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ORIGINAL ARTICLE

Short-term pain trajectories in patients with knee osteoarthritis

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Abstract

Aim: It is unknown if pain in knee osteoarthritis (KOA) follows distinct patterns over the short term. Therefore, the aim of this study was to identify whether persons with a previous history of KOA pain fluctuations have distinct trajectories of pain over 90 days and to examine associations between baseline characteristics and pain trajectories.

Method: People with a previous history of KOA were selected from a web-based longitudinal study. Baseline variables were sex, age, being obese/overweight, years of KOA, knee injury, knee buckling, satisfactory Lubben Social Support Score, pain and stress scales, Intermittent Constant Osteoarthritis Pain Score (ICOAP), medication use, and physical activity. Participants completed a Knee Injury and Osteoarthritis Outcomes Score (KOOS) pain subscale (KOOS-p, rated 0 = extreme to 100 = no knee problems) at 10-day intervals for 90 days. Short-term KOOS-p trajectories were identified using latent growth mixture modeling and the baseline risk factors for these pain trajectories were examined.

Results: Participants (n = 313) had a mean age of 62.2 (SD ± 8.1) years and and a body mass index of 29.8 (SD ± 6.6) kg/m^2. The three-class latent growth mixture modeling quadratic model with best fit indices was chosen (based on lowest sample-size-adjusted Bayesian Information Criterion, high probability of belonging, interpretability). Three distinct pain trajectory clusters (over 90 days) were identified: low-moderate pain at baseline with large improvement (n = 11), minimal change in pain over 90 days (n = 248), and moderate-high pain with worsening (n = 46). Higher ICOAP (intermittent scale), perceived stress, negative affect score, and knee buckling at baseline were associated with a worse knee pain trajectory ($P < 0.05$).

Conclusions: Persons with KOA showed unique short-term pain trajectories over 90 days, with distinct characteristics at baseline associated with each trajectory.

KEYWORD
knee joint osteoarthritis pain, short-term pain, trajectory,

1 | INTRODUCTION

Pain is the dominant symptom in knee osteoarthritis (KOA) and is the main reason that people seek health care. The evolution of pain in KOA has been the subject of considerable interest because improved understanding of the pattern of longitudinal pain progression would better inform the pathogenesis of this disease, as KOA is essentially still without a cure. Previous studies of individuals with KOA, assessing pain at 12-18 month intervals, demonstrated that the stereotype portraying KOA as being slowly progressive is most likely inaccurate and that mild or improving symptom trajectories are present in a minority.[1] Further, it is unknown if fluctuations of knee pain over a short time period in individuals with symptomatic KOA follow distinct patterns, and which risk factor(s) are attributed to short-term pain fluctuation. As KOA pain fluctuations (KOAF) are disabling and negatively impact a person's life, limiting social participation and engagement, knowledge of short-term pain trajectories will provide valuable insights into the individual experience of pain in KOA.[2] It is envisaged that further knowledge on KOAF pain trajectories will provide valuable information for clinicians to counsel and educate patients and healthcare resource allocators to plan and organize healthcare services; and will give researchers more insight on the pathogenetic process that occurs in the initial phases in individuals who experience KOAF, who potentially have earlier stages of KOA.[3]

Large-scale studies on KOA pain trajectories have mainly explored long-term KOA pain trajectories.[4-7] Short-term changes in pain, for example periods of less than 3 months,[8] particularly in those with KOAF, are less well understood.[9] Exploration of short-term changes in pain provides the opportunity to identify modifiable risk factors early in the disease process, through characterization of early progressors, which may later inform management strategies. Therefore, it is pertinent to examine pain at shorter intervals in order to meaningfully ascertain the shorter-term pain patterns in KOA, especially in those reporting KOAF, to develop a full understanding of the disease. The aim of our study was to describe the trajectory of the Knee Injury and Osteoarthritis Outcomes Score pain (KOOS-p) scores in a group of individuals from the SPARK-Web Study at 10-day intervals over 90 days and examine the risk factors for these trajectories.[10]

2 | MATERIALS AND METHODS

Data were obtained from SPARK-web (web-based study of risk factors for pain exacerbation in KOA), an Australian longitudinal study, designed to examine associations between risk factors and pain exacerbation in KOA.[10] This study recruited individuals with a previous diagnosis of symptomatic KOA from existing databases or social media and followed the individuals longitudinally for 3 months collecting data including the KOOS at 10-day intervals (control points) and at points of flare. Data were collected via a specially constructed secure website designed to obtain self-reported information of risk factors.

The study inclusion criteria were as follows: persons aged more than 40 years,with an active email address with internet connectivity, who had experienced knee pain in at least one knee for most days in the preceding month with fluctuations in the level of knee pain.[10] In addition, it was necessary for those selected to have not had/have no plans for a knee joint replacement in the most painful knee. Those diagnosed with inflammatory joint disease or fibromyalgia were excluded.[10]

The participants' most recent knee radiographs were evaluated by the study physician as only persons with radiographic tibiofemoral osteoarthritis (at least Kellgren and Lawrence grade ≥2) or patellofemoral osteoarthritis on radiograph were recruited for the study as part of the eligibility criteria.

2.1 | Assessment of outcome

We used the KOOS score, a valid and reliable knee-specific instrument that was developed with the intent of assessing patient self-report on their KOA-related problems.[11,12] The KOOS examines 42 items, which are examined within five subscales. Each of these five subscales; Pain (KOOS-p), Symptoms, Function in daily living, Function in Sports and Recreation, and knee-related Quality of Life; are scored separately by a Likert scale with five possible options (0 = No problems to 4 = Extreme problems). Each subscale is calculated by the sum of the items that were included in it. These scores are then transformed on a 0–100 scale with 0 and 100 representing extreme knee problems and no knee problems, respectively.[11,12] This project examined the trajectory of KOOS-p subscales, which were assessed every 10 days for a period of 3 months.

2.2 | Assessment of risk factors

Participant characteristics evaluated at baseline were chosen a priori based on importance to understanding KOA and KOAF[10,13] and their potential to describe identified clusters. These included the following demographic variables: age (years), race (white Australian/Asian/other), weight (kg), and height (cm) (from which body mass index was calculated); and pain scores; background/usual and worst pain reported at baseline (on a 0–10 point numeric rating scale). In addition, information on whether an injury to the index knee occurred in the preceding 7 days or whether any buckling of the index knee happened during the preceding 2 days was assessed. The Intermittent and Constant Osteoarthritis Pain Score (ICOAP), which evaluates constant pain and intermittent pain (or "pain that comes and goes") by two separate subscales (0-100).[2] The Positive/Negative Affect Scores (score from 10 to 50), which assesss psychological/mood-related factors; the Perceived Stress Score (score from 0 to 40), which measures an individual's appraisal of their level of stress; and the Lubben Social Support Score (satisfactory score >12), a self-reported measure of social engagement[14-18] were assessed at baseline using previously validated questionanaires. The medication use

during the previous week was assessed and classified as daily, none, or intermittent. Similarly, self-reported physical activity during the previous week (using the previously validated Seven-Day Physical Activity Recall questionnaire) was assessed at baseline,[19] and the physical activity was classified as mild physical activity only or any moderate or any vigorous activity.[20]

Ethical approval was obtained from the University of Sydney Human Ethics Committee (Protocol No.: 14 435), University of Melbourne Human Research Ethics Committee (No. 0709220) and Radiation Safety Committee.

2.3 | Analysis

2.3.1 | Latent variable modeling

Latent variable longitudinal mixture modeling was used to explore the heterogeneity in KOOS-p scores over 90 days to classify individuals into unique groups ('classes' or 'clusters') based on their KOOS-p trajectory. A systematic approach to model selection was applied and followed the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) reporting guidelines[21] (Appendix 1). A three-class quadratic growth model based on latent growth mixture modeling (LGMM) was selected above others based on superior model fit indices (Akaike information criterion, sample-size-adjusted Bayesian Information Criterion, Vuong-Lo-Mendell-Rubin Likelihood Ratio Test) and a range of pragmatic criteria (entropy, probability of membership, and interpretation). Missing data for KOOS-p scores were handled under missing at random and estimated using maximum likelihood. No imputation of KOOS-p scores was undertaken (Appendix 1).

2.3.2 | Multinomial logistic regression

After short-term pain trajectories were determined, univariate multinomial logistic regression analysis was used to investigate the association (odds ratio) of baseline characteristic for each trajectory cluster compared with a reference trajectory with poorest progression.[22]

3 | RESULTS

3.1 | Sample characteristics

A total of 313 individuals were included in the study. These persons had a mean age of 62.2 (SD ± 8.1) years with a mean body mass index of 29.8 (SD ± 6.6) kg/m^2. They reported having a mean duration of 10.2 (SD ± 10.6) years of KOA. The description of the entire study cohort and the description of characteristics in the individual clusters derived from the final trajectory model are given in Table 1. The medians (interquartile ranges) for the ICOAP constant subscale and the intermittent subscale are 35 (15-50) and 41.2 (29.2-54.2), respectively. The medians (interquartile ranges) for KOOS-p, KOOS-symptoms, KOOS-activities of daily living, KOOS-sport/recreation, and KOOS-quality of life were 55.6 (44.4-66.7), 42.8 (35.7-53.6), 63.2 (48.5-77.9), 15 (0-32.5), and 43.8 (31.2-56.3), respectively.

3.2 | Selection of a latent variable model

Model fit was tested for one to five trajectories using latent class growth analysis (LCGA) and LGMM, with both linear and quadratic growth curves tested (20 models in total), from which a single model was selected. All modeling used KOOS scores as the dependent variable. We used 100 random sets of starting values in the initial stage with 20 final-stage optimizations for each of the 20 separate models[23] (Table A1).

3.3 | Characteristics of cluster membership and between-cluster comparison

Table 1 describes the characteristics of individuals classified into each cluster in the three-trajectory model. Figure 1 shows both the averaged and individual trajectory patterns for each cluster in the final model (Figure A1 in the Appendix shows Averaged KOOS-p scores with 95% CI for each cluster). Figure 2(A, B) show the mean and individual KOOS trajectories for individuals assigned to each cluster in the final model with panel A depicting the KOOS scores reported by individuals and panel B showing the KOOS scores predicted by the growth model.

Cluster 1 (Low-moderate pain with large improvement over 90 days) comprised the smallest group of individuals (n = 11, average probability of belonging = 0.86) and was characterized by a baseline average KOOS score of 54.5 (SD ± 17.2), followed by large improvement over the study period (Day 90 KOOS score 78.3 (SD ± 16.0)).

Cluster 2 (Minimal change in pain over 90 days) comprised the largest group of individuals (n = 248, $P = 0.90$) and was characterized by a baseline average KOOS score of 62.5 (SD ± 8.1) followed by a small increase in average pain or relative stability over the study period (Day 90 KOOS score 63.7 [SD 14.5]).

Cluster 3 (Moderate-high pain with worsening over 90 days) comprised a group of individuals (n = 46, $P = 0.78$) who were characterized by a baseline average KOOS score of 38.2 (SD ± 12.7) followed by minimal worsening over the study period (Day 90 KOOS score 31.9 [SD ± 13.4]).

3.4 | Comparison of cluster membership characteristics

Table 2 reports the odds ratios (OR) for baseline characteristics for Clusters 1 and 2 compared with Cluster 3. No apparent associations were observed between sex, age over 65 years, social

TABLE 1 Baseline characteristics for the whole population and each cluster in the final three-cluster model

Variable	Pain improving Cluster 1 (n = 11)	Pain stable Cluster 2 (n = 248)	Pain worsening Cluster 3 (n = 46)	*P* value[b]
Continuous variables	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Demographics				
Age, y	61.1 (6.5)	62.5 (8.1)	60.7 (8.1)	0.347
Years since KOA diagnosis	9.7 (11.5)	10.0 (10.2)	11.8 (12.5)	0.58
Body mass index, kg/m^2	26.9 (2.8)	29.3 (6.2)	33.6 (2.8)	<0.001
Pain levels				
Background level of pain[a]	4.8 (2.2)	3.9 (1.8)	6.3 (1.6)	<0.001
Worst level of pain	8.5 (1.1)	7.7 (1.7)	9 (1.0)	<0.001
Intermittent constant osteoarthritis pain score (ICOAP)				
ICOAP (constant subscale)	43.6 (23.2)	27.7 (21.4)	60.9 (22.9)	<0.001
ICOAP (intermittent subscale)	40.9 (24.6)	37.2 (18.7)	61.6 (20.6)	<0.001
ICOAP (total score)	42.1 (23.1)	32.9 (17.8)	61.3 (18.7)	<0.001
Positive-negative affect scores				
Positive affect score	36.4 (9.9)	34.6 (7.7)	31.4 (7.6)	0.025
Negative affect score	14.5 (0.7.8)	15.8 (5.7)	19.9 (8.0)	<0.001
KOOS subscales				
KOOS pain	54.5 (17.2)	58.9 (14.5)	38.2 (12.7)	<0.001
KOOS symptoms	43.8 (10.4)	45.6 (12.1)	37.6 (15.6)	<0.001
KOOS activities of daily living	62.0 (22.9)	66.9 (16.3)	40.6 (15.5)	<0.001
KOOS sport and recreation	18.2 (14.0)	25.0 (24.2)	6.5 (9.3)	<0.001
KOOS quality of life	32.4 (16.5.)	43.6 (16.5)	24.6 (15.7)	<0.001
Perceived stress scale	10.8 (8.4)	12.8 (6.7)	17.8 (7.8)	<0.001
Dichotomous variables	**N (%)**	**N (%)**	**N (%)**	
Female	5 (45.4)	153 (61.7)	31 (67.4)	0.396
Race				
White Australian	10 (90.9)	233 (94.7)	41 (89.1)	0.29
Asian	1 (9.1)	8 (3.2)	2 (4.4)	
Other	–	5 (2.0)	3 (6.5)	
Injury (yes)	2 (18.2)	9 (3.6)	4 (8.7)	0.029
Knee buckling (yes)	2 (18.2)	42 (16.9)	16 (34.8)	0.020
Obese/overweight (yes)	9 (81.8)	194 (78.2)	40 (87.0)	0.395
Satisfactory Lubben Score	7 (63.6)	175 (70.6)	33 (71.7)	0.868
Medication during past week				
None	8 (72.7)	149 (58.7)	14 (29.2)	<0.001
Intermittent	2 (18.2)	52 (20.5)	11 (22.9)	
Daily	1 (9.1)	53 (20.9)	23 (47.9)	
Physical activity category				
Mild physical activity only	5 (45.4)	4 (1.6)	2 (4.4)	0.684
Any moderate physical activity	6 (54.6)	112 (45.2)	21 (45.7)	
Any vigorous physical activity	–	132 (53.2)	23 (50.0)	

[a]The numeric rating scale 0-10 was used to assess background and worse levels of pain.

[b]Analysis of variance was used for continuous variables, chi-square test for dichotomous (or exact test if chi-square assumptions were not met).

support, and years of osteoarthritis with short-term pain trajectories. However, individuals with higher intermittent ICOAP pain subscales were less likely to be in Cluster 1 (OR 0.90, 95% CI 0.81-0.99) and Cluster 2 (OR 0.88 95% CI 0.83-0.94) than to be in Cluster 3. Interestingly, individuals in Cluster 2 were less likely to have high constant ICOAP subscales than Cluster 3 (OR 0.87, 95% CI 0.80-0.96) though a similar difference was not detected between Cluster 3 and Cluster 1.

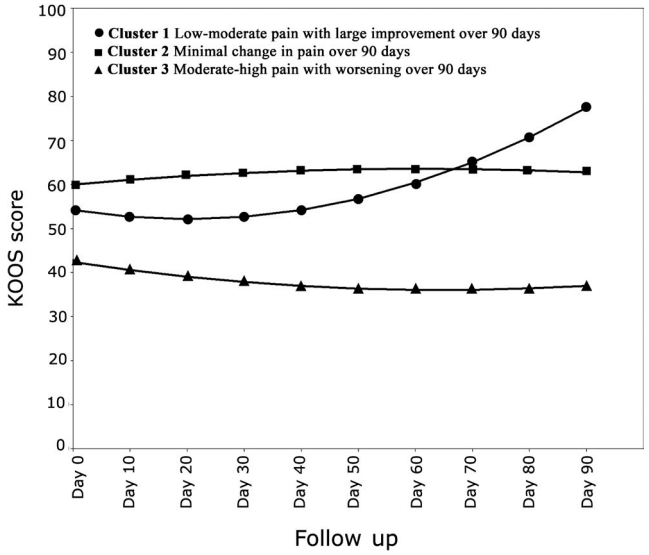

FIGURE 1 KOOS trajectory for individuals assigned to each cluster in the final model

Compared with Cluster 3, individuals in Cluster 1 and Cluster 2 were less likely to have higher negative affect scores (OR 0.46, 95% CI 0.31-0.70; OR 0.88, 95% CI 0.82-0.95, respectively), higher perceived stress (OR 0.79, 95% CI 0.64-0.98; OR 0.86, 95% CI 0.78-0.95), and higher pain scores (OR 0.57, 95% CI 0.33-0.98; OR 0.39, 95% CI 0.29-0.51).

Individuals in Cluster 2 were less likely to report a recent knee injury compared with individuals in Cluster 3 (OR 0.24, 95% CI 0.13-0.47), but there was no difference between Cluster 1 and Cluster 3 in terms of recent injury. On average, individuals in Cluster 1 and Cluster 2 were less likely to have knee buckling than those in Cluster 3 (OR 0.32, 95% CI 0.15-0.68; OR 0.26 95% CI 0.18-0.38, respectively). Similarly, individuals in Cluster 2 were less likely to be obese or overweight when compared with Cluster 3 (OR 0.38, 95% CI 0.22-0.68).

4 | DISCUSSION

This study identified three distinct short-term pain trajectories among individuals with symptomatic KOA over 90 days. Unlike

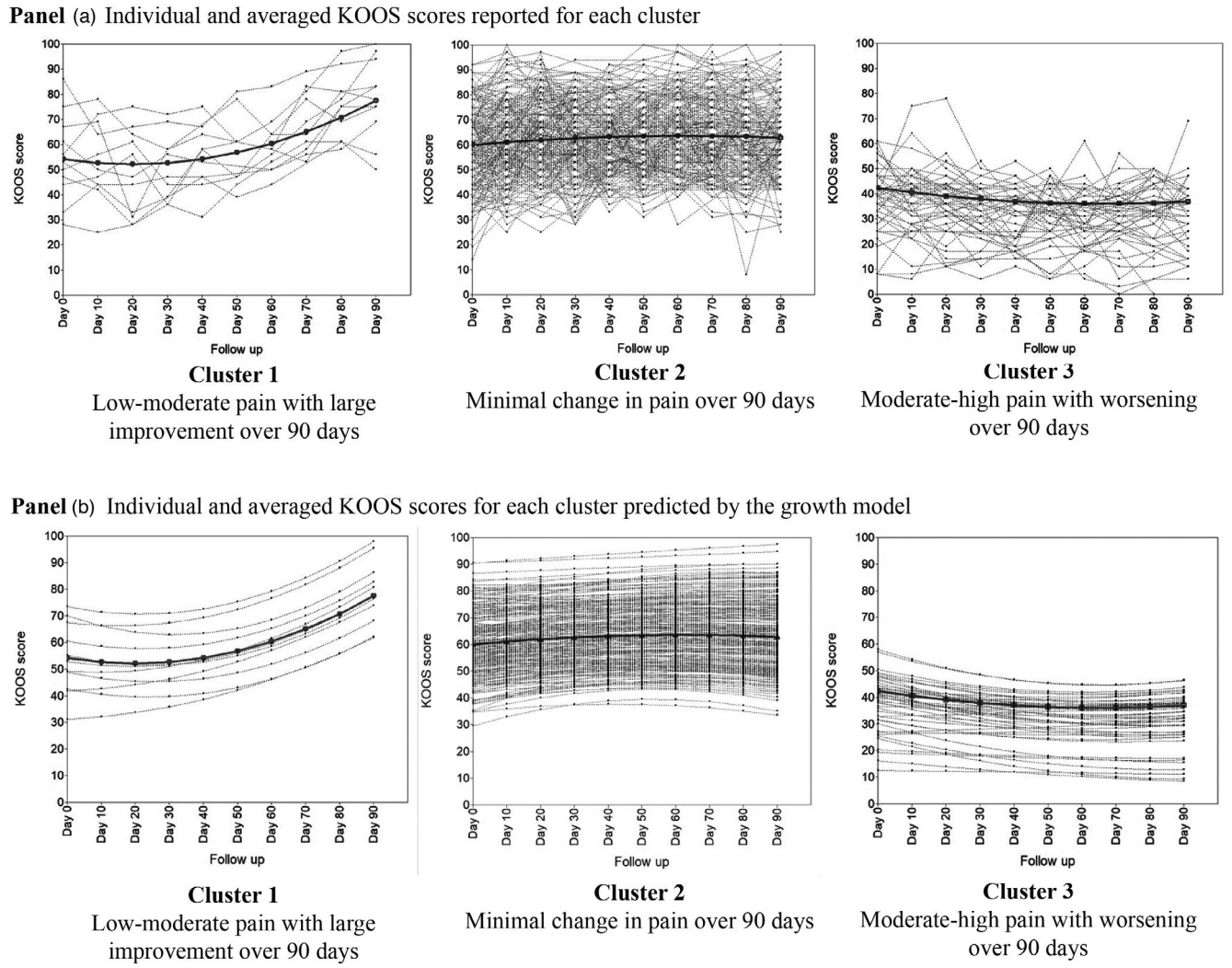

FIGURE 2 Mean and individual KOOS-pain trajectory for individuals assigned to each cluster in the final model

TABLE 2 Univariate multinomial logistic regression using three-step analysis (Cluster 3 as reference)

Baseline factor		Comparator	Odds ratio	95% CI	*P* value
Sex (female = 1)	n = 305*	Cluster 1 v 3	0.33	0.06-1.72	0.105
		Cluster 2 v 3	0.71	0.27-1.87	0.406
Age (≥65 y = 1)	n = 305*	Cluster 1 v 3	2.80	0.02-434.80	0.461
		Cluster 2 v 3	2.68	0.14-49.75	0.256
Years since diagnosis of KOA (continuous)	n = 303*	Cluster 1 v 3	0.98	0.90-1.06	0.615
		Cluster 2 v 3	0.98	0.95-1.02	0.287
Body mass index (obese/overweight = 1)	n = 313	Cluster 1 v 3	0.50	0.22-1.15	0.406
		Cluster 2 v 3	0.38	0.22-0.68	**0.037**
Background level of pain reported (continuous) (0-10 NRS)[a]	n = 303*	Cluster 1 v 3	0.57	0.33-0.98	**0.006**
		Cluster 2 v 3	0.39	0.29-0.51	**<0.001**
Worst level of pain reported (continuous) (0-10 NRS)[a]	n = 313	Cluster 1 v 3	0.28	0.15-0.54	**0.005**
		Cluster 2 v 3	0.15	0.15-0.54	**<0.001**
Perceived stress score-10 (continuous) (0-40)	n = 313	Cluster 1 v 3	0.79	0.64-0.98	**0.017**
		Cluster 2 v 3	0.86	0.78-0.95	**0.001**
ICOAP-intermittent (continuous) (0-100)	n = 303*	Cluster 1 v 3	0.90	0.81-0.99	**0.033**
		Cluster 2 v 3	0.88	0.83-0.94	**<0.001**
ICOAP-constant (continuous) (0-100)	n = 303*	Cluster 1 v 3	0.91	0.81-1.04	0.154
		Cluster 2 v 3	0.87	0.79-0.96	**0.002**
ICOAP-total (continuous) (0-100)	n = 303*	Cluster 1 v 3	0.91	0.80-1.04	0.147
		Cluster 2 v 3	0.87	0.80-0.96	**0.003**
Positive affect Score (continuous) (10-50)	n = 313	Cluster 1 v 3	1.12	0.92-1.36	0.272
		Cluster 2 v 3	1.07	1.02-1.13	**0.014**
Negative affect Score (continuous) (10-50)	n = 305*	Cluster 1 v 3	0.46	0.31-0.70	**<0.001**
		Cluster 2 v 3	0.88	0.82-0.95	**<0.001**
KOOS pain (0-100)[b]	n = 313	Cluster 1 v 3	1.13	1.02-1.26	**0.031**
		Cluster 2 v 3	1.18	1.11-1.26	**<0.001**
KOOS symptoms (0-100)[b]	n = 313	Cluster 1 v 3	1.06	0.10-1.13	0.067
		Cluster 2 v 3	1.08	1.02-1.14	**0.008**
KOOS activities of daily living (0-100)[b]	n = 313	Cluster 1 v 3	1.11	1.01-1.20	**0.03**
		Cluster 2 v 3	1.14	1.10-1.18	**<0.001**
KOOS sports and recreation (0-100)[b]	n = 313	Cluster 1 v 3	1.09	1.02-1.17	**0.017**
		Cluster 2 v 3	1.11	1.04-1.19	**0.003**
KOOS quality of life (0-100)[b]	n = 313	Cluster 1 v 3	1.04	0.10-1.09	0.141
		Cluster 2 v 3	1.10	1.07-1.14	**<0.001**
Knee injury (yes=1)	n = 305*	Cluster 1 v 3	2.30	0.04-130.0	0.589
		Cluster 2 v 3	0.24	0.13-0.47	**0.001**
Knee buckling (yes =1)	n = 305*	Cluster 1 v 3	0.32	0.15-0.68	**0.039**
		Cluster 2 v 3	0.26	0.18-0.38	**<0.001**
Satisfactory Lubben Social Support Score (yes = 1)	n = 305*	Cluster 1 v 3	0.64	0.39-1.05	0.511
		Cluster 2 v 3	0.93	0.84-1.02	0.878
Any use of medication over the previous week	n = 313	Cluster 1 v 3	0.08	0.05-0.12	**<0.001**
		Cluster 2 v 3	0.16	0.11-0.23	**<0.001**
Any vigorous physical activity over the previous week	n = 313	Cluster 1 v 3	1.26	0.78-2.07	0.798
		Cluster 2 v 3	1.20	0.98-1.46	0.715

Note: Missing data for covariates was not imputed.

[a]NRS-Numeric Rating Scale (0-10).

[b]KOOS (0-100, with 0 = extreme and 100 = no knee problems).

Bold indicates statistical significant $P < 0.05$).

previous studies on the subject, the unique feature of this study was that it was able to both identify pain trajectories of individuals who had previous pain fluctuations and examine their change in pain over a short period of time.[1,4,5] We found that the majority of individuals (n = 248) reported minmal change in their pain on average, over the study period. The second largest cluster (n = 46) reported on average moderate-high pain that worsened, whereas the third and smallest cluster (n = 11) reported large improvement in pain over the study period. The characteristics of individuals allocated to each cluster were compared with characteristics of those in the cluster with the poorest outcome KOOS-p trajectory. This comparison identified that individuals in the cluster with the poorest outcome had a higher body mass index, poorer pain scores, higher negative affect, lower positive affect, higher perceived stress scores, and an increased propensity for buckling of knee or knee injury at baseline.

This study demonstrates that short-term pain trajectories in persons with previous KOAF are largely unaltered with a large cluster of individuals showing little improvement/deterioration in pain over 90 days. This contrasts with some of the previous studies on long-term pain trajectories in persons with KOA. Most assessed pain and physical function trajectories, but one study, with more than 3 years of follow up, identified four osteoarthritis phenotypes characterized by the following pain patterns: low-fluctuating pain, mild-increasing pain, and treatment sensitivity: moderate-treatment-sensitive and severe-treatment-insensitive pain.[24-26] In addition, another examined pain and physical function combined trajectories.[26] But, none of these studies examined short-term changes in pain, nor did they explore the pain trajectories in persons with previous KOAF. We selected individuals with a previous history of KOA pain fluctuations in the previous month; ie persons more prone to pain exacerbations; as our intent was to document pain trajectories in persons who have greater potential for pain progression. Pain fluctuation is a phenomenon that is possibly seen in earlier disease.[3] Therefore, the difference in our results when compared with the longer pain trajectories examined previously may be due to the different pathogenic mechanisms operational in KOAF compared with chronic KOA.[3,27]

Conceptually, knees with pain fluctuations (at least in the early stages) retain the capacity to resolve after a disruption/challenge to the baseline state[3] and it has been postulated that KOAF are of inflammatory origin and that these usually settle within a week.[28-31] As most cases of KOAF settle approximately within a week, it is felt that the 90-day pain trajectory was largely unaltered because pain resolves within the 10 days.[31] But it is noteworthy that in our study, these pain flucutations, in general, did not impact the short-term 90-day pain trajectory as a whole.

The differences we detected between the clusters are in keeping with existing knowledge on patient profiles observed in KOAF. Our study demonstrated that there was a difference in cluster membership based on pain trajectories in terms of knee injuries and buckling of knee, with individuals in the worsening pain cluster more likely to report recent injury or knee buckling than those in the small or large improvement clusters. This is in keeping with the current postulated mechanisms of KOAF, which are believed to be triggered by local perturbations in joint stress.[3,32] Similarly, individuals in the worsening pain cluster were more likely to be obese or overweight when compared with those in improving pain clusters. These findings further lend support to the micro-trauma KOAF relationship because heavier individuals are more likely to load the knee than others.[3,32,33]

The pain experience was different in the three clusters, with significant differences detected between clusters in terms of the ICOAP score. The ICOAP examines the constructs of 'constant' and 'intermittent' pain in KOA. It comprehensively evaluates the pain experience in KOA assessing pain (intensity, frequency) and the impact of pain on quality of life, mood, and sleep independently of physical function, and differentiates the pain experience between the intermittent and constant pain construct. As expected, the ICOAP intermittent subscale was significantly different between the three clusters, whereas the ICOAP constant subscale was only significantly different between Cluster 3 and Cluster 2. This finding adds strength to the different clusters identified by the trajectory analysis by demonstrating that these clusters are indeed different using previously validated robust measures used in osteoarthritis studies.

There were notable differences in negative affect between the clusters and we demonstrated that persons in Cluster 1 and Cluster 2 were less likely to have higher negative affect scores and higher pain scores compared with Cluster 3. It has been demonstrated that poorer mood and lower pain thresholds are associated with KOA pain.[34-36] Negative affect, in particular, has been demonstrated to be associated with clinically perceived pain in osteoarthritis as well as pain in other musculoskeletal diseases.[37-39] In addition, this study demonstrated a significantly higher positive affect between those with Cluster 2 compared with those with Cluster 3. Loss of positive affect makes a person more vulnerable to negative affect; whereas an increase in positive affect improves resilience and buffers a person from negative affect, which explains these findings in Cluster 3.[38,40] Further, a short-term increase in positive affect may dampen the effects of pain by minimizing and reducing the sensitization gating of central pain processing pathways.[40] There were significantly higher perceived stress scores in Cluster 3 compared with Clusters 1 and 2. This is in keeping with previous findings that perceived that stress scores play a role in pain perception.[37] All of these characteristics of our identified clusters are compatible with the study population and add further support to the findings of previous studies.[4]

Our study did not find a difference between the three clusters with regard to years of KOA, age over 65 years, female sex, and social support. This is in contrast to other longer-term pain trajectory studies, which assessed persons at yearly intervals and demonstrated that the participants in older age groups were more likely to have worse pain trajectories than those with minimal pain.[4,26] Another study that assessed participants annually found that younger age was associated with a poorer activity limitation trajectory. It is likely that the effect of age is more likely to be seen only in studies with longer assessment points than the short-term assessment in ours. There were no previous studies that assessed the association between years of osteoarthritis with cluster membership.

The key strengths of our study are that it was conducted in a targeted population with KOA, with distinct and narrow eligibility criteria, in a cohort who also had a history of previous KOAF. We believe that examining this targeted study population facilitates an important deeper understanding of the pain trajectory in persons with a tendency to have KOAF. In addition, this study has examined this population at smaller 10-day time intervals, thereby giving a better perspective of the pain trajectory in the short-term, which we feel is better suited to identify our study question. The 10-day assessment interval permitted better applicability of the KOOS-p instrument, which is designed to capture symptoms and disabilities in the preceding 7 days.[41] Robust methodology in accordance with the GRoLTS checklist was applied to explore heterogeneity in the study population and to identify distinct trajectories based on KOOS-p score (Appendix 1). Thereafter the characteristics of each cluster were described.[21] This approach uncovered unique patterns of pain progression in the short-term, which have not been documented previously in the literature. The majority of previous studies have focused on much longer pain windows of 3 months or more and there are no studies to date that have focused on a shorter window of pain evolution, ie time-points as short as 10 days.

This study has the following limitations. First, this study collected data from a pre-existing cohort in a relatively smaller group of participants compared with other studies. The reason for this sample size is in part due to one of the advantages of the study, in that it assessed data in real time and at shorter time intervals. It is not feasible to study individuals at this frequency of reporting using larger sample sizes because of participant burden and financial constraints. Assessing individuals at closer intervals in turn increases the validity and reduces recall bias while creating the potential to examine a smaller window of time than previous studies. In addition, this study was carried out in a predominantly White Australian population with ready access to the internet and may need replication in other more varied populations, ideally with a larger sample size.

Although the cluster with large pain improvement (n = 11) was small, the decision to adopt the model that included the smallest cluster was based both on model fit statistics and on clinical importance, especially given that this cluster showed a large improvement in pain over 90 days. Accordingly, further investigations are needed to verify the trajectory patterns observed in our study, especially that of the cluster with greater pain improvement over a short period. It is significant that pain improvement was detected at all within this relatively small window of 10 days of observation, even in this small sample size.

Cluster 3 had higher levels of pain at baseline and showed a trend towards worsening over the following 90 days. It is noteworthy that longer assessment points (ie 2 years) have identified greater KOOS-p Minimum Clinically Important Difference (MCID) thresholds—particularly in surgical interventions—than that identified in our Cluster 3.[42,43] But there are no currently established thresholds to identify (MCID) in KOOS-p at short-term assessments As the three clusters in this study were identified by best-fit modeling using a robust methodology, characterized by different clinical characteristics compatible with current evidence, it is likely that smaller MCID are relevant in the shorter term.

This study does not seek to provide prediction of recovery, but does offer new information towards profiling individuals who are more likely to follow one of the identified three trajectories. However, it is noteworthy that only the univariate relationships of the characteristics of the clusters were examined. Therefore, the collinearity of predictor variables could not be ascertained.

In addition, a web-based study design was used in data collection. KOA is a disease of older persons, but many older persons may not be internet savvy. Therefore, it is possible that these findings may not be generalizable to the entire population of persons with osteoarthritis. However, web-based study designs have been used in the multiple rheumatological diseases that are prevalent in older individuals.[13] Therefore, these findings are considered as valid. In addition, there is a potential for recall bias with self-reported information. But, the real-time data collection, with regular reminders, may have minimized delays in reporting information. In addition, pain scores were collected at regular intervals, during control periods, reducing the potential for recall bias.

Despite these limitations, we assert that this study has identified three clinically meaningful pain clusters based on pain trajectories in this KOA cohort. The three clusters identified broadly agree with previous osteoarthritis research and extend this knowledge to provide unique insights into pain trajectories in persons who have fluctuating pain. This is useful for both clinicians and policy-makers in that these findings indicate that individuals with episodes of pain fluctuations have different trajectories and may need different levels of care and support. Similarly, researchers need to enrol larger cohorts of individuals with pain fluctuations to further investigate mechanisms underlying the heterogeneity that our study uncovered. We also recommend that further imaging, genetic and molecular studies be carried out to better understand the unique characteristics in these different phenotypes.

5 | CONCLUSIONS

In conclusion, this study demonstrated that the short-term pain trajectories in knee osteoarthritis diverge during a period as short as 90 days. Each cluster identified in this cohort was also described by characteristics at baseline.

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CONFLICT OF INTEREST

The work reported in this manuscript has not received any financial support or other benefits from commercial sources. The authors

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AUTHOR CONTRIBUTIONS

All authors fulfil the International Committee of Medical Journal Editors criteria for authorship.

DISCLOSURES

DJH provides consulting services on the scientific advisory board for Pfizer, Lilly, Kolon TG, and TLCBio.

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APPENDIX 1

MISSING DATA MECHANISM AND LATENT VARIABLE MODELING APPROACHES

Exploration of missing data

Most longitudinal studies are affected by drop-outs of participants and missing data points.[1,2] As the mechanism by which the data are missing can impact or bias findings, we examined the missing data patterns. The missing data mechanism was explored using Little's MCAR (missing completely at random) test and its extension to test the covariate-dependent missingness using STATA v15.1 (StataCorp, College Station, TX, USA).

Complete data were available for the first two time points. To identify the pattern of missingness across all other time points, we used Little's MCAR test and its extension to test the covariate-dependent missingness (CDM) STATA v15.1. Without inclusion of covariates the missing data were not MCAR (n = 313, χ^2 distance = 817, df = 2420, P = 0.0016). When the following covariates were added individually: age (<65 or >65 years), years of osteoarthritis, ICOAP (intermittent, constant, and total scores), positive negative affect score, usual level of background pain, or worst level of background pain reported at baseline, being overweight/obese, a satisfactory Lubben Social Support Score, knee injury or knee buckling in the 7 days or 2 days before, respectively, the missing data satisfied MCAR (all tests, $P > 0.9$). Similarly, when important covariates were considered together—age (<65 or >65 years), years of osteoarthritis, ICOAP (intermittent, constant, and total scores), positive negative affect score, usual level of background pain—the missing data satisfied MCAR (n = 301, χ^2 distance = 650, df = 1540, P = 1.0).

Latent variable modeling

Latent variable longitudinal mixture modeling was used to model the heterogeneity in KOOS-p scores over 90 days in an attempt to classify individuals into unique groups (classes or clusters) based on their KOOS-p trajectory. A systematic approach to modeling latent variables was explored as recommended by the Guidelines for Reporting Latent Trajectory Studies (GRoLTS) reporting guidelines.[3] Latent class growth analysis (LCGA) was followed by latent growth mixture modeling (LGMM). LCGA is a special type of LGMM, where the within-class variance of latent intercept and slope are fixed to zero within class (individuals vary only between classes), which leads to a solution where classes differ mainly by intercept (initial KOOS score).[4-6] In contrast, LGMM permits within-group variability for the latent intercepts and slope for each class (individuals can vary within and between classes), which leads to a solution where classes differ by both intercept and shape.[7] GMM is more computationally intensive, which can result in model convergence issues.[8-10] Both modeling approaches were explored in this data set using linear and quadratic growth curves.

For each model, individuals with similar trajectories were classified into a single class based on posterior probability.[11] The optimal number of classes considered both data-driven (goodness-of-fit indices) and pragmatic (model parsimony, model interpretability) criteria. Goodness-of-fit indices included the sample-size-adjusted Bayesian Information Criterion (sBIC) and Akaike information criterion (AIC) where lower values represent a better fitting model.[11] In addition, the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR LRT) and the Lo-Mendell-Rubin Adjusted Ratio Test (LMR-LRT) where the model with *k* classes is favored against the model with *k-1* classes, were used.[11,12] Models were then tested until no further improvement in model fit occurred (LRT $P \geq 0.05$). Pragmatic model selection criteria considered acceptable entropy values and posterior probabilities per cluster (>0.7), potential clinical relevance, cluster membership size in each model tested without pre-specifying a minimum cluster size, and other practical concerns (eg model convergence).[13] Mplus version 8 (Muthén & Muthén, Los Angeles, CA) was used for all latent class modeling. In MPlus, missing data for KOOS-p scores are handled using MAR with estimating using maximum likelihood. No imputation of KOOS-p scores was undertaken.

When all models were considered, the three-class LGMM-quadratic model was chosen based on the best fit indices: (lowest sBIC = 21 402), ideal VLMR-LRT (three-class vs two-class LGMM, P = 0.058); high posterior probability (0.81-0.91), and acceptable entropy (0.73). The three-class LGMM-quadratic model identified the greatest number of improvers (n = 11) over the study period (Figure A1). Compared with LCGA models, LGMM models had superior goodness-of-fit indices for both AIC and sBIC. The three-class LGMM-quadratic model had the best fit indices with a combination of the lowest sBIC (21 402.21), ideal VLMR-LRT (P = 0.058) and LMR-LRT (P = 0.065).

Models had an acceptable average posterior probability of belonging to each class and acceptable entropy (>0.7). All LCGA models had higher posterior probability and entropy than the LGMM models (which was expected because of LCGA fixing within-class variance to zero). Minimum class size ranged from 11 to 137 for LCGA models, and from 1 to 33 for LGMM models. In addition, LGMM models identified one cluster of individuals that had a large improvement in KOOS scores over the study period with the three-class quadratic model capturing the greatest number of improvers (n = 11). The quadratic model had superior fit indices compared with the linear model, which suggests that individuals improved at a greater rate later in the study period (Table A1).

Overall, the three-class LGMM-quadratic model was chosen based on the best fit indices, acceptable posterior probability and entropy, parsimony, and potential clinical relevance. Table A1 details the goodness-of-fit indices and trajectory characteristics for each model (Figure A1).

A split validation of the data set (sequential 1:1 allocation) was conducted to explore: (a) ideal number of clusters in each "split" sample" and (b) stability of class membership for each individual (ie were the individuals in each split data set classified differently compared with full data set). This process confirmed that the three-class model remained ideal in each split solution, and that the classification of participants compared with the full model was high (Table A2).

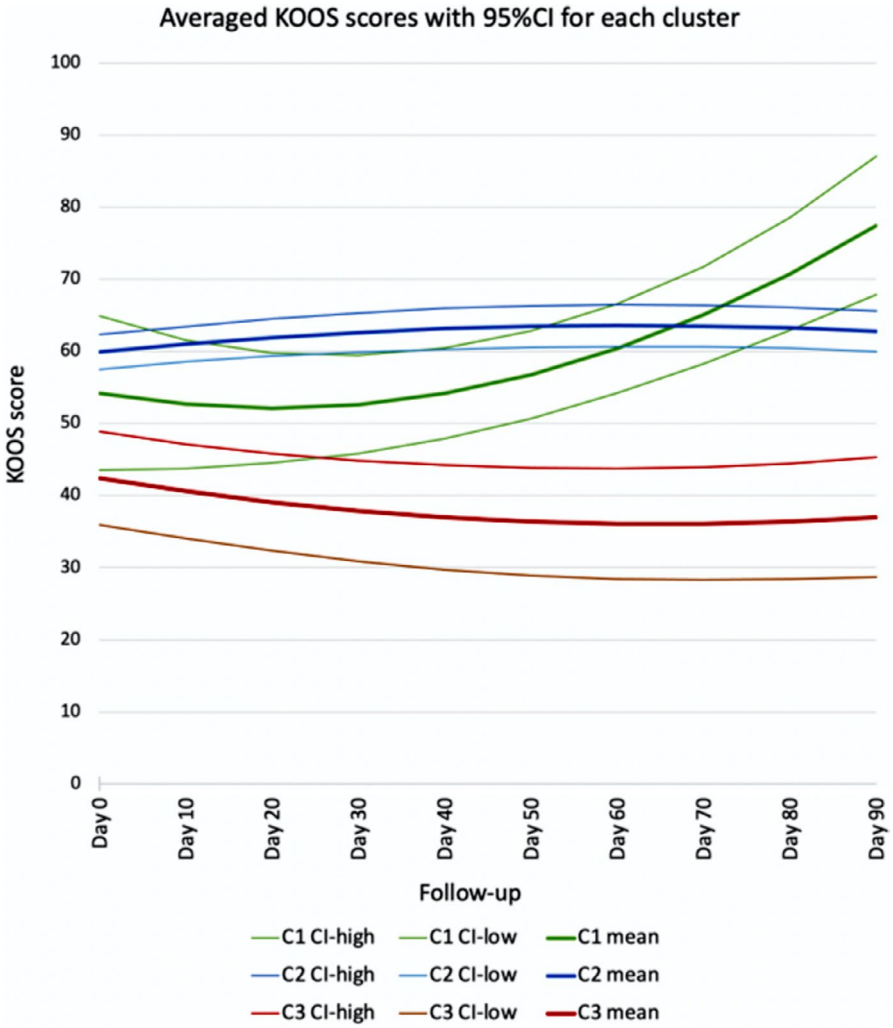

FIGURE A1 Averaged KOOS-p scores with 95% CI for each cluster

TABLE A1 Fit indices and model selection

Model	Fit indices	1-cluster model	2-cluster model	3-cluster model	4-cluster model	5-cluster model
LCGA-linear	Log likelihood	−12 420.42	−11 572.01	−11 166.22	−10 967.32	−10 856.52
	AIC	24 864.86	23 174.04	22 368.45	21 976.66	21 761.05
	sBIC	24 871.75	23 182.66	22 378.79	21 988.72	21 774.84
	VLMR LRT (*P* value)		0.008	0.165	0.085	0.078
	LMR LRT (*P* value)		0.010	0.175	0.091	0.085
	Entropy		0.92	0.94	0.92	0.92
	Posterior probabilities (range)	1.00	0.97-0.97	0.97-0.97	0.93-0.96	0.93-0.99
	Cluster membership (C1/C2/C3..)	313	176/137	59/143/111	107/69/97/40	91/49/98/64/11
LCGA-quadratic	Log likelihood	−12 420.27	−11 571.65	−11 164.45	−10 964.33	−10 854.62
	AIC	24 866.55	23 177.29	22 370.89	21 978.66	21 767.24
	sBIC	24 874.02	23 187.06	22 382.96	21 993.02	21 783.90
	VLMR LRT (*P* value)		0.008	0.183	0.185	0.178
	LMR LRT (*P* value)		0.009	0.190	0.193	0.185
	Entropy		0.92	0.94	0.93	0.93
	Posterior probabilities (range)		0.97-0.97	0.96-0.97	0.93-0.97	0.93-0.98
	Cluster membership (C1/C2/C3..)	313	137/176	143/59/111	107/40/69/97	11/98/92/48/64

Model	Fit indices	1-cluster model	2-cluster model	3-cluster model	4-cluster model	5-cluster model
LGMM-linear	Log likelihood	−10 693.88	−10 688.68	−10 683.85	−10 680.70	Model did not converge[a]
	AIC	21 417.75	21 413.37	21 409.69	21 409.39	
	sBIC	21 426.37	21 423.71	21 421.76	21 423.18	
	VLMR LRT (*P* value)		0.018	0.082	0.605	
	LMR LRT (*P* value)		0.022	0.092	0.623	
	Entropy		0.67	0.77	0.72	
	Posterior probabilities (range)		0.76-0.92	0.76-0.92	0.82-0.86	
	Cluster membership (C1/C2/C3..)	313	33/280	4/35/274	5/156/132/20	
LGMM-quadratic	Log likelihood	−10 683.61	−10 673.62	−10 667.35	−10 662.87	Model did not converge[a]
	AIC	21 405.22	21 393.24	21 388.70	21 387.74	
	sBIC	21 416.13	21 406.45	21 404.21	21 405.55	
	VLMR-LRT (*P* value)		0.017	0.058	0.185	
	LMR-LRT (*P* value)		0.019	0.065	0.193	
	Entropy		0.89	0.73	0.74	
	Posterior Probabilities (range)		0.98-0.85	0.81-0.91	0.78-0.99	
	Cluster membership (C1/C2/C3..)	313	301/12	11/254/48	251/1/12/49	

Abbreviations: AIC, Akaike information criterion; LMR-LRT, Lo-Mendell-Rubin Adjusted Ratio Test; sBIC, Bayesian Information Criterion; VLMR-LRT, Vuong-Lo-Mendell-Rubin Likelihood Ratio Test.

[a]The latent variable covariance matrix (psi) was not positive definite (initial conditions: random start sets = 500, final stage optimizations = 100).

TABLE A2 Stability of cluster membership when split cohorts were compared

		Proportion assigned to original cluster after split		
		C1	C2	C3
Cluster membership full data set (n_{full} = 313)	C1 = 11	**0.82**	0.18	0.00
	C2 = 248	0.01	**0.97**	0.02
	C3 = 46	0.00	0.14	**0.86**

Note: C1 = Cluster 1: Low-moderate pain with large improvement over 90 days, C2 = Cluster 2: Minimal change in pain over 90 days, C3 = Cluster 3: Moderate-high pain with worsening over 90 days. Shaded boxes represent participants from each data set half (n_a|n_b) classified into the same cluster as full data set (n_{full}).

Mplus code for final model

```
(Auxiliary variable modeling [R3step] not shown)

Title:
GMM 3-class Quadratic model
Data: File = Koos Data set.dat;
Variable:
Names = ID pa1-pa10;
Usevariables = pa1-pa10;
Classes = c(3);
IDVariable = ID;
Missing = ALL(-99);
Analysis:
Type = Mixture;
PROCESSORS = 8;
Starts = 100 20;
Model:
%Overall%
i s q&#x007C; pa1@0 pa2@1 pa3@2 pa4@3 pa5@4 pa6@5
pa7@6 pa8@7 pa9@8 pa10@9;
! for 95%CI plot
%c#1%
[i s q] (p1 p2 p3);
%c#2%
[i s q] (p4 p5 p6);
%c#3%
[i s q] (p7 p8 p9);
Output:
TECH1 TECH8 CINTERVAL;
PLOT: SERIES = pa1-pa10 (s);
TYPE = PLOT3;
MODEL CONSTRAINT:
PLOT(class1 class2 class3);
LOOP(time,0,10,0.1);
class1 = p1+time*p2+time*time*p3;
class2 = p4+time*p5+time*time*p6;
class3 = p7+time*p8+time*time*p9;
```

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