Defining pain and interference recovery trajectories after acute non-catastrophic musculoskeletal trauma through Growth Mixture Modeling

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Joshua Lee
Western University
_emails jlee2793@uwo.ca Corresponding Author
ORCiD: https://orcid.org/0000-0001-7480-6291

David M. Walton
Western University

Paul Tremblay
Western University

Curtis May
The University of British Columbia

Wanda Millard
Western University

James M. Elliott
Northern Sydney Local Health District

Joy C. MacDermid
Western University

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Abstract
Background Recovery trajectories support early identification of delayed recovery and can inform personalized management or phenotyping of risk profiles in patients. The objective of this study was to investigate the trajectories in pain severity and functional interference following non-catastrophic musculoskeletal (MSK) trauma in an international, mixed injury sample.

Methods A prospective longitudinal cohort of n= 241 was formed from patients identified within 4 weeks of trauma, from attendance at emergency or urgent care centres located in London, ON, Canada, or Chicago, IL, USA. Pain interference was measured via the Brief Pain Inventory (London cohort) or the Neck Disability Index (Chicago cohort). Pain severity was captured in both cohorts using the numeric pain rating scale. Growth mixture modeling and RM ANOVA approaches identified distinct trajectories of recovery within pain interference and pain severity data.

Results For pain interference, the 3 trajectories were labeled accordingly: Class 1 = Rapid recovery (lowest intercept, full or near full recovery by 3 months, 32.0% of the sample); Class 2 = Delayed recovery (higher intercept, recovery by 12 months, 26.7% of the sample); Class 3 = Minimal or no recovery (higher intercept, persistently high interference scores at 12 months, 41.3% of the sample).
For pain severity, the 2 trajectories were labeled: Class 1 = Rapid recovery (lower intercept, recovery by 3 months, 81.3% of the sample); and Class 2 = Minimal or no recovery (higher intercept, flat curve, 18.7% of the sample). The “Minimal or No Recovery” trajectory could be predicted by female sex and axial (vs. peripheral) region of trauma with 74.3% accuracy across the 3 classes for the % Interference outcome. For the Pain Severity outcome, only region (axial trauma, 81.3% accuracy) predicted the “Minimal or No Recovery” trajectory.

Conclusions These results suggest that 3 meaningful recovery trajectories can be identified in an international, mixed-injury sample when pain interference is the outcome, and 2 recovery trajectories emerge when pain severity is the outcome. Females in the sample or people who suffered axial injuries (head, neck, or low back) were more likely to be classed in poor outcome trajectories.

Background
While patient reports of pain are a common feature following musculoskeletal trauma, the
phenomenon is complex and the experience is unique to each patient. Early biological models conceptualized the pain experience to be the direct result of tissue damage, though newer models endorse multifaceted drivers recognizing the pain experience as highly subjective and influenced by interactions of biology, psychology and social influences (1). Inconsistent relationships between clinical pain outcomes and key physiological mechanisms (2) has made management of post-trauma pain and interference difficult. Chronic pain is recognized as a distinct pathological condition (3) that disrupts daily life (4). The incidence and prevalence of chronic pain is estimated to be nearly 20% of adults in Canada (5) and the United States (6) with large economic and social burden (7). The inability to consistently predict or prevent the transition from acute-to-chronic is partially related to the lack of clear understanding of the mechanisms involved (8). Adding to the confusion is that many prior longitudinal studies have evaluated outcomes and differences at specific time-points rather than actual trajectories. As a result clinicians are too often left to adopt a ‘wait and see’ approach to identify those patients who do not appear to be recovering, though by the time such a case arises it is often too late to prevent persistent problems. We and others in the field suggest that better mechanism-based prognostic models are needed to accurately and consistently identify those at greatest risk of transitioning from acute to chronic pain (9, 10) that will allow more targeted interventions to mitigate the risk and improve distal outcomes.

Pain prognosis as a field of study has evolved considerably over the past two decades, with emphasis added in areas such as acute whiplash-associated disorder (11) and acute low back pain (12). However, considerable challenges persist, including i) the nature and importance of the outcomes being predicted and ii) the multitude of confounding factors influencing the value of, and confidence in, prognostic models (13). Traditionally, pain intensity (or severity) has been the most common outcome predicted in prognostic research of musculoskeletal trauma, and acute pain intensity has also been a consistent predictor of those outcomes (14, 15). For example, Panken and colleagues (16) conducted growth mixture modeling to identify 3 trajectories that best described the trajectory of pain intensity in 622 participants with low back pain of median 5.8 weeks duration (2 to 780 weeks). Their results showed 3 distinct categories of recovery wherein people either had consistently low
pain, consistently high pain, or showed a gradual recovery over a period of 12 months. This type of 3-class trajectory model appears to be showing consistency across other traumatic injuries, such as whiplash (17). Outstanding questions persist including the translation of these findings to injuries affecting other parts of the body, and how choice of outcome may affect these. A better understanding of recovery trajectories will inform prognostic assessment of patients, regardless of the trauma or diagnosis, helping to direct healthcare diagnostic and theranostic (individualized treatment) resources to those who would benefit most, while reducing wasted resources for those likely to quickly recover.

The purpose of this study was to investigate the trajectories in pain and functional interference following non-catastrophic musculoskeletal (MSK) trauma in a mixed sample of both axial and peripheral non-catastrophic trauma drawn from two different countries. This was conceptualized as a first step towards a non-body-region-specific approach to prognostic phenotyping of people with acute, non-catastrophic MSK trauma.

Methods
Participant recruitment
Data for this analysis were drawn from two longitudinal cohorts, one in London Ontario, Canada (SYMBIOME, Systematic Merging of Biology, Mental Health and Environment, clinicaltrials.gov ID no. NCT02711085) and one in Chicago, Illinois, United States (Neuromuscular Mechanisms Underlying Poor Recovery from Whiplash Injuries, clinicaltrials.gov ID no. NCT02157038). Eligible participants were identified by emergency or acute-care nursing or medical clinicians, all within hours to 4 weeks of musculoskeletal (MSK) trauma. Participants were 18 to 65 years old, had to have suffered a non-catastrophic MSK injury that did not require inpatient admission or surgical correction, and could speak and understand conversational (at least grade 8) English. The London cohort included participants with non-catastrophic acute MSK injury affecting any body region, while the Chicago cohort included only those with acute whiplash-associated symptoms about the neck arising from a motor vehicle collision. Exclusion criteria were those with one or more prior motor vehicle collisions (Chicago cohort only), any metabolic systems disorders (Chicago cohort only), and any nervous
system or major systemic disorders that would be expected to otherwise impair recovery independently of the trauma (e.g. active cancer, neuromuscular disease, autoimmune diseases). Co-treatment or other chronic comorbidities were captured as part of the intake and follow-up packages. After being medically cleared, interested participants provided permission for a member of the research team to describe the study, answer questions, and obtain consent to participate before leaving the hospital. Participants were provided a package of self-report questionnaires to be completed and returned within 24 hours. While follow-up periods differed slightly between the two cohorts, consistent were follow-up within 2–4 weeks from inception, and again 3 and 12 months after injury.

Demographics and outcomes
The constructs being captured through self-reported questionnaires were similar enough to allow meaningful pooling of the two cohorts. Both studies captured demographic and social data including age, sex, body mass index (BMI, kg/m$^2$), work status, medicolegal status, and significant comorbidities (e.g. depression or other mood disorders, existing pain conditions). The outcomes for defining recovery trajectory were pain severity using a 0–10 Numeric Pain Rating Scale (NPRS) where 0 = no pain and 10 = extreme pain, and pain-related functional interference as measured by the Interference subscale of the Brief Pain Inventory (BPI (18), London cohort) or the Neck Disability Index (NDI (19), Chicago cohort). The BPI is one of the most widely used pain interference scales globally (20) and has considerable evidence of validity across many clinical populations including musculoskeletal pain (21). The NDI is one of the most widely used region-specific scales for neck disorders and captures pain interference with function on most items. The two tools share several items including work ability, sleep, and recreation, but the NDI excludes walking interference that is less relevant to those with neck pain. Both the NDI and the BPI Interference subscale have demonstrated acceptable reliability, validity, and responsiveness for capturing interference (18, 19, 21–24) and both show a strong and similar correlation with pain severity rating scales (NDI: $r = 0.64$ (25), BPI: $r = 0.67$, current database). Both can easily be converted into a percentage of the total scale range (0% = no interference, 100% = complete interference) for meaningful pooling.
Intervention between follow-up periods, if any, occurred at the discretion of the participant and their healthcare providers without influence by the research team. Type of intervention was captured in general terms (e.g. physical therapy, chiropractic, pharmaceuticals, massage therapy, work hardening) for descriptive purposes as the balance of evidence available in the field does not consistently support the superiority of any treatment modality over others (26–29).

Ethics approval was obtained by the respective research and hospital institutional ethics boards prior to recruiting participants into the study. Participants were reimbursed up to the equivalent of $240 Canadian dollars ($175 US dollars) for expenses and time incurred during participation across all follow-up periods.

Analysis
Pre-Analysis
Participant demographics and baseline scores on the two outcomes were evaluated descriptively (frequencies, means, ranges). The primary (% Interference) and secondary (pain severity out of 10) outcomes were first explored for missing data and normality. Region of injury was coded according to the primary area of symptoms: presence of any head, neck or back injuries (regardless of any less significant peripheral injuries) were classified as “axial” while those affecting the upper or lower extremities (shoulder, elbow, wrist, hip, knee, ankle) were classed as “peripheral”. As it was anticipated that recovery would occur in the majority of patients by 12 months, scores were square-root transformed across collection periods to reduce the skewness and kurtosis of the distribution to within acceptable limits for statistical modeling.

Growth Mixture Modeling
Maximum likelihood-based latent growth curve analysis (LGCA) using the Growth-mixture modelling (GMM) procedure in MPlus v6.12 software (Muthen & Muthen, Los Angeles USA) was conducted, following the steps of DiStefano and Kamphaus (30), to identify the number of trajectories definable by each of the 2 primary outcomes. A series of models were constructed for both % Interference and Pain Severity, starting with a base single trajectory model and increasing classes until i) the model fit no longer improved substantially, ii) the estimation could not derive a mathematically valid model, or iii) one of the classes possessed fewer than 10% of participants. The fit indicators of interest were the
Akaike Information Criterion (AIC) (31–33), the Bayesian Information Criterion (BIC) (31–33), and entropy (32). While no set criteria exist for deeming an acceptable model fit (33), the cluster solution providing the lowest AIC and BIC and the highest entropy value (ideally > 0.70) that also conforms to theory is generally considered optimal (34). An additional statistical analysis was conducted using the k-means approach, where the Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (LMR-LRT) (31, 33) was used to statistically compare the fit of the k cluster solution (e.g. 3) with that of the k-1 class solution (e.g. 2). When fit did not statistically improve (p > 0.05) with the addition of a new class, the solution with the smaller number of classes is generally accepted for reasons of parsimony (33, 35). All models included a quadratic (non-linear) growth function as pre-analysis revealed the quadratic growth factor was significant in the base model. ‘Region’ (axial or peripheral) was then included as a covariate in each model to control for the effect of the different cohorts and tools. After identifying the optimal model, each participant received an assignment to the most likely trajectory (termed ‘class’) based on the highest posterior probability from the modeling procedure.

Missing data
Only those participants with at least 2 data points were included in the modeling procedure. Maximum Likelihood Estimation (MLE)-based curve estimation is useful for datasets with missing data as it makes use of all available data to estimate an appropriate trajectory that can be used to describe the entire sample as long as the data are missing at random (36, 37). To provide some evidence of randomness, independent samples t-tests were conducted between those with full datasets and those with missing data to identify any differences in baseline participant characteristics (age, sex, BMI, pain severity or interference) that could indicate any potential systematic biases in those lost to follow-up.

Model validation
To improve confidence in the model structures we statistically compared the observed data (using all available data) to the MLE-based estimated values from the non-region-adjusted modeling procedure using paired samples t-tests. No significant difference between observed and estimated values would indicate the predictive model was adequately accurate for estimating the data including missing
values.

Description of trajectories
Forward-entry binary logistic regression was conducted to determine the extent to which sex, age, BMI, and region of injury (in that order) could predict trajectories using odds ratios as a standardized metric of effect size comparison across the variables. Age and BMI were dichotomized through median split (Age ≤ 38 years, BMI ≤ 25.09 kg/m²). For this analysis, the anticipated ‘worst’ (persistent problems) trajectory was coded as the state to be predicted against any other trajectories that emerged. Model fit was explored according to the recommendations of Peng and colleagues (38) using the Hosmer-Lemeshow (H-L) test wherein a non-significant effect indicates good fit to the data, supported by the Nagelkerke $R^2$ and overall accuracy of the regression-predicted trajectory classifications. The supporting indices were needed as there were fewer than 5 groups to be predicted rendering the H-L test vulnerable to potentially biased estimates. (38)

Sample size estimation
Sample size estimates for GMM are difficult to establish through traditional effect size metrics, though previous studies investigating pain recovery trajectories using GMM and ANOVA-based approaches have identified distinct classes with a medium-sized standardized difference between the classes. (39) The planned intention to conduct between-group regression analyses led to an a priori decision that a minimum of 30 participants in the smallest class was necessary. Based on work of prior authors, we anticipated the smallest class to represent about 15% of the sample, leading us to target a total sample of 200 usable datasets.

Results

Participant characteristics
A total of 241 participants were recruited within 28 days (4 weeks) of non-catastrophic MSK trauma, with 225 (93.4%) providing complete baseline data. Of those, 134 were from the London, Ontario sample and 97 from the Chicago, Illinois sample. The combined sample was 54.9% male, mean age of 39.7 years, BMI of 26.1 kg/m², and the modal cause of injury was motor vehicle collision (50.5% of responses). Table 1 presents the remaining participant characteristics including baseline mean
values on the primary outcomes. The sample was mixed between those with primarily axial (59.9%) or extremity (40.1%) injuries. Over the 12-month period, 27% of participants reported taking over-the-counter pharmaceuticals for symptom management, 18% received physiotherapy, 10% filled and used a prescription opioid, 9% received massage therapy, and 38% received ‘other’ interventions.

**Growth Mixture Modeling**

The dataset for the base model included 205 participants (axial and peripheral combined) after removing 20 further participants with only a single baseline data point. Comparisons between those excluded and retained showed no difference in sex, age, BMI, or baseline pain and interference scores, supporting a random effect of missing data. **Table 2** presents the results of the 2, 3, and 4-class models for both outcomes. The square-root transformed % Interference data were best described by the 3 classes after controlling for region of injury (axial or peripheral) and including a quadratic growth factor. This solution was optimal in terms of fit indicators and clinical utility with a significant LMR-LRT (LR = 60.77, p<0.01) vs. the 2-class model. The 3 trajectories were labeled: Class 1 = Rapid recovery (lowest intercept, full or near full recovery by 3 months, 32.0% of the sample); Class 2 = Delayed recovery (higher intercept, recovery by 12 months, 26.7% of the sample); Class 3 = Minimal or no recovery (higher intercept, persistently high interference scores at 12 months, 41.3% of the sample).

Fit indicators for the pain severity outcome were optimal for a 2-trajectory quadratic growth model (AIC = 2935.51, BIC = 2983.58, Entropy = 0.79, LMR-LRT = 81.03, p<0.01 vs. the single class). A 3-class model also satisfied most a priori criteria save for the proportions, where a middle 3rd “persistent moderate severity” class included only 8.3% of the sample and was therefore not retained. The two retained trajectories were labeled: Class 1 = Rapid recovery (lower intercept, recovery by 3 months, 81.3% of the sample); and Class 2 = Minimal or no recovery (higher intercept, flat curve, 18.7% of the sample). **Figures 1** (% Interference) and **2** (Pain Severity) present the trajectories graphically while **Table 3** provides means and 95% confidence intervals by class and time.

The region covariate (axial vs. peripheral injury) showed a significant effect on the latent class
variables for both outcomes ($\Delta F \ p< 0.01 \ for \ both$). A $\chi^2$ comparison of proportions revealed the effect: 92.6% (% Interference) and 91.7% (Pain Severity) of participants in the ‘Minimal or No Recovery’ trajectories were those with axial injuries, while 75.6% (% Interference) and 56.2% (Pain Severity) of those in the ‘Rapid Recovery’ trajectories described extremity injuries ($\chi^2$ for proportions = 83.3, $p < 0.01$ for % Interference; $\chi^2 = 16.0, p<0.01$ for Pain Severity).

Model Validation

Paired t-tests between the available observed data and the non-adjusted, unstandardized estimated values for both outcomes revealed no significant differences at any of the 4 time points, indicating the model provided accurate estimates of the observed data.

Class predictors

Binary logistic regression was used to explore the predictive value of the person-level variables in classifying participants into the worst (Minimal or No Recovery) trajectory as the index state with the other trajectory/trajectories grouped together as a single ‘recovery predicted’ trajectory. The regression models were an acceptable fit to the data (% Interference: H-L $\chi^2 = 4.91, p = 0.77$, Nagelkerke $R^2 = 0.45$; Pain Severity: H-L $\chi^2 = 11.89, p = 0.16$, Nagelkerke $R^2 = 0.16$). Table 4 presents the results. For % Interference as the outcome, the Minimal or No Recovery trajectory could be predicted by female sex and axial (vs. peripheral) region of trauma with 74.3% accuracy. For the Pain Severity outcome, only region (axial trauma) predicted the Minimal or No Recovery trajectory.

Discussion

This study has defined anticipated recovery trajectories following non-catastrophic MSK trauma in mixed geographic and body region samples. The models were created using a mixed sample of working-age adults across two different institutions, in two different countries, with injuries affecting different body regions. Growth Mixture Modeling adequately identified 3 trajectories of pain-related interference and 2 trajectories for pain severity in adult participants followed for up to 52 weeks after non-catastrophic musculoskeletal trauma. These trajectories have been labeled on the basis of their intercept, slope, and quadratic function for use in future prognostic phenotyping work.
The trajectories for functional interference are qualitatively similar to those derived by other authors in region-specific samples though potentially important differences may exist. For example, Sterling and colleagues (17) identified 3 curvilinear classes of recovery from traumatic neck pain that could be discriminated by baseline (y-intercept) disability score. In contrast our model has identified a ‘Delayed Recovery’ group that entered the study with high functional interference not different from the Minimal or No Recovery class, but had recovered by the final 12-month follow-up. Our model is more similar to that of Panken and colleagues (16) who also identified a ‘Delayed Recovery’ class in a sample of adults with low back pain, though the outcome was pain severity rather than functional interference. Regardless of the construct, the existence of this middle trajectory casts some doubt on previous findings, including our own prior meta-analysis (40), that suggests those most likely to develop chronic problems can be reliably identified through higher interference or pain scores at baseline. In the current analysis those in the delayed interference recovery group would be misclassified on the basis of baseline interference scores alone. Risk phenotyping for this group will require further exploration in future studies. This work does however lend further support to the notion that those who enter a longitudinal study with lower pain or interference scores are less likely to report persistent problems, and this appears to be independent of which body region is injured.

The identification of a trajectory representing over 41% of the sample that shows little or no improvement in functional scores over all time-points is a concern, but is consistent with prior primary and secondary evidence that indicates approximately 50% of people following acute neck or low back injuries do not fully recover (41). The proportion of participants in this trajectory is nearly identical to that identified by Panken and colleagues (45.2% of their sample) (16). The Rapid Recovery group, representing 32.0% of the sample, has also been consistently identified in both neck (17, 42) and low back pain (43). Despite some differences in shape, the 3-trajectory model has now been identified with striking consistency across clinical populations worldwide. This includes trajectories of pain and disability in a large population-level study of people with chronic pain in Canada (44), and post-operative pain in Belgium and the United States (45, 46). Even in studies that have identified more trajectories in hip (Netherlands) (47) and low back pain (UK) (48), the existence of 3 stable classes
represent the highest proportions with other smaller classes representing participants with fluctuating symptoms. Our a priori criterion of rejecting class structures with fewer than 10% of the sample may have masked some of these smaller groups with irregular symptoms, so they may yet emerge with larger samples though we suggest it may be time for the field to move with more vigor towards predicting and defining those in each trajectory. 

Pain Severity as an outcome favoured a 2-class model. Contrary to the functional interference findings, the largest proportion for pain severity was the rapid recovery trajectory. We considered endorsing a 3-class model for consistency with interference to facilitate clinical translation; a 3rd ‘moderate persistent symptoms’ trajectory could be identified using a base (unadjusted) model but included only 8.3% of the sample and was therefore rejected. Again our trajectories appear similar to those of prior research. Downie and colleagues (43) followed a sample of participants with acute low back pain for 12 weeks and also identified 70.1% that showed rapid recovery. The difference in proportions between the outcomes highlights an important reminder that pain severity and functional interference, while related, are distinct constructs that warrant separate investigation and may lead to different recovery status. While we personally favour functional interference over pain severity as a meaningful outcome, the 2-trajectory model for Severity does fit with prior prognostic and epidemiologic work indicating that persistent pain symptoms can be predicted by pain severity at baseline (15) and that approximately 15–20% of the North American adult population will report daily chronic pain (5, 6). 

The person-level variables that best predicted Minimal or No Recovery class membership are potentially useful for future study design. Prior work has shown that females (40) and older participants (49) are at greater risk of poor outcomes following acute neck trauma. In our sample, the odds of being in the poor interference trajectory was also approximately 2.4x greater for females than males, while age did not predict class membership for either outcome. The strongest predictor of class membership regardless of outcome however was region of injury. Those who endorsed neck or low back injuries were 23x more likely to be assigned to the poor interference trajectory and 7x more likely to be assigned to the higher pain outcome group. These results are generally in keeping with
prior work showing that patients who have experienced non-catastrophic axial traumas tend to rate symptoms as more severe and more distressing than those with non-catastrophic traumas involving the extremities (50). Taken together these results would also seem to indicate that clinicians and researchers might expect a greater proportion of poor outcomes in females reporting neck or back injuries.

Limitations
The most notable risk of potential confounding in this study is the combination of two separate databases from two different countries. While the important aspects of data collection were consistent across the two cohorts, there were also obvious differences. One is the medicolegal context between the private payer system in the United States and the socialized health system in Canada. There has yet to be any compelling evidence to suggest that the rate or amount of improvement in these common MSK traumas is different between the two neighboring countries, however we acknowledge that work in other countries with less established personal injury insurance systems (e.g. Lithuania (51, 52), Greece (52, 53)) have been previously associated with different rates of chronic post-trauma neck pain compared to other western countries. Dedicated international research collaborations with standardized case definitions and outcomes are required to more fully explore the effect of personal injury insurance claims. The two cohorts also used a different standardized patient reported outcome for measuring functional interference, with the Chicago cohort using the NDI and the London cohort using the BPI. As far as we know the two scales have never been directly compared for equality of measurement properties, though each have been independently explored against other standardized tools and shown to have similar associations (18, 19, 23, 24). Both share two nearly identical items (sleep, work) and also include items pertaining to activity and recreation. The BPI is intended as a more generic tool, including walking, which is less relevant to those reporting neck pain only. As these databases were combined after collection was complete, we could not standardize the tools used, though we are confident that converting each to a percent of total scale score ensures similar constructs of “functional interference” and justifies combining the two databases for this analysis. Importantly, there was no significant difference in baseline %
Interference scores between the two cohorts (not shown) and the inclusion of ‘region’ as a covariate in the models provided some protection against spurious findings, as the majority of those in the database with neck trauma came from the Chicago cohort. A well-recognized reciprocal tension exists between internal and external validity, and in this case we have chosen to favor the latter through the inclusion of mixed samples, countries, and outcomes, though acknowledge the effect on internal validity of doing so. Another potential limitation is sample size, though 205 is not considered small by LGCA standards. Some research groups have identified smaller trajectory classes hidden within larger samples (though these tend to represent 10% or less of the overall proportion), while other large scale analyses have similarly reported 3 trajectories (16, 44). While it is possible that other trajectories comprised of smaller proportions exist in our data but were not identified, we propose that these would be rare enough to not substantively affect prognosis or treatment decisions. Finally, the use of the quadratic term made clinical and statistical sense, though it should be noted that a purely linear model could be identified that resulted in qualitatively similar class structures with some differences in proportions assigned to each. The posterior validation steps in this study were undertaken to strengthen our confidence in the results of the quadratic models, with the added advantage of better prediction for missing data and a clear indication of recovery in the rapid class by 3 month follow-up after which the curve flattened considerably.

Conclusion
An international mixed-injury sample of adults from with non-catastrophic musculoskeletal trauma was followed from the acute peri-injury stage through 12 months post-injury. Growth Mixture Modeling identified 3 meaningful trajectories of recovery when functional interference was the outcome, and 2 trajectories when pain severity was the outcome. Those who reported injuries affecting the axial spine (neck or low back) were more likely to be classed into the poor outcome trajectories (pain severity or interference), and females were more likely than males to be classed into the Minimal or No Recovery group only when functional interference was the outcome. Further exploration of person-level differences for predicting the trajectory class is a priority area for ongoing research.
Abbreviations
MSK - Musculoskeletal
RM ANOVA - Repeated-measures Analysis of Variance
ANOVA - Analysis of Variance
SYMBIOME - Systematic Merging of Biology, Mental health, and Environment
BMI - Body mass index
NPRS - numeric pain rating scale
BPI - Brief Pain Inventory
NDI - Neck Disability Index
LGCA - Latent Growth Curve Analysis
GMM - Growth Mixture Modeling
AIC - Akaike Information Criterion
BIC - Bayesian Information Criterion
LMR-LRT - Lo-Mendell-Rubin Adjusted Likelihood Ratio Test
MLE - Maximum Likelihood Estimation
H-L - Hosmer-Lemeshow

Declarations

Ethics approval and consent to participate

The study was approved by the office of Human Research Ethics at Western University and the Lawson Health Research Institute, and written, informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

Datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

JME reports payment for lectures/workshops on assessment and management of the patient with pain
that is outside the submitted work. DMW reports payment for lectures/workshops on assessment and management of the patient with pain that is irrespective of the submitted work.

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**Authors’ contributions**

JYL contributed to study design, data analysis, and drafted the manuscript. DMW contributed to study design, data analysis and was a major contributor to the manuscript. PT contributed to data correction and consultation on growth mixture modeling and latent growth curve analysis. JME provided the Chicago cohort data and contributed to data correction and critical revisions on the manuscript. CM, WM, and JCM made critical revisions to the manuscript.

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Tables
| Variable (N = 231)                                      | Proportion or Mean (SD, range) |
|--------------------------------------------------------|-------------------------------|
| Sex (% male)                                           | 54.9%                         |
| Age (years)                                            | 39.7 (13.8, 18 to 66)         |
| Body Mass Index (kg/m²)                                | 26.1 (5.4, 14.4 to 51.5)      |
| Cause (%)                                               |                               |
| Motor vehicle collision                                | 50.5%                         |
| Fall / Slip                                            | 14.2%                         |
| Hit by person or object (not MVC)                      | 9.4%                          |
| Awkward lift or twist                                  | 8.0%                          |
| Other                                                  | 17.9%                         |
| Body Region Injured (%)                                 |                               |
| Neck                                                   | 52.7%                         |
| Shoulder                                               | 9.1%                          |
| Elbow                                                  | 3.6%                          |
| Wrist or Hand                                          | 15.5%                         |
| Lower Back                                             | 9.1%                          |
| Hip                                                    | 2.3%                          |
| Knee                                                   | 8.6%                          |
| Foot or Ankle                                          | 16.4%                         |
| Employment (%)                                          |                               |
| Full or Part-Time paid work                            | 73.7%                         |
| Off Work (temporary)                                   | 2.6%                          |
| Not Employed for Pay                                   | 23.7%                         |
| Pain Interference (% of total score)²                  | 37.6% (21.0%, 0 to 96)        |
| Pain Severity (0-10 NRS)                               | 4.6 (2.2, 0 to 10)            |

**TABLE 1.** Participant characteristics for the entire sample (N = 231)

1: The total proportions will exceed 100% as participants were free to choose more than one body region.

2: Disability, or functional interference was captured using the interference subscales of the Neck Disability Inventory or the Brief Pain Inventory and have been reported as a percentage of total scale score.
### TABLE 2. Fit indices for maximum likelihood-based latent growth curve models of pain severity and interference dimensions when controlling for effect of body region injured.

1: The 4-class model for % Interference would only converge when variance in both slope and quadratic growth function were constrained to zero.

#### % Interference

| Class   | %      | Baseline | 1-month | 3-month | 6-month | Slope | Quadratic | Region-adjusted estimate |
|---------|--------|----------|---------|---------|---------|-------|-----------|--------------------------|
| Rapid   | 32.0%  | 22.0 (19.9, 24.3)\(^1\) | 4.1 (3.1, 5.3)\(^1\) | 0.4 (0.1, 0.7)\(^2\) | 0.2 (0.0, 0.4) | -15.3 | 0.63 | |
| Delayed | 26.7%  | 40.6 (37.0, 44.3) | 24.8 (21.6, 28.1) | 9.7 (7.8, 11.8)\(^2\) | 0.6 (0.2, 1.2) | -0.5 | -0.1\(^1\) | |
| Minimal | 41.3%  | 40.7 (38.1, 43.4) | 29.1 (26.6, 31.7) | 21.9 (19.8, 24.2)\(^2\) | 18.1 (16.1, 20.1)\(^3\) | -1.0 | 0.02 | |

#### Pain Severity

| Trajectory | n     | Baseline | 1-month | 3-month | 6-month | Slope | Quadratic | Region-adjusted estimate |
|------------|-------|----------|---------|---------|---------|-------|-----------|--------------------------|
| Rapid      | 82.2% | 4.5 (4.2, 4.7)\(^2\) | 2.6 (2.5, 2.8)\(^2\) | 1.3 (1.2, 1.4)\(^2\) | 0.5 (0.4, 0.6)\(^2\) | -2.0 | | |
| Minimal    | 17.8% | 5.6 (5.1, 6.1)\(^2\) | 5.5 (5.1, 5.8)\(^2\) | 5.3 (5.1, 5.6)\(^2\) | 5.1 (4.9, 5.3)\(^2\) | -0.4 | | |
**TABLE 3.** Proportions and estimated means for % Interference (Top) and Pain Severity (Bottom) trajectory classes with 95% confidence intervals (n = 215). Differences between classes were explored using Bonferroni-corrected post-hoc analyses for significant Class x Time interactions.

1: Mean % Interference in the *Rapid Recovery* group is significantly lower than the other two groups, with no difference between *Delayed* and *Minimal* recovery groups by virtue of overlapping confidence intervals.

2: Mean % Interference / mean pain severity is significantly different across all groups.

3: Mean % Interference is significantly higher in the *Minimal* recovery group than the other two groups, with no difference between the *Rapid* and *Delayed* groups.

|                  | % Interference (Minimal or No Recovery) | Pain Severity (Minimal or No Recovery) |
|------------------|----------------------------------------|----------------------------------------|
|                  | B                                      | OR (95%CI)                             | P           |
| **Sex (Female)** | 0.87                                   | 2.39 (1.18, 4.82)                      | 0.02        |
| Age >38          | -0.13                                  | 0.88 (0.42, 1.83)                      | 0.73        |
| BMI > 25.09      | 0.64                                   | 1.90 (0.93, 3.88)                      | 0.08        |
| **Axial injury** | 3.14                                   | 23.13 (8.43, 63.48)                    | <0.01       |

**TABLE 4.** Results of binary logistic regression for predicting class membership to the worst (Minimal or no recovery) class trajectories. B = unstandardized beta, OR = odds ratio. **BOLD** are variables that contributed significant predictive value to the model.

**Figures**
Recovery Trajectories for Pain Interference in Axial and Peripheral Injuries

Figure 1

Graphical representation of a 3-class LGCA model of pain interference recovery for axial and peripheral injury over a 12-month follow-up period, where dashed lines indicate 95% confidence intervals for each class. The x-axis denotes time in months (from zero at intake to 12-month follow-up) and the y-axis denotes pain interference expressed as a square-root transformed percentage. Rapid recovery (34.9%) is depicted as having a moderate intercept and rapidly declining slope. Delayed recovery (19.2%) is depicted as having a high intercept and steadily declining slope. Minimal or No Recovery (45.9%) is depicted as having a high intercept and minimally declining slope.
Figure 2

Recovery Trajectories for Pain Severity for Axial and Peripheral Injuries Graphical representation of a 2-class LGCA model of pain severity recovery for axial and peripheral injury over a 12-month follow-up period, where dashed lines indicate 95% confidence intervals for each class. The x-axis denotes time in months (from zero at intake to 12-month follow-up) and the y-axis denotes their pain severity score out of 10. Rapid recovery (83.4%) is depicted as having a moderate intercept and steadily declining slope. Minimal or No Recovery (16.6%) is depicted as having a high intercept and minimal slope.