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Trajectories of femorotibial cartilage thickness among persons with or at risk of knee osteoarthritis: development of a prediction model to identify progressors

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SUMMARY

Objective: There is significant variability in the trajectory of structural progression across people with knee osteoarthritis (OA). We aimed to identify distinct trajectories of femorotibial cartilage thickness over 2 years and develop a prediction model to identify individuals experiencing progressive cartilage loss.

Methods: We analysed data from the Osteoarthritis Initiative (OAI) (n = 1,014). Latent class growth analysis (LCGA) was used to identify trajectories of medial femorotibial cartilage thickness assessed on magnetic resonance imaging (MRI) at baseline, 1 and 2 years. Baseline characteristics were compared between trajectory-based subgroups and a prediction model was developed including those with frequent knee symptoms at baseline (n = 686). To examine clinical relevance of the trajectories, we assessed their association with concurrent changes in knee pain and incidence of total knee replacement (TKR) over 4 years.

Results: The optimal model identified three distinct trajectories: (1) stable (87.7% of the population, mean change −0.08 mm, SD 0.19); (2) moderate cartilage loss (10.0%, −0.75 mm, SD 0.16) and (3) substantial cartilage loss (2.2%, −1.38 mm, SD 0.23). Higher Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) pain scores, family history of TKR, obesity, radiographic medial joint space narrowing (JSN) ≥1 and pain duration ≤1 year were predictive of belonging to either the moderate or substantial cartilage loss trajectory [area under the curve (AUC) 0.79, 95% confidence interval (CI) 0.74, 0.84]. The two progression trajectories combined were associated with pain progression (OR 1.99, 95% CI 1.34, 2.97) and incidence of TKR (OR 4.34, 1.62, 11.62).

Conclusions: A minority of individuals follow a progressive cartilage loss trajectory which was strongly associated with poorer clinical outcomes. If externally validated, the prediction model may help to select individuals who may benefit from cartilage-targeted therapies.

Introduction

There is considerable variability in the structural disease trajectory among patients with knee osteoarthritis (OA). Using radiographic joint space width (JSW) and magnetic resonance imaging (MRI)-based measures of articular cartilage, it has been

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shown that most individuals remain structurally stable over several years, while others experience structural progression[1–3]. As yet, there is no widely accepted risk stratification to better select individuals at risk for progressive joint pathology for targeted treatment[4]. To further advance OA management, it is necessary to better understand the different structural disease trajectories and to prospectively identify individuals following a progressive course who might benefit from treatment. Sparing those with good prognosis from unnecessary interventions would optimize the efficiency of clinical trials and contribute to the development of new effective therapies[4,5].

Cartilage pathology is a hallmark feature of OA. Although all synovial joint tissues play a role in promoting the structural and symptomatic disease[6], loss of cartilage thickness has been associated with clinically important outcomes in knee OA patients such as progression to total knee replacement (TKR)[7–9]. As yet, radiographic JSW is currently the standard technique for assessment of structural progression in trials formally accepted by regulatory agencies. However, this method has inherent shortcomings, such as limited responsiveness to change over time[10–12], limited responsiveness to structural treatment effects[13,14] and the inability to distinguish cartilage loss from meniscal lesions[15]. Cartilage evaluation on MRI is a valuable method to more accurately detect cartilage loss and efforts are underway to attain regulatory approval for MRI cartilage measures as a structural endpoint in clinical trials.

Previous studies have demonstrated distinct structural disease trajectories based on radiographic JSW using group-based mixture modelling, an emerging data-driven statistical approach used to identify subgroups of individuals sharing similar patterns of change in longitudinal data[1,16,17]. Other recent studies have also used similar methods to describe heterogeneity in the trajectory of knee pain[18–20] and disability in persons with early symptomatic knee OA[21]. However, there have been no studies to date using this approach to investigate the heterogeneity in the longitudinal structural disease trajectory based on MRI-detected quantitative cartilage thickness.

A number of patient and disease factors have been identified as potential determinants of structural disease progression and have previously been summarized in literature reviews[5,22–24]. Therefore, the aims of this study were to identify distinct cartilage thickness trajectories in knees with or at risk of OA, and to subsequently develop a prediction model to identify individuals experiencing progressive cartilage loss. Potential key predictors that were tested were baseline clinical (e.g., obesity, history of joint injury, knee pain duration and severity) and radiographic characteristics with literature evidence of an association with structural progression[5,22–26]. In order to examine the clinical relevance of the cartilage thickness trajectories, we further investigated the association of the trajectories with concurrent changes in knee pain and incidence of TKR over 4 years.

Methods

Study population

Our study population consisted of individuals in the Osteoarthritis Initiative (OAI), a prospective observational cohort including 4796 participants aged 45–79 years, with publicly accessible data collected at baseline and annually. For this analysis, we included individuals from two sub-studies within the OAI (projects 9B and 22; $n = 1014$)[27]. These sub-studies were selected based on available MRI data on quantitative cartilage measures in at least one knee at baseline, 1 and 2 years and the use of the same method and definition of anatomical regions across the knee[28]. Individuals in project 9B ($n = 414$) were selected for presence of frequent knee symptoms and Kellgren Lawrence grade (KLG) 2 or 3 at baseline in the same knee (index knee). Project 22 included individuals from the Foundation for the National Institutes of Health (FNIH) OA Biomarkers Consortium[29], a nested case–control study within OAI including 600 individuals with KLG 1, 2 or 3 at baseline and potential to meet criteria for radiographic and pain progression. Participants in the FNIH study were retrospectively selected to include 1/4 OA progressors (both clinical and radiographic progression), 1/4 non-progressors and 1/2 either clinical only or radiographic only progressors. The Institutional Review Board for the University of California, San Francisco (UCSF), and its affiliates approved the OAI study.

MRI assessment of cartilage thickness

Sagittal double echo steady state (DESS) sequence of either the right or left knee (one knee per participant) was available for all participants and read centrally for quantitative cartilage morphology measures using Chondrometrics software (Chondrometrics, Ainring, Germany) blinded to the chronological order of image acquisition. Further details of the MRI acquisition protocol have been described previously[28] and can be found at http://www.oai.ucsf.edu/datarelease/OperationsManuals.asp. The reliability of the quantitative cartilage measurements in the OAI has been previously reported[28].

Mean cartilage thickness assessed in the central (weight-bearing) medial tibiofemoral compartment at baseline, 1 and 2 years was used to define cartilage thickness trajectories. This measure represents a combination of the cartilage thickness at the central subregion of the medial tibia and the central subregion of central (weight-bearing) medial femur, with the central weight-bearing femoral condyle being defined using 75% of the distance between the trochlear notch and the posterior end of the femoral condyle[28]. We focused on this region due to its greater sensitivity to change when compared to peripheral cartilage regions, and due to its associations with subsequent radiographic and clinical progression[7,28,30].

Comparison of baseline characteristics between distinct trajectories

We investigated associations between cartilage thickness trajectories and the following baseline characteristics, selected based on evidence of an association with structural OA progression in previous studies[5,22–26]: age; gender; race; body mass index (BMI) (kg/m^2); knee pain, assessed by the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (0–100, higher scores representing worse pain); pain duration; knee alignment (central assessment of anatomic alignment on knee radiograph); history of knee injury which limited the ability to walk for at least 2 days (self-reported); history of knee surgery (any type; self-reported); isometric quadriceps strength (maximum torque [in newtons] among 3 trials); presence of contralateral knee OA (KLG $\geq$ 2); family history of TKR; presence of hand OA (bilateral nodes or bony enlargement on physical examination); intra-articular glucocorticoid injection in the last 6 months; physical activity (score of 2 [sometimes] or 3 [often] for strenuous sport/recreation activities on the Physical Activity Scale for the Elderly questionnaire); KLG; and radiographic medial joint space narrowing (JSN) score, centrally scored from 0 to 3 according to the Osteoarthritis Research Society International (OARSI) atlas[31].

Association with clinical outcomes

To determine the clinical relevance of the trajectory-based subgroups, we investigated if membership to each trajectory predicted knee pain progression over 2 years (i.e., change concurrent to the cartilage thickness change) and incidence of TKR over 4 years. Knee pain progression was defined as an increase in the WOMAC pain subscale $\geq$9 points (0–100)[32].

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Comparison of radiographic-defined progression between trajectories

To assess the relationship between the MRI-based cartilage thickness trajectories and the standard definition of structural progression based on radiographic criteria, we compared the proportion of individuals in each trajectory classified according to the OARSI-Outcome Measures in Rheumatology (OMERACT) definition of radiographic progression[33]. Progression was defined as a decrease in minimum JSW in the medial tibiofemoral compartment of ≥0.7 mm, the smallest detectable difference of this method[33].

Statistical analysis

Trajectories of cartilage thickness were identified using latent class growth analysis (LCGA), a type of mixture modelling for longitudinal data which assigns individuals with similar trajectories to a single class based on posterior probability[34]. LCGA assumes that there is no or minimal inter-individual variability within trajectories-based subgroups, making it possible to identify possible distinct subgroups within a population. The optimal number of classes was determined using data driven (goodness of fit indices) and pragmatic criteria (model parsimony, high entropy, and interpretability)[34,35]. We aimed to select a model with a combination of the smallest Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC), high entropy values and posterior probabilities (the nearest to 1.0 for each), and a bootstrap likelihood ratio test (BLRT) *P*-value <0.05 which represents that the model with *k* classes is favoured against the model with *k*−1 classes. Models were tested until no further improvement was found (BLRT *P*-value ≥0.05). We have used a pragmatic consideration based on the potential clinical relevance and subgroup sizes in each model tested, without prespecifying a minimum percentage of individuals required in each trajectory. To test stability of the trajectories we split the full dataset into two halves and repeated the LCGA analysis in each dataset. Additionally, we conducted LCGA analysis for each sub-study to check for robustness of results across study populations. We have used the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS)-Checklist[36] to guide the reporting of the trajectory analysis (Supplementary Table 1).

Differences in participants' baseline characteristics between trajectories were investigated using chi-square for dichotomous variables and analysis of variance (ANOVA) for continuous variables. Differences in clinical outcomes (concurrent knee pain progression and incidence of TKR over 4 years) between the trajectories were investigated using logistic regression using the trajectories as the predictor variable and adjusting for age, gender, baseline KLG and baseline femorotibial cartilage thickness. Counts and percentages were used to compare the proportion of individuals fulfilling the radiographic progression definition between the MRI-based cartilage thickness trajectories.

In a second step, trajectory-based subgroups showing cartilage loss progression (i.e., moderate and severe cartilage loss) were combined into one *progression* subgroup and logistic regression was used to assess the odds of belonging to the progression subgroup compared to the *non-progression* subgroup (i.e., no cartilage loss trajectory). Only cases with complete data available were analysed. Variables with a *P*-value <0.2 in univariable analysis were included in multivariable analysis, after which backwards selection was used to arrive at a final model. Only variables with a *P*-value <0.05 were included in this final model. Bootstrapping (1000 samples) was used in the multivariable model for internal validation, optimizing precision of the final model. Non-ignorable bias (the difference between parameter estimates obtained for the study population and the average of 1000 bootstrap samples) was defined as >0.25 × standard error (SE)[37,38]. Furthermore, we adjusted the intercept of the prediction model by adding the intercept estimate of the logistic regression model in the sub-study 9B with the linear predictor from the derived predicted model included as the offset variable[39]. Area under the Receiver Operating Characteristic (ROC) curve (AUC) was used to assess the discriminant ability of the final model to identify individuals in the progression subgroup. Model calibration was assessed using a calibration plot and the Hosmer and Lemeshow test.

We used the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) checklist to ensure the quality of reporting of the prediction model[40]. Mplus software version 8.0 was used for the LCGA and SPSS version 22.0 was used for the other analyses (SPSS, Chicago, IL, USA). STATA version 14.0 was used to obtain bootstrapped AUCs.

Results

Cartilage thickness trajectories

Model fit was tested for one to five-trajectory models as the BLRT *P*-value became ≥0.05 for the model with five trajectories. Supplementary Table 2 displays the fit indices and trajectory characteristics for each model. The four-trajectory model was not selected due to the extremely small size of one of the classes (0.8% of the population). Compared to the model with two trajectories, the three-trajectory model displayed lower BIC and AIC, similar entropy values, and included a trajectory with the greatest slope and similar intercept compared to the stable trajectory which we considered potentially clinically relevant. Thus, a three-trajectory model was selected and is displayed in Fig. 1. The average posterior probabilities were all above 0.7 which is considered appropriate[41]. Additional details concerning the trajectory model used can be found in the Supplementary Table 1.

Participants in trajectory 1 (stable trajectory) comprised the majority of the population ($n = 889$, 87.7%) and had no significant progression over 2 years (mean change in cartilage thickness = −0.08 mm; SD 0.19). Participants in trajectory 2 (moderate decline; $n = 102$, 10.0%) demonstrated intermediate rates of progression (mean change = −0.75 mm; SD 0.16) and those in trajectory 3 (greatest decline; $n = 23$, 2.3%) had the greatest rate of cartilage loss (mean change = −1.38 mm; SD 0.22). Table I describes the cartilage thickness values at each time point as well as the change in each trajectory over 2 years. Baseline cartilage thickness was greater in the stable trajectory compared to the moderate decline trajectory, although it was similar to the greatest decline trajectory. Similar trajectories and trajectory membership were identified when the analysis was performed in each half of the dataset and in each sub-study (Supplementary Figs. 1 and 2, respectively).

Characteristics of the participants in each trajectory

Table II shows the baseline characteristics of participants in each trajectory. Missing data was infrequent and maximum for the quadriceps strength variable ($n = 71$, 7.0%). Obesity (but not baseline BMI), varus malalignment, and baseline WOMAC pain score each increased from the stable trajectory to the trajectories with moderate and the greatest decline. The percentages of participants with a history of an intra-articular glucocorticoid injection and OA in the contralateral knee were higher in trajectories with cartilage thickness loss, while any JSN (score > 0) and severe JSN[2,3] were most frequent in the moderate decline trajectory. There was a lower proportion of African Americans and a higher percentage of males and individuals with previous knee injury in the trajectory with the

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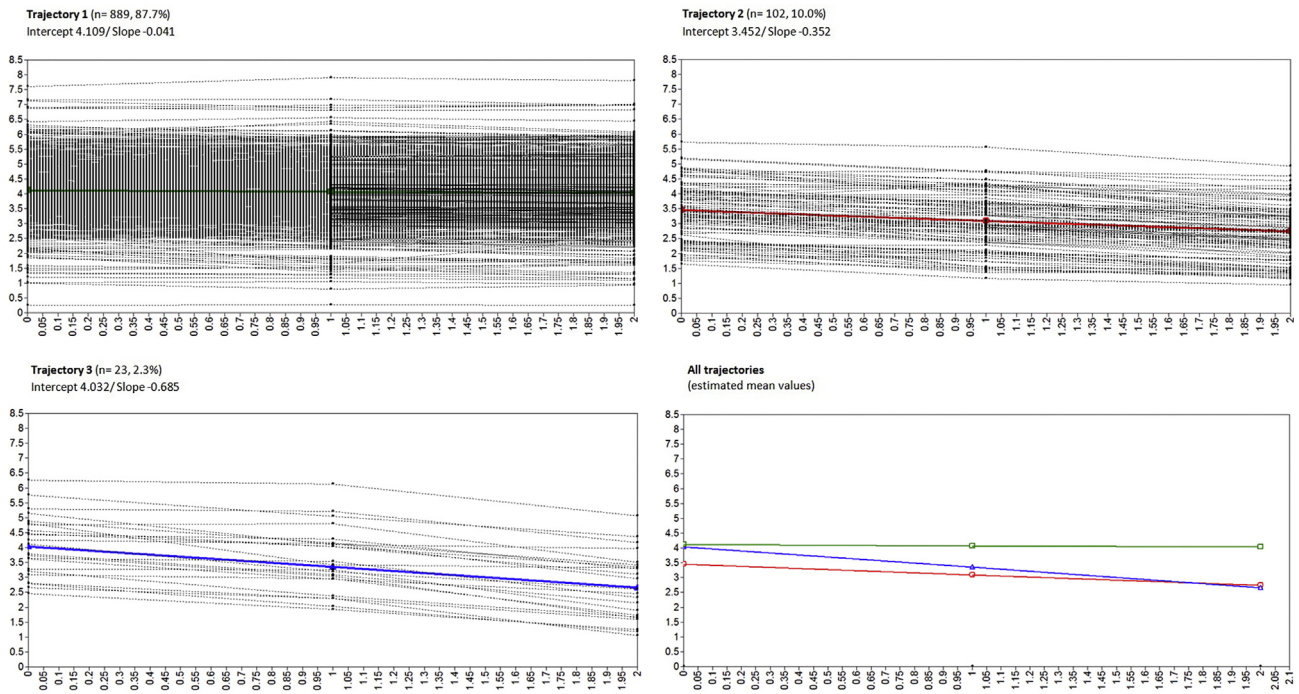

Fig. 1. Three distinct trajectories of cartilage thickness change in the central medial tibiofemoral 551 compartment over 2 years (observed values and estimated means).

Table I
Change in cartilage thickness (mm) in the central medial tibiofemoral compartment in each trajectory subgroup

	All participants *n* (%) missing*	Trajectory 1 (stable)	Trajectory 2 (moderate decline)	Trajectory 3 (greatest decline)	*P*-value		
					1 vs 2	2 vs 3	1 vs 3
Cartilage thickness, mm							
Baseline	0 (0.0)	4.10 (0.93)	3.38 (0.87)	4.07 (1.02)	**<0.001**	**0.004**	0.986
12 months	41 (4.2)	4.06 (0.96)	3.01 (0.93)	3.55 (1.11)	**<0.001**	**0.048**	**0.038**
24 months	0 (0.0)	4.02 (0.96)	2.63 (0.88)	2.69 (1.11)	**<0.001**	0.961	**<0.001**
Change in cartilage thickness over 24 months, mm	–	−0.08 (0.19)	−0.75 (0.16)	−1.38 (0.22)	**<0.001**	**<0.001**	**<0.001**

Mean (SD) is displayed in the table for cartilage thickness values. Statistically significant *P*-values are displayed in bold.
* Missing at random assumption; missing data was not imputed.

greatest decline, although the latter differences did not reach statistical significance.

Association with clinical outcomes

The odds of undergoing TKR over 4 years were higher in the trajectories with moderate and greatest cartilage loss compared to the stable trajectory [OR 3.73, 95% confidence interval (CI) 1.22, 11.38 and 6.71, 95% CI 1.38, 32.52, respectively] (Table III). Similarly, pain progression concurrent to the cartilage thickness change was more likely to occur in individuals in the moderate decline trajectory (OR 2.04, 95% CI 1.32, 3.16) and in the greatest decline trajectory (OR 1.80, 95% CI 0.76, 4.25), although the latter did not reach statistical significance. Individuals in the cartilage loss trajectories combined (i.e., progressors) had nearly twice the odds of experiencing pain progression compared to the ones in the stable trajectory (OR 1.99, 95% CI 1.34, 2.97). Unadjusted analyses revealed similar results (results not shown).

Prediction model

Table IV shows the univariable and multivariable regression analyses. Pain duration was available for those individuals who reported frequent knee symptoms at the baseline visit ($n = 686$) and only these individuals were included in the multivariable model. The final model included baseline WOMAC pain (OR 1.02, 95% CI 1.01, 1.03), radiographic JSN (OR 10.75, 95% CI 4.22, 27.42 for medial JSN > 0 vs = 0), pain duration (OR 2.16, 95% CI 1.19, 3.92 for ≤ 1 year of knee pain vs > 1 year), family history of TKR (OR 2.15, 95% CI 1.22, 3.78) and obesity (OR 1.09, 95% CI 1.03, 2.79). The bias obtained from the bootstrap analysis was below the threshold for non-ignorable bias. The model had good discriminant ability to identify individuals in the progression subgroup, with a bootstrapped AUC of 0.79 (95% CI 0.74, 0.84) (Fig. 2). The Supplementary Fig. 3 displays the calibration plot which showed good model calibration (Hosmer and Lemeshow test value = 0.93). The equation for the logit of the probability of being in the progression group is provided below (the intercept was increased by 0.133 for the adjustment):

$$\text{LP (linear predictor)} = -5.240 + 0.768 \times \text{family history} + 0.024 \times \text{WOMAC pain} + 0.773 \times \text{pain duration} + 2.376 \times \text{medial JSN} + 0.530 \times \text{obesity}.$$

Comparison with radiographic-defined progression

Among individuals in the cartilage thickness loss trajectories (moderate and greatest decline combined), 66% were classified as

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Table II
Baseline characteristics of participants in each trajectory subgroup

	All participants $n = 1014$	Trajectory 1 (stable) $n = 889$	Trajectory 2 (moderate decline) $n = 102$	Trajectory 3 (greatest decline) $n = 23$	*P*-value (all three trajectories)
Age, years	61.53 (8.86)	61.38 (8.86)	62.57 (8.88)	62.95 (8.34)	0.320
Female, %	59.2	58.7	66.7	43.5	0.091
BMI, kg/m^2	30.19 (4.87)	30.27 (4.84)	29.66 (5.16)	29.66 (4.73)	0.422
% Obese*	48.5	47.0	58.8	60.9	**0.038**
Alignment (degrees)†	−5.65 (2.58)	−5.46 (2.58)	−7.01 (2.24)	−7.02 (1.73)	**<0.001**
Baseline WOMAC pain (0–100)	16.77 (18.11)	15.83 (17.47)	23.11 (21.05)	25.43 (20.99)	**<0.001**
Race, %					**<0.001**
White or Caucasian	76.9	77.1	75.5	78.3	
Black or African American	19.9	20.6	16.7	8.7	
Others	3.1	2.4	7.8	13	
Baseline medial JSN‡, %					**<0.001**
0	32.3	35.7	4.9	26.1	
1	33.1	34.6	23.5	17.4	
2–3	34.5	29.7	71.6	56.5	
Baseline KLG, %					0.081
1	9.0	9.2	8.8	0.0	
2	49.7	49.0	53.9	56.5	
3	40.8	41.4	36.3	39.1	
4	0.5	0.3	1.0	4.3	
Previous knee injury, %	37.2	37.2	32.4	56.5	0.095
Previous knee surgery, %	21.6	21.7	21.8	17.4	0.883
Quadriceps strength, N	342.79 (133.42)	342.35 (132.68)	341.57 (128.37)	363.63 (178.90)	0.790
Physically active, %	15.5	15.5	14.7	17.4	0.945
Presence of hand OA, %	20.4	20.2	23.5	13.0	0.498
Family history of TKR, %	17.3	16.3	23.8	27.3	0.079
Intra-articular glucocorticoid injection past 6 months, %	2.1	1.5	6.9	4.3	**0.001**
Pain duration, %					0.124
1 year or less	15.5	14.1	24.6	25.0	
2–5 years	43.3	43.4	43.5	37.5	
More than 5 years	41.3	42.4	31.9	37.5	
OA contralateral knee, %	63.4	61.6	76.5	73.9	**0.007**
Comorbidity score	0.42 (0.85)	0.41 (0.82)	0.53 (1.07)	0.26 (0.61)	0.253
>1 Comorbidities, %	27.1	27.0	30.4	17.4	0.436

Mean (SD) displayed for continuous variables and percentages for categorical variables. Statistically significant *P*-values are displayed in bold.
* Obesity was defined as BMI ≥30 kg/m^2.
† Negative values represent varus malalignment.
‡ Medial tibiofemoral joint space narrowing. WOMAC = Western Ontario & McMaster Universities Osteoarthritis Index; JSN = joint space narrowing.

Table III
Association between the trajectories and clinical outcomes

	Trajectory 1 (stable)	Trajectory 2 (moderate decline)	Trajectory 3 (greatest decline)	Trajectories 2 and 3 combined ("progressors")
Pain progression (index knee), *n* (%)	239 (26.9)	43 (42.2)	9 (39.1)	52 (41.6)
OR (95% CI)	REF	**2.04 (1.32, 3.16)**	1.80 (0.76, 4.25)	**1.99 (1.34, 2.97)**
TKR rate over 4 years, *n* (%)	13 (1.5)	5 (4.9)	2 (8.7)	7 (5.6)
OR (95% CI)	REF	**3.73 (1.22, 11.38)**	**6.71 (1.38, 32.52)**	**4.34 (1.62, 11.62)**

Pain progression defined as an increase in WOMAC pain score >9 points over 2 years. Adjusted for age, gender, baseline Kellgren and Lawrence grade and baseline cartilage thickness. Statistically significant *P*-values are displayed in bold. TKR = total knee replacement.

radiographic progressors while 34% were classified as non-radiographic progressors (Supplementary Table 3). Conversely, 14% of the individuals in the stable trajectory were classified as progressors and 86% as non-progressors according to the radiographic definition (kappa coefficient 0.402).

Discussion

In this study, we used an emerging statistical approach to identify distinct trajectories of cartilage thickness over 2 years and develop a prediction model to identify individuals following progressive cartilage loss trajectories. Understanding the heterogeneous course of OA as well as predicting progression was highlighted as a research priority in OA[42] and has become a growing research focus more recently. LCGA has been increasingly used in OA research as it is a useful statistical technique to model heterogeneity "by classifying individuals into groupings with similar patterns" using longitudinal data[34]. To our knowledge this is the first study to use quantitative cartilage thickness detected on MRI to identify trajectories of structural progression. We additionally used a comprehensive set of baseline patient and disease characteristics to characterize the individuals in each trajectory and develop a model to predict progression. We found that cartilage thickness remained relatively stable in the vast majority of participants, while a minority demonstrated moderate or substantial cartilage loss which was significantly associated with adverse clinical outcomes. The prediction model included WOMAC pain scores, family history of TKR, radiographic medial JSN, pain duration and obesity and would be easily applicable in future studies.

A few limitations of this study need to be mentioned. We included individuals from two distinct sub-studies within OAI with different inclusion criteria. Particularly for the FNIH study, a pre-

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Table IV
Univariable and multivariable logistic regression. Odds for belonging in the progression subgroup (trajectories 2 and 3) compared to the non-progression subgroup (trajectory 1)

	Univariable analysis		Multivariable analysis	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Baseline WOMAC pain	1.02 (1.01, 1.03)	**<0.001**	1.02 (1.01, 1.03)	**<0.001**
Family history	1.60 (1.02, 2.53)	**0.040**	2.15 (1.22, 3.78)	**0.008**
Obesity*	1.70 (1.15, 2.50)	**0.007**	1.69 (1.03, 2.79)	**0.037**
Baseline medial JSN†				
0	Ref		Ref	
≥1	5.74 (3.04, 10.82)	**<0.001**	10.75 (4.22, 27.42)	**<0.001**
Pain duration				
More than 1 year	Ref		Ref	
1 year or less	2.04 (1.18, 3.52)	**0.010**	2.16 (1.19, 3.92)	**0.011**
Alignment	1.30 (1.19, 1.42)	**<0.001**		
Intra-articular glucocorticoid injection past 6 months	4.65 (1.88, 11.47)	**0.001**		
Radiographic OA contralateral knee	2.01 (1.29, 3.11)	**0.002**		
Age	1.02 (0.99, 1.03)	**0.146**		
Gender (female)	1.16 (0.79, 1.72)	0.430		
Race				
White or Caucasian	Ref			
Others	1.03 (0.66, 1.61)	0.875		
Baseline KLG				
1	Ref			
2	1.42 (0.68, 1.96)	0.348		
3 or 4	1.14 (0.53, 2.42)	0.783		
Knee injury	0.97 (0.66, 1.44)	0.904		
Knee surgery	0.97 (0.61, 1.55)	0.923		
Quadriceps strength	1.00 (0.99, 1.00)	0.725		
Physically active	0.99 (0.59, 1.68)	0.992		
Presence of hand OA	1.06 (0.67, 1.69)	0.791		
Comorbidities, >1	1.07 (0.70, 1.62)	0.753		

Variables with a *P* value <0.2 in the univariate analysis were included in the multivariate regression model. Statistically significant *P*-values are displayed in bold.
* Obesity was defined as BMI ≥30 kg/m2.
† Medial tibiofemoral joint space narrowing. WOMAC = Western Ontario & McMaster Universities Osteoarthritis Index; JSN = joint space narrowing; KLG = Kellgren and Lawrence grade.

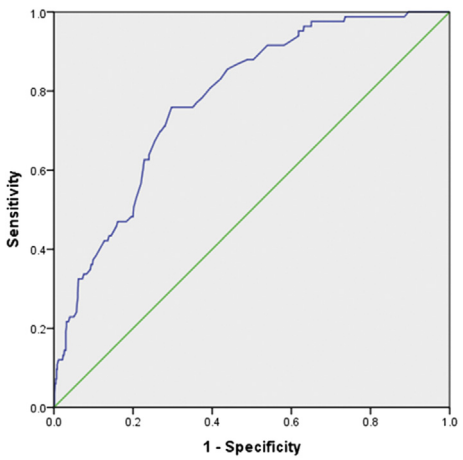

Fig. 2. ROC curve of significant baseline characteristics (final multivariate model) for predicting cartilage loss progression on MRI over 2 years. *Footnote*: Model included baseline WOMAC knee pain, radiographic JSN, family history of TKR, obesity and pain duration. Bootstrapped AUC = 0.79, 95% CI 0.74 to 0.84.

specified number of radiographic and pain progressors was selected and it is unclear if the results would have been different in an unselected OA population. However, we found very similar trajectories when the LCGA was performed separately in each substudy, supporting validity of this trajectory model. It is of note that despite the inclusion of the FNIH study data, the rate of progression to TKR was low which may be related to the relatively short follow up duration and to the fact that most individuals had mild to moderate OA at baseline. Furthermore, we used bootstrapping for internal validation of the prediction model. Nevertheless, there was no other large longitudinal cohort with publicly accessible MRI data for quantitative cartilage measures to follow the preferred approach of external validation. Such external validation in a similar population (predominantly mild to moderate radiographic OA) is necessary before our model could be tested for selecting patients in clinical studies. In addition, as posterior probabilities were lower than 1.0, certainty that individuals were classified into the correct trajectory-based subgroup is not 100% and misclassification cannot completely be ruled out. However, as all posterior probabilities were high (≥0.87) it is unlikely that this substantially affected the results. Finally, although LCGA is a data-driven technique, the final selection of trajectories is based on a combination of fit indices and pragmatic reasoning[35]. This relative subjectivity may create differences in results across studies using similar approaches. Although we combined the two trajectories of progression in the second step of our analysis, a two-trajectory model would have resulted in miss-classification of these individuals across both stable and progression subgroups.

Although there is no widely accepted cut-off defining what a significant change in cartilage thickness on MRI is[15], the mean change in the stable trajectory (mean = −0.08 ± 0.19) was similar to previously observed changes in the FNIH study in individuals classified as non-progressors according to clinical and radiographic criteria (mean = −0.12 ± 0.28)[43], supporting that the change in this trajectory is unlikely to be clinically important. In contrast, the trajectories with moderate (mean = −0.75 ± 0.16) or greatest decline (mean = −1.38 ± 0.22) displayed substantial cartilage thinning which was independent of baseline KLG but significantly associated with baseline medial JSN score. As an interesting finding, the subgroup with moderate decline had lower baseline cartilage thickness compared to the stable trajectory group; however, this

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was not observed for the greatest decline trajectory. In addition, there was great variation in baseline cartilage thickness among individuals experiencing similar rates of progression. These observations support that, besides baseline disease status, other patient and disease characteristics may influence the trajectory of cartilage loss and may aid in the identification of individuals at risk for progression[23,25,26].

In another study, Bartlett *et al.* identified seven trajectories of radiographic JSW in knee OA individuals using group-based trajectory modelling, four of them (70% of the population) with no significant JSW loss over 2 years. Similar to our findings, baseline pain was greater in the progression subgroups. In addition, individuals with intermediate rates of progression (i.e., slow and moderate progression) were predominantly females, while males outnumbered females in the greatest decline group[1]. A direct relationship between baseline knee pain and cartilage loss progression has also been found in studies using cartilage thickness on MRI[44,45], although not in others[46]. In our study, baseline knee pain according to the WOMAC pain subscale was an independent predictor of progression despite adjustment for baseline medial JSN score in the multivariable model.

A few studies have previously developed prediction models for incident radiographic and/or symptomatic knee OA[25,47–50], knee OA progression[25,51,52] and incident knee OA with fast progression[26]. Most studies used easily available demographic, clinical and radiographic characteristics to facilitate implementation of the models in the clinical and research settings. Different definitions of progression were used across these studies, such as an increase in KLG ($\geq$1 grade)[25] and any increase in medial radiographic semi-quantitative JSN score[52]. In contrast to these studies, we first used a data-driven approach to identify trajectories of progression sharing similar rates of cartilage thickness on MRI and subsequently developed a prediction model to identify individuals belonging to the trajectories displaying moderate or substantial cartilage loss. The robust associations between the trajectory-based subgroups and clinical outcomes corroborate the meaningfulness and clinical relevance of this approach and support a relationship between structural progression (i.e., cartilage loss) and symptomatic OA progression. We focused our analysis on baseline characteristics that would be easily obtainable in the clinical and/or research settings. A previous study showed that adding genetic, biochemical and other questionnaire data on general health and disability did not change significantly the prediction value of a model including only demographic characteristics to predict incident knee OA[49]. Interestingly, we found that individuals with shorter pain duration (i.e., one year or less) were much more likely to lose cartilage over 2 years compared with those with longer disease duration.

We found that one-third of the individuals in the progression trajectories were classified as non-progressors according to the standard radiographic criteria based on changes in minimum JSW. Direct comparisons of the sensitivity to change of minimum medial JSW loss and quantitative MRI measurements of cartilage loss have shown greater responsiveness of MRI measures, particularly when assessed in the central medial tibiofemoral compartment[10,15]. Although there may be differences in location of assessment between the two imaging methods in our study, our findings suggest that classifying progression status based on radiographic criteria might result in misclassification, which is relevant for studies using this measure as a structural endpoint.

In conclusion, this data-driven approach revealed that individuals in this population with or at risk of knee OA follow one of three main cartilage thickness trajectories assessed quantitatively on MRI over 2 years. While most individuals had no or minimal loss of cartilage, those in the trajectories of moderate or substantial cartilage loss were more likely to experience worse clinical outcomes, supporting an influence of structural progression on symptoms and emphasizing the need for better treatment stratification for targeted treatment in future studies. Among a comprehensive set of possible determinants of progression assessed at baseline, presence of radiographic medial JSN, higher WOMAC knee pain score, family history of TKR, obesity and pain duration $\leq$1 year were predictive of cartilage loss progression trajectories, with good discriminant ability of the final model. After external validation, this model may help selecting patients more likely to experience cartilage loss who would potentially benefit from cartilage-targeted therapies.

Authors contribution

LAD, AD and DJH contributed to the study conception and design. LAD conducted the data analyses; AD and JGTP provided input to the LCGA. All authors contributed to the interpretation of the data and LAD wrote the first draft of the manuscript. All authors revised it critically for important intellectual content and read and approved the final manuscript.

Conflict of interest

LAD, WVS and AD declare no competing interests. DJH reports personal fees from Merck Serono, Flexion and Tissuegene. FE reports grants from Foundation of the NIH and NIH; grants and personal fees from Merck, Servier and Samumed, personal fees from Roche, Abbvie and Medtronic; grants from Tissuegene and Orthotrophix/BICL. Dr Tamez-Pena reports personal fees from Qmetrics Technologies, outside the submitted work.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2018.09.015.

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