Title:

Identifying Multiple Knee Pain Trajectories and the Prediction of Opioid and NSAID Medication Used: A Latent Class Growth Approach

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Abstract

Background: Knee pain is a major source of distress and disability, with pain progression highly variable between individuals. Previous studies defining pain trajectories have all used a single measure of pain, and these differ across studies. Different measures reflect diverse pain mechanisms. To ascertain the clinical utility of pain trajectories we explored associations between opioid and non-steroidal anti-inflammatory drug (NSAID) use.

Methods: We model pain trajectories using two measures - Intermittent and Constant Osteoarthritis Pain (ICOAP) and the painDETECT, in 2141 participants, across 3 waves (the baseline, 1- and 3-year assessments) of the Knee Pain In the Community (KPIC) cohort.

Results: Latent class growth analysis identified 6 trajectories using ICOAP subscales (High Stable, Low Stable, Moderate Worsening, Moderate Recovering, Worsening, and Recovering), and 4 trajectories using painDETECT (High stable, Low stable, Moderate Worsening, and Moderate Recovering). There was a high degree of correspondence between people assigned to pain trajectories between ICOAP intermittent and constant subscales, but less so using painDETECT. Opioid use was associated with ICOAP trajectories only (e.g., High Stable and Worsening intermittent ICOAP trajectories) and in women.

Conclusion: Different measures of pain produce different patterns of pain progression and these are differentially related to medication use. Opioid use is linked to trajectories of pain based on the impact of pain on behaviour and not pain symptoms. Thus, managing pain's behavioural impact is more central to understanding opioid use than managing pain symptoms. These findings support more in-depth questioning about the type of pain and its progression in clinical practice.

Keywords: Knee pain, Pain progression, Osteoarthritis, Latent class growth analysis, knee pain trajectories.

Introduction

Knee pain (KP) is the usual presenting symptom of knee osteoarthritis (OA) [1], varying both across people [2] and over time [3, 4]. While many studies have modelled variation in pain progression for OA [5-12], a major gap in this literature remains. That is all studies to date have used a single measure of pain. This gap results in two unanswered questions. First, are different patterns of pain progress observed for different measures of pain within the same individuals? Second, what is the degree of overlap between patterns of pain progression derived from different measures? These questions are important for avoiding any erroneous assumption that two similar-looking and named pain trajectories are assessing the same pattern of pain or even identifying the same people.

Widely used measures of pain assess different aspects of the pain experience [13] and potentially different patterns of pain progression. For example, painDETECT is designed to assess the experience of neuropathic pain-like symptoms (e.g., burning sensation) [14]. In contrast, the Intermittent and Constant Osteoarthritis Pain (ICOAP) assesses transient and continuous pain, and their effects on behaviour (e.g., sleep) and psychological states (e.g., frustration and worry) [15]. Thus, these two widely used assessments measure very different aspects of pain (symptoms vs patterns linked to behaviour and feelings). Therefore, they may reveal very different pain trajectories, and there is a need to explore how well ostensibly similar trajectories identify the same patients [16] and whether those identified as having worsening pain on both the ICOAP and painDETECT are the same people. This has clinical implications concerning treatment decisions. Studies show that pain trajectories are potential treatment moderators [17-19]. Indeed, patients with different pain trajectories may benefit from different treatments [19]. Furthermore, pain treatments could also shift the patients'

pain trajectories into different patterns [17, 18]. This can help to determine whether successful treatments can shift a patient's pain trajectory to a more normal one that poses less burden on both patient's pain behaviour and the healthcare system. Pain trajectories can also be used as a tool to discuss the treatment goals and to help patients to understand the mood and behaviour linked to their conditions.

Thus, to explore if pain trajectories have utility rather than just offering a description of pain progression, we explored if pain trajectories are linked to medication use. Understanding the association between pain trajectories and medication use is of particular importance given concerns raised in recent years around potential adverse events associated with opioid [20] or non-steroidal anti-inflammatory drug (NSAID) use [21]. To examine these, we used scores from both ICOAP and PainDETECT at three-time points using data from the Knee Pain and Health In the Community (KPIC) cohort study [22]. The current study provides the first-ever analysis of the associations between various pain trajectories and prescription-based opioid and NSAID use.

Methods

Study design and Participants

Data for this study were taken from the Nottinghamshire KPIC cohort [22]. KPIC is an ongoing prospective study designed to understand the natural history of knee pain including incidence, prevalence, progression, and risk factors in community-derived adults. This study was approved by the Nottingham University Hospitals NHS Trust and the Nottingham Research Ethics Committee. We analysed three waves of data: baseline, and two follow ups at 1 and 3 years. The full KPIC study protocol, including details about recruitment, sampling

and measures have been reported elsewhere [22]. As indicated in Figure 1, the KPIC study included 4294 participants who reported knee pain at baseline and were asked to complete the constant and intermittent ICOAP and painDETECT of whom 3418, 3484, and 3375, respectively, answered these three pain questionnaires. The inclusion criteria were 1) to respond to one of the three baseline pain questionnaires and 2) to respond to the same pain questionnaire in at least one of the follow-ups. This resulted in a total of 2141 participants including 1768 and 1590 baseline cases for Intermittent and constant OA, respectively, as well as 1860 baseline cases for painDETECT, which also included participants who recovered from knee pain at years 1 and 3 follow-ups. Of the total sample, 1381 cases had responded to all three pain questionnaires at all three time points.

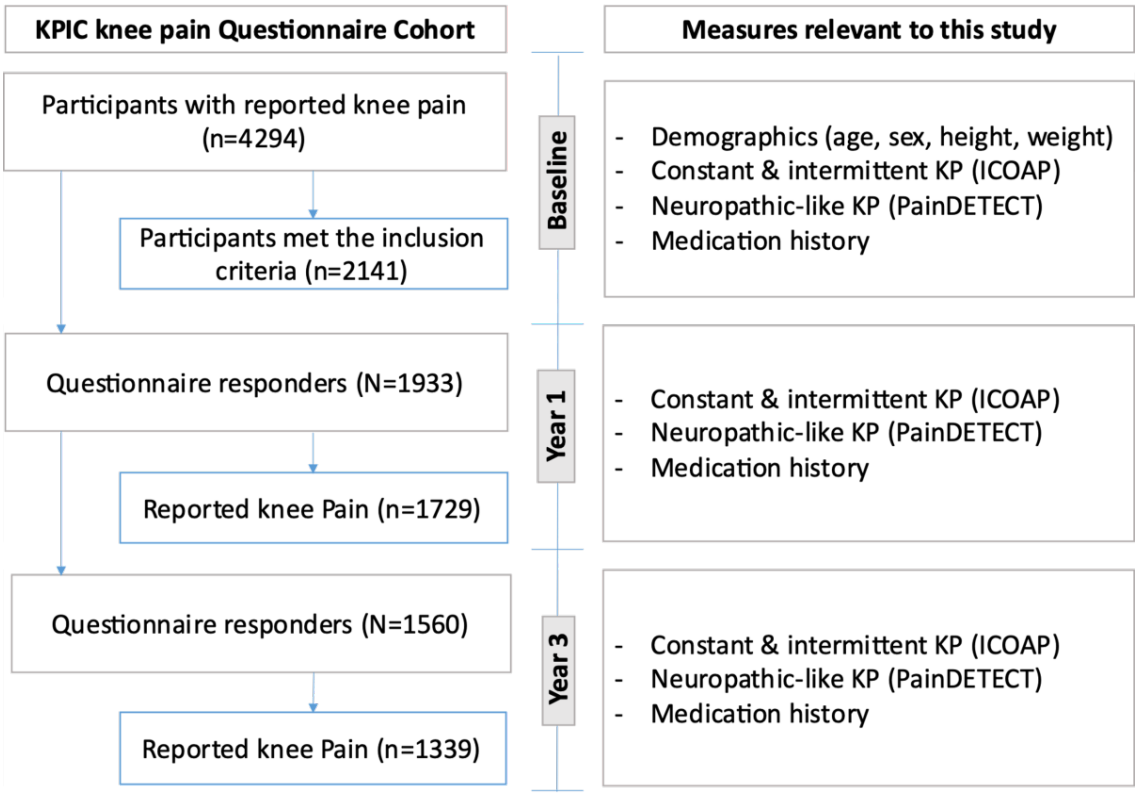

Figure 1. Knee Pain and health In the Community (KPIC) cohort design and measures relevant to the current study. Abbreviations: ICOAP Intermittent and Constant Osteoarthritis Pain, painDETECT Neuropathic-like knee pain.

Measures

Demographics

Age, sex, height, and weight, and BMI were obtained from the baseline survey.

Knee pain

Knee pain was defined by a response of "yes" to the question "*Have you ever had pain in or around a knee on most days of the past month?"* [23]. Respondents who answered "Yes" at baseline to the question were then asked to complete in-depth pain assessments (i.e. ICOAP, painDETECT), and thus had eligible data for the trajectory analysis.

Intermittent and Constant Osteoarthritis Pain (ICOAP)

The ICOAP questionnaire assesses pain in individuals with hip or knee osteoarthritis using two sub-scales: constant and intermittent [15, 24]. In both scales, pain is assessed from 0 (not at all) to 4 (extremely). These assess the impact of constant and intermittent pain on quality of life, sleep, and mood. Constant pain (hereafter: constant ICOAP) is measured using five items (range = 0-20), measuring pain that patients "have all the time" (α=0.94. at all three-time points). Intermittent pain (hereafter: intermittent ICOAP) is measured using six items (range = 0-24), assessing pain that "comes and goes". Cronbach's alphas for this sub-scale were 0.94, 0.93, and 0.94 at baseline, years 1 and 3 follow-ups, respectively.

Neuropathic-like knee pain.

The quality of knee pain was assessed using a modification of the painDETECT instrument [25] that focused on knee pain, at all three waves, to measure symptoms of neuropathic pain (e.g, burning, tingling, numbness) in relation to external stimuli (e.g., heat, cold, pressure). The painDETECT measure used in this study consists of seven pain gradation items that measure different sensory aspects of neuropathic pain, and an additional item that measures the pain

course pattern. The pain gradation items are assessed using a five-point Likert scale (0 = never, 5 = very strongly), and the pain course has four response options: persistent pain with pain attacks (scored -1), persistent pain (scored 0), pain attacks without pain between them (scored 1), and pain attacks with pain between them (scored 1). The two parts of the painDETECT questionnaire were summed together and ranged from 0 to 38. Cronbach's alphas were 0.82, 0.86, and 0.85 at baseline, years 1 and 3 follow-ups, respectively.

Medication history

Medication history was assessed by asking the participants to list all their current medication including those prescribed by their doctor. From this list, the medications were screened (see Supplementary Table S3 for the list of drugs for each category) to classify whether respondents had been prescribed drugs from two kinds of pain medications: opioids and NSAIDs (both topical and oral).

Statistical analysis

Descriptive statistics including frequencies, percentage, mean, and SD were used to characterise the samples at the three waves of the cohort. Crosstabulation with adjusted standardised residual (a ratio that applies the standard deviation to calculate the difference between the observed count and the expected count in chi-square testing) and post hoc χ^2 test with Bonferroni p-value corrections were used to test whether there were any overlaps between the pain trajectories extracted by the three pain measures. Latent class growth analysis (LCGA) was applied to estimate the class-based trajectories of knee pain. We estimated three separate LCGAs for constant ICOAP, intermittent ICOAP, and painDETECT. We used the procedure suggested by Jung and Wickrama [26]. We first use the conventional model parametrisation [27] to fit a latent growth model where the three time measures of

OA pain regressed on two latent factors: intercept and slope. Each model was adjusted for the three time-points of opioids and NSAIDs as the time-varying covariates (TVCs). In the adjusted latent growth model, the TVCs regressed on their corresponding pain measures at each time-point as well as covaried with both intercept and slope. After this, we added a latent class variable to the original model to predict the different classes of people with pain experience. We used random intercept and random slope, where individuals were allowed to vary at both starting points and trajectories of change. Determining the number of classes was guided by iteratively comparing models with k classes with those of with k-1 classes using several fit indices such as Bayesian information criterion (BIC), bootstrap likelihood ratio test (BLRT), Vuong-Lo-Mendell-robin adjusted likelihood ratio test (VLMR-LRT), and Entropy. As recommended by Nylund et al. [28], models with low BIC, Entropy approaching 1, significant BLRT and VLMR-LRT were considered as a good fit. Models with non-significant BLRT or VLMR-LRT were rejected. Interpretability and theoretical significance were also used to determine the final number of classes. To validate the true classification of the sample, the final models were investigated for problems with local solutions [29]. The associations between pain trajectories and medication use were assessed using a panel-based random-effect logistic regression. LCGA was performed using Mplus version 7.4 [30], random effect logistic regression was performed using Stata 16 [31] and the rest of the quantitative analyses were performed using IBM SPSS 26 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

Missing data analysis

Little's test of Missing Completely At Random (MCAR) [32] was used to test whether the observed dropouts were completely at random. If the results failed an MCAR mechanism, the

Diggle and Kenward selection model [33] was used to examine whether the dropouts were missing at random (MAR) or missing not at random (MNAR). We used the procedure proposed by Enders [34] to test the missing mechanisms: If the probability of missing data for the outcome variable was unrelated to other measured variables at the previous wave and unrelated to the values of the outcome itself at the follow-up, an MCAR mechanism was inferred. However, if the probability of missing data on the outcome variable was related to other measured variables at the previous wave but not to the values of the outcome itself at the follow up a MAR mechanism was inferred. Finally, if the probability of missing data on the outcome variable was related to other measured variables at the previous wave as well as to the values of the outcome itself at the follow up an MNAR mechanism was inferred. If dropouts at follow up years 1 and 3 follow-ups were MNAR we used Roy's latent class dropout method [35] to model missingness due to the attrition. In the Roy's model, dropout times influence both the latent class variable and the random-effect means for the outcomes.

Results

Demographics of participants

Characteristics of the study sample across the 3 study waves are presented in Table 1. Of the 2141 participants who met the inclusion criteria for this study, the mean age at baseline was 62.28 (range 40 to 86) years, and at 1 and 3 years follow up were 63.31 and 65.66 years, respectively. At each time point, 59% to 60% of participants were women, and the baseline mean for BMI was 28.76, and at 1 and 3 years follow up were 28.96 and 28.52, respectively. As to the medication use, among all the participants, opioid use at baseline was 17.7%, and at 1 and 3 years follow up were 18.7 and 19.5, respectively. Also, NSAID use at baseline was 6.8%, and at 1 and 3 years follow up were 7.7 and 4.1, respectively.

Pain Trajectories

Constant ICOAP

A total of 1590 participants had constant ICOAP scores at baseline plus at one or both follow-ups were included in latent class growth analysis (74.3% of the baseline sample, see Table 1). The Little's MCAR test rejected a missing completely at random (MCAR) mechanism (χ^2 =48.36, df=24, p=.002) and thus a Diggle and Kenward selection model [33] was tested and the results of logistic regression indicated a missing not at random (MNAR) mechanism: the probability of missingness at year 1 depended on the outcome variables at baseline and year 1 (OR=4.24, p<.001 and OR=3.47, p=.001, respectively). Likewise, the probability of missingness at year 3 depended on the outcome variables at year 1 and year 3 (OR=2.85, p=.004 and OR=2.79, p=.005, respectively). Therefore, Roy's latent dropout class model was used to model the missing data for the LCGA. To remove the confounding effects of medication used on identifying the pain trajectories, we adjusted the LCGA for the three time-points of opioids and NSAIDs. We selected the best model-fit based on the fit statistics. In this LCGA on Constant ICOAP data, Vuong-Lo-Mendell-robin adjusted likelihood ratio test (VLMR-LRT) was the key statistics to decide how many classes fit our data best. The results (see Table S1a) showed that a 6-class model was the best fit for the Constant ICOAP data. We named the trajectories relative to the scale ranges (0 to 20): *High Stable* (includes 124, 7.8%, of the participants), *Moderate Recovering* (includes 478, 30.1%, of the participants), *Moderate Worsening* (includes 281, 17.7%, of the participants), *Low Stable* (includes 537, 33.8%, of the participants), *Worsening* (includes 77, 4.8%, of the participants), and *Recovering* (includes 93, 5.8%, of the participants) trajectories (see Figure 2a).

Table 1 Characteristics of the study samples by pain measure type and waves of cohort who reported knee pain.

Pain measures	**ICOAP: Constant**			**ICOAP: Intermittent**			**painDETECT**		
Waves	**Baseline**	**Year 1**	**Year 3**	**Baseline**	**Year 1**	**Year 3**	**Baseline**	**Year 1**	**Year 3**
N (%)[a]	1590 (74.3)	1448 (67.6)	1127 (52.6)	1768 (82.6)	1622 (75.8)	1231 (57.5)	1860 (86.9)	1669 (78)	1441 (67.3)
Age in year**,** mean (DS)[b]	62.41(9.99)	63.41 (10.02)	65.86 (9.56)	62.43 (10.02)	63.45 (10.03)	65.80 (9.69)	62.00 (9.95)	63.06 (9.94)	65.32 (9.68)
Men, n (%)[c]	645 (40.8)	582(40.4)	446 (39.7)	719 (40.8)	649 (40.2)	492 (40.1)	756 (40.8)	679 (40.9)	583 (40.6)
Women, n (%)[c]	937 (59.2)	858 (59.6)	677 (60.3)	1042 (59.2)	966 (59.8)	735 (59.9)	10.96 (59.2)	983 (59.1)	853 (59.4)
BMI, mean (SD)	28.97 (6.01)	28.96 (5.97)	28.81 (5.63)	28.72 (6.06)	28.67 (6.03)	28.43 (5.58)	28.60 (5.94)	28.56 (5.86)	28.33 (5.58)
ICOAP: Constant, mean (SD)[d]	6.88 (5.22)	6.94 (5.15)	6.92 (5.37)	6.79 (5.22)	6.84 (5.12)	6.80 (5.37)	7.09 (5.08)	7.00 (5.12)	7.02 (5.35)
ICOAP: Intermittent, mean (SD)[e]	8.87 (5.77)	9.21 (5.42)	8.83 (5.94)	8.34 (5.65)	9.07 (5.26)	8.52 (5.83)	8.73 (5.44)	9.10 (5.27)	8.63 (5.82)
painDETECT, mean (SD)[f]	10.42 (6.99)	11.21 (7.38)	8.86 (7.39)	9.91 (6.77)	10.91 (7.27)	8.19 (7.14)	9.43 (6.74)	10.95 (7.30)	7.00 (7.28)
Medication history									
Opioids, n (%)[g]	302 (19)	289 (20)	230 (20.4)	306 (17.3)	296 (18.2)	241 (19.6)	315 (16.9)	297 (17.8)	266 (18.5)
NSAIDs, n (%)[g]	119 (7.5)	121 (8.4)	48 (4.3)	117 (6.6)	121 (7.5)	50 (4.1)	116 (6.2)	121 (7.2)	55 (3.8)

[a] % = each N divided by the total sample (N=2141). [b] Age at year 1 = baseline age +1 year etc. (3 baseline missing values). [c] Gender variable had 8 baseline missing values. [d] Score range: 0–20, [e] Score range: 0–24. [f] score range: -1–38. [g] % = frequencies divided by each wave's N. Abbreviations: SD standard deviation, KP knee pain, BMI body mass index, ICOAP Intermittent and Constant Osteoarthritis Pain, painDETECT Neuropathic-like knee pain, NSAIDs non-steroidal anti-inflammatory drugs.

Intermittent ICOAP

For this LCGA, 1768 participants had intermittent ICOAP scores at baseline plus one or both follow-ups and were included for analysis (82.6% of the baseline sample, see Table 1). The results of the Little's MCAR test rejected a MCAR mechanism (χ^2 =52.48, df=24, p=.001). The Diggle and Kenward selection analysis indicated MNAR mechanism: the probability of missingness at year 1 depended on the outcome variables at baseline and year 1 (OR=4.16, p<.001 and OR=9.68, p<.001, respectively). Likewise, the probability of missingness at year 3 depended on the outcome variables at year 1 and year 3 (OR=7.23, p<.001 and OR=6.02, p<.001, respectively). Roy's latent dropout class model was, therefore, used to model the missing data for the LCGA. To remove the confounding effects of medication used on identifying the pain trajectories, we adjusted the LCGA for the three time-points of opioids and NSAIDs. We selected the best model-fit based on the fit statistics. In this LCGA on Intermittent ICOAP data, the VLMR-LRT was the key statistics to decide how many classes fit the data best. The results showed that a 6-class model fit the Intermittent ICOAP data best (Table S1b). We name these relative to the scale ranging from 0 to 24: *High Stable* (includes 88, 5.0%, of the participants), *Moderate Recovering* (includes 498, 28.2%, of the participants), *Moderate Worsening* (includes 242, 13.7%, of the participants), *Low Stable* (includes 735, 41.6%, of the participants), *Worsening* (includes 152, 8.6%, of the participants), and *Recovering* (includes 53, 3.0%, of the participants) trajectories (see Figure 2b).

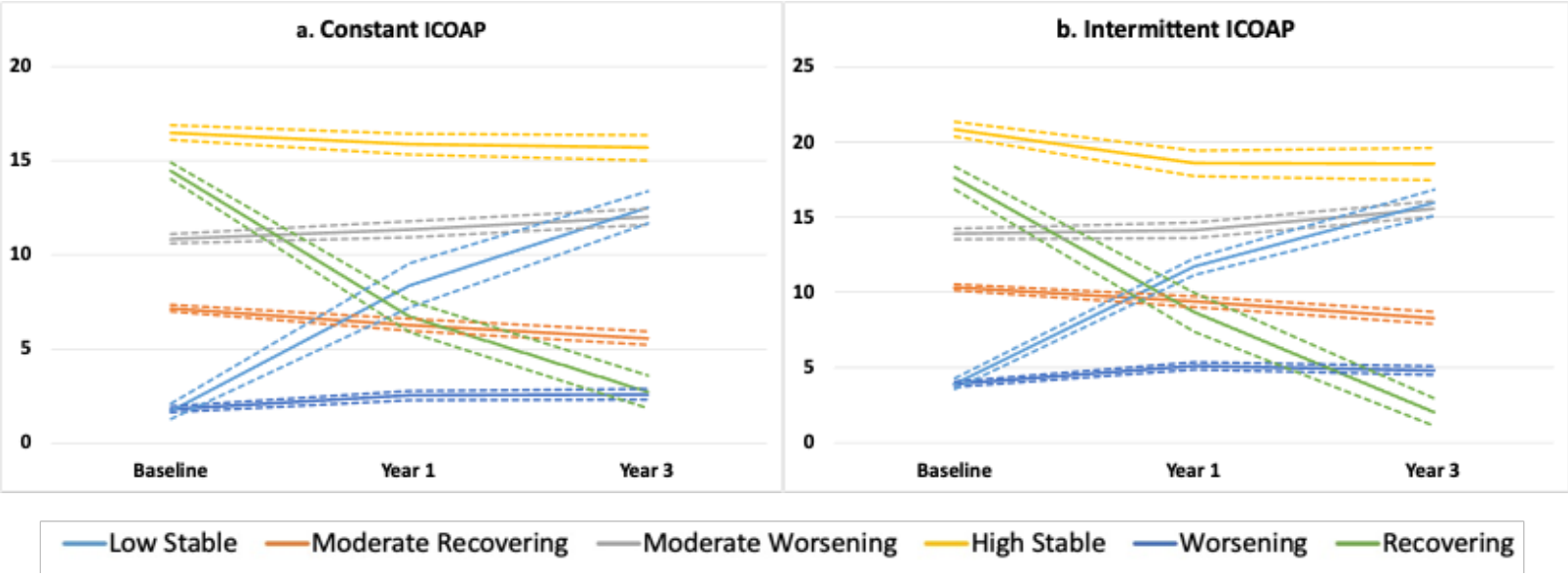

Figure 2 Sample mean Plot for ICOAP pain trajectories. The doted-lines above and below the main trajectory lines are Upper and Lower 95%CI, respectively. Abbreviations: ICOAP Intermittent and Constant Osteoarthritis Pain.

Neuropathic-like knee pain

A total of 1860 participants had painDETECT scores at baseline plus at one or both follow-ups and so were included in this LCGA (86.9% of the baseline sample, see Table 1). The missing analysis (Little's MCAR test) rejected a MCAR mechanism (χ^2 =267.61, df=18, p=.000). The Diggle and Kenward selection analysis indicated a MNAR mechanism: the probability of missingness at year 1 depended on the outcome variables at baseline and year 1 (OR=7.63, p<.001 and OR=19.61, p<.001, respectively). Likewise, the probability of missingness at year 3 depended on the outcome variables at year 1 and year 3 (OR=5.88, p<.001 and OR=2.30, p=.021, respectively). Roy's latent dropout class model was, therefore, used to model the missing data for the LCGA. To remove the confounding effects of medication used on identifying the pain trajectories, we adjusted the LCGA for the three time points of opioids and NSAIDs. We selected the best model-fit based on the fit statistics. In this LCGA on painDETECT data, the VLMR-LRT was the key statistics to decide how many classes fit the data best. The results showed that a 4-class model fitted the painDETECT data best (Table S1c). We named the four trajectories relative to the scale ranging from 0 to 38: *High Stable* (includes 120, 6.5%, of the participants), *Moderate Recovering* (includes 60, 3.2%, of the participants), *Moderate Worsening* (includes 520, 28%, of the participants), and *Low Stable* (includes 1160, 62.4%, of the participants) trajectories of neuropathic-like pain (see Figure 3).

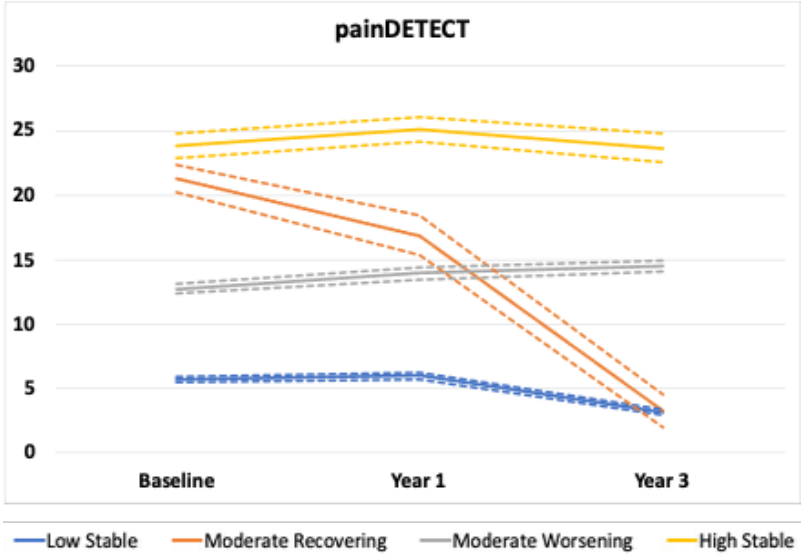

Figure 3 Sample mean Plot for PainDETECT trajectories. The doted-lines above and below the main trajectory lines are Upper and Lower 95%CI, respectively. Abbreviation: painDETECT Neuropathic-like knee pain.

Baseline differences. Participants differed between ICOAP pain trajectory groups for most of the baseline variables (for full results, see Supplementary Table S2). Women were more likely than men to be allocated to the Moderate Worsening trajectory in both constant ICOAP (68.9%, p=.002) and intermittent ICOAP (67.2%, p=.042). Participants allocated to the trajectories of Moderate Worsening and High Stable neuropathic-like pain (painDETECT) were more likely to be women (63.2% and 73.3%, p<0.001). Participants allocated to the High Stable trajectory for all three pain measures had higher BMI, ranging from 31.70 to 33.43 (see Tables S2).

Co-distribution of the three pain measures.

The extent to which the pain trajectories of intermittent ICOAP covaries with the pain trajectories of constant ICOAP is shown in Table 2. The two ICOAP subscales were similar in assigning participants to the comparable trajectories (χ^2=2065.39, df=16, p=.000). Adjusted

standardised residuals (ASR) indicate that the High-, Moderate- and Low-stable trajectories classified the same people with a high degree of accuracy, but less so for the Worsening and Recovering groups (see highlighted cells diagonally in Table 2). For example, 657 out of the 728 people allocated to the Low Stable trajectory of constant ICOAP were also allocated to the Low Stable trajectory of intermittent ICOAP with 90.2% overlap (ASR=27.9, $p<.001$). We calculated Bonferroni corrected post hoc χ^2 test [36] to adjust the p-value for testing whether the observed ASRs are significantly different from the expected ASRs. The results confirmed that the trajectories of constant ICOAP overlap positively and significantly with similar trajectories of intermittent ICOAP.

The degrees of overlap between ICOAP and painDETECT were complex but in expected directions (Table 3). As highlighted in Table 3, the Low-Recovering painDETECT trajectory was found to have a stronger overlap with Low Stable ICOAP (72%) trajectory. That is, most people with Recovering neuropathic-like pain have been identified by ICOAP having a Low Stable trajectory.

Table 2 Class membership frequencies crosstab for both latent trajectories of ICOAP.

	ICOAP: Intermittent, n (%) [ASR [a]]						
ICOAP: Constant	Low Stable	Moderate Recovering	Moderate Worsening	High Stable	Worsening	Recovering	Total (%)
Low stable	419 (**82.2**) [24.9]***	54 (10.6) [-11.3]***	3 (0.6)	0 (0)	33 (6.5)	1 (0.2)	510 (100)
Moderate Recovering	131 (29.2)	263(**58.7**) [16.5]***	20 (**4.5**) [-7.8]**	0 (0)	29 (6.5)	5 (1.1)	448 (100)
Moderate Worsening	3 (1.2)	79 (30.9) [21.2]***	152 (**59.4**) [21.2]***	11 (4.3)	9 (3.5)	2 (0.8)	256 (100)
High Stable	1 (0.9)	3 (2.7)	35 (31.5) [4.8]*	68 (**61.3**) [26.0]***	1 (0.9)	3 (2.7)	111 (100)
Worsening	19 (25.7)	8 (10.8)	6 (8.1)	1 (1.4)	40 (**54.1**) [15.4]***	0 (0)	74 (100)
Recovering	1 (1.2)	24 (28.6)	15 (17.9)	6 (7.1)	1 (1.2)	37 (**44.0**) [21.8]***	84 (100)
Total	574 (38.7)	431 (29.1)	231 (15.6)	86 (5.8)	113 (7.6)	48 (3.2)	1483 (100)

[a] only statistically significant ASRs are shown in the table. * p<.05, ** p<.01, *** p<.001. Note: P-values were calculated for post hoc χ^2 test and compared to adjusted Bonferroni p-values. Abbreviations: ICOAP Intermittent and Constant Osteoarthritis Pain, painDETECT Neuropathic-like knee pain, ASR Adjusted standardised residuals. The highlighted cells in orange with positive ASR indicate that the observed cell frequency is larger than the expected frequency, and the highlighted cells in blue with negative ASR indicate that the observed cell frequency is smaller than the expected frequency.

Table 3 Class membership frequencies crosstabs for ICOAP trajectories with painDETECT.

	ICOAP: Constant, n (%) [ASR [a]]						
painDETECT:	Low Stable	Moderate Recovering	Moderate Worsening	High Stable	Worsening	Recovering	Total (%)
Low stable	390 (**51.2**) [16.9]***	251 (32.9)	65 (8.5) [-10.4]**	6 (0.8)	22 (2.9) [-3.1]*	28 (3.7) [-3.7]*	762 (100)
Moderate Recovering	5 (9.3)	12 (22.2)	9 (16.7)	6 (11.1)	0 (0)	22 (**40.7**) [11.2]**	54 (100)
Moderate Worsening	54 (11.1) [-12.0]**	167 (43.4)	149 (**30.7**) [8.5]**	48 (9.9)	40 (8.2) [5.0]**	27 (5.6)	485 (100)
High Stable	2 (1.7) [-7.4]**	19 (16.0) [-6.2]***	40 (33.6)	52 (**43.7**) [15.1]***	1 (0.8)	5 (4.2)	119 (100)
Total	451 (31.8)	449 (31.6)	263 (18.5)	112 (7.9)	63 (4.4)	82 (5.8)	1420(100)
painDETECT:	**ICOAP: Intermittent**, n (%) [ASR [a]]						
Low stable	489 (**56.8**) [15.1]***	231 (26.8)	55 (6.4) [-10.4]**	6 (0.7) [-8.9]**	59 (6.9)	21 (2.4)	861 (100)
Moderate Recovering	10 (**19.2**)	13 (25.0)	8 (15.4)	5 (9.6)	1 (1.9)	15 (**28.8**) [11.0]**	52 (100)
Moderate Worsening	103 (21.4) [-10.3]**	182 (37.8) [4.6]*	111 (**23.1**) [6.4]**	33 (6.9)	44 (9.1)	8 (1.7)	481 (100)
High Stable	2 (1.9) [-8.3]**	22 (21.2)	44 (42.3) [8.3]**	31 (**29.8**) [12.0]***	3 (2.9)	2 (1.9)	104 (100)
Total	604 (40.3)	448 (29.9)	218 (14.6)	75 (5.0)	107 (7.1)	46 (3.1)	1498 (100)

[a] only statistically significant ASRs are shown in the table. * p<.05, ** p<.01, *** p<.001. Note: P-values were calculated for post hoc χ^2 test and compared to adjusted Bonferroni p-values. Abbreviations: ICOAP Intermittent and Constant Osteoarthritis Pain, painDETECT Neuropathic-like knee pain, ASR Adjusted standardised residuals. The highlighted cells in orange with positive ASR indicate that the observed cell frequency is larger than the expected frequency, and the highlighted cells in blue with negative ASR indicate that the observed cell frequency is smaller than the expected frequency.

Medication history and pain trajectories. Descriptive statistics for participant self-reported medication use are presented in Table 4 (Figure S1). We used two separate random-effect logistic panel regression models with each of the pain trajectories identified in the ICOAP and painDETECT predicting either opioid or NSAID use (Tables 5 and 6). We adjusted the models for age, sex, study wave, and the drug not being predicted. In terms of opioid usage, the odds of patients with High Stable Intermittent pain using opioids was 10.99 (95%CI, 2.14 to 56.28) times that of Low Stable intermittent pain trajectory (Table 5). Also, the odds of patients with worsening Intermittent pain using opioids was 3.56 (95%CI, 1.18 to 10.76) times that of Low Stable intermittent pain trajectory. As to constant ICOAP, the odds of patients with Moderate Recovering and Moderate Worsening constant pain using opioids were 3.47 (95%CI, 1.16 to 10.37) times and 2.13 (95%CI, 1.00 to 4.54) times that of Low Stable intermittent pain trajectory, respectively (Table 5). Compared to men, women were nearly 1.98 (95%CI, 1.18 to 3.31) times more likely to take opioids. No significant associations were found between the painDETECT trajectories and opioid use. Compared to baseline, opioid use had a slight but non-significant increase in wave 3 (OR=1.44, 95%CI, 1.03 to 2.00).

Table 4 Participants' self-reported medication use changed over time

Medication categories	**Baseline** n (%)	**Year 1** n (%)	**Year 3** n (%)
Opioid	887 (9.3)	514 (5.4)	375 (10.7)
NSAIDs	351 (3.7)	195 (2)	75 (2.1)
Total medication use	1238	709	450

Abbreviations: NSAIDs Nonsteroidal anti-inflammatory. % is for people how used medications compared to those who did not.

Table 5 Random-effect logistic regression (RELR) for ***opioids*** adjusted for age, sex, waves, and NSAIDs.

Predictors	Coef.	SE	z	P	OR	OR [95% CI]	
Age	-0.005	0.007	-0.54	0.589	0.996	0.982	1.010
Female [a]	0.682	0.263	2.59	0.010	1.977	1.181	3.312
Wave 2 [b]	0.138	0.157	0.88	0.381	1.147	0.844	1.560
Wave 3 [b]	0.363	0.169	2.15	0.031	1.438	1.033	2.001
NSAIDs	1.773	0.327	5.43	0.000	5.892	3.107	11.174
Constant ICOAP [c]							
Moderate Recovering	0.758	0.385	1.97	0.049	2.134	1.003	4.540
Moderate Worsening	1.244	0.559	2.23	0.026	3.469	1.160	10.373
High Stable	0.639	0.807	0.79	0.428	1.894	0.390	9.204
Worsening	-0.205	0.707	-0.29	0.772	.815	0.204	3.254
Recovering	0.163	0.786	0.21	0.836	1.177	0.252	5.489
Intermittent ICOAP [c]							
Moderate Recovering	-0.007	0.383	-0.02	0.986	0.993	0.469	2.103
Moderate Worsening	0.498	0.553	0.90	0.367	1.646	0.557	4.862
High Stable	2.397	0.834	2.88	0.004	10.986	2.144	56.284
Worsening	1.269	0.564	2.25	0.025	3.558	1.177	10.758
Recovering	0.208	0.924	0.23	0.821	1.232	0.201	7.530
painDETECT [c]							
Moderate Recovering	0.319	0.694	0.46	0.646	1.376	0.353	5.365
Moderate Worsening	0.575	0.309	1.86	0.063	1.778	0.970	3.259
High Stable	0.335	0.541	0.62	0.535	1.395	0.485	4.037

[a] Reference category is Male. [b] Compared to baseline. [c] Reference category is Low Stable. SE: Standard Error, P: p-value, OR: Odds Ratio. Participants' N=1318.

The results relating to NSAID use showed that all trajectories of constant ICOAP were using NSAIDs significantly higher than the Low Stable one. We found strong results for the odds of patients with High Stable and Worsening constant pain using NSAIDs, which were 24.53 (95%CI, 3.45 to 174.31) times and 30.31 (95%CI, 4.97 to 184.78) times those of with Low Stable constant pain trajectory, respectively (Table 6). There were no significant differences between the Low Stable trajectory and the trajectories of intermittent ICOAP as well as that for the trajectories of painDETECT in terms of NSAIDs use. Compared to baseline, NSAIDs use had a slight but non-significant increase in wave 2. (OR=1.50, 95%CI, 0.99 to 2.27).

Table 6 Random effect logistic regression (RELR) for ***NSAIDs*** adjusted for age, sex, waves, and NSAIDs.

Predictors	Coef.	SE	z	P	OR	OR [95% CI]	
Age	-0.042	0.016	-2.63	0.009	0.959	0.929	0.989
Female [a]	-0.280	0.320	-0.88	0.381	0.755	0.403	1.415
Wave 2 [b]	0.408	0.211	1.93	0.053	1.504	0.994	2.274
Wave 3 [b]	-1.069	0.278	-3.85	0.000	0.343	0.199	0.592
Opioid	1.699	0.291	5.83	0.000	5.467	3.089	9.676
Constant ICOAP [c]							
Moderate Recovering	1.500	0.491	3.06	0.002	4.480	1.712	11.719
Moderate Worsening	1.693	0.718	2.36	0.018	5.434	1.330	22.200
High Stable	3.200	1.000	3.20	0.001	24.534	3.453	174.312
Worsening	1.947	0.808	2.41	0.016	7.007	1.438	34.140
Recovering	3.412	0.922	3.70	0.000	30.311	4.972	184.777
Intermittent ICOAP [c]							
Moderate Recovering	-1.265	0.476	-2.66	0.008	0.282	0.111	0.718
Moderate Worsening	-1.708	0.690	-2.47	0.013	0.181	0.047	0.702
High Stable	-3.094	1.072	-2.89	0.004	0.045	0.006	0.371
Worsening	-0.318	0.670	-0.47	0.635	0.728	0.196	2.706
Recovering	-2.859	1.185	-2.41	0.016	0.057	0.006	0.585
painDETECT [c]							
Moderate Recovering	-0.063	0.864	-0.07	0.942	0.939	0.173	5.104
Moderate Worsening	0.107	0.374	0.29	0.775	1.113	0.534	2.318
High Stable	0.096	0.671	0.14	0.887	1.100	0.295	4.102

[a] Reference category is Male. [b] Compared to baseline. [c] Reference category is Low Stable. SE: Standard Error, P: p-value, OR: Odds Ratio. Participants' N=1318.

Discussion

We show that ICOAP and painDETECT describe relatively similar patterns of pain progression. Specifically, both ICOAP and painDETECT revealed stable and recovering pain trajectories. However, there were some dissimilarities too. The painDETECT measure neither capture severe Worsening nor severe Recovering pain trajectories, whereas the ICOAP scales were able to identify severity in both Worsening and Recovering pain trajectories. The variation between pain measures in capturing a trajectory for severe OA pain, though not examined in a single study, was found by comparing studies on OA pain trajectories (See supplementary Table S3 for details). For example, while cohort studies using Western Ontario and McMaster

Universities Osteoarthritis Index (WOMAC) were able to identify severe OA pain [5, 6, 8], studies using the Visual Analog Scale (VAS) did not identify any trajectories for severe pain [11, 12]. Our results also, as discussed below, showed that the within-individual correspondences between conceptually similar trajectories were good. They also show a differential relationship with medication use. A key finding for this was that the pain trajectories identified for intermittent and constant ICOAP were differently associated with the medication use. The pain trajectories of constant ICOAP were associated only with NSAIDs, whereas pain trajectories of intermittent ICOAP were associated only with opioid use. Also, while all pain trajectories of constant ICOAP were strongly associated with higher NSAID use, only, the High Stable and the Worsening pain trajectories of intermittent were associated with higher opioid use.

Different Measures, Different Trajectories

We reliably identified that different pain measures produce non-equivalent descriptions of pain progression. Using pain measures other than ICOAP and painDETECT, several studies have identified low, moderate, and high stable trajectories [5-7, 12], a few studies have identified worsening [8, 10, 12, 37], and some report recovering [8, 10, 11, 37] trajectories. Using two measures of pain we show that because trajectories appear similar does not mean they are identifying the same patients across these studies [5, 6].

Specifically, our results showed that the two ICOAP scales (intermittent and constant) classified the same individual with some degree of accuracy as falling into the same trajectories, especially for the stable high, moderate, and low trajectories, although less so for the changing pain trajectories (i.e., recovering or worsening). The correspondence

between the 4 painDETECT trajectories and the 6 ICOAP trajectories captured high overlaps for Low Stable, Moderate Worsening, and High Stable. However, the Moderate Recovering trajectories of the two measures did not correspond: the Moderate Recovering painDETECT was found to have stronger overlap with Recovering ICOAP, which shows that most people with Moderate Recovering neuropathic-like pain have been identified by ICOAP to have complete Recovering pain pattern.

Medication Change and Pain Progression

There is an extensive literature on the role of medication in pain management [38, 39]. However, this has typically not considered the role of pain trajectories, instead the focus has been on exploring overall relationships between pain and medication use. When it has examined pain trajectories, it has not used robust techniques to determine the number of trajectories such as LCGA [39] or not explored medication in detail, examining medication frequency in general [5].

Thus, our results offer new insights into the associations between opioid medication use and pain trajectories. These are observed for the ICOAP, but not for neuropathic-like pain progression. Thus, opioid use is associated with pain trajectories that focus on the impact of pain on quality of life and behaviour, rather than neuropathic symptoms. Opioid use is associated with the management of the impact of pain of behaviour and mood and not the management of symptoms of pain per se. This is especially the case when the impact of intermittent or constant symptoms on behaviour and mood is worsening or the impact of the intermittent symptoms is high and stable over time. For example, compared to the Low Stable trajectory, people with the High Stable intermittent ICOAP trajectory or with Worsening

intermittent ICOAP trajectory were more likely to report opioid use. Thus, clinicians may wish to consider how patients are reporting the pain (symptoms vs impact on life) and to consider alternative treatment options when the impact on life is reported. Similarly, for NSAIDs it was trajectories that assess the impact of constant and intermittent pain (ICOAP) on behaviour and mood that were associated with greater NSAID use. For example, compared to the Low Stable trajectory, all the constant ICOAP trajectories were associated with greater reports of NSAID use. Thus, while there is some degree of overlap between pain trajectories it is the experience of a particular type of pain progression based on the constant or constant–intermittent nature of pain and its influence on behaviour and feelings that is associated with opioid and NSAID use and not neuropathic pain symptoms. To the best of our knowledge, this is the first study to explore and identify these associations [40, 41]. This clear distinction is a novel finding of this work.

Limitations of the study and direction for future studies

The present study had some limitations: First, we have only assessed knee pain at 3 time points, and the pain questionnaires were time limited. Therefore, we do not know their more detailed overall pain experience over the 3 years. The study also represents a large group of knee pain patients. This heterogenic data for knee pain may limit extrapolating our finding to mark OA-induced knee pain. Also, we do not know how effective opioids and NSAIDs are for their differing types and phases of knee OA pain. Second, we had missing values around 45 to 53 percent, which needs cautious generalisations of the findings. Although attrition is inevitable in longitudinal designs, its incremental effects can be decreased by either advanced imputation techniques or modelling the missingness. In our study, because of The non-random nature of dropouts, we adjusted our models using latent class dropout method.

Furthermore, our sample size was large enough for the given statistical modelling even at phase 3.

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Ethics: All aspects of the KPIC study were approved by the Nottingham University Hospitals NHS Trust and the Nottingham Research Ethics Committee 1 (NREC Ref: 14EM0015) and registered (clinicaltrials.gov portal: NCT02098070).

***Declarations of conflict interest*:** None

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Consents: Completion of the KPIC baseline questionnaire and willingness to answer follow-up questionnaire were taken as implicit consent.

Author contributions: The KPIC cohort study was designed by DW, MD, WZ and VA. All authors contributed to the design and conception of the current paper. SH performed data analysis with input from RJ, and EF. SH prepared the draft of the manuscript with inputs from RJ, EF, DW, MD, GR, AV and WZ. All authors discussed the results and commented on the manuscript.

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Online supplementary files

Table S1 Model fit indices of LCGA (Constant ICOAP, Intermittent ICOAP, and painDETECT)

Class	BIC (AIC)	Entropy	VLMR-LRT *p*	Average posterior probability (min-max)	Number of subjects per class
a. Constant ICOAP					
1	24995.331 (24689.156)	-		1.00	**1590**
2	22900.927 (22814.983)	.759	P< 0.000	.918(.884-.952)	495/1095
3	22758.296 (22645.495)	.715	P< 0.000	.852 (.820-.912)	587/798/205
4	22714.324 (22574.665)	.709	P= 0.023	.784 (.578-.913)	509/746/107/228
5	22685.731 (22519.214)	.739	P=0.007	.747 (.516-.923)	726/94/218/60[b]/492
6	**22621.851 (22428.478)**	**.744**	**P=0.006**	**.777 (.562-.899)**	**93/124/281/77[b]/478/537**
7[a]	22633.082 (22412.851)	.752	P=0.124	.747(.598-.898)	282/79[b]/28[b]/459/129/98/515
b. Intermittent ICOAP					
1	27556.428 (27244.205)	-	-	1.00	**1768**
2	26149.668 (26062.026)	0727	P< 0.000	.887 (.819-.954)	439/1329
3	26053.955 (25938.925)	0.693	P< 0.000	.816 (.758-.898)	127/591/1050
4	26035.869 (25983.441)	0.721	P= 0.006	.730 (.434-.925)	1040/48[b]/553/127
5	26028.465 (25858.659)	0.697	P=0.032	.667 (.334-.917)	54b/552/954/239/70[b]
6	**26016.958 (25819.764)**	**0.666**	**P= 0.004**	**.702 (.508-.876)**	**242/735/53[b]/152/498/88[b]**
7 [a]	26033.190 (25808.609)	0.715	P= 0.240	.725 (.376-.920)	519/234/490/88[b]/322/60[b]/55[b]
c. painDETECT					
1	29972.061 (29656.946)	-	-	1.00	**1860**
2	28753.427 (28664.973)	0.862	P< 0.000	.940 (.900-.979)	406/1454
3	28366.020 (28249.925)	0.834	P< 0.000	.897 (.766-.958)	1230/120/510
4	**28237.010 (28093.273)**	**0.844**	**P= 0.006**	**.827 (.599-.953)**	**120/60[b]/1160/520**
5 [a]	28100.831 (27929.452)	0.803	P= 0.167	.815 (.655-.937)	268/76b/471/997/48[b]

[a] VLMR-LRT test does not reject the H_0 that a model with k classes significantly improves a model with k-1 classes, and therefore the highest number of classes that fits the data significantly is a model with k-1 classes.

[b] A class with most likely latent membership <5%. Statistics highlighted in **bold** are the selected best-fit indices.

Note: All extracted classes in the table had most likely latent membership >1%. All models' Bootstrapped likelihood ratio test (BLRT) had p<.001. Abbreviations: ICOAP Intermittent and Constant Osteoarthritis Pain, painDETECT Neuropathic-like knee pain, **AIC** Akaike information criterion, **BIC** Bayesian information criterion, **VLMR-LRT** Vuong-Lo-Mendell-robin adjusted likelihood ratio test.

Table S2 Baseline characteristics of the latent classes for ICOAP and painDETECT

	Low stable	Moderate Recovering	Moderate Worsening	High stable	Worsening	Recovering	p-value [a]
Constant ICOAP							
Age, mean (SD)	62.31 (10.03)	62.71 (9.89)	62.96 (9.96)	60.81 (10.43)	61.13 (10.25)	63.02 (9.53)	0.293
Women, N (%)[b]	293 (54.7)	270 (57)	193 (68.9)	81 (66.4)	45 (58.4)	55 (59.2)	0.008
BMI, mean (SD)	27.31 (4.41)	28.82 (5.92)	29.86 (6.17)	33.43 (8.53)	28.84 (5.71)	30.84 (6.36)	<0.001
Intermittent ICOAP							
Age, mean (SD)	62.49 (9.85)	62.53 (9.76)	63.59 (10.12)	59.70 (10.18)	61.41 (11.03)	62.58 (10.46)	0.044
Women, N (%) [b]	410 (55.9)	288 (58.2)	162 (68.2)	55 (64)	95 (62.5)	32 (60.4)	.042
BMI, mean (SD)	27.59 (4.91)	28.61 (6.18)	30.62 (6.83)	32.95 (7.73)	28.45 (6.13)	30.69 (7.25)	<0.001
painDETECT							
Age, mean (SD)	61.81 (10.03)	27.59 (4.93)	27.59 (4.93)	27.59 (4.93)	-	-	.184
Women, N (%)	648 (56.1)	34 (56.7)	326 (63.2)	88 (73.3)	-	-	<0.001
BMI, mean (SD)	27.59 (4.93)	30.67 (6.12)	29.94 (6.57)	31.70 (8.92)	-	-	<0.001

[a] Heterogeneity for count data was assessed using χ^2 and that for continuous data was assessed using ANOVA (independent t-test for the two painDETECT classes). [b] Percentage of the total number of women, compared to men, in each subgroup. Abbreviations: ICOAP Intermittent and Constant Osteoarthritis Pain, painDETECT Neuropathic-like knee pain.

Table S3 Studies examining the trajectories of OA or RA pain with original trajectories' names

Paper	Sample	Pain Measure in trajectory analysis	Number and names of pain trajectories (%)	Baseline variables	Trajectory analysis
Collins et al. (2014) [5]	Patients with diagnosed radiographic evidence of knee OA in OAI cohort.	WOMAC	**5**: severe (6), high moderate (17), low moderate (32) mild (35), and no pain (11)	Sex, race, education, comorbidities, age, BMI, alignment, KL, and depression.	GBTA
Dai et al. (2017) [6]	People (45-79 years) with or at risk of knee OA, annual follow-ups for 8 years	WOMAC	**4**: no pain (34.5), mild pain (38.1), moderate pain (21.2), and severe pain (6.2).	Fibre Intake	GBTA
Holla et al. (2014) [7]	CHECK cohort, participants with early symptomatic knee OA	WOMAC	**3**: mostly stable trajectories differing in baseline and follow-up pain: good (47), moderate (37) and poor outcomes (16)	age, knee flexion range, BMI, NRS, hip pain, comorbidity, SF-36 vitality, bony tenderness, OA,	LCGA
Nicholls et al. (2014) [8]	CAS-K cohort: Adults with or at high risk of knee OA.	WOMAC	**5**: Mild, non-progressive (35) Progressive (28), Moderate (22), Improving (12), and Severe, non-improving (3).	age, sex, WOMAC Pain, WOMAC Function BMI, and KL score for tibiofemoral osteoarthritis	LCGA
Bastick et al. (2016) [37]	CHECK cohort: Patients with symptomatic knee OA. A 5-year cohort knee follow-up study of knee OA.	NRS	**6**: constant mild (26) or severe (10), severe (5) or moderate progression (24), major (3) or moderate regression (29)	BMI, education, comorbidity, WOMAC physical, knee joint space tenderness, painful knee flexion	LCGA
Wesseling et al. (2015) [10]	Patients with symptomatic knee OA severity at baseline and 5 annual follow-ups.	NRS	**3**: marginal (31), mild (42), and moderate (26)	BMI, Education, hip pain, comorbidities, PCI worrying, and resting.	LCGA
Mills et al. (2019) [11]	Patients with Predominant Patellofemoral OA. Assessed at baseline and follow-up assessments of 6, 12, 18, and 26 weeks.	VAS	**3**: high-persistent (28), moderate-persistent (57), and low improving (15)	Sex, age, BMI, unilateral or bilateral knee symptoms, KOOS, Depression, Anxiety and Stress (DASS-21)	LCGA
Verkleij et al. (2012) [12]	previously performed RCT: patients with clinically and radiographically determined hip OA	VAS	**5**: three stables, two changing: mild (31) or moderate pain (14), always in pain (14) and regular (22) or rapidly (19) progressing	age, sex and BMI, comorbidity, medication adherence and activity level	LCGA

Abbreviations: CAPS Childhood Arthritis Prospective Study, GBTA Group-Based Trajectory Analysis, KL Kellgren-Lawrence, KOOS Knee Injury and Osteoarthritis Outcome Score, LCGA Latent Class Growth Analysis, NRS Numerical Rating Scale, VAS Visual Analog Scale, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

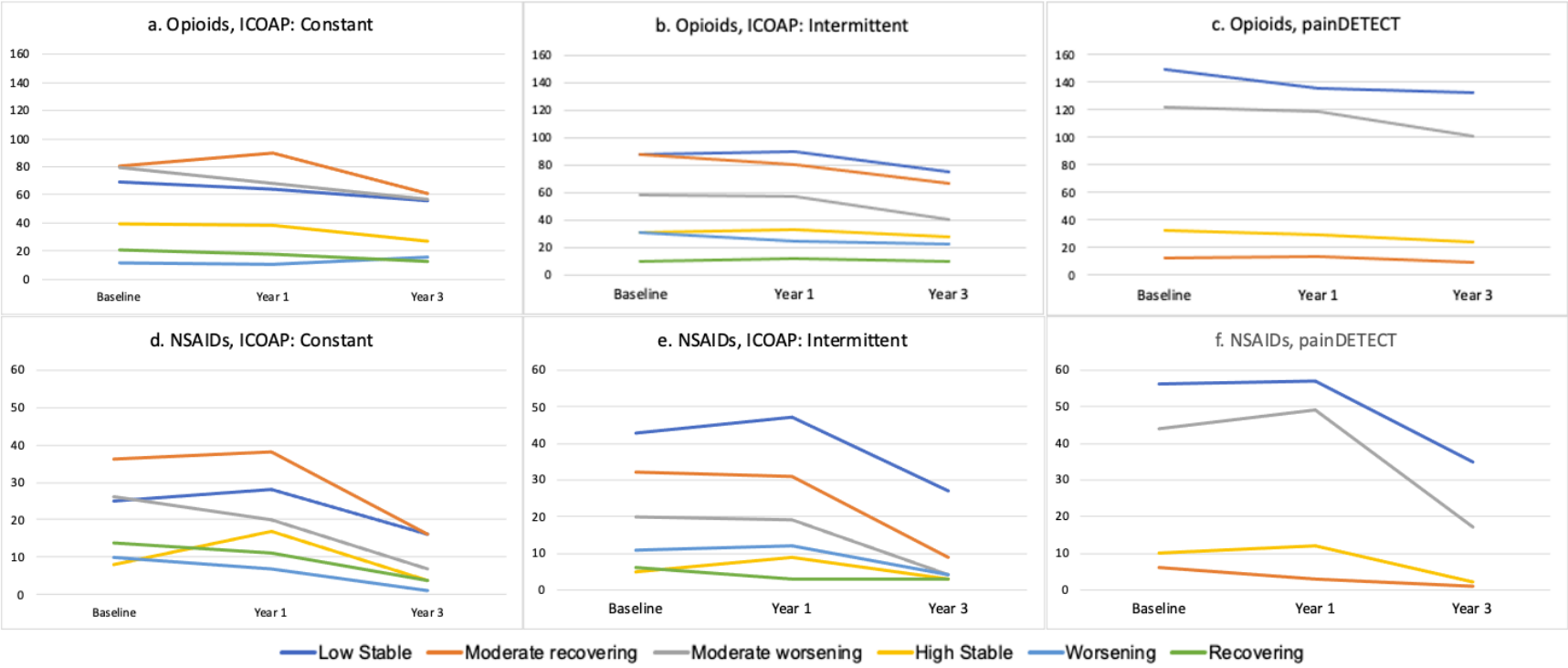

Figure S1. Medication used by the trajectories of Constant OA pain, Intermittent OA pain, and PainDETECT. Abbreviations: ICOAP Intermittent and Constant Osteoarthritis Pain, painDETECT Neuropathic-like knee pain, NSAIDs Nonsteroidal anti-inflammatory.