



BMJ Open Do measures of physical function enhance the prediction of persistent pain and disability following a whiplash injury? Protocol for a prospective observational study in Spain

Ahmed Alalawi ¹, Alejandro Luque-Suarez,² Manuel Fernandez-Sanchez,³ Alessio Gallina,¹ David Evans,¹ Deborah Falla ¹

To cite: Alalawi A, Luque-Suarez A, Fernandez-Sanchez M, *et al*. Do measures of physical function enhance the prediction of persistent pain and disability following a whiplash injury? Protocol for a prospective observational study in Spain. *BMJ Open* 2020;**10**:e035736. doi:10.1136/bmjopen-2019-035736

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-035736>).

Received 13 November 2019
Revised 17 February 2020
Accepted 28 July 2020



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¹Centre of Precision Rehabilitation for Spinal Pain (CPR Spine), School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK
²Physiotherapy, University of Malaga, Malaga, Spain
³Facultad de Ciencias de la Educacion Enfermeria y Fisioterapia, Universidad De Almeria, Almeria, Spain

Correspondence to
Professor Deborah Falla;
d.falla@bham.ac.uk

ABSTRACT

Introduction Not all factors that predict persistent pain and disability following whiplash injury are known. In particular, few physical factors, such as changes in movement and muscle behaviour, have been investigated. The aim of this study is to identify predictive factors that are associated with the development of persistent pain and disability following a whiplash injury by combining contemporary measures of physical function together with established psychological and pain-related predictive factors.

Methods and analysis A prospective observational study will recruit 150 consecutive eligible patients experiencing whiplash-related symptoms, admitted to a private physiotherapy clinic in Spain within 15 days of their whiplash injury. Poor outcome will be measured using the Neck Disability Index (NDI), defined as an NDI score of 30% or greater at 6 months post injury. Candidate predictors, including demographic characteristics, injury characteristics, pain characteristics, self-reported psychosocial factors and physical factors, will be collected at baseline (within 15 days of inception). Regression analyses will be performed to identify factors that are associated with persistent neck pain and disability over the study period.

Ethics and dissemination The project has been approved by the Ethics Committee of the province of Malaga, Spain (#30052019). The results of this study will be published in peer-reviewed journals.

INTRODUCTION

The term ‘whiplash’ refers to an acceleration-deceleration motion of the neck, most commonly following a motor vehicle collision, that can result in tissue injury.¹ Following whiplash, individuals may develop a variety of clinical signs and symptoms, collectively termed whiplash-associated disorders (WADs).¹ Soft tissue damage has been detected in some individuals with WAD; however, this has not been linked to the progression of symptoms.^{2–4} WAD is associated with a significant

Strengths and limitations of this study

- This protocol describes, a priori, the methods and analysis of identifying predictors of persistent pain and disability following a whiplash injury.
- Specific physical measures together with established self-reported measures will be captured within 15 days of inception.
- Candidate predictors are selected using a combination of best available knowledge and theory, and their applicability in clinical practice.
- Trajectories of self-reported pain and disability will be recorded over the 12-month study period.
- Physical measures will not be measured throughout the course of the study.

socioeconomic burden;⁵; the cost to the UK economy is ~£3 billion per year.⁶ This burden is primarily acquired by those developing chronic, long-term symptoms and half of those with WAD continue to report neck pain at least 1 year after the injury.⁷ This highlights the importance of early identification (ID) of features associated with ongoing pain and disability; this would facilitate personalised treatment approaches to mitigate the risk associated with the development of chronic WAD.⁸

High-quality evidence has shown higher pain and disability immediately post injury to be the most consistent factor predicting longer-term pain and disability.^{9,10} Studies have examined other factors that might predict the development of ongoing pain following whiplash covering all three elements of the biopsychosocial model: demographic factors,^{7 11–14} pre-existing comorbidities,^{11 13 14} collision factors,^{7 11–13 15–18} physical factors,^{14 19–24} radiological changes,^{2 25–30} societal factors³¹ and psychological factors.^{7 32 33} Yet, there is

controversial evidence concerning the predictive ability of other factors including: general psychological distress, depression, previous neck pain, gender and the use of a seatbelt at the time of the collision.^{9 14 32 34 35} This illustrates an incomplete picture regarding the predictive factors for recovery versus ongoing pain in WAD.

There has been little investigation of the predictive utility of physical factors following whiplash injury; of the studies conducted, measures of physical function have been limited to measures such as range of motion^{19 20 36 37} and craniocervical flexion test performance.^{38 39} Yet, physical factors may offer potential to improve prediction accuracy. For example, there is a wealth of evidence describing changes in movement and muscle behaviour.^{40–42} Decreased maximum angular velocity of neck movements has been observed in individuals with chronic WAD when compared with healthy individuals.⁴⁰ Such changes in movement behaviour have been confirmed in individuals with WAD and insidious neck pain, where lower peak velocity was observed in both groups.⁴¹ In addition, a significantly larger Jerk Index (measure of the smoothness of neck movement) has been reported in individuals with chronic neck pain of both insidious and traumatic onset, when compared with asymptomatic individuals.⁴¹ Another feature reported in those with chronic neck pain is increased coactivation of the neck flexors and extensors,⁴² which is associated with reduced neck strength.⁴² These additional features have not been investigated in individuals with acute WAD, but results from experimental pain studies suggest these adaptations occur soon after pain onset and may, therefore, have relevance for ongoing symptoms in individuals with chronic WAD.^{43–50}

A number of methodological limitations of previously published studies in the field of WAD prognosis have been identified. For instance, a review conducted by Walton *et al*¹⁰ found that many predictors have conflicting results.^{11 12 32} Inconsistent outcome measures have previously been used by to define recovery in WAD,⁵¹ with a different definition of recovery used in each study.^{7 52} Other reasons for inconsistency can be attributed to poor reporting^{11 53} and the inclusion of subjects from different settings and at different inception points. Another recent review found controversial evidence with regards to which demographic factors, prior pain and psychological factors are associated with the transition to chronic WAD.⁹

Collectively, these limitations impact on our understanding of factors associated with the transition to chronic WAD following a whiplash injury and highlight the need for an adequately powered, methodologically robust observational study to provide useful predictive estimates. Such knowledge could lead to the development of a new clinical care pathway that matches early interventions to risk factors for poor recovery.

Aims of study

The aim of the study is to identify factors soon after a whiplash injury that predict the occurrence of persistent pain and disability 6 months later. We will include a broad

range of candidate predictors, including measures of physical function with self-reported measures of pain, disability and established psychological constructs.

METHODS

Study design

The study will be a prospective observational design. This protocol has been developed in accordance with guidelines from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement,⁵⁴ the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) statement,⁵⁵ the Quality In Prognosis Studies (QUIPS) tool,⁵⁶ the CHECKlist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)⁵⁷ and the PROGNosis RESearch Strategy (PROGRESS) framework.⁵⁸

Participants

We aim to recruit 150 individuals presenting to a private physiotherapy clinic in Malaga, Spain, with symptoms attributed to a recent (within the previous 15 days) whiplash injury. Consecutive eligible individuals will be invited to participate in the study for a follow-up period of 12 months until this target is achieved. Study recruitment will commence on November 2019 and will be completed by November 2020.

Eligibility criteria

Inclusion criteria: Adults aged 18 years or older, who are experiencing acute neck pain with or without other whiplash-related symptoms such as headache, upper limb symptoms or dizziness⁵⁹ following a whiplash injury, attributed to a recent (previous 15 days) motor vehicle collision or sports injury. An ability to understand written and verbal Spanish language is also necessary.

Exclusion criteria: Individuals who experienced cervical spine fractures or dislocations during or since their whiplash injury (WAD grade IV),¹ loss of consciousness during or since their whiplash injury⁶⁰ or have ever received neck surgery⁶¹ will be excluded from participation. Individuals with malignant spinal disorders, mental disorders^{62 63} or regular use of analgesic medication prior to the injury due to chronic pain will also be excluded.

Recruitment

Participants will be recruited from a single private physiotherapy clinic in Malaga, Spain. Based on feasibility data (clinical records), we estimate that at least 300 eligible individuals will be eligible for recruitment over a 12-month period, and that at least 50% can be expected to consent to participation.

We will recruit eligible patients within 15 days of their whiplash injury. One designated physiotherapist working at the physiotherapy clinic will manually check electronic clinical records of all consecutive patients attending the clinic. Once an eligible patient

is identified at the clinic, the designated clinic physiotherapist will contact the patient to invite them to participate in the study; this invitation will be done either in-person at the clinic after the first treatment session or via telephone after patients have returned home from their clinic appointment. A verbal and written description of the study will be provided during the invitation. Those patients interested in participation will be invited to attend an initial study session at the physiotherapy clinic. At this session, the researcher will again explain the study design and context, patients will be given a detailed information

sheet and written informed consent will be sought. The English version of the consent form is provided in the online supplemental file. Once recruited, participants (figure 1) will be asked to complete a baseline self-reported questionnaire, after which physical data will be collected (table 1). Participants will be informed that they can withdraw from the study at any time, without having to provide a reason. They will also be advised to carry on with their daily routines as usual, and that any interventions received during their physiotherapy sessions will be recorded for a descriptive analysis.

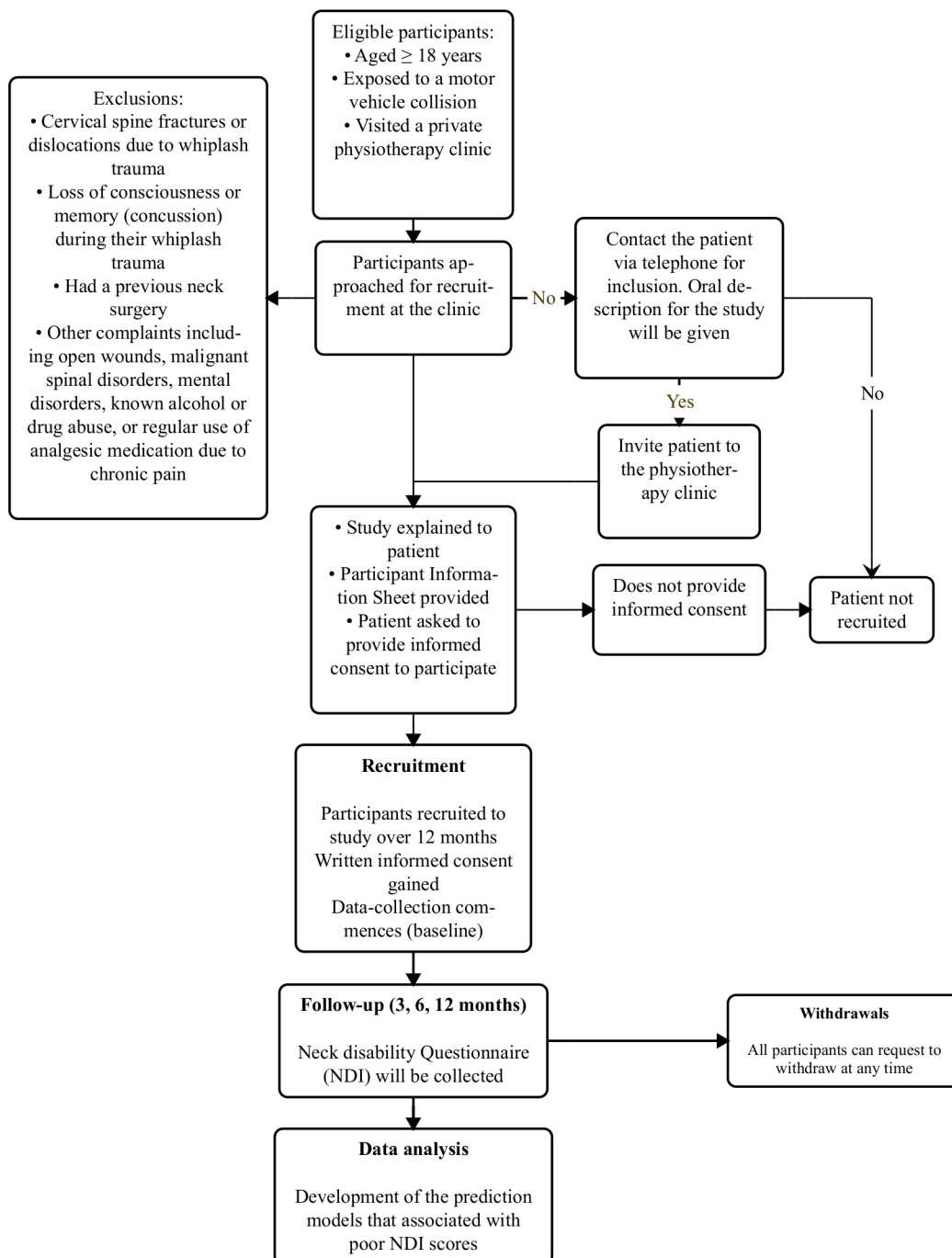


Figure 1 Participant flow through the study.

**Table 1** Summary of self-reported and physical measures that will be collected

Domain/candidate predictor	Data collection instrument	Baseline commencing ≤15 days post injury	3–12 months, clinical course; 6 months, outcome assessment point
General patient characteristics including previous musculoskeletal pain			
Gender at birth	Male/female	✓	
Education	Highest educational level attained	✓	
Psychosocial features			
Catastrophising	Pain Catastrophizing Scale	✓	
Kinesiophobia	Tampa Scale of Kinesiophobia	✓	
Recovery expectation	Numeric Rating scales (NRSs)	✓	
Injury characteristics			
Disability	Neck Disability Index	✓	✓
Pain characteristics			
Current neck pain intensity	NRSs	✓	
Neck pain intensity at the end of neck range of motion tasks	NRSs	✓	
Neck pain intensity at the end of maximum contraction tasks of craniocervical flexion, neck flexion and neck extension	NRSs	✓	
Neck pain intensity at the end of submaximum contraction tasks of craniocervical flexion, neck flexion and neck extension	NRSs	✓	
Physical measures			
Neck range of motion	G-Walk (flexion, extension, rotation and side flexion)	✓	
Neck angular velocity	G-Walk (flexion, extension, rotation and side flexion)	✓	
Smoothness of neck movement	G-Walk (flexion, extension, rotation and side flexion)	✓	
Neck proprioception	G-Walk (rotation with eyes closed)	✓	
Maximal and submaximal isometric contractions	Dynamometer–evaluation of craniocervical flexion, flexion, and extension maximum voluntary contraction and control of submaximal force	✓	
Coactivation of the sternocleidomastoid and splenius capitis	Surface electromyography during physical tests described above	✓	

Outcome

Outcome will be measured using the Neck Disability Index (NDI);⁶⁴ a neck-specific self-reported questionnaire used to assess neck pain-related disability. The NDI consists of 10 items of daily activities including personal care, lifting, reading, work, driving, sleeping and recreation.⁶⁴ Each item has five ordinal response options from 0 (no disability) to 5 (complete disability), producing a maximum total score of 50, which can be expressed as a percentage (0%–100%). The reliability of NDI and validity have been established in individuals with neck pain disorders.⁶⁵

Outcome will be assessed at 6 months for the prediction model.⁶⁶ Using 6 months as a cut-off for identifying outcome is supported by the finding that most individuals

recover within 3 months of the whiplash injury, with fewer recovering after this,^{11 67} and a plateau after 6 months.⁶⁸ To investigate the course of neck pain and disability, the NDI scores will additionally be collected at 3 and 6 months.

Candidate predictors

Due to the current lack of consensus on predictive factors of poor outcome, several self-reported and physical measures will be collected.⁹ Factors have been selected based on current knowledge of prognosis in whiplash^{2 7 9 11–13 24 31–34 69} and a theoretical association with prognosis in individuals with neck pain, as informed by the biopsychosocial model of pain.⁷⁰ These factors are also chosen due to being feasible to measure in clinical

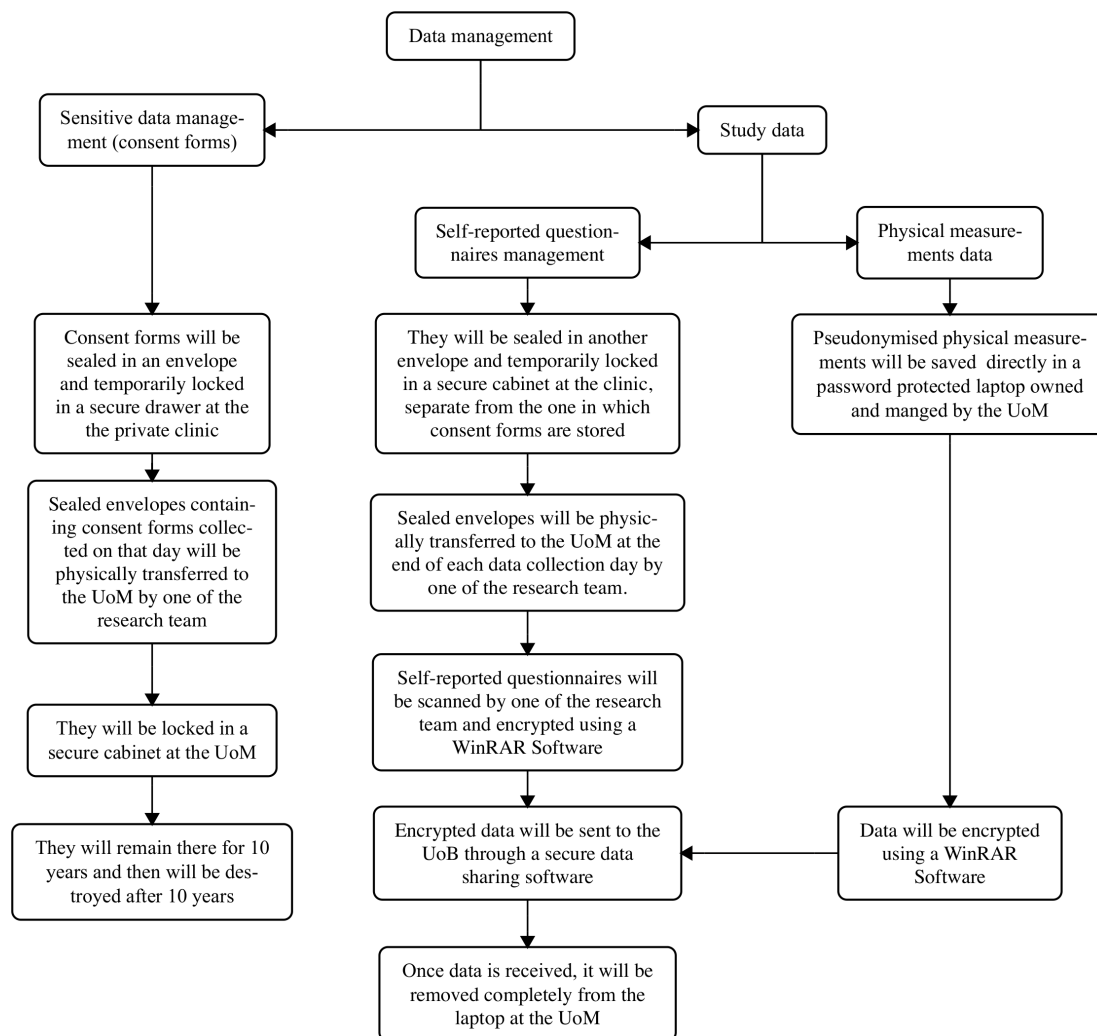


Figure 2 Process for data management. UoM, University of Malaga; UoB, University of Birmingham.

practice. Candidate predictors are summarised in [table 1](#) with further information available in the online supplemental file S1. All data collection will be standardised through protocols and clinical report forms

Data collection

Baseline and follow-up

Baseline data including self-reported questionnaires and physical assessments will be collected immediately following recruitment, at the physiotherapy clinic, by a trained assessor within 15 days of injury. Participants will be contacted by the same assessor by telephone at the University of Malaga (UoM) at 3, 6 and 12 months follow-up, in order to complete the NDI, as used previously.⁷¹

Data management

Participant data privacy will be maintained throughout data handling (collection transfer, storage and processing) and will comply with data protection requirements as set out by the General Data Protection Regulation of the European Union and UK Data Protection Act 2018 ([figure 2](#)). Participant data will be tracked using

only study ID numbers. Study ID numbers will be kept separate from study research data, which will be accessible only by members of the UoM research team.

Sensitive data management

Some participant data will be sensitive in nature; in particular consent forms which contain identifiable data, name, phone, contact address and study ID numbers. Once each participant has completed a consent form in the clinic, it will then be sealed in an envelope and temporarily locked in a secure drawer at the physiotherapy clinic, with access only available to members of the UoM research team. Once daily data collection has ended, all sealed envelopes containing consent forms collected on that day will be physically transferred to the UoM by one of the research team and locked in a secure filing cabinet there. Identifiable data will be securely stored at UoM for a period of 10 years, after which they will be destroyed. No identifiable data will be transferred outside of the UoM.

Self-reported questionnaires management

Self-reported paper questionnaires, identifiable only by study ID number for each participant, will be sealed in

another envelope and temporarily locked in a secure cabinet at the clinic, separate from the one in which consent forms are stored. Sealed envelopes containing the pseudonymised self-reported questionnaires will be physically transferred to the UoM at the end of each data collection day by one of the research team. Once transferred, self-reported questionnaires will be scanned by one of the research team and saved in a password protected laptop computer, owned and managed by UoM. Scanned self-reported electronic data will be encrypted using a WinRAR Software before transit to the University of Birmingham (UoB) (via Power Folder data sharing software, hosted locally at the University). Once received, this pseudonymised data will be uploaded directly to physically secure servers at the UoB, where they will remain indefinitely on secure UoB servers with access restricted to members of the study team. Once uploaded to UoB servers, data will be removed completely from the laptop at UoM. The same procedures will be followed for follow-up NDI data at 3, 6 and 12 months.

Physical data management

Pseudonymised physical data will be saved in a password protected laptop owned and managed by UoM, while at the clinic study session. Access to the UoM laptop is restricted and only available to the local research team. As with other data, pseudonymised electronic data will be encrypted using a WinRAR Software, transferred to the UoB team, and uploaded to the physically secure servers at UoB, where they will remain indefinitely with access restricted to study researchers. Again, once data have been received by the team at UoB, they will be removed from UoM computers.

Data analysis

Numbers of individuals will be recorded that are: potentially eligible, examined for eligibility, confirmed eligible, recruited into the study, completing follow-up and analysed. Loss to follow-up and withdrawals will be reported, with reasons where available. Descriptive analyses of participants at baseline will include participant demographics, self-reported questionnaires and physical assessment data.

Linear and logistic regression analysis

Linear regression analysis will be used as the primary analysis to develop a linear model to determine the association between candidate predictors and neck pain and disability (measured by NDI) at 6 months post injury. Linear regression analysis was included as a primary analysis to allow for the inclusion of the outcome (NDI) without dichotomisation. This approach follows the recommendations by PROGRESS series recommending of analysing continuous variables on their continuous scale,⁷² as well as to the fact that this approach method increases the statistical power and reduces information loss.

In addition to the linear regression analysis, logistic regression will be included as a secondary analysis to identify factors that are associated with poor outcomes. Outcome (NDI) scores will be dichotomised into good or poor categories with a NDI score of $\geq 30\%$ at 6 months post injury defined as poor outcome, as described previously.

Variable selection

Penalisation (shrinkage) approach will be used to avoid overfitting the final prognostic model, given the minimum number of events¹⁰ per variable will be adopted in this study to develop prognostic models.⁷³

First a full model will be constructed including all baseline candidate predictors (table 1) with their estimated adjusted regression coefficients calculated by standard methods. Next, a shrinkage method, a least absolute shrinkage and selection operator (LASSO) regression, will be used to effectively exclude candidate predictors from the final model by shrinking their coefficients to exactly zero.⁷⁴ Candidate predictors with zero coefficients will be excluded from the model, leaving the remaining candidate predictors with regression coefficients of more than zero. This approach is in line with the current recommendations for variable selection in prognostic models to address overfitting.⁷⁵ Moreover, this approach is preferred when a model with fewer predictors is desired without affecting the predictive ability of the model, making it more applicable in clinical practice.⁷³

Model performance

The predictive performance of the prognostic screening tool will be assessed using the established traditional measures of overall prognosis, discrimination and calibration.⁷⁶ Brier score will be used to quantify the overall performance of the screening tool where the score ranges from 0 ('perfect model') to 0.25 ('not informative model').⁷⁶ The receiver operator characteristic curve will be used to discriminate between those who did or did not develop chronic whiplash. Finally, the calibration will be assessed through plotting the mean predicted against observed chronic whiplash cases.

Sample size

This study will consider the association between 16 candidate predictors (table 1) and neck pain and disability at 6 months. The authors will ensure that at least ten participants per predictor will be used to develop an adequately powered linear regression analysis.^{77 78} Because the shrinkage method by LASSO method creates models with fewer predictors,⁷³ it is anticipated that the number of final predictors retained in the final linear model will fall below 12 predictors. Therefore, a sample size target of 120 participants is required to adequately powered a maximum of 12 candidate predictors into the multiple linear regression, with the addition of 30 participants to allow for possible loss of follow-up (total=150).

For the sample size of a logistic regression model derived following the LASSO shrinkage method, a minimum of

5 events per predictor is sufficient as established previously.⁷³ Based on the current knowledge about the transition rate from acute to chronic WAD, it is expected that 50% of patients will report persistent neck pain and disability.^{11 17 79} This leaves 60 out of our potential participants who might develop persistent neck pain and disability 6 months post WAD. Therefore, a sample size of 60 participants is adequate to power a logistic regression analysis of 12 candidate predictors with 5 events per predictor.

Management of missing data

For each variable of interest, numbers of participants with missing data will be reported. Any potential bias due to loss of follow-up will be assessed and compared using baseline data of subjects who withdraw or lost at follow-up.⁶⁶ Multiple imputation⁸⁰ will be used to deal with missing outcome data, if appropriate and necessary. Participants will be excluded from the predictive model and subsequent analyses if they request to withdraw from the study following recruitment.⁶⁶

Patients and public involvement

The research question in this study was developed following consultations with patients. Patients will not be involved in the analysis and data collection of study. The results of the study will be presented to members of the public and patients during one of our regular Patient and public involvement meetings.

Ethics and dissemination

The study will be conducted according to the Declaration of Helsinki. The project has been approved by the ethics committee of the province of Malaga, Spain, (#30052019). The results of the study will be disseminated via reports published in peer-reviewed journals and national and international conferences. No datasets will be created as part of this work for deposition or curation. Participant burden has been taken into consideration when developing this study. The number of measures has been kept to a minimum. To ensure the privacy of each patient, a unique ID number will be assigned to each participant at the time of recruitment. Only pseudonymised or anonymised data will be used during analyses. Participants will be informed that they can withdraw from the study at any time, without having to provide a reason; however, where a reason is given, it will be recorded. If a participant withdraws, no further data will be collected but data already collected will be retained for analyses. Baseline characteristics of any participants that withdraw will be compared with retained participants to assess for any differences.

At each data collection session, confirmation to proceed will be gained before any data are collected. Any concerns and/or adverse events will be noted and fed back to clinical staff, according to the good clinical practice principles. For ethical reasons, routine treatment will not be withheld from individuals at any point during the study. The details and frequency of any received treatment will

be recorded and reported. The protocol and conduct of this study are strengthened by the inclusion of patient and public involvement, who contributed to the development of study design and documentation. In addition, they will contribute to the processes of performing data analysis, interpretation of results and producing a lay summary of findings.

DISCUSSION

This is the first protocol to describe, a priori, the methods and analysis for identifying predictive factors for ongoing pain and disability following acute whiplash injury. In particular, self-reported measures together with novel physical measure will be incorporated including angular velocity, smoothness of movements, force steadiness and neck muscle coactivation to predict poor outcome in individuals with WAD recruited within 15 days of the injury. The selected candidate predictors are included based on current knowledge and the possible utilisation in clinical practice. The knowledge gained through this study can assist in the ID of personalised interventions to facilitate recovery and therefore minimise the transition to chronic whiplash.

SPIRIT 2013 statement, TRIPOD, PROGRESS, QUIPS and CHARMS statements and frameworks have informed design to ensure rigorous conduct of this study.^{54–58} The results from this study will provide new insights into who is likely to recover versus who is likely to develop persistent symptoms following a whiplash injury. Using a novel combination of outcome measures will allow the future development of a tool to predict development of chronic and disabling pain following a whiplash injury providing new opportunities to identify precision intervention.

Twitter David Evans @drdaviddevans and Deborah Falla @Deb_Falla

Contributors All authors contributed to the focus of this study. AA is a PhD student with DF as Lead Supervisor and AG as Co-Supervisor. AA drafted the initial protocol with guidance from DF and DE at all stages. AL-S and MF-S will be involved in collecting data from participants. All authors approved the final version for publication. DF is guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iDs

Ahmed Alalawi <http://orcid.org/0000-0001-5667-8150>

Deborah Falla <http://orcid.org/0000-0003-1689-6190>

REFERENCES

- Spitzer WO, Skovron ML, Salmi LR, et al. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. *Spine* 1995;20:1S-73.
- Li Q, Shen H, Li M. Magnetic resonance imaging signal changes of alar and transverse ligaments not correlated with whiplash-associated disorders: a meta-analysis of case-control studies. *Eur Spine J* 2013;22:14-20.
- Kongsted A, Sorensen JS, Andersen H, et al. Are early MRI findings correlated with long-lasting symptoms following whiplash injury? A prospective trial with 1-year follow-up. *Eur Spine J* 2008;17:996-1005.
- Ichihara D, Okada E, Chiba K, et al. Longitudinal magnetic resonance imaging study on whiplash injury patients: minimum 10-year follow-up. *J Orthop Sci* 2009;14:602-10.
- Holm LW, Carroll LJ, Cassidy JD, et al. The burden and determinants of neck pain in whiplash-associated disorders after traffic collisions: results of the bone and joint decade 2000-2010 Task force on neck pain and its associated disorders. *J Manipulative Physiol Ther* 2009;32:S61-9.
- Melody J. *Whiplash associated disorder training pack*. London: British Association for Accident and Emergency Medicine, 2003.
- Carroll LJ, Holm LW, Hogg-Johnson S, et al. Course and prognostic factors for neck pain in whiplash-associated disorders (WAD): results of the bone and joint decade 2000-2010 Task force on neck pain and its associated disorders. *Spine* 2008;33:S83-92.
- Jull GA, Söderlund A, Stemper BD, et al. Toward optimal early management after whiplash injury to lessen the rate of transition to chronicity: discussion paper 5. *Spine* 2011;36:S335-42.
- Sarrami P, Armstrong E, Naylor JM, et al. Factors predicting outcome in whiplash injury: a systematic meta-review of prognostic factors. *J Orthop Traumatol* 2017;18:9-16.
- Walton DM, Carroll LJ, Kasch H, et al. An overview of systematic reviews on prognostic factors in neck pain: results from the International collaboration on neck pain (ICON) project. *Open Orthop J* 2013;7:494-505.
- Kamper SJ, Rebeck TJ, Maher CG, et al. Course and prognostic factors of whiplash: a systematic review and meta-analysis. *Pain* 2008;138:617-29.
- Scholten-Peeters GGM, Verhagen AP, Bekkering GE, et al. Prognostic factors of whiplash-associated disorders: a systematic review of prospective cohort studies. *Pain* 2003;104:303-22.
- Côté P, Cassidy JD, Carroll L, et al. A systematic review of the prognosis of acute whiplash and a new conceptual framework to synthesize the literature. *Spine* 2001;26:E445-58.
- Walton DM, Macdermid JC, Giorgianni AA, et al. Risk factors for persistent problems following acute whiplash injury: update of a systematic review and meta-analysis. *J Orthop Sports Phys Ther* 2013;43:31-43.
- Atherton K, Wiles NJ, Lecky FE, et al. Predictors of persistent neck pain after whiplash injury. *Emerg Med J* 2006;23:195-201.
- Hartling L, Pickett W, Brison RJ. Derivation of a clinical decision rule for whiplash associated disorders among individuals involved in rear-end collisions. *Accid Anal Prev* 2002;34:531-9.
- Hendriks EJM, Scholten-Peeters GGM, van der Windt DAWM, et al. Prognostic factors for poor recovery in acute whiplash patients. *Pain* 2005;114:408-16.
- Radanov BP, Sturzenegger M, Di Stefano G. Long-term outcome after whiplash injury. A 2-year follow-up considering features of injury mechanism and somatic, radiologic, and psychosocial findings. *Medicine* 1995;74:281-97.
- Kasch H, Bach FW, Jensen TS. Handicap after acute whiplash injury: a 1-year prospective study of risk factors. *Neurology* 2001;56:1637-43.
- Kasch H, Qerama E, Kongsted A, et al. Clinical assessment of prognostic factors for long-term pain and handicap after whiplash injury: a 1-year prospective study. *Eur J Neurol* 2008;15:1222-30.
- Brijnath B, Bunzli S, Xia T, et al. General practitioners knowledge and management of whiplash associated disorders and post-traumatic stress disorder: implications for patient care. *BMC Fam Pract* 2016;17:82.
- Sterling M, Jull G, Vicenzino B, et al. Physical and psychological factors predict outcome following whiplash injury. *Pain* 2005;114:141-8.
- Sterling M, Jull G, Kenardy J. Physical and psychological factors maintain long-term predictive capacity post-whiplash injury. *Pain* 2006;122:102-8.
- Goldsmith R, Wright C, Bell SF, et al. Cold hyperalgesia as a prognostic factor in whiplash associated disorders: a systematic review. *Man Ther* 2012;17:402-10.
- Knackstedt H, Kråkenes J, Bansevicius D, et al. Magnetic resonance imaging of craniovertebral structures: clinical significance in cervicogenic headaches. *J Headache Pain* 2012;13:39-44.
- Vetti N, Kråkenes J, Damsgaard E, et al. Magnetic resonance imaging of the alar and transverse ligaments in acute whiplash-associated disorders 1 and 2: a cross-sectional controlled study. *Spine* 2011;36:E434-40.
- Dullerud R, Gjertsen O, Server A. Magnetic resonance imaging of ligaments and membranes in the craniocervical junction in whiplash-associated injury and in healthy control subjects. *Acta Radiol* 2010;51:207-12.
- Myran R, Kvistad KA, Nygaard OP, et al. Magnetic resonance imaging assessment of the alar ligaments in whiplash injuries: a case-control study. *Spine* 2008;33:2012-6.
- Krakenes J, Kaale BR. Magnetic resonance imaging assessment of craniovertebral ligaments and membranes after whiplash trauma. *Spine* 2006;31:2820-6.
- Richter M, Ferrari R, Otte D, et al. Correlation of clinical findings, collision parameters, and psychological factors in the outcome of whiplash associated disorders. *J Neurol Neurosurg Psychiatry* 2004;75:758-64.
- Spearing NM, Connelly LB, Gargett S, et al. Does injury compensation lead to worse health after whiplash? A systematic review. *Pain* 2012;153:1274-82.
- Williamson E, Williams M, Gates S, et al. A systematic literature review of psychological factors and the development of late whiplash syndrome. *Pain* 2008;135:20-30.
- Walton DM, Pretty J, MacDermid JC, et al. Risk factors for persistent problems following whiplash injury: results of a systematic review and meta-analysis. *J Orthop Sports Phys Ther* 2009;39:334-50.
- Williams M, Williamson E, Gates S, et al. A systematic literature review of physical prognostic factors for the development of late whiplash syndrome. *Spine* 2007;32:E764-80.
- Sterling M. Does knowledge of predictors of recovery and nonrecovery assist outcomes after whiplash injury? *Spine* 2011;36:S257-62.
- Sterling M, Jull G, Vicenzino B, et al. Development of motor system dysfunction following whiplash injury. *Pain* 2003;103:65-73.
- Dall'Alba PT, Sterling MM, Treleaven JM, et al. Cervical range of motion discriminates between asymptomatic persons and those with whiplash. *Spine* 2001;26:2090-4.
- Falla DL, Jull GA, Hodges PW. Patients with neck pain demonstrate reduced electromyographic activity of the deep cervical flexor muscles during performance of the craniocervical flexion test. *Spine* 2004;29:2108-14.
- Jull GA. Deep cervical flexor muscle dysfunction in whiplash. *J Musculoskelet Pain* 2000;8:143-54.
- Baydal-Bertomeu JM, Page AF, Belda-Lois JM, et al. Neck motion patterns in whiplash-associated disorders: quantifying variability and spontaneity of movement. *Clin Biomech* 2011;26:29-34.
- Sjölander P, Michaelson P, Jaric S, et al. Sensorimotor disturbances in chronic neck pain—range of motion, peak velocity, smoothness of movement, and repositioning acuity. *Man Ther* 2008;13:122-31.
- Fernández-de-las-Peñas C, Falla D, Arendt-Nielsen L, et al. Cervical muscle co-activation in isometric contractions is enhanced in chronic tension-type headache patients. *Cephalalgia* 2008;28:744-51.
- Falla D, Farina D, Dahl MK, et al. Muscle pain induces task-dependent changes in cervical agonist/antagonist activity. *J Appl Physiol* 2007;102:601-9.
- Madeleine P, Leclerc F, Arendt-Nielsen L, et al. Experimental muscle pain changes the spatial distribution of upper trapezius muscle activity during sustained contraction. *Clin Neurophysiol* 2006;117:2436-45.
- Madeleine P, Mathiassen SE, Arendt-Nielsen L. Changes in the degree of motor variability associated with experimental and chronic neck-shoulder pain during a standardised repetitive arm movement. *Exp Brain Res* 2008;185:689-98.
- Muceli S, Falla D, Farina D. Reorganization of muscle synergies during multidirectional reaching in the horizontal plane with experimental muscle pain. *J Neurophysiol* 2014;111:1615-30.
- Smith M, Coppieters MW, Hodges PW. Effect of experimentally induced low back pain on postural sway with breathing. *Exp Brain Res* 2005;166:109-17.
- Tucker KJ, Hodges PW. Changes in motor unit recruitment strategy during pain alters force direction. *Eur J Pain* 2010;14:932-8.

- 49 Hug F, Hodges PW, Tucker K. Task dependency of motor adaptations to an acute noxious stimulation. *J Neurophysiol* 2014;111:2298–306.
- 50 Gizzi L, Muceli S, Petzke F, et al. Experimental muscle pain impairs the synergistic modular control of neck muscles. *PLoS One* 2015;10:e0137844.
- 51 Walton D. A review of the definitions of 'recovery' used in prognostic studies on whiplash using an ICF framework. *Disabil Rehabil* 2009;31:943–57.
- 52 Gabel CP, Burkett B, Neller A, et al. Can long-term impairment in general practitioner whiplash patients be predicted using screening and patient-reported outcomes? *Int J Rehabil Res* 2008;31:79–80.
- 53 Holm LW, Carroll LJ, Cassidy JD, et al. Expectations for recovery important in the prognosis of whiplash injuries. *PLoS Med* 2008;5:e105–7.
- 54 Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
- 55 Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMC Med* 2015;13:1.
- 56 Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280–6.
- 57 Moons KGM, de Groot JAH, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the charms checklist. *PLoS Med* 2014;11:e1001744.
- 58 Steyerberg EW, Moons KGM, van der Windt DA, et al. Prognosis research strategy (progress) 3: prognostic model research. *PLoS Med* 2013;10:e1001381.
- 59 Sterling M. Differential development of sensory hypersensitivity and a measure of spinal cord hyperexcitability following whiplash injury. *Pain* 2010;150:501–6.
- 60 Cantu RC. Cerebral concussion in sport. *Sport Med* 1992;14:64–74.
- 61 Crawford JR, Khan RJK, Varley GW. Early management and outcome following soft tissue injuries of the neck—a randomised controlled trial. *Injury* 2004;35:891–5.
- 62 Rosenfeld M, Gunnarsson R, Borenstein P. Early intervention in whiplash-associated disorders: a comparison of two treatment protocols. *Spine* 2000;25:1782–7.
- 63 Rosenfeld M, Seferiadis A, Carlsson J, et al. Active intervention in patients with whiplash-associated disorders improves long-term prognosis: a randomized controlled clinical trial. *Spine* 2003;28:2491–8.
- 64 Vernon H, Mior S. The neck disability index: a study of reliability and validity. *J Manipulative Physiol Ther* 1991;14:409–15.
- 65 MacDermid JC, Walton DM, Avery S, et al. Measurement properties of the neck disability index: a systematic review. *J Orthop Sports Phys Ther* 2009;39:400–12.
- 66 Rushton A, Evans D, Middlebrook N. Development of a prognostic screening tool to predict the risk of chronic pain and disability following musculoskeletal trauma: protocol for a prospective observational study. *Orthopaedic Proceedings*, The British Editorial Society of Bone & Joint Surgery, 2018.
- 67 Carroll LJ, Hogg-Johnson S, van der Velde G, et al. Course and prognostic factors for neck pain in the general population: results of the bone and joint decade 2000–2010 Task force on neck pain and its associated disorders. *J Manipulative Physiol Ther* 2009;32:S87–96.
- 68 Sterling M, Hendrikz J, Kenardy J. Compensation claim lodgement and health outcome developmental trajectories following whiplash injury: a prospective study. *Pain* 2010;150:22–8.
- 69 Daenen L, Nijs J, Raadsen B, et al. Cervical motor dysfunction and its predictive value for long-term recovery in patients with acute whiplash-associated disorders: a systematic review. *J Rehabil Med* 2013;45:113–22.
- 70 Pincus T, Kent P, Bronfort G, et al. Twenty-five years with the biopsychosocial model of low back pain—is it time to celebrate? A report from the twelfth international forum for primary care research on low back pain. *Spine* 2013;38:2118–23.
- 71 Kivioja J, Jensen I, Lindgren U. Neither the WAD-classification nor the Quebec Task force follow-up regimen seems to be important for the outcome after a whiplash injury. A prospective study on 186 consecutive patients. *Eur Spine J* 2008;17:930–5.
- 72 Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis research strategy (progress) 2: prognostic factor research. *PLoS Med* 2013;10:e1001380.
- 73 Pavlou M, Ambler G, Seaman SR, et al. How to develop a more accurate risk prediction model when there are few events. *BMJ* 2015;351:h3868.
- 74 Tibshirani R. Regression shrinkage and selection via the LASSO. *J R Stats Soc B* 1996;58:267–88.
- 75 Riley RD, van der Windt D, Croft P, et al. *Prognosis research in healthcare: concepts, methods, and impact*. Oxford University Press, 2019.
- 76 Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;21:128.
- 77 Royston P, Moons KGM, Altman DG, et al. Prognosis and prognostic research: developing a prognostic model. *BMJ* 2009;338:b604.
- 78 Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007;165:710–8.
- 79 Carroll LJ, Holm LW, Hogg-Johnson S, et al. Course and prognostic factors for neck pain in whiplash-associated disorders (WAD): results of the bone and joint decade 2000–2010 Task force on neck pain and its associated disorders. *J Manipulative Physiol Ther* 2009;32:S97–107.
- 80 Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.