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Pain and functional trajectories in symptomatic knee osteoarthritis over up to 12 weeks of exercise exposure☆

A.C. Lee †, W.F. Harvey †, X. Han †, L.L. Price ‡ §, J.B. Driban †, R.R. Bannuru † ‖, C. Wang † *

† Center for Complementary and Integrative Medicine, Division of Rheumatology, Tufts Medical Center, Boston, MA, USA
‡ Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA
§ Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA, USA
‖ Center for Treatment Comparison and Integrative Analysis, Division of Rheumatology, Tufts Medical Center, Boston, MA, USA

SUMMARY

Objective: Exercise is the recommended treatment for knee osteoarthritis (OA). However, heterogeneous patterns in treatment response are poorly understood. Our purpose was to identify pain and functional trajectories from exercise interventions in knee OA, and to determine their association with baseline factors.

Methods: Prospective cohort of 171 participants (mean age 61 years; BMI 32 kg/m², 71% female; 57% white) with symptomatic knee OA from a randomized trial comparing 12-week Tai Chi and Physical Therapy. We analyzed weekly Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain (0 −500) and function (0−1700) scores using group-based trajectory models. Associations between baseline factors and trajectories were examined using multinomial logistic regression.

Results: We identified four pain trajectories: Lower-Early Improvement (43%), Moderate-Early Improvement (32%), Higher-Delayed Improvement (15%), and Higher-No Improvement (10%). We found similar trajectories for function, except that the lower function trajectories diverged into gradual (12%) or delayed-improvement (15%). Compared with the Lower-Early Improvement pain trajectory, moderate and higher trajectories were associated with poorer physical and psychosocial health. A similar pattern of associations were found among the function trajectories.

Conclusions: We found four distinct trajectories for pain and function over up to 12-weeks of exercise interventions. While most participants experienced improvements over a short-term exposure, subgroups with greater baseline pain/physical disability had either gradual, delayed, or no improvements. These findings help disentangle the heterogeneity of treatment response and may advance patient-centered care in knee OA.

Introduction

Symptomatic knee osteoarthritis (OA) is a leading cause of chronic pain and functional disability among older adults worldwide[1]. Exercise is strongly recommended for the conservative treatment of all patients[2]. However, there is little evidence to formulate patient-centered exercise programs given the heterogeneity in treatment response[3,4]. This has contributed to an under-utilization of prescriptive exercise by clinicians and poor exercise adherence by patients[5–12].

Treatment effects of exercise are commonly described as average change in pain/physical function among all participants. Moreover, prior studies have found baseline factors (e.g., muscle strength, depressive symptoms, etc.) that predict response after intervention[13]. However, by analyzing frequently-measured short-term outcomes, group-based trajectory modeling can ascertain patterns of longitudinal change over increasing treatment exposure. This knowledge may help to identify patients that require

proactive monitoring to encourage better adherence and confirm treatment progression; or patients that do not respond to exercise intervention. Observational studies have explored long-term trajectories of pain and function over several years in OA[14–17]. In addition, interventional studies have examined short-term trajectories in response to surgery[18,19]. To date, however, pain and functional trajectory patterns remain unknown among patients receiving exercise interventions.

Therefore, the aims of this study were (1) to identify subgroups of individuals with symptomatic knee OA who have similar trajectories in pain and physical function over up to 12 weeks of exercise exposure; (2) to characterize those participants and their pain and functional trajectories; and (3) to explore the associations of pain and functional trajectories with baseline factors of health. We hypothesized that multiple trajectory patterns exist among participants with symptomatic, radiographic knee OA. These results may identify novel patient phenotypes and help contextualize the heterogeneous treatment responses commonly observed among these patients.

Methods

Study design

This was a secondary analysis of a National Institutes of Health-funded, single-blind, randomized trial comparing Tai Chi and Physical Therapy among adults with symptomatic knee OA (Trial Registry #NCT01258985). As no difference was detected for pain and function between the two intervention groups in the primary trial, we have combined them together for this study to increase the power and precision of the analysis. In addition, we found that intervention-specific trajectories were predominantly similar for both pain and function (Supplementary Fig. 1). Detailed descriptions of the methodology, protocol, and primary results for this trial have been previously published[20,21].

Inclusion criteria were: 1) age ≥40 years, 2) fulfillment of the American College of Rheumatology criteria for symptomatic knee OA, and 3) Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score ≥40/100 on at least one of five questions. Exclusion criteria were: 1) prior experience with complementary medicine or Physical Therapy programs for knee OA within the past year, 2) severe medical limitations precluding full participation, 3) intra-articular steroid injections or surgery in the prior 3 months, 4) intra-articular hyaluronic acid injections in the prior 6 months, 5) Mini-Mental Status examination score <24, or 6) inability to walk without an assistive device.

Participants were randomly assigned in a 1:1 ratio to either 12-weeks of Tai Chi or Physical Therapy. The physical function assessors were blinded to the treatment assignments during enrollment, and did not have access to the data until collection was complete. All participants signed an informed consent form before enrollment and the study was approved by the Tufts University/Tufts Medical Center Institutional Review Board. In order to provide an adequate number of data points for trajectory analysis[22], we only included participants who had at least three total visits: their first week of class and at least two additional weeks of attendance.

Interventions

The 60-min Tai Chi sessions occurred twice per week for 12 weeks. We recruited three experienced Tai Chi instructors and developed a standardized classical Yang-style Tai Chi protocol for knee OA that was based on the literature[23]. Before study initiation, the principal investigator and the Tai Chi master (who was also one of the three instructors) reviewed the concepts of knee OA and trained the other instructors on the standardized delivery of the classical Yang-style Tai Chi protocol. In the first session, participants received printed materials on Tai Chi principles, practice techniques, and safety precautions. The instructor explained mind–body exercise theory and procedures. Subsequent sessions started with a warm-up and a review of Tai Chi principles and movement, breathing techniques, and relaxation methods[20].

The physical therapy protocol followed U.S. guidelines for knee OA treatment[24] and consisted of two 30-min outpatient sessions per week for 6 weeks. Before enrollment, the supervising physical therapist trained three physical therapists, observed evaluations and interventions during each treatment cycle to ensure consistency in documentation, and provided feedback for program progression. Depending on the diagnostic findings in the initial musculoskeletal examination, the therapist targeted physical therapy regimens to address specific treatment goals developed collaboratively with the participant. At each session, the physical therapist examined the participant for adverse signs and symptoms before proceeding with manual therapy or exercise. After 6 weeks, participants were instructed to continue exercises in 30-min sessions four times per week for 6 weeks. These were monitored weekly by telephone by using standardized forms to ascertain frequency, exercises completed, adverse events, and adherence[20]. Throughout both interventions, participants were asked to practice for at least 20 min daily at home.

Weekly measures

The WOMAC is a validated, visual analog scale that measures pain intensity and functional disability in OA[25]. Participants completed the WOMAC at the beginning of the first attended-session of each week. During the home-exercise portion of the Physical Therapy intervention, WOMAC data were collected during weekly monitoring phone calls by study staff. Baseline measurements were collected at screening, prior to randomization. For baseline WOMAC scores, however, the post-randomization data (collected at their first session) was used in this analysis to mitigate the influence of self-inclusion bias and regression to the mean.

Baseline measures

The *Patient Global Assessment* is a single-item visual analog scale that measures patient-perceived global health[26]. The *Short Form-36* measures health-related quality of life and consists of 36 questions related to eight dimensions of health[27]. In this analysis, the *Mental Health* and *Energy and Vitality* subscales were used to complement domains already measured in other instruments. Scores were also combined to obtain two aggregate scores: *Physical Component Summary* and M*ental Component Summary* scores. The Patient-Reported Outcomes Measurement Information Systems *Sleep Disturbance Short Form* measures sleep quality, sleep depth, and sleep restoration[28]. The *Beck Depression Inventory, second edition,* measures depressive symptom severity[29]. The *Perceived Stress Scale* measures the degree to which situations are appraised as uncontrollable/overwhelming[30]. The *Arthritis Self-Efficacy Scale*-8 measures self-efficacy, the belief that one can successfully take action to produce a desired outcome[31]. The *Outcome Expectations for Exercise Scale* measures perceived benefits of exercise among older adults[32]. The *Medical Outcomes Study Social Support Survey* measures functional social support in community-dwelling, chronically-ill persons[33]. The *Six-minute Walk Test* measures functional exercise capacity[34] by having participants walk as far as possible within a 6-

min period. The *20-Meter Walk Test* measures gait speed[35], in seconds, over 20 m. *The Berg Balance Scale* is a performance-based test of balance[36]. Described in further detail elsewhere[37], *leg extensor muscle strength* was assessed according to bilateral leg-press apparatus using the one-repetition maximum technique. L*eg extensor peak muscle power* and *peak contraction velocities* were subsequently measured after a 5-min rest. Briefly, each participant completed a total of five repetitions, each separated by 30 s, as quickly as possible through their full ROM at 40% and then at 70% of the one-repetition maximum. The highest measured power output (measured in watts) and corresponding contraction velocity (meters/second) were recorded. Baseline *radiographic knee alignment* of participants was measured by one reader using anatomic axis on weight-bearing semi-flexed antero-posterior knee radiographs according to previously validated methods (Intra-rater reliability ICC [3,1 model] = 0.94)[38]. We adjusted anatomic axis measures by sex (female, $-3.5°$; male, $-6.4°$) to better reflect mechanical axis and categorized them using standard definitions: valgus ($>182°$), normal ($178-182°$), or varus ($<178°$).

Statistical analysis

Descriptive statistics were computed for baseline variables and presented as mean ± SD unless otherwise stated. In this investigation, time was defined according to treatment duration, measured as the number of weeks attended, i.e., attendance-weeks, which is concordant with those used in related-Cochrane Reviews to quantify exercise dosage as a function of treatment duration[39]. Time was defined in this manner in order to investigate the trajectories of pain and function as a function of exercise exposure vs a function of time.

Group-based trajectory models utilizing the PROC TRAJ macro in SAS were used to identify subgroups within the participant cohort that share a similar underlying trajectory in pain or function[40]. We did not pre-specify cutpoints or trajectory groups, but allowed PROC TRAJ to find the best trajectories based on the data. Following the recommended methodology, the number of trajectory groups was varied until the best-fitting model was obtained as indicated by the Bayesian Information Criterion (values closest to zero indicate the best fitting model)[40–42]. We modeled intercept linear, quadratic, or cubic polynomial terms for each trajectory and optimized the final model by removing non-significant polynomial terms. Before final optimization, we required the smallest trajectory group to include at least 10% of the participant sample to exclude groups with reduced interpretability or power, which is concordant with the approach used in prior studies[22]. If a group had less than 10% of the sample, the number of groups was reduced and the analysis was re-run. Thus, all participants were placed into one of the trajectories. To check robustness of the final optimized models, we used the posterior probabilities of group membership from each individual to assess the fit of the models[22]. High probability of membership into a single group represents a good model fit. After the final optimization, we applied descriptive labels to each of the trajectories, based on the shape of the trajectory.

We used multinomial logistic regression to examine the association of baseline factors with the probability of membership in one of the trajectories. A list of baseline variables was selected prior to analyses from among domains that were associated with exercise treatment outcomes in the OA literature. We also considered variables that could conceptually or biologically influence treatment response from exercise. As we were looking at potential associations and not aiming to make any causal inference between pain trajectories and baseline variables, we performed univariate analyses. Analyses were adjusted for age, sex, and BMI. All

continuous variables were checked for a linear association with the outcome, and continuous variables violating this assumption were dichotomized according to clinically-relevant cut-points. Clinically relevant cut-points used to dichotomize continuous variables that violated the assumption of linearity: 1) *Short Form-36 Physical Component Summary*-a 40 point score represents one full SD below the general population average[27]. 2) *Community Healthy Activities Model Program for Seniors (CHAMPS)*- 1,123.3 mod-high calories/ week are expended by older adults when completing the 150 min of weekly physical activity recommended by the American Heart Association and the American College of Sports Medicine[43]. 3) *20-Meter Walk Test*- Because gait speeds <1 m/second (i.e., ≥20 s) identify a high risk of poor health-related outcomes in well-functioning older adults[44]. 4) *The Berg Balance Scale*- Scores <50 points are associated with a history of falls among the elderly[45]. 5) L*eg extensor peak muscle power*- Average muscle power among mobility-limited older adults is 228 W[46]. Threshold for statistical significance was a global test $P \leq 0.05$. If the global test was not significant for a given variable, the pairwise comparisons were not assessed. All data were analyzed using SAS statistical software (SAS Institute Inc., Cary, NC, version 9.4). Due to the hypothesis-generating nature of this investigation, analyses were not adjusted for multiple comparisons.

Results

There were 171 participants from the parent trial who met inclusion criteria for this analysis (attended both their first week of class and at least two additional weeks). These participants were predominantly female (71%), white (57%), had some postsecondary education (84%), and normal radiographic alignment (46%). Mean age was 61 ± 10 years and BMI was 32 ± 7 kg/m². According to baseline factors that significantly distinguished trajectories, the 33 excluded participants from the parent trial were generally similar to participants included in this analysis, except that the excluded group had a relatively larger proportion of black participants, more people with diabetes, and lower scores in the physical component of SF-36 (Table I). Time constraints were a common reason why participants stopped attending the intervention.

Pain trajectories

We identified four trajectories of pain over 12 weeks [Fig. 1(A), Table II]. The *Lower Pain, Early Improvement* trajectory included the largest proportion of participants (43%), and was characterized by an initial WOMAC pain score of 139.2 points and a meaningful decline in pain (98.7 point reduction; minimally important difference for WOMAC pain = 85 points) that plateaus after five attended weeks[47]. 32% of participants were on a *Moderate Pain, Early Improvement* trajectory with an initial WOMAC pain score of 230.4 points and a decline in pain (98.6 point reduction) overfive attendance-weeks. 15% of participants had a *Higher Pain, Delayed Improvement* trajectory characterized by higher initial levels of pain (329.5 points) and a small improvement through 4–5 attendance-weeks, but large improvements (159.6 point reduction) after attending 5 through 11 weeks of intervention. In contrast, around 10% of participants had a *Higher Pain, No Improvement* trajectory, characterized by higher initial levels of pain (317.7 points) without improvement throughout intervention.

Functional trajectories

We identified four trajectories of physical function over 12 weeks [Fig. 1(B), Table III]. The *Higher Function, Early Improvement*

Table I
Baseline characteristics of all participants and excluded participants

Characteristic	Total $n = 171$	Excluded parent trial participants§ $n = 33$
Demographic		
Age, years	60.8 ± 10.4	57.2 ± 10.2
Female sex, n (%)	122 (71.4)	21 (63.6)
Race, n (%)		
Black	54 (31.6)	18 (54.6)
Other	117 (68.4)	15 (45.4)
Body mass index, kg/m^2	32.4 ± 7.0	34.6 ± 7.9
Duration of knee pain, years	8.3 ± 10.6	8.3 ± 6.8
Kellgren−Lawrence grade, n (%)*		
0−2	75 (45.2)	13 (40.6)
3−4	91 (54.8)	19 (59.4)
Highest level of education, n (%)		
High school graduate or less	28 (16.4)	6 (18.2)
Some college or more	143 (83.6)	27 (81.8)
Self-reported comorbidities, n (%)		
Heart disease	13 (7.6)	3 (9.1)
Hypertension	84 (49.1)	18 (54.6)
Diabetes	27 (15.8)	11 (33.3)
Opioid use, n (%)	18 (10.8)	5 (15.2)
NSAID use, n (%)	100 (58.8)	23 (71.9)
Intervention assignment, n (%)		
Tai Chi	93 (54.4)	13 (39.4)
Patient-reported physical health		
WOMAC pain (range: 0−500)	214.2 ± 109.0	238.7 ± 100.1
WOMAC physical function (range: 0−1700)	740.6 ± 372.6	804.8 ± 368.5
Patient global assessment (range: 0.0−10.0 cm)	5.1 ± 2.2	5.7 ± 2.2
SF-36 physical component summary (range: 0−100)¶	37.1 ± 9.1	33.7 ± 8.7
SF-36 energy and vitality (range: 0−100)¶	57.0 ± 19.3	55.9 ± 16.0
CHAMPS physical activity mod-high calories/week¶	1,496.2 ± 1816.8	1,143.4 ± 1,465.1
PROMIS Sleep Disturbance Short Form, v.8a (range: T-score: 28.9−76.5)	50.5 ± 9.7	47.9 ± 9.1
Physical performance		
6-Minute Walk Test, meters (normal range: 400−700)†,¶	400.1 ± 88.1	372.3 ± 97.8
20-Meter Walk Test, seconds	18.7 ± 5.3	20.4 ± 5.3
Leg extensor muscle strength‡, newtons¶; 1RM	974.3 ± 395.1	1,080.5 ± 448.1
Muscle contraction velocity‡, meters/second (40% of 1RM)¶	0.5 ± 0.2	0.5 ± 0.2
Muscle contraction velocity‡, meters/second (70% of 1RM)¶	0.3 ± 0.1	0.3 ± 0.1
Muscle power‡, watts (40% of 1RM)¶	265.9 ± 166.4	300.0 ± 210.8
Muscle power‡, watts (70% of 1RM)¶	307.3 ± 176.4	324.6 ± 207.0
Berg balance score (range: 0−56)¶	52.2 ± 4.9	50.4 ± 6.0
Psychosocial health		
SF-36 mental component summary (range: 0−100)¶	52.4 ± 9.4	53.1 ± 8.6
SF-mental health (range: 0−100)¶	74.4 ± 16.3	77.0 ± 15.2
Beck-II Depression Inventory (range: 0−63)	7.7 ± 8.6	7.2 ± 8.9
Perceived stress (range: 0−40)	13.4 ± 6.9	12.5 ± 7.3
MOS social support (range: 19−95)¶	68.0 ± 22.4	65.1 ± 25.5
Arthritis Self-Efficacy Scale-8 (range: 0−10)¶	6.2 ± 2.1	6.4 ± 2.2
Outcome expectations (range: 1.0−5.0)¶	3.9 ± 0.6	3.9 ± 0.8
Biomechanical factors		
Radiographic leg alignment‖, n (%)		
Normal	52 (45.6)	14 (73.7)
Malalignment	62 (54.4)	5 (26.3)

1RM = one-repetition maximum; CHAMPS = Community Healthy Activities Model Program for Seniors; MOS = Medical Outcomes Survey; PROMIS = Patient-Reported Outcomes Measurement Information Systems; SF-36 = Short Form-36; WOMAC = Western Ontario and McMasters Osteoarthritis Index.
All values are mean ± standard deviation, unless otherwise specified.
* Osteophyte was confirmed in the patellofemoral joint region for those with Kellgren/Lawrence grade 0 or 1.
† Normal range reported for the general population.
‡ For muscle strength, power, and velocity, total $n = 165$ to 168: 86 to 88 for Tai Chi and 78 to 80 for Physical Therapy.
§ Participants were only included if they attended both their first week of class and ≥2 additional weeks.
‖ For radiographic leg alignment, total $n = 121$: 62 for Tai Chi and 59 for Physical Therapy.
¶ Higher score indicates greater health.

trajectory included the largest proportion of participants (44%), and was characterized by an initial WOMAC function score of 452.7 points and an improvement in function (301.8 point reduction) that plateaus after five attended weeks. 29% of participants were on a *Moderate Function, Early Improvement* trajectory that had a poorer initial WOMAC function score of 816.8 points and a similar

improvement in function (407.4 point reduction) that plateaus after six attendance-weeks. 12% of participants had a *Lower Function, Gradual Improvement* trajectory characterized by high initial levels of functional disability (1,064.7 points) and large improvements (737.7 point reduction) through 11 attendance-weeks. Finally, 15% of participants had a *Lower Function, Delayed Improvement*
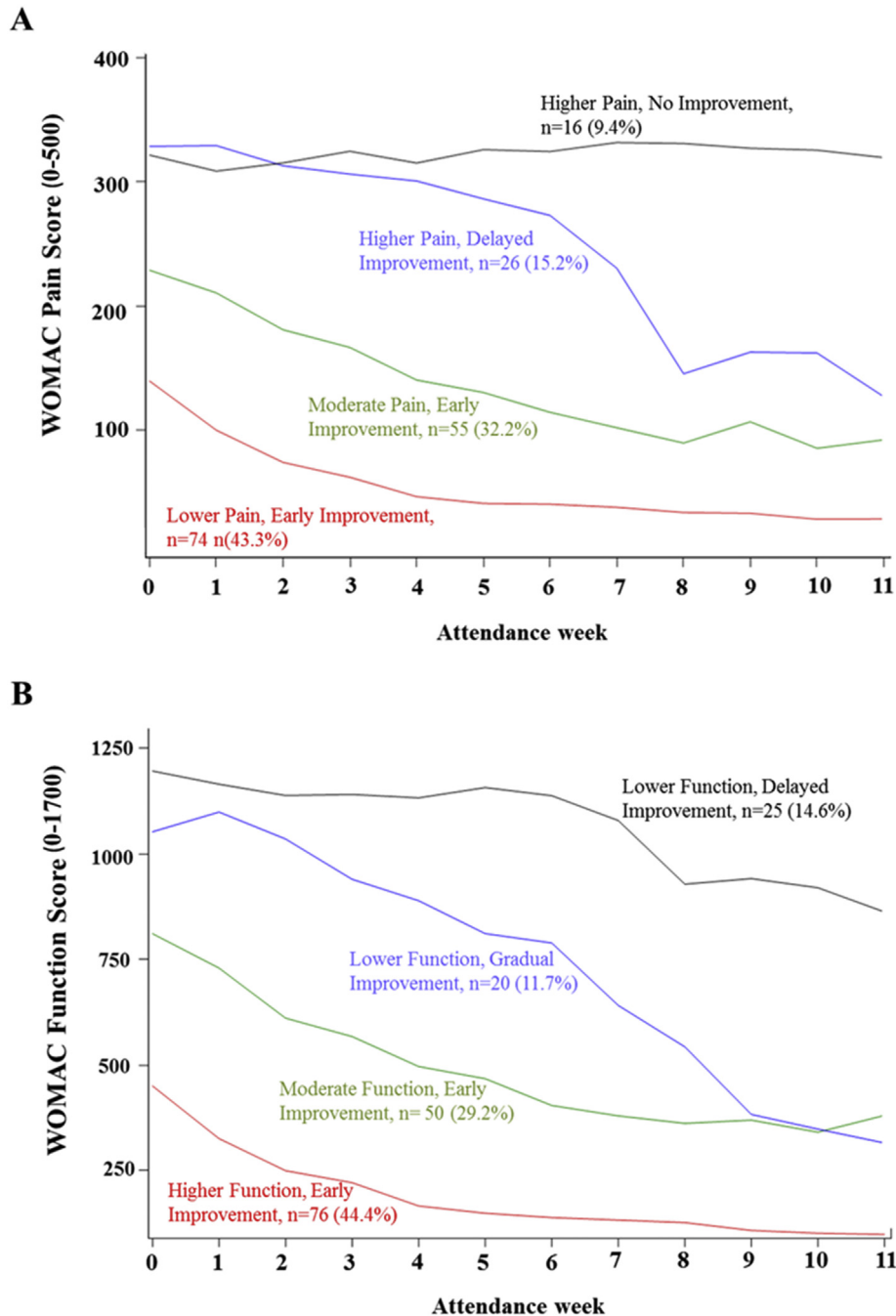
Fig. 1. Trajectories of Pain and Function during Interventions: WOMAC = Western Ontario and McMasters Osteoarthritis Index. **Panel A:** Pain Trajectories. WOMAC Pain subscale range: 0–500, higher scores = greater pain. **Panel B:** Function Trajectories. WOMAC Function subscale range: 0–1700, higher scores = poorer physical function.

trajectory characterized by higher initial levels of functional disability (1,204.0 points) and small improvements (117.4 point reduction) up to seven attended weeks, but meaningful improvements (216.8 point reduction; minimally important difference for WOMAC function = 204 points)[47] from attending 7 through 11 weeks of treatment.

For both pain and function trajectories, the overall posterior group probabilities of allocating each participant into their respective trajectories ranged from 0.92 to 0.98 for each group, which can be interpreted as an 'excellent' model fit and exceeds the recommended minimum of 0.7[22]. In other words, there was a 92–98% probability on average of each individual trajectory fitting the respective group trajectory (See Supplemental Tables S1 and S2 for further information on fit indices across models and participant distributions across posterior probability subcategories.).

Characteristics and association within trajectories

As shown in Tables II and III, higher pain or physical disability trajectory groups had larger proportions of black participants, and poorer physical health and self-efficacy than those from trajectories with lower or moderate baseline pain or physical disability. Conversely, Kellgren–Lawrence grade, and comorbidities were evenly distributed among trajectory groups. As shown in Table IV,

Table II
Baseline characteristics of participants among pain trajectories

Characteristic	Lower pain, early improvement $n = 74$	Moderate pain, early improvement $n = 55$	Higher pain, delayed improvement $n = 26$	Higher pain, no improvement $n = 16$	Overall P value
Demographic					
Race, n (%)					
Black	13 (17.6)	19 (34.6)	12 (46.2)	10 (62.5)	
Odds ratio (vs white and others)	Reference	2.17 (0.93, 5.08)	2.84 (1.00, 8.06)	6.92 (2.07, 23.09)	0.01
Duration of knee pain, years	9.4 ± 11.7	6.7 ± 7.5	11.3 ± 15.4	4.9 ± 3.5	
Odds ratio (1 unit increase)	Reference	0.98 (0.93, 1.02)	1.03 (0.99, 1.07)	0.91 (0.81, 1.03)	0.10
Kellgren–Lawrence grade, n (%)*					
3–4	34 (46.6)	33 (62.3)	16 (64.0)	8 (53.3)	
Odds ratio (vs 0–2)	Reference	1.89 (0.88, 4.07)	2.05 (0.75, 5.60)	1.67 (0.52, 5.37)	0.32
Highest level of education, n (%)					
Some college or more	65 (87.8)	45 (81.8)	23 (88.5)	10 (62.5)	
Odds ratio (vs high school graduate or less)	Reference	0.62 (0.23, 1.69)	1.67 (0.32, 8.69)	0.23 (0.07, 0.83)	0.08
Self-reported comorbidities, n (%)					
Heart disease	6 (8.11)	4 (7.3)	2 (7.7)	1 (6.3)	
Odds ratio	Reference	1.05 (0.26, 4.27)	1.37 (0.23, 8.31)	1.23 (0.12, 12.10)	0.99
Hypertension	34 (46.0)	33 (60.0)	12 (46.2)	5 (31.3)	
Odds ratio	Reference	1.78 (0.85, 3.73)	0.96 (0.37, 2.50)	0.63 (0.19, 2.08)	0.26
Diabetes	11 (14.9)	10 (18.2)	3 (11.5)	3 (18.8)	
Odds ratio	Reference	1.04 (0.40, 2.73)	0.59 (0.15, 2.40)	1.09 (0.26, 4.62)	0.87
Opioid use, n (%)	7 (9.6)	4 (7.6)	4 (16.0)	3 (18.8)	
Odds ratio	Reference	0.90 (0.24, 3.41)	1.84 (0.40, 8.49)	3.16 (0.66, 15.15)	0.42
NSAID use, n (%)	39 (53.4)	39 (70.9)	15 (57.7)	7 (43.8)	
Odds ratio	Reference	1.76 (0.81, 3.84)	1.02 (0.38, 2.74)	0.68 (0.22, 2.12)	0.34
Intervention assignment					
Tai Chi	35 (47.3)	33 (60.0)	16 (61.5)	9 (56.3)	
Odds ratio (vs physical therapy)	Reference	1.64 (0.80, 3.40)	1.64 (0.63, 4.24)	1.55 (0.51, 4.71)	0.52
Patient-reported physical health					
WOMAC pain (range: 0–500)	139.2 ± 72.4	230.4 ± 81.2	329.5 ± 94.4	317.7 ± 85.6	
Odds ratio	———	———	———	———	
WOMAC physical function (range: 0–1700)	485.4 ± 266.5	810.1 ± 287.5	1,081.8 ± 335.4	1,127.2 ± 204.9	
Odds ratio (100 unit increase)	Reference	**1.54 (1.31, 1.82)**	**2.21 (1.73, 2.82)**	**2.32 (1.75, 3.08)**	**<0.0001**
Patient global assessment (range: 0.0–10.0 cm)	4.0 ± 1.9	5.4 ± 2.0	7.0 ± 1.2	6.1 ± 2.4	
Odds ratio (1 unit increase)	Reference	**1.37 (1.13, 1.66)**	**2.32 (1.66, 3.23)**	**1.65 (1.22, 2.23)**	**<0.0001**
SF-36 physical component summary, n (%)	29 (39.2)	32 (58.2)	24 (92.3)	12 (75.0)	
<40 points (range: 0–100)‖					
Odds ratio (vs ≥40 points)	Reference	2.00 (0.96, 4.16)	**16.00 (3.44, 74.36)**	**4.13 (1.19, 14.32)**	**0.001**
SF-36 energy and vitality, (range: 0–100)‖	63.0 ± 18.8	56.4 ± 17.1	47.5 ± 20.3	46.9 ± 17.3	
Odds ratio (10 unit increase)	Reference	0.83 (0.67, 1.02)	**0.63 (0.48, 0.83)**	**0.66 (0.49, 0.90)**	**0.003**
CHAMPS physical activity, n (%) mod-high calories/week‖ <1,123.3	34 (47.2)	32 (60.4)	14 (60.9)	12 (75.0)	
Odds ratio (vs ≥1,123.3)	Reference	1.49 (0.70, 3.18)	1.39 (0.51, 3.79)	3.15 (0.89, 11.14)	0.31
PROMIS Sleep Disturbance Short Form, v.8a (range; T-score: 28.9–76.5)	48.8 ± 9.0	48.6 ± 9.6	56.2 ± 7.6	55.6 ± 11.3	
Odds ratio (10 unit increase)	Reference	0.98 (0.66, 1.45)	**2.52 (1.41, 4.50)**	**2.13 (1.12, 4.08)**	**0.003**
Physical performance					
6-Minute Walk Test, meters (normal range: 400–700)†,‖	427.6 ± 96.7	389.5 ± 73.7	362.1 ± 67.6	364.8 ± 83.1	
Odds ratio (50 unit increase)	Reference	**0.76 (0.60, 0.97)**	**0.58 (0.42, 0.81)**	**0.60 (0.42, 0.85)**	**0.003**
20-Meter Walk Test, n (%) seconds, <20	57 (77.0)	37 (67.3)	14 (58.3)	10 (62.5)	
Odds ratio (vs ≥20)	Reference	0.57 (0.25, 1.30)	0.35 (0.12, 1.00)	0.39 (0.12, 1.31)	0.17
Leg extensor muscle strength‡ newtons‖; 1RM	1,051.2 ± 428.7	927.5 ± 365.4	909.8 ± 342.7	880.7 ± 378.6	
Odds ratio (100 unit increase)	Reference	**0.83 (0.73, 0.95)**	**0.78 (0.65, 0.94)**	0.84 (0.68 1.03)	**0.01**
Muscle contraction velocity‡, meters/second (40% of 1RM)‖	0.5 ± 0.2	0.5 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	
Odds ratio (0.1 unit increase)	Reference	0.99 (0.78, 1.25)	**0.67 (0.48, 0.94)**	**0.68 (0.47, 0.99)**	**0.03**
Muscle contraction velocity‡, meters/second (70% of 1RM)‖	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	
Odds ratio (0.1 unit increase)	Reference	0.92 (0.67, 1.25)	0.70 (0.45, 1.08)	0.66 (0.41, 1.07)	0.21
Muscle power‡, n (%) watts, <228.4 (40% of 1RM)‖	29 (42.0)	27 (50.9)	12 (52.2)	11 (68.8)	
Odds ratio (vs ≥228.4)	Reference	1.83 (0.77, 4.36)	2.16 (0.69, 6.83)	4.25 (1.02, 17.67)	0.17
Muscle power‡, n (%), watts, <228.4 (70% of 1RM)‖	24 (34.8)	19 (37.3)	12 (54.6)	10 (62.5)	
Odds ratio (vs ≥228.4)	Reference	1.48 (0.62, 3.50)	**4.25 (1.32, 13.71)**	**4.72 (1.25, 17.85)**	**0.03**
Berg balance score, n (%) ≤50 points (range: 0–56)‖	10 (13.5)	14 (25.5)	10 (40.0)	4 (25.0)	
Odds ratio (vs >50 points)	Reference	2.31 (0.88, 6.06)	**5.30 (1.68, 16.67)**	3.01 (0.74, 12.17)	**0.04**
Psychosocial health					
SF-36 mental component summary (range: 0–100)‖	54.1 ± 8.5	52.4 ± 10.4	49.2 ± 9.4	50.0 ± 8.4	
Odds ratio (10 unit increase)	Reference	0.75 (0.49, 1.14)	0.52 (0.31, 0.87)	0.65 (0.36, 1.18)	0.08
SF-mental health (range: 0–100)‖	77.2 ± 15.0	74.3 ± 17.5	70.3 ± 16.6	67.8 ± 14.9	
Odds ratio (10 unit increase)	Reference	0.85 (0.67, 1.08)	0.73 (0.54, 0.98)	0.73 (0.53, 1.01)	0.12
Beck-II Depression Inventory (range: 0–63)	6.1 ± 7.3	7.8 ± 9.5	10.2 ± 8.5	11.1 ± 9.7	
Odds ratio (1 unit increase)	Reference	1.04 (0.99, 1.09)	1.07 (1.01, 1.14)	1.06 (1.00, 1.13)	0.07
Perceived stress (range: 0–40)	12.6 ± 6.4	12.3 ± 7.7	15.1 ± 6.2	17.9 ± 5.7	

Table II (continued)

Characteristic	Lower pain, early improvement $n = 74$	Moderate pain, early improvement $n = 55$	Higher pain, delayed improvement $n = 26$	Higher pain, no improvement $n = 16$	Overall P value
Demographic					
Odds ratio (1 unit increase)	Reference	1.00 (0.95, 1.06)	1.07 (1.00, 1.15)	**1.12(1.02, 1.22)**	**0.03**
MOS social support (range: 19–95)‖	67.8 ± 23.3	69.0 ± 21.5	64.5 ± 25.6	72.0 ± 15.5	
Odds ratio (1 unit increase)	Reference	1.00 (0.99, 1.02)	0.99 (0.97, 1.01)	1.01 (0.98, 1.04)	0.64
Arthritis Self-Efficacy Scale-8 (range: 0–10)‖	6.9 ± 1.9	6.1 ± 2.1	5.3 ± 1.8	4.5 ± 2.3	
Odds ratio (1 unit increase)	Reference	**0.80(0.65, 0.97)**	**0.65(0.50, 0.84)**	**0.54(0.39, 0.74)**	**0.0002**
Outcome expectations (range: 1.0–5.0)‖	4.0 ± 0.6	3.9 ± 0.6	3.9 ± 0.6	3.9 ± 0.6	
Odds ratio (1 unit increase)	Reference	1.03 (0.53, 2.01)	1.11 (0.47, 2.61)	0.95 (0.35, 2.59)	0.99
Biomechanical factors					
Radiographic leg alignment§, n (%)					
Malalignment	26 (53.1)	18 (48.7)	10 (58.8)	8 (72.7)	
Odds ratio (vs normal)	Reference	0.76 (0.31, 1.85)	1.07 (0.33, 3.45)	2.50 (0.58, 10.88)	0.49

Bolded values indicate statistical significance ($P < 0.05$).
1RM = one-repetition maximum; CHAMPS = Community Healthy Activities Model Program for Seniors; MOS = Medical Outcomes Survey; PROMIS = Patient-Reported Outcomes Measurement Information Systems; SF-36 = Short Form-36; WOMAC = Western Ontario and McMasters Osteoarthritis Index.
All values are mean ± standard deviation, unless otherwise specified.
Note: Odds ratios >1.00 favor the first category in dichotomized comparisons.
* Osteophyte was confirmed in the patellofemoral joint region for those with Kellgren/Lawrence grade 0 or 1.
† Normal range reported for the general population.
‡ For muscle strength, power, and velocity, total $n = 165$ to 168: 86 to 88 for Tai Chi and 78 to 80 for Physical Therapy.
§ For radiographic leg alignment, total $n = 121$: 62 for Tai Chi and 59 for Physical Therapy.
‖ Higher score indicates greater health.

all pain and function trajectories had between 70% and 88% of participants who attended at least 8 weeks of treatment. Overall, attendance rates were similar among trajectory groups. Among the pain trajectories, the Lower Pain, Early Improvement trajectory had the smallest proportion (47%) with perfect attendance while the other pain trajectories had between 50% and 68% of participants with perfect attendance. Among the functional trajectories, the Lower Function, Gradual Improvement trajectory had the smallest proportion (35%) with perfect attendance, whereas the other functional trajectories had between 43% and 52%. There was a relatively similar balance of treatment assignment (40–60%) among participants within each of the pain or functional trajectories.

Table II summarizes the associations between baseline characteristics and pain trajectory group membership (in reference to Lower Pain, Early Improvement), and Table III summarizes the same for functional trajectory group membership (in reference to Higher Function, Early Improvement). We found a general pattern wherein black race and poorer physical health were associated with membership in the moderate-to-higher pain/function severity trajectories. For example, poorer Patient Global Assessment was significantly associated with increased odds of being in the Moderate Pain, Early Improvement (OR = 1.37; 95% Confidence Intervals [CI]: 1.13, 1.66); Higher Pain, Delayed Improvement (OR = 2.32; 95% CI: 1.66, 3.23); and Higher Pain, No Improvement trajectories (OR = 1.65; 95% CI: 1.22, 2.23). Similarly among the functional trajectories, poorer Patient Global Assessment was significantly associated with increased odds of being in the Moderate Function, Early Improvement (OR = 1.33; 95% CI: 1.10, 1.61); Lower Function, Gradual Improvement (OR = 1.45; 95% CI: 1.12, 1.89); and Lower Function, Delayed Improvement trajectories (OR = 1.84; 95% CI: 1.40, 2.41). In general, we found that participants with poorer physical health and worse sleep quality had higher odds of being in the higher pain and lower function trajectories groups. We found another general pattern wherein participants with poor psychological health, such as low self-efficacy and high perceived stress, had higher odds of being in the higher pain/poorer function trajectories groups. Furthermore, the less favorable trajectories (i.e., 'no improvement' for pain and 'delayed improvement' for function) were significantly associated with a greater number of psychological health variables than their more favorable counterparts (i.e., 'delayed improvement' for pain and 'gradual improvement' for function).

Discussion

This investigation provides a unique insight into the heterogeneous patterns of change in pain and function from exercise interventions among adults with symptomatic knee OA. By identifying distinct trajectories of symptomatic improvement, our findings provide a more realistic understanding of treatment response to exercise compared with traditional group mean-based analyses. These newer group-based trajectory modeling techniques revealed four distinct pain and functional trajectory patterns over 12 weeks of treatment that showed most participants had improvements in pain/function over a short-term exposure, while some had no improvements in pain/function. In addition, we found a novel delayed-response pattern characterized by intractable symptoms that eventually improved after 6–7 weeks of treatment. Importantly, we found a pattern wherein poorer physical and psychological morbidities at baseline were associated with these delayed- and non-response patterns.

Concordant with our results, a similar number of distinct trajectories were found in prior studies that describe the natural history of disease over several years[14–17] or recovery from knee surgery[18,19]. Major findings of this investigation were the divergent trajectories observed among severely symptomatic participants at baseline. In OA research, these findings are discordant with the conventional approach to exclude participants with severe pain/functional disability based on the presumption that exercise will have little effect on those with severe disease[48]. Moreover, the divergent severe pain/function trajectories found in our study have clinically important implications. Patients with severe pain or physical disability are less likely to initiate clinician-prescribed exercise programs, and tend to have poor exercise adherence, especially when symptomatic benefits are not perceived in the early stages of treatment[5–12]. Thus, our findings may be used by clinicians at the onset of treatment to curtail future frustrations and non-compliance by informing severely symptomatic patients about the potential for delayed improvements.

Characterizing these trajectories is important to help establish phenotypes that are readily identifiable in the clinical setting. We

Table III
Baseline characteristics of participants among physical function trajectories

Characteristic	Higher function, early improvement $n = 76$	Moderate function, early improvement $n = 50$	Lower function, gradual improvement $n = 20$	Lower function, delayed improvement $n = 25$	Overall P value
Demographic					
Race, n (%)					
Black	12 (15.8)	21 (42.0)	6 (30.0)	15 (60.0)	
Odds ratio (vs white and others)	Reference	**3.61(1.51, 8.64)**	1.68 (0.50, 5.59)	**7.22(2.55, 20.51)**	0.0009
Duration of knee pain, years	9.5 ± 11.5	6.9 ± 8.5	4.8 ± 3.3	10.1 ± 14.3	
Odds ratio (1 unit increase)	Reference	0.98 (0.93, 1.02)	0.90 (0.80, 1.02)	1.01 (0.97, 1.05)	0.26
Kellgren−Lawrence grade, n (%)†					
3–4	37 (50.0)	31 (63.3)	10 (50.0)	13 (56.5)	0.57
Odds ratio (vs 0−2)	Reference	1.51 (0.69, 3.29)	0.92 (0.32, 2.63)	1.66 (0.61, 4.46)	
Highest level of education, n (%)					
Some college or more	70 (92.1)	37 (74.0)	18 (90.0)	18 (72.0)	
Odds ratio (vs high school graduate or less)	Reference	**0.25(0.09, 0.74)**	0.80 (0.14, 4.58)	**0.21(0.06, 0.71)**	0.02
Self-reported comorbidities, n (%)					
Heart disease	5 (6.6)	3 (6.0)	3 (15.0)	2 (8.0)	
Odds ratio	Reference	0.99 (0.21, 4.67)	3.75 (0.68, 20.77)	2.34 (0.38, 14.60)	0.39
Hypertension	33 (43.4)	33 (66.0)	7 (35.0)	11 (44.0)	
Odds ratio	Reference	2.39 (1.11, 5.15)	0.70 (0.24, 2.05)	1.18 (0.46, 3.03)	0.08
Diabetes	10 (13.2)	9 (18.0)	4 (20.0)	4 (16.0)	
Odds ratio	Reference	1.31 (0.48, 3.59)	1.35 (0.36, 5.03)	1.02 (0.28, 3.70)	0.94
Opioid use, n (%)	4 (5.33)	8 (16.7)	3 (15.8)	3 (12.0)	
Odds ratio	Reference	3.60 (0.95, 13.71)	5.09 (0.93, 27.87)	3.65 (0.70, 18.98)	0.18
NSAID use, n (%)	41 (54.7)	34 (68.0)	14 (70.0)	11 (44.0)	
Odds ratio	Reference	1.60 (0.73, 3.54)	1.58 (0.51, 4.87)	0.63 (0.24, 1.64)	0.29
Intervention assignment					
Tai Chi	36 (47.4)	33 (66.0)	10 (50.0)	14 (56.0)	
Odds ratio (vs physical therapy)	Reference	1.64 (0.80, 3.40)	1.64 (0.63, 4.24)	1.55 (0.51, 4.71)	0.52
Patient-reported physical health					
WOMAC pain (range: 0−500)	143.4 ± 73.6	228.5 ± 85.8	287.6 ± 93.6	342.0 ± 86.3	
Odds ratio (50 unit increase)	Reference	**1.92(1.46, 2.54)**	**2.85(1.94, 4.18)**	**3.90(2.58, 5.88)**	<0.0001
WOMAC physical function (range: 0−1700)	452.7 ± 239.7	816.8 ± 233.6	1,064.7 ± 262.1	1,204.0 ± 228.2	
Odds ratio	−−−	−−−	−−−	−−−	
Patient global assessment (range: 0.0−10.0 cm)	4.2 ± 2.1	5.5 ± 1.8	6.0 ± 2.1	6.6 ± 2.1	
Odds ratio (1 unit increase)	Reference	**1.33(1.10, 1.61)**	**1.45(1.12, 1.89)**	**1.84(1.40, 2.41)**	<0.0001
SF-36 physical component summary, n (%) <40 points (range: 0−100)‖	25 (32.9)	35 (70.0)	17 (85.0)	20 (80.0)	
Odds ratio (vs ≥40 points)	Reference	**4.47(2.03, 9.84)**	**10.38(2.71, 39.70)**	**7.70(2.54, 23.35)**	<0.0001
SF-36 energy and vitality (range: 0−100)‖	64.1 ± 18.3	54.1 ± 18.3	48.3 ± 20.6	48.4 ± 15.9	
Odds ratio (10 unit increase)	Reference	**0.72(0.57, 0.90)**	**0.64(0.47, 0.85)**	**0.65(0.50, 0.85)**	0.001
CHAMPS physical activity, n (%) mod-high calories/week‖ <1,123.3	34 (46.0)	27 (57.5)	14 (77.8)	17 (68.0)	
Odds ratio (vs ≥1,123.3)	Reference	1.52 (0.71, 3.27)	3.59 (1.03, 12.52)	2.18 (0.81, 5.84)	0.14
PROMIS Sleep Disturbance Short Form, v.8a (range; T-score: 28.9−76.5)	48.5 ± 9.1	50.0 ± 9.8	53.4 ± 8.3	55.3 ± 10.2	
Odds ratio (10 unit increase)	Reference	1.19 (0.80, 1.77)	1.76 (1.00, 3.09)	**2.08(1.23, 3.53)**	0.03
Physical performance					
6-Minute Walk Test, meters (normal range: 400−700)*,‖	435.0 ± 92.2	373.0 ± 75.9	378.9 ± 60.5	359.4 ± 77.1	
Odds ratio (50 unit increase)	Reference	**0.61(0.47, 0.80)**	**0.61(0.42, 0.88)**	**0.51(0.37, 0.72)**	0.0002
20-Meter Walk Test, n (%) seconds, <20	61 (80.3)	30 (62.5)	14 (70.0)	13 (52.0)	
Odds ratio (vs ≥20)	Reference	**0.38(0.16, 0.90)**	0.47 (0.14, 1.52)	**0.22(0.08, 0.62)**	0.02
Leg extensor muscle strength‡, newtons‖; 1RM	1,029.4 ± 441.4	951.5 ± 353.4	987.0 ± 306.9	830.6 ± 366.2	
Odds ratio (100 unit increase)	Reference	0.87 (0.76, 0.99)	0.87 (0.73, 1.04)	0.83 (0.70, 1.00)	0.08
Muscle contraction velocity‡, meters/second (40% of 1RM)‖	0.5 ± 0.2	0.5 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	
Odds ratio (0.1 unit increase)	Reference	0.99 (0.78, 1.26)	0.87 (0.63, 1.21)	0.66 (0.47, 0.92)	0.08
Muscle contraction velocity‡, meters/second (70% of 1RM)‖	0.3 ± 0.1	0.3 ± 0.1	0.4 ± 0.2	0.3 ± 0.1	
Odds ratio (0.1 unit increase)	Reference	0.95 (0.69, 1.31)	1.05 (0.68,1.60)	0.60 (0.39, 0.93)	0.12
Muscle power‡, n (%) watts, <228.4 (40% of 1RM)‖	32 (44.4)	22 (47.8)	8 (73.9)	17 (73.9)	
Odds ratio (vs ≥228.4)	Reference	1.51 (0.62, 3.67)	1.07 (0.33, 3.46)	4.05 (1.18, 13.88)	0.15
Muscle power‡, n (%) watts, <228.4 (70% of 1RM)‖	24 (33.3)	18 (40.9)	7 (36.8)	16 (69.6)	
Odds ratio (vs ≥228.4)	Reference	2.05 (0.84, 5.00)	1.98 (0.59, 6.61)	**6.42(1.97, 20.85)**	0.02
Berg balance score, n (%) ≤50 points (range: 0−56)‖	10 (13.2)	14 (28.6)	5 (25.0)	9 (36.0)	
Odds ratio (vs >50 points)	Reference	**2.67(1.02, 6.99)**	2.56 (0.70, 9.38)	**5.00(1.59, 15.72)**	0.04
Psychosocial health					
SF-36 mental component summary (range: 0−100)‖	54.6 ± 7.7	51.6 ± 10.5	50.6 ± 11.6	48.8 ± 8.4	
Odds ratio (10 unit increase)	Reference	**0.63(0.41, 0.97)**	**0.57 (0.33, 1.00)**	**0.51(0.30, 0.85)**	0.03
SF-mental health (range: 0−100)‖	77.2 ± 14.7	74.6 ± 17.4	70.7 ± 18.8	68.3 ± 15.1	
Odds ratio (10 unit increase)	Reference	0.87 (0.68, 1.12)	0.75 (0.55, 1.03)	0.73 (0.55, 0.97)	0.11

Table III (continued)

Characteristic	Higher function, early improvement n = 76	Moderate function, early improvement n = 50	Lower function, gradual improvement n = 20	Lower function, delayed improvement n = 25	Overall P value
Demographic					
Beck-II Depression Inventory (range: 0–63)	5.5 ± 6.7	8.0 ± 8.7	10.7 ± 10.2	11.7 ± 10.3	
Odds ratio (1 unit increase)	Reference	**1.06(1.00, 1.12)**	**1.09(1.02, 1.16)**	**1.09(1.03, 1.16)**	**0.01**
Perceived stress, (range: 0–40)	12.1 ± 6.0	12.6 ± 7.1	16.0 ± 8.7	16.8 ± 6.3	
Odds ratio (1 unit increase)	Reference	1.03 (0.97, 1.09)	**1.10(1.02, 1.19)**	**1.11(1.03, 1.20)**	**0.01**
MOS social support, (range: 19–95)‖	67.9 ± 22.6	70.0 ± 20.9	61.2 ± 26.8	71.1 ± 21.2	
Odds ratio (1 unit increase)	Reference	1.00 (0.99, 1.02)	0.99 (0.96, 1.01)	1.01 (0.99, 1.03)	0.42
Arthritis Self-Efficacy Scale-8 (range: 0–10)‖	7.0 ± 1.9	5.9 ± 2.0	5.5 ± 1.9	4.8 ± 2.3	
Odds ratio (1 unit increase)	Reference	**0.75(0.61, 0.91)**	**0.69(0.53, 0.90)**	**0.57(0.44, 0.74)**	**0.0002**
Outcome expectations (range: 1.0–5.0)‖	4.0 ± 0.5	3.9 ± 0.6	3.8 ± 0.4	3.9 ± 0.7	
Odds ratio (1 unit increase)	Reference	0.93 (0.47, 1.83)	0.78 (0.31, 1.97)	0.94 (0.41, 2.17)	0.96
Biomechanical factors					
Radiographic leg alignment§, n (%)					
Malalignment	26 (53.1)	19 (52.8)	6 (50.0)	11 (64.7)	0.70
Odds ratio (vs normal)	Reference	0.81 (0.33, 1.99)	0.87 (0.24, 3.19)	1.69 (0.53, 5.38)	

Bolded values indicate statistical significance (P < 0.05).

1RM = one-repetition maximum; CHAMPS = Community Healthy Activities Model Program for Seniors; MOS = Medical Outcomes Survey; PROMIS = Patient-Reported Outcomes Measurement Information Systems; SF-36 = Short Form-36; WOMAC = Western Ontario and McMasters Osteoarthritis Index.

All values are mean ± standard deviation, unless otherwise specified.

Note: Odds ratios >1.00 favor the first category in dichotomized comparisons.

* Normal range reported for the general population.
† Osteophyte was confirmed in the patellofemoral joint region for those with Kellgren/Lawrence grade 0 or 1.
‡ For muscle strength, power, and velocity, total n = 165 to 168: 86 to 88 for Tai Chi and 78 to 80 for Physical Therapy.
§ For radiographic leg alignment, total n = 121: 62 for Tai Chi and 59 for Physical Therapy.
‖ Higher score indicates greater health.

Table IV
Number of participants among trajectories by attendance-weeks

	Attendance-weeks*									
	0–2	3	4	5	6	7	8	9	10	11
PAIN Trajectory Groups										
Lower pain, early improvement	74	73	72	70	60	59	56	48	45	35
Moderate pain, early improvement	55	53	53	51	48	48	46	42	41	34
Higher pain, delayed improvement	26	25	23	23	22	19	19	19	16	14
Higher pain, no improvement	16	16	16	16	15	14	14	14	12	10
FUNCTION Trajectory Groups										
Higher function, early improvement	76	76	75	72	63	62	61	52	47	33
Moderate function, early improvement	50	47	47	45	43	41	38	37	35	26
Lower function, gradual improvement	20	19	18	18	17	15	14	13	10	7
Lower function, delayed improvement	25	25	24	24	22	21	21	21	17	13

* Attendance-weeks indicate the total number of weeks participants attended their assigned intervention.

found that poorer physical factors were associated with trajectories of moderate or higher initial severity, which is concordant with studies that show physical health to predict treatment response from exercise[13]. Our other finding was that some poorer psychological health factors were associated with the delayed response/non-response trajectories. An emerging body of evidence shows that psychological factors (e.g., depressive symptoms, mental health, etc.) may influence treatment response from exercise among patients with OA[3,6]. Our findings extend upon this evidence by showing that psychological health factors may help clinicians to distinguish patients who will have a delayed response or no response to exercise. There are many potential mechanisms through which psychological factors may modulate the effects of exercise in OA. Psychological morbidities may negatively modulate symptoms in chronic pain via symptom amplification, pain sensitization[49,50], and the fear-avoidance model[51]. Although greater psychological health may modulate exercise outcomes through better attendance, this is unlikely to have influenced our findings because we quantified exercise dose according to attendance-weeks. While a definitive rationale is beyond the scope of this study, our results provide an indication that psychological status may play a role in stratifying patients according to their trajectory of treatment response from exercise.

This study has limitations. First, because some people did not attend the minimum required number of intervention sessions, this may have affected our results and interpretation. Second, the effects of treatment from higher amounts of exercise exposure may be biased towards those who were more adherent to the intervention. Third, owing to the hypothesis-generating nature of this investigation, analyses were not adjusted for multiple comparisons which could have led to some spurious associations. Furthermore, some trajectory groups had small sample sizes, especially in the higher pain and worse function groups. . This in combination with overall low sample size may have led to sparse data bias[52]. In addition, although group-based trajectory modeling assumes that data is missing at random, it is possible that some of the missing data from this investigation were non-random. However, this does not detract from the primary value of our findings from this exploratory study, which is that various, meaningful trajectories of treatment response exist in OA, and that some patients had a delayed response to exercise. Furthermore, we utilized several other methods to reduce bias, including blinded assessors of

physical performance, radiographic and symptomatic verification of diagnosis, and our use of post-randomization WOMAC pain/function data as the baseline measure, which likely reduced the influence of self-selection bias and regression to the mean.

Despite these limitations, our investigation found novel information to better understand who may benefit from treatment and how their symptomatic trajectories actively change with increasing exercise exposure. To fully characterize and understand these subgroups, additional study among larger samples is imperative. We therefore call for strong consideration of this approach (i.e., frequently measured outcomes during intervention) as a part of standard investigative practice for consensus guidelines of exercise trials in OA. In addition, future studies could investigate whether modifications in the exercise dose (e.g., greater frequency, longer durations, different exercise types, etc.) lead to better outcomes among trajectories with delayed or no improvements.

In conclusion, this exploratory study suggests that there are distinct trajectories for both pain and function over 12 weeks of exercise exposure among adults with symptomatic knee OA. While the majority of participants experienced improvements over short-term exposure, we found a subset of participants with higher baseline symptom severities who do not respond. By helping to disentangle the heterogeneity of treatment response in OA, these findings may advance the delivery of patient-centered care for this large patient population.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.joca.2018.01.016.

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