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Pain Susceptibility Phenotypes in Those Free of Knee Pain with or at Risk of Knee Osteoarthritis: The Multicenter Osteoarthritis Study.

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Abstract

Objectives: Why some individuals develop pain with knee osteoarthritis (OA) is not clear. We sought to identify pain susceptibility phenotypes (PSPs) and their relation to incident persistent knee pain (PKP) 2 years later.

Methods: We identified individuals free of PKP from the Multicenter Osteoarthritis Study, a longitudinal cohort of older adults with or at risk of knee OA. Latent class analysis was used to determine PSPs that may contribute to development of PKP apart from structural pathology: widespread pain, poor sleep, psychological factors and quantitative sensory tests (QST) (i.e., pressure pain threshold and temporal summation (TS)). We evaluated the association of

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sociodemographic factors with PSPs and the relation of PSPs to developing PKP over two years with logistic regression.

Results: 852 participants were included (mean age 67; BMI 29.5 kg/m^2, 55% women). Four PSPs were identified, primarily characterized by varying proportions (low/absent, moderate, or high) of the presence of pressure pain sensitivity and of facilitated TS, reflecting different measures of sensitization. The PSP with high proportion of pressure pain sensitivity + moderate proportion of facilitated TS was twice as likely to develop incident PKP over 2 years OR 2.11 (95% CI 1.06 4.22) compared with the PSP having low proportion of sensitization by both measures.

Conclusions: Four PSPs were identified, of which three were predominated by QST evidence of sensitization, and one was associated with developing PKP 2 years later. Prevention or amelioration of sensitization may be a novel approach to preventing onset of persistent knee pain in OA.

Keywords

pain sensitization; phenotype; knee osteoarthritis; latent class analysis

The recognized structure-symptom discordance in knee OA points to the importance of factors other than structural joint pathology in explaining the differences in pain experienced by people with knee osteoarthritis (OA), and by extension, the susceptibility to developing knee pain in OA.(1) It is possible that, independent of structural pathology, multiple characteristics such as psychological factors, sleep, and nervous system sensitization may increase the risk of an individual developing symptoms.(2–4) Pain in knee OA has intermittent and constant components, with the former defining the early stages of the disease where pain, often absent for periods of time, is triggered by activities with high force or loads.(5) As the disease progresses, pain becomes more constant or persistent, often punctuated by intense intermittent pain.(6) Why the transition from intermittent to constant pain occurs and who may be at risk for developing persistent pain is not known.

Sensitization of the peripheral or central nervous system is a known contributor to pain in people with knee OA.(7) Defined as an amplification of neural signaling which manifests as widespread hyperalgesia, spinal hyperexcitability and impaired descending modulation, this process allows typically innocuous stimuli to induce and maintain a pain state.(8) There is no gold standard to assess sensitization, which has been observed in chronic pain populations, though studies often use quantitative sensory testing (QST) to assess sensitization. (9–11)

Phenotyping of pain, identified by OA treatment guidelines as a research priority,(12, 13) is an approach that can account for the multifactorial nature of pain, establish pain prognosis, and enable a rational mechanism-based approach to pain management. Phenotyping of those who are susceptible to the *development* of persistent knee pain related to knee OA may provide novel insights into pain mechanisms. Understanding how various risk factors are associated with different pain susceptibility phenotypes (**PSP**s) would facilitate targeted

preventive strategies by helping clinicians identify patients who are most at risk for developing persistent pain and likely to benefit from a given treatment.

Initial studies of pain phenotypes in people with knee OA have exclusively examined people who are symptomatic in cross-sectional analyses and therefore have not enhanced our understanding of the *development* of pain, particularly that of developing persistent knee pain or transitioning from acute (intermittent) to chronic (persistent) pain. Further, these previous studies vary methodologically in their use of phenotypic variables by including various combinations of psychological factors, surrogate measures of sensitization, and measures of radiographic and pain severity.(9, 14–18) No studies have included multiple psychological measures and direct QST measures of pain sensitization to define and enable more complete phenotyping in people who have not yet developed persistent knee pain but may be at risk for transitioning to persistent knee pain irrespective of structural pathology.

We sought to understand what factors other than structural pathology may be associated with the risk of developing persistent knee pain as a first step towards understanding factors that may contribute to the transition from acute, activity-related pain to chronic, persistent knee pain in OA. Thus, the objectives of this study were three-fold: 1) to identify PSPs related to psychological factors, measures of sensitization (i.e., **QST**), widespread pain (**WSP**), and sleep among persons with or at risk of knee OA who were free of knee pain; 2) to determine risk factors for these identified phenotypes; and 3) to determine the relation of the PSPs to the development of persistent knee pain (**PKP**).

MATERIALS and METHODS

Study sample

The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal cohort of community dwelling adults between the ages of 50–79 years who had or were at risk of developing knee OA at baseline. Subjects were recruited from Birmingham, Alabama and Iowa City, Iowa. Details of the cohort have been published elsewhere, and approved by the relevant institutional review boards that were in compliance with the Helsinki Declaration.(19) The current sample comprised participants who attended the 60-month visit (baseline for this study; the first visit at which measures of sensitization were obtained) who were free of PKP, defined as those who did not have frequent knee pain (i.e., pain, aching or stiffness on most days of the past month at both the telephone screen occurring on average one month prior to the clinic visit and at the clinic visit. Thus, some participants included could have experienced intermittent knee pain, though *not* on most days of the month. Participants who screened positive for peripheral neuropathy(20) or who had a prior total knee replacement were excluded from this study.

Pain Susceptibility Phenotype (PSP) Determination

To determine PSPs related to factors other than structural pathology, we hypothesized that psychological factors (pain catastrophizing, depressive symptoms), sleep, WSP, and QST measures of pain sensitization (pressure pain threshold (**PPT**), temporal summation (**TS**)) would identify distinct groups of people based on patterns of grouping by these variables.

(21–24) As we were seeking to identify pain phenotypes and not overall clinical phenotypes, we based our choice of variables on multidimensional factors known to have a direct relationship with the experience of pain in people with or at risk of knee OA, informed by evidence-based recommendations for pain phenotypying, the relationship of WSP to knee pain and the availability of variables in the MOST study.(21–24)

Pain catastrophizing was measured using a single item from the Coping Strategies Questionnaire which has a correlation of 0.74–0.81 with the full scale.(25) Pain catastrophizing was defined as being present if the score was >1. The Center for Epidemiologic Studies Depression Scale (CES-D) was utilized as a measure of depressive symptoms, defined as a score of ≥16.(26) WSP was defined using a validated standard homunculus.(27) Sleep quality was measured on a 4-point Likert scale, with very bad or bad sleep designated as poor sleep quality. QST methods have been previous described elsewhere.(11) In brief, PPT was assessed by applying an algometer (1 cm2 rubber tip; Wagner, FDIX25) at a rate of 0.5 kg/s on the centre of the patellae bilaterally, tibial tuberosities and distal radioulnar joint (control site; right side unless contraindicated) as the point at which participants indicated the pressure first changed to slight pain. The PPT at each anatomical site was calculated by averaging three trials, and categorized into sex-specific tertiles. Those in the lowest tertile, demonstrating lower PPTs represent a higher degree of pressure pain sensitivity; they are hereafter referred to as being the group that demonstrated evidence of ‘pressure pain sensitivity’. Mechanical temporal summation was assessed using a weighted 60 g von Frey monofilament at the wrist and patellae (Aalborg University, Denmark). Subjects first provided a numerical pain rating to a trial of four stimulations. Subsequently, the monofilament was applied repeatedly over the skin of the same site at a frequency of 1 Hz for 30 s. Subjects provided a pain rating at the completion of the train of 30 simulations, and 15 s post stimulation. TS was defined as being facilitated when a positive value was found after the initial trial was subtracted from the greater of the two subsequent trials. This group is hereafter referred to as demonstrating evidence of facilitated TS.

Subject Characteristics Associated with Pain Susceptibility Phenotypes

Subject characteristics associated with the PSPs were hypothesized to include age, sex, race (Caucasian vs. other), education (≤high school vs. ≥postsecondary education), body mass index (BMI), comorbidities (using the Charlson Comorbidity index), and Kellgren and Lawrence (KL) grade. All were collected at the baseline for this study.

Incident Persistent Knee Pain Definition

To examine the face validity of the identified PSPs, we sought to examine the relation of the identified PSPs with the development of persistent knee pain. This was operationalized as “persistent knee pain” (PKP), and defined as a participant answering ‘yes’ to having knee pain on most days of the past 30 days at both the telephone screen and at the clinic visit occurring on average 30 days apart, thus spanning a 2-month period. A participant was considered as having incident PKP if either knee met the definition at the 2-year follow-up from among this study sample at baseline (60 months), all of whom were free of PKP at this study’s baseline, i.e., had answered ‘no’ to having knee pain on most days of the past 30 days at both the telephone screen and at the clinic visit.

ANALYSIS

To identify PSPs, we applied an agnostic approach using latent class analysis (LCA). LCA is a model-based approach that employs fit statistics combined with evidence based knowledge of the concept being analyzed to decide on the appropriate number of classes. Although the phenotypes are identified in a data-driven approach, we imposed a requirement that each class must have at least 10% of the sample to ensure meaningful interpretation of the classes and to limit possible errors in their estimates. The posterior probability of subgroup membership was generated from the LCA model and the maximum-probability approach assigned each subject to one of the subgroups. Posterior fit statistics of Bayesian Information Criterion (BIC), adjusted BIC, the Vuong-Lo-Mendell Rubin test (VLMR) and the Bootstrapped Likelihood Ratio test (BLRT) were used to determine the optimal number of classes, along with clinical reasoning.(28) Once the ideal number of classes were determined, profiles of each class were interpreted using class-specific proportions of each included factor. Sample characteristics were described using class specific proportions. Next, we ran a separate model using the R3Step method, a 3-step method used to assess the association of latent class predictors with the latent classes.(29)(see supplementary material Table 4 for details of steps) Finally, we assessed the relation of the PSPs to incident PKP using the method described by Lanza.(30) As this method does not allow for covariates to be included in the model,(31) we ran adjusted models using logistic regression. Sensitivity analyses were conducted to assess more parsimonious models, as well as variable contribution to the original model. In two sensitivity analyses, we examined a model with fewer QST variables and the second using QST variables only. Correlation analysis of the QST variables demonstrated low to high significant correlations (Table 5 supplementary material). We therefore chose to employ a model with one TS variable measured at the wrist, and, to maintain the representation of peripheral and central sensitivity, we retained the variable measuring PPT at the wrist and created one variable that reflected the average patellar PPT from both knees. Those at the tibia were discarded as it is likely that they represented the same construct given their proximity to the patella. Latent class analysis was then performed with a 7-variable model (these limited QST measures plus the other variables originally included). Due to the dominance of the QST variables in our main LCA model (see Table 6 of supplementary material for correlations of remaining indicator variables), a second sensitivity analysis was run using a model with only the original QST variables. Analyses were conducted with Mplus v7.3 (Muthen & Muthen) and SPSS (v22 IBM, Chicago Ill.).

RESULTS

There were 852 subjects included in this study (55% female, mean age 67, mean BMI 29.5 kg/m^2), all of whom were free of PKP at baseline. We ran models starting with 2 classes to determine the optimal number of classes (i.e., PSPs). With 6 classes, less than 10% of the sample was forming a class, which violated our desire to have each class comprise at least 10% of the sample. Of the 2 to 5 class solutions, the 4 and 5 class solutions were considered superior to the 2 and 3 class solutions. The BIC and aBIC indicated 5 classes were better, the VLMR suggested that 4 classes were ideal and the BLRT statistics indicated that either the 4 or 5 class solution was acceptable. The 4-class solution was chosen because it was more

readily interpretable clinically and in line with our current understanding of contributing mechanisms, i.e., nervous system sensitivity as evidenced in the current literature. (21–24) The model entropy value, an indicator of the quality of classification, was 0.86 (1=perfect) (see Supplementary Table 7) indicating good quality of classification(32) and the classification probabilities for each class were all ≥0.87.

The four PSPs were primarily distinguished by differences in the proportion of sensitization as indicated by demonstration of pressure pain sensitivity (both peripherally and centrally) and/or facilitated TS at each of the anatomic sites tested (proportions of each anatomic site are reported in Table 1). The classes are described in order of their sample size. PSP 1, comprising 34% of the sample, had a low-moderate proportion of people with both pressure pain sensitivity (~16–26%) and facilitated TS (33–35%). PSP 2, comprising 31% of the sample, had low proportions-to-none with pressure pain sensitivity (0–6%) and facilitated TS (2–10%). PSP 3, comprising 23% of the sample, had a high proportion with pressure pain sensitivity (75–89%) and moderate proportion with facilitated TS (53–58%). Finally, PSP 4 (12% of the sample) had high proportion of facilitated TS (82–90%) but very low proportion-to-none with pressure pain sensitivity (0–4%). We labelled the PSPs according to the proportions with pressure pain sensitivity and facilitated TS in each class: **PSP-1**. Low-moderate proportions with both pressure pain sensitivity + facilitated TS; **PSP-2**. Low/none with both pressure pain sensitivity + facilitated TS; **PSP-3**. High proportion with pressure pain sensitivity + moderate proportion with facilitated TS; **PSP-4**. Low proportion-to-none with pressure pain sensitivity + high proportion with facilitated TS. The PSPs are presented in Figure 1.

As can be seen in Figure 1, there were few differences in the proportion of other factors examined (e.g., WSP, psychological factors, sleep) among the phenotypes. Specifically, there were no significant differences in the proportions with poor quality sleep across all classes. Statistically significant (though small) differences in pain catastrophizing and WSP were only found between PSP 2 (which had low proportions of both pressure pain sensitivity and facilitated TS) and PSP 3 (which had high proportion with pressure pain sensitivity and moderate proportion with facilitated TS). Table 1 provides the frequency for the variables for the whole sample.

Associations of subject characteristics with pain susceptibility phenotype class membership

Subject characteristics for each PSP are presented in Figure 2. The proportion of females was highest in PSP 3 at 74%, in contrast to PSP 4 that had low proportion of pressure pain sensitivity + high proportion of facilitated TS (26%). Proportions of non-Caucasians were greatest in PSP 2 and 4 (22 and 23% respectively, while the oldest participants were found in PSP 4 (mean 70 years). Proportions of KL grade ≥ 2, BMI, comorbidities and post-secondary education were similar across classes.

The associations between each subject characteristic with PSP membership are presented in Table 2, with PSP 2 (i.e., low proportions with both pressure pain sensitivity + facilitated TS class) as the referent group. Neither BMI, education level nor KL grade were significantly associated with membership in any class compared with membership in PSP 2. Female sex

was significantly associated with 3-to-4 times higher odds of being in the two PSPs that had moderate to high proportions with pressure pain sensitivity (PSPs 1 and 3), compared with PSP 2, whereas it was negatively associated with being in PSP 4 which had low proportion of pressure pain sensitivity but high proportion of facilitated TS (OR 0.46 (95% CI 0.27, 0.79)). Non-Caucasians and those 65 years of age or older had 3.5 and 3.0 greater odds, respectively, of being in PSP 4 (low proportion of pressure pain sensitivity + high proportion of facilitated TS) and 1.9 and 2.5 greater odds of being in PSP 3 (High proportion of low PPT + moderate proportion of facilitated TS) compared with PSP 2.

Relation of Pain Susceptibility Phenotypes to Incident Persistent Knee Pain Outcome

PSP 3, which had high proportion of pressure pain sensitivity + moderate proportion of facilitated TS class, was twice as likely to develop incident PKP over two years compared with PSP 2, the group with low proportion-to-none that had both pressure pain sensitivity or facilitated TS class (OR 1.98 (1.07, 3.68)). The other classes were not statistically significantly associated with development of PKP (Table 3).

Sensitivity analyses

The models for both sensitivity analyses are presented in supplementary materials Figures 3 and 4. The first sensitivity analysis, using a model with fewer QST variables had a lower overall entropy of 0.835 but improved model fit BIC= 7896. Class proportions differed from the original, as well as the values for each of the 7 indicator variables (Figure 3, supplementary materials). The QST only model (Figure 4, supplementary materials) using variables from the original model resulted in very similar class structure essentially replicating the pattern of the classes from the original model. Entropy was similar at 0.855 and model fit was lower, BIC=10132 (see supplementary Table 7 for fit statistics and entropy values)

DISCUSSION

We found 4 distinct PSPs among individuals who were free from PKP that were primarily differentiated by measures indicative of sensitization. Other factors traditionally associated with knee pain, such as psychological factors, poor sleep, and WSP did not differ substantially between the groups. The group with the highest proportion of pressure pain sensitivity at both the knee and the wrist (indicating more sensitization both locally and centrally) had a 2-fold increased risk of developing persistent knee pain over a two-year period. This work lends further support for the importance of sensitization in the knee pain experience of people with symptomatic knee OA,(9, 33) and provides new insights into the influence of pre-existing sensitization on the transition from intermittent to persistent knee pain among those who were free of persistent pain to begin with. Interestingly, the group who had primarily predominant evidence of central sensitization with facilitated TS at either the wrist or the knee were not at increased risk of developing persistent knee pain in this sample.

Different from previous phenotyping studies of people with symptomatic knee OA which have concentrated on QST measures or psychological factors,(9, 15, 33) we employed a

multifactorial approach similar to that recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.(21) This work represents an initial step in helping to more clearly understand symptom persistence, and the transition from intermittent to persistent pain. It is noteworthy that the individual entropy values in our LCA model (an indicator of the influence of a variable on class formation; see supplementary table 8) for PPT and TS testing had the highest values while minimal between class differences were noted amongst the remaining indicator variables. This means that in our community-based cohort, features of pain sensitization had the greatest influence in phenotype formation in those free from PKP, but the psychological constructs (e.g., depressive symptoms, pain catastrophizing), sleep quality or WSP did not. Our findings indicate that, while other studies have highlighted the importance of these latter factors, the presence of sensitization appears to have a far greater influence on the development of persistent pain.

We found female sex, age, and non-Caucasian race to be significant predictors of class membership in PSP3 compared to PSP2, with the former two having the highest risk estimates of any group. Studies of pain phenotypes in people with symptomatic OA have found similar associations,(9, 15, 17, 33) but others have also reported associations with BMI and education.(9, 15, 33) Few have reported any association of radiographic severity.(17, 34) In previous studies, female sex has had greater positive associations with facilitated TS as opposed to our finding of an association with greater pressure pain sensitivity and a negative association with facilitated TS,(9, 33) while reports of the association of non-Caucasian race with increased TS are conflicting.(9, 33) How these characteristics are related to neurophysiologic tests at different pain stages requires further clarification.

We focused on subjects who were free of persistent pain to evaluate which grouping or cluster of features tended to occur together, and their relation to the development of persistent knee pain. In studies of symptomatic groups, there is disagreement as to whether trajectories of pain change or stay stable over periods of 5 to 6 years.(34, 35) Our results, while not trajectory based, indicate that the group with the highest proportion with sensitization, as reflected by local, extra-segmental, and distant pressure pain sensitivity, are at higher risk of developing persistent knee pain compared with those who have a relative absence of sensitization as reflected by pressure pain sensitivity.

Our first sensitivity analysis revealed that in using fewer QST variables, similar patterns of pain susceptibility groupings amongst the classes can be found; however the proportion of individuals found in each respective class changed. By comparison, our second sensitivity analysis using only the QST measures from our main model provided almost identical results, thereby demonstrating how these variables drove the model, with psychosocial, WSP and sleep variables offering little influence in differentiating the groups and the risk of developing persistent knee pain. The lack of effect of WSP was further substantiated by a model that we ran without the inclusion of WSP which did not changes the estimates of the remaining variables (see Table 9 supplementary data)

Our study has several limitations to consider. While we included variables known to have a direct relationship with the experience of pain in people with or at risk of knee OA and

guided by the availability of variables in the MOST study, the ideal representation and/or combination of variables for pain susceptibility phenotyping may not be fully characterized. Generalizability of our findings is limited in the application to different geographic regions and different racial classes. We used a limited set of QST measures and our sample may not be representative of the spectrum of OA disease. Lastly as with all latent class models, our findings are exploratory and require external validation. There are equally several strengths to consider. Our study is the first to focus on people with or at risk of knee OA who are free of PKP to understand the development of the clinically relevant entity in knee OA of persistent knee pain. This is an important subgroup to consider given the intermittent nature of pain in knee OA that typically evolves to become more persistent over time. We have shown that phenotypes vary according to the degree of sensitization as detected by QST and that specific sociodemographic factors are associated with PSP membership. Compared with other clustering methods, the use of LCA, an agnostic data-driven model-based approach, is less subjective in class formation creating potentially more valid subgroups.

In conclusion, we identified 4 distinct PSPs in people with or at risk of knee OA who were free of PKP at baseline. We found that the PSP with the highest degree of sensitization, namely the group with the highest proportion of people with pressure pain sensitivity across all sites tested (locally, extrasegmentally and remotely), was at greatest risk of developing persistent knee pain. Understanding the mechanisms that contribute to pain susceptibility and identifying prognostic phenotypes is an important step towards the goal of phenotypic, mechanism-based management of pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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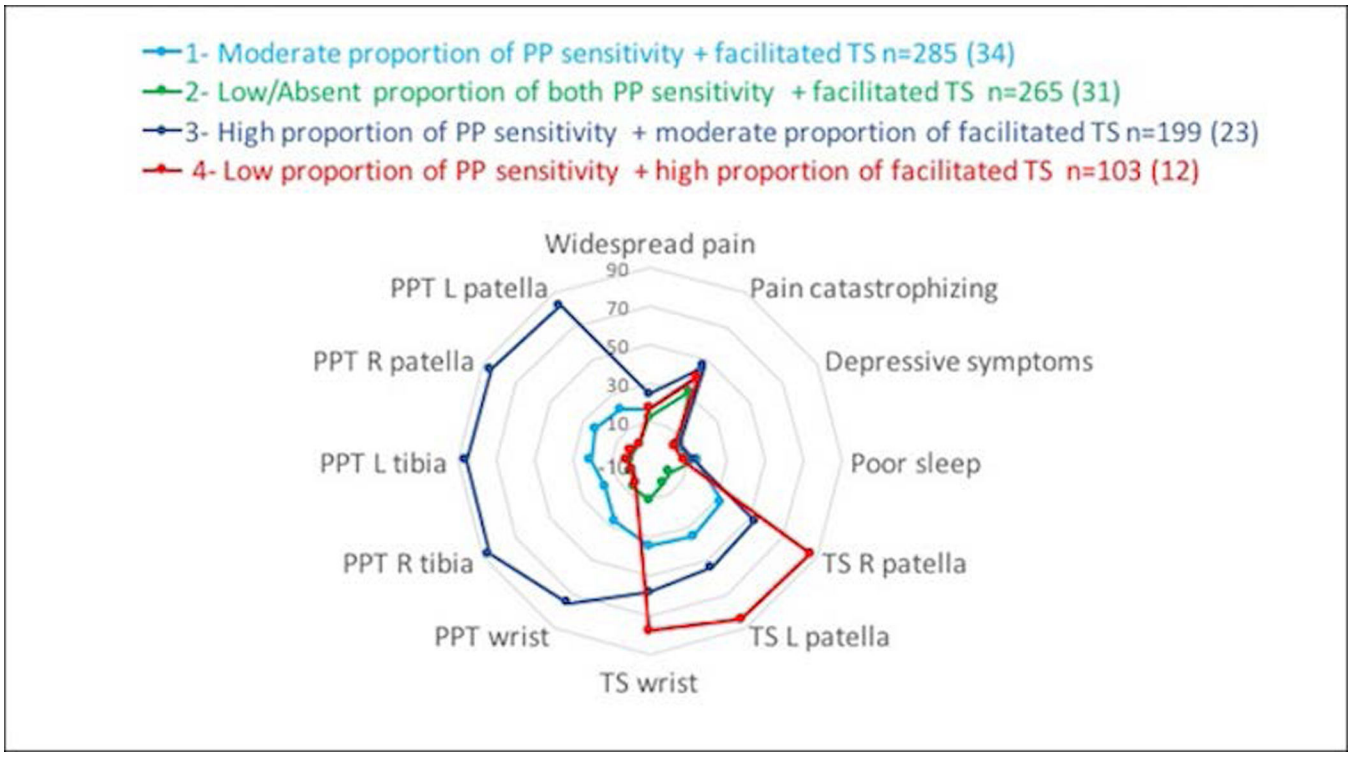

Figure 1.

Spidergram plot of identified classes showing proportions of each indicator variable in each of the respective phenotypes.

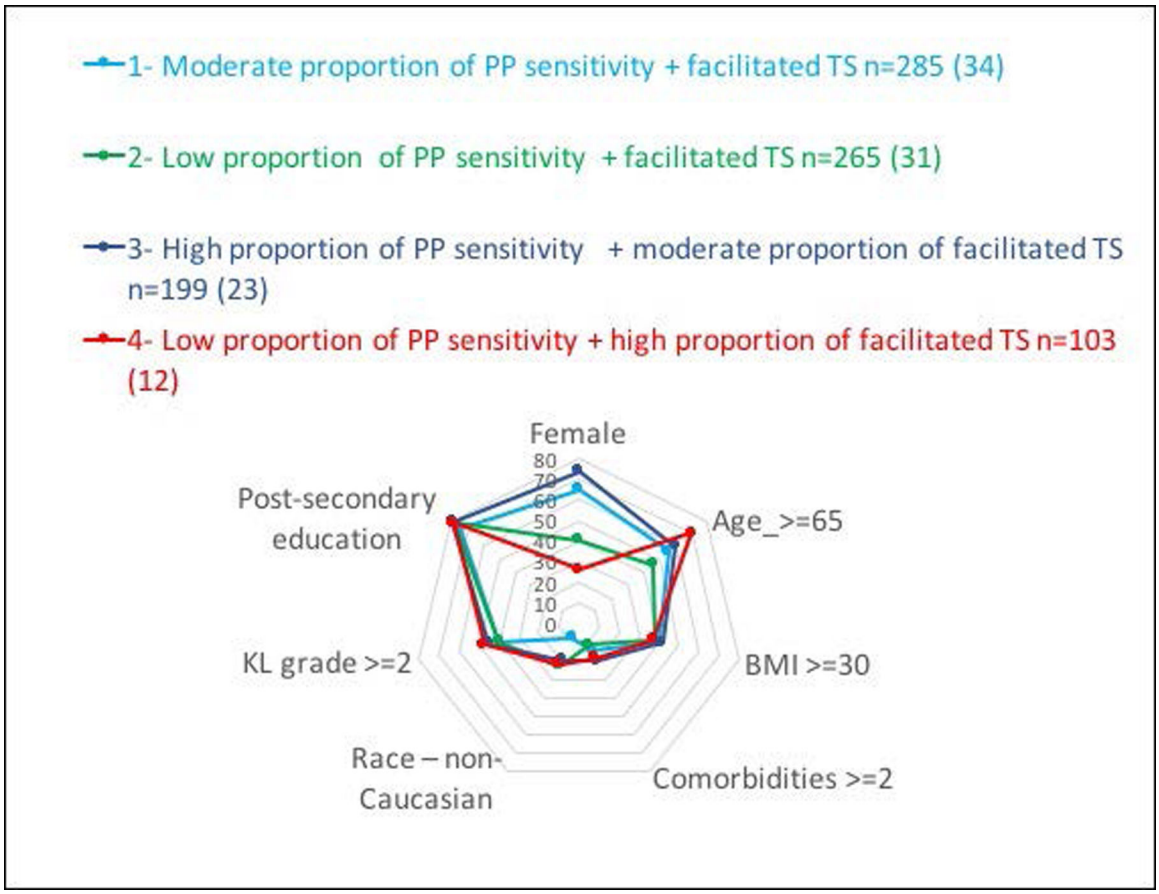

Figure 2.

Spidergram plot of subject characteristics showing proportions of each characteristic in each of the respective phenotypes.

Table 1.

Frequency of indicator variables in the whole sample and each pain susceptibility phenotype

Class indicator variables	Whole sample N=852 (%)
Widespread pain	17.3
Pain catastrophizing	39.6
Depressive symptoms	6.5
Poor sleep	12.9
TS R patella	35.0
TS L patella	36.8
TS wrist	38.4
PPT wrist †	29.1
PPT R tibia †	26.6
PPT L tibia †	27.9
PPT R patella †	28.2
PPT L patella †	27

† refers to lower tertile of values i.e. most sensitive, with referent group being the upper tertile. i.e. least sensitive. The upper limit for the lowest tertile for each anatomic site listed in the table was as follows: 2.76, 4.54, 4.32, 4.22 and 3.97.

PPT= pressure pain thresholds, TS= Temporal summation, L= left, R= right.

Table 2.

Association of subject characteristics with PSP class membership

Characteristics	Moderate proportion of both PP sensitivity + facilitated TS (PSP Class 1) OR (95% CI)	High proportion of PP sensitivity + moderate proportion of facilitated TS (PSP Class 3) OR (95% CI)	Low proportion of PP sensitivity + high proportion of facilitated TS (PSP Class 4) OR (95% CI)	Low/Absent proportion of both PP sensitivity + facilitated TS (PSP Class 2) OR (95% CI)
Age_>=65	1.42 (0.99, 2.06)	*1.88 (1.24, 2.85)*	*3.03 (1.78, 5.15)*	1
Sex: Female	*2.69 (1.87, 3.87)*	*4.08 (2.68, 6.22)*	*0.46 (0.27, 0.79)*	1
BMI >=30 kg/m^2	1.17 (0.81, 1.70)	1.18 (0.78, 1.77)	0.99 (0.60, 1.64)	1
Race: Non-Caucasian	0.80 (0.42, 1.52)	*2.47 (1.36, 4.49)*	*3.53 (1.78, 6.98)*	1
KL grade >=2	0.85 (0.59, 1.23)	1.15 (0.76, 1.73)	1.60 (0.97, 2.62)	1
Education: Post-secondary	0.99 (0.65, 1.53)	1.33 (0.82, 2.17)	1.40 (0.77, 2.55)	1
Comorbidities ≥1	1.38 (0.84, 2.27)	0.92 (0.51, 1.65)	1.32 (0.66 2.63)	1

PP= pressure pain; BMI= Body mass index; KL = Kellgren Lawrence

Table 3.

Risk of Incident Persistent Knee Pain

Class	**Incident PKP (n=82/773; 10.6%) *OR (95% CI)**
Moderate proportion of both pressure pain sensitivity + facilitated TS (**PSP 1**) (N=261)	0.84 (0.43, 1.64)
High proportion of pressure pain sensitivity + moderate proportion of facilitated TS (N=182) (**PSP 3**)	*1.98 (1.07, 3.68)*
Low proportion of pressure pain sensitivity + high proportion of facilitated TS (N=96) (**PSP 4**)	0.96 (0.41, 2.27)
Low proportion of both pressure pain sensitivity + facilitated TS (N=234) (**PSP 2**)	1 (referent)

* adjusted for BMI, race, education, sex, comorbidities, KL grade, age.