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PII: S1526-5900(19)30845-4
DOI: https://doi.org/10.1016/j.jpain.2019.10.008
Reference: YJPAI 3808

To appear in: *Journal of Pain*

Received date: 15 March 2019
Revised date: 6 October 2019
Accepted date: 30 October 2019

Please cite this article as: Mari Glette , Tore C. Stiles , Petter C. Borchgrevink , Tormod Landmark , The natural course of chronic pain in a general population: Stability and change in an eight-wave longitudinal study over four years (the HUNT pain study), *Journal of Pain* (2019), doi: https://doi.org/10.1016/j.jpain.2019.10.008

Highlights

- We identified five pain trajectories in individuals with chronic pain in the general population
- The majority of individuals with chronic pain in the general population have stable pain trajectories over an extended period
- A substantial proportion of individuals fluctuate between mild and moderate pain, which is an often-used cut-off
- Pain trajectories are associated with key biopsychosocial characteristics

The natural course of chronic pain in a general population: Stability and change in an eight-wave longitudinal study over four years (the HUNT pain study)

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Disclosures

The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre, (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. The HUNT pain study was funded by the Research Council of Norway. This current study was funded by the Liaison Committee between the Central Norway Regional Health Authority and NTNU (Grant number: 46056914). The authors declare no conflict of interest.

Abstract

Epidemiological studies have to a little extent addressed the potential fluctuations of chronic pain over time, and there is a lack of information about the long-term course of pain using repeated measurements. We wanted to identify different trajectories of pain during eight waves of follow-up over four years among individuals in the general population reporting pain lasting at least six months at baseline. Secondarily, we wanted to investigate whether biopsychosocial factors at baseline were associated with the different pain trajectories. Longitudinal Latent Class Analysis (LLCA) was performed to classify 1905 random participants from a larger population-based study (HUNT3) into groups based on their longitudinal pain severity reporting. A five-class solution gave the best fit. The terms chosen to describe the pain trajectories were: "fluctuating" (n = 586 [31 %]), "persistent mild" (n = 449 [24 %]), "persistent moderate" (n = 414 [22 %]), "persistent severe" (n = 251 [13 %]), and "gradual improvement" (n = 205 [11 %]). In a multinomial logistic regression model using "gradual improvement" as the reference category, the "persistent moderate", "persistent severe", and "fluctuating" pain groups were associated with chronic widespread pain (CWP), elevated levels of catastrophizing, and poorer mental health. The "persistent

mild" group was associated with sleep difficulties only. This study finds that although most individuals have a stable pain course, individuals in the largest distinct trajectory reports pain that fluctuate between mild and moderate levels, thus fluctuating under and above the chronic pain definition using moderate pain or more as a criterion.

Perspective: When examining the long-term course of chronic pain in the general population, five trajectories emerge. Although most individuals have stable pain, the largest distinct trajectory fluctuated under and above the chronic pain cut-off, using moderate pain or more as a criterion. A dichotomous categorization of chronic pain may be overly simplistic.

Introduction

Estimates of prevalence of chronic pain vary from 9% to 64% in the general population[24, 42]. One of the most important factors accounting for this substantial variance is inconsistency in the operational definitions used in various studies[42]. This problem stems mainly from lack of a clear and standardized definition of chronic pain. The International Association for the Study of Pain (IASP) proposed that pain lasting for longer than three months[32, 46] and for research purposes, six months, should be the working definition of chronic pain[32]. However, a recent meta-analysis found that variations in prevalence estimates are not related to the different duration criteria[42]. The IASP Task Force which has developed the definition for chronic pain for ICD-11, specified additional criteria such as pain severity or interference[46], but without a standard way of measuring these and without a predefined cut-off that has been agreed upon.

With the possible recurrent nature of pain in mind, a dichotomized cut-off seems to indicate that some individuals may fluctuate under and above the chronic pain classification. However, epidemiological studies have to a little extent addressed the potential fluctuations

of chronic pain over time, and there is a lack of information about the long-term course of pain using repeated measurements in chronic pain epidemiology. Existing studies of chronic pain have often had only one follow-up time point which prevents longitudinal fluctuating patterns from being studied[13, 14]. One statistical method suitable for identifying course patterns using repeated measures is Longitudinal Latent Class Analysis (LLCA), which is a data-driven method that aims to reduce within-group variability and increase between group heterogeneity. The use of LLCA in previous studies has identified four or five subgroups of low back pain (LBP) sufferers[3, 8, 10-12, 20, 21, 31, 44, 45], showing that most individuals with LBP experience a persistent or fluctuating pain of low or medium intensity, whereas one sub-group develops chronic severe pain and another recovers[20]. These sophisticated analyses have been limited to specified pain conditions such as LBP and not applied to chronic pain as one distinct entity[9, 34]. Further, most studies have been on treatment-seeking individuals. Now standing as its own diagnosis in ICD-11[54], we believe there is a need for more information on the long-term natural course of chronic pain measured as a distinct disease entity.

The primary aim of the present study was therefore to describe the natural course of chronic pain in the general population by identifying underlying patterns of pain in repeated measures over four years. Secondarily, we wanted to determine the relevance of the pain trajectories, by investigating several biopsychosocial characteristics measured at baseline.

Methods

Study sample and procedures

This is a longitudinal population-based study, part of the larger ongoing HUNT study. To date, three HUNT studies have been conducted in which the total population of Nord Trøndelag County in Norway was invited to participate: HUNT 1 (1984–86), HUNT 2 (1995–97), and HUNT 3 (2006–08) and a fourth study (HUNT 4) is expected to be finished

in 2019. The overall participation rates in the completed studies have been 90%, 70%, and 54%, respectively [23]. In HUNT 3, the response rate was higher among women (59%) than men (50%) and lowest among the youngest age groups (31% for the age group 20 to 29 years). A nonparticipation analysis has shown that nonparticipants had lower socioeconomic status, higher mortality, and higher prevalence of several chronic diseases relative to participants, and that participants reported a higher prevalence of musculoskeletal pain, urinary incontinence, and headache, relative to nonparticipants [27].

A random sample of 6419 individuals from two municipalities that participated in HUNT 3 was invited to answer questionnaires about pain and associated characteristics at quarterly intervals for 12 months (five questionnaires), followed by three questionnaires at annual intervals for three additional years. Among these, 4782 (75%) agreed to participate, and all participants gave informed consent. Questionnaires were mailed every three months for 12 months (five questionnaires in total). Reminder questionnaires were mailed to non-responders after one month. If the reminder was not returned, no new questionnaires were mailed until the 12 months follow up. The study has been described in more detail elsewhere [24-26]. The study was approved by the Regional Committee for Medical and Health Research Ethics Central Norway.

The inclusion criteria for the current study was all individuals answering reporting having had pain for at least six months at baseline (n=2196), thus excluding individuals with acute pain.

Measures

Chronic pain case definition

Chronic pain was assessed by the question: "*Do you have bodily pain which has lasted for more than 6 months?"* which was constructed to meet the IASP proposal for classification of chronic pain [32]. Pain severity was assessed by the question: "*How much*

bodily pain have you had during the past week?". The question is included in the SF-8 and the SF-36 health surveys, and has evidence supporting its validity as a single item measure of pain intensity [51]. Responses are provided on a 6-point verbal rating scale (i.e., "None", "Very mild", "Mild"," Moderate", "Severe", or "Very severe"). A cut-off between mild and moderate has been demonstrated to identify individuals with pain of a more complex nature[16]. For the LLCA of the current study the scale was divided into four categories: no pain ("None"), mild pain ("Very mild" or "Mild"), or moderate pain ("Moderate") and severe pain ("Severe" or "Very severe").

Chronic widespread pain (CWP)

A body map was used to measure location and spatial distribution of pain. The map displays a full body figure in frontal and dorsal views. Included beside the body map are check boxes with predefined layman labels of 16 body regions including left and right sided: *jaw/teeth, shoulder/arm, wrists/hands, elbows, calves, hips, thighs, knees, feet/ankles,* in addition to *chest, stomach, pelvis/genitalia, neck, low back, upper back and head*, which gives 23 possible areas. CWP was defined according to the American College of Rheumatology (ACR) criteria: pain on the left side of the body, pain on the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) need to be present[53].

Mental health

Mental health was assessed using the Mental Health Inventory-5 (MHI-5) which is a five-item scale with three questions assessing depression and two assessing anxiety symptoms [2]. These questions are included in the SF-36 health survey[52], and are published as an independent screening test. The items are scored on a 6-point Likert scale (1 = "*All of the time*" to 6 = "*None of the time*"). A total score is calculated by reversing two of the items and summing the ratings, and the score is then transformed to a scale from 0-100 using a standard

linear transformation where a higher score indicates better mental health. To ease comprehensibility, we further transformed this variable, so a one unit increase in MHI-5 represents 10% of the scale. The MHI-5 is validated as a screening tool for detecting mood disorders [5, 39]. The Norwegian version of the MHI-5 has been validated and has shown acceptable psychometric properties [43]. The Cronbach α for the MHI-5 in the current sample was .83, indicating good reliability.

Catastrophizing

Catastrophizing was assessed using the two-item version of the catastrophizing subscale of the Coping Strategies Questionnaire [17]. The scale measures subjective evaluations of helplessness and threat when experiencing pain [38]. The items are rated on a 7-point Likert scale (0 = *"never do"*, 6 = *"always do that"*). The two-item version has shown good psychometric properties, correlates strongly with the full scale, and has been shown to be sensitive to change [17].

Sleep difficulties

Sleep satisfaction was measured by the question:" *During the past week, have you had trouble sleeping?"* The item is a 4-point Likert scale (*"Not at all"*, "*Little", "Some*", "*Very much*"). A similar one-item measure of global sleep satisfaction has previously been shown to be a good indicator of the presence of a sleep disorder and discriminator of the severity of sleep disturbance in the general population [36]. For this study, the scale was dichotomized with a cut-off between "Not at all" and "Some" indicating sleep difficulties to a significant degree.

Organ disease comorbidity

Information on organ-specific diseases was obtained by self-report of the following: "*During the past 12 months, have you had the following*: *cardiovascular disease, lung*

disease, cancer, gastrointestinal disease, kidney disease, neurological disorder or diabetes". Self-report of these chronic diseases have been found to be fairly accurate [22]. Arthritis (rheumatoid arthritis, psoriasis arthritis, Bechterew's disease), osteoarthritis, osteoporosis, other musculoskeletal disorders, fractures and nerve injuries were not included due to the close relation with pain. Responses to these questions were dichotomized into no disease or any comorbid disease.

Statistical analyses

To investigate whether it is possible to identify different trajectories of pain in the general population based on the eight measurement occasions, we applied Longitudinal Latent Class Analysis (LLCA). LLCA is a statistical approach that assumes that there is a certain number of distinct time trends or trajectories to be identified in reports over time of a certain variable, in this case pain severity. In this approach, within-class variation is minimized and between-class variation is maximized. The variable "time" was entered as a nominal predictor, so the time estimations could take any pattern.

We included one-class to eight-class model solutions in our analyses and inspected improvements in statistical fit to identify the optimal number of classes. We based our decision on the likelihood-ratio statistic (LL^2) and the Bayes Information Criterion (BIC)[40] and for both, a lower value indicates a better statistical fit. We also calculated the percentage of reduction in LL^2 per model increase. The bootstrapped likelihood ratio test was performed to evaluate whether an increasing number of classes would significantly improve model fit. Further, the average posterior probability of class membership of the possible models was considered. Each participant has a probability for belonging to each class (between 0 and 1), and participants are allocated to the class for which this probability is the largest. An average posterior probability above 0.7 in each class is considered acceptable for the separation of individuals[33]. Entropy, which is a rescaling of the posterior probability was considered for

overall class distinctiveness. Lastly, other factors such as class size and clinical interpretability of the classes were considered.

The series of models with one-class to eight-class model solutions were repeated ten times to assure that the best final model reached a global maximum likelihood solution [28]. When the potential best model was chosen, a bootstrapped parametric likelihood test was run to compare the chosen model with K classes to a model with one less (K-1) class, to evaluate if the addition of a class significantly improved the model fit [35]. Results from the analysis are given in probabilities of a positive response to the categorical variables (a probability of 1 means that all individuals in the subgroup responded positively to that category). Three individual cases were chosen randomly from each trajectory group and visual plots was made for inspection of the course trend. The labelling of the trajectory groups was based both on the observed pain severity levels over time and individual trajectories within each group.

To investigate whether baseline biopsychosocial characteristics are associated with membership in the different pain trajectories, a multinomial logistic regression analysis with group membership as the outcome variable were performed. Baseline characteristics of interest as predictors were chosen a priori based on existing literature. Preliminary analyses were first conducted to ensure there was no violation of the assumption of linearity for the continuous predictor variables. If departure from linearity was detected, the variables were dichotomized or trichotomized. The risk of belonging to each trajectory group for a given characteristic was compared to the reference category with least severe pain. First, separate multinomial regression analyses were performed for each independent baseline variable, adjusted for age and sex. In the second model, we added all the variables simultaneously. Results from the multinomial logistic regression are given in relative risk ratios (RRR).

The level of significance for all statistical tests was set at $p < 0.05$. The LLCA was conducted using Latent GOLD 5.1[49]. Information about class membership and estimated posterior class membership probabilities was exported and further analyzed in Stata 15[41].

Results

Participants, design and procedure

For all individuals invited to participate in the HUNT pain study (n=6420), response rates on the pain variable ranged from 73% (4620/6420) at baseline to 53% (3372/6420) at the 48 months follow-up time point. Among those reporting chronic pain at baseline, a total of 291 (13%) individuals were excluded due to high level of missing follow-up values, leaving 1905 individuals for further analysis. The mean age was 56.6 years (SD 13.5) and 61% had female gender. Further characteristics of the sample are presented in Table 1.

Model development and descriptions of trajectories

There was a rapid decrease in BIC from one- to four-class models (Table 2). For the subsequent models, the reduction evened out. When calculating the percentage of reduction in LL^2 from the H_0 model, there was little benefit in reducing further than five classes, which after had a 1% or less reduction. The LL^2 and BIC favored a seven-class solution. However, as the gains in model fit was so minimal from four classes, we chose to evaluate the four and five and class solutions according to further criteria. The average posterior probabilities values were within the 0.7 criteria for all models. The bootstrap likelihood test supported a continuous adding of new models with $p < 0.001$ for all solutions.

One is encouraged to choose the most parsimonious model, as an increasing number of classes often will not give new distinct classes itself, but rather divide larger groups into subgroups with slightly different pattern while the main pattern is similar. As the fifth group

in the five-class solution was a clinically meaningful group where a new distinct type of main pattern was added (improvement), it was therefore chosen as the best model fit for the data. Further, this was not the case when adding a sixth class, as this solution rather divided one of the main patterns (fluctuating) from the five-class solution into two smaller subgroups.

Three of the groups had a very stable pattern of pain reports across all follow-up measurements and were labeled: “Persistent mild” (n = 449 [24 %]), “persistent moderate” (n = 414 [22 %]), and “persistent severe” (n = 251 [13%]). The “persistent mild” group had a high probability of reporting mild pain (range: 0.76- 0.80) at all occasions, the “persistent moderate” group had a high probability of reporting moderate pain (range: 0.71- 0.80) at all occasions, and “persistent severe” group had a high probability of severe pain (range: 0.60 - 0.77) at all occasions. Of note, among individuals in the “persistent moderate” group, the probability of reporting severe pain increased gradually from 0.12 at baseline to 0.26 at the 48 months follow up. This type of development was not seen in the other stable groups. In sum, the proportion of individuals within a persistent pain group was altogether 59% (n=1114) of the sample, indicating that most individuals are stable in their pain level.

A fourth group was labelled “fluctuating” (n = 586 [31 %]) as individuals showed a fluctuating course between pain levels. This was the largest single group, as one of every three individuals was classified here. Individuals in this group had highest probability of reporting mild pain (range: 0.34 - 0.41), and moderate pain (range: 0.50 - 0.55). Individuals in this group had almost zero probability for reporting no pain, and the probability for severe pain was also low (range: 0.07-0.09). indicating that their fluctuations were mainly around mild to moderate pain. A fifth group was labelled “gradual improvement” (n = 205 [11 %]) as they displayed an increasing probability of reporting no or less severe pain throughout the follow up period. Accordingly, the probability of reporting no pain doubled, from 0.25 at baseline and stabilizing around 0.50 at nine months and continuing throughout follow-up.

The mean posterior probabilities with their respective 95% confidence intervals indicated acceptable distinctiveness and precision for assigned membership to each group (Table 3).

Figure 2 shows the mean pain intensity scores at all follow-up time points for each trajectory group. It is important to note that a fluctuating pattern cannot be seen on group means. This is because two individuals in the same group may have increases or decreases in pain at different time points and this is illustrated by individual curves (Supplementary Figure 1).

Associations between baseline factors and trajectory group membership

A multinomial logistic regression analysis was performed to compare biopsychosocial characteristics at baseline of individuals in each trajectory group with the "gradual improvement" group (Table 4).

Compared with the "gradual improvement" group, older age was significantly associated with membership in all groups but the "persistent mild" group. Sex was not associated with membership in any of the groups. Sleep difficulties showed a strong association with the "persistent severe" group (RRR 3.10, [95% CI 1.80-5.34]), followed by the "persistent moderate" group (RRR 3.05, [95% CI 1.99-4.68), the "fluctuating" group (RRR 2.68, [95% CI 1.83-3.93]) and the "persistent mild" group (RRR 2.13, [95% CI 1.45-3.13]). Having a comorbid organ disease, as compared to not, was associated with the "persistent severe" group (RRR 2.84, [95% CI 1.66-4.86]. Having CWP, higher levels of catastrophizing and poorer mental health was significantly associated with all but the "persistent mild" group. For CWP, the strength of association was largest for the "persistent severe" group (RRR 10.89, [95% CI 5.08-23.33]), followed by "persistent moderate" (RRR 8.12, [95% CI 3.94-16.71]), and "fluctuating" groups (RRR 4.06, [95% CI 1.99-8.29]). For catastrophizing, the strength of association was largest for the "persistent severe" group

(RRR 4.02, [95% CI 3.24-4.99]), followed by the "persistent moderate" group (RRR 2.01, [95% CI 1.67-2.40]), and "fluctuating" group (RRR 1.48, [95% CI 1.26-1.76]). For poorer mental health, the strength of association was largest for the for the "persistent severe" group (RRR .76 per 10% increase [95% CI .64-.90]), followed by the "persistent moderate" group (RRR .79 per 10% increase [95% CI .68-.93]), and "fluctuating" group (RRR .83 per 10% increase [95% CI .71-.97]).

Sensitivity analyses

The LLCA using cases with complete data only (n=1318, 69%) yielded a similar five-class solution as the main analysis (data not shown).

Discussion

Our main finding is that most individuals with chronic pain in the general population have stable pain trajectories over an extended period of time. Five discrete pain trajectories were identified, of which three represented stable courses of " persistent mild" (24%), "persistent moderate" (22 %), and "persistent severe" (13%), a fourth fluctuated mainly between mild and moderate pain levels ("fluctuating", [31%]), and the fifth and smallest group showing an important pain improvement ("gradual improvement", [11%]). Similar trajectories have been found in LBP cohorts of treatment-seeking individuals. Our study extends previous findings by demonstrating that the same patterns are shared by heterogenous pain conditions in the general population. Also, our follow-up period was substantially longer than the 12 months which has been examined earlier.

The "fluctuating" group comprised a third of the sample (31%). The size of this group has been considerably smaller in other studies[8, 10, 11]. However, the only previous study from the general population found similar groups (although follow-up was limited to 12 months) [45]. An argument has been made that these individuals stabilize over time[10]. In fact, we found

that this group had high probabilities of both mild and moderate pain at all follow-up points. It may be argued that these individuals have a rather stable trajectory, only fluctuating between mild and moderate pain, and thus seems to go under and above the definition of chronic pain using moderate pain or more as a criterion. In an epidemiological context, this fluctuation has potential for confusing prevalence estimates of chronic pain.

A crucial finding is that an improving group was identified, with most substantial improvement happening within the first three to six months. This group is common in studies with treatment-seeking individuals[7, 8, 11, 21, 31], but not in general population studies[45]. Possibly some of them had an acute onset about six months prior to the study and then the pain gradually improved. In that case, this reflects a single episode of chronic pain. In previous longitudinal studies having two measurement occasions, the proportion of individuals recovering from chronic pain has been 5% - 8%[13, 24] using various case definitions, length of follow-up and definitions of recovery. Since these studies have one follow-up time point, longitudinal fluctuating patterns cannot be studied. A recent study from HUNT defined recovery as a transition from chronic pain of at least moderate intensity to no chronic pain, and found that of the 8% who recovered at one year follow up, a substantial proportion re-transitioned into chronic pain later[24]. Our findings are more refined in that the dichotomized value of pain severity is not used and show that one of every tenth participant has improvements, both to no pain and to mild pain. A rapid and later stabilized improving pattern is similar to that found in inception cohorts of neck and low back pain[47]. Whether this improvement is lasting, is a result of the episodic nature of the pain or due to treatment, remains a question unanswered.

A second aim was to investigate whether baseline biopsychosocial characteristics were associated with trajectory membership. Earlier studies have shown trajectories to be associated with factors across biopsychosocial domains such as general health and

comorbidity [7, 8, 10, 45], activity limitation [11, 21, 45], work participation [11, 45], symptoms of depression and anxiety [10, 11, 21], recovery expectations [7, 8, 21], and in a single study, also catastrophizing and health care utilization [11]. Our results are in line with and extends these findings to heterogenous pain conditions in the general population. Of note, the "persistent moderate" and "persistent severe" groups were associated with all biopsychosocial factors at baseline, compared with the "gradual improvement" group, whereas few differences were found between "persistent mild" and "gradual improvement". In general, the number and strength of associations with negative predictors tended to increase as a function of mean longitudinal pain severity. Identifying the factors associated with pain trajectories are important as these might be factors modifiable if targeted in treatment.

People seeking treatment for pain contemplates on whether their pain will get worse or can be improved[37]. It has been suggested that the word "chronic" is misleading as it gives the impression that pain is static and not subject to change[50]. Although our data show that pain tend to be stable, they do not show that the pain is a static trait. A large proportion of individuals experienced fluctuations to some degree, and in all groups, there was a possibility of experiencing mild pain. Thus, our results do not imply that one should refrain from giving hope that pain might improve, but they may guide health providers and patients to set realistic expectations and goals.

Although we did not identify a worsening trajectory, one can see from Figure 1 that the "persistent moderate" group has a tendency towards a higher probability of severe pain at the later follow-up time points. This is a group, which in addition to the "persistent severe" group (who could not transition towards worse pain categories), should receive extra attention regarding treatment interventions. Although we know from studies in multidisciplinary treatments[19], psychological treatments[48], and drug treatments[4] that pain intensity is not generally reduced by treatment, measures should be taken to help these

individuals to prevent the chronic pain to become worse. Psychological distress, sleep problems, and adverse coping might be relevant targets for obtaining this.

Strengths and limitations

A strength of the current study is the large sample size and the frequency of follow-up time points contributing to estimates that are more precise. This study has a follow up period of four years, which is a considerably longer than earlier studies, usually limited to 12-months and less intervals. When the study was planned, sample size was calculated to determine incidence as low as 2% with sufficient precision[24]. Although we used only 1905 participants from the sample, we considered our smallest group, being 11%, as well within the limit of acceptable precision.

A limitation to be considered is loss to follow-up, which may reduce the representativeness of our estimates. This study is part of the HUNT study, which had a 54% participation rate, and this is likely to limit representativeness of the participants. The current study had a 29% attrition rate from baseline to the four-year follow-up. However, the attrition has been shown to not be largely influenced by pain[24], and research suggests that declines in participation rates of survey studies are not likely to have substantial influence on studies of associations [15]. The male-female ratio was similar at every measurement follow-up, whereas the proportion of the youngest age group declined and the proportion of middle-aged individuals increased from baseline to four-year follow-up[24]. Our results may therefore better reflect the course of chronic pain among middle-aged and older individuals than younger adults. Although some studies exist [12, 30], more research should focus on adolescence and young adults to see if these replicate other age groups, to confirm or reject whether these pain trajectories are stabilized in older age.

A limitation of the LLCA methodology is that evaluating the right number of classes is based on several statistical stopping rules which often do not indicate one specific model solution as the best fit. Several factors might affect which trajectories are found. Episodic pain is defined as pain which is interrupted by a period of no pain lasting at least one month[6]. Our time intervals prevented us from identifying episodic pain following this definition. For instance, one can speculate whether individuals in the "gradual improvement" group may have had episodes between the yearly measurements. To confirm or reject this hypothesis, we would need more frequent measurements.

Although pain intensity is the most common outcome measure, "bothersomeness" [1] and "days in pain" [21, 29] have been used and might affect the results. Future research should explore trajectories of other factors than pain intensity, such as pain interference [18] or function, and also time-varying covariates more distantly related to pain such as depression or sleep problems.

Finally, when investigating associations between baseline factors and trajectories some considerations need to be taken into account. Some predictors, either continuous or ordinal, were dichotomized to ease interpretation or to meet the assumptions of the regression model. This might have reduced some precision, but probably did not changed our conclusions. We used the "gradual improvement" group as reference category as we considered this group most meaningful to compare the other groups with. However, choosing another reference category could have displayed other relevant differences between the trajectories. The level of significance for the statistical tests was set at $p < .05$, and multiple comparisons were made without adjusting for this, which might increase the risk for type I errors.

Conclusions

Five trajectories emerged when examining the natural long-term course of chronic pain in the general population. Although most individuals have a stable pain course, the largest distinct trajectory had pain levels that fluctuated between mild and moderate pain. Thus, the same distinct types of pain trajectories found in treatment-seeking samples, limited to LBP, also exist in a population-based sample reporting diverse types of chronic pain. These different pain trajectories are associated with different key characteristics not used in the subgroup formation, which further supports their relevance and may act as potential targets for treatment.

References

1. Axén I, Bodin L, Bergström G, Halasz L, Lange F, Lövgren PW, Rosenbaum A, Leboeuf-Yde C, Jensen I. Clustering patients on the basis of their individual course of low back pain over a six month period. *BMC musculoskeletal disorders.* 12:99, 2011 https://doi.org/10.1186/1471-2474-12-99

2. Berwick DM, Murphy JM, Goldman PA, Ware JE, Jr., Barsky AJ, Weinstein MC. Performance of a five-item mental health screening test. *Medical care.* 29:169-176, 1991 http://dx.doi.org/10.1097/00005650-199102000-00008

3. Chen Y, Campbell P, Strauss VY, Foster NE, Jordan KP, Dunn KM. Trajectories and predictors of the long-term course of low back pain: cohort study with 5-year follow-up. *Pain.* 159:252, 2018 https://doi.org/10.1016/j.pain.2007.10.032

4. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of internal medicine.* 162:276-286, 2015 https://doi.org/10.7326/M14-2559

5. Cuijpers P, Smits N, Donker T, Ten Have M, de Graaf R. Screening for mood and anxiety disorders with the five-item, the three-item, and the two-item Mental Health Inventory. *Psychiatry research.* 168:250-255, 2009 https://doi.org/10.1016/j.psychres.2008.05.012

6. de Vet HC, Heymans MW, Dunn KM, Pope DP, van der Beek AJ, Macfarlane GJ, Bouter LM, Croft PR. Episodes of low back pain: a proposal for uniform definitions to be used in research. *Spine.* 27:2409-2416, 2002 https://doi.org/10.1097/01.BRS.0000030307.34002.BE

7. Deyo RA, Bryan M, Comstock BA, Turner JA, Heagerty P, Friedly J, Avins AL, Nedeljkovic SS, Nerenz DR, Jarvik JG. Trajectories of symptoms and function in older adults with low back disorders. *Spine.* 40:1352-1362, 2015 https://doi.org/10.1097/BRS.0000000000000975

8. Downie AS, Hancock MJ, Rzewuska M, Williams CM, Lin C-WC, Maher CG. Trajectories of acute low back pain: a latent class growth analysis. *Pain.* 157:225-234, 2016 https://doi.org/10.1097/j.pain.0000000000000351

9. Dowsey M, Smith A, Choong P. Latent class growth analysis predicts long term pain and function trajectories in total knee arthroplasty: a study of 689 patients. *Osteoarthritis and cartilage.* 23:2141-2149, 2015 https://doi.org/10.1016/j.joca.2015.07.005

10. Dunn KM, Campbell P, Jordan KP. Long-term trajectories of back pain: cohort study with 7-year follow-up. *BMJ open.* 3:e003838, 2013 https://doi.org/10.1136/bmjopen-2013-003838

11. Dunn KM, Jordan K, Croft PR. Characterizing the Course of Low Back Pain: A Latent Class Analysis. *American Journal of Epidemiology.* 163:754-761, 2006 https://doi.org/10.1093/aje/kwj100

12. Dunn KM, Jordan KP, Mancl L, Drangsholt MT, Le Resche L. Trajectories of pain in adolescents: a prospective cohort study. *Pain.* 152:66-73, 2011 https://doi.org/10.1016/j.pain.2010.09.006

13. Elliott AM, Smith BH, Hannaford PC, Smith WC, Chambers WA. The course of chronic pain in the community: results of a 4-year follow-up study. *Pain.* 99:299-307, 2002 https://doi.org/10.1016/S0304-3959(02)00138-0

14. Eriksen J, Ekholm O, Sjogren P, Rasmussen NK. Development of and recovery from long-term pain. A 6-year follow-up study of a cross-section of the adult Danish population. *Pain.* 108:154-162, 2004 https://doi.org/10.1016/j.pain.2003.12.018

15. Galea S, Tracy M. Participation rates in epidemiologic studies. *Annals of epidemiology.* 17:643-653, 2007 https://doi.org/10.1016/j.annepidem.2007.03.013

16. Jensen MK, Sjøgren P, Ekholm O, Rasmussen NK, Eriksen J. Identifying a long-term/chronic, non- cancer pain population using a one- dimensional verbal pain rating scale: an epidemiological study. *European Journal of Pain.* 8:145-152, 2004 https://doi.org/10.1016/S1090-3801(03)00088-0

17. Jensen MP, Keefe FJ, Lefebvre JC, Romano JM, Turner JA. One- and two-item measures of pain beliefs and coping strategies. *Pain.* 104:453-469, 2003 https://doi.org/10.1016/S0304-3959(03)00076-9

18. Jordan KP, Sim J, Croft P, Blyth F. Pain that does not interfere with daily life—a new focus for population epidemiology and public health? *Pain.* 160:281-285, 2019 https://doi.org/10.1097/j.pain.0000000000001374

19. Kamper SJ, Apeldoorn A, Chiarotto A, Smeets R, Ostelo R, Guzman J, Van Tulder M. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. *Bmj.* 350:444, 2015 https://doi.org/10.1136/bmj.h444

20. Kongsted A, Kent P, Axen I, Downie A, Dunn KM. What have we learned from ten years of trajectory research in low back pain? *BMC Musculoskeletal Disorders.* 17, 2016 https://doi.org/10.1186/s12891-016-1071-2

21. Kongsted A, Kent P, Hestbaek L, Vach W. Patients with low back pain had distinct clinical course patterns that were typically neither complete recovery nor constant pain. A latent class analysis of longitudinal data. *The spine journal.* 15:885-894, 2015 https://doi.org/10.1016/j.spinee.2015.02.012

22. Kriegsman DM, Penninx BW, Van Eijk JTM, Boeke AJP, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly: a study on the accuracy of patients' self-reports and on determinants of inaccuracy. *Journal of clinical epidemiology.* 49:1407-1417, 1996 https://doi.org/10.1016/S0895-4356(96)00274-0

23. Krokstad S, Langhammer A, Hveem K, Holmen T, Midthjell K, Stene T, Bratberg G, Heggland J, Holmen J. Cohort profile: the HUNT study, Norway. *International journal of epidemiology.* 42:968-977, 2012

24. Landmark T, Dale O, Romundstad P, Woodhouse A, Kaasa S, Borchgrevink PC. Development and course of chronic pain over 4 years in the general population: The HUNT pain study. *European Journal of Pain.* 0, 2018 https://doi.org/10.1002/ejp.1243

25. Landmark T, Romundstad P, Dale O, Borchgrevink PC, Kaasa S. Estimating the prevalence of chronic pain: validation of recall against longitudinal reporting (the HUNT pain study). *Pain.* 153:1368-1373, 2012 https://doi.org/10.1016/j.sjpain.2013.07.022

26. Landmark T, Romundstad PR, Borchgrevink PC, Kaasa S, Dale O. Longitudinal associations between exercise and pain in the general population-the HUNT pain study. *PloS one.* 8:e65279, 2013 https://doi.org/10.1371/journal.pone.0065279

27. Langhammer A, Krokstad S, Romundstad P, Heggland J, Holmen J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC medical research methodology.* 12:143, 2012 https://doi.org/10.1186/1471-2288-12-143

28. Lanza ST, Rhoades BL. Latent class analysis: An alternative perspective on subgroup analysis in prevention and treatment. *Prevention Science.* 14:157-168, 2013 https://doi.org/10.1007/s11121-011-0201-1

29. Leboeuf-Yde C, Fejer R, Nielsen J, Kyvik KO, Hartvigsen J. Pain in the three spinal regions: the same disorder? Data from a population-based sample of 34,902 Danish adults. *Chiropractic & manual therapies.* 20:11, 2012 https://doi.org/10.1186/2045-709X-20-11

30. Leino-Arjas P, Rajaleid K, Mekuria G, Nummi T, Virtanen P, Hammarström A. Trajectories of musculoskeletal pain from adolescence to middle age: the role of early depressive symptoms, a 27-year follow-up of the Northern Swedish Cohort. *Pain.* 159:67-74, 2018 https://doi.org/10.1097/j.pain.0000000000001065

31. Macedo LG, Maher CG, Latimer J, McAuley JH, Hodges PW, Rogers WT. Nature and determinants of the course of chronic low back pain over a 12-month period: a cluster analysis. *Physical therapy.* 94:210-221, 2014 https://doi.org/10.2522/ptj.20120416

32. Merskey H, Bogduk N: Task force on taxonomy of the international association for the study of pain. In: Classification of chronic pain, second edition (revised). , International Association for the Study of Pain, Seattle (WA), 1994.

33. Nagin DS: Group-based modeling of development, Harvard University Press, 2005.

34. Nicholls E, Thomas E, van der Windt DA, Croft PR, Peat G. Pain trajectory groups in persons with, or at high risk of, knee osteoarthritis: findings from the Knee Clinical Assessment Study and the Osteoarthritis Initiative. *Osteoarthritis and cartilage.* 22:2041-2050, 2014 https://doi.org/10.1016/j.joca.2014.09.026

35. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural equation modeling: A multidisciplinary Journal.* 14:535-569, 2007 https://doi.org/10.1080/10705510701575396

36. Ohayon MM, Paiva T. Global sleep dissatisfaction for the assessment of insomnia severity in the general population of Portugal. *Sleep medicine.* 6:435-441, 2005 https://doi.org/10.1016/j.sleep.2005.03.006

37. Richardson JC, Ong BN, Sim J. Remaking the future: contemplating a life with chronic widespread pain. *Chronic Illness.* 2:209-218, 2006 https://doi.org/10.1177/17423953060020030201

38. Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low back pain patients: relationship to patient characteristics and current adjustment. *Pain.* 17:33-44, 1983 https://doi.org/10.1016/0304-3959(83)90125-2

39. Rumpf HJ, Meyer C, Hapke U, John U. Screening for mental health: validity of the MHI-5 using DSM-IV Axis I psychiatric disorders as gold standard. *Psychiatry research.* 105:243-253, 2001 https://doi.org/10.1016/S0165-1781(01)00329-8

40. Schwarz G. Estimating the dimension of a model. *The annals of statistics.* 6:461-464, 1978

41. StataCorp: Stata Statistical Software: Release 15. College Station, StataCorp LP, TX, 2015.

42. Steingrímsdóttir ÓA, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies: a systematic review and meta-analysis. *Pain.* 158:2092-2107, 2017

43. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nordic journal of psychiatry.* 57:113-118, 2003 https://doi.org/10.1080/08039480310000932

44. Stynes S, Konstantinou K, Ogollah R, Hay EM, Dunn KM. Novel approach to characterising individuals with low back-related leg pain: cluster identification with latent class analysis and 12-month follow-up. *Pain.* 159:728-738, 2018 https://doi.org/10.1097/j.pain.0000000000001147

45. Tamcan O, Mannion AF, Eisenring C, Horisberger B, Elfering A, Müller U. The course of chronic and recurrent low back pain in the general population. *Pain.* 150:451-457, 2010 https://doi.org/10.1016/j.pain.2010.05.019

46. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB. A classification of chronic pain for ICD-11. *Pain.* 156:1003, 2015

47. Vasseljen O, Woodhouse A, Bjørngaard JH, Leivseth L. Natural course of acute neck and low back pain in the general population: The HUNT study. *Pain.* 154:1237-1244, 2013 https://doi.org/10.1016/j.pain.2013.03.032

48. Veehof MM, Oskam M-J, Schreurs KM, Bohlmeijer ET. Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. *Pain.* 152:533-542, 2011 https://doi.org/10.1016/j.pain.2010.11.002

49. Vermunt JK, Magidson J: Latent GOLD 4.0 user's guide, Statistical Innovations Inc., Belmont, Massachusetts, 2005.

50. Von Korff M, Dunn KM. Chronic pain reconsidered. *Pain.* 138:267-276, 2008 https://doi.org/10.1016/j.pain.2007.12.010

51. Ware JE, Kosinski M, Dewey JE, Gandek B. How to score and interpret single-item health status measures: a manual for users of the SF-8 health survey. *Lincoln, RI: QualityMetric Incorporated.* 15:5, 2001

52. Ware Jr J, Sherbourne C. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical care.* 30:473-483, 1992 https://doi.org/10.1097/00005650-199206000-00002

53. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology.* 33:160-172, 1990

54. World Health Organization. International statistical classification of diseases and related health problems (11th Revision). Retrieved from: https://icd.who.int/browse11/l-m/en. 2018

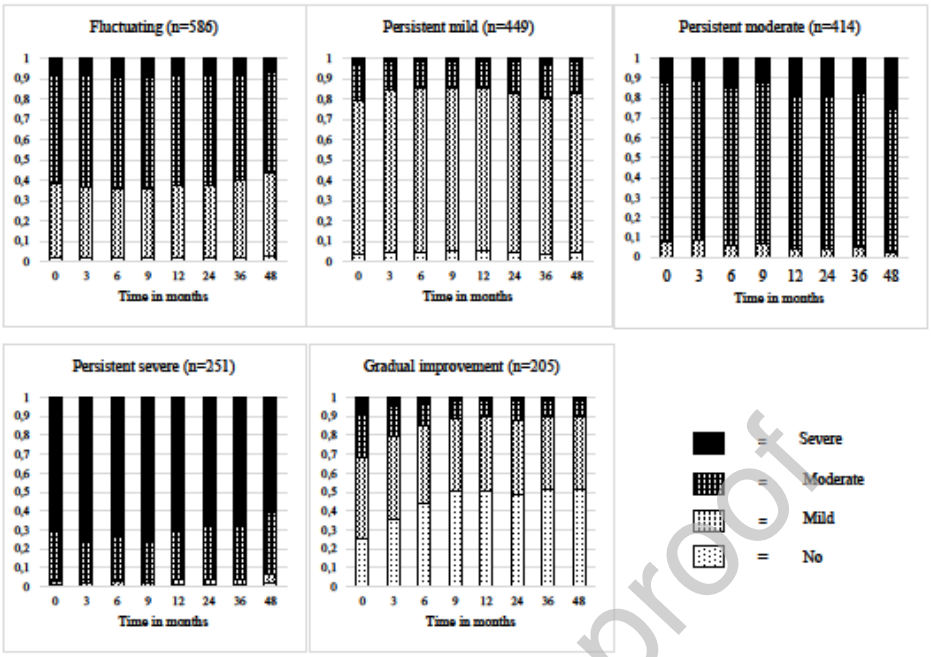

Figure 1. Proportion of individuals reporting no, mild, moderate and severe pain in the five different pain trajectories identified by the LLCA of the individuals with pain 6< months at baseline (n=1905). Proportions are shown for each follow-up time point.

Figure 1. Proportion of individuals reporting no, mild, moderate and severe pain in the five different pain trajectories identified by the longitudinal latent class analysis of the individuals with pain 6< months at baseline (n=1905). Proportions are shown for each follow-up time point.

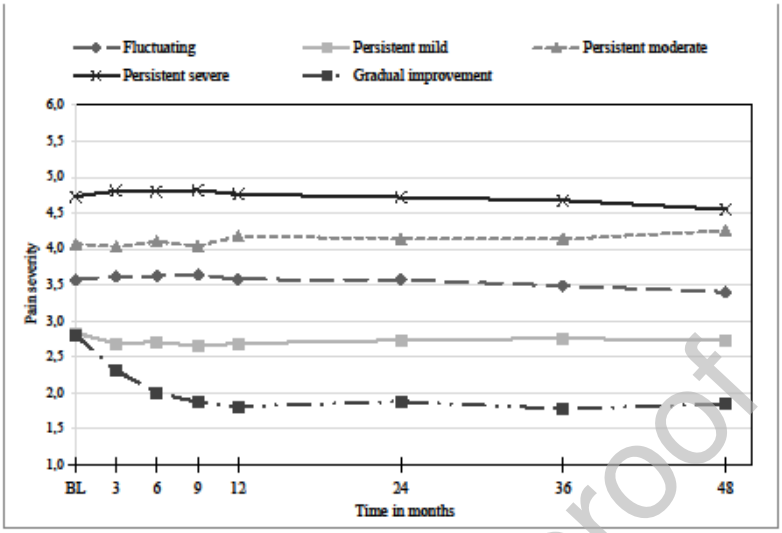

Figure 2. Average pain intensity values for all the five trajectory groups identified over all eight follow-up measures.

Figure 2. Average pain intensity values for all the five trajectory groups identified over all eight follow-up measures.

Supplementary figure 1. Examples of individual trajectories in the five trajectories identified.

The individual curves are chosen randomly.

Table 1. *Descriptive characteristics of the whole sample (n=1905) and of the five pain trajectory groups identified.*

		Trajectory groups				
	Whole cohort	Fluctuating	Persistent mild	Persistent moderate	Persistent severe	Gradual improvement
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total N (%)	1905	586 (31)	449 (24)	414 (22)	251 (13)	205 (11)
Sex (male)	738 (39)	210 (36)	213 (47)	142 (34)	82 (33)	91 (44)
Age						
19-44	386 (20)	106 (18)	124 (28)	48 (12)	41 (16)	67 (33)
45-64	1002 (53)	328 (56)	219 (49)	230 (56)	127 (51)	98 (48)
65+	517 (27)	152 (26)	106 (24)	136 (33)	83 (33)	40 (20)
Organ disease [y/n]	497 (26)	135 (23)	99 (22)	119 (29)	111 (44)	33 (16)
LBP [y/n]	838 (44)	255 (44)	145 (32)	231 (56)	161 (64)	46 (22)
CWP [y/n]	489 (26)	135 (23)	47 (10)	167 (40)	131 (52)	9 (4)
Sleep problems [y/n]	1231 (65)	393 (67)	343 (54)	316 (76)	208 (84)	71 (35)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Catastrophizing [0-6]	1.99 (1.34)	1.89 (1.14)	1.26 (1.10)	2.38 (1.16)	3.48 (1.18)	1.26 (1.09)
Pain intensity [1-6]	3.56 (1.01)	3.57 (.83)	2.83 (.76)	4.07 (.46)	4.73 (.70)	2.70 (1.10)
Mental health [0-100]	78.91 (16.05)	79.16 (14.7)	83.19 (12.3)	75.89 (17.5)	69.82 (19.5)	86.0 (12.5)

Table 2. *Goodness of fit statistics of the longitudinal latent class analysis models using data from all eight follow-up measures of the individuals reporting chronic pain 6< months at baseline (n=1905).*

	LL^2	% reduction in LL from H_0	BIC (LL)	Average posterior probabilities	Entropy	Smallest group size (%)
Model 1 (H_0)	13236.3	-	33603.3	-	-	-
Model 2	8953.3	32	29403.4		.86	50
Model 3	7704.1	42	28237.3	.92-.94	.83	14
Model 4	7049.2	47	27665.4	.90-.93	.82	11
Model 5	6864.5	48	27563.8	.80-.92	.75	11
Model 6	6739.7	49	27522.1	.73-.90	.72	10
Model 7	6647.4	50	27512.9	.70-.90	.69	9
Model 8	6564.5	50	27513.0	.70-.90	.69	4

Note. LL = Log likelihood, BIC = Bayes Information Criterion

Table 3. *Mean posterior probability with 95% Confidence intervals (CI) for the five classes obtained from the longitudinal latent class analysis*

Assigned class	Posterior probability
Fluctuating (n=586)	0.80 (0.78-0.81)
Persistent mild (n=449)	0.84 (0.83-0.86)
Persistent moderate (n=414)	0.81 (0.80-0.83)
Persistent severe (n=251)	0.91 (0.90-0.94)
Gradual improvement (n=205)	0.90 (0.87-0.92)

Table 4. *Results from the multinomial logistic regression analysis showing the association between trajectory membership and baseline factors for all individuals reporting chronic pain 6< months at baseline. Results based on individuals with no missing values at any of the baseline measures (n=1769).*

	Persistent severe pain compared to gradual improvement			Persistent moderate pain compared to gradual improvement			Fluctuating to gradual improvement			Persistent mild to gradual improvement		
	N	RRR[a]	95% CI	N	RRR[a]	95% CI	N	RRR[a]	95% CI	N	RRR[a]	95% CI
Sex												
Female	161	1.0	Ref.	250	1.0	Ref.	344	1.0	Ref.	227	1.0	Ref.
Male	71	.80	.50-1.29	133	.93	.63-1.39	199	.91	.64-1.31	198	1.22	.85-1.74
Age												
19-44	40	1.0	Ref.	46	1.0	Ref.	104	1.0	Ref.	123	1.0	Ref.
45-64	123	1.49	.84-2.66	214	2.53**	1.54-4.16	312	1.78*	1.17-2.70	209	1.01	.67-1.52
65+	69	2.29*	1.16-4.51	123	3.95**	2.19-7.13	127	1.91*	1.13-3.23	93	1.14	.68-1.92
CWP												
No	112	1.0	Ref.	227	1.0	Ref.	418	1.0	Ref.	381	1.0	Ref.
Yes	120	10.89**	5.08-23.33	156	8.12**	3.94-16.71	125	4.06**	1.99-8.29	44	2.06	.98-4.36
Sleep difficulties												
No	38	1.0	Ref.	93	1.0	Ref.	174	1.0	Ref.	194	1.0	Ref.
Yes	194	3.10**	1.80-5.34	290	3.05**	1.99-4.68	369	2.68**	1.83-3.93	231	2.13**	1.45-3.13
Organ disease												
No	132	1.0	Ref.	274	1.0	Ref.	420	1.0	Ref.	335	1.0	Ref.
Yes	100	2.84**	1.66-4.86	109	1.58	.98-2.56	123	1.27	.81-1.99	90	1.25	.79-1.97
Catastrophizing [0-6][b]	232	4.02**	3.24-4.99	383	2.01**	1.67-2.40	543	1.48**	1.26-1.76	425	.95	.80-1.12

Mental health [0-10][b]	23 2	.76*	.64-.90	38 3	.79*	.68-.93	54 3	.83*	.71-.97	42 5	.92	.78-1.08

Note. RRR = relative risk ratio; CI = confidence interval.

[a] RRR of each variable for each trajectory group compared to the rapid improvement trajectory group (reference category). Adjusted for age and sex.

[b] RRR per 10 % unit increase. Variable is reversed (higher score indicates better mental health).