral condyle cartilage loss at 24 months in the OA-ACL group was -0.25 and -0.16 respectively. These values are similar to other studies (r=0.07 to 0.30) that investigated the relationship between knee alignment and cartilage loss in similar regions [22,28,34]. Knee alignment is one of many factors that play a role in knee OA progression and these other factors likely account for the unexplained variance. Regardless, FTA was significantly related to medial compartment cartilage loss in both groups and lateral compartment cartilage loss in the OA-ACL group.

These current findings have potential research and clinical implications. Firstly, they demonstrate that pathways to joint failure differ between patients with and without an intact ACL. Alignment and load distribution might play a different role in knee OA initiation and progression in these patients and these differences might be compartment specific. Secondly, some knee OA interventions change alignment and/or modify joint loading in order to decrease symptoms or potentially slow disease progression. For instance, high tibial osteotomy has been shown to improve patient outcomes and decrease varus malalignment in patients with knee OA [35]. Another study demonstrated similar improvements in patients that had combined high tibial osteotomy and ACL reconstruction, although it is not clear which part of the surgery was responsible for the improvement [36]. Future studies should examine if treatment effects and disease progression are similar between knee OA patients with and without intact ACLs. Thus, the results have potential clinical implications, but additional research is required to examine these hypotheses.

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This study has several limitations. Partial and full ACL ruptures were included in the OA-ACL group to increase sample size. Differences in OA-related structural changes could exist between patients with full and partial ACL ruptures; however, a previous study found no differences in meniscal morphology between these groups and cartilage morphology was similar in most regions (19 of 22 regions) [37]. In addition, it is not clear how many participants in the OA-ACL group sustained traumatic ACL injuries, when exactly these ACL ruptures occurred, and the ACL rupture was diagnosed from MRI without a clinical assessment. The OAI [12] asks participants if they were, “ever injured badly enough to limit ability to walk at least 2 days.” Less than half of the participants (30 out of 66) in the OA-ACL groups responded “yes” to this question, and a traumatic ACL tear is possible. However, the recall accuracy of this question has not been determined. It is possible that some participants that responded “no” actually had sustained trauma, but were unable to recall the incident. Regardless, a deficient ACL did impact cartilage volume change in patients with knee OA. It is not clear if these results can be generalized to other types of knee trauma (e.g. meniscal tear without ACL damage). Finally, participants were from different OAI projects (projects #22, 30, 63, 65) [13-15]. Each project had different inclusion/exclusion criteria, which likely increased the variability of the current study sample. However, this would ensure the results are more generalizable to patients with knee OA or people at risk of developing knee OA.

In conclusion, an interaction existed between knee alignment and ACL status when examining their impact on cartilage volume loss. Greater valgus alignment was associated with decreased cartilage volume in the lateral compartment in participants with knee OA or at risk of knee OA if they had an ACL disruption. This relationship diminished in participants with a normal ACL. Varus alignment was related to cartilage loss in the medial compartment in both groups. These findings indicate that alignment impacts knee OA initiation and progression in the lateral compartment differently in patients with knee OA that have an intact versus a disrupted

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ACL. Future studies should examine if the effectiveness of interventions that aim to modify knee alignment or loading differs between these groups.

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CONFLICT OF INTEREST STATEMENT

Jean-Pierre Pelletier and Johanne Martel-Pelletier are shareholders in ArthroLab Inc. François Abram is an employee of ArthroLab Inc. There are no other conflicts of interest to report.

DATA AVAILABILITY

The datasets used in the current study are available through the Osteoarthritis Initiative website: https://nda.nih.gov/oai/

ETHICAL STANDARDS

Ethics approval for the OAI database was made by the Institutional Review Board of the University of California (approval number 10-00532) and from the clinical sites that participated in the study. Informed consent was obtained from participants during enrollment into the OAI.

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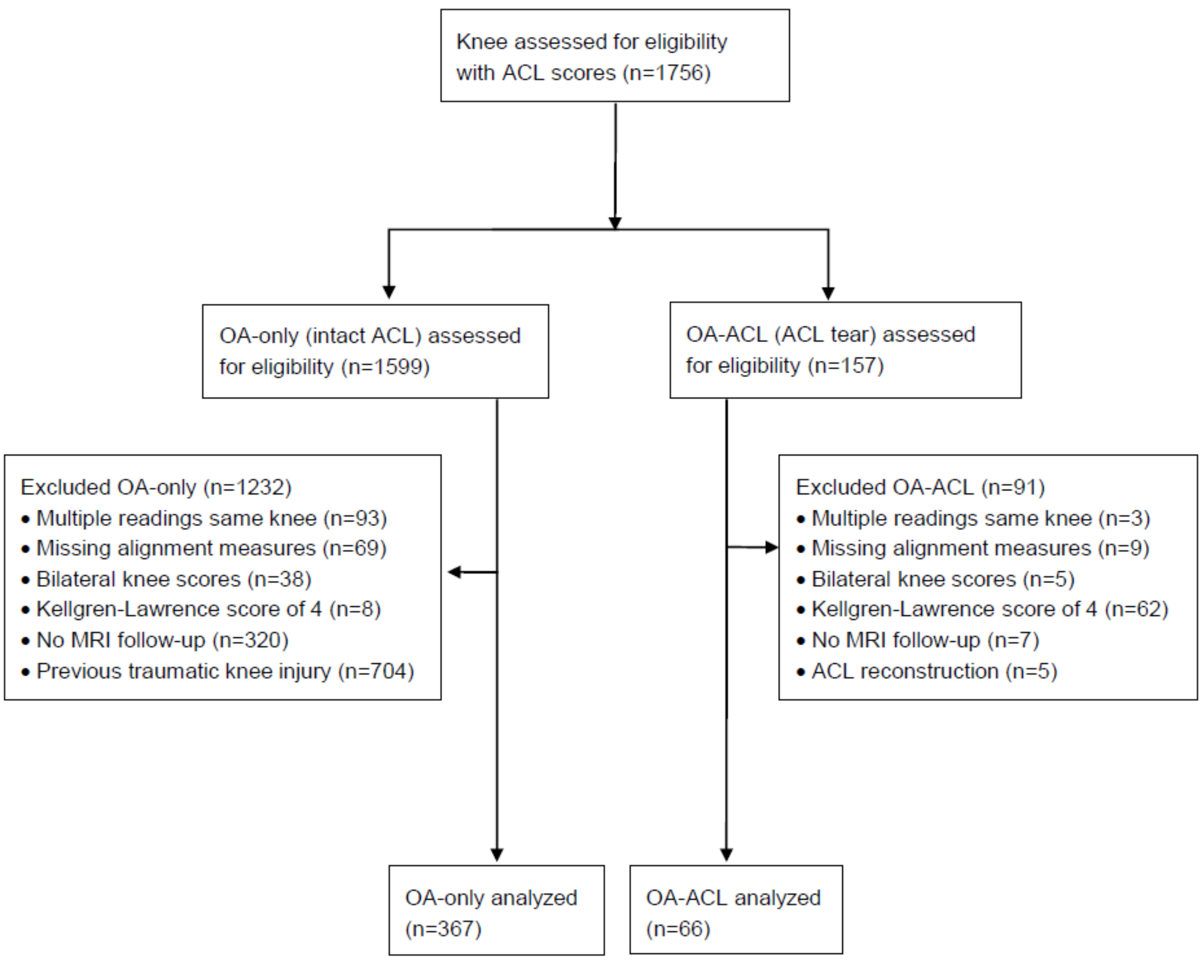

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Fig. 1 A flow diagram of the participants in the two groups and reasons for exclusions. Note:

OA, osteoarthritis; ACL, anterior cruciate ligament

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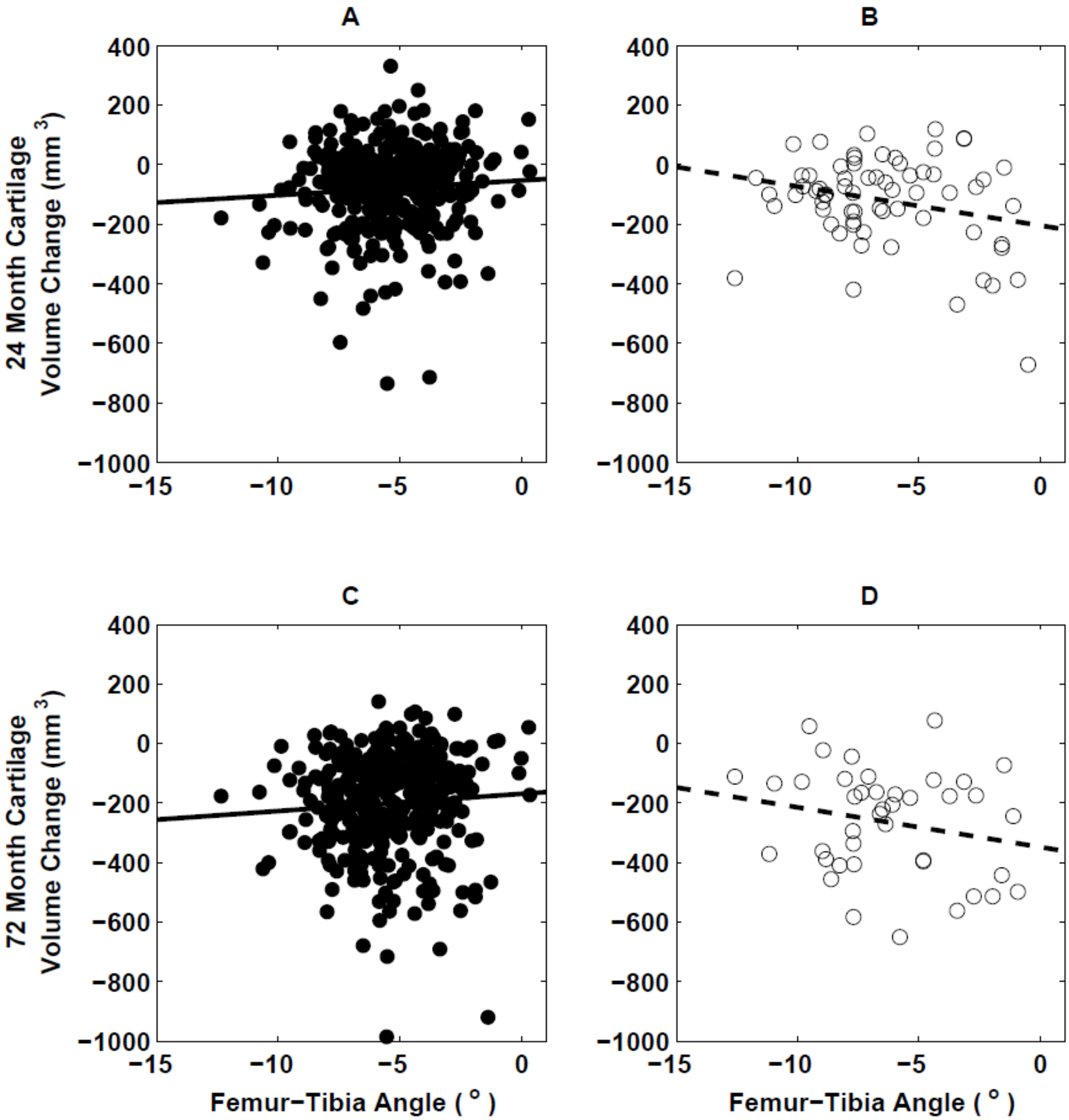

Fig. 2 The relationship between femur-tibia angle (FTA) and lateral tibial plateau cartilage volume change over 24 months (A) for the knee osteoarthritis only group (OA-only; black, filled dots) and (B) the group with combined anterior cruciate ligament rupture and knee osteoarthritis (OA-ACL; unfilled dots). This relationship is also demonstrated over 72 months for (C) OA-only and (D) OA-ACL groups. The lines of best fit (unadjusted, bivariate relationships) for the OA-only and OA-ACL groups are represented by the solid and dashed lines respectively. Extreme values (i.e. decreases in cartilage volume by more than 1000 mm^3) were not represented on the plots

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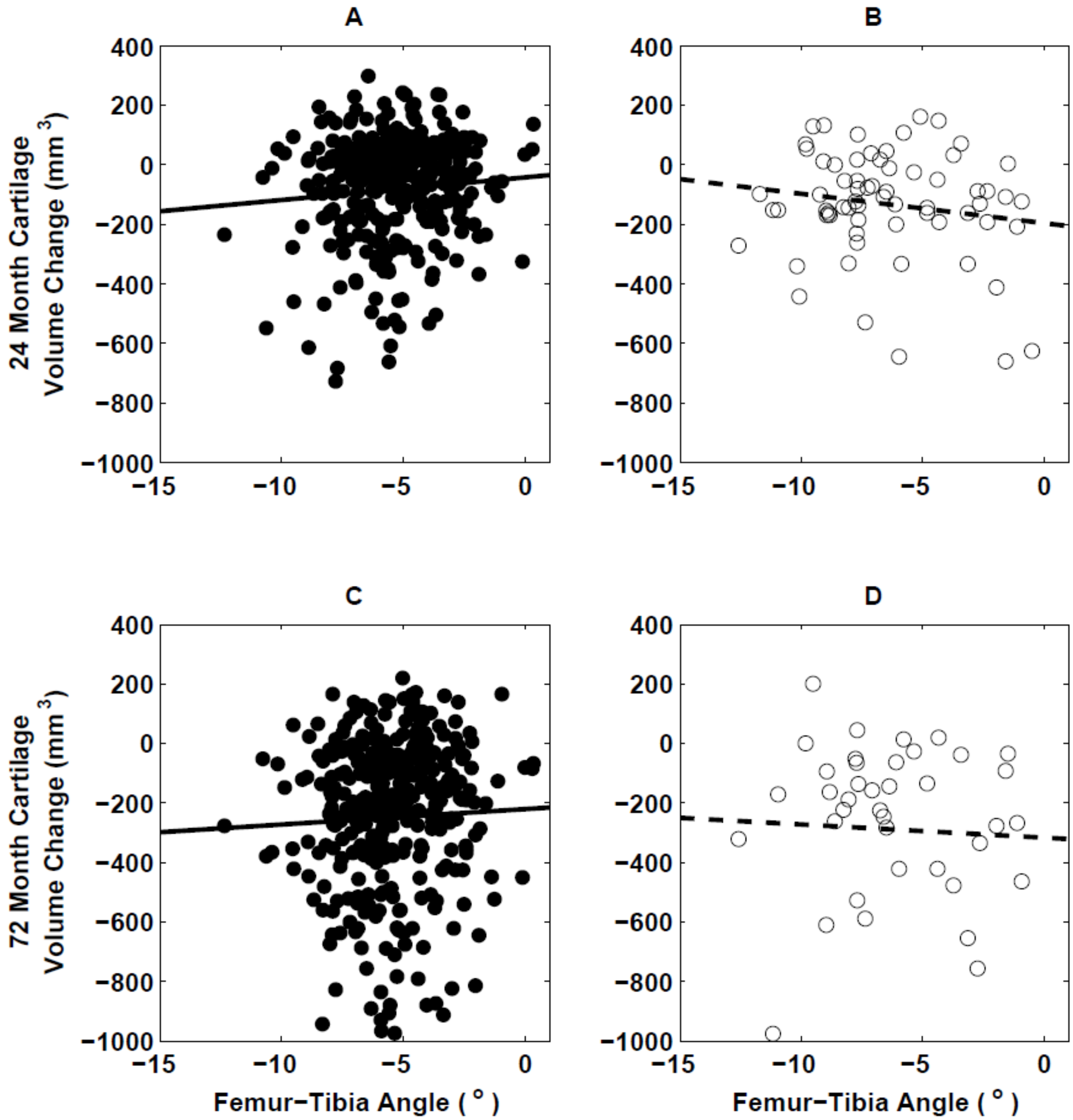

Fig. 3 The relationship between femur-tibia angle (FTA) and lateral femoral condyle cartilage volume change over 24 months (A) for the knee osteoarthritis only group (OA-only; black, filled dots) and (B) the group with combined anterior cruciate ligament rupture and knee osteoarthritis (OA-ACL; unfilled dots). This relationship is also demonstrated over 72 months for (C) OA-only and (D) OA-ACL groups. The lines of best fit (unadjusted, bivariate relationships) for the OA-only and OA-ACL groups are represented by the solid and dashed lines respectively. Extreme values (i.e. decreases in cartilage volume by more than 1000 mm^3) were not represented on the plots.

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Table 1: Participants' characteristics at baseline.

Variable		OA-only (n=367)	OA-ACL group (n=66)	p value*
Women (%)		256 (70)	27 (41)	<0.001**
Age (y)		62 (9)	62 (9)	0.742
Height (m)		1.67 (0.09)	1.70 (0.11)	0.008
Weight (kg)		82.30 (15.53)	89.35 (17.19)	0.003
Body Mass Index (kg/m^2)		29.59 (4.62)	30.74 (5.20)	0.096
Meniscus Tear (%)		167 (46)	55 (83)	<0.001**
Femur-Tibia Angle (^{o})[a]		-5.40 (1.96)	-6.46 (2.92)	0.006
Hip-Knee-Ankle Angle (^{o})[a]		-0.89 (2.15)	-2.34 (2.95)	<0.001
Baseline Cartilage Volume (mm^3)				
	<u>Medial Compartment</u>			
	Tibial Plateau	1411.7 (557.0)	1542.2 (654.0)	0.131
	Femoral Condyle	3275.9 (982.8)	3608.8 (1134.3)	0.028
	<u>Lateral Compartment</u>			
	Tibial Plateau	1921.5 (564.2)	2233.0 (773.2)	0.002
	Femoral Condyle	3182.9 (885.0)	3837.5 (1317.1)	<0.001
KL-scores frequency (%)	0 (none)	61 (17%)	6 (9%)	<0.001
	1 (questionable)	115 (31%)	6 (9%)	
	2 (mild)	127 (35%)	11 (17%)	
	3 (moderate)	64 (17%)	43 (65%)	

Means (standard deviation) are provided for the study variables. Frequencies (percentages) are provided for sex, meniscus tear, and Kellgren-Lawrence scores (KL-scores).
*p values are from Welch t-tests or Mann-Whitney U tests, **χ^2.
OA, osteoarthritis; ACL, anterior cruciate ligament.
[a]Lower values for the femur-tibia angle and hip-knee-ankle angle represent varus alignment and higher values represent valgus alignment. The hip-knee-ankle angle was calculated from the femur-tibia angle using previously published equations [21].

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Table 2: Slope parameters (95% confidence intervals) over the different regions for the final hierarchical linear models with femur-tibia angle.*

Factor	Medial		Lateral	
	Tibial Plateau	Femoral Condyle	Tibial Plateau	Femoral Condyle
Age	**-2.13 (-3.65, -0.61)**	**-3.26 (-6.15, -0.37)**	0.86 (-0.77, 2.49)	0.50 (-1.68, 2.68)
Sex	**-43.49 (-78.07, -8.90)**	-43.37 (-111.00, 24.25)	12.89 (-22.90, 48.68)	**66.33 (15.43, 117.24)**
Body Mass Index	0.26 (-2.50, 3.01)	-4.56 (-9.77, 0.64)	-1.92 (-4.88, 1.03)	-0.97 (-4.89, 2.95)
KL-scores	-5.75 (-20.48, 8.98)	**-42.04 (-69.89 -14.19)**	-0.38 (-15.43, 16.18)	-3.90 (-24.95, 17.15)
OAI subcohort	-4.55 (-30.72, 21.62)	31.49 (-17.91, 80.88)	-3.15 (-31.36, 25.06)	14.80 (-22.44, 52.04)
Meniscus	-18.91 (-47.46, 9.63)	7.45 (-45.56, 61.45)	-22.64 (-53.24, 7.95)	-28.10 (-68.88, 12.69)
Time	**-109.98 (-129.24, -90.73)**	**-244.35 (-281.63, -207.08)**	**-122.99 (-142.31, -103.67)**	**-164.58 (-192.83, -136.33)**
Baseline Cartilage Volume	**-0.06 (-0.09, -0.03)**	**-0.05 (-0.08, -0.02)**	**-0.07 (-0.09, -0.04)**	**-0.11 (-0.13, -0.08)**
Group	3.52 (-88.49, 95.53)	-121.38 (-296.57, 51.81)	**-146.72 (-244.98, -48.45)**	**-133.63 (-264.94, -2.32)**
FTA[a]	**7.49 (0.17, 14.80)**	**19.70 (5.96, 33.44)**	2.21 (-5.54, 9.95)	1.61 (-8.65, 11.87)
Group x FTA interaction	3.42 (-10.13, 16.96)	-22.80 (-48.45, 2.85)	**-20.19 (-34.65, -5.73)**	**-23.64 (-43.06, -4.23)**

*Significant slope parameters ($p<0.05$) are bolded.
KL-scores, Kellgren Lawrence disease severity scores; OAI, Osteoarthritis Initiative; FTA, femur-tibia angle.
[a]For the FTA, lower values represent varus alignment and higher values represent valgus alignment.
Sex was coded as 0=women and 1=men. OAI subcohort was coded as 0=incidence and 1=progression. Meniscus was coded as 0=no tear and 1=tear. Time was coded as 0=24 months and 1=72 months. Group was coded as 0=OA-only and 1=OA-ACL.

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Table 3: Slope parameters (95% confidence intervals) over the different regions for the hierarchical linear models with hip-knee-ankle angle.*

Factor	Medial		Lateral	
	Tibial Plateau	Femoral Condyle	Tibial Plateau	Femoral Condyle
Age	**-2.13 (-3.65, -0.60)**	**-3.19 (-6.09, -0.29)**	0.89 (-0.75, 2.52)	0.53 (-1.65, 2.71)
Sex	-31.72 (-70.23, 6.79)	-19.80 (-94.13, 54.53)	10.66 (-28.20, 49.52)	**62.02 (7.06, 116.98)**
Body Mass Index	0.25 (-2.50, 3.01)	-4.44 (-9.64, 0.76)	-1.84 (-4.80, 1.11)	-0.87 (-4.79, 3.04)
KL-scores	-5.93 (-20.66, 8.79)	**-42.96 (-70.77, -15.15)**	-0.10 (-15.89, 15.69)	-4.54 (-25.57, 16.48)
OAI subcohort	-4.74 (-30.92, 21.45)	32.65 (-16.73, 82.03)	-2.22 (-30.45, 26.00)	15.91 (-21.34, 53.16)
Meniscus	-19.04 (-47.58, 9.51)	7.95 (-46.02, 61.91)	-22.05 (-52.65, 8.54)	-27.40 (-68.18, 13.39)
Time	**-109.97 (-129.22, -90.71)**	**-244.40 (-281.68, -207.12)**	**-123.05 (-142.37, -103.73)**	**-164.66 (-192.91, -136.41)**
Baseline Cartilage Volume	**-0.06 (-0.09, -0.03)**	**-0.05 (-0.08, -0.02)**	**-0.07 (-0.09, -0.04)**	**-0.11 (-0.13, -0.08)**
Group	-10.45 (-57.70, 36.80)	-29.30 (-118.63, 60.04)	**-60.96 (-111.44, -10.47)**	-33.38 (-100.66, 33.91)
HKA[a]	**7.55 (0.14, 14.95)**	**20.02 (6.11, 33.92)**	1.63 (-6.22, 9.48)	0.76 (-9.64, 11.15)
Group x HKA interaction	3.53 (-9.74, 16.81)	-23.64 (-48.73, 1.45)	**-19.29 (-33.44, -5.13)**	**-22.62 (-41.65, -3.59)**

*Significant slope parameters ($p<0.05$) are bolded.
KL-scores, Kellgren Lawrence disease severity scores; OAI, Osteoarthritis Initiative; HKA, hip-knee-ankle angle.
[a]For the HKA, lower values represent varus alignment and higher values represent valgus alignment. HKA was converted from femur-tibia angles.
Sex was coded as 0=women and 1=men. OAI subcohort was coded as 0=incidence and 1=progression. Meniscus was coded as 0=no tear and 1=tear. Time was coded as 0=24 months and 1=72 months. Group was coded as 0=OA-only and 1=OA-ACL.

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