



# BMJ Open Are physical factors associated with poor prognosis following a whiplash trauma?: a protocol for a systematic review and data synthesis

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## ABSTRACT

**Introduction** Mitigating the transition from acute to chronic whiplash-associated disorders (WAD) is fundamental, and this could be achieved through early identification of individuals at risk. Several physical factors such as angular velocity, smoothness of neck movement and coactivation of neck flexors and extensors, have been observed in patients with WAD, but their predictive ability after a whiplash injury have not been considered in previous reviews. Therefore, the aim of the current protocol is to outline the protocol for a systematic review that synthesises the current evidence of which physical factors can predict ongoing pain and disability following a whiplash trauma.

**Methods and analysis** Two independent reviewers will search for studies in several electronic databases including MEDLINE, Embase, CINAHL, PsycINFO, Scopus and Web of Science as well as grey literature. Observational cohort studies will be considered if they involve participants with acute WAD followed for at least 3 months post-injury. Studies will be required to assess the prognostic ability of one or more physical factors that directly involve a body function and/or structure and can be measured objectively. Further, patient-reported outcomes of physical function will be considered. The primary outcome for this review is Neck Disability Index, while all other validated measures will be considered as secondary outcomes. Risk of bias across individual studies will be assessed using the Quality In Prognostic Studies tool along with the Grades of Recommendation, Assessment, Development and Evaluation method to assess the quality of evidence. A meta-analysis will be conducted depending on homogeneity and the number of available studies. If appropriate, data will be pooled and presented as odds ratios, otherwise, a qualitative synthesis will be conducted.

**Ethics and dissemination** Ethical approval is not required for this systematic review. The result from this review will be published in peer-reviewed journals.

**PROSPERO registration number** CRD42019122559

## INTRODUCTION

Whiplash is a term used to describe an injury mechanism associated with a sudden forward and backward movement of the head that is usually due to car collision.<sup>1</sup> This sudden impact may result in injuries to multiple

## Strengths and limitations of this study

- This systematic review will be the first to rigorously summarise and evaluate the current body of evidence regarding the predictive ability of physical factors following a whiplash trauma, using a combination of clinical and patient-reported outcome measures.
- Several methodological limitations across included studies are anticipated such as substantial heterogeneity, high risk of bias, variabilities in whiplash severity and source of participants, which may lead to potential difficulty in interpreting and applying the results.
- This review will consider studies reported in English language only and therefore may miss studies published in other languages.

structures in the neck,<sup>1</sup> which lead to the development of a wide range of clinical manifestations commonly termed as whiplash-associated disorder (WAD).<sup>1</sup> WAD has a substantial socioeconomic burden,<sup>2</sup> with costs to the UK economy ~£3 billion per year.<sup>3</sup> It is a source of disability<sup>4,5</sup> with common negative consequences including limited work ability, fatigue, restricted participation in sports, depression, frustration and anger.<sup>6,7</sup>

The rate of transition from acute to chronic WAD is high. It has been found that 50% of patients with acute WAD develop chronic WAD,<sup>5,8,9</sup> a condition that tends to be resistant to treatment with limited evidence of effective interventions.<sup>10,11</sup> Additionally, there is a large variability between individuals in how they respond to a specific intervention.<sup>12</sup> For example, only up to 44% of patients with chronic WAD reported a significant reduction in pain following a 12-week programme of specific neck exercise.<sup>12</sup> Due to this general lack of responsiveness to interventions, mitigating the transition to chronic WAD, in the first place, is fundamental. This could be achieved through early identification

of physical factors that increase the risk of developing persistent symptoms, among whom, a better allocation of treatments could be prescribed.<sup>13</sup>

Many syntheses have been conducted in the field of WAD prognosis aiming to identify factors that are associated with the outcomes following a whiplash trauma. To this end, 12 systematic reviews focused on prognosis following a whiplash injury were found,<sup>5 8 14–23</sup> and covered a myriad factors including social, psychological and physical factors. A review of these reviews found that an initial high level of neck pain and disability following a whiplash injury is associated with poor outcome.<sup>24 25</sup> However, there is still inconsistency in the reported evidence concerning the predictive ability of other factors including post-injury anxiety, catastrophizing, cold hyperalgesia, legal and compensation factors, WAD grading and early healthcare use.<sup>24</sup> Additionally, there is inconsistency in the results among systematic reviews regarding the predictive ability of physical factors (eg, restricted cervical range of motion (ROM)).

Qualitative synthesis from systematic reviews showed limited evidence about the association between restricted cervical ROM and persistent disability,<sup>16 21 22</sup> whereas no such association was found in another review.<sup>8</sup> This was also shown in a meta-analysis of six cohorts investigating the prognostic ability of restricted ROM on persistent neck pain and disability.<sup>19</sup> Due to this controversy and to the fact that it has been 6 years since the last systematic review on physical factors,<sup>16</sup> a systematic review is needed.

Several other physical factors have been observed to be impaired in patients with WAD, yet they have not considered in current reviews. These include changes in motor function and muscle behaviour such as decreased maximum angular velocity,<sup>26 27</sup> larger jerk index (a measure of the smoothness of neck movement)<sup>27</sup> and increased coactivation of neck flexors and extensors.<sup>28</sup> The presence of these adaptations was also observed in experimental pain studies,<sup>29–36</sup> where patients injected with a hypersaline solution inducing an immediate pain similar to a traumatic event. Besides, patient-reported outcome measures to assess physical function could be useful in predicting outcomes following a whiplash trauma.

Physical functioning was recommended by an international multidisciplinary panel as one of the core domains to be reported in clinical studies involving patients with WAD,<sup>37</sup> and low back pain.<sup>38–40</sup> ‘Physical function is a broad domain that can encompass various aspects of a person’s life including ability to carry out daily activities, eg, household tasks, recreational activities or self-care to specific strength, endurance and functional capacity’.<sup>37</sup> Yet, there is no consensus on the measurement instruments of physical functioning in the field on whiplash. Recommendations on selecting measurement interments to measure physical functioning were formulated in individuals with low back pain,<sup>40</sup> including Oswestry Disability Index V.2.1a and 24-item Roland-Morris Disability Questionnaire.

Therefore, the aim of this systematic review is twofold: (1) To inform and summarise the objective physical measures that have been used to date in prognostic research in this population and (2) To synthesise the evidence regarding the predictive ability of these physical factors on neck pain and disability in individuals following a whiplash trauma.

## METHODS AND ANALYSIS

### Registration and methodology

This is a protocol for conducting a systematic review aiming to identify whether physical factors are associated with ongoing pain and disability following a whiplash trauma. The protocol was planned according to the guidelines proposed by Moons *et al* for conducting prognostic reviews,<sup>41</sup> and reported according to the guidelines from Preferred reporting items for systematic review and meta-analysis protocols,<sup>42</sup> the Cochrane Handbook<sup>43</sup> and the Cochrane Back Review Group guidelines.<sup>44</sup>

### Protocol registration

The protocol of this review was registered on PROSPERO (International Prospective Register of Systematic Reviews).

## ELIGIBILITY CRITERIA

### Inclusion criteria

#### Studies

Observational studies will be included if they describe the association between physical factors and prognosis in individuals who have sustained a whiplash injury and who have been followed up over time for a minimum of 3 months. Other study designs such as case reports or case-control studies will be excluded from this review, as well as any review articles, letters, editorials, conference proceedings and studies with only abstracts. Only articles published in English will be considered.

#### Participants

Studies will be included if they involve populations with the characteristics below:

1. Participants with acute WAD (<6 weeks) attributed to a motor traffic collision or sports injury and classified as grade I, II or III on Quebec Task Force (QTF) classification.<sup>1</sup> If the cause of acute WAD was not specified, the paper will be considered as well.
2. Participants were followed up over time for at least 3 months. Studies with different time-points beyond 3 months will be considered.
3. Aged >16 years old

#### Exposure or intervention (potential prognostic factors)

Studies will be required to assess the prognostic ability of one or more physical factors measured at baseline regardless of the measurement used. Because there is no consensus on the definition of physical factors specifically

in the field of WAD, physical factors will be selected, for the purpose of this review, if they directly involve a body function and/or structure and can be measured objectively. These include neck self-reported measures of physical functioning (eg, patient specific functional scale, physical component of the SF-36), joint position sense, movement sense, proprioception, onset and amplitude of muscle activation, range of neck movement, quality of neck movement, velocity of neck movement, tests of eye movement control, neck muscle strength and endurance, neck muscle fatigue, balance and the morphology of the cervical spine muscles. Any spinal structural changes or findings in X-ray will not be considered in this review.

## Outcome

The primary outcome of interest is the Neck disability Index<sup>45</sup> measured at least at 3 months follow-up. All other validated outcomes that were used in primary studies to describe the association between physical factors and an outcome will be included in the review and considered as secondary outcomes of interest such as pain intensity, psychological status, health-related quality of life, self-rated recovery and functional recovery.

## Exclusion criteria

Other study designs such as case reports or case-control studies will be excluded from this review, as well as any review articles, letters, editorials, conference proceedings and studies with only abstracts. Only articles published in English will be considered. Also, studies will be excluded if they include patients with previous cervical pain, surgery or combine subjects with WAD and other musculoskeletal injuries.

## Search strategy

Several databases will be searched from 1995 to August 2019 including MEDLINE (OVID), Embase (OVID), Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO (OVID), Scopus and Web of Science as well as grey literature through Zetoc database which includes any document that usually not published commercially as a peer-reviewed article.<sup>46</sup> The identified key words in box 1 will be used to search for relevant studies including unpublished articles. We limit our search to 1995 as the standardised definition of WAD was provided by the QTF monograph, an approach used previously in a systematic reviews.<sup>14 19</sup> Notable authors in the field will be contacted to identify relevant unpublished literature which is currently in preparation. Moreover, reference lists of retrieved individual studies will be screened for relevant studies as well as any relevant published reviews on prognosis in WAD to ensure all related studies have been identified. The searching process will be limited to the English language.

A combination of free text and Medical Subject Heading (MeSH) will be used to retrieve all related studies. The related search terms related to WAD, whiplash trauma and physical prognostic factors have been informed from

## Box 1 Example of searching strategy for MEDLINE (OVID) electronic database

### Search terms

1. Whiplash Injuries/pa, pp, rh, th [Pathology, Physiopathology, Rehabilitation, Therapy]
2. Whiplash Injur\*.mp.
3. (Whiplash or WAD).mp.
4. (Motor adj accident\*).mp.
5. (Motor adj crash\*).mp.
6. Neck Injuries/pa, pp, rh, th [Pathology, Physiopathology, Rehabilitation, Therapy]
7. (Neck adj2 injurie\*).mp.
8. (Neck adj2 Sprain\*).mp.
9. (Neck adj2 strain\*).mp.
10. OR/ 1-9
11. "cervical dysfunction\*".mp.
12. (Neck adj2 dysfunction\*).mp.
13. ('Joint adj2 sense').mp.
14. joint position error'.mp.
15. sensorimotor control.mp
16. motor control.mp.
17. motor system dysfunction.mp.
18. sensorimotor dysfunction\$.mp.
19. (neck adj3 sense).mp.
20. Proprioception/ or neck sense.mp.
21. neuromuscular control.mp.
22. Muscle\* activation\*.mp.
23. Co?activation\*.mp.
24. movement\* quality.mp.
25. (quality adj movement).mp.
26. (Neck adj2 motion).mp.
27. angular velocity.mp. or Rotation/
28. Eye Movements/ or Pursuit, Smooth/ or 'movement smooth\*.mp. or Motion Perception/
29. ('neck adj3 strength').mp.
30. ('neck adj3 endurance').mp.
31. ('Deep adj3 muscle\*).mp.
32. ('superficial adj3 muscle\*).mp.
33. onset of activation\$.mp.
34. Somatosensory Disorders/et, pp, rh [Etiology, Physiopathology, Rehabilitation]
35. ('Smooth adj3 movement').mp.
36. ('Alter\* adj3 strategy\*).mp.
37. Isometric Contraction/ or Co?contraction\*.mp.
38. Fatigue/ or Muscle Fatigue/ or Muscle\* fatigue.mp.
39. Muscle, Skeletal/ or Adaptation, Physiological/ or Peripheral adaptation.mp.
40. Fatty infiltration\*.mp. or Magnetic Resonance Imaging/
41. physical measure\*
42. Self adj3 measure\*
43. Patient\* adj3 measure\*
44. Physical adj function\*
45. Patient\* adj2 outcome\*
46. Muscular Atrophy/ or Immobilization/ or Muscle\* disuse.mp.
47. Balance.mp. or POSTURAL BALANCE/
48. Atrophy.mp. or ATROPHY/
49. OR/ 11-48
50. Validat\$.mp. or Predict\$.ti. or Rule\$.mp. or (Predict\$ and (Outcome\$ or Risk\$ or Model\$)).mp. or ((History or Variable\$ or Criteria or Scor\$ or Characteristic\$ or Finding\$ or Factor\$) and

Continued



## Box 1 Continued

- (Predict\$ or Model\$ or Decision\$ or Identif\$ or Prognos\$).mp. or (Decision\$.mp. and ((Model\$ or Clinical\$).mp. or Logistic Models/)) or (Prognostic and (History or Variable\$ or Criteria or Scor\$ or Characteristic\$ or Finding\$ or Factor\$ or Model\$)).mp.
51. (Predict\* or Predictive value of tests or Scor\* or Observ\* or Observer variation).mp.
  52. ('Stratification' or 'ROC Curve' or 'Discrimination' or 'Discriminate' or 'c-statistic' or 'c statistic' or 'Area under the curve' or 'AUC' or 'Calibration' or 'Indices' or 'Algorithm' or 'Multivariable').mp.
  53. Risk Factors/ or Predict\$ factor\$.mp.
  54. Predict\$ variable\$.mp.
  55. Prognos\$ factor\$.mp.
  56. Prognos\$ variable\$.mp.
  57. (Candidate adj3 factor\*).mp.
  58. Candidate predictor\*.mp.
  59. Prognosis/ or Progn\*.mp.
  60. Predic\*.mp.
  61. OR/ 50-60
  62. 10 AND 49 AND 61

previously published reviews in prognosis following WAD trauma,<sup>8 14-16 18 19 24</sup> and from our scoping searches. To increase the sensitivity of retrieving all related prognosis studies, the proposed prognosis filters that identified by Geersing *et al.*<sup>47</sup> will be utilised in addition to other filters identified previously.<sup>48 49</sup> The use of relevant phrases and MeSH terms are expected to be varied between databases. A total number of hits in each database and the excluded papers with the reasons will be reported in the main review. The search will be conducted by the lead author (AA) and has been informed by subject specific expertise and the completion of scoping searches. An example search in MEDLINE (OVID) is demonstrated in [box 1](#).

### Data management

Relevant citations and abstracts will be managed using EndNote V.X9 (Clarivate Analytics) software programme during the process of storing, removing duplicates and screening processes. Relevant forms will be developed to aid the screening process. A Microsoft Excel spreadsheet will be used to store all the extracted data.

### Study selection

Once duplicates have been removed, two reviewers will independently conduct searches and screen titles and abstracts of the studies against the predetermined eligibility criteria to avoid missing related studies. Full text of the studies will be retrieved if eligibility were met or in case a conclusion could not be possible to be made based on the title or abstract. In the case where multiple papers were published from the same cohort that investigated the same predictor, the original cohort will be selected and then extracted for this review, an approach was used previously in published systematic reviews.<sup>14 19 22</sup> The same two reviewers will screen full texts eligibility and review relevant references lists. A third reviewer (DF)

will be consulted to resolve any agreement by discussion if consensus could not be reached.

### Data collection process

Data will be extracted using a modified data extraction form. The form will be reviewed and finalised through a pilot test of a small number of eligible studies during the process of data extraction. Both reviewers will extract the data independently, who will then meet to check the accuracy of the extracted data. A third reviewer (DF) will mediate any disagreement in data extraction.

### Data items

The data extraction items were informed by the CChecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies.<sup>41</sup> Although this tool was designed for reviews of primary prediction modelling studies, some domains have been selected to inform selecting data items of this review. The following data will be extracted from each study: authors and year of publication, study location, study design, participants characteristics, outcomes of interest, candidate predictors, sample size, length of follow-up, items associated with risk of bias, summary statistics and methods for statistical analysis. The corresponding author of the original studies will be contacted for clarification and missing data if required. If no response is received from a corresponding author and the inquiry affects the eligibility of the study, it will be excluded from this review.

### Risk of bias

To evaluate the risk of bias of included individual studies, the Quality In Prognostic Studies tool<sup>50</sup> will be used. The tool was designed to assess bias in review questions related to prognostic factors<sup>51</sup> and showed acceptable inter-rater reliability.<sup>50</sup> It considers six domains when assessing bias in prognostic studies; study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement and analysis and reporting.<sup>51</sup> Each risk of bias domain is rated as a 'high', 'moderate' or 'low' based on consensus judgement from at least two assessors.<sup>50</sup> To assess the overall risk of bias of individual study, a study gets overall of low risk of bias, when all six domains rated as a low risk, while study judged as having a high risk a bias if  $\geq 1$  domain assessed as a high risk of bias. Two reviewers will assess the risk of bias independently. Any disagreement will be resolved by discussion or by a third reviewer (DF) if consensus could not be reached.

### Quality of evidence

The overall quality of evidence for a prognostic factor per outcome across studies will be assessed using The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.<sup>52</sup> The GRADE approach criteria was modified to be used in prognostic factor research.<sup>53 54</sup> The adapted GRADE for prognostic factors research includes six factors that decrease the quality of evidence including 'phase of investigation', 'study limitations', 'inconsistency', 'indirectness, imprecision', 'publication bias', while two

factors increase the quality 'moderate or large effect size', 'exposure-response gradient'.<sup>53</sup> The *phase of investigation* GRADE domain is a district for prognostic studies phase 3 and phase 2 considered the highest quality of evidence.<sup>53</sup> The GRADE system will be applied to assess the overall quality of evidence of confirmed prognostic factors generated from univariate results, as used previously.<sup>55</sup>

### Data synthesis and analysis

A quantitative synthesis will be planned depending on homogeneity between included studies. If meta-analysis is not possible, a qualitative synthesis of the results will be conducted.

### Summary statistics

When outcomes are binary, they expected to be presented as OR in primary studies calculated by the logistic regression model.<sup>56</sup> Therefore, pooled ORs will be used to calculate the effect estimate of a prognostic ability of predictors on an outcome of interest. Since it is expected that primary studies have used different effect estimators to calculate the prognostic ability of a factor on an outcome, some statistical conversions may be required. For example, if OR and risk ratio (RR) were not provided, they could be estimated manually based on the number of events among two comparative groups.<sup>57</sup> In case where potential predictors or outcome are continuous variables, the mean difference or adjusted mean difference will be used to represent a summary effect.<sup>57</sup> If needed, the mean difference may be converted into standardised mean difference when combined.<sup>58</sup> If estimation from available data is unfeasible, authors will be contacted to provide data. If no response is received, the study will be excluded from the meta-analysis. All statistical conversions will be reported in the main manuscript.

### Data synthesis

The results will be pooled if an association between an outcome and specific prognostic factor was presented by the same summary statistics in two or more cases. OR or RR will be summarised separately if the outcome is binary whereas continuous outcome will be combined using mean difference or standardised mean difference. When continuous variables are presented using the median instead of the mean, they will not be combined and handled as it is.<sup>57</sup>

Because this review includes studies with univariate and multivariate analysis, it is expected that some studies will report univariate analysis and others with multivariate analysis. In this case, only the unadjusted estimates of prognostic factors will be pooled. This is because of the confounding effect of factors within a multivariate model which could give misleading results; therefore, effect estimates from multivariate models will be summarised qualitatively.

### Meta-analysis

If meta-analysis is feasible, the random-effect model (DerSimonian and Laird method) will be conducted,<sup>58</sup> utilising the Statistical Software Package, Review Manager V.5.3.<sup>59</sup>

A significant univariate association between a factor and outcome will be considered present if the reported p value is <0.05 or 95% of CIs of OR or similar statistical methods do not get below one.<sup>8</sup> If combined results are presented, the 95% prediction interval will be calculated.<sup>60</sup>

### Heterogeneity

Heterogeneity of the pooled estimate will be assessed using Q statistic and the I<sup>2</sup> test. Statistical heterogeneity will be considered significant between studies if p<0.1, as this test has low power.<sup>61</sup> Beside the Q statistic and to measure the magnitude of heterogeneity, the I<sup>2</sup> test will be used which gives a score range from 0% to 100%, where scores from (0% to 30%), (30% to 50%), (50% to 70%) and (70% to 100%) indicates low, moderate, considerable and substantial heterogeneity, respectively.<sup>58</sup> In the case of low heterogeneity, the fixed-effect model will be used as it gives weight better than the random-effect model, otherwise, the random effect model will be used.<sup>62</sup> However, both tests may be affected by the number of included studies which could not detect heterogeneity in some cases. Because of this, heterogeneity will also be investigated using forest plots to see if the estimated effect overlaps with all CIs across studies. If heterogeneity is present, further exploration will be performed including subgroup analysis and sensitivity analysis.

### Subgroup analysis

Subgroup analysis is planned to clarify the source of heterogeneity if present between studies. High heterogeneity among studies is more likely to be present. A priori potential sources of heterogeneity could arise from WAD grade, study design, source of participants, follow-up time.

### Sensitivity analysis

Sensitivity analysis will be performed to examine the robustness of the results by including studies with only high-quality.

### Reporting bias

A funnel plot will be used to examine publication bias within studies. Also, Egger's test will be used statistically to examine publication bias,<sup>63</sup> with statistical power set at p<0.1 due to the low power of this test, which shows evidence of publication bias. If it is suspected, the trim and fill method will be applied.<sup>64</sup>

### Confirmation of prognostic factors

The overall decision of judging whether a factor is prognostic will be based on two criteria, an approach used previously.<sup>55</sup> First, the same factor must show statistical univariate association with an outcome in at least 75% of all included studies. Second, the effect of prognostic factors is consistently in the same direction of effect across all studies. Further, if a multivariate analysis about the prognostic ability of a factor is available, it will be used to confirm such association. These criteria would allow a quantitative and robust methodology which allows replicable results.

## 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 the systematic review.

## Ethics and dissemination

No ethical approval is required for this systematic review, as there is no patient data being collected. The result of this review will be published in peer-reviewed journals and presented in national and international conferences.

## Implication of results

The results obtained from this review will have implications for understanding the recovery after whiplash trauma. In particular, information on physical factors following whiplash injury will be synthesised and their predictive ability will be demonstrated, if present. This will inform future research agenda on the predictive ability of physical factors in patients with acute whiplash. Particularly, future studies could be designed to create and test screening tools to categorise patients with acute WAD into low risk and high risk of developing persistent symptoms, which will inform early intervention and management. Additionally, intervention resources could be targeted towards those with the risk of poor outcomes which could mitigate their risk of developing ongoing symptoms, informing health policy and clinical management. Although this systematic review focuses on physical measures only, the findings will be discussed with consideration of the current knowledge on which psychosocial factors can predict ongoing pain and disability following whiplash trauma.

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**Contributors** All authors contributed to the focus of the systematic review topic. AA is a PhD student with DF as Lead Supervisor and AG as Co-Supervisor. AA drafted the initial protocol with guidance from DF at all stages. MS and AG provided feedback on manuscript drafts and all authors approved the final version for publication. DF is guarantor.

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