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Exploring different models of pain phenotypes and their association with pain worsening in people with early knee osteoarthritis: The MOST cohort study

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SUMMARY

Objective: To determine i) pain phenotypes (PP) in people with early-stage knee osteoarthritis (EKOA); ii) the longitudinal association between the phenotypes and pain worsening at two years.

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Author Contributions

All authors contributed to drafting the article or revising it critically for important intellectual content and final approval of the submitted version. In addition, LCC contributed to study conception and design, analysis, and interpretation of the data; TN, TB, TA and DK to study conception and design and acquisition of the data; YVRN, MJ, LM, DK, SH, LFL, CL, MN to analysis and interpretation of data.

Declaration of Competing Interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2023.09.003.

Design: We studied participants with EKOA from the Multicenter Osteoarthritis Study defined as pain intensity ≤3/10, Kellgren and Lawrence grade ≤2, intermittent pain none to sometimes, and no constant pain. Two models of PP were explored. Model A included pressure pain thresholds, temporal summation, conditioned pain modulation, pain catastrophizing, sleep quality, depression, and widespread pain (WSP). In Model B, gait characteristics, quadriceps strength, comorbidities, and magnetic resonance imaging features were added to Model A. Latent Class Analysis was used to create phenotypes, and logistic regression was used to determine their association with pain worsening.

Results: 750 individuals (60% females), mean age [standard deviation (SD)]: 60.3 (9.4) were included in Model A and 333 individuals (60% females), mean age (SD): 59.4 (8.1) in Model B. 3-class and 4-class solutions were chosen for Model A and Model B. In Model A, the most "severe" phenotype was dominated by psychosocial factors, WSP, and measures of nervous system sensitization. Similarly in Model B, the Model A phenotype plus gait variables, quadriceps strength, and comorbidities were dominant. Surprisingly, none of the phenotypes in either model had a significant relationship with pain worsening.

Conclusion: Phenotypes based upon various factors thought to be important for the pain experience were identified in those with EKOA but were not significantly related to pain worsening. These phenotypes require validation with clinically relevant endpoints.

Keywords

Phenotypes; Early-onset knee OA; Pain progression

Introduction

Osteoarthritis (OA) is a highly prevalent disorder affecting approximately 500 million individuals globally.[1] The knee is the most commonly affected joint accounting for the majority of OA costs to North American healthcare.[2] Arguably, the driver of those costs is the pain of knee OA, which is also the leading reason for medical consultation.[3] Currently, there is a lack of effective treatment options to alleviate pain in knee OA, with most treatments having small to moderate effect sizes at best.

Pain mechanisms in knee OA are multi-factorial with nervous system sensitization, poor sleep, and psychological variables in addition to the structural changes contributing to the pain experience.[3] However, inter-patient pain variability and accompanying clinical heterogeneity demands a tailored treatment approach rather than the current 'one size fits all'.[4] Therefore, the development of personalized treatment strategies using phenotyping to target the underlying pain mechanisms is necessary and recommended.[5] This is particularly important in the early stages of the disease, where prevention of pain progression can minimize the long-term burden.[6–8]

Pain phenotyping has been proposed to effectively represent the multidimensional pain experience.[5] Phenotypes are defined as a collection of observable traits that can identify and characterize a subgroup in a defined population.[9] Previous phenotyping studies in people with established knee OA have reported clinical (including chronic pain/sensitization),

inflammatory, metabolic syndrome, bone and cartilage metabolism, mechanical overload, imaging features, and minimal joint disease phenotypes.[9,10] However, heterogeneity in the number and type of indicator variables across domains was present in multiple studies. For studies examining pain phenotypes, factors with direct (e.g., pain sensitization), and indirect associations with pain (e.g., muscle strength) have been analyzed,[10] fueling an ongoing debate regarding how to best model pain phenotypes that inform symptomatic progression.

The majority of phenotyping studies have been cross-sectional,[11–15] with some using measures of nervous system sensitization (i.e., quantitative sensory testing (QST)) alone,[11,12] or in combination with clinical (e.g., muscle strength), or psychological measures.[13–15] Other factors such as imaging features, and mechanical overload have also been shown to contribute to phenotyping and have an association with pain outcomes,[16,17] indicating that disease-related domains may also be useful for pain phenotype creation.

Only two larger prospective cohort studies have reported the longitudinal relationship of pain phenotypes to changes in pain over time.[18,19] Carlesso et al., identified four persistent pain susceptibility phenotypes using QST and psychological measures in individuals at risk or with knee OA, who were initially free of persistent pain.[18] Those with the highest proportion of pressure pain sensitivity had twice the odds of developing persistent knee pain at 2 years.[18] Pan et al, used psychological, structural, and lifestyle factors, and demographic data, to identify a subgroup with high levels of emotional factors and low levels of structural factors having a greater association with knee pain at 10 years, but did not include pain sensitivity measures.[19]

Recently, there has been an emphasis on understanding sex differences for various outcomes in knee OA as studies have shown important sex- differences with greater pain sensitivity,[20] and lower quadriceps strength,[21] in females than in males with little or no exploration of sex-specific analysis in phenotyping literature in knee OA. Lastly, to our knowledge, no pain phenotyping studies have been conducted in people with early-stage knee OA, a subgroup for which no standard definition exists.

Therefore, our study attempted to address the current gaps in knee OA phenotyping literature by exploring different phenotype models and their association with pain worsening in people exclusively with early-stage knee OA.

Objectives of the study

The specific objectives of our study were to determine:

- **i.** Phenotypes using two different modeling strategies in people with early-stage KOA.
- **ii.** Participant characteristics and whether there are sex differences associated with the identified phenotypes.
- **iii.** The longitudinal association between the identified phenotypes from the different models and pain worsening at two-year follow-up.

Methods

Study design and sample

We used data from participants in the Multicenter Osteoarthritis (MOST) study, a National Institutes of Health–funded longitudinal cohort of community-dwelling adults.[22] Participants in MOST were recruited from Birmingham, Alabama, and Iowa City, Iowa.[22] We used data from MOST to identify two different models of phenotypes (Model A consisting of pain variables and Model B consisting of pain plus disease-related variables) using cross-sectional data and determined their longitudinal relationship with pain worsening, respectively. The current sample comprised participants from the original study cohort at 12 years follow-up and baseline data from a new cohort that was added at this same time point. Participants exclusively with early-stage knee osteoarthritis (KOA) were defined as those with pain intensity ≤3/10 in the past 30-days, Kellgren and Lawrence (KL) grade 0, 1, 2, having intermittent pain with a frequency of 'none to sometimes' whereas those with KL = 0 had to have at least intermittent pain of 'sometimes', and no constant pain, measured using the Intermittent and Constant Osteoarthritis Pain (ICOAP) Questionnaire. Those with complete data for the 14th year follow-up visit were selected. For those with bilateral eligible knees, one was randomly selected, and individuals with positive peripheral neuropathy were excluded. The details of the cohort have been published elsewhere,[22] and the study was approved by the relevant institutional review boards and was in compliance with the Helsinki Declaration.[22]

Pain phenotype creation

We chose to use variables based on our previous work on pain susceptibility phenotypes in people with established OA[18] (i.e., pressure pain threshold (PPTs) (patella and forearm), temporal summation (TS), conditioned pain modulation (CPM), pain catastrophizing, sleep quality, depression, and widespread pain (WSP)) which were associated with the development of persistent pain. The detailed procedures for the measurement of indicator variables are described in the supplementary file.

PPTs

PPTs were assessed with a pressure algometer (1 cm^2 rubber tip, FDIX25 Wagner) at the patella and forearm to capture peripheral and central sensitization, where higher values indicate lower pain sensitivity. Due to known differences in PPTs by sex, values were standardized for males and females seperately.[22]

TS

TS was assessed using a standard set of weighted probes from 64 to 512 mN where pain ratings were reported after 10 stimulations and 15 s post-stimulation. TS is calculated by subtracting the first pain rating from the last,[23] where higher values indicate greater pain facilitation.

CPM

CPM was assessed following recommended testing,[24–26] with values < 100 indicating pain facilitation.

Depressive symptoms

The Center for Epidemiologic Studies Depression (CES-D) scale was used to measure the severity of depression symptoms.[27] The total CES-D score was analysed as a continuous indicator variable.[27]

WSP

WSP was measured with a validated homunculus using a modified American College of Rheumatology definition.[28] The responses were categorized as WSP present or absent.

Pain Catastrophizing

Pain catastrophizing was measured using one item from the Pain Coping Strategies Questionnaire, which was shown to have a good correlation with the full scale.[29] The responses were dichotomized as pain catastrophizing present or absent.

Sleep Quality

Sleep quality was measured using a Likert scaled item categorized as very good, fairly good (good sleep quality), fairly bad, very bad (poor sleep quality).[19]

In Model B, variables of gait characteristics (gait speed, step length, ground reaction force [GRF]), quadriceps strength, comorbidities, and magnetic resonance imaging (MRI) features were considered along with the pain variables in Model A.

Comorbidities

Charlson comorbidity index[30] was used to quantify the number of comorbid conditions, which was analyzed as a continuous variable.

Gait Characteristics

All participants completed two trials of a 20-meter walk task where they were asked to walk at their self-selected pace while inertial sensors (OPAL, APDM Inc., Portland, OR, USA) on both ankles and lower back. Gait speed was determined as the total distance walked (20 m) divided by the total walking time. The average step length was calculated by dividing the total distance walked (20 m) with the total number of steps. For both measures, average of the two trials was used for analyses. Lastly, three-dimensional GRF data were recorded while walking over a force platform (AccuGait, AMTI, Inc, Watertown, MA, USA).

Quadriceps strength

The one repetition-maximum (1RM) of quadriceps was used as a measure of strength measured using an instrumented dynamometer (HUMAC NORM, Computer Sports Medicine Inc, Stoughton, MA, USA).

MRI features

Semiquantitative features were obtained using the MRI Osteoarthritis Knee Score (MOAKS) grading systems.[31] In the MOST Study at each clinical visit, a single knee was randomly selected for longitudinal MRI readings, thus limiting the sample size for this analysis. The MRI variables selected were medial and lateral meniscal extrusion, trochlear and femoral cartilage loss, and effusion-synovitis which were categorized as Present or Absent.[20] These particular features were selected to align with measures available on ultrasonography for a planned future external validation project within another cohort (Western Ontario Registry of Early Osteoarthritis (WOREO) knee cohort).

Definition of pain worsening at 2-year follow-up

Pain worsening was defined as those having intermittent pain of a frequency that is 'often or very often', and having any constant pain measured by the ICOAP scale, and in addition, they must have had an increase ≥2 on the pain VAS at the 2-year follow-up compared with the baseline VAS pain rating.

Statistical analysis

Descriptive characteristics of the sample were reported (age, sex, body mass index (BMI), Kellgren Lawrence grade, race, education) using means and standard deviations for continuous variables and counts and percent for categorical variables.

Objective 1

Latent Class Analysis (LCA) was used to create the phenotypes for both models, which is a data-driven clustering technique recommended by the OA consensus statement on phenotyping.[32] LCA is a flexible unsupervised model-based analysis which provides fit statistics to inform objective indices of classes that do not require subjective investigator assessment. These fit statistics can then be complemented by a current understanding of the topic of interest. In addition, posterior probabilities of class assignment are provided. The optimal number of classes in each model was decided using fit statistics (sample size adjusted Bayesian Information Criterion (BIC), Bootstrapped Likelihood Ratio Test (BLRT), and Vo-Loung Mendel Ruben test (VLMRT)) ensuring each class had a minimum of 10% of the total sample, contextualizing with current understanding of the clinical presentation of early-stage knee OA.[33] We started with a 2-class model for each of Models A and B and proceeded to evaluate larger number of classes until the fit statistics indicated poor fit (e.g., increase in BIC, BLRT, VLMRT > 0.05) or if there was less than 10% of the sample per class. Once the ideal number of classes was determined for both models, profiles of each class were interpreted using class-specific means/proportions of the indicator variables.

Objective 2

Next, once the number of classes was decided upon, we profiled the classes with our selected covariates of age, sex, KL grade, BMI, race, and education, considered in both models, whereas comorbidities were also considered in Model A (not considered for Model B because these were included in the model). A sex-stratified analysis was then conducted which included the assessment of measurement invariance (i.e., the extent to which latent

class models are similar across groups) to assess whether class values (i.e., item response probabilities and item means) for males and females were equivalent. This included the comparison of unconstrained (no restriction of class probabilities or class sizes), semi-constrained (class probabilities equal), and fully constrained models (class probabilities and class numbers equal), compared using the fit statistics (BIC).[34]

Sensitivity analysis

Two sensitivity analyses were conducted. First, we ran Model B with an additional MRI variable, Hoffa's synovitis, to determine its contribution. This variable was not included in the main model as it was not available in the WOREO study which will be used for external validation; however, previous studies have shown that Hoffa's synovitis has associations with pain sensitization.[35] Next given that the sample for Model B included a sub sample of Model A, we re-ran Model A with participants included in Model B to assess their similarity.

Objective 3

We evaluated the relation of the identified phenotypes to risk of pain worsening using logistic regression, adjusted for age, sex, KL grade, BMI, race, and education. Given that this method allows for uncertainty in class membership, we also performed the Lanza method for distal outcome analysis which determines classes and their relationship to a distal outcome in one model but does not allow for adjustment of covariates or confounders. All analyses were performed using Mplus software and STATA version B/E 17.0.

Results

At the 12th year of the MOST study, there were 2177 participants from the original cohort and 1525 participants from the new cohort. After applying the inclusion criteria, 759 participants were eligible. Those having complete data resulted in 750 individuals (60% females) with mean age [standard deviation (SD)]: 60.3 years (9.4) and mean BMI (SD): 28.5(5.3) in Model A and 333 individuals (60% females) with mean age (SD): 59.4 years (8.1) and BMI (SD): 27.8(4.6) in Model B. In the MOST Study at each clinical visit, a single knee was randomly selected for longitudinal MRI readings, thus limiting the sample size for this analysis in model B. The participant's characteristics are shown in Table I.

Objective 1

Three class and four class solutions were chosen for Model A and Model B, respectively, considering fit statistics (specifically the sample size adjusted BIC and BLRT) and current knowledge of the pain and disease-related variables in early-stage KOA. Figs. 1 and 2 show radar plots of the indicator variables of both models with standardized values for the continuous variables and proportions for the categorical variables.

Model A

Class 1 (n = 476, 62%) is distinguished by the lowest PPTs (most sensitive), middle values of TS and depressive symptoms, and moderate proportions of individuals with WSP. Class 2 (n = 98, 13%) included individuals with the highest levels of TS and depressive symptoms

(average score was above the cut-score (16/60) for depressive symptoms), and the highest proportion of individuals with pain catastrophizing, poor sleep quality, and WSP. Class 3 (n = 186, 25%) comprised people with the highest PPTs (least sensitive), the lowest values for CPM (inefficient) and depressive symptoms, and the smallest proportion of individuals with WSP (see Table II, and Fig. 1).

Model B

MRI findings were generally of low proportions and somewhat similar across all classes with the exception of medial meniscus extrusion which occurred in low (classes 1–3; 11–22%) to moderate (class 4; 39–41%) proportions of individuals. Lateral meniscus extrusion was generally absent. Cartilage loss at the medial anterior femur ranged from 2% (class 2) to 7% (class 4), while the lateral anterior femur ranged from 2% (class 2) to 4% (class 4). Joint effusion-synovitis ranged from 0 (class 4) to 4% (classes 1 and 2). See Table III for summary values of all indicator variables.

Class 1 (n = 167, 50%) was characterized by the second to lowest values of PPTs, depressive symptoms, and comorbidities second to highest values on gait speed and step length, and the second highest proportion of people with WSP. Class 2 (n = 68, 20%) was characterized by people with the lowest PPTs, gait speed, step length and quadriceps strength, highest TS, CPM (efficient), depressive symptoms, comorbidities, and the largest proportion of individuals with WSP, pain catastrophizing and poor sleep. In class 3 (n = 53, 16%) PPTs were the highest (least sensitive), with the lowest TS (least sensitive), CPM (inefficient), depressive symptoms, and comorbidities. In Class 4 (n = 45, 13%) highest GRFs, quadriceps strength, step length, and gait speed were observed with second to highest values for PPTs, depressive symptoms, and proportions of people with pain catastrophizing (see Table III).

Fit of Model A vs. Model B: The 3-class solution of Model A had a sample size adjusted BIC of 21020.693, whereas in Model B the BIC value was 17755.050 indicating a relatively better model fit.

Objective 2

In Model A, covariates with significant class associations included age, KL grade 1–2, BMI, high school education, and comorbidities whereas in Model B, all the covariates were associated with latent classes (see Table IV).

Sex-specific analysis: The fit statistics (BIC) indicated that measurement invariance (i.e., equal conditional response probabilities or similar responses to indicator variables) held across the latent classes in both models. Therefore, the running of sex specific models was unnecessary[34] and sex-specific values for indicator variables were obtained by class assignment (see supplementary files Tables VI and VII). Female sex was significantly associated with the latent classes in both models. We did not conduct tests of significance due to small cell sizes in Model B.

Objective 3

Overall, 255 (34%) individuals in Model A and 90 (27%) individuals in Model B met the criteria of pain worsening at 2-year follow-up. In neither model were any significant associations identified between the latent classes and pain worsening after adjusting for covariates. The odds ratios with 95% confidence intervals are shown in Table V. The results of the Lanza method (supplementary file, table 8), also remain nonsignificant, however, the odds ratios were slightly higher likely due to the lack of covariate adjustment.

Sensitivity analysis 1

The inclusion of Hoffa's synovitis in Model B did not result in any substantive changes either in the number or distribution of classes. The mean/proportion of the indicator variables with 95% CI are summarized in Table IX of supplementary file. The original model had an overall entropy value of 0.808 whereas the model with Hoffa's synovitis resulted in a similar entropy of 0.812.

Sensitivity analysis 2

The LCA results of model A (with model B sample) are summarized in table 10 of the supplementary material, which indicates that the number and profiles of latent classes were similar to the original model A (n = 750)'.

Discussion

We identified different early-stage KOA phenotypes based on the factors included in the pain model (Model A) and the pain plus disease-related variables model (Model B). Model B showed slightly better fit than Model A, indicating that perhaps a more robust model in this sample may be preferred. However, this may be due to larger number of indicator variables in the model.[36] Measures of nervous system sensitivity (QST) and psychosocial variables were distinguishing features in both models, with gait characteristics, quadriceps strength, comorbidities, and meniscal extrusion contributing to the classes in Model B. However, surprisingly, we found no significant associations with pain worsening two years later in either model. This indicates that all groups had a similar propensity for pain worsening, with no single cluster of features substantially increasing that risk over the other clusters. Nonetheless, our study is unique in exploring what we believe are the first phenotypes in an early-stage knee OA sample using variables from various domains for phenotype creation. This knowledge can provide insights on potentially important indicator variables for future studies.

Earlier studies on pain phenotype creation using pain-related variables (similar to Model A) in people with established KOA have also reported greater contributions from both QST factors and psychological factors.[18,19] Our phenotypes (Model A) also differed with respect to QST and psychosocial constructs with relatively greater separation between classes on PPTs (patella and forearm), depressive symptoms, pain catastrophizing, WSP, and sleep quality indicating their importance throughout the disease course. However, none of the classes in Model A were found to have significantly different associations with longitudinal pain worsening. Two previous trajectory analyses of pain in people with early

symptomatic knee OA (KL 0–1) have been reported. Bastick et al reported 6 different types of pain trajectories ranging from constant mild pain to constant severe pain, with stable, regressing, and progressing courses were highlighted.[37] Wesseling et al., analyzed pain severity trajectories and found minimal, mild, and moderate trajectories, all three of which were stable over 5 years.[38] Importantly our definition of pain worsening differs from previous work and includes a composite of pain intensity and pain qualities that have been linked to disease progression.[39] Future studies are needed with longer follow-up using this outcome to determine its value, including response to tailored treatments or other prognostic markers (e.g., structural worsening).

Model B classes were distinguished by Model A variables and disease-related variables of quadriceps strength, comorbidities, and gait characteristics. Lower quadriceps strength has been correlated with greater pain levels in people with early stage KOA[40] and found to be associated with pain worsening and structural progression in people with or at risk of knee OA.[41,42] Quadriceps strength also correlates with stride length and gait speed/velocity in people with both early-stage and established KOA.[43,44] Though there is no strong evidence for the relationship between quadriceps strength and knee joint loading,[45] class 4 of model B was comprised of mostly men, had highest quadriceps strength, GRFs, and features of meniscal extrusion. It could be theorized that greater muscle co-contraction during walking may have contributed to imaging features observed in this group, however, other factors such as alignment that were not accounted for in our study could confound this relationship.

Despite previous work associating QST with joint effusion,[35] this feature and the contribution of other MRI findings was very low with the exception of medial meniscal extrusion. Evidence for synovitis and increased cartilage metabolism in early disease has been reported by others.[46–48] Part of the challenge in comparing study findings of imaging in this population has been a lack of consensus on a standardized definition of early KOA.[49] Therefore, results may differ across cohorts when different thresholds are used for early KOA. Nonetheless, our initial findings are informative and will serve as a foundation for future research in this area.

Strengths and limitations

Strengths of our study include addressing the current gaps in literature by exploring phenotypes in a sample of people with early-stage KOA, using different modeling strategies with multiple constructs representing the multi-dimensional nature of pain in relation to a longitudinal composite pain outcome. Our phenotypes using the agnostic data-driven approach of LCA, are known to be superior to other clustering methods. Identifying phenotypes in this population may lead to the development of targeted treatments that may prevent pain progression and lessen the disease burden.

A few limitations of our study should be considered. Model B differed from Model A due to the inclusion of different variables and our complete case analysis approach resulted in a smaller sample size. This combination of changes appears to have resulted in a different make-up of classes in Model B from Model A as the participants in Model A did not directly map onto Model B classes. We cannot be certain whether these differences are due to changes in sample size or the variables included. We were unable

to consider significant quantitative sex differences. Also, considering the exploratory nature of our study, the phenotypes derived in our study need further validation using clinically meaningful endpoints and external validation in an independent sample. Lastly, the variables used to capture pain worsening only covered the prior 30-day period and may not be indicative of pain worsening over a longer period.

Conclusion

Similar to established KOA, distinct phenotypes exist in a cohort of people with early-stage KOA. We explored two phenotype models, one using pain variables only, and the other using pain and disease-related variables. Our results support the value of measures of nervous system sensitization and other psychosocial variables for phenotyping and suggest that gait variables, quadriceps strength, and comorbidities could add valuable information. However, it appears that these MRI features, except for medial meniscal extrusion, do not contribute meaningfully to early-stage knee OA phenotypes. No class from either model was significantly related to our composite outcome of pain worsening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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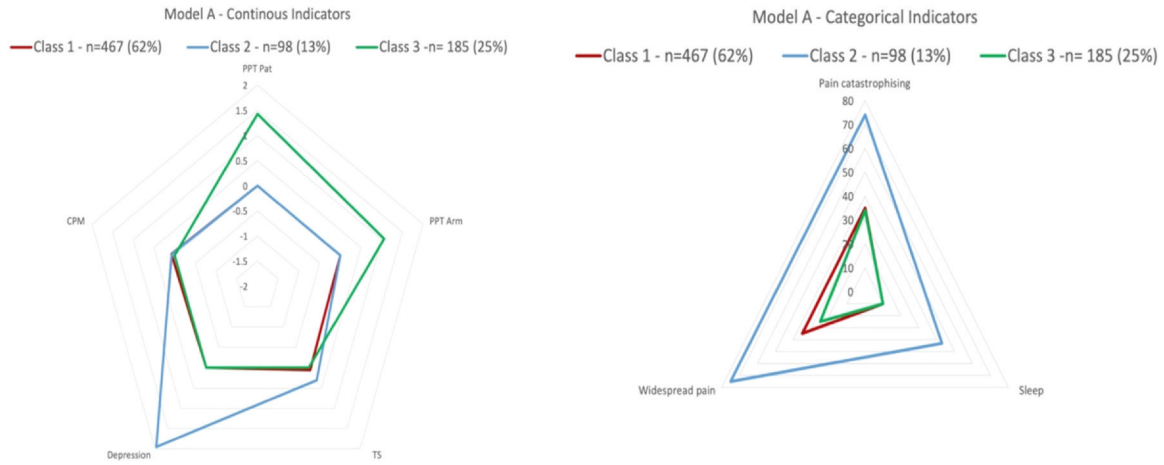

Fig. 1.

Spider gram of indicator variables and latent classes in model A. Continuous values are standardized. PPT pat: Pressure Pain Thresholds Patella; PPT Arm: Pressure Pain Thresholds forearm: TS: Temporal Summation; CPM: Conditioned Pain Modulation.

Fig. 2.

Spider gram of indicator variables and latent classes in model B. Continuous values are standardized PPT pat: Pressure Pain Thresholds Patella; PPT Arm: Pressure Pain Thresholds forearm: TS: Temporal Summation; CPM: Conditioned Pain Modulation; Sleep: Poor Sleep Quality; PIF: Peak Inertial Force; Q´ceps strength: Quadriceps strength; CDMAF: Cartilage Loss Medial Anterior Femur; CDLAF: Cartilage Loss Lateral Anterior Femur; MEMMM: Meniscal Extrusion Medial Meniscus Medial; MEMMA: Meniscal Extrusion Medial Meniscus Anterior; MELMA: Meniscal Extrusion Lateral Meniscus Anterior; MELML: Meniscal Extrusion Lateral Meniscus Lateral.

Table I

Osteoarthritis and Cartilage

Variable	Whole sample (Model A) (N = 750)	Model B (n = 333)
Age	60.3 (9.4)	59.4 (8.1)
Mean (SD)		
Females (n, %)	457 (61%)	203 (61%)
BMI	28.5 (5.3)	27.8 (4.7)
Mean (SD)		
VAS at baseline	13.0 (8.5)	12.7 (8.2)
Mean (SD)		
VAS = 0 (n, %)	236 (31%)	113 (33%)
VAS = 1 (n, %)	279 (39%)	122 (36%)
VAS = 2 (n, %)	176 (23%)	75 (22%)
VAS = 3 (n, %)	59 (7%)	23 (6%)
Race:	643 (85%)	288 (86%)
Caucasian (n, %)		
KL grade (n, %)	Grade 0: n = 380 (50%)	Grade 0: n = 198 (60%)
	Grade 1: n = 185 (25%)	Grade 1: n = 114 (34%)
	Grade 2: n = 185 (25%)	Grade 2: n = 21 (6%)

SD: Standard Deviation; BMI: body mass index; VAS: Visual Analogue Scale; KL: Kellgren and Lawrence

Descriptive characteristics of the sample.

Table II

Osteoarthritis and Cartilage

Indicator variable	Class 1 (n = 467, 62%)	Class 2 (n = 98, 13%)	Class 3 (n = 185, 25%)
PPT patella (kg/cm^2)	4.4 (1.4)	4.8 (1.8)	9.3 (1.2)
Mean (SD)	(4.3–4.6) *	(4.5–5.2) *	(9.1–9.5) *†
PPT forearm (kg/cm^2)	3.2 (1.1)	3.4 (1.2)	5.9 (2.1)
Mean (SD);	(3.1–3.4) *	(3.2–3.7) *	(5.6–5.2) *†
TS (0–10 NRS)	1.5 (1.6)	1.9 (1.8)	0.8 (1.2)
Mean (SD)	(1.4–1.6) *	(1.5–2.2) *	(0.7–1.0) *†
CPM (% difference)	109.7 (28.3)	109.4 (29.7)	99.9 (25.9)
Mean (SD)	(107.6–112.4) *	(103.7–116.3) *	(96.0–102.8) *†
Depression	4.2 (3.5)	17.8 (6.0)	3.5 (3.5)
Mean (SD)	(3.7–4.7) *	(14.8–19.5) *†	(3.0–4.3) *
Widespread Pain	35% (n = 160)	75% (n = 74)	25% (n = 46)
(Proportion)	(30–39) *	(67–83) *†	(19–31) *
Pain Catastrophizing	34% (n = 159)	76% (n = 75)	35% (n = 64)
(Proportion)	(30–39) *	(66–83) *†	(28–40) *
Sleep Quality	10% (n = 46)	43% (n = 42)	11% (n = 20)
(Proportion)	(7–13) *	(34–53) *†	(6–15) *

SD: Standard Deviation: PPT: Pressure Pain Thresholds; TS: Temporal Summation; CPM: Conditioned Pain Modulation

*95%CI

†indicates class different from the other two.

Summary values for indicator variables: Model A.

Table III

Osteoarthritis and Cartilage

Indicator variable	Class 1 (n = 167, 50%)	Class 2 (n = 68, 20%)	Class 3 (n = 53, 16%)	Class 4 (n = 45, 14%)
PPT patella (kg/cm^2)	4.9 (1.6)	4.2 (1.7)	9.5 (1.0)	5.8 (2.4)
Mean (SD)	(4.6–5.1) *	(3.8–4.6) *	(9.2–9.7) *†	(5.0–6.5) *
PPT forearm (kg/cm^2)	3.5 (1.0)	2.9 (1.4)	5.8 (2.0)	4.3 (1.7)
Mean (SD)	(3.4–3.9) *	(2.6–3.3) *	(5.3–6.4) *†	(3.7–4.7) *
TS (0–10 NRS)	1.3 (1.4)	2.3 (1.9)	0.8 (1.1)	1.1 (1.5)
Mean (SD)	(1.0–1.4) *	(1.8–2.9) *†	(0.6–1.0) *	(0.8–1.5) *
CPM (% difference)	111.9 (32.7)	111.5 (24.0)	97.5 (23.1)	100.7 (22.3)
Mean (SD)	(106.8 – 116.9) *	(105.7–117.3) *	(92.0–103.0) *†	(92.6–108.9) *
Depression	4.8 (4.8)	10 (6.9)	3.5 (3.3)	6.7 (7.2)
Mean (SD)	(3.3–6.4) *	(7.2–12.7) *†	(2.6–4.3) *	(4.5–9.0) *
Comorbidities	0.2 (0.5)	0.7 (1.4)	0.3 (0.6)	0.2 (0.6)
Mean (SD)	(0.1–0.2) *	(0.4–1.0) *†	(0.1–0.4) *	(0.0–0.4) *
Quad Strength (Nm.)	47.7 (13.8)	43.8 (14.5)	51.3 (14.2)	94.1 (23.8)
Mean (SD)	(44.0–51.3) *	(39.3–48.4) *	(46.9–55.6) *	(84.3–104.0) *†
Step length (m.)	0.7 (0.0)	0.6 (0.0)	0.7 (0.0)	0.7 (0.0)
Mean (SD)	(0.7–0.7) *	(0.5–0.6) *	(0.6–0.7) *	(0.7–0.8) *
Gait speed (m/sec)	1.4 (0.1)	1.2 (0.1)	1.3 (0.1)	1.5 (0.1)
Mean (SD)	(1.4–1.5) *	(1.0–1.2) *	(1.2–1.4) *	(1.4–1.5) *
PIF (%BW)	799.5 (138.4)	822.5 (176.9)	833.7 (132.9)	1059.2 (140.7)
Mean (SD)	(765.3–834.6) *	(771.9–873.2) *	(793.0–874.4) *	(1019.5–1099.0) *†
Widespread Pain	35% (n = 19)	57% (n = 38)	28% (n = 47)	28% (n = 12)
(Proportion)	(26–44) *	(44–70) *†	(15–38) *	(14–42) *
Pain Catastrophizing	35% (n = 19)	54% (n = 34)	37% (n = 62)	44% (n = 20)
(Proportion)	(24–47) *	(34–74) *†	(22–47) *	(28–60) *
Sleep Quality	12% (n = 7)	42% (n = 30)	9% (n = 15)	6% (n = 3)
(Proportion)	(4–20) *	(27–57) *	(2–17) *	(0–14) *

Indicator variable	Class 1 (n = 167, 50%)	Class 2 (n = 68, 20%)	Class 3 (n = 53, 16%)	Class 4 (n = 45, 14%)
CDMAF	5% (n = 3)	2%	3% (n = 5)	7% (n = 4)
(Proportion)	(1–9) *	(0–6) *	(0–8) *	(0–16) *†
CDLAF	4% (n = 3)	10% (n = 6)	2% (n = 3)	4% (n = 2)
(Proportion)	(0–9) *	(3–17) *†	(0–11) *	(0–10) *
MEMMM	14% (n = 8)	12% (n = 9)	16% (n = 27)	38% (n = 16)
(Proportion)	(8–20) *	(1–24) *	(6–27) *	(22–54) *†
MEMMA	13% (n = 7)	11% (n = 7)	24% (n = 43)	40% (n = 20)
(Proportion)	(7–19) *	(0–24) *	(13–35) *	(24–55) *†
MELMA	0% (0) *	0% (0) *	0% (0) *	0% (0) *
(Proportion)				
MELML	0% (0) *	1%	1% (0–4)*	0% (0) *
(Proportion)		(0–3) *		
Effusion	1%	4% (n = 3)	4% (n = 5)	2% (n = 1)
(Proportion)	(0–4) *†	(0–9) *	(0–12) *	(0–6) *

SD: Standard Deviation; PPT: Pressure Pain Thresholds; TS: Temporal Summation; CPM: Conditioned Pain Modulation; PIF: Peak Inertial Force; Quad strength: Quadriceps strength; PIF: Peak Inertial Force CDMAF: Cartilage Loss Medial Anterior Femur; CDLAF: Cartilage Loss Lateral Anterior Femur; MEMMM: Meniscal Extrusion Medial Meniscus Medial; MEMMA: Meniscal Extrusion Medial Meniscus Anterior; MELMA: Meniscal Extrusion Lateral Meniscus Anterior; MELML: Meniscal Extrusion Lateral Meniscus Lateral:

*95%CI

†indicates class different from the others.

Summary values for indicator variables: Model B.

Table IV

Osteoarthritis and Cartilage

Covariates	Model A			Model B			
	Class 1 OR 95% CI	Class 2 OR 95% CI	Class 3 Referent	Class 1 OR 95% CI	Class 2 OR 95% CI	Class 3 Referent	Class 4 OR 95% CI
Age	*1.04 (1.01–1.06)*	1.00 (0.96–1.03)	1	1.00 (0.96–1.04)	*1.09 (1.0 –1.16)*	1	*0.92 (0.87–0.98)*
Female sex	1.03 (0.69–1.38)	1.43 (0.9–1.97)	1	*2.59 (1.3–5.13)*	*5.23 (2.25–12.14)*	1	*0.04 (0.01–0.16)*
KL grade: 1–2	*0.60 (0.41–0.93)*	*0.55 (0.31–0.98)*	1	0.76 (0.47–1.24)	*0.52 (0.28–0.93)*	1	1.09 (0.53–2.23)
BMI	*0.74 (0.62–0.87)*	*0.67 (0.32–0.56)*	1	0.99 (0.91–1.09)	*1.20 (1.10–1.32)*	1	*1.24 (1.11–1.37)*
Race: Non-Caucasian	1.66 (0.88–3.12)	1.18 (0.51–2.74)	1	0.48 (0.21–1.11)	0.94 (0.29–3.05)	1	0.44 (0.11–1.81)
Education: ≤ high school	1.18 (0.57–2.42)	0.40 (0.17-0.94)	1	2.18 (0.57–8.3)	*0.40 (0.11 –1.38)*	1	2.77 (0.62–12.40)
Comorbidities	1.12 (0.89–1.39)	*1.53(1.19–1.96)*	1	-	-	-	-

CI: Confidence Interval; BMI: body mass index; KL: Kellgren and Lawrence

Association of covariates with latent classes.

Table V

Osteoarthritis and Cartilage

Classes	Model A (n = 750)		Model B (n = 333)	
	n (%) pain worsening	OR (95% Cl)	n (%) pain worsening	OR (95% Cl)
Class 1	160 (21.3)	0.98 (0.68–1.41)	25 (7.5)	1.23 (0.54–2.77)
Class 2	30 (4)	0.77 (0.45–1.32)	36 (10.8)	0.57 (0.28–1.16)
Class 3	35 (4.7)	1	17 (5.1)	1
Class 4		NA	12 (3.6)	0.79 (0.31–2.04)

Adjusted for age, sex KL grade, BMI, race, education, and comorbidities for Model A.

Adjusted Association between Latent classes and Pain Worsening.