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

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CHAPTER 3

ASSOCIATIONS OF CHANGES IN HAND PAIN WITH BMI, EMPLOYMENT AND MENTAL WELL-BEING OVER FOUR YEARS IN PATIENTS WITH HAND OSTEOARTHRITIS

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ABSTRACT

Objective

We aimed to characterize hand osteoarthritis (OA) patients with deteriorating or improving hand pain, and to investigate patients achieving good clinical outcome after four years.

Methods

We used four-year annual Australian/Canadian hand osteoarthritis index (AUSCAN) pain subscale (range 0-20) measurements from the HOSTAS cohort (patients with hand OA).

Pain changes were categorized as deterioration, stable and improvement using the Minimal Clinical Important Improvement (MCII). Good clinical outcome was categorized using the Patient Acceptable Symptom State (PASS).

Associations between baseline characteristics (patient and disease characteristics, coping styles, illness perceptions) and outcomes were investigated using multinomial or binary logistic regression, adjusted for baseline pain, age, sex and BMI.

Results

356 patients (83% female, mean age 60.6 years, mean AUSCAN 9.1) were analyzed. Pain improved for 38% of patients, deteriorated for 30% of patients and remained stable for 32% of patients over four years. Four-year pain development followed annual trends. At baseline, 44% of patients reached PASS, 49% of patients reached PASS at follow-up.

Higher BMI, coping through comforting cognitions and illness comprehension were positively associated with pain deterioration. Higher AUSCAN function score, mental wellbeing and illness consequences were negatively associated with pain improvement. Employment (positively) and emotional representations (negatively) were associated with both improvement and deterioration. Higher baseline AUSCAN function, tender joint count and symptoms attributed to hand OA were associated negatively with PASS after four years.

Conclusions

The pain course of hand OA patients is variable, not inevitably worsening, and various factors may play a role. Whether modification of these risk factors can influence pain outcomes requires further investigation.

Significance and Innovations

- Similar numbers of patients show an increase, a decrease or a stable course of pain over four years
- The number of patients at an acceptable level of pain increases from 44% to 49% over four years
- Changes in pain were associated with BMI, employment status, mental wellbeing, illness perceptions and coping styles
- These factors may be used for patient stratification, both in clinical and research settings

INTRODUCTION

Osteoarthritis (OA) is a chronic disease that progresses over the course of multiple years. Hand osteoarthritis (OA) is a prevalent OA subtype, resulting in structural damage and symptoms including disability, loss of quality of life (QoL) and pain in the hand. (1, 2) Different processes are thought to underly this hand pain, such as nociceptive pain (both mechanical and inflammatory in origin) and nociplastic pain (due to sensitization). (3-5) Inflammatory pain can arise from local processes, for example synovitis, (6) or from systemic processes, such as obesity and the accompanying adipokines. (7) Mechanic pain can arise through structural damage to the joint and mechanical loading developed, for example, during intense manual labor. (8, 9) Mental factors are also thought to contribute to pain in OA. These include coping styles and illness perceptions. (8, 10, 11) Due to its multifactorial nature and the plethora of underlying mechanisms, treating pain in hand OA is challenging.

Little is known about the course of hand OA pain over time and what determines this course. Given the chronic nature of the disease and the known gradual increase in structural damage, one would expect the pain to increase over time. However, studies on the development of pain both over the short term (2 years), and the long term (6 or 10 years) found that pain on the group level largely remains stable. (12-14) Similar results were seen over four years in a previous study by our group. (15) However, individual patients may experience a deterioration or an improvement in pain. (12) These patients can be categorized using the minimal clinical important improvement (MCII), a measure used to categorize clinically meaningful improvements, enabling investigation of changes on the patient level. (16) Little is known about what influences the development of pain. Change in pain has been associated with change in synovitis measured on MRI, but not with radiographic signs. (17) It is currently unknown whether other mechanisms and risk factors that contribute to the occurrence of pain also influence the course of pain.

Perhaps even more clinically relevant for the patient is the acceptability of a given level of pain. The limit of acceptability for a symptom can be defined with the Patient Acceptable Symptom State (PASS). The PASS describes the highest level of symptoms at which patients regard the symptom as acceptable, should it remain at that level for the rest of their life. (16) Little is known regarding determinants of reaching a PASS for pain in hand OA, with a previous study showing that patients with worse pain and function scores at baseline, as well as more painful joints at baseline, were more likely to not reach PASS after 6 years. (12)

Therefore, this study aimed to evaluate the change in hand pain on the mid-term for individual patients, and, after four years, to characterize the patients with improving or deteriorating pain, and to investigate which patients are likely to achieve a good clinical outcome. We aimed to identify potential modifiable risk factors, to support the move towards personalized medicine and to enable optimal patient inclusion in clinical trials.

PATIENTS AND METHODS

Study design

The data were derived from the Hand OSTeoArthritis in Secondary care (HOSTAS) cohort. The HOSTAS is an observational cohort study of consecutively referred patients with primary hand OA, collected from the Leiden University Medical Center rheumatology outpatient clinic between June 2009 and October 2015. The HOSTAS included patients who had a clinical diagnosis of hand OA, determined by their treating rheumatologist. Exclusion criteria included any pathological conditions that could otherwise explain the symptoms of the hand (e.g., carpal tunnel syndrome, strain, fibromyalgia, other rheumatic musculoskeletal diseases) and secondary OA (e.g. due to inflammatory joint diseases such as rheumatoid arthritis or psoriatic arthritis; bone diseases such as osteitis deformans and osteochondritis; fractures; metabolic diseases such as hemochromatosis; bone dysplasia; endocrine diseases such as acromegaly; major congenital or developmental diseases; and major local diseases such as hypermobility or gout). Finally, patients with a language barrier or psychological limitations precluding participation or informed consent were excluded. Patients answered questionnaires yearly and underwent physical examinations biannually for four years. Full details on the cohort have been published previously. (18)

The HOSTAS cohort consists of 538 patients. Only patients with AUSCAN pain measurements at both baseline and year 4 (required for the main outcome), were included in the analysis (n=356).

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.

Outcome

The primary outcome for this study was the validated AUSCAN pain score. The AUSCAN pain score is calculated by summing five individual component questions, each worth 0-4 for a total score of 0-20, with higher scores indicating more pain, collected through a questionnaire. (19)

The AUSCAN questionnaire further contains a function domain (9 questions, total score 0-36).

Covariates

Additional validated questionnaires collected included the Hospital Anxiety and Depression (HADS) scale for signs of anxiety and depression (7 questions for each domain, scored 0-3 for 0-21 domain scores). (20) Illness perceptions associated with hand OA were investigated using the Illness Perception Questionnaire (IPQ), with questions stating that they concerned hand OA. (21) This questionnaire measures eight domains of illness perceptions and attributions, with higher scores indicating stronger beliefs in the investigated concept. A detailed explanation is attached in the supplementary files. Coping strategies were investigated using the Coping with Rheumatic Stressors (CORS) questionnaire, which investigates eight different coping styles and was developed for use in rheumatic musculoskeletal diseases. (22) Higher scores indicate more use of a particular coping style. Details can be found in the supplementary file. Demographic information including age, sex, marital status (categorized into married/living together or not), working status (categorized into currently working or not, excluding pensioners and patients replying "other" from the analysis), education level (categorized into low education level and other [mid and high education level]) were collected through a questionnaire. Furthermore, the time of first symptoms was collected from this questionnaire and used to calculate symptom duration. Height and weight were measured and used to calculate BMI. Information on comorbidities was collected using the modified Charlson Index. (23) Given the distribution of the information on comorbidities, this was dichotomized to comorbidities or no comorbidities for the analyses. Finally, information on use of analgesics (including paracetamol, NSAIDs, opioids or other types of analgesics) was collected by questionnaire.

Radiographic signs (Kellgren-Lawrence (KL) sum score over 30 joints (24) and presence of erosive disease in interphalangeal joints according to Verbruggen-Veys (defined as ≥1

interphalangeal joint in the E or R phase) (25)) were investigated from hand radiographs made at baseline. T2 MRI images without contrast, made using a 1.5T MRI scanner, were scored while blinded for patient characteristics using the Hand Osteoarthritis Magnetic Resonance Imaging Scoring System (HOAMRIS) system for synovitis and effusion, with the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints scored on a scale of 0-3 for the right hand. (26) Reliability of scoring was excellent, with an intra-class correlation of 0.93, based on 25 scans scored twice in a random order. Physical examination was performed to determine the tender joint count (TJC) and establish fulfilment of the ACR criteria. (27)

Annual data from the AUSCAN pain score from baseline up to and including year 4 were used. Baseline data were used for all other variables.

AUSCAN scores were regarded as missing when more than one component question was missing, or two in case of the function score. IPQ scores were regarded as missing in case of 1 or 2 missing components, depending on the domain. HADS and CORS scores were regarded as missing if any component question was missing. Missing data were <5% for most variables. The few variables with more than 5% missing are explained by the addition of those specific measurements after the start of data collection. Patients who entered before inclusion of these measurements have missing values for these variables. These missing values are considered missing completely at random. Another variable with more than 5% than 5% missing data was "currently working", in which retired patients were excluded. These patients were not part of the group of interest. Missing data were not imputed.

Statistical analysis

Baseline characteristics were described using mean with standard deviation [SD] or median with interquartile range [IQR] for continuous measures, as appropriate, and as number with percentages for categorical variables.

Change scores in AUSCAN pain from baseline to year four were calculated and used to classify patients as having stable, deteriorated or improved pain after four years of participation in the study, based on the MCII, previously established at 1.6. (28) Based on this classification, an increase of >1.6 was classified as a deterioration of the pain status of the patient, a decrease <-1.6 as an improvement and changes between -1.6 and 1.6 were classified as stable. Good clinical outcome was categorized according to the PASS of 8.2, with scores lower than this cutoff counting as having attained PASS. (28)

Annual changes in pain in the three change groups (stable, improvement, deterioration) were visualized using heatmaps. Differences between patients experiencing a deterioration or an improvement in pain from baseline to year four and the stable group were investigated using multinomial logistic regression analysis, with the change categories stable, improvement or deterioration as the dependent, and no change in pain (the stable group) as the index. Baseline variables hypothesized to influence pain development in hand OA were tested and used as independent variables. Separate models were run for independent variables, each model adjusted for baseline pain, age, sex and BMI. Associations between the independent variables and change in pain from baseline to year 4 were determined using the adjusted odds ratio's (ORs) obtained from these multinomial logistic regression models. Baseline values for all independent variables were used.

Analyses for variables showing an effect in these analyses were repeated after stratification for presence of comorbidities and use of analgesics at baseline.

Patients reaching the PASS at year four were investigated using binary logistic regression, with patients not reaching the PASS as the index group. The same variables hypothesized to influence pain in hand OA were tested in separate models, adjusted for baseline age, sex, baseline BMI and baseline pain.

All analyses were performed using Rstudio running R version 4.0.3.

RESULTS

Patient characteristics

An overview of patient characteristics at entry is shown in table 1. Of 356, there were 296 (83%) female participants and the mean (SD) age was 60.6 (8.2), range 39.6-86.3 years. The ACR criteria were fulfilled by 326 (92%) of the cohort, and the mean (SD) AUSCAN pain score at baseline was 9.1 (4.3). There were no major differences between the included and excluded patients for the longitudinal analysis groups (table A1).

Annual change in AUSCAN pain between visits

Changes over four years were used to categorize patients into improvement, deterioration and stable groups (table A2). Over four years, AUSCAN pain improved in 137 patients (38%, mean (SD) baseline pain 10.8 (3.9), change score -4.8 [2.8]), was stable in 113 patients (32%, mean (SD) baseline pain 8.6 (4.3), change score -0.1 [0.8]) and deteriorated in 106 patients (30%, mean (SD) baseline pain 7.3 (3.9), change score 3.8

Table 1. Patient characteristics at baseline

	N=356
Patient characteristics	
Female sex; N (%)	296 (83)
Age, years	60.6 (8.2)
BMI, kg/m2	26.8 (4.5)
Married or living together; N (%)	291 (82)
Low education level; N (%)	80 (23)
Currently working*; N (%)	163 (75)
Number of Comorbidities (range 0-18); median (IQR)	0 (0-1)
Presence of any comorbidities; N (%)	146 (42)
Current use of analgesics	232 (65)
Disease characteristics	
ACR criteria fulfilled; N (%)	326 (92)
Symptom duration, years; median (IQR)	5.6 (2.0-12.6)
Erosive disease; N (%)	106 (30)
KL sum score (range 0-120); median (IQR)	17 (9-31)
Synovitis on MRI (range 0-24); median (IQR)	0 (0-1)
If any synovitis present (range 0-24); median (IQR)	2 (1-3)
Tender joint count (range 0-30); median (IQR)	3 (1- 6)
Patient reported outcome measures	
AUSCAN	
Pain (range 0-20)	9.1 (4.3)
PASS at baseline; N (%)	155 (44)
Function (range 0-36)	14.9 (8.4)
HADS	
Depression (range 0-21); median (IQR)	2 (1-5)
Anxiety (range 0-21); median (IQR)	4 (2-7)

Data are mean (SD) unless indicated otherwise. BMI = Body mass index. HADS = Hospital Anxiety and Depression scale. ACR = American college of Rheumatology criteria for hand OA. KL = Kellgren-Lawrence. AUSCAN = Australian/Canadian osteoarthritis hand index. VAS = Visual analog scale. Percentage of missing data was lower than 5%, unless indicated otherwise. Currently working n = 216. Synovitis n=207. HADS n = 254. *Excluding pensioners

[1.9]). Annual changes also reflected the course of the changes over four years, as can be seen in figure 1. These annual changes in pain ranged from -12 to +11. Comparing the annual changes between the groups, patients with improvement over four years showed improvement (decreased pain) on annual intervals (green bars) more frequently than patients in the stable and deterioration groups. Similarly, patients in the deterioration group showed more annual intervals with deterioration (increased pain, red bars). The stable pain group showed the most heterogeneity in annual intervals of the three groups.

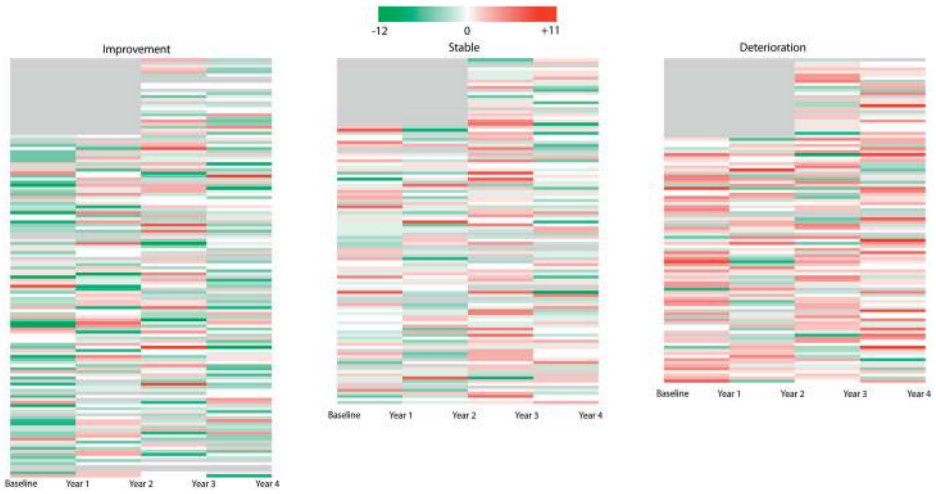

Figure 1. Heatmaps for annual change in AUSCAN pain between visits
Change in AUSCAN pain between visits for individual patients. First column is change from baseline to year 1, the second is year 1 to year 2, the third is year 2 to year 3 and the final column is year 3 to year 4. White indicates a change of 0, green indicates improvement in pain and red indicates deterioration. Gray indicates a missing value. Darker colour means a larger change (range from -12 to +11). The heatmaps on the left contain data for patients that had an improvement in pain (n=137), the middle shows patient with stable pain (n=113) and the right shows patients with a deterioration in pain (n=106). Categorization on change from baseline to year 4, with the MCII of 1.6 as the cut off.

Associations with a deterioration or an improvement in pain

BMI at baseline was positively associated with deterioration in pain (OR 1.08), with an increase of 1 kg/m^2 multiplying the odds of experiencing a deterioration in pain with 1.08, or an increase of 5 kg/m^2 multiplying the odds by 1.40. Age and sex were not associated with changes in pain over four years. Patients who were currently employed had a higher chance to report either deteriorated or improved pain after four years than to report a stable level of pain, whereas those unemployed or on sick leave were more likely to report stable levels of pain. (table 2)

Only a few of the patient reported outcome measures showed an association with a deterioration in pain. Use of the coping style comforting cognitions and the IPQ domain "illness coherence" (with higher scores indicating less understanding of the disease) were positively associated with a deterioration in pain over four years, while the IPQ domain "emotional representations" (with higher scores indicating more negative emotions attributed to hand OA) was negatively associated with a deterioration in pain. Baseline AUSCAN function (higher scores equals worse function), HADS depression and anxiety scores (higher scores equal more signs of depression and anxiety) and the IPQ domains

Table 2. Associations of baseline characteristics with clinically important deterioration or improvement in pain

	Adjusted odds ratio (95% confidence interval)	
	Deterioration (n=106)	**Improvement (n=137)**
Patient characteristics at baseline		
Female sex[1]	1.02 (0.49-2.15)	0.80 (0.39-1.63)
Age, years[2]	0.98 (0.94-1.01)	0.99 (0.96-1.02)
BMI, kg/m2[3]	1.08 (1.01-1.14)	0.99 (0.93-1.05)
Married or living together	1.79 (0.82-3.88)	1.01 (0.53-1.94)
Low education level	0.99 (0.50-1.96)	1.05 (0.54-2.03)
Currently working*	3.35 (1.39-8.11)	4.44 (1.83-10.7)
Presence of any comorbidities	1.03 (0.57-1.85)	0.98 (0.57-1.70)
Current use of analgesics	0.81 (0.44-1.50)	0.96 (0.53-1.75)
Disease characteristics at baseline		
Erosive disease present	1.19 (0.64-2.22)	0.87 (0.48-1.57)
KL sum score (range 0-120)	1.01 (0.99-1.03)	1.00 (0.98-1.02)
Symptom duration, years	1.02 (0.99-1.06)	0.97 (0.94-1.01)
Tender joint count (range 0-30)	1.06 (0.99-1.13)	0.96 (0.90-1.03)
Synovitis on MRI (range 0-24)	0.97 (0.78-1.21)	0.90 (0.73-1.13)
Patient reported outcome measures at baseline		
AUSCAN function (range 0-36)	1.01 (0.95-1.06)	0.95 (0.91-1.00)
HADS		
Depression (range 0-21)	0.92 (0.82-1.03)	0.89 (0.80-0.98)
Anxiety (range 0-21)	0.92 (0.82-1.03)	0.91 (0.82-1.00)
CORS		
Pain		
Comforting cognitions (9-36)	1.10 (1.02-1.19)	1.04 (0.97-1.11)
Decreasing activity (8-32)	0.99 (0.91-1.07)	0.95 (0.88-1.02)
Diverting attention (8-32)	1.04 (0.97-1.12)	1.05 (0.98-1.12)
Limitations		
Optimism (5-20)	1.07 (0.95-1.20)	1.03 (0.93-1.14)
Pacing (10-40)	1.02 (0.97-1.08)	0.96 (0.91-1.02)
Creative solutions (8-32)	1.04 (0.97-1.11)	0.99 (0.92-1.05)
Dependency		
Accepting (6-24)	1.00 (0.92-1.09)	1.00 (0.92-1.08)
Consideration (7-28)	1.02 (0.93-1.12)	0.99 (0.91-1.07)

Table 2. Associations of baseline characteristics with clinically important deterioration or improvement in pain (continued)

	Adjusted odds ratio (95% confidence interval)	
	Deterioration (n=106)	**Improvement (n=137)**
IPQ		
Identity (0-14)	1.03 (0.86-1.24)	0.91 (0.78-1.06)
Timeline (Chronic) (6-30)	1.02 (0.92-1.12)	1.00 (0.92-1.09)
Consequences (6-30)	0.94 (0.86-1.03)	0.91 (0.84-0.98)
Personal control (6-30)	0.97 (0.89-1.07)	1.04 (0.95-1.13)
Treatment control (5-25)	1.03 (0.91-1.17)	0.97 (0.87-1.09)
Illness coherence (5-25)	1.11 (1.01-1.22)	1.07 (0.99-1.17)
Timeline cyclical (4-20)	0.99 (0.90-1.10)	0.98 (0.90-1.08)
Emotional representations (6-30)	0.92 (0.86-1.00)	0.93 (0.88-1.00)

Associations with changes in AUSCAN pain, defined by MCII, adjusted for baseline AUSCAN pain, age, sex and BMI. N=356. Stable group as index. [1] Adjusted for baseline pain, age and BMI. [2] Adjusted for baseline pain, sex and BMI. [3]Adjusted for baseline pain, age and sex. *Compared to currently not working, excluding retirees (n=161). BMI = Body mass index. HADS = Hospital Anxiety and Depression scale. ACR = American college of Rheumatology criteria for hand OA. KL = Kellgren-Lawrence. AUSCAN = Australian/Canadian osteoarthritis hand index. VAS = Visual analog scale. CORS = Coping with Rheumatic Stressors. IPQ = Illness Perception Questionnaire.

"emotional representations" and "consequences" (measuring consequences attributed to hand OA) were all negatively associated with an improvement in pain after four years.

No associations were found for disease characteristics, including erosive disease, synovitis or radiographic signs with changes in pain. (table 2) Models that showed effects on change in pain were stratified for presence or absence of comorbidity and use or no use of analgesics. The stratified analyses showed similar results as the unstratified analyses (tables A3-A5 and A8-A11).

Associations with good clinical outcome

At baseline, 155 (44%) patients were at PASS. At year four, 176 (49%) were. Of those at PASS at baseline, 112 (72%) were still at PASS at year four. 43 patients lost PASS, and 64 patients reached PASS. Being at PASS at baseline was strongly associated with being at PASS at year four, but the effect attenuated with adjustment (crude OR [95% CI] 5.6 [3.5-8.9], OR adjusted for age, sex and BMI 6.1 [3.8-9.9], OR adjusted for baseline pain, age, sex and BMI 1.21 [0.53-2.77]). Patients with worse hand function (AUSCAN function score) and higher tender joint count at baseline were less likely to reach a good clinical outcome at year 4. The identity scale of the IPQ, indicating how many symptoms are considered related to the OA by the patient, was also negatively associated with reaching good clinical outcome at year 4. No further associations were seen. (Table 3)

Table 3. Associations with good clinical outcome

	Adjusted odds ratio (95% confidence interval)
	PASS (n=176)
Patient characteristics at baseline	
Female sex[1]	1.14 (0.59-2.21)
Age, years[2]	1.00 (0.97-1.03)
BMI, kg/m2[3]	0.96 (0.91-1.02)
Married or living together	0.66 (0.35-1.26)
Low education level	1.09 (0.60-1.99)
Currently working*	1.42 (0.68-3.00)
Presence of any comorbidities	0.73 (0.44-1.22)
Current use of analgesics	0.97 (0.57-1.67)
Disease characteristics at baseline	
Erosive disease present	0.85 (0.49-1.47)
KL sum score (range 0-120)	1.00 (0.98-1.01)
Symptom duration, years	0.98 (0.95-1.01)
Tender joint count (range 0-30)	0.91 (0.84-0.97)
Synovitis on MRI (range 0-24)	0.92 (0.75-1.12)
Patient reported outcome measures at baseline	
AUSCAN function (range 0-36)	0.95 (0.91-0.99)
HADS	
Depression (range 0-21)	0.93 (0.84-1.03)
Anxiety (range 0-21)	0.97 (0.88-1.06)
CORS	
Pain	
Comforting cognitions (9-36)	0.96 (0.90-1.03)
Decreasing activity (8-32)	0.96 (0.90-1.03)
Diverting attention (8-32)	0.98 (0.93-1.05)
Limitations	
Optimism (5-20)	0.98 (0.89-1.08)
Pacing (10-40)	0.99 (0.94-1.04)
Creative solutions (8-32)	0.98 (0.93-1.04)
Dependency	
Accepting (6-24)	1.02 (0.95-1.10)
Consideration (7-28)	0.98 (0.90-1.06)

Table 3. Associations with good clinical outcome (continued)

	Adjusted odds ratio (95% confidence interval)
	PASS (n=176)
IPQ	
Identity (0-14)	0.81 (0.69-0.95)
Timeline (Chronic) (6-30)	0.96 (0.89-1.04)
Consequences (6-30)	0.96 (0.89-1.03)
Personal control (6-30)	1.01 (0.94-1.10)
Treatment control (5-25)	1.00 (0.90-1.11)
Illness coherence (5-25)	0.97 (0.90-1.05)
Timeline cyclical (4-20)	1.00 (0.92-1.09)
Emotional representations (6-30)	1.03 (0.97-1.09)

Associations with reaching PASS at year 4, adjusted for baseline AUSCAN pain, age, sex and BMI. N=356. Group not reaching PASS as index. [1] Adjusted for baseline pain, age and BMI. [2] Adjusted for baseline pain, sex and BMI. [3]Adjusted for baseline pain, age and sex. *Compared to currently not working, excluding retirees (n=161). BMI = Body mass index. HADS = Hospital Anxiety and Depression scale. ACR = American college of Rheumatology criteria for hand OA. KL = Kellgren-Lawrence. AUSCAN = Australian/Canadian osteoarthritis hand index. VAS = Visual analog scale. CORS = Coping with Rheumatic Stressors. IPQ = Illness Perception Questionnaire.

DISCUSSION

This study aimed to investigate pain development and good clinical pain outcomes in patients with hand OA. We followed 356 patients with hand OA over four years and found that 137 experienced an improvement in pain, 106 experienced a deterioration and 113 experienced a stable level of pain. The changes over four years were consistent with annual changes. An improvement in pain after four years (38% of patients) was seen most in patients who at baseline had a better hand function, fewer mental problems, a paid job, and who attributed fewer negative emotions and consequences to the disease than other patients. A deterioration in pain over four years was seen in 30% of patients, and most prevalent in patients with a higher BMI and a job at baseline, who used comforting cognitions as a coping strategy and who perceived they understood the disease better. A good clinical outcome, defined as being at PASS after four years, was seen in 49% of patients, a slight increase from 44% at baseline. Being at PASS at baseline was strongly associated with being at PASS at year four. Furthermore, patients with better hand function, fewer painful joints on palpation and who attributed less symptoms to their hand OA at baseline were more likely to be at PASS at year four.

Previously we found that pain remained stable on a group level in patients with hand OA over four years. (15) This stable group level may mask a mixture of patients experiencing a deterioration or an improvement. This was confirmed by our findings reported here.

Part of the change in pain over time can be explained by regression to the mean. Investigation of the annual changes showed that changes over four years were consistent with annual changes as well. Participants experiencing a deterioration over four years also experienced a deterioration in pain per year more often than patients in the stable and improvement groups. This makes it unlikely that the changes seen in this study are solely due to regression to the mean or chance. A previous study with six years follow-up reported more participants experiencing deterioration in pain (40%) than improvement (26%). (12) There may be a number of explanations: the difference in average baseline pain between the studies (6.7 in the previous study vs 9.1 in the current study), differences in type of patients with OA studied (hand OA vs polyarticular familiar hand OA), or the difference in follow-up duration (four vs six years).

It should be noted that changes in pain were based on yearly measurements in this study, which may not adequately capture fluctuations in pain between these timepoints. An alternative approach might be a pain dairy, which provides more detailed data. However, a diary is very time consuming for participants. It is also likely to bias the results due to response shift. (29) Filling in a pain diary may also influence pain awareness, leading to further bias. This makes it difficult to determine the optimal interval duration for pain questionnaires.

The changes over time found in this study were associated with various factors. BMI was associated with a deterioration in pain after four years. The positive association between BMI and pain in hand OA has previously been reported cross-sectionally, and is thought to stem from the systemic inflammation caused by adipokines. (7, 8) Our study contributes an association between BMI and clinically relevant changes in pain over time, which means that pain modulation by BMI may be a continuous process. Currently working was both associated with both deterioration and improvement of pain. Having paid work may be a proxy for being in a more active phase of life with more varying demands. This could translate to changing pain scores, reported in response to changes in the strain placed upon the hands (e.g. switching from a manual to a desk job). This hypothesis requires further validation.

Having less signs of anxiety or depression (measured with the HADS) was associated with an improvement in pain, highlighting the previously described effect of overall mental wellbeing on pain. (8) Interestingly, better wellbeing at baseline was associated with an improvement in pain, whereas worse wellbeing showed no association with a deterioration in pain. Mental wellbeing is reinforced as a potential therapeutic target for pain in hand OA. Whether treatment of the mental wellbeing of patients leads to improvement in their pain outcomes requires further investigation.

Better hand function at baseline was associated with improvement in pain. It has previously been shown that functional limitations at baseline are associated with poor pain outcomes. (12) As such, an association between better function at baseline and an improvement in pain was expected. Mechanistically, we expect that a change in function follows a change in pain. However, patients reporting worse function may feel more limited by their hand symptoms. They may then report those symptoms, including pain, as more severe due to increased attention on those symptoms. This could lead to a negative spiral and changes in reported pain. Therapy supporting hand function might relieve pain and should be investigated further.

Previous studies indicated that illness perceptions and coping styles may be targets for interventions to improve hand function. (30, 31) Additional work showed that developing more negative illness perceptions was associated with a worsening of functional hand OA outcomes over six years. (32) We add to this that perceiving less consequences of hand OA is associated with an improvement in pain and that understanding the disease better was associated with a deterioration in pain, indicating illness perceptions can also have effects on pain. Illness perceptions may be a target to improve pain as well as function. The positive association of coping using comforting cognitions with a deterioration in pain reinforces that different coping styles may also influence pain development. Increasing the patient's resilience to pain through education may thus be of value in treating pain in hand OA. It should be noted that perceiving fewer negative emotions due to the hand OA was associated with both a deterioration and an improvement in pain. Illness perceptions can potentially have different effects in different patients, possibly dependant on other patient beliefs and personality traits.

Presence of comorbidities and usage of analgesics were not added to the models as covariates, due to the size of the confidence intervals obtained when attempting to do so. This could be explained by the small strata underlying these analyses, as the categorical variables yielded strata of <10 participants when combined, before adding continuous variables (tables A6 and A7). We employed stratification instead. Some variables showed slightly different associations over the strata, but no major differences or changes in the direction of the association were seen. The resulting confidence intervals were wider, which can be explained by the smaller number of participants per stratum of the analyses. The low number of participants per stratum precludes drawing reliable conclusions from these data.

Change may not be relevant to patients unless it leads to "good" or "bad" outcomes. Good clinical outcome, defined as the PASS, was positively associated with baseline hand function and negatively with the "identity" scale of the IPQ, meaning that patients

who attribute fewer symptoms to hand OA are more likely to reach a PASS. These determinants are associated with both change in pain and with patient satisfaction after four years, emphasizing their importance. Being at PASS after four years was also associated with a lower tender joint count at baseline after adjustment for baseline pain, age, sex and BMI, indicating the number of affected joints may independently influence patient satisfaction measured through pain.

No other associations between change in pain or pain outcome and disease characteristics (Kellgren-Lawrence score, presence of erosions, synovitis, and symptom duration) were found after adjustment. This indicates that a cross-sectional association with pain, which is known to exist for erosive disease, does not necessarily indicate an association with change in pain as well. (1, 33) The discordance between radiographic damage and pain in hand OA has been described previously, and is again confirmed by our study. (2) Regarding symptom duration, no association was expected given the lack of change in pain over time on the group level. Change in synovitis measured on MRI was previously shown to be associated with change in pain on the joint level. (17) Previous ultrasonography studies have also shown that the association between synovitis and pain is stronger on the joint level than on the patient level. (6) In the current study we found no effect between synovitis and pain on the patient level, indicating the effect may have been diluted due to the large number of joints contributing to the pain on patient level. This is exacerbated by the fact that synovitis was only scored in 8 joints (the PIP and DIP joints of the right hand), which is a limitation in our study.

We used data from a large cohort, consisting of consecutively referred hand OA patients presenting at the rheumatology outpatient clinic, only excluding patients who suffered from secondary OA or hand symptoms due to other causes. This sample is therefore expected to be representative of hand OA patients seeking care from a rheumatologist.

There were a few limitations to our study in addition to the ones mentioned previously. Patients recruited from a secondary/tertiary centre may be only partly generalizable to the larger hand OA population, as not all hand OA patients will visit a rheumatologist. Another limitation is that this study investigated progression of hand OA pain in a cohort of hand OA patients, and could have been affected by collider stratification bias or selective loss to follow-up, most likely biasing found effects towards the null. (34) The real effects would then be larger than what was found in this study. As stated above, this study could also suffer from residual confounding due to unmeasured variables, skewing the results in either direction. As such, replication and validation of these results is essential. We did not have data on all potential factors of interest, such as repeated hand

movements. This is also a limitation of the current study that should be complemented in future studies.

To conclude, in this study we found that over four years, about 40% of patients will remain stable in their level of pain, with 30% experiencing a deterioration and 30% experiencing an improvement. The patients experiencing deteriorations are identified by higher BMI, having paid work, coping through comforting cognitions and illness coherence. Patients experiencing improvements are identified by having paid work, mental wellbeing (less signs of anxiety and depression), more perceived consequences of HOA as well as better hand function. Over four years, the number of patients at a PASS slightly increased, which was associated with a lower number of tender joints and better hand function at baseline. These results can help inform patients and physicians. They may support the selection of patients for trials. These observational results require validation, but could represent modifiable risk factors, and require further study in future trials.

Conflict of interest statement:
This work was supported by the Dutch Arthritis Society

Conflicts of interest: CvdM, LvdS, SJB, FR and SEST 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.

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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 8-32] 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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Table A1. Patient characteristics of patients excluded from change in AUSCAN pain analysis

	N=182
Patient characteristics	
Female sex; N (%)	167 (92%)
Age, years	61.9 (9.4)
BMI, kg/m2	27.7 (5.3)
Married or living together; N (%)	136 (79%)
Low education level; (N (%)	61 (36%)
Currently working; N (%)	52 (55%)
Number of Comorbidities (range 0-18); median (IQR)	0 (0-1)
Disease characteristics	
Symptom duration, years; median (IQR)	4.8 (1.7-11.7)
Erosive disease; N (%)	39 (22%)
KL sum score (range 0-120); median (IQR)	18 (8-29)
Synovitis on MRI (range 0-24); median (IQR)	0 (0-0)
If any synovitis present (range 0-24); median (IQR)	2 (1-3)
Tender joint count (range 0-30); median (IQR)	4 (1-8)
Patient reported outcome measures	
AUSCAN	
Pain (range 0-20)	9.7 (4.4)
PASS at baseline; N (%)	67 (40)
Function (range 0-36)	16.9 (8.5)
HADS	
Depression (range 0-21); median (IQR)	3 (1-6)
Anxiety (range 0-21); median (IQR)	4 (3-7)

Data are mean (SD) unless indicated otherwise. BMI = Body mass index. HADS = Hospital Anxiety and Depression scale. ACR = American college of Rheumatology criteria for hand OA. KL = Kellgren-Lawrence. AUSCAN = Australian/Canadian osteoarthritis hand index.

Table A2. Patient characteristics per pain change group

	Stable (n=113)	Deterioration (n=106)		Improvement (n=137)	
Patient characteristics			OR (95% CI)		OR (95% CI)
Female sex; N (%)	93 (82)	88 (83)	1.05 (0.52-1.70)	115 (84)	1.12 (0.58-2.19)
Age, years	61.5 (7.7)	59.8 (7.9)	0.98 (0.94-1.01)	60.5 (8.7)	0.99 (0.96-1.02)
BMI, kg/m2	26.5 (4.3)	27.7 (5.2)	1.06 (1.02-1.13)	26.5 (4.2)	1.00 (0.94-1.06)
Married or living together; N (%)	90 (80)	92 (87)	1.68 (0.81-3.47)	109 (80)	0.99 (0.54-1.85)
Low education level; (N (%)	24 (21)	25 (24)	1.15 (0.61-2.16)	31 (23)	1.12 (0.61-2.04)
Currently working*; N (%)	36 (61)	56 (82)	2.98 (1.32-6.73)	71 (80)	2.52 (1.21-5.26)
Presence of any comorbidities; N (%)	46 (41)	41 (39)	0.93 (0.54-1.61)	59 (45)	1.18 (0.71-1.96)
Disease characteristics					
Symptom duration, years; median (IQR)	6.5 (2.4-11.9)	5.4 (3.3-13.7)	1.01 (0.98-1.04)	5.1 (1.4-12.0)	1.37 (0.96-1.95)
Erosive disease; N (%)	34 (30)	32 (30)	1.01 (0.56-1.79)	40 (29)	0.96 (0.56-1.65)
KL sum score (range 0-120); median (IQR)	18 (11-31)	18 (9.3-31.5)	1.00 (0.98-1.02)	16 (8-29)	0.99 (0.98-1.01)
Synovitis on MRI (range 0-24); median (IQR)	0 (0-1)	0 (0-1)	0.87 (0.70-1.07)	0 (0-1)	0.84 (0.69-1.02)
If any synovitis present (range 0-24); median (IQR)	2 (2-5)	2 (1-3)	0.83 (0.61-1.12)	1 (1-2)	0.76 (0.56-1.02)
Tender joint count (range 0-30); median (IQR)	3 (1-6)	3 (1-6)	1.01 (0.95-1.08)	3 (2-7)	1.02 (0.96-1.08)
Patient reported outcome measures					
AUSCAN					
Pain (range 0-20)	8.6 (4.3)	7.3 (3.9)	0.92 (0.86-0.98)	10.8 (3.9)	1.14 (1.07-1.22)
PASS at baseline; N (%)	48 (43)	68 (64)	2.42 (1.41-4.18)	39 (29)	0.54 (0.32-0.91)
Function (range 0-36)	14.8 (8.9)	12.8 (8.2)	0.97 (0.94-1.00)	16.7 (7.8)	1.03 (1.00-1.06)
HADS					
Depression (range 0-21); median (IQR)	3 (1-6)	2 (1-4)	0.92 (0.83-1.02)	2 (1-4)	0.95 (0.86-1.03)
Anxiety (range 0-21); median (IQR)	5 (2-7)	3 (2-6)	0.91 (0.82-1.01)	4 (2-7)	0.64 (0.89-1.05)

Patient characteristics and crude analyses. Data are mean (SD) unless indicated otherwise. Odds ratio's shown are the odds ratio to be in the deterioration/improvement group compared to the stable group, per point increase in the variable shown in the left most column. BMI = Body mass index. HADS = Hospital Anxiety and Depression scale. ACR = American college of Rheumatology criteria for hand OA. KL = Kellgren-Lawrence. AUSCAN = Australian/Canadian osteoarthritis hand index. * Excluding pensioners

Table A3.

	Stable (n=112)	Deterioration (n=104)	Improvement (n=131)
No comorbidities	66 (58.9)	63 (60.6)	72 (55.0)
At least 1 comorbidity	46 (41.1)	41 (39.4)	59 (45.0)

Number (%) of patients with no comorbidities or at least one comorbidity per pain change group. Group sizes are slightly smaller, reflecting missing comorbidity data.

Table A4. Outcomes of multinomial logistic regression for change in pain group stratified by presence of comorbidity: Improvement group

Stable (n=112) vs Improvement (n=131)	Adjusted odds ratio (95% confidence interval)		
	All	>0 comorbidities (N=105)	0 comorbidities (N=138)
Patient characteristics at baseline			
Currently working*	4.44 (1.83-10.7)	8.81 (1.70-45.6)	3.20 (1.08-9.55)
Patient reported outcome measures at baseline			
AUSCAN function (range 0-36)	0.95 (0.91-1.00)	0.93 (0.85-1.00)	0.97 (0.91-1.03)
HADS			
Depression (range 0-21)	0.89 (0.80-0.98)	0.85 (0.72-1.00)	0.88 (0.76-1.02)
Anxiety (range 0-21)	0.91 (0.82-1.00)	0.92 (0.80-1.07)	0.88 (0.77-1.01)
IPQ			
Consequences (0-30)	0.91 (0.84-0.98)	0.85 (0.75-0.97)	0.94 (0.85-1.03)
Emotional representations (0-30)	0.93 (0.88-1.00)	0.87 (0.79-0.97)	0.98 (0.90-1.08)

Associations with changes in AUSCAN pain, defined by MCII, adjusted for baseline AUSCAN pain, age, sex and BMI. N=356. *Stable group as index. Models were run both improvement and deterioration, but split in the table for readability.* *Compared to currently not working, excluding retirees (n=148). HADS = Hospital Anxiety and Depression scale. AUSCAN = Australian/Canadian osteoarthritis hand index. VAS = Visual analog scale. IPQ = Illness Perception Questionnaire.

Table A5. Outcomes of multinomial logistic regression for change in pain group stratified by presence of comorbidity: Deterioration group

Stable (n=112) vs Deterioration (n=104)	Adjusted odds ratio (95% confidence interval)		
	All	**>0 comorbidities (n=87)**	**0 comorbidities (n=129)**
Patient characteristics at baseline			
[1]BMI, kg/m^2	1.08 (1.01-1.15)	1.05 (0.96-1.15)	1.10 (1.01-1.21)
Currently working*	3.35 (1.39-8.11)	3.85 (0.82-18.0)	3.35 (1.08-10.4)
CORS			
Pain			
Comforting cognitions (9-36)	1.10 (1.02-1.19)	1.11 (0.99-1.24)	1.10 (0.98-1.22)
IPQ			
Illness coherence (0-20)	1.11 (1.01-1.22)	1.09 (0.94-1.27)	1.12 (0.99-1.26)
Emotional representations (0-30)	0.92 (0.86-1.00)	0.87 (0.76-0.99)	0.96 (0.86-1.07)

Associations with changes in AUSCAN pain, defined by MCII, adjusted for baseline AUSCAN pain, age, sex and BMI. N=356. *Stable group as index. Models were run both improvement and deterioration, but split in the table for readability.* [1]Adjusted for baseline pain, age and sex. *Compared to currently not working, excluding retirees (n=127). BMI = Body mass index. CORS = Coping with Rheumatic Stressors. IPQ = Illness Perception Questionnaire.

Table A6.

	Stable	**Deterioration**	**Improvement**
Currently working	9	18	27
Currently not working	8	6	7

Number of participants working or not working, excluding retirees, per pain change stratum, within the group that has at least 1 comorbidity.

Table A7.

	Stable	**Deterioration**	**Improvement**
Currently working	27	37	40
Currently not working	15	6	9

Number of participants working or not working, excluding retirees, per pain change stratum, within the group that has no comorbidities.

Table A8.

	Stable (n=113)	**Deterioration (n=106)**	**Improvement (n=137)**
No analgesics	40 (35.4)	45 (42.5)	39 (28.5)
Use of analgesics	73 (64.6)	61 (57.5)	98 (71.5)

Number (%) of patients using analgesics or not per pain change group.

Table A9.

Use of analgesics	Adjusted odds ratio (95% confidence interval)	
	Improvement (n=137)	**Deterioration (n=106)**
Crude	1.38 (0.81-2.35)	0.74 (0.43-1.28)
Adjusted for baseline AUSCAN pain	0.92 (0.52-1.65)	0.97 (0.55-1.72)
Adjusted for baseline pain, age, sex and BMI	0.81 (0.44-1.50)	0.96 (0.53-1.75)

Associations of use of analgesics with changes in AUSCAN pain, defined by MCII=356. Stable group as index.

Table A10. Outcomes of multinomial logistic regression for change in pain group stratified by use of analgesics: Improvement group

Stable (n=113) vs Improvement (n=137)	Adjusted odds ratio (95% confidence interval)		
	All	**Use of analgesics (N=171)**	**No use of analgesics (N=79)**
Patient characteristics at baseline			
Currently working*	4.44 (1.83-10.7)	2.76 (1.00-7.59)	17.0 (1.90-151)
Patient reported outcome measures at baseline			
AUSCAN function (range 0-36)	0.95 (0.91-1.00)	0.95 (0.90-1.01)	0.93 (0.85-1.02)
HADS			
Depression (range 0-21)	0.89 (0.80-0.98)	0.89 (0.79-1.00)	0.80 (0.64-0.99)
Anxiety (range 0-21)	0.91 (0.82-1.00)	0.87 (0.78-0.98)	0.95 (0.79-1.15)
IPQ			
Consequences (6-30)	0.91 (0.84-0.98)	0.93 (0.85-1.01)	0.83 (0.70-0.98)
Emotional representations (6-30)	0.93 (0.88-1.00)	0.93 (0.86-1.00)	0.91 (0.80-1.04)

Associations with changes in AUSCAN pain, defined by MCII, adjusted for baseline AUSCAN pain, age, sex and BMI. N=356. Stable group as index. Models were run both improvement and deterioration, but split in the table for readability. *Compared to currently not working, excluding retirees (n=148). HADS = Hospital Anxiety and Depression scale. AUSCAN = Australian/Canadian osteoarthritis hand index. VAS = Visual analog scale. IPQ = Illness Perception Questionnaire.

Table A11. Outcomes of multinomial logistic regression for change in pain group stratified by use of analgesics: Deterioration group

Stable (n=113) vs Deterioration (n=106)	Adjusted odds ratio (95% confidence interval)		
	All	**Use of analgesics (N=134)**	**No use of analgesics (N=85)**
Patient characteristics at baseline			
[1]BMI, kg/m^2	1.08 (1.01-1.15)	1.10 (1.01-1.19)	1.06 (0.95-1.18)
Currently working*	3.35 (1.39-8.11)	2.11 (0.71-6.30)	4.90 (0.81-29.5)
CORS			
Pain			
Comforting cognitions (9-36)	1.10 (1.02-1.19)	1.07 (0.97-1.17)	1.20 (1.03-1.39)
IPQ			
Illness coherence (5-25)	1.11 (1.01-1.22)	1.05 (0.93-1.19)	1.18 (1.00-1.39)
Emotional representations (6-30)	0.92 (0.86-1.00)	0.98 (0.89-1.07)	0.82 (0.71-0.95)

Associations with changes in AUSCAN pain, defined by MCII, adjusted for baseline AUSCAN pain, age, sex and BMI. N=356. Stable group as index. Models were run both improvement and deterioration, but split in the table for readability. [1]Adjusted for baseline pain, age and sex. *Compared to currently not working, excluding retirees (n=127). BMI = Body mass index. CORS = Coping with Rheumatic Stressors. IPQ = Illness Perception Questionnaire.