Doctor, why does my hand hurt? The nature, course and treatment of pain in hand osteoarthritis

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CHAPTER 2

DETERMINATION AND CHARACTERIZATION OF PATIENT SUBGROUPS BASED ON PAIN TRAJECTORIES IN HAND OSTEOARTHRITIS

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ABSTRACT

Objectives

To investigate pain, pain trajectories and their determinants in hand osteoarthritis (OA).

Methods

Data from the HOSTAS (Hand OSTeoArthritis in Secondary care) consisting of consecutive hand OA patients were used. Australian Canadian Osteoarthritis Hand Index (AUSCAN) pain was measured yearly for four years. Patients with complete AUSCAN at ≥2 time points were eligible for longitudinal analysis.

Associations between variables of interest and baseline AUSCAN pain were investigated with linear regression. Development of pain over time was modelled using latent class growth analysis (LCGA). Associations of LCGA classes with variables of interest were analyzed using multinomial logistic regression adjusted for baseline pain.

Results

A total of 484/538 patients (mean [SD] age 60.8 [8.5] years, 86% women, mean [SD] AUSCAN pain 9.3 [4.3]) were eligible for longitudinal analysis.

Sex, marital and working status, education, disease duration and severity, anxiety and depression scores, lower health-related quality of life (HR-QoL), specific illness perceptions and coping styles were associated with baseline pain.

LCGA yielded three classes, characterized by average pain levels at baseline; average pain remained stable over time within classes. Classes with more pain were positively associated with BMI, tender joint count, symptom duration, hand function scores and depression scores, negatively with physical HR-QoL, and education level.

Conclusion

Baseline pain was associated with patient and disease characteristics, and psychosocial factors. LCGA showed three pain trajectories in hand OA patients, with different baseline pain levels and stable pain over time. Classes were distinguished by BMI, education level, disease severity, depression, and HR-QoL.

Key messages

- Subgroups with different pain trajectories exist within the hand OA population
- Trajectories show different intercepts and stable average pain levels over time.
- Subgroups can be characterized by patient and disease characteristics, and mental and physical wellbeing.

INTRODUCTION

Hand osteoarthritis (OA) is a frequently occurring, invalidating disease (1, 2). Pain is the primary symptom, along with loss of function and destruction of the joints (1, 2). Previous studies have identified various factors associated with pain in hand osteoarthritis, including sex, disease subtype and distribution, rapid radiological progression, and signs of depression and anxiety, indicating it is a multifactorial problem (3, 4). The etiology of hand OA pain is as of yet unclear, but both nociceptive mechanisms (joint damage, inflammation) and non-nociceptive mechanisms (sensitization) are thought to play a role. These mechanisms require different therapies, which complicates treatment (3, 5). This indicates the importance of investigating factors associated with pain in hand OA, as it may provide insights leading to new treatment options. For example, differences in coping strategies and illness perceptions have been shown to influence functional disability in hand OA, which in turn has been associated with pain (3, 6-9).

Along with the uncertainty regarding the etiology, the development of hand OA pain over time is also unclear. Much previous research has focused on radiographic signs to study progression. Large cohort studies investigating the development of pain in hand osteoarthritis are still few in number. The studies that have been performed indicate that pain does not seem to increase on average. (10, 11) However, the lack of changes in average pain does not preclude the existence of subgroups within the hand OA population, in which increasing or decreasing pain trajectories may be found.

For knee and hip OA, subgroups with different pain trajectories have been identified. (12, 13) These subgroups were identified using latent class growth analysis (LCGA), a statistical technique to investigate inter-individual differences in intra-individual development. This technique identifies subgroups based on the course of a variable of interest over time.

Knowledge regarding subgroups with different pain trajectories within hand OA and their characteristics may help guide clinical decision making and patient education. Additionally, knowledge of factors associated with pain in hand OA, both cross-sectional and over time, may provide insights into potential treatments. Therefore, this study aimed: i) to investigate the cross-sectional associations of disease and patient characteristics with pain in hand OA; ii) to identify subgroups based on pain trajectories within the hand OA population; iii) to describe these trajectories; and iv) to characterize the subgroups of patients that follow these trajectories.

METHODS

Study design

Data from the Hand OSTeoArthritis in Secondary care (HOSTAS) cohort, an ongoing observational cohort consisting of consecutive patients from the Leiden University Medical Center rheumatology outpatient clinic, were used. Between June 2009 and October 2015, consecutive patients diagnosed with primary hand OA by their treating rheumatologist were included. Patients diagnosed with secondary hand OA or hand symptoms due to other diseases were excluded. Patients were followed for four years, filling in questionnaires yearly and undergoing physical examinations and imaging every second year. Full details on the cohort have been published previously. (14)

All 538 HOSTAS patients were included in the cross-sectional analysis. Patients with complete Australian Canadian Osteoarthritis Hand Index (AUSCAN) pain measurements at a minimum of two visits were included in the longitudinal analyses.

The HOSTAS study was approved by the medical ethics committee at the LUMC and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Patient and public involvement

Patients were not involved in the execution of this analysis, but were involved in designing the original cohort study.

Study variables

The primary outcome of the present study was AUSCAN pain score. (15) The AUSCAN pain score consists of 5 questions scored 0-4, for a total score of 0-20, with higher scores indicating more pain.

Other questionnaires used included the short form (SF)-36 for health related quality of life (used to calculate norm-based physical (PCS) and mental (MCS) component scales, using age- and sex-specific Dutch-population based norms, with higher scores indicating better outcomes), (16) the Hospital Anxiety and Depression Scale (HADS) for depression and anxiety (7 questions scored 0-3 per domain, for domain scores of 0-21), (17) and a modified Charlson comorbidity index to assess comorbidities. The Charlson comorbidity index collects information on 18 comorbidities, summarized here as a sum score (0-18). (18) Hand function was assessed using the function domain of the AUSCAN questionnaire (range 0-36, with higher scores indicating worse function). (15) Illness perceptions and attributions were investigated using the Illness Perception Questionnaire (IPQ).

The domains of this questionnaire are explained in the supplementary methods. For all domains, higher scores indicate a stronger belief in the investigated construct. (19) Coping strategies were explored using the Coping with Rheumatic Stressors questionnaire (CORS). (20) The coping strategies are detailed in the supplementary methods. Higher scores indicate more use of that particular strategy. Additionally, patient characteristics including age, sex, BMI, education level, and working and marital status were collected (education level was categorized as lower [no schooling, primary school only or lower vocational education], middle [lower general secondary education or secondary vocational education] or high [all higher education]. Working status was categorized as currently employed [fulltime or parttime], currently not employed, disabled/sick leave [completely or partially disabled, or sickness leave] or retired. Marital status was categorized as living together [married or unmarried] or not [single, widowed or divorced]. Finally, disease characteristics including symptom duration and fulfilment of American College of Rheumatology (ACR) criteria for hand OA (21) were collected at baseline.

The examinations included a physical examination of the distal interphalangeal (DIP), proximal interphalangeal (PIP), metacarpophalangeal (MCP) and first carpometacarpal (CMC-I) joints as well as the wrist, during which amongst others the tender joint count was collected (0-3 per joint, total score 0-90, dichotomized to pain or no pain and summed to a score of 0-30). During the visits, a VAS pain was also collected on paper for each hand.

Dorsal-volar radiographs of the hands were taken at baseline and scored using the Kellgren-Lawrence method (score 0-120) (22) and Verbruggen-Veys method to assess presence of erosive disease. (23) Erosive disease was defined as having ≥1 PIP/DIP joint of digits 2-5 in the erosive or remodelling phase according to the Verbruggen-Veys system. Intra-observer reliability of scoring was good. (14)

Summed scores were regarded as missing in case of any missing component, in case of > 1 missing component for the AUSCAN pain subscale or >2 for the function subscale, in case of more than 1 or 2 missing components for the IPQ questionnaire depending on the specific domain, and in case of more than half of the components per scale for the SF-36.

Statistical analysis

Variables were described using mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables and absolute and relative frequencies (number [%]) for categorical variables.

Associations of variables of interest with baseline AUSCAN pain, selected based on existing evidence regarding factors associated with pain in OA, were investigated using univariate linear regression.

To investigate the presence of subgroups with different AUSCAN pain development trajectories, latent class growth analysis (LCGA) was used. LCGA divides the data into classes with different trajectories of the variable of interest. The trajectories are described based on the intercept (measure of baseline value) and slope (measure of development over time). The slope and intercept have a fixed variance of zero within the classes, allowing only for variance between classes.

Models were run with varying numbers of classes (two up to six) and varying formulae for the slopes (linear, quadratic or cubic). The optimal model was selected based on a combination of factors: fit indices, clinical plausibility of the modelled phenomenon, size of classes, parsimony and interpretability. The following model fit indices were used and judged as follows: The smallest Bayesian information criterion (BIC) value, high entropy value (maximum 1.0), a significant Vuong-Lo-Mendell-Rubin likelihood ratio test (LRT) and a significant bootstrap LRT. These LRTs indicate if the model with n classes describes the data better than the model with n-1 classes. A significant p-value (<0.05) indicates statistical superiority of the model with 1 more class.

Differences in baseline characteristics between the identified classes were investigated using multinomial logistic regression analysis, with the classes as the dependent variable. The class with the lowest baseline pain was chosen as the reference group. The independent variables, selected based on previous evidence regarding factors associated with pain in hand OA, were first tested univariately in multinomial logistic regression to assess their total effect, after which the regression models were adjusted for baseline AUSCAN pain to assess direct effects of potential factors of influence by excluding the indirect effect through baseline pain. As a sensitivity analysis, the models were further adjusted for age, sex and BMI.

Mplus version 8.0 was used for the LCGA. All other analyses were performed using R version 4.0.3.

RESULTS

Patient characteristics

Patient characteristics are summarized in table 1. A total of 463 patients (86%) were female. Mean (SD) age was 61.0 (8.6) years. A total of 485 patients (90%) fulfilled the ACR criteria for hand OA. Mean AUSCAN pain score was 9.3 (SD 4.6). No clinically relevant

Table 1. Patient characteristics

	N=538
Patient characteristics	
Female sex; N (%)	463 (86)
Age, years	61.0 (8.6)
BMI, kg/m2	27.1 (4.8)
Living together; N (%)	427 (81)
Low education level; (N (%)	141 (27)
Currently working; N (%)	215 (46)
Comorbidities, number (range 0-18); median (IQR)	0 (0-1)
HADS	
Depression (range 0-21); median (IQR)	2 (1-5)
Anxiety (range 0-21); median (IQR)	4 (2-7)
Disease characteristics	
ACR criteria fulfilled; N (%)	485 (90)
Erosive disease; N (%)	154 (29)
KL sum score (range 0-120); median (IQR)	17 (8-29)
Symptom duration, years; median (IQR)	5.3 (2.0-12.2)
Tender joint count (range 0-30); median (IQR)	3 (1- 7)
Patient reported outcome measures	
AUSCAN	
Pain (range 0-20)	9.3 (4.6)
Function (range 0-36)	15.6 (8.5)
VAS pain (range 0-100)	
Left hand	33.6 (22.5)
Right hand	36.7 (21.8)
SF-36	
MCS	51.7 (8.7)
PCS	44.7 (8.2)

N=484. Data are mean (SD) unless indicated otherwise. ACR = American college of Rheumatology criteria for hand OA. BMI = Body mass index. AUSCAN = Australian/Canadian osteoarthritis hand index. VAS = Visual analog scale. SF-36 = Short-form 36, with norm-based scores with a mean of 50 and SD of 10 using age and sex-specific Dutch population-based norms. MCS = mental component scale. PCS = physical component scale. KL = Kellgren-Lawrence. HADS = Hospital Anxiety and Depression scale. BMI N=511. Living together N=529. Education level N=524. Working status N=471. HADS depression N=382. HADS anxiety N=381. Erosive disease N=534. KL sum score N=534. Symptom duration N=500. AUSCAN pain N=523. AUSCAN function N=523. VAS pain = 388. SF-36 N=511.

mean changes in AUSCAN pain score were seen over time (Appendix table S1). Of 538 participants, 484 (90%) were included in the longitudinal analysis. Included participants did not show marked differences from the excluded participants (data not shown).

Associations with baseline pain

Baseline AUSCAN pain scores showed positive associations with female sex, low education level, the number of comorbidities, HADS anxiety and depression scores, presence of erosive disease, symptom duration, tender joint count, and AUSCAN function scores. Negative associations were found for living together, currently working, and SF-36 PCS and MCS scores. Of the IPQ domains, baseline pain was positively associated with the identity domain (indicating more complaints are attributed to the disease), the consequences domain (indicating more consequences experienced are attributed to the disease), and emotional representations (indicating more emotions experienced due to the disease), and negatively with illness coherence (indicating less understanding of the disease). Among the coping strategies, baseline pain was positively associated with accepting, decreasing activity, pacing and finding creating solutions, and negatively with comforting cognitions. (table 2)

Table 2. Association with baseline AUSCAN pain

Baseline	β (95% confidence interval) AUSCAN pain (n=534)
Patient characteristics	
Female sex	1.19 (0.12 to 2.26)
Age, years	0.02 (-0.02 to 0.07)
BMI, kg/m2	0.04 (-0.04 to 0.12)
Living together	-1.02 (-1.96 to -0.07)
Education level low	0.97 (0.13 to 1.81)
Currently working	-1.22 (-2.01 to -0.43)
Excluding retirees	-1.92 (-3.00 to -0.85)
Number of Comorbidities	0.99 (0.60 to 1.38)
HADS	
Depression	0.36 (0.24 to 0.49)
Anxiety	0.31 (0.19 to 0.43)
Disease characteristics	
Erosive disease	0.84 (0.02 to 1.67)
Symptom duration, years;	0.07 (0.03 to 0.11)
KL sum score	0.01 (-0.02 to 0.03)
Tender joint count	0.31 (0.24 to 0.38)

Table 2. Association with baseline AUSCAN pain (continued)

Baseline	β (95% confidence interval) AUSCAN pain (n=534)
Patient reported outcome measures	
VAS pain	
Left hand	0.09 (0.08 to 0.11)
Right hand	0.11 (0.10 to 0.13)
AUSCAN function	0.40 (0.37 to 0.42)
SF-36	
PCS	-0.26 (-0.30 to -0.22)
MCS	-0.11 (-0.16 to -0.07)
Illness perceptions (N=351)	
Identity (0-14)	0.69 (0.52 to 0.87)
Timeline (Chronic) (6-30)	0.01 (-0.11 to 0.12)
Consequences (6-30)	0.34 (0.25 to 0.43)
Personal control (6-30)	-0.02 (-0.13 to 0.10)
Treatment control (5-25)	-0.10 (-0.25 to 0.06)
Illness coherence (4-20)	-0.17 (-0.28 to -0.06)
Timeline cyclical (4-20)	-0.01 (-0.14 to 0.12)
Emotional representations (6-30)	0.21 (0.13 to 0.30)
Coping styles (N=349)	
CORS domains	
Dependency	
Accepting (6-24)	0.13 (0.03 to 0.23)
Consideration (7-28)	0.07 (-0.04 to 0.18)
Pain	
Comforting cognitions (9-36)	-0.10 (-0.18 to -0.01)
Decreasing activity (8-32)	0.29 (0.19 to 0.38)
Diverting attention (8-32)	0.08 (-0.01 to 0.17)
Limitations	
Optimism (5-20)	-0.10 (-0.24 to 0.04)
Pacing (10-40)	0.16 (0.09 to 0.23)
Creative solutions (8-32)	0.12 (0.04 to 0.20)

N=538. BMI = Body mass index. HADS = Hospital Anxiety and Depression scale. KL = Kellgren-Lawrence. VAS = Visual analog scale. AUSCAN = Australian/Canadian osteoarthritis hand index. SF-36 = Short-form 36, with norm-based scores with a mean of 50 and SD of 10 using age and sex-specific Dutch population-based norms. PCS = physical component scale. MCS = mental component scale. IPQ = Illness Perception Questionnaire. CORS = Coping with Rheumatic Stressors. BMI N=511. Living together N=529. Education level N=524. Working status N=471. HADS depression N=382. HADS anxiety N=381. Erosive disease N=534. KL sum score N=534. Symptom duration N=500. AUSCAN pain N=523. AUSCAN function N=523. VAS pain = 388. SF-36 N=511. IPQ identity N=383, all other domains N=384. CORS accepting N=375, consideration N=372, comforting cognitions N=377, decreasing activity N=380, diverting attention N=378, optimism N=376, pacing N=379, creative solutions N=370.

LCGA classes

The quadratic LCGA model with three classes was determined to be the best, based on the combination of fit indices, the size of the classes and interpretability (Appendix tables S2 and S3). The resulting classes each had a trajectory described by an intercept (I), linear (S) and quadratic (Q) term (with formula $Y=a+bX+bX^2$). The three classes were termed low, middle and high, based on the trajectory intercepts. For the low class, the trajectory intercept was 4.841, the linear term was -1.052 and the quadratic 0.176. The middle class had a trajectory described by intercept 8.849, linear term -0.273 and quadratic term 0.030. Finally, the high class had a trajectory described by intercept 13.039, linear term 0.249 and quadratic term -0.071. Patient characteristics of each of the three LCGA classes can be found in Appendix table S4.

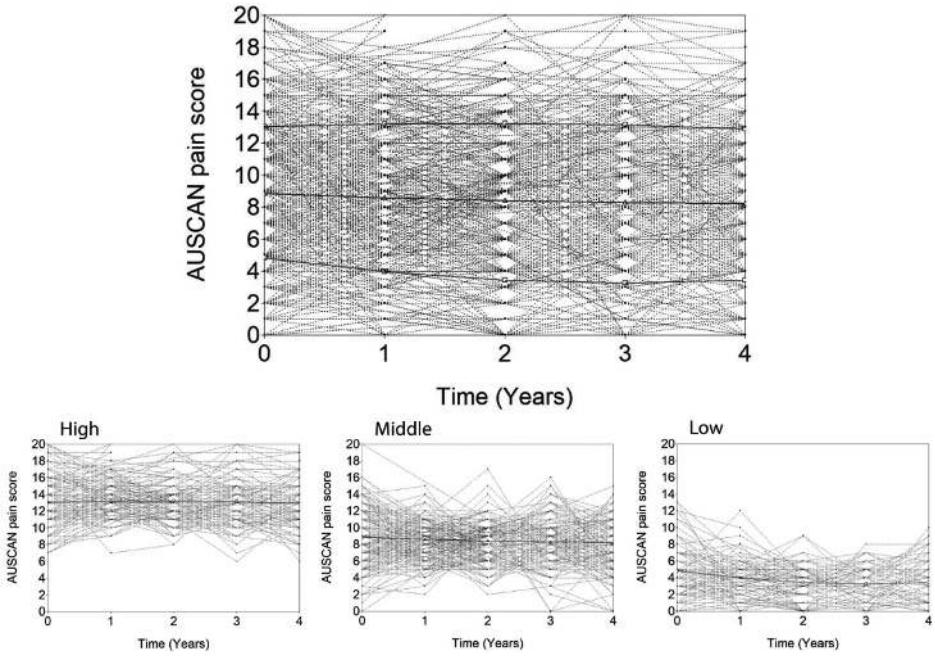

Figure 1. LCGA classes

The three classes determined by latent class growth analysis. Each class shows the average (solid line) trajectory of the group, as well as the individual observed pain scores (dashed lines) of the participants in that class. Time in years (0-4) on the X axis, AUSCAN pain score (0-20) on the Y axis.

Associations with LCGA classes

After adjustment for baseline AUSCAN pain scores, membership of the middle or high class compared to the low class was positively associated with BMI, symptom duration, tender joint count, VAS pain scores, HADS depression scores, AUSCAN function scores, low education level, and negatively with SF-36 scores (table 3). Most of these associations (excluding those for education level and HADS scores) remained after further adjustment for age, sex and BMI (Appendix table S5). None of the IPQ domains were associated with the LCGA classes after adjustment for baseline AUSCAN pain (table 4). Amongst the coping styles, only the consideration style was associated with LCGA class membership (table 5). This style was employed more frequently in the middle and high classes compared to the low class.

Table 3. Association of LCGA classes with variables of interest

Baseline	Adjusted odds ratio (95% confidence interval) AUSCAN pain trajectory over 4 years		
	Low (N=101)	Middle (N=226)	High (N=157)
Female sex	1	1.43 (0.68-3.01)	0.98 (0.37-2.61)
Age, years	1	0.97 (0.94-1.00)	1.00 (0.96-1.04)
BMI, kg/m2	1	1.07 (1.00-1.15)	1.11 (1.02-1.20)
Erosive disease	1	0.94 (0.49-1.78)	1.03 (0.47-2.26)
Symptom duration, years;	1	1.03 (0.99-1.07)	1.07 (1.03-1.12)
KL sum score	1	1.00 (0.97-1.01)	1.01 (0.99-1.03)
Tender joint count	1	1.12 (1.02-1.24)	1.20 (1.07-1.33)
VAS pain			
Left hand	1	1.01 (1.00-1.03)	1.04 (1.01-1.06)
Right hand	1	1.03 (1.00-1.05)	1.06 (1.03-1.09)
AUSCAN			
Function	1	1.05 (1.00-1.11)	1.15 (1.08-1.23)
SF-36			
PCS	1	0.94 (0.90-0.99)	0.87 (0.83-0.93)
MCS	1	0.98 (0.94-1.02)	0.96 (0.91-1.00)
HADS			
Depression	1	1.13 (0.97-1.33)	1.19 (1.01-1.41)
Anxiety	1	1.10 (0.97-1.25)	1.13 (0.98-1.30)
Living together; N (%)	1	1.25 (0.59-2.63)	1.31 (0.52-3.30)
Low education level	1	1.62 (0.80-3.28)	2.23 (0.96-5.19)
Currently working	1	1.16 (0.64-2.11)	0.74 (0.35-1.57)
Excluding retirees	1	0.67 (0.26-1.70)	0.37 (0.12-1.10)
Comorbidities, number	1	1.11 (0.75-1.64)	1.43 (0.91-2.24)

Multinomial logistic regression with LCGA classes as outcome, adjusted for baseline AUSCAN pain. N=484. BMI = Body mass index. KL = Kellgren-Lawrence. VAS = Visual analog scale. AUSCAN = Australian/Canadian osteoarthritis hand index. SF-36 = Short-form 36, with norm-based scores with a mean of 50 and SD of 10 using age and sex-specific Dutch population-based norms. MCS = mental component scale. PCS = physical component scale. HADS = Hospital Anxiety and Depression scale.

Table 4. Multinomial logistic regression of illness perceptions on LCGA classes

IPQ domain	Adjusted odds ratio (95% confidence interval) AUSCAN pain trajectory over 4 years		
	Low	Middle	High
Identity (0-14)	1	1.13 (0.91 to 1.41)	1.25 (0.98 to 1.58)
Timeline (Chronic) (6-30)	1	1.04 (0.94 to 1.14)	1.07 (0.96 to 1.20)
Consequences (6-30)	1	1.06 (0.97 to 1.17)	1.10 (0.99 to 1.23)
Personal control (6-30)	1	0.99 (0.90 to 1.09)	1.01 (0.90 to 1.13)
Treatment control (5-25)	1	0.97 (0.85 to 1.10)	0.95 (0.81 to 1.11)
Illness coherence (4-20)	1	0.99 (0.90 to 1.09)	0.96 (0.85 to 1.07)
Timeline cyclical (4-20)	1	1.01 (0.91 to 1.13)	1.07 (0.94 to 1.21)
Emotional representations (6-30)	1	1.04 (0.96 to 1.13)	1.05 (0.95 to 1.15)

Multinomial logistic regression of IPQ domains with LCGA classes as outcome, adjusted for baseline AUSCAN pain. N=484. AUSCAN = Australian/Canadian osteoarthritis hand index. IPQ = Illness Perception Questionnaire

Table 5. Multinomial logistic regression of coping styles on LCGA classes

CORS domain	Adjusted odds ratio (95% confidence interval) AUSCAN pain trajectory over 4 years		
	Low	Middle	High
Dependency			
Accepting (6-24)	1	0.93 (0.85 to 1.01)	1.00 (0.90 to 1.10)
Consideration (7-28)	1	1.02 (0.93 to 1.11)	1.13 (1.00 to 1.26)
Pain			
Comforting cognitions (9-36)	1	0.99 (0.92 to 1.06)	0.99 (0.91 to 1.08)
Decreasing activity (10-40)	1	1.04 (0.96 to 1.13)	1.07 (0.97 to 1.18)
Diverting attention (8-32)	1	0.98 (0.92 to 1.05)	1.01 (0.93 to 1.10)
Limitations			
Optimism (5-20)	1	0.94 (0.83 to 1.06)	0.99 (0.86 to 1.14)
Pacing (10-40)	1	1.02 (0.97 to 1.08)	1.05 (0.98 to 1.12)
Creative solutions (8-32)	1	0.98 (0.92 to 1.04)	1.02 (0.94 to 1.11)

Multinomial logistic regression of CORS domains with LCGA classes as outcome, adjusted for baseline AUSCAN pain. N=484. AUSCAN = Australian/Canadian osteoarthritis hand index. CORS = Coping with Rheumatic Stressors.

DISCUSSION

In this study, AUSCAN pain scores in patients with hand OA were cross-sectionally associated with disease characteristics (severity of symptoms, symptom duration, hand function), patient characteristics (sex and education level), and patient reported outcome measures (quality of life, anxiety and depression). LCGA identified three classes, with trajectories differing primarily on baseline pain levels rather than on development

of average pain over time. Membership of classes with more pain was associated with many variables also associated with pain at baseline. Membership of the classes showed little to no associations with illness perceptions and coping styles after adjustment for baseline pain.

The associations between baseline pain and disease characteristics are in accordance with previous literature; erosive hand OA has been described to have a higher disease burden, including more pain. (1) The association between self-reported pain and function is similarly known. (2) Previous literature has also described positive correlations between AUSCAN pain scores and tender joint counts, albeit of limited magnitude. (6, 7) A positive association of tender joint counts with sensitization has also recently been described, which may also lead to higher AUSCAN pain scores, given that sensitization contributes to pain. (24) The association found with female sex is in accordance with previous literature, as is the association with low education level. (3, 25) The associations between baseline pain and patient reported outcome measures regarding mental and physical wellbeing are also in line with previous literature, which described a mutual influence between pain in hand OA and mood and coping styles. (3) We add to this that having more pain is associated specifically with the coping styles accepting, comforting cognitions, decreasing activity, pacing and finding creating solutions. One previous study described associations between the CORS domains and disability. (8) Illness perceptions have also previously been investigated in hand OA, similarly with focus on disability. (9, 26) In those studies, changes in disability were associated with changes in illness perceptions and illness perceptions at baseline were associated with worse function after six years, indicating these perceptions as possible targets for intervention. In the current study, associating more symptoms with the disease, less understanding of the disease, attributing more consequences to the disease and experiencing more negative emotions due to the disease were all associated with higher pain scores. Illness perceptions may therefore be used to similarly influence pain outcomes. Our findings thus support and expand on evidence that psychological and social characteristics may provide potential targets for treating pain in hand OA.

However, in treating pain, one has to consider the expected development of pain over time, as well as the baseline level, as this can help tailor treatment to subgroups of patients. Thus, we studied pain longitudinally using LCGA. We identified three classes with different trajectories of pain development, characterized by the intercept rather than by the slope. This is different from previous studies in knee and hip OA, which yielded trajectories that showed more heterogeneous slopes. (12, 13) In the case of knee OA pain, three classes have been found. The groups were characterized by low baseline pain (intercept) and a slight decrease over time, medium baseline pain and a stable course

and high baseline pain with an increase of pain over 5 years. (12) LCGA analyses over 5 years in hip OA pain yielded four classes with different trajectories (constant mild, moderate pain with moderate regression, moderate pain with progression and constant severe pain). (13) A possible explanation for the difference between hand OA versus knee or hip OA is that hand OA is polyarticular rather than monoarticular. Pain in the hands is a summary of the pain in all the individual joints, which may fluctuate in their symptoms. This could potentially cause the increased complaints of one joint to cancel out the improvement of another joint when asking about pain in the entire hand. Furthermore, there is a difference in studied disease stage; both the knee and hip studies were performed on patients with early OA, whereas the current study did not specifically select early hand OA patients. The progression of symptoms may differ between disease stages. This may indicate that development of pain in hand OA occurs more slowly or in a different stage of the disease than was captured in this study. However, the finding that average pain levels remain stable over time can be of great use in informing patients with hand OA, as they often expect the disease to continually worsen over time, whereas our results indicate that symptoms remain stable on average. Our findings can thus be used to reassure patients that the symptoms need not necessarily progress.

It should however be noted that despite the average trajectory in a class being stable over time, this average is made up of many individual trajectories that fluctuate over time. Given this heterogeneity of individual trajectories within the classes, the intercept cannot be the only determining factor. For example, someone with a baseline AUSCAN score of 9 could be classified into either of the three classes (figure 1). To investigate what other factors could discriminate classes apart from baseline pain, multinomial logistic regression analysis was performed with adjustment for baseline pain after the unadjusted analysis. The unadjusted analysis yielded associations for many factors also found to associate with baseline pain. However, the analysis with adjustment for baseline pain still yielded a number of risk factors for the various classes independent of baseline pain. Amongst these, higher BMI, low education level and higher HADS depression score all associated with membership of more painful classes, in accordance with previous studies in hip and knee OA. (12, 13, 27) We could find no previous literature regarding the associations of LCGA classes with tender joint count and AUSCAN function. However, these have been associated with pain previously, as stated earlier. We add to the knowledge that these factors not only associate with pain, but also with trajectories of pain over time. Health-related quality of life as measured with the SF-36 has also previously been associated both with chronic musculoskeletal pain and with changes thereof. (28) Interestingly, membership of a class with more pain was associated with longer symptom duration, another indication that changes over time may occur in different timeframes than were captured in this study.

Just one association was found between IPQ and CORS domains and the pain trajectories after adjustment for baseline AUSCAN pain scores: an association with the consideration coping style. Possibly this indicates that coping styles are most strongly associated with pain at baseline, and that they have no direct effect on the trajectory of the pain beyond the effect through baseline pain.

Our study has some limitations, including the selection of patients from secondary and tertiary care, which may have led to selection of patients with more severe disease and thus more severe symptoms, limiting the generalizability of these results. Furthermore, the current follow-up time was only 4 years; the stability of the determined trajectories may be in part due to the relatively short time of follow-up relative to the total disease course of hand OA. Also, AUSCAN pain scores were collected yearly. Collecting pain measurements at more time points leading to more dense data may improve precision of these results. We therefore encourage replication of these results in cohorts with longer follow-up time and more frequent pain measurements to confirm these findings.

In conclusion, this study further confirms the multifactorial nature of pain reported by patients with hand OA, depending on psychological, social and disease specific variables. Given the trajectories found average pain levels appear to remain stable in hand OA, although differences and fluctuations in individual pain trajectories occur. These data can be used to inform patients of their prospects, as in our clinical experience patients often expect the disease to get worse with time; these results show that this need not be the case. Furthermore, associations with the different pain trajectories were found even after adjustment for baseline pain, indicating the expected level of pain may be influenced through various factors. BMI, psychological and social factors are thus reinforced as targets of interest in the treatment of pain in hand OA.

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Conflict of interest
Conflicts of interest: CvdM, LvdS, FR and JR report no conflicts of interest. MK reports consultancy/lecture fees outside the submitted work from Pfizer, Novartis, UCB, Galapagos, Flexion, Kiniksa, Jansen, Abbvie, CHDR, all paid to institution. Royalties from Wolters Kluwer and Springer Verlag, paid to institution.

Data availability statement

No data are available. The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. However, some aspects of the data can be shared on reasonable request to the corresponding author.

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APPENDIX

Supplementary methods

Illness perceptions and attributions were investigated using the Illness Perception Questionnaire (IPQ). The IPQ consists of 9 domains: Identity (how many other symptoms are present and if the patient associates these with their hand OA, scored 0-14), timeline acute/chronic (whether the disease is regarded as chronic, 6-30), timeline cyclical (whether the disease is experienced as fluctuating, 4-20), consequences (perceived severity of consequences of the disease, 6-30), personal control (perceived personal control over the disease, 6-30), treatment control (perceived control the treatment has on the disease, 5-25), emotional representations (amount and severity of negative emotions experienced due to the disease, 6-30), illness coherence (how well the patient understands the disease, 5-25) and attributions (which factors patients think caused their disease, further divided into psychological, risk factors, immunity and chance domains). For all domains, higher scores indicate a stronger belief in the investigated construct. For illness coherence, a higher score indicates better understanding. (1)

Coping strategies were explored using the Coping with Rheumatic Stressors questionnaire (CORS). The CORS consists of questions on the use of 8 coping styles. The examined coping styles are divided into three categories: 1) Coping with dependency (accepting [accepting the incurred dependency, scored 6-24] and consideration [taking others into consideration, for example by not asking too much of one person or returning favours if possible, scored 7-28]), 2) coping with pain (comforting cognitions [various positive cognitions in reaction to the pain, scored 9-36], decreasing activity [pausing, stopping or avoiding strenuous physical activities, scored 10-40] and diverting attention [diverting oneself or seeking distractions from the pain, scored 8-32]), and 3) coping with limitations (optimism [cultivating an optimistic outlook on the limitations, scored 5-20], pacing [avoiding or spreading out heavy activities over longer periods of time, scored 10-40] and creative solutions [altering methods and timing of activities, scored 8-32]). Higher scores indicate more use of that particular coping style. (2)

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SUPPLEMENTARY RESULTS

Table S1. Mean change in AUSCAN pain score between study visits

From To	Year 1	Year 2	Year 3	Year 4
Baseline (n=479)	-0.3 (3.5)	-0.5 (3.8)	-0.2 (4.2)	-0.7 (4.1)
Year 1(n=345)	-	-0.4 (3.0)	0.1 (3.4)	-0.4 (3.5)
Year 2(n=443)	-	-	0.3 (3.2)	0.0 (3.4)
Year 3 (n=377)	-	-	-	-0.4 (3.2)
Year 4 (n=361)	-	-	-	-

Data are presented as mean change (SD).

Table S2. LCGA statistics

No. of classes	Smallest group	AIC	BIC	Entropy
2				
Linear	232	10813	10855	0.784
Quadratic	232	10814	10864	0.785
Cubic	230	10817	10875	0.785
3				
Linear	103	10545	10599	0.808
Quadratic	**101**	**10545**	**10612**	**0.811**
Cubic	102	10548	10627	0.812
4				
Linear	51	10455	10522	0.785
Quadratic	52	10456	10539	0.787
Cubic	51	10461	10561	0.787
5				
Linear	40	10409	10489	0.766
Quadratic	37	10408	10508	0.774
Cubic	38	10414	10535	0.774
6				
Linear	17	10396	10488	0.767
Quadratic	20	10399	10516	0.765
Cubic	18	10403	10545	0.770

Latent class growth analysis statistics. AIC = Akaike information criterion. BIC = Bayesian information criterion.

Table S3 LCGA likelihood ratio tests

No. of classes	LRT	p-value	LMR-LRT	p-value	BLRT	p-value
2						
Linear	-5758	0.0001	704	0.0001	-5768	0.0000
Quadratic	-5768	0.0001	716	0.0001	-5768	0.0000
Cubic	-5767	0.0001	723	0.0001	-5767	0.0000
3						
Linear	-5396	0.0021	260	0.0027	-5396	0.0000
Quadratic	**-5395**	**0.0015**	**266**	**0.0018**	**-5395**	**0.0000**
Cubic	-5394	0.0007	270	0.0009	-5394	0.0000
4						
Linear	-5259	0.0138	91	0.0161	-5259	0.0000
Quadratic	-5257	0.0255	94	0.0283	-5257	0.0000
Cubic	-5255	0.0313	94	0.0339	-5255	0.0000
5						
Linear	-5211	0.0070	49	0.0086	5211	0.0000
Quadratic	-5208	0.0161	53	0.0182	-5208	0.0000
Cubic	-5206	0.0391	55	0.0421	-5206	0.0000
6						
Linear	-5186	0.6536	18	0.6641	-5186	0.0000
Quadratic	-5180	0.4825	17	0.4984	-5180	0.0000
Cubic	-5178	0.4909	21	0.5043	-5178	0.0200

LRT = likelihood ratio test. LMR-LRT = Lo-Mendell-Rubin likelihood ratio test. BLRT = Bootstrap likelihood ratio test.

Table S4. Cohort description per LCGA class

	Low (N=101)	Middle (N=226)	High (N=157)
Female sex; N (%)	80 (79)	197 (87)	138 (88)
Erosive disease; N (%)	26 (26)	62 (28)	51 (33)
Age, years	61.4 (9.2)	60.1 (8.3)	61.5 (8.3)
BMI, kg/m2	25.8 (3.6)	27.3 (4.8)	27.4 (5.2)
AUSCAN			
Pain (range 0-20)	4.6 (3.3)	8.9 (3.1)	13.0 (3.0)
Function (range 0-36)	7.9 (5.9)	14.4 (7.0)	22.6 (6.4)
VAS pain (range 0-100)			
Left hand	17.6 (18.4)	31.9 (19.8)	46.3 (21.0)
Right hand	17.7 (14.6)	35.4 (18.4)	51.1 (19.6)
SF-36			
MCS	54.2 (6.3)	52.2 (8.0)	48.8 (10.2)
PCS	50.3 (6.7)	45.9 (6.8)	39.5 (7.5)
KL sum score (range 0-120); median (IQR)	18 (10-31)	16 (7-27)	18 (10-31)
Symptom duration, years; median (IQR)	4.2 (0.9-8.6)	4.6 (1.6-10.5)	8.2 (3.5-17.8)
HADS			
Depression (range 0-21); median (IQR)	1 (1-3)	2 (1-5)	3 (1-8)
Anxiety (range 0-21); median (IQR)	3 (2-4)	4 (3-6)	5 (3-8)
Number of Comorbidities (range 0-18); median (IQR)	0 (0-1)	0 (0-1)	1 (0-2)
Living together; N (%)	83 (82)	189 (84)	120 (76)
Education level			
Low; N (%)	16 (16)	58 (26)	49 (31)
Mid; N (%)	36 (36)	95 (42)	58 (37)
High; N (%)	48 (48)	69 (31)	49 (31)
Work status			
Working; N (%)	50 (50)	100 (44)	52 (33)
Not currently working; N (%)	5 (5)	11 (5)	8 (5)
Disabled/Sick leave; N (%)	5 (5)	25 (11)	30 (19)
Retired; N (%)	34 (34)	66 (29)	48 (31)
Tender joint count (range 0-30); median (IQR)	2 (0-4)	3 (1-6)	5 (3-9)

BMI = Body mass index. AUSCAN = Australian/Canadian osteoarthritis hand index. VAS = Visual analog scale. SF-36 = Short-form 36, with norm-based scores with a mean of 50 and SD of 10 using age and sex-specific Dutch population-based norms. MCS = mental component scale. PCS = physical component scale. KL = Kellgren-Lawrence. HADS = Hospital Anxiety and Depression scale.

Table S5. Multinomial logistic regression adjusted for baseline AUSCAN pain, age, sex and BMI

Baseline	Odds ratio (95% confidence interval) AUSCAN pain trajectory over 4 years		
	1 (N=101)	**2 (N=226)**	**3 (N=157)**
Erosive disease	1	1.00 (0.50-1.98)	0.85 (0.37-1.95)
Symptom duration, years;	1	1.03 (0.99-1.08)	1.07 (1.02-1.13)
KL sum score	1	0.99 (0.97-1.02)	1.00 (0.98-1.03)
Tender joint count	1	1.13 (1.02-1.25)	1.20 (1.07-1.34)
VAS pain			
Left hand	1	1.1 (0.99-1.03)	1.03 (1.01-1.06)
Right hand	1	1.03 (1.01-1.06)	1.06 (1.03-1.10)
AUSCAN function	1	1.08 (1.02-1.14)	1.19 (1.10-1.28)
SF-36			
PCS	1	0.94 (0.90-0.99)	0.87 (0.82-0.93)
MCS	1	0.99 (0.94-1.03)	0.96 (0.91-1.01)
HADS			
Depression	1	1.11 (0.94-1.32)	1.17 (0.97-1.40)
Anxiety	1	1.07 (0.94-1.22)	1.11 (0.96-1.29)
Married or living together; N (%)	1	1.29 (0.59-2.83)	1.40 (0.53-3.69)
Education level	1	1.31 (0.62-2.78)	1.53 (0.62-3.80)
Work status	1	0.62 (0.26-1.45)	0.49 (0.17-1.36)
Number of Comorbidities	1	1.16 (0.76-1.78)	1.39 (0.85-2.28)

BMI = Body mass index. KL = Kellgren-Lawrence. VAS = Visual analog scale. AUSCAN = Australian/Canadian osteoarthritis hand index. SF-36 = Short-form 36, with norm-based scores with a mean of 50 and SD of 10 using age and sex-specific Dutch population-based norms. MCS = mental component scale. PCS = physical component scale. HADS = Hospital Anxiety and Depression scale.