

4-26-2023

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### NSUWorks Citation

Callan, Bradford; Walton, David M.; Cleland, Joshua; Kolber, Morey J.; and Elliott, James M., "Exploring sex as a moderator of other prognostic variables in whiplash associated disorder: An observational study." (2023). *HPD Articles*. 418.  
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RESEARCH ARTICLE

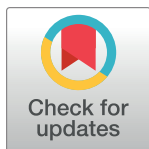
# Exploring sex as a moderator of other prognostic variables in whiplash associated disorder: An observational study

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**Citation:** Callan B, Walton DM, Cleland J, Kolber MJ, Elliott JM (2023) Exploring sex as a moderator of other prognostic variables in whiplash associated disorder: An observational study. PLoS ONE 18(4): e0282640. <https://doi.org/10.1371/journal.pone.0282640>

**Editor:** Juan Antonio Valera-Calero, Complutense University of Madrid: Universidad Complutense de Madrid, SPAIN

**Received:** September 1, 2022

**Accepted:** February 14, 2023

**Published:** April 26, 2023

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**Data Availability Statement:** Data cannot be shared publicly because of data security and ownership under the current approved protocol. Data are available from Prof. J. Elliott ([jim.elliott@sydney.edu.au](mailto:jim.elliott@sydney.edu.au)) for researchers who meet the criteria for access to confidential data. Data are available from the Northwestern University Institutional Review Board ([irb@northwestern.edu](mailto:irb@northwestern.edu)) for researchers who meet the criteria for access to confidential data.

## Abstract

### Background

Prognostic variables for assessing people with whiplash associated disorder (WAD) following a motor vehicle collision (MVC) have been evaluated in numerous studies. However, there is minimal evidence assessing how these variables may differ between males and females.

### Question/Purpose

1) To assess if the sex of a person interacts with known prognostic variables within the development of chronic WAD. 2) To determine if commonly used outcome measures used in the assessment of chronic WAD differ between sexes.

### Methods

The study was a secondary analysis of an observational study with an inception cohort immediately following an MVC in an emergency department in Chicago, IL, USA. Ninety-seven adults aged 18 to 60 (mean 34.7 years old; 74% female) participated in the study. The primary outcome was long-term disability as determined by Neck Disability Index (NDI) scores at 52-weeks post-MVC. Data was collected at baseline (less than 1-week), 2, 12, 52-weeks post MVC. Hierarchical linear regression was used to determine significance ( $\Delta F$ -score,  $p < 0.05$ ) and  $R^2$  for each of the variables. The primary variables of interest were sex of the participant, age, baseline scores on the numeric pain rating scale (NPRS) and NDI and created interaction terms for sex x z-baseline NPRS and sex x z-NDI.

**Funding:** Data supplied originated from a parent study, Neuromuscular Mechanisms Underlying Underlying Poor Recovery from Whiplash Injuries NIH R01 HD079076. ClinicalTrials.gov Identifier: NCT02157038. No funding was obtained specifically for the analyses here.

**Competing interests:** The authors have declared no competing interests exist.

## Results

From analysis 1, both NDI ( $R^2 = 8.7\%$ ,  $p < 0.01$ ) and NPRS ( $R^2 = 5.7\%$ ,  $p = 0.02$ ) collected at baseline predicted significant variance in NDI score at 52-weeks. The interaction term of sex  $\times$  z-NPRS was also significant ( $R^2 = 3.8\%$ ,  $p = 0.04$ ). In analysis 2 the regression models when disaggregated by sex showed that baseline NDI was the significant predictor of 52-week outcome in males ( $R^2 = 22.4\%$ ,  $p = 0.02$ ) while it was the NPRS as the significant predictor in females ( $R^2 = 10.5\%$ ,  $p < 0.01$ ).

## Introduction

Non-catastrophic motor vehicle collisions (MVC) (those that do not result in fractures, loss of limbs, or death) are common in the United States with over 6 million reported each year [1]. It is estimated over one-million people will present immediately to the emergency department (ED), or to their physician for sustained injuries, with the most common being ‘whiplash-associated disorder’ (WAD) [1, 2]. Signs and symptoms of WAD include, but are not limited to: neck or widespread pain, weakness, psychological distress, tinnitus, headache, swallowing deficits, balance, and oculomotor deficits [3]. Longitudinal modeling studies indicate that about 50% of those with WAD will fully recover in the first 6 to 12-weeks, while the remaining 50% will continue to report persistent symptoms in the long-term [3, 4]. There remains no gold standard diagnostic test for WAD. Rather, it is generally diagnosed by the presence of neck pain, stiffness, or tenderness only (no physical signs—Quebec Task Force (QTF) grade I); neck pain and stiffness (QTF grade II); neck pain and peripheral neurological signs (QTF grade III); and neck pain and fracture or dislocation (QTF grade IV) following an MVC or other mechanical event (e.g., sports injury, slips, and falls) through which energy is rapidly transmitted between the trunk and head through the neck [5].

Recovery from WAD is usually recorded using patient self-reported outcome measures (PROMs). Two of the most common PROMs are the Neck Disability Index (NDI) [6] and the 0–10 Numeric Pain Rating Scale (NPRS) [4]. The NDI is a 10-item scale intended to capture self-ratings of disability associated with neck pain [6]. It is one of the most widely used neck-specific disability scales, with a recognizable scoring system that is commonly reported between 0% (no disability) and 100% (complete disability) [7]. The NPRS is a single-item tool that is used to estimate the intensity of pain a person is experiencing and is amongst the most ubiquitous PROMs used globally [8]. Two prior latent growth curve analyses have found that PROM-based recovery from acute WAD can be defined through a 3-trajectory model: a rapid/full recovery group, a delayed recovery/mild disability group, and a non-recovery/severe disability group [3, 9] with proportions roughly matching the 50% recovered and 50% not recovered estimates. Subsequently, in the interest of identifying more homogenous subgroups and more informed early management decisions to prevent persistent problems, considerable prognostic work has been conducted to help clinicians and researchers better estimate the most likely recovery outcomes of people with acute WAD. Through this body of work, baseline (acute) pain severity (NPRS) and disability scores (NDI) have been consistently endorsed as strong predictors of 12-month outcomes [4].

To date, the majority of prognostic work has not considered the potential for differential functioning of prognostic factors across clinically relevant subgroups. One of the most obvious would be the possibility that the accuracy of prognostic variables is moderated by the sex of the injured person. Some prior work in the field has identified sex itself as a

potential prognostic variable, wherein females are more likely to report persistent pain than are males following WAD [10]. However, as a target for intervention, it is unclear how sex can or should be considered to improve outcomes. Rather we are informed by the Sex and Gender Equity in Research (SAGER) initiative [11], endorsing exploration of research findings disaggregated by sex, whereby more equitable evidence for clinical decision making can be realized, rather than assuming variables function the same in both males and females.

While both high NDI and high NPRS scores have established evidence as risk factors for persistent pain and disability post-WAD, the purpose of this study was to follow the SAGER guidelines and explore the potential that the strength of that prognosis varies as a function of the respondent's sex.

## Methods

### Participants

This study was a secondary analysis of data collected during a parent study investigating recovery from WAD (ClinicalTrials.gov Identifier: NCT02157038). In all, data were collected from 97 participants (72 females) who were recruited from an academic emergency department (ED) in Chicago, IL, USA from September 2014 through May 2019. To be eligible for the study, the following inclusion criteria had to be met: an MVC within the previous week with a QTF whiplash grade of 2 or 3 [5], and be between 18 to 65 years of age. Exclusion criteria were a previous MVC at any time, treatment for neck pain disorders in the past ten years, any nervous system disorder (e.g., stroke, Parkinson's), metabolic system disorder (e.g., diabetes), or those who, by standard emergency medical services' protocols were deemed to be at risk for multi-system trauma. The Institutional Review Board of Northwestern University Feinberg School of Medicine granted approval and all participants provided written informed consent (STU00090769-MODCR0003).

### Primary outcome measure

The primary recovery outcome of the parent study was NDI score, reported as 0–100% disability. The NDI has been extensively studied in people with traumatic and non-traumatic neck pain [12], and it has demonstrated adequate reliability and validity and has been deemed appropriate to use in both clinical and research settings based on its reported psychometric properties [13, 14]. NDI scores were captured at inception ( $\leq 1$  week from injury) and again at 2, 12, and 52 weeks follow-up. For this study only inception and 52-week scores were extracted, ostensibly indicating where participants started and where they ended in the study. For those lost to follow-up ( $n = 19$ ), the 12-week score was carried forward as prior modeling and reviews evaluating participants with WAD grades 2 and 3 has revealed very little change occurs between 12 and 52 weeks [3, 4].

### Predictor variables

The variables collected for this study were sex-at-birth (male/female), age in years, and scores on the NDI and NPRS at inception. The NPRS is an 11-point scale that ranges from 0 to 10 with scores on each whole integer [15]. The anchors for the scores are 0 = no pain and 10 = the worst pain imaginable. The psychometrics of the NPRS have been reported across various subgroups, including those with WAD, and it is reported to be an adequately valid, reliable, and responsive tool [13, 16].

## Statistical analysis

Participant characteristics (sex, age, baseline NDI and NPRS) were reported descriptively (proportions or means and range), see Table 1. Missing data were first assessed with Little's Missing Completely At Random (MCAR) test, and then handled on a case-by-case basis. As a first pass analyses, we explored the potential for differences in mean NDI and NPRS scores at baseline when the sample was disaggregated by sex using independent t-tests or Mann-Whitney U-tests dependent on the structure of the data, see Table 1.

For the primary analyses, we used multiple stepwise (hierarchical) linear regression. The dependent variable was NDI score at 52-weeks, and the potential predictor variables in the first analysis were (in order of entry): sex, age, NPRS, and NDI scores at baseline. In the second model we added two interaction terms after the same four variables: sex  $\times$  z-NPRS and sex  $\times$  z-NDI. We transformed the baseline NPRS and NDI scores to z-scores to reduce the risk of multicollinearity as both baseline NPRS and NDI scores were used in the first steps of the model.

For both models, variables were retained when their inclusion led to a significant ( $p < 0.05$ ) change in F-value, and the size of the effect was interpreted through the  $R^2$  as a percent of unique variance in 52-week NDI score explained by that variable. Where inclusion of the interaction terms was significant, we interpreted that as an indication the prognostic value of that variable was different between the sexes. For illustrative purposes and in accordance with SAGER guideline [11], when a significant interaction was identified we repeated the first regression model with the sample disaggregated by sex to enable reporting of estimated variance in 52-week NDI score explained by each variable for each sex.

Prior to evaluating the models, all assumptions regarding linear regression were assessed. Linearity was assessed by partial regression plots of all IV's (except sex as it is categorical) against the DV 52-week NDI score, homoscedasticity was evaluated by plotting standardized residuals against the predicted residuals, multicollinearity was assessed by looking for correlation coefficients greater than 0.75 and tolerance less than 0.1, standardized residuals were assessed with a P-P plot, outliers were determined if any of the standardized residuals were greater than 3 standard deviations from a mean of 0, a leverage point was considered significant if it was greater than 0.2, and data were considered to be an influential point if Cook's distance was greater than 1 [17].

An a priori sample size estimate was performed, and with an 80% power and alpha set at 0.05, assuming a 10% dropout rate, 100 participants, with an expected 10% drop-out rate (n of 90), were necessary to achieve the desired results within the original NIH study parameters. Secondary sex-disaggregated analyses were expected to be underpowered when the sample was split, so these were considered exploratory hypothesis-generating analyses only.

All analyses were performed using SPSS Statistics for Windows Version 26.0 (IBM Corporation, Armonk, NY).

**Table 1. Based on participant sex: Independent *t*-test for age and baseline NDI scores, and Mann-Whitney U test for baseline NPRS.**

	Male (n = 25) Mean (95%CI)	Female (n = 72) Mean (95% CI)	<i>p</i> -value
Age	32.1 (28.0 to 36.3)	35.6 (32.9 to 38.2)	0.19
NPRS at baseline	5.2 (4.1 to 6.2)	5.0 (4.5 to 5.5)	0.88
NDI at baseline	32.2 (24.2 to 40.2)	37.6 (33.9 to 41.1)	0.17

Abbreviations: NPRS: numeric pain rating scale; NDI: neck disability index; CI: confidence interval.

<https://doi.org/10.1371/journal.pone.0282640.t001>

## Results

### Participants

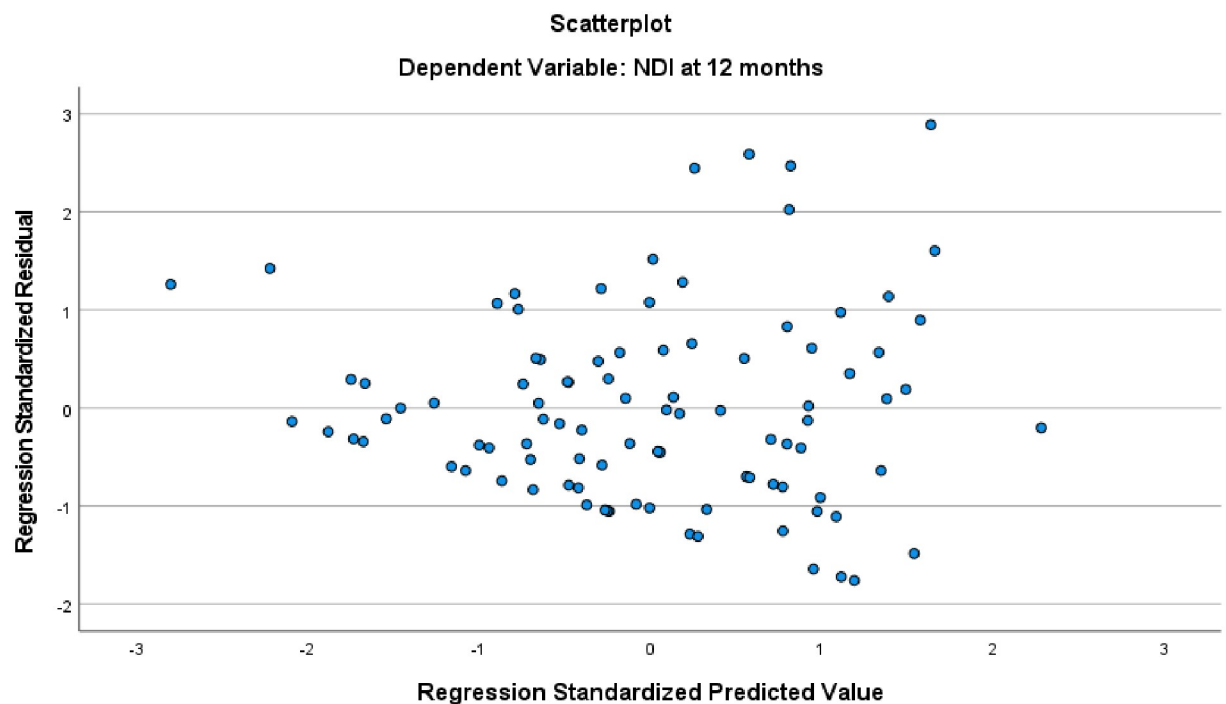
A total of 100 people consented to participate of which 97 (72 female) presented for their initial assessment. All 97 provided data at baseline, 2- and 12 weeks, while 78/97 provided data at all 4 timepoints. Of the 19 (19.6% of baseline) that were lost to follow up between 12 and 52 weeks, 5 were male and 14 were female. Proportions of males and females were not different between the baseline and 52-week collection periods ( $\chi^2 = < 0.01$ ,  $p = 0.95$ ). MCAR test indicated a random pattern of missing data ( $\chi^2 = 4.59$ ,  $p = 0.47$ ). Considering this, and prior evidence revealing no significant difference in mean NDI scores between 12 and 52-weeks, the 12-week NDI scores for those 19 lost to follow-up were carried forward to 52-weeks for purposes of the predictive analysis.

### Baseline analysis

Table 1 presented the mean age, NPRS, and NDI scores between the sexes. None of the differences were significant by independent samples t-tests ( $p \geq 0.17$ ) or Mann-Whitney U test ( $p = 0.88$ ).

### Primary analysis

The results from our study demonstrated that the NDI is a more robust tool for males in predicting 52-week disability scores for those with WAD when compared to females, while the NPRS was a more robust tool for females in the same population. Assumptions of linear regression were satisfied, though the scedasticity plot indicated a pattern of increasing residuals proportional to the higher level of NDI scores (Fig 1). Neither age nor sex in isolation



**Fig 1.** Scedasticity plot of standardized and predicted residuals for the full sample population.

<https://doi.org/10.1371/journal.pone.0282640.g001>

Table 2. Results of stepwise multiple linear regression using the entire sample.

Variable	$\beta$ ( $\beta$ )	$\Delta R^2$	$\Delta F$ (p)
Age	0.10 (0.07)	0.6	0.57 (0.45)
Sex (male = 1, female = 2)	1.2 (0.04)	1.5	1.41 (0.24)
NPRS at baseline	0.39 (0.06)	5.7	5.75 (0.02)
NDI at baseline	0.30 (0.34)	8.7	9.52 (<0.01)
Interaction of sex and NDI baseline	-2.79 (-0.21)	0.4	0.45 (0.50)
Interaction of sex and NPRS baseline	3.31 (0.24)	3.8	4.37 (0.04)

Abbreviations: NPRS, numeric pain rating score; NDI, neck disability index;  $\beta$ : unstandardized beta value;  $\beta$ : standardized beta value; p-value significance  $\leq 0.05$ .

<https://doi.org/10.1371/journal.pone.0282640.t002>

explained significant variance in 52-week NDI scores (p of F change  $\geq 0.24$ ). In accordance with prior work [4], both baseline NPRS ( $\Delta F = 5.75$ ,  $p = 0.02$ ,  $\Delta R^2 = 5.7\%$ ) and baseline NDI ( $\Delta F = 9.52$ ,  $p < 0.01$ ,  $\Delta R^2 = 8.7\%$ ) explained significant unique variance in 52-week NDI scores. In the second model, the sex  $\times$  z-NDI term was non-significant, while the sex  $\times$  z-NPRS term led to a significant increase in variance explained ( $\Delta F = 4.37$ ,  $p = 0.04$ ,  $\Delta R^2 = 3.8\%$ ). The three significant independent variables explained a cumulative 18.2% of variance in NDI scores captured 52 weeks later. Table 2 presents the results of the second regression model including the interaction terms.

The significant interaction term and pattern of non-random residuals supported the decision to conduct the secondary sex-disaggregated regression analyses shown in Table 3. For males, only NDI at baseline was a significant predictor of 52-week NDI score ( $\Delta F = 6.22$ ,  $p = 0.02$ ,  $\Delta R^2 = 22.4\%$ ). Conversely in females, only NPRS at baseline was a significant predictor of 52-week NDI score ( $\Delta F = 8.28$ ,  $p < 0.01$ ,  $\Delta R^2 = 10.5\%$ ). Despite the smaller samples in these secondary disaggregated analyses, all assumptions for regression were satisfied after splitting the sample.

## Discussion

The primary focus of this study was to explore the possibility that common prognostic variables in the field of WAD recovery research exhibit differential functioning by sex of the injured person. The results support this presupposition, that the response to key prognostic

Table 3.  $\beta$  value (unstandardized and standardized), changes in  $R^2$ , and change in F at each step with significance values for each variable for the regression analyses when disaggregated by sex.

Variable	$\beta$ ( $\beta$ )	$\Delta R^2$	$\Delta F$ (p)
<b>Males (n = 25)</b>			
Age	-0.01 (-0.01)	1.9	0.44 (0.52)
NPRS at baseline	-2.19 (-0.30)	0.2	0.04 (0.85)
<i>NDI at baseline</i>	<i>0.57 (0.62)</i>	<i>22.4</i>	<i>6.22 (0.02)</i>
<b>Females (n = 72)</b>			
Age	0.12 (0.11)	2.0	1.43 (0.24)
<i>NPRS at baseline</i>	<i>1.29 (0.21)</i>	<i>10.5</i>	<i>8.28 (&lt;0.01)</i>
NDI at baseline	0.20 (0.23)	3.8	3.13 (0.08)

Abbreviations: NPRS, numeric pain rating score; NDI, neck disability index;  $\beta$ , beta value; p-value significance  $\leq 0.05$ . *Italicized*: significant predictor variables.

<https://doi.org/10.1371/journal.pone.0282640.t003>



variables appear to be different between males and females, and the results of this work should lead to sex-specific prognostic models and screening tools in the interest of more equitable and person-centric research and practice. The significant sex  $\times$  z-NPRS interaction term indicated that a difference in prognostic performance exists, and the secondary sex-disaggregated analyses indicate that initial NDI score may be a more robust prognostic variable in males, while initial NPRS (pain intensity) score may be more robust in females. We are unaware of prior work that has considered moderating or interaction effects in prognostic models in WAD. The results herein indicate that doing so may result in even more accurate prognostic screening tools.

Prior work has identified, for people with WAD, three recovery trajectories people most often follow: rapid/full recovery, delayed/mild persistent problems, and non-recovery/ severe persistent problems [3, 18]. At least one published prognostic screening tool prioritizes baseline NDI score as the first-pass screen for 'risk of poor outcome' following WAD [19], though our results indicate that such associations may be considerably more complex than previously considered. Two such findings are worth exploration in this regard: the first is the scedasticity plot in Fig 1, the second are the significant sex interaction term and sex-disaggregated analyses. These will be considered in turn.

The pattern of residuals in Fig 1 suggests the predictive value of the regression model is better when 52-week NDI scores are on the lower end of the scale, and less precise as 52-week scores increase. These findings fit with a recent publication using quantile regression on a dataset of which the current sample was a subset but using different predictor variables [18]. In that study, Modarresi and colleagues similarly found the prognostic accuracy of many commonly reported variables (post-traumatic distress) was better when recovery outcomes were good, but less accurate when recovery outcomes were poor. In practice, such results make analysis and interpretation of any such work in the field more complex, but for injured people these offer promise—while those deemed 'low risk' at baseline are indeed likely to recover quickly, those deemed 'higher risk' are part of a group with considerable variation in 52-week outcomes, some of which is presumably modifiable. From a screening and social justice perspective this is also valuable—most current clinical practice guidelines endorse minimal intervention for acutely injured people deemed low risk, so accuracy of such judgements is of critical importance at the lower ends of the scale. Conversely, those deemed higher risk usually move on to more fulsome clinical workup, meaning that even when risk screening is inaccurate the salient impact on the injured person is undergoing more evaluation.

The differential prognostic functioning by sex demands further exploration and replication in other samples, especially considering the smaller sample sizes in the disaggregated analyses. If replicated, such a finding will demand a rethinking in how prognostic screening tools and decision rules are created. The findings herein may go some way towards explaining the inconsistencies in prior work around sex itself as a prognostic variable. For example, a meta-analysis by Walton and colleagues [10] found that females showed a small but significant 1.5-fold increased odds of non-recovery after WAD, but work since then has rarely found sex to be an important prognostic discriminator [20–22]. Perhaps, per the findings of this study, it is not sex itself that is the prognostic variable, but rather the effect that sex has on other variables that has led some groups to find it significant while others have not. If replicated, the simple interpretation of such findings is that prognostic tools should be created and interpreted separately for males and females, an endorsement that has been supported by the SAGER group and several other critical feminist and disability scholars [23–25]. The mechanisms to explain why pain intensity appears to be more relevant for females while pain-related disability is more relevant for males is a novel finding for which we are unable to find supporting prior evidence, suggesting this is another area that demands further quantitative and qualitative exploration.



We acknowledge an important drawback to the interpretations of this work that are borne by the level of data collected in the original parent study. We have consistently used the term 'sex' throughout this study, as the initial intake data form offered respondents binary response options of selecting male or female. This is most closely aligned with the biological concept of sex-assigned-at-birth, referring to biological differences such as reproductive organs and circulating hormones. However, it is now well-recognized that sex, as a biological construct, should be considered distinct from the concept of gender, including socially or culturally constructed traits, roles, and behaviors. Gender is a difficult construct to quantify in post-positivist research, though some tools exist and may be useful for components of such research [26]. Members of our group have recently found that constructs of relationship-orientation and emotiveness, commonly ascribed to more feminine-leaning traits by Western cultural standards, were more strongly associated with acute pain and post-traumatic distress in an independent sample analysis using the Gender, Pain, and Expectations Scale [manuscript currently under review]. So, while the results reported herein appear to indicate that it is sex, rather than gender, that requires differential consideration in prognostic studies, we need to make clear this is a side-effect of the data available and instead suggest these concepts require considerable further exploration to better determine what are the important constructs, and how biological sex and cultural gender norms may interact to better predict outcomes from WAD.

Finally, we support the SAGER guidelines in endorsing sex- and gender-based analyses not only in prognostic research described here, but also in intervention trials. It is widely-recognized the evidence base to support many interventions for WAD, whether acute or chronic, is weak and/or demonstrates generally small clinical effects [27, 28]. Based on our recent results including those described here, we propose one explanation for limited empirical support for one intervention over another is that prior work in the field has rarely been designed with sex-disaggregated sub-analyses in mind. It seems possible, and very reasonable, to believe the effects of interventions, be they pharmaceutical, rehabilitative, surgical, or otherwise, may vary by sex. This seems like a ripe area for further exploration.

## Limitations

The primary limitation in this study was the unequal numbers of males (25) and females (72). While not equal, the nearly 1:3 ratio is reflective of the proportions commonly reported in research studies and clinical practice [14, 29, 30], and preparatory analyses of between-group variance indicated similar variances despite the unequal sizes. As a secondary analysis of previously collected data we were unable to recruit more acutely injured male participants, and as such these analyses should be considered exploratory and hypothesis generating at this stage. Future studies should aim to have equal numbers between the sexes.

A second limitation was the loss of 19 participants between 12 and 52 weeks. Although we felt comfortable carrying NDI and NPRS scores forward from the 12 to the 52-week time point, as this allowed data from all 97 people to be included in the analysis using an intention-to-treat approach, we recognize it is unlikely that all followed the same trajectory during that time. Our decision was based on previous research showing minimal change in these scores between 12 and 52 weeks [3].

A final limitation is the examination of just three primary variables (age, baseline NDI scores, and baseline NPRS). The purpose of this study was not to evaluate all potential variables; thus, we used these three established variables [4, 21] as a proof-of-concept to explore possible sex-related differences and to better inform future research designs in the area. While there are numerous variables associated with the development of chronic WAD such as hyperarousal scores on the post-traumatic diagnostic scale [21], increased levels of muscle fatty

infiltrate within the cervical musculature [31], or levels of post-traumatic stress [32]; evaluating how males and females react to each one should be included in future research designs [11].

## Summary

The results from this study reproduce prior findings of an association between NDI scores when captured 52-weeks apart [33]. The data provide at least preliminary evidence that males and females may have different prognostic variables associated with the development of chronic WAD following an MVC, with baseline NDI scores predictive for males and baseline NPRS for females. Such information could potentially assist in the development of and a greater understanding for the prognostic profiles of people following an MVC with a target to explore, test, and establish more efficient treatment strategies.

## Supporting information

**S1 Checklist. STROBE statement—Checklist of items that should be included in reports of cohort studies.**

(DOCX)

## Acknowledgments

This study was completed as partial fulfillment of a PhD dissertation at Nova Southeastern University and under a data share agreement with Northwestern University, Chicago, IL, USA.

## Author Contributions

**Conceptualization:** Bradford Callan, David M. Walton, James M. Elliott.

**Data curation:** Bradford Callan, James M. Elliott.

**Formal analysis:** Bradford Callan, David M. Walton.

**Funding acquisition:** James M. Elliott.

**Investigation:** James M. Elliott.

**Methodology:** David M. Walton, Joshua Cleland, Morey J. Kolber, James M. Elliott.

**Project administration:** James M. Elliott.

**Supervision:** David M. Walton, Joshua Cleland, Morey J. Kolber, James M. Elliott.

**Validation:** David M. Walton, James M. Elliott.

**Writing – original draft:** Bradford Callan.

**Writing – review & editing:** David M. Walton, Joshua Cleland, Morey J. Kolber, James M. Elliott.

## References

1. Centers for Disease Control and Prevention. Motor Vehicle Crash Injuries. 2014. <https://www.cdc.gov/vitalsigns/crash-injuries/index.html>. Accessed 6/13/2018.
2. Naumann RB, Dellinger AM, Zaloshnja E, Lawrence BA, Miller TR. Incidence and total lifetime costs of motor vehicle-related fatal and nonfatal injury by road user type, United States, 2005. *Traffic injury prevention*. 2010; 11:353–360. <https://doi.org/10.1080/15389588.2010.486429> PMID: 20730682
3. Ritchie C, Sterling M. Recovery Pathways and Prognosis After Whiplash Injury. *J Orthop Sports Phys Ther*. 2016; 46:851–861. <https://doi.org/10.2519/jospt.2016.6918> PMID: 27594661

4. Walton DM, Carroll LJ, Kasch H, Sterling M, Verhagen AP, Macdermid JC, et al. An Overview of Systematic Reviews on Prognostic Factors in Neck Pain: Results from the International Collaboration on Neck Pain (ICON) Project. *The open orthopaedics journal*. 2013; 7:494–505. <https://doi.org/10.2174/1874325001307010494> PMID: 24115971
5. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, et al. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. *Spine (Phila Pa 1976)*. 1995; 20:1s–73s. PMID: 7604354
6. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. *J Manipulative Physiol Ther*. 1991; 14:409–415. PMID: 1834753
7. Croft AC, Workman JA, Szatalowicz MP, Roberts PE, Suiter LR. Classifying Whiplash Recovery Status Using the Neck Disability Index: Optimized Cutoff Points Derived From Receiver Operating Characteristic. *J Chiropr Med*. 2016; 15:95–101. <https://doi.org/10.1016/j.jcm.2016.04.011> PMID: 27330511
8. Boonstra AM, Stewart RE, Koke AJ, Oosterwijk RF, Swaan JL, Schreurs KM, Schiphorst Preuper HR. Cut-Off Points for Mild, Moderate, and Severe Pain on the Numeric Rating Scale for Pain in Patients with Chronic Musculoskeletal Pain: Variability and Influence of Sex and Catastrophizing. *Frontiers in psychology*. 2016; 7:1466. <https://doi.org/10.3389/fpsyg.2016.01466> PMID: 27746750
9. Walton D, Elliott J, Lee J, Fakhereddin M, Seo W. Identification of clinically-useful cut scores of the Traumatic Injuries Distress Scale (TIDS) for predicting rate of recovery following musculoskeletal trauma. *PloS one*. 2021; 16:e0248745. <https://doi.org/10.1371/journal.pone.0248745> PMID: 33755664
10. Walton DM, Macdermid JC, Giorgianni AA, Mascarenhas JC, West SC, Zammit CA. 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. <https://doi.org/10.2519/jospt.2013.4507> PMID: 23322093
11. Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Research integrity and peer review*. 2016; 1:1–9.
12. MacDermid JC, Walton DM, Avery S, Blanchard A, Etruw E, McAlpine C, et al. Measurement properties of the neck disability index: a systematic review. *J Orthop Sports Phys Ther*. 2009; 39:400–417. <https://doi.org/10.2519/jospt.2009.2930> PMID: 19521015
13. Cleland JA, Childs JD, Whitman JM. Psychometric properties of the Neck Disability Index and Numeric Pain Rating Scale in patients with mechanical neck pain. *Arch Phys Med Rehabil*. 2008; 89:69–74. <https://doi.org/10.1016/j.apmr.2007.08.126> PMID: 18164333
14. Hoving JL, O'Leary EF, Niere KR, Green S, Buchbinder R. Validity of the neck disability index, Northwick Park neck pain questionnaire, and problem elicitation technique for measuring disability associated with whiplash-associated disorders. *Pain*. 2003; 102:273–281. [https://doi.org/10.1016/S0304-3959\(02\)00406-2](https://doi.org/10.1016/S0304-3959(02)00406-2) PMID: 12670669
15. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *Journal of clinical nursing*. 2005; 14:798–804. <https://doi.org/10.1111/j.1365-2702.2005.01121.x> PMID: 16000093
16. Bijur PE, Latimer CT, Gallagher EJ. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Academic emergency medicine: official journal of the Society for Academic Emergency Medicine*. 2003; 10:390–392. <https://doi.org/10.1111/j.1553-2712.2003.tb01355.x> PMID: 12670856
17. Meyers L, Gamst G, Guarino A. *Applied Multivariate Research Design and Interpretation*. Los Angeles, CA: SAGE; 2013.
18. Modarresi S, MacDermid JC, Suh N, Elliott JM, Walton DM. How Is the Probability of Reporting Various Levels of Pain 12 Months After Noncatastrophic Injuries Associated with the Level of Peritraumatic Distress? *Clin Orthop Relat Res*. 2022; 480:226–234. <https://doi.org/10.1097/CORR.0000000000002024> PMID: 34705736
19. Ritchie C, Hendrikz J, Jull G, Elliott J, Sterling M. External validation of a clinical prediction rule to predict full recovery and ongoing moderate/severe disability following acute whiplash injury. *J Orthop Sports Phys Ther*. 2015; 45:242–250. <https://doi.org/10.2519/jospt.2015.5642> PMID: 25827122
20. Linnstaedt SD, Riker KD, Walker MG, Nyland JE, Zimny E, Lewandowski C, et al. MicroRNA 320a Predicts Chronic Axial and Widespread Pain Development Following Motor Vehicle Collision in a Stress-Dependent Manner. *J Orthop Sports Phys Ther*. 2016; 46:911–919. <https://doi.org/10.2519/jospt.2016.6944> PMID: 27690835
21. Ritchie C, Hendrikz J, Kenardy J, Sterling M. Derivation of a clinical prediction rule to identify both chronic moderate/severe disability and full recovery following whiplash injury. *Pain*. 2013; 154:2198–2206. <https://doi.org/10.1016/j.pain.2013.07.001> PMID: 23831865
22. Zetterqvist V, Holmstrom L, Maathz P, Wicksell RK. Pain avoidance predicts disability and depressive symptoms three years later in individuals with whiplash complaints. *Acta anaesthesiologica Scandinavica*. 2017; 61:445–455. <https://doi.org/10.1111/aas.12874> PMID: 28233304

23. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth*. 2013; 111:52–58. <https://doi.org/10.1093/bja/aet127> PMID: 23794645
24. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL 3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. *The journal of pain: official journal of the American Pain Society*. 2009; 10:447–485.
25. Jones A, Zachariae R. Investigation of the interactive effects of gender and psychological factors on pain response. *British Journal of Health Psychology*. 2004; 9:405–418. <https://doi.org/10.1348/1359107041557101> PMID: 15296686
26. Ghodrati M, Walton DM, MacDermid JC. Exploring the Domains of Gender as Measured by a New Gender, Pain and Expectations Scale. *Womens Health Rep (New Rochelle)*. 2021; 2:87–96. <https://doi.org/10.1089/whr.2020.0109> PMID: 33937906
27. Willaert W, Leysen L, Lenoir D, Meeus M, Cagnie B, Nijs J, et al. Combining Stress Management With Pain Neuroscience Education and Exercise Therapy in People With Whiplash-Associated Disorders: A Clinical Perspective. *Physical therapy*. 2021; 101. <https://doi.org/10.1093/ptj/pzab105> PMID: 33764474
28. Wong JJ, Shearer HM, Mior S, Jacobs C, Côté P, Randhawa K, et al. Are manual therapies, passive physical modalities, or acupuncture effective for the management of patients with whiplash-associated disorders or neck pain and associated disorders? An update of the Bone and Joint Decade Task Force on Neck Pain and Its Associated Disorders by the OPTIMA collaboration. *The spine journal: official journal of the North American Spine Society*. 2016; 16:1598–1630. <https://doi.org/10.1016/j.spinee.2015.08.024> PMID: 26707074
29. Jonsson B, Tingvall C, Krafft M, Bjornstig U. The risk of whiplash-induced medical impairment in rear-end impacts for males and females in driver seat compared to front passenger seat. *IATSS Research*. 2013; 37:8–11.
30. Pool JJ, Ostelo RW, Hoving JL, Bouter LM, de Vet HC. Minimal clinically important change of the Neck Disability Index and the Numerical Rating Scale for patients with neck pain. *Spine (Phila Pa 1976)*. 2007; 32:3047–3051. <https://doi.org/10.1097/BRS.0b013e31815cf75b> PMID: 18091500
31. Elliott JM, Pedler AR, Jull GA, Van Wyk L, Galloway GG, O'Leary SP. Differential changes in muscle composition exist in traumatic and nontraumatic neck pain. *Spine (Phila Pa 1976)*. 2014; 39:39–47. <https://doi.org/10.1097/BRS.0000000000000033> PMID: 24270932
32. Sterling M, Jull G, Kenardy J. Physical and psychological factors maintain long-term predictive capacity post-whiplash injury. *Pain*. 2006; 122:102–108. <https://doi.org/10.1016/j.pain.2006.01.014> PMID: 16527397
33. Sterling M, Hendrikz J, Kenardy J. Similar factors predict disability and posttraumatic stress disorder trajectories after whiplash injury. *Pain*. 2011; 152:1272–1278. <https://doi.org/10.1016/j.pain.2011.01.056> PMID: 21396780