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Article type : Original Article

Determining one-year trajectories of low back related leg pain in primary care patients: growth mixture modelling of a prospective cohort study

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Role of the funders

The ATLAS study was funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-0707-10131). Dr Kika Konstantinou is supported by a Higher Education Funding Council for England Senior Clinical Lectureship. Siobhán Stynes was supported by a National Institute for Health Research/Chief Nursing Officer Clinical Doctoral Research Fellowship (CDRF-2010-055).

ABSTRACT

Objective: The clinical presentation and outcome of patients with back and leg pain in primary care are heterogeneous and may be better understood by identification of homogeneous and clinically meaningful subgroups. Subgroups of patients with different back pain trajectories have been identified, but little is known about the trajectories for patients with back-related leg pain. This study sought to identify distinct leg pain trajectories, and baseline characteristics associated with membership of each group, in primary care patients.

Methods

Monthly data on leg pain intensity were collected over 12 months for 609 patients participating in a prospective cohort study of adult patients seeking healthcare for low back and leg pain including sciatica, of any duration and severity, from their general practitioner. Growth mixture modelling was used to identify clusters of patients with distinct leg pain trajectories. Trajectories were characterised using baseline demographic and clinical examination data. Multinomial logistic regression was used to predict latent class-membership with a range of covariates.

Results: Four clusters were identified: (1) improving mild pain (58%), (2) persistent moderate pain (26%), (3) persistent severe pain (13%), and (4) improving severe pain (3%). Clusters showed statistically significant differences with a number of baseline characteristics.

Conclusion: Four trajectories of leg pain were identified. Clusters 1, 2 and 3 were generally comparable to back pain trajectories, while cluster 4, with major improvement in pain, is infrequently identified. Awareness of such distinct patient groups improves understanding of the course of leg pain and may provide a basis of classification for intervention.

Keywords: Leg pain, pain trajectories, sciatica, primary care, growth mixture modelling, prospective

Significance and Innovations

- In primary care patients with low back-related leg pain, using growth mixture modelling, we identified four distinct trajectories – "improving mild", "persistent moderate", "persistent severe" and "improving severe" leg pain – with the majority of patients on average following stable patterns.
- Three of the trajectories – "improving mild", "persistent moderate", and "persistent severe" leg pain– are generally comparable to back pain trajectories. The "improving severe" cluster represented a group with severe leg pain, whose symptoms improved over time– this group is less often identified in back pain patients.
- The identification of trajectory patterns of leg pain in patients presenting with low back-related leg pain in primary care may potentially improve understanding of the course of leg pain and guide interventions.
- For the majority of this patient group, it might be justifiable to mainly consider conservative management options, such as medication and physiotherapy input.

However, for those patients presenting with very severe pain who do not improve in the first few weeks, perhaps more invasive management options should be considered earlier in the course of pain, if these options are appropriate and desirable.

INTRODUCTION

Low back pain (LBP) is a common condition and a major cause of disability globally[1] and results in an immense economic burden[2]. More than half of patients consulting in primary care for LBP also report leg pain[3, 4]. LBP with leg pain has been shown to be associated with worse health outcomes and increased use of health care compared to LBP alone[4, 5].

Studies on the clinical course of most musculoskeletal pain conditions[6-9] have mainly shown a marked improvement in pain within the first few weeks, but after that point improvement slows considerably. These findings are based on single growth trajectories with the assumption that individuals are drawn from a single homogeneous population with common population parameters. However, the moderate to high person-to-person variability in pain at follow-up time points reported in these studies[7] clearly points to the heterogeneity in the clinical course of pain. This has led to a number of studies in the past decade focussing on investigation of the underlying averaged course of LBP, and has demonstrated that different trajectory patterns exist[10, 11].

Despite this growing body of research focused on identifying distinct trajectory patterns of LBP over time, little is known about the temporal evolution of leg pain intensity for patients with back and leg pain. Identification of homogeneous and clinically meaningful subgroups of low back-related leg pain (LBLP) patients would be important as it better reflects individuals' course patterns and may provide a basis of classification for intervention.

The aim of this study was to identify distinct leg pain trajectory groups in primary care patients consulting with LBLP, and to identify baseline patient characteristics associated with membership of each trajectory group.

MATERIALS AND METHODS

Data source

This study used data from a prospective cohort study (ATLAS) of 609 patients aged 18 years and over, visiting their family doctor (general practitioner (GP)) with symptoms of LBLP (including sciatica), of any severity and duration, at GP practices in North Staffordshire and Stoke-on-Trent, UK. Details of the protocol and results have been published elsewhere[12-14]. In brief, potentially eligible patients were sent a letter with information about the study, an invitation to attend the initial research clinic, and baseline questionnaires capturing sociodemographic, pain, psychological and health variables. At the research clinic, patients underwent a standardised clinical assessment by one of seven musculoskeletal physiotherapists, and were diagnosed as having sciatica (spinal nerve root involvement) or referred (non-specific) leg pain, based on the examiner's clinical opinion. Providing there were no clinical contraindications to the procedure, patients had a lumbar spine magnetic resonance imaging (MRI) scan within two weeks of their baseline assessment. As part of the study, monthly data for leg pain intensity were collected over 12 months, using brief postal questionnaires. Leg pain intensity was measured using the mean of three 0 to 10 numerical rating scales (NRS) for least, usual and current leg pain over the previous 2 weeks[15]. Most participants received physiotherapy treatments, a small number were referred for specialist opinion and management. The ATLAS study care pathways are described in detail elsewhere[14]. Ethical Approval for this study was obtained by the South Birmingham

Research Ethics Committee (REC ref. 10/H1207/82).

Baseline patient characteristics

There are no known baseline factors associated with leg pain trajectory class membership. Therefore, based on previous research in other musculoskeletal pain conditions, a number of patient baseline sociodemographic, pain, psychological and health variables were selected to describe the characteristics of participants in each of the trajectory groups. These included: age; gender; employment status; currently smoking; Body Mass Index (BMI); sleep disturbances due to patients' back and/or leg pain; sciatica clinical diagnosis (made by clinician without knowledge of MRI findings); disability measured with the Roland Morris Disability Questionnaire (RMDQ) leg pain version[16, 17]; neuropathic pain measured using the self-report Leeds Assessment Neuropathic Symptoms and Signs (S-LANSS)[18]; Sciatica Bothersomeness Index (SBI) composite score (0 to 24)[16]; leg pain duration; anxiety and depression measured using the Hospital Anxiety and Depression scale (HADs)[19]; whether pain extended below the knee; whether leg pain was worse than back pain; evidence of nerve root compression on MRI; and whether a patient was referred to secondary care for spinal specialist opinion. Supplemental Table 2 summarises these variables.

Statistical analysis

To identify possible homogeneous and clinically meaningful trajectory groups based on the observed longitudinal trend of pain over time, we applied growth mixture models (GMM)[20-22]. GMM is a statistical approach that captures patients' heterogeneity (individual differences in pain intensity over time) in terms of the growth intercept

(individual differences in pain at the beginning of the study) and growth slope (individual differences with respect to their pain profile over time), by classifying individuals into unobserved groupings with more homogenous patterns, called latent trajectory classes, with each subject belonging exclusively to one latent class. We fitted a random effects model, which allows for within class variability as opposed to assuming that all individual growth trajectories within classes are homogeneous.

To decide on the optimal number of classes, we fitted several sets of models successively (two-class through to six-class solution) and compared their fit by considering: (i) Bayesian Information Criterion (BIC) statistic – a low BIC value indicates a well-fitting model; (ii) bootstrapped parametric likelihood ratio test, which compares the model with *K* classes to a model with (*K*-1) classes; (iii) classification quality determined by the posterior probabilities ensuring that the average of the posterior probabilities of group membership for individuals assigned to each group exceeds a minimum threshold of 0.7[23, 24]; (iv) face validity of the clusters in terms of their clinical interpretability; and (v) class size– the number of individuals in each class[25]. Baseline characteristics of the identified latent trajectory classes were described. Longitudinal plots of the raw individual-level leg pain data were presented as well as the overall trajectory smoothed mean curve estimated using LOESS regression. Multinomial logistic regression models were used to determine the baseline factors independently associated with the latent trajectory class membership. The univariable association between each baseline characteristic and trajectory group was estimated and those with *p*-values <0.25 were selected for inclusion in the multivariable models. Tests of multicollinearity were performed between the predictors. Manual backward elimination was performed using likelihood ratio tests and the BIC statistic to remove non-significant variables from the multivariable model until only predictors with a *p*-value<0.05 were retained in the final model. Using the same modelling process, we performed a subgroup

analysis comparing baseline characteristics between those assigned to the 'improving severe' and 'persistent severe' trajectory.

Latent class analyses were carried out by maximum likelihood estimation using R[26] and MPlus[27]. Subsequent analyses were carried out using Stata 14[28]. The maximum likelihood estimation makes use of all available data points, so missing values are handled without need for imputation, assuming that missing data is missing at random (MAR), meaning that given the observed outcomes and covariates, missingness does not depend on unobserved outcomes. As sensitivity analysis, we repeated the analyses to determine the optimal number of latent trajectory classes by analysing only subjects with complete follow-up data and also by relaxing the assumption of within-class normality using a skew-t growth mixture model.

RESULTS

Participants and monthly response rates

At baseline, 609 participants (mean (SD) age: 50 (13.9) years; 63% female) were included in the study and completed the baseline questionnaire and clinical assessment. Characteristics of these participants have previously been reported [13]. As described, responders and non-responders to follow-up questionnaires showed reasonable comparability in key baseline characteristics (age, gender, and area-level deprivation). On average, leg pain intensity for the whole sample reduced over the first three months and thereafter remained almost unchanged (Figure 1). Monthly response rates ranged from 46% (282/609) at month 5 to 75% (455/609) at month 1, with month 12 having a 74% (450/609) response rate. Twenty-nine percent (n=176) of participants had complete data for leg pain at all follow-up time points, while 61(10%) participants did not provide any follow-up data. There were no systematic differences in follow-up rates across the clusters.

Trajectories of low back-related leg pain

The individual-level patient leg pain profile (trajectories) over the 12 months revealed a heterogeneous population with a wide range of patterns in the clinical course of back and leg pain for individuals (Figure 1).

The BIC statistics indicated that the four-class model was the best fitting solution (Supplemental Table 1). The bootstrapped parametric likelihood ratio test for three classes versus four classes also showed that four classes had a better fit than the three classes ($p<0.001$). The four-model solution also reflected good clinical interpretability and was chosen as the final model. The average posterior probability for each class ranged from 72% to 85% (Supplemental Table 3) showing acceptable precision of classification of individuals into classes. Figure 2 shows the mean trajectories obtained from the 4-class model, with Supplemental Figure 2 adding 95% confidence bounds. Similar results were obtained when normality assumptions were relaxed. Figure 2 reveals four distinct trajectories that differ from each other in their mean levels and changes in pain. Detailed observed individual-level raw data for each trajectory group (Figure 3) shows that the groups identified are clearly different, but also that there are fluctuations around the means within the groups. Based on the growth patterns (Figure 2 and 3), the largest trajectory class (Cluster 1, n=352, 58%) was labelled "improving mild" pain. Members of this class began with mild to moderate leg pain averaging 4.2 at baseline that reduced gradually with time to no pain and had total amount of growth across the entire time interval of -0.23 (time-averaged slope: $p < 0.001$). Cluster 2 contained around a quarter of the sample (n=161; 26%), and was named "persistent moderate" pain. Members of this class began with an average leg pain of 5.6 at baseline, with a total amount of growth across the entire time interval of -0.03 (slope: $p = 0.23$) indicating

little change in leg pain intensity. Cluster 3 (n=79; 13%) was named "persistent severe" pain. Members of this class began with an average leg pain of 8.1, had total amount of non-significant growth across the entire time interval of -0.01 (slope: p = 0.65), i.e. almost no change over time; this group still had severe leg pain averaging 7.2 by 12 months. Cluster 4 (n=17; 3%) was named "improving severe" pain. Members of this class began with an average leg pain of 8.4, which remained high up to around 4 months and afterwards started reducing with a significant (negative) growth across the entire 12-months follow-up time of -0.56 (slope: p <0.001). The sensitivity analysis based on a subgroup of participants with complete leg pain data at all time-points, gave similar cluster structures (Supplemental Figure 1 and Supplemental Figure 3), with n=102, 48, 21, and 5 for clusters 1 to 4, respectively.

The characteristics of the latent trajectory groups

The baseline characteristics of the latent trajectory groups are presented in Table 1. Both the "persistent severe" and "improving severe" leg pain groups had higher scores on anxiety, depression, disability, and sciatica bothersomeness than the "improving mild" and "persistent moderate" groups. The proportion of patients clinically diagnosed with sciatica was highest in the "persistent severe" group (94%), followed by "improving severe" (85%), "persistent moderate" (74%) and least among the "improving mild" group (71%). The "persistent severe" group participants were characterised by the highest level of possible neuropathic pain (73%). The "improving severe" group of participants were characterised by the highest proportion of females, self-reported sleep disturbance due to back and/or leg pain, sciatica clinical diagnosis, leg pain being worse than back pain, reporting having pins and needles and/or numbness, evidence of nerve root compression on MRI, referrals for spinal specialist opinion, and all having pain below the knee.

Relationships between baseline patient characteristics and the latent trajectory groups

The Multinomial logistic regression model results comparing the baseline variables of interest among the latent trajectory groups, with the "improving mild" group (Cluster 1) as the reference, are shown in Table 2. The table presents the risk of belonging to each cluster for a given characteristic compared to the reference cluster expressed as a relative risk ratio (RRR). The final multivariable model included baseline measures of being in full time work, SBI, leg pain duration, leg pain being worse than back pain, anxiety, and referred to spinal specialist for opinion. Controlling for other variables in the model, patients with longer leg pain duration, higher anxiety scores, and those referred for a specialist opinion, were more likely to be in the "persistent moderate" class than "improving mild" class. Patients were significantly more likely to be in the "persistent severe" class relative to "improving mild" if they were not in full time jobs, had higher SBI scores, had longer pain duration, with leg pain worse than back pain and higher anxiety scores. Patients were more likely to be in the "improving severe" class relative to the "improving mild" class if they were in full time jobs, had higher SBI scores, leg pain worse than back pain, and referred for spinal specialist opinion.

Differentiation of the 'improving severe' from the 'persistent severe' groups at baseline

Table 3 compares the baseline characteristics between those assigned to the 'improving severe' and 'persistent severe' trajectory groups for only significant predictors. Participants in the "improving severe" class were significantly more likely to have evidence of nerve root compression on MRI and be referred for spinal specialist opinion than those in the "persistent severe" class, but were less likely to have neuropathic pain.

DISCUSSION

Summary of findings

We identified four distinct trajectories of leg pain over 12 months. To our knowledge, this is the first study reporting trajectories of leg pain. The first cluster with more than half of the participants, which we labelled "improving mild" leg pain, comprised of patients who, on average, presented with mild to moderate leg pain at baseline and gradually improved over the 12-month follow-up. The second cluster labelled "persistent moderate" leg pain, comprised of patients presenting with moderate leg pain at baseline which persisted throughout the 12 months. The third cluster, labelled "persistent severe" leg pain consisted of patients whose leg pain was consistently severe over the year. The final cluster, labelled "improving severe", though with few participants had a very distinctive feature as they presented with very severe leg pain at baseline, followed by slow recovery up to around 4 months, then rapid recovery, to almost no pain, by 12 months.

The four trajectory groups differed significantly regarding specific patient sociodemographic, pain, psychological and clinical characteristics (obtained from clinical examination data). Patients who presented with severe leg pain at baseline (Cluster 3 and 4) had on average higher scores on anxiety, depression, disability, sciatica bothersomeness and were more likely to have a sciatica diagnosis than patients who presented with moderate to mild leg pain. In our final multivariable model examining the predictors of trajectory group membership, the baseline variables that significantly differentiated the other trajectory groups from the "mild improving" one, included being in full time work, SBI, leg pain duration, leg pain being worse than back pain, anxiety, and whether referred for spinal specialist opinion.

Comparison with previous studies

Since the first paper reporting statistically derived trajectories in back pain was published in 2006[29], several studies have investigated trajectories of back pain and other musculoskeletal pain conditions, but to our knowledge, no study has investigated trajectories specifically in patients with LBLP. A recent overview of previous studies on LBP trajectories, from ten cohorts over the past decade[11] found that most cohorts identified four or five patterns as the optimal number of trajectory patterns, with 'persistent mild', 'recovering mild', 'fluctuating' and 'severe chronic' pain patterns, as the common trajectory patterns. An overview of LBP studies also found that most people who experience LBP will have trajectories of either persistent or episodic pain rather than a one-off well-defined episode[30]. Similar features, common between our study and those previous LBP cohort studies, include the "improving mild", "persistent moderate", and "persistent severe" trajectory patterns. Despite such similarity in patterns with the previous LBP studies, the proportion of patients in each trajectory differs significantly with our study. For example, the proportion of "recoverers" ('improving mild') in our study (58%) was much higher than most of the LBP studies (ranging from 7% to 54%)[11], or studies in other musculoskeletal pain conditions such as knee (12%)[31] and hip osteoarthritis (17%)[32].

Despite many LBP studies identifying trajectory groups of episodic/fluctuating patterns comprising of between 15 to 34% of the sample[3, 29, 33], our study of LBLP patients did not discover a trajectory predominantly representing such a group of patients. However, since the identified trajectories allow for individual variations within trajectories as evidenced in Figure 3, fluctuations are likely to be super-imposed on these underlying trajectories but are not the predominant patterns. Since we used data spanning only 12 months, it is not known how the patterns we identified may develop over a longer follow-up, so we cannot tell

whether the recoveries observed in two of the trajectory groups are definite recoveries with no future recurrences. However, a study that investigated the stability of LBP trajectories over time by following the same cohort over two six-month periods that were seven years apart[34] found that the majority of patients with back pain remain in a particular LBP trajectory over long time periods.

Noteworthy in our study is the "improving severe" cluster which represented a group with severe leg pain on average, whose symptoms improved over time. This cluster, however contained only 17 participants, hence should be interpreted with caution until replicated in other studies. This group is less often identified in back pain patients of longer term follow-up. However, studies on short term follow-up[35][36] have observed an early improvement group with a more rapid improvement than in our study.

Implications

The results from our study have important implications for the way we understand LBLP. We have shown that distinct leg pain clinical course patterns exist; therefore leg pain may not be fully described by measuring pain intensity at only one or a few points in time, or by single growth trajectories. Identification of such trajectory patterns in LBLP patients may potentially improve understanding of the course of leg pain and guide targeted interventions. More than half of our study sample showed improving mild-moderate pain. For the majority of participants in this group, it might be justifiable to mainly consider conservative management options, such as medication and physiotherapy input. Indeed, as the ATLAS study was a treatment cohort, the majority of patients did receive physiotherapy input. We also identified subgroups of patients with persistent moderate and persistent severe pain trajectories. Whether these patients may benefit from consideration of more aggressive

treatment options for pain relief, early on, assuming these options are appropriate for the individual patient, we are not able to say.

Even though the "persistent severe" and the "improving severe" groups presented with severe leg pain at baseline and seemed to have similar characteristics compared to the other groups, there were a few characteristics which could distinguish them at baseline. Participants in the "persistent severe" group were more likely to report leg pain of possible neuropathic nature than those in the "improving severe" group. Conversely, all participants in the "improving severe" group had leg pain extending below the knee, had significantly higher likelihood of having nerve root compression on MRI, and were more likely to be referred for spinal specialist opinion. However, the results of MRI directly influence the decision to refer to spinal specialists, in these cases with very severe pain which do not improve over time with conservative management, and are, in principle, appropriate candidates for invasive management options, such as injections and spinal surgery. It is not possible to disentangle the effects of treatment from those of natural course. We are unsure if it is possible for clinicians to differentiate early in patients' presentation, between the two groups with severe leg pain at baseline. However, it is normal clinical practice to re-assess patients regularly, especially those with more severe symptoms, and to consider further appropriate investigations for those with severe pain and lack of improvement.

Future research

Similarly to research in the LBP field [37], future studies may develop simple approaches easily used in a clinical setting to identify patients likely to belong to a particular pain trajectory at an early stage of leg pain presentation. The ability to predict leg pain trajectories early, could guide patient care in terms of not waiting for all conservative management

options to be exhausted before opting for more invasive treatments, such as spinal injections and surgery, where appropriate.

Strengths and limitations

This study benefits from the use of longitudinally collected data with monthly follow-up measurements up to a year. Moreover, we used a robust statistical method, GMM, for identifying the latent trajectory groups. A further novelty of this cohort is the availability of clinical examination data including a clinical diagnosis of sciatica, as opposed to many studies that have relied purely on self-report.

As a limitation of this study, similar to all prospectively collected observational data; there were high numbers of drop-outs from the original sample. The problem of missing data could influence the selection and the pattern of trajectories, although our sensitivity analysis results showed similar patterns of trajectories, and the differences between the participants and the drop-outs were minimal in terms of the key baseline characteristics. In addition, the possible biases arising from such a problem were minimised by use of full-information maximum likelihood. Given that the fourth cluster contained less than 5% of the participants we would suggest obtaining further evidence from future studies on leg pain trajectories to confirm that this group is also identified in other datasets. Further, the small size of the fourth cluster may have inhibited our ability to detect differences in baseline characteristics between clusters 3 and 4.

CONCLUSIONS

In primary care patients with back-related leg pain, we identified four distinct and clinically meaningful trajectories of leg pain over 12 months and a number of baseline patient characteristics associated with membership of each trajectory class. Three of the trajectory classes– "improving mild", "persistent moderate", and "persistent severe" leg pain– are generally comparable to back pain trajectories. The "improving severe" cluster represented a group with severe leg pain, whose symptoms improved over time– this group is less often identified in back pain patients. These findings could help to gain a better understanding of the nature of LBLP presenting in primary care. The findings also confirm that describing an entire LBLP population using a single growth trajectory is oversimplifying the leg pain growth patterns. Identification of such distinct groups of patients could improve understanding of the course of leg pain and may provide a basis of classification for further diagnostic tests and treatment choice from potential and appropriate interventions.

Acknowledgements

We would like to thank the members of the ATLAS study research team; Elaine M Hay, Martyn Lewis, Sue Jowett, Danielle AWM van der Windt, Samantha L Hider, Steve Vogel, and all the participating patients, clinicians and managers.

Author contributions

All the authors contributed substantially to conception and design of the study, drafting the article or revising it critically for important intellectual content, analysis of data and interpretation of results, and all authors approved the final version to be submitted for publication. Dr. Reuben Ogollah had full access to all of the data in the study, led the

analysis, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer: The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethics approval: South Birmingham Research Ethics Committee (REC ref. 10/H1207/82)

Data sharing statement

The Arthritis Research UK Primary Care Centre has established data sharing arrangements to support joint publications and other research collaborations. Applications for access to anonymised data from our research databases are reviewed by the Centre's Data Custodian and Academic Proposal (DCAP) Committee, and a decision regarding access to the data is made subject to the NRES ethical approval first provided for the study and to new analysis being proposed. Further information on our data sharing procedures can be found on the Centre's website (http://www.keele.ac.uk/ pchs/publications/datasharingresources/) or by emailing the Centre's data manager (primarycare.datasharing@keele.ac.uk

References

1. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S *et al*: **Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010**. *Lancet* 2012, **380**(9859):2197-2223.

2. Kent PM, Keating JL: **The epidemiology of low back pain in primary care**. *Chiropractic & Osteopathy* 2005, **13**(1):13.

3. 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**. *Spine J* 2015, **15**(5):885-894.

4. Hill JC, Konstantinou K, Egbewale BE, Dunn KM, Lewis M, van der Windt D: **Clinical outcomes among low back pain consulters with referred leg pain in primary care**. *Spine (Phila Pa 1976)* 2011, **36**(25):2168-2175.

5. Konstantinou K, Hider SL, Jordan JL, Lewis M, Dunn KM, Hay EM: **The impact of low back-related leg pain on outcomes as compared with low back pain alone: a systematic review of the literature**. *Clin J Pain* 2013, **29**(7):644-654.

6. Heuch I, Foss IS: **Acute low back usually resolves quickly but persistent low back pain often persists**. *J Physiother* 2013, **59**(2):127.

7. Pengel LH, Herbert RD, Maher CG, Refshauge KM: **Acute low back pain: systematic review of its prognosis**. *BMJ* 2003, **327**(7410):323.

8. Menezes Costa LdC, Maher CG, Hancock MJ, McAuley JH, Herbert RD, Costa LOP: **The prognosis of acute and persistent low-back pain: a meta-analysis**. *CMAJ : Canadian Medical Association Journal* 2012, **184**(11):E613-E624.

9. Artus M, van der Windt D, Jordan KP, Croft PR: **The clinical course of low back pain: a meta-analysis comparing outcomes in randomised clinical trials (RCTs) and observational studies**. *BMC Musculoskelet Disord* 2014, **15**:68.

10. Enthoven WT, Koes BW, Bierma-Zeinstra SM, Bueving HJ, Bohnen AM, Peul WC, van Tulder MW, Berger MY, Luijsterburg PA: **Defining trajectories in older adults with back pain presenting in general practice**. *Age and ageing* 2016, **45**(6):878-883.

11. Kongsted A, Kent P, Axen I, Downie AS, Dunn KM: **What have we learned from ten years of trajectory research in low back pain?** *BMC Musculoskelet Disord* 2016, **17**(1):220.

12. Konstantinou K, Beardmore R, Dunn KM, Lewis M, Hider SL, Sanders T, Jowett S, Somerville S, Stynes S, van der Windt DA *et al*: **Clinical course, characteristics and prognostic indicators in patients presenting with back and leg pain in primary care. The ATLAS study protocol**. *BMC Musculoskelet Disord* 2012, **13**:4.

13. Konstantinou K, Dunn KM, Ogollah R, Vogel S, Hay EM: **Characteristics of patients with low back and leg pain seeking treatment in primary care: baseline results from the ATLAS cohort study**. *BMC Musculoskelet Disord* 2015, **16**:332.

14. Konstantinou K, Dunn KM, Ogollah R, Lewis M, van der Windt D, Hay EM: **Prognosis of sciatica and back-related leg pain in primary care: the ATLAS cohort**. *The Spine Journal* 2017.

15. Dunn KM, Jordan KP, Croft PR: **Recall of medication use, self-care activities and pain intensity: a comparison of daily diaries and self-report questionnaires among low back pain patients**. *Primary Health Care Research & Development* 2010, **11**(1):93-102.

16. Patrick DL, Deyo RA, Atlas SJ, Singer DE, Chapin A, Keller RB: **Assessing health-related quality of life in patients with sciatica**. *Spine (Phila Pa 1976)* 1995, **20**(17):1899-1908; discussion 1909.

17. Roland M, Morris R: **A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain**. *Spine (Phila Pa 1976)* 1983, **8**(2):141-144.

18. Bennett MI, Smith BH, Torrance N, Potter J: **The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research**. *J Pain* 2005, **6**(3):149-158.

19. Zigmond AS, Snaith RP: **The Hospital Anxiety and Depression Scale**. *Acta Psychiatrica Scandinavica* 1983, **67**(6):361-370.

20. Muthén B: **Latent variable analysis. Growth mixture modeling and related techniques for longitudinal data**. In: *The SAGE Handbook of Quantitative Methodology for the Social Sciences.* Edited by Kaplan D. Thousand Oaks: SAGE Publications; 2004: 345-368.

21. Ram N, Grimm KJ: **Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups**. *International journal of behavioral development* 2009, **33**(6):565-576.

22. Muthén BO: **Beyond SEM: General latent variable modeling**. *Behaviormetrika* 2002, **29**(1):81-117.

23. Nagin DS, Odgers CL: **Group-based trajectory modeling in clinical research**. *Annual review of clinical psychology* 2010, **6**:109-138.

24. Nagin D: **Group-Based Modeling of Development**: Harvard University Press; 2005.

25. Jung T, Wickrama KAS: **An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling**. *Social and Personality Psychology Compass* 2008, **2**(1):302-317.

26. Proust-Lima C, Philipps V, Liquet B: **Estimation of extended mixed models using latent classes and latent processes: the R package lcmm**. *arXiv preprint arXiv:150300890* 2015.

27. Muthén LK, Muthén BO: **Mplus User's Guide. Sixth Edition**. In. Los Angeles, CA: Muthén & Muthén; 1998-2011.

28. StataCorp: **Stata Statistical Software: Release 14. College Station, TX: StataCorp LP**. 2015.

29. Dunn KM, Jordan K, Croft PR: **Characterizing the course of low back pain: a latent class analysis**. *Am J Epidemiol* 2006, **163**(8):754-761.

30. Axen I, Leboeuf-Yde C: **Trajectories of low back pain**. *Best Pract Res Clin Rheumatol* 2013, **27**(5):601-612.

31. 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 Cartilage* 2014, **22**(12):2041-2050.

32. Bastick AN, Verkleij SP, Damen J, Wesseling J, Hilberdink WK, Bindels PJ, Bierma-Zeinstra SM: **Defining hip pain trajectories in early symptomatic hip osteoarthritis - 5 year results from a nationwide prospective cohort study (CHECK)**. *Osteoarthritis Cartilage* 2016, **24**(5):768-775.

33. Tamcan O, Mannion AF, Eisenring C, Horisberger B, Elfering A, Muller U: **The course of chronic and recurrent low back pain in the general population**. *Pain* 2010, **150**(3):451-457.

34. Dunn KM, Campbell P, Jordan KP: **Long-term trajectories of back pain: cohort study with 7-year follow-up**. *BMJ Open* 2013, **3**(12):e003838.

35. Kongsted A, Leboeuf-Yde C: **The Nordic back pain subpopulation program - individual patterns of low back pain established by means of text messaging: a longitudinal pilot study**. *Chiropractic & Osteopathy* 2009, **17**(1):11.

36. 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* 2011, **12**(1):99.

37. Dunn KM, Campbell P, Jordan KP: **Validity of the Visual Trajectories Questionnaire for Pain**. *J Pain* 2017, **18**(12):1451-1458.

Tables

Table 1: Baseline characteristics of the four pain trajectory groups obtained from the GMM

Baseline characteristics	Leg pain trajectory groups			
	Improving mild; n=352, 58%	**Persistent moderate; n=161, 26%**	**Persistent severe; n=79, 13%**	**Improving severe; n=17, 3%**
Age (years), mean (SD)	49.0 (13.7)	51.4 (13.7)	51.4 (14.8)	56.9 (12.8)
Gender, Female, n (%)	213 (60.5)	110 (68.3)	48 (60.8)	12 (70.6)
BMI categories (kg/m^2), n (%)				
Normal (18.5 to <25)	79 (22.5)	36 (22.4)	15 (19.2)	6 (35.3)
Overweight (25 to<30)	129 (36.8)	61 (37.9)	28 (35.9)	5 (29.4)
Obese/Morbidly obese (30 +)	143 (40.7)	64 (40.0)	35 (44.9)	6 (35.3)
Current smoker, n (%)	95 (27.0)	58 (36.0)	35 (44.3)	7 (41.2)
Currently in paid job, n (%)	245 (70.0)	88 (55.0)	27 (34.6)	7 (41.2)
Sleep disturbances due to back and/or leg pain, n (%)	228 (64.8)	127 (78.9)	58 (73.4)	15 (88.2)
Co-morbidities[*:] – at least one other health problem, n (%)	123 (34.9)	65 (40.4)	41 (51.9)	9 (52.9)
RMDQ disability score (0-23), mean (SD)	11.4 (5.4)	13.3 (5.6)	16.4 (5.5)	15.4 (4.8)
Sciatica clinical diagnosis, n (%)	250 (71.0)	119 (73.9)	67 (84.8)	16 (94.1)
Sciatica Bothersomeness Index (SBI), mean (SD)	12.4 (5.0)	15.1 (4.6)	19.3 (3.9)	19.6 (3.3)
Leg pain duration, n (%)				
<6 weeks	167 (49.4)	60 (39.7)	21 (27.3)	3 (17.7)
6-12 weeks	77 (22.8)	25 (16.6)	11 (14.3)	7 (41.2)

Over 3 months	94 (27.8)	66 (43.7)	45 (58.4)	7 (41.2)
S-LANSS (possible neuropathic pain), n (%)	139 (39.6)	89 (55.6)	57 (73.1)	8 (47.1)
Pain below the knee, n (%)	210 (62.1)	105 (69.1)	62 (80.5)	17 (100.0)
Leg pain is worse than back pain (patient report), n (%)	145 (41.2)	79 (49.1)	43 (54.4)	13 (76.5)
HADs depression subscale, mean (SD)	5.7 (3.6)	6.3 (3.9)	8.9 (4.7)	8.2 (3.7)
HADs anxiety subscale, mean (SD)	6.8 (3.8)	8.3 (4.0)	10.5 (4.5)	9.6 (4.0)
Pins and needles and/or numbness (patient reports having these symptoms), n (%)	205 (58.2)	103 (64.0)	60 (76.0)	14 (82.4)
Mild or severe muscle weakness, n (%)	62 (17.6)	26 (16.2)	13 (16.7)	4 (23.5)
Reduced or loss of pin prick sensation, n (%)	135 (38.4)	70 (43.5)	39 (49.4)	9 (52.9)
Patient referred to secondary care, n (%)	22 (6.3)	26 (16.2)	14 (17.7)	8 (47.1)
Had surgery for back or leg pain over 12 months, n (%)	3 (0.9)	2 (1.2)	4 (5.1)	5 (29.4)
Evidence of nerve root compression on MRI, n (%)	161 (50.8)	78 (53.8)	44 (57.9)	14 (87.5)

*The health problems included chest problems, heart problems, raised blood pressure, diabetes, and circulation problems in the leg

Table 2: Univariable (unadjusted) and multivariable (adjusted) risk estimates: Relative risk ratios (RRR) and 95% Confidence intervals (CI) for belonging in each trajectory groups relative to "improving mild" trajectory group (reference trajectory group)

Baseline characteristics	Univariable (Unadjusted)			Multivariable (Adjusted)*		
	2: Persistent moderate, n=161	3: Persistent severe, n=79	4: Improving severe; n=17	2: Persistent moderate, n=161	3: Persistent severe, n=79	4: Improving severe, n=17
Age in years	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.04 (1.00, 1.08)	-	-	-
Gender, Female (Male) †	1.41 (0.95, 2.09)	1.01 (0.61, 1.67)	1.57 (0.54, 4.54)	-	-	-
BMI categories (kg/m^2) (Normal (18.5 to <25)						
Overweight (25 to<30)	1.04 (0.63, 1.71)	1.14 (0.57, 2.27)	0.51 (0.15, 1.73)	-	-	-
Obese/Morbidly obese (30 +)	0.98 (0.60, 1.61)	1.29 (0.66, 2.50)	0.55 (0.17, 1.77)	-	-	-
Current smoker (Non-smoker)	1.52 (1.02, 2.27)	2.15 (1.30, 3.56)	1.89 (0.70, 5.12)	-	-	-
Currently in paid job (not currently in paid job)	0.52 (0.36, 0.77)	0.23 (0.13, 0.38)	0.30 (0.11, 0.81)	0.50 (0.32, 0.76)	0.24 (0.13, 0.46)	0.26 (0.09, 0.79)
Sleep disturbances due to back and/or leg pain (no disturbance)	2.03 (1.31, 3.14)	1.50 (0.87, 2.59)	4.08 (0.92, 18.12)	-	-	-
Co-morbidities: – at least one other health problem (None)	1.26 (0.86, 1.85)	2.01 (1.23, 3.29)	2.09 (0.79,5.57)	-	-	-
RMDQ disability score (0-23)	1.06 (1.03, 1.10)	1.20 (1.14, 1.26)	1.15 (1.04, 1.26)	-	-	-
Sciatica clinical diagnosis (referred leg pain)	1.16 (0.76, 1.76)	2.28 (1.18. 4.39)	6.52 (0.85, 49.8)	-	-	-
Sciatica Bothersomeness Index (SBI)	1.12 (1.07, 1.16)	1.41 (1.31, 1.52)	1.43 (1.24, 1.66)	1.10 (1.05, 1.15)	1.36 (1.25, 1.47)	1.35 (1.16, 1.57)
Leg pain duration (<6 weeks)						
6-12 weeks	0.90 (0.53, 1.55)	1.14 (0.52, 2.47)	5.06 (1.27, 20.10)	0.84 (0.47, 1.47)	1.22 (0.50, 3.00)	3.61(0.80, 16.33)
Over 3 months	1.95 (1.27, 3.01)	3.81 (2.13, 6.77)	4.14 (1.04, 16.41)	1.62 (1.02, 4.57)	2.68 (1.32, 5.42)	2.56(0.58, 11.34)

S-LANSS (possible neuropathic pain) (No)	1.91 (1.31, 2.79)	4.13 (2.40, 7.13)	1.36 (0.51, 3.60)	-	-	-
Pain below the knee (pain above the knee)	1.36 (0.91, 2.05)	2.52 (1.38, 4.61)	Perfect prediction	-	-	-
Leg pain is worse than back pain (back pain worse)	1.38 (0.95, 2.00)	1.71 (1.04, 2.79)	4.64 (1.48, 14.51)	1.47 (0.96, 2.24)	1.99 (1.05, 3.76)	3.64(1.04, 12.81)
HADs depression subscale	1.04 (0.99, 1.09)	1.21 (1.14, 1.28)	1.16 (1.03, 1.31)	-	-	-
HADs anxiety subscale	1.10 (1.04, 1.15)	1.25 (1.17, 1.32)	1.18 (1.05, 1.33)	1.06 (1.01,1.12)	1.14 (1.05, 1.23)	1.11 (0.97, 1.28)
Pins and needles and/or numbness (patient reports having these symptoms) (None)	1.27 (0.87, 1.87)	2.26 (1.30, 3.96)	3.34 (0.94, 11.85)	-	-	-
Mild or severe muscle weakness (Normal)	0.90 (0.54, 1.49)	0.94 (0.49, 1.80)	1.44 (0.45, 4.56)	-	-	-
Reduced or loss of pin prick sensation (None)	1.24 (0.85, 1.81)	1.57 (0.96, 2.55)	1.80 (0.68, 4.80)	-	-	-
Patient referred to secondary care (No)	2.89 (1.58, 5.28)	3.23 (1.57, 6.64)	13.33 (4.69, 37.93)	2.05 (1.06, 3.94)	1.42 (0.58, 3.50)	5.40(1.65, 17.65)
Evidence of nerve root compression on MRI (None)	1.12 (0.76, 1.67)	1.33 (0.80, 2.21)	6.78 (1.52, 30.33)			

*All the variables in the univariable model except BMI and muscle weakness were significant ($p<0.25$) and were included in the initial multivariable model. For the multivariable model, depression and anxiety were highly correlated and only anxiety was left in the model as it had stronger univariable association with class membership; [†]The reference categories for all categorical variables are presented in parentheses

Table 3: Odds ratios and 95% CI for being in the 'improving severe' class vs. 'persistent severe' class

Baseline characteristics (reference category)	Unadjusted*	Adjusted
	OR (95% CI)	OR (95% CI)
S-LANSS (possible neuropathic pain) (No)	0.34 (0.11, 0.96)	0.27 (0.08, 0.87)
Referred for specialist opinion (No)	4.13 (1.35, 12.57)	5.28 (1.59, 17.47)
Evidence of nerve root compression on MRI (None)	5.09 (1.08, 23.98)	-

Note: Pain extending below the knee was a perfect predictor for being in the improving severe class since all members of that cluster had pain extending below the knee

*All the baseline variables considered in Table 2 were examined for the univariable association but were all non-significant (p>0.25), hence are excluded from this table

Figure Legends

Figure 1: Observed individual-level raw data and smoothed mean curve for patient leg pain profile over 12 months

Figure 2: Course of pain over 12 months among primary care low back-related leg pain consulters: Mean trajectories obtained from the 4-class model

Figure 3: Observed individual-level raw data and smoothed mean curve for each trajectory group for patient leg pain profile over 12 months

Supplemental Figure 1: Mean trajectories obtained from the 4-class model for those with 12 months complete data, n=176

Supplemental Figure 2: Subject-specific mean predicted trajectories with time (presented with the dot) and class-specific weighted mean observed trajectories (solid lines) and their 95% confidence bounds (dotted lines) for the whole sample. The predicted and observed class-specific values are weighted means within each time interval

Supplemental Figure 3: Subject-specific mean predicted trajectories with time (presented with the dot) and class-specific weighted mean observed trajectories (solid lines) and their 95% confidence bounds (dotted lines) for those with 12 months complete data, n=176. The predicted and observed class-specific values are weighted means within each time interval