New Directions for Physical Rehabilitation of Musculoskeletal Pain Conditions
Research Paper
OPEN
PAIN REPORTS®

The mechanisms of effect of a physiotherapist-delivered integrated psychological and exercise intervention for acute whiplash-associated disorders: secondary mediation analysis of a randomized controlled trial

Rachel A. Elphinston[a,b,c,d,*], Michele Sterling[a,b], Justin Kenardy[c], Rob Smeets[e], Nigel R. Armfield[a,f]

Abstract

Introduction: Integrated psychological and physical treatments can improve recovery for whiplash-associated disorders (WADs). Little is known about how these interventions work.

Objective: To examine the mechanisms by which a physiotherapist-delivered integrated intervention for acute WAD improves health outcomes.

Methods: Secondary analysis using structural equation modelling of a randomized controlled trial comparing integrated stress inoculation training and exercise to exercise alone for acute WAD. Outcomes were disability, pain self-efficacy, pain intensity, and health-related quality of life at 12 months. The intended intervention target and primary mediator, stress was tested in parallel with pain-related coping, an additional cognitive behavioral mediator that significantly improved at posttreatment (Model 1). Stress-related constructs that commonly co-occur with stress and pain were also tested as parallel mediators: depression and pain-related coping (Model 2); and posttraumatic stress and pain-related coping (Model 3).

Results: Reductions in stress mediated the effect of the integrated intervention on disability ($\beta = -0.12$, confidence interval [CI] = -0.21 to -0.06), pain self-efficacy ($\beta = 0.09$, CI = 0.02–0.18), pain ($\beta = -0.12$, CI = -0.21 to -0.06), and health-related quality of life ($\beta = 0.11$, CI = 0.04–0.21). There was an additional path to pain self-efficacy through pain-related coping ($\beta = 0.06$, CI = 0.01–0.12). Similar patterns were found in Models 2 and 3.

Conclusions: Improvements in stress and related constructs of depression and posttraumatic stress, and pain-related coping were causal mechanisms of effect in a physiotherapist-delivered integrated intervention. As integrated interventions are growing in popularity, it is important to further personalize interventions for improved benefit.

Keywords: Integrated interventions, Cognitive behavioral therapy, Physical rehabilitation, Physiotherapy, Whiplash, Change processes

1. Introduction

Musculoskeletal pain conditions are among the leading causes of disability worldwide.[40] Motor vehicle crashes are a common cause of musculoskeletal pain, with neck pain or whiplash-associated disorders (WADs) being the most frequent injury. Up to 50% of people with whiplash injuries do not fully recover[4] and will experience a complicated recovery trajectory characterized by chronic pain, mental health problems, and disability.[16,35]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] RECOVER Injury Research Centre, The University of Queensland, Brisbane, Australia, [b] NHMRC CRE in Road Traffic Injury Recovery, The University of Queensland, Brisbane, Australia, [c] School of Psychology, The University of Queensland, Brisbane, Australia, [d] Metro South Addiction & Mental Health Service, Metro South Health, Brisbane, Australia, [e] Department of Rehabilitation Medicine, Research School CAPHRI, Maastricht University, Maastricht, the Netherlands, [f] Centre for Health Services Research, Faculty of Medicine, the University of Queensland, Brisbane, Australia

**Corresponding author. Address: RECOVER Injury Research Centre, The University of Queensland, Level 7, 288 Herston Rd, Herston, Brisbane, Australia 4006. Tel.: +61 7 3365 5560. E-mail address: rachelel@uq.edu.au (R.A. Elphinston).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painrpts.com).

PR9 5 (2020) e835

http://dx.doi.org/10.1097/PR9.0000000000000835

There are few effective treatments for acute WAD. Physical rehabilitation has only small effects[18,33,37] and early multidisciplinary treatment is no more effective than usual care.[15] In contrast, recent evidence indicates that identifying patients at risk of poor recovery and targeting both psychological and physical factors delivers more beneficial effects. The StressModex randomised clinical trial (RCT) compared a 6-week physiotherapist-delivered integrated psychological and exercise intervention to 6 weeks of exercise alone. The integrated intervention delivered greater decreases in pain-related disability (primary outcome) as well as improvements in secondary outcomes of pain intensity, pain self-efficacy, and quality of life that were clinically relevant and sustained for 12 months.

The psychological component of the integrated intervention aimed to target early stress based on evidence that acute stress is an important psychological risk factor for poor recovery.[3,17] Termed stress inoculation training, techniques including education about the effects of stress on pain and recovery, relaxation strategies, problem-solving and coping self-statements teach individuals to manage stress (see supplementary materials of the main trial,[36] http://links.lww.com/PR9/A71). It applies cognitive behavioral theory, which hypothesizes that treatments work through therapeutic changes in emotions (ie, stress) and cognitive and behavioral patterns (eg, coping; catastrophizing). Techniques were delivered within a self-management framework, enhancing individuals' confidence in managing stress and their recovery.

The approach of identifying "at-risk" patients and targeting early psychological risk factors in addition to physical rehabilitation is gaining momentum. In addition to WAD, studies of low back pain and injured workers have demonstrated clinically relevant benefits from this approach.[9,12,27] To date, no study has tested the theoretically relevant mechanisms of therapeutic change (mediators) in these integrated interventions. Information about change processes would help to inform refinement of theoretical models, clinical decision-making, design of more personalized treatment approaches,[2,19] and targeted skills training of care providers.

The aim of this study was to examine the potential causal mechanisms by which an integrated intervention for acute WAD improves health outcomes through a secondary mediation analysis of data from the StressModex RCT. Stress was a key intervention target and the primary mediator to be tested using the stress subscale of the Depression Anxiety and Stress Scale (DASS-21).[22] We hypothesized that the effects of the integrated psychological and exercise intervention on disability, pain-related self-efficacy, pain intensity, and health-related quality of life at 12 months would be mediated by reductions in levels of stress. We also considered potential cognitive behavioral mediators that had significantly improved 6-weeks posttreatment. It was also hypothesized that in addition to stress, pain-related coping would be a parallel mediator of the relationship between the integrated intervention and pain-related outcomes. In subsequent models, stress-related constructs that commonly co-occur with stress and pain and also share features of stress (eg, physiological arousal; anger/irritability) were tested as alternative mediators. In each model, parallel mediators were depressive symptoms and pain-related coping; and posttraumatic stress symptoms and pain-related coping.

2. Method

2.1. Participants and setting

The StressModex RCT was prospectively registered (ACTRN12614001036606) and the protocol[29] and results published.[36] The study received ethical approval from the human ethics research committees of The University of Queensland (2011000206), Griffith University (AHS/14/14/HREC), and the Gold Coast University Hospital (HREC/15/QGC/34). The sample has been previously described in detail.[36] Briefly, inclusion criteria were: acute (<4 weeks) WAD grade II/III (no fracture/dislocation), at least moderate neck pain-related disability (≥32%, on the Neck Disability Index[39]), and hyperarousal symptoms (≥3 on the hyperarousal subscale of the Posttraumatic Diagnostic Scale[7]). Participants were excluded if there was known or suspected spinal cord injury; confirmed fracture or dislocation; fracture or injuries to other body areas; spinal surgery in the past 12 months; met the criteria for probable acute stress disorder or major depression; or a history of psychosis, bipolar disorder, or depression. Refer to the methods of the main trial[36] for a summary of the number of individuals excluded due to severe levels of stress or major depression. After completion of baseline assessment measures, 108 patients were randomly allocated to receive the physiotherapist-delivered integrated stress inoculation and exercise intervention (n = 53) or exercise only (n = 55). The mean age of the sample was 41 years (SD = 14.1), the majority of participants were female (68%), had at least 10 years of schooling (77%), and were employed (64%). Outcomes were assessed at 6-weeks posttreatment, and at 6- and 12-month follow-ups. On the primary outcome, follow-up rates were 94% and 87% at 12 months for the integrated intervention vs physiotherapy exercise only group, respectively, with some variation in completion of secondary outcomes measures. Patient adherence to treatment was good; median number of sessions for both groups was 10 out of a possible 10 sessions. Physiotherapist adherence to the session protocols was excellent in both groups (>93%).[36]

2.2. Interventions

Detailed information on the interventions including the treatment manual can be found in the primary report and supplementary materials (http://links.lww.com/PR9/A71).[36] In short, the integrated intervention consisted of 6 physiotherapist-delivered sessions of stress inoculation and 10 sessions of physiotherapy exercise delivered over 6 weeks. The stress inoculation intervention comprised 3 main components: (1) identifying and understanding stress and its influence on pain and recovery, (2) developing skills for managing stress, and (3) applying skills in various situations to develop tolerance and confidence. Participants were encouraged to practice these skills each week during home practice. The physiotherapy exercise programme adhered to the Australian Guidelines for the Management of Acute Whiplash[34] and included exercises to improve movement, strength, and endurance of the neck and shoulder girdle muscles, eye/head coordination, and balance. Participants were encouraged to practice the exercises at home on a daily basis. The physiotherapy exercise only group received the 10-session exercise programme only.

2.3. Measures

For this secondary post hoc analysis, we chose all significant outcomes as in the main analyses except for the global impression of recovery scores because these were only collected immediately after treatment. These included 4 pain-related outcomes measures at 12 months: the Neck Disability Index,[39] Pain Self-Efficacy Questionnaire,[28] average pain intensity in the last 24 hours (0–10 scale), and the health-related quality of life (HRQoL) mental health component score from the SF-36.[10] The

mediating variables at 6 weeks included the following: stress subscale from the DASS-21,[22] as well as the DASS-21 depression subscale,[22] the Posttraumatic Diagnostic Scale symptom score,[7] and the Coping Strategies Questionnaire.[30] These measures have been previously described in detail.[36]

2.4. Summary of previously reported StressModex randomised clinical trial results

As previously reported,[36] a linear mixed modelling and intention-to-treat analysis was used. Each outcome was analysed separately. Findings at 6-weeks posttreatment and 12-months follow-up are reported here because these are the time-points of interest for this secondary analysis. A significant and clinically important between-group difference in the primary outcome of pain-related disability was found, favoring the integrated intervention at 6 weeks and 12 months. **Table 1** provides a summary. At 6 weeks, there was a significant treatment effect on secondary outcomes of posttraumatic stress symptoms, depression, stress, pain-related coping skills, pain intensity and HRQoL (mental health), but no effect on pain catastrophizing or anxiety symptoms. Significant treatment effects were also found at 12 months for pain intensity, pain self-efficacy, pain-related coping skills, and HRQoL (mental health).

2.5. Analyses

Only variables with treatment effects at 6 weeks were tested as potential mediators. These were: stress symptoms (primary mediator) and pain-related coping skills as well as stress-related constructs of depressive and posttraumatic stress symptoms. Pearson correlations were performed in STATA (version 16) to examine potential multicollinearity among the mediators at 6 weeks (**Table 2**). Because stress, depressive, and posttraumatic stress symptoms at 6 weeks were highly correlated with each other (*r* values between 0.71–0.77; again, **Table 2**), it was not possible to enter them into a single model. We therefore created 3 separate simplex lagged parallel mediation models. In Model 1, stress symptoms and pain-related coping were entered as mediators; depressive symptoms and pain-related coping were entered in Model 2; and posttraumatic stress symptoms and pain-related coping were entered in Model 3. We used structural equation modelling to assess whether the primary mediator stress, or alternative mediators depressive or posttraumatic stress symptoms, and pain-related coping skills mediated the treatment effects (integrated intervention vs exercise control) on pain-related disability, pain self-efficacy, pain intensity, and HRQoL (mental health) at 12 months with the outcomes tested simultaneously. Structural equation modelling allows testing of multiple mediators and/or dependent variables simultaneously. For consistency with the primary analysis, we adjusted for baseline variables. The direct effect of the integrated intervention vs exercise control on each outcome (controlling for the mediators) and the average causal mediation effect (indirect effect) of the integrated intervention vs exercise control on 12-month health outcomes that is mediated by the hypothesized mediators were estimated. Indirect effects were computed using 95% confidence intervals (CIs) using bootstrapped standard errors (1,000 iterations), with estimates considered significant when CIs did not include zero. Standardized and unstandardized estimates, CIs, and R^2 values were reported, as well as proportions of specific and total indirect effects. Absolute model fit was assessed and is represented by a non-significant χ^2 statistic. Comparative fit indices were also assessed: comparative fit index (CFI), root mean-square error of approximation (RMSEA), and the standardized root mean-square residual (SRMR).[13] Cutoffs $\geq$0.95 for CFI, $\leq$0.06 for RMSEA, and $\leq$0.08 for SRMR represent good fit.[24] We note that these cutoffs are considered only as a guide, and models approaching these values were interpreted as having acceptable fit.[24] Missing data were handled using list-wise deletion. Mediational analyses were performed in MPlus Version 8.3.[26]

3. Results

After excluding cases due to missing data at follow-up, 103 of the 108 participants in the StressModex RCT were included. Standardized and unstandardized parameter estimates of the direct and indirect effects, significance levels, and CIs as well as proportions of the total effects are provided in **Table 3** and **Figures 1–3**. Results are reported separately for each model.

3.1. Model 1: testing stress and pain-related coping as mediators

The results of Model 1 are depicted in **Figure 1**. In line with the findings of the StressModex RCT, there was a direct

Table 1

Treatment effects reported in the primary study at 6 weeks and 12 months.[35]

	6 weeks		12 months	
	Mean difference	95% CI	Mean difference	95% CI
Primary outcome				
NDI (0–100)	−10.0*	−15.5 to −4.48	−10.1*	−16.3 to −4.0
Secondary outcomes				
PDS (0–51)	−3.7†	−6.9 to 0.5	−3.2	−6.7 to 0.4
DASS-stress (0–42)	−5.6‡	−8.4 to −2.8	−2.2	−5.1 to 0.8
DASS-anxiety (0–42)	−2.3	−4.6 to 0.1	−0.8	−3.7 to 2.1
DASS-depression (0–42)	−3.8*	−6.5 to −1.1	−2.5	−5.8 to 0.9
PCS (0–52)	−2.5	−5.6 to 0.5	−1.2	−4.8 to 2.4
PSEQ (0–60)	3.9	−1.2 to 9.0	6.7†	1.3 to 12.0
CSQ (−72 to 180)	12.9†	0.8 to 25	16.8*	4.8 to 28.8
HRQoL (MCS)	6.6*	2.1 to 11.2	4.5	0.2 to 8.7
24-hour pain intensity (0–10)	−1.5*	−2.3 to −0.6	−1.0†	−2.0 to −0.1

Baseline and 6-month measures omitted for clarity; results from linear mixed models with each outcome analysed separately, participant_id as the random effect and models adjusted for baseline values.

* $P < 0.001$.

† $P < 0.01$.

‡ $P < 0.05$.

CI, confidence intervals; CSQ, Coping Strategies Questionnaire; DASS, Depression, Anxiety, and Stress Scale; HRQoL (MCS), Health-related Quality of Life (Mental Health Component scores) from the SF-36; NDI, Neck Disability Index; PDS, Posttraumatic Diagnostic Scale; PCS, Pain Catastrophizing Scale; PSEQ, Pain-related Self-Efficacy Questionnaire.

Table 2

Bivariate correlations of potential mediators at 6 weeks.

	1	2	3
1 Depression subscale (DASS)	1.00		
2 Stress subscale (DASS)	0.77*	1.00	
3 Posttraumatic stress (PDS)	0.71*	0.73*	1.00
4 Pain-related coping (CSQ)	−0.22†	−0.24†	−0.09

Total sample was used.
* $P < 0.001$.
† $P < 0.05$.
CSQ, coping strategies questionnaire; DASS, Depression, Anxiety, and Stress Scale; PDS, Posttraumatic Diagnostic Scale.

intervention effect on 6-week stress and pain-related coping favouring the integrated intervention. There was a direct effect of stress on pain-related disability, pain self-efficacy, pain intensity, and HRQoL (mental health) at 12 months and a direct effect of pain-related coping on pain self-efficacy only. The integrated intervention had indirect effects on pain-related disability (β = −0.12, CI = −0.21 to −0.06), pain self-efficacy (β = 0.09, CI = 0.02–0.18), pain intensity (β = −0.12, CI = −0.21 to −0.06), and HRQoL (mental health) (β = 0.11, CI = 0.04–0.21) at 12 months through changes in levels of stress at 6 weeks. Changes in stress symptoms explained 50%, 45%, 53%, and 64% of the total integrated intervention effect on disability, pain-related self-efficacy, pain intensity, and quality of life, respectively. Indirect intervention effects on pain self-efficacy at 12 months through changes in pain-related coping skills at 6 weeks were also found (β = 0.06, CI = 0.01–0.12). Approximately 31% of the total effect of the integrated intervention on pain-related self-efficacy was mediated by coping. The direct effects of the integrated intervention on pain-related disability, pain self-efficacy, pain intensity, and HRQoL (mental health) at 12 months were not significant. Model 1 showed a good fit for the data (χ^2 (31) = 47.30, $P = 0.03$, CFI = 0.96, RMSEA = 0.07, SRMR = 0.08). The total variance accounted for by each of the health outcomes ranged from 30% to 46% in Model 1. Refer to Table S1 in the supplementary materials for R^2 values for the mediators and outcome variables (available at http://links.lww.com/PR9/A71).

3.2. Model 2: testing depression and pain-related coping as mediators

The results of Model 2 are depicted in **Figure 2**. There was a direct effect of the integrated intervention on depression and pain-related coping skills at 6 weeks. There were direct effects of depression on pain-related disability, pain self-efficacy, pain intensity, and HRQoL (mental health) at 12 months and a direct effect of pain-related coping on pain self-efficacy only. The integrated intervention showed indirect effects on pain-related disability (β = −0.09, CI = −0.16 to −0.02), pain self-efficacy (β = 0.06, CI = 0.01–0.12), pain intensity (β = −0.08, CI = −0.15 to −0.02), and HRQoL (mental health) (β = 0.10, CI = 0.03–0.18) at 12 months through changes in levels of depression at 6 weeks. Changes in depressive symptoms explained 33%, 27%, 31%, and 52% of the total integrated intervention effect on disability, pain-related self-efficacy, pain intensity, and quality of life,

Table 3

Direct, indirect, and total effects.

	Outcomes at 12 mo											
	Pain-related disability			Pain-related self efficacy			Pain intensity			HRQoL (mental health)		
	B	β	95% CI	B	β	95% CI	B	β	95% CI	B	β	95% CI
Model 1												
Direct	−4.03	−0.11	−0.27 to 0.08	1.44	0.05	−0.14 to 0.22	−0.41	−0.08	−0.26 to 0.10	1.22	0.05	−0.14 to 0.23
Indirect through stress	**−4.49**	**−0.12**	**−0.21** to **−0.06**	**2.70**	**0.09**	**0.02** to **0.18**	**−0.61**	**−0.12**	**−0.21** to **−0.06**	**2.64**	**0.11**	**0.04** to **0.21**
Indirect through coping skills	−0.42	−0.01	−0.06 to 0.02	**1.89**	**0.06**	**0.01** to **0.12**	−0.14	−0.03	−0.08 to 0.01	0.23	0.01	−0.03 to 0.05
Total indirect	**−4.92**	**−0.14**	**−0.24** to **−0.06**	**4.58**	**0.14**	**0.05** to **0.25**	**−0.75**	**−0.15**	**−0.24** to **−0.08**	**2.87**	**0.12**	**0.04** to **0.22**
Total	**−8.94**	**−0.25**	**−0.40** to **−0.08**	**6.02**	**0.19**	**0.04** to **0.35**	**−1.16**	**−0.24**	**−0.41** to **−0.06**	**4.09**	**0.17**	**0.01** to **0.33**
Proportion mediated	55%			76%			64%			70%		
Model 2												
Direct	−6.26	−0.17	−0.34 to 0.01	2.78	0.09	−0.07 to 0.26	−0.73	−0.15	−0.34 to 0.03	2.06	0.08	−0.08 to 0.26
Indirect through depression	**−3.24**	**−0.09**	**−0.16** to **−0.02**	**1.76**	**0.06**	**0.01** to **0.12**	**−0.39**	**−0.08**	**−0.15** to **−0.02**	**2.37**	**0.10**	**0.03** to **0.18**
Indirect through coping skills	−0.27	−0.01	−0.06 to 0.03	**1.84**	**0.06**	**0.01** to **0.12**	−0.13	−0.03	−0.07 to 0.01	0.09	0.004	−0.04 to 0.04
Total indirect	**−3.52**	**−0.10**	**−0.18** to **−0.03**	**3.60**	**0.11**	**0.04** to **0.20**	**−0.52**	**−0.11**	**−0.18** to **−0.04**	**2.46**	**0.10**	**0.02** to **0.18**
Total	**−9.77**	**−0.27**	**−0.43** to **−0.10**	**6.39**	**0.20**	**0.05** to **0.36**	**−1.25**	**−0.25**	**−0.43** to **−0.08**	**4.52**	**0.19**	**0.03** to **0.36**
Proportion mediated	36%			56%			41%			54%		
Model 3												
Direct	**−6.91**	**−0.19**	**−0.34** to **−0.03**	3.15	0.10	−0.06 to 0.26	−0.80	−0.16	−0.33 to 0.01	2.59	0.11	−0.05 to 0.27
Indirect through posttraumatic stress	**−2.54**	**−0.07**	**−0.14** to **−0.01**	**1.57**	**0.05**	**0.01** to **0.11**	**−0.38**	**−0.08**	**−0.15** to **−0.02**	**1.92**	**0.08**	**0.02** to **0.15**
Indirect through coping skills	−0.60	−0.02	−0.07 to 0.02	**1.99**	**0.06**	**0.01** to **0.13**	−0.16	−0.03	−0.08 to 0.002	0.31	0.01	−0.03 to 0.05
Total indirect	**−3.14**	**−0.09**	**−0.17** to **−0.03**	**3.55**	**0.11**	**0.04** to **0.20**	**−0.54**	**−0.11**	**−0.20** to **−0.04**	**2.23**	**0.09**	**0.02** to **0.16**
Total	**−10.05**	**−0.27**	**−0.43** to **−0.11**	**6.71**	**0.21**	**0.06** to **0.37**	**−1.34**	**−0.27**	**−0.44** to **−0.09**	**4.81**	**0.20**	**0.04** to **0.36**
Proportion mediated	31%			53%			40%			46%		

Significant effects are shown in bold; unstandardized (B) and standardized (β) estimates shown. Bootstrapped 95% CIs for indirect paths.
Proportion mediated is the unstandardized total indirect effects divided by the total effects.
CI, confidence intervals; HRQoL, Health-related Quality of Life.

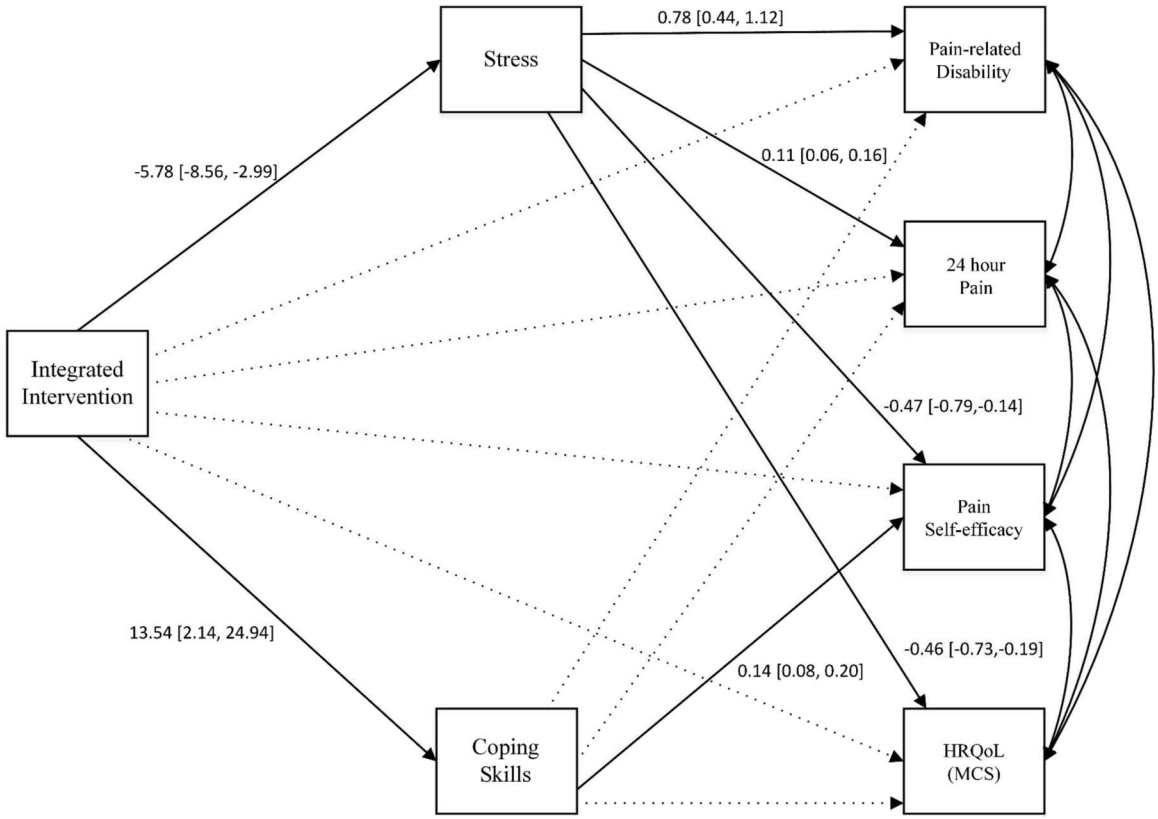

Figure 1. Model 1: Paths between the integrated intervention and 12-month outcomes through changes in stress and coping skills at 6 weeks; solid lines represent significant paths; dotted lines are nonsignificant; HRQoL (MCS), health-related quality of life (mental component score). Baseline variables not shown for clarity.

respectively. Indirect intervention effects on pain self-efficacy at 12 months were also found through changes in pain-related coping skills at 6 weeks (β = 0.06, CI = 0.01–0.12). Improvements in coping skills accounted for approximately 29% of the total integrated intervention effect on pain-related self-efficacy. There were no significant direct effects of the integrated intervention on disability, pain self-efficacy, pain intensity, and HRQoL. Model 2 showed a good fit for the data (χ^2 (31) = 44.75, P = 0.05, CFI = 0.97, RMSEA = 0.07, SRMR = 0.08). The total variance accounted for by each of the health outcomes ranged from 27% to 45% in Model 2 (refer to Table S1 in the supplementary materials for R^2 values, available at http://links.lww.com/PR9/A71).

3.3. Model 3: testing posttraumatic stress and pain-related coping as mediators

The results of Model 3 are depicted in **Figure 3**. There was a direct effect of the integrated intervention on posttraumatic stress symptoms and pain-related coping skills at 6 weeks. There were direct effects of posttraumatic stress symptoms on pain-related disability, pain self-efficacy, pain intensity, and HRQoL (mental health) at 12 months and a direct effect of pain-related coping on pain self-efficacy only. There were indirect effects of the integrated intervention on pain-related disability (β = −0.07, CI = −0.14 to −0.01), pain self-efficacy (β = 0.05, CI = 0.01–0.11), pain intensity (β = −0.08, CI = −0.15 to −0.02), and HRQoL (mental health) (β = 0.08, CI = 0.02–0.15) at 12 months through changes in posttraumatic stress symptoms at 6 weeks. Changes in posttraumatic symptoms explained 25%, 23%, 28%, and 40% of the total integrated intervention effect on disability, pain-related self-efficacy, pain intensity, and quality of life, respectively. There was an indirect intervention effect on pain self-efficacy at 12 months through changes in pain-related coping skills at 6 weeks (β = 0.06, CI = 0.01–0.13). Approximately 30% of the total effect of the integrated intervention on pain-related self-efficacy was mediated by coping skills. The direct effect of the integrated intervention on pain-related disability at 12 months was significant but not on pain intensity, pain self-efficacy, and HRQoL. Model 3 showed a good fit for the data (χ^2 (31) = 37.51, P = 0.20, CFI = 0.98, RMSEA = 0.05, SRMR = 0.07). The total variance accounted for by each of the health outcomes ranged from 33% to 48% (again, refer to Table S1 in the supplementary materials, available at http://links.lww.com/PR9/A71).

4. Discussion

Establishing effectiveness of integrated psychological and physical treatments for musculoskeletal pain in RCTs is important. Also important is to determine how these treatments work according to theory or other yet unidentified mechanisms. This secondary analysis of an RCT examined the underlying change mechanisms of an integrated physiotherapist-delivered psychological and exercise intervention for patients at risk of poor recovery after acute whiplash injury. Overall, the results support our hypothesis that improvements in multiple health outcomes are mediated by improvements in the intended intervention target of stress, as well as improvements in pain-related coping, which led to improvements in pain self-efficacy only. Stress-related constructs of depressive and posttraumatic stress symptoms were also important mechanisms of effect in an integrated intervention on health outcomes.

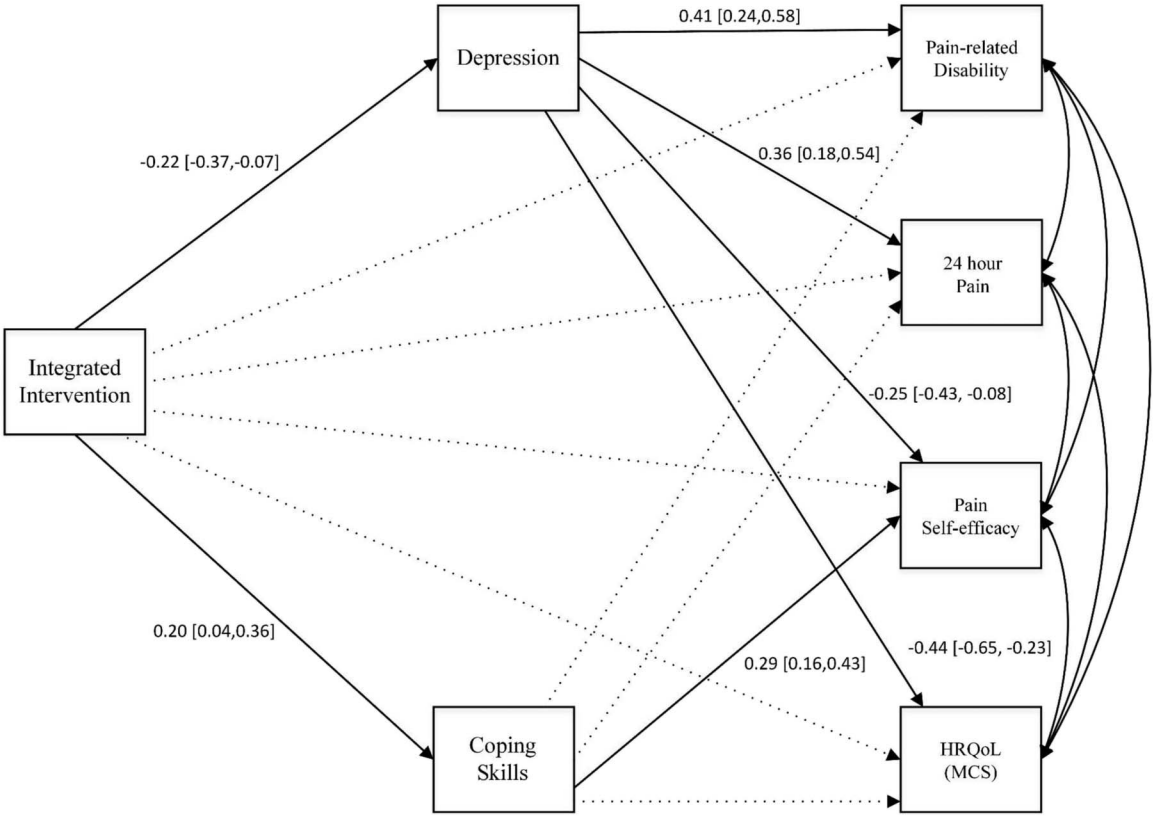

Figure 2. Model 2: Paths between the integrated intervention and 12-month outcomes through changes in depression and coping skills at 6 weeks; solid lines represent significant paths; dotted lines are nonsignificant; HRQoL (MCS), health-related quality of life (mental component score). Baseline variables not shown for clarity.

Intervention approaches that target early psychological risk factors known to delay recovery in addition to physical rehabilitation can lead to improved health outcomes for individuals with musculoskeletal pain.[9,12,27,36] No studies have been conducted examining if integrated psychological and exercise interventions for acute WAD exert their effects through intended intervention targets. Consistent with the StressModex RCT,[36] stress, depression, posttraumatic stress symptoms, and pain-related coping skills improved at 6 weeks after the integrated intervention compared with physiotherapy exercise alone. Stress was shown to be an important causal mechanism of therapeutic improvement, explaining 45% to 64% of the total effects of the integrated intervention on pain-related disability, pain intensity, pain self-efficacy, and HRQoL; 31% of the total intervention effects on pain self-efficacy were mediated by improvements in pain-related coping. The findings suggest that integrated interventions designed to target stress as a psychological risk factor after acute WAD can be beneficial for achieving a range of patient-relevant recovery outcomes. Components of the integrated intervention were explicitly designed to target levels of stress by enhancing patients' ability to cope with stress associated with pain and injury. For example, relaxation strategies were incorporated to address physiological arousal, and positive coping statements were used to address negative cognitions.

Broadly, the results of this study are in line with cognitive behavioral theory and previous investigations of psychological change processes over the course of cognitive behavioral therapies including acceptance and commitment therapy for chronic pain conditions.[21,38] Generally, in these studies, psychological interventions are delivered by psychologists. Our findings suggest that physiotherapists as well as psychologists can elicit changes in psychological variables in patients who have mild to moderate baseline scores and that these are the mechanisms by which the integrated intervention worked. They add to the emerging research in low back pain, which shows that the effects of psychologically informed vs usual primary care physiotherapy are associated with improved disability through changes in pain-related distress and pain severity.[23]

Causal mechanisms of change had consistent effects on health outcomes in each model. Similar to the pattern of findings in Model 1, 27% to 52% of the total effects of the integrated intervention on the 4 outcomes at 12 months were mediated by reductions in depressive symptoms and 29% of the total intervention effects on pain self-efficacy by improvements in pain-related coping (Model 2); 23% to 40% of the total integrated intervention effects on health outcomes were mediated by posttraumatic stress and 30% of the total integrated intervention effects on pain self-efficacy by pain-related coping (Model 3). These findings suggest that a number of stress-related constructs including depressive and posttraumatic stress symptoms are underlying mechanisms of therapeutic improvement for acute WAD. Measures of stress, depression, and posttraumatic stress symptoms used in this study were highly correlated, indicating a significant degree of overlap. Stress occurs when perceived environmental demands exceed the adaptive capacity to cope while measures of depression and posttraumatic stress capture more individual differences in affective and behavioral experiences suggestive of psychopathology.[5,6,20] Perceptions of stress are not the same construct as depressive or posttraumatic stress

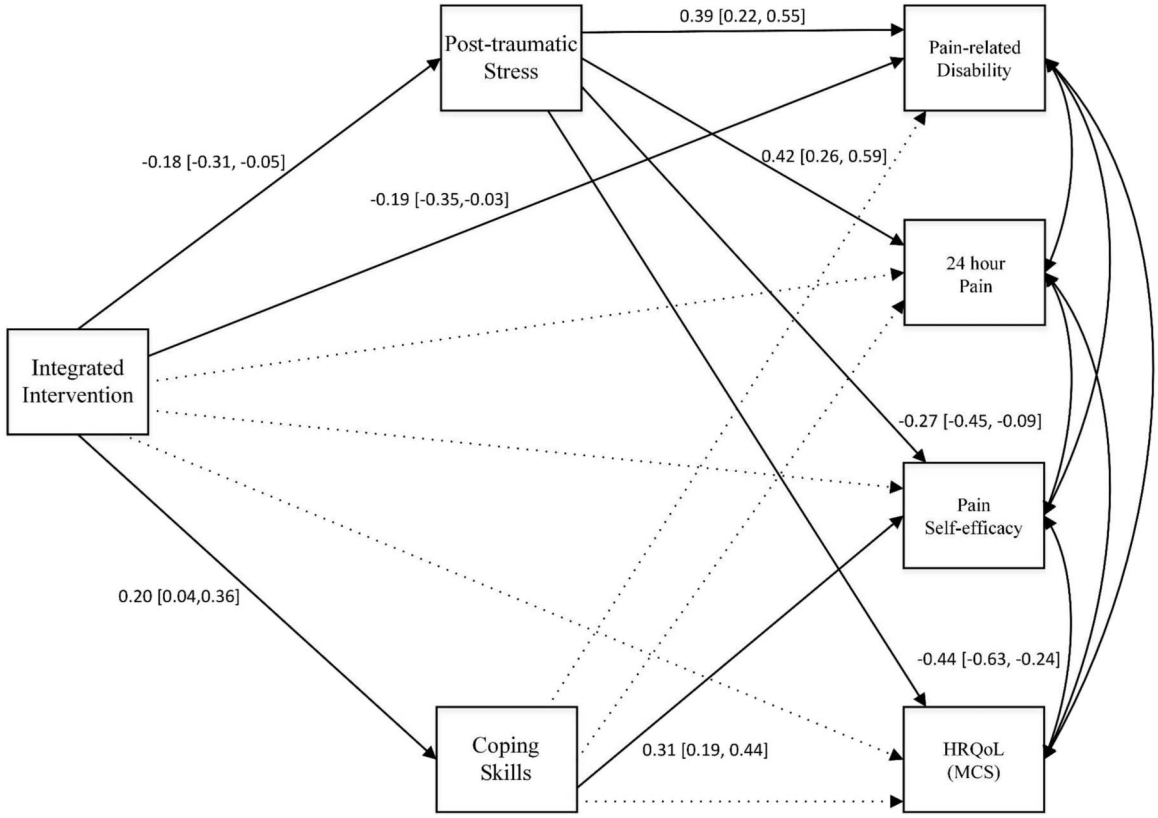

Figure 3. Model 3: Paths between the integrated intervention and 12-month outcomes through changes in posttraumatic stress and coping skills at 6 weeks; solid lines represent significant paths; dotted lines are nonsignificant; HRQoL (MCS), health-related quality of life (mental component score). Baseline variables not shown for clarity.

symptoms, although there is overlap.[6] Previous research has shown depressive symptoms and posttraumatic stress symptoms to be highly correlated.[8] However, validation studies of the DASS in clinical samples indicate correlations between 0.45 and 0.66 and distinguish between 3 separate factors.[1] Other research using community samples suggests there may be a common underlying factor of psychological distress as well as specific depression, anxiety, and stress factors.[11]

Changes in pain-related coping skills were also shown to mediate the effects of the integrated intervention but on pain self-efficacy only. For patients who received the integrated intervention, improvements in their ability to cope with pain led to improvements in their beliefs about their ability to perform certain activities when experiencing pain but not their functional ability to carry these out, or levels of pain. In the integrated intervention, coping strategies such as relaxation and developing coping statements aimed to help patients manage stress rather than pain. One session consisted of cognitive skill development, which involved patients developing positive coping statements to help them manage stressful situations. Coping strategies measured by the Coping Strategies Questionnaire[30] such as using distraction, ignoring sensations, and reinterpreting sensations were not included in the sessions. Therefore, it is possible that the integrated intervention failed to cause sufficient change in pain-related coping skills to improve disability-related outcomes. Previous research has suggested that changes in pain coping may not mediate specific treatment outcomes.[14,38] Failure to find mediation effects for pain-related coping on pain and disability does not mean it is not a critical mechanism. It is possible that coping with daily stressors and problems not measured in this study could be important. Temporal ordering of coping and stress-related variables or interactions between mediators could be considered in future studies. Finally, it may be possible to produce functional gains if pain-related coping skills are increased using other intervention techniques.

4.1. Limitations

This study had some limitations. We adjusted for baseline variables but did not control for possible confounders such as the number of treatment sessions patients completed or the extent to which physiotherapists adhered to the treatment protocol. As reported in the main trial, treatment completion and therapist adherence were high (>90%). The relatively small sample size may have resulted in insufficient power to detect small indirect effects through pain-related coping on other outcome variables. To enhance precision, we used bootstrapping methods to estimate 95% CIs, which is recommended when estimating indirect effects in mediation models with small to moderate sample sizes.[31] Because mediational analyses were designed post hoc, other potential cognitive behavioral and physical mediating factors were not measured. Due to multicollinearity, we did not include stress, depression, and posttraumatic stress mediators in a single model and were unable to account for the effects of correlated measurement error. We only investigated changes in mediating factors at 6-weeks post-intervention and did not account for subsequent changes that may have occurred over time. The results are also limited to individuals with acute WAD who have mild to moderate symptoms of stress.

4.2. Strengths and future directions

This is one of the first studies to apply causal test of mediation to examine mechanisms of effect within the context of an RCT for acute WAD. It contributes to the emerging evidence base in favour of a theory-driven CBT approach by showing that changes in stress and pain-related coping are the processes by which a physiotherapist-delivered integrated psychological and exercise intervention worked. We assessed more than one mediator and included cognitive behavioral and alternative stress-based mediators. We also studied the effect of the mediators on multiple recovery outcomes and were able to show that improvements in self-efficacy can be reached through more than one path.

The results suggest that the integrated intervention effects could also be mediated through other pathways. Potential mediating variables such as pain-related fear known to be associated with poor recovery[25] and general (process) variables such as the clinician–patient alliance and patient expectations could be tested. Because the integrated intervention also included 10 exercise sessions, changes in measures targeted by this component of the intervention such as strength, coordination, and physical activity levels could be explored. Future research could consider incorporating objective measures of physiological stress reactivity as well as self-report measures of stress in childhood and cumulative life stress. Despite research showing that reductions in pain catastrophizing can mediate improvements in functioning,[32] it is possible that it might be a mediator in both integrated interventions and physical therapy only interventions because we did not find pain catastrophizing scores were different between the 2 groups. Possible shared vs specific mechanisms associated with the integrated and exercise interventions require further attention. Future RCTs should plan and design a priori mediational analyses to identify potential causal mechanisms. Potential moderators could also be tested such as number of completed sessions. Although the stress inoculation training did not specifically address depressive or posttraumatic stress symptoms, the findings also suggest that patients with acute WAD and at risk of poor recovery could benefit from a more targeted approach that specifically addresses these risk factors. This information could guide the development of more personalized integrated treatment approaches.

5. Conclusions

Improvements in stress, and related constructs of depressive and posttraumatic stress symptoms, as well as pain-related coping were causal mechanisms through which a physiotherapist-delivered integrated intervention exerted its effects on multiple health outcomes. Knowledge that reducing stress is an important treatment target in integrated interventions is useful for patients with WADs, clinicians, and researchers to understand how treatments work, or why they can fail. It also guides which skills of physiotherapists need to be trained. Given scarce health resources, we argue that shifting attention towards further developing and personalizing components of integrated interventions and designing future RCTs with a priori mediational analyses is critical to optimizing treatment effects for individuals with whiplash.

Disclosures

The authors have no conflicts of interest to declare.

Funding for the initial StressModex RCT was received from the National Health and Medical Research Council of Australia (Grant ID: APP1069443).

Acknowledgements

The authors acknowledge Joan Carlisle and Tania Manning for their work coordinating recruitment for the trial. The authors thank the participants who volunteered for the study and the physiotherapy clinics that conducted the treatments. The authors also thank Simone Scotti Requena for assistance with data checking. The authors have no conflicts of interest to declare.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A71.

Article history:
Received 8 February 2020
Received in revised form 25 May 2020
Accepted 15 June 2020
Available online 23 September 2020

References

[1] Brown TA, Chorpita BF, Korotitsch W, Barlow DH. Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. Behav Res Ther 1997;35:79–89.
[2] Burns JW. Mechanisms, mechanisms, mechanisms: it really does all boil down to mechanisms. PAIN 2016;157:2393–4.
[3] Campbell L, Smith A, McGregor L, Sterling M. Psychological factors and the development of chronic whiplash-associated disorder(s): a systematic review. Clin J Pain 2018;34:755–68.
[4] Carroll LJ, Holm LW, Hogg-Johnson S, Cote P, Cassidy JD, Haldeman S, Nordin M, Hurwitz EL, Carragee EJ, van der Velde G, Peloso PM, Guzman J. 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(4 suppl):S83–92.
[5] Cohen S, Kessler RC, Gordon LU. Strategies for measuring stress in studies of psychiatric and physical disorders. Measuring stress: a guide for health and social scientists. New York: Oxford University Press, 1995. p. 3–26.
[6] Epel ES, Crosswell AD, Mayer SE, Prather AA, Slavich GM, Puterman E, Mendes WB. More than a feeling: a unified view of stress measurement for population science. Front Neuroendocrin 2018;49:146–69.
[7] Foa EB, Cashman L, Jaycox L, Perry K. The validation of a self-report measure of posttraumatic stress disorder: the Posttraumatic Diagnostic Scale. Psychol Assess 1997;9:445–51.
[8] Foa EB, Meadows EA. Psychosocial treatments for posttraumatic stress disorder: a critical review. Annu Rev Psychol 1997;48:449–80.
[9] Hansen Z, Daykin A, Lamb SE. A cognitive-behavioural programme for the management of low back pain in primary care: a description and justification of the intervention used in the Back Skills Training Trial (BeST; ISRCTN 54717854). Physiotherapy 2010;96:87–94.
[10] Hawthorne G, Osborne RH, Taylor A, Sansoni J. The SF36 Version 2: critical analyses of population weights, scoring algorithms and population norms. Qual Life Res 2007;16:661–73.
[11] Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. Br J Clin Psychol 2005;44:227–39.
[12] Hill JC, Whitehurst DGT, Lewis M, Bryan S, Dunn KM, Foster NE, Konstantinou K, Main CJ, Mason E, Somerville S, Sowden G, Vohora K, Hay EM. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. Lancet 2011;378:1560–71.
[13] Hu L-T, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Structural Equation Modeling: A Multidisciplinary Journal, 1999;6:1–55.
[14] Jensen MP, Turner JA, Romano JM. Correlates of improvement in multidisciplinary treatment of chronic pain. J Consult Clin Psychol 1994;62:172–9.

[15] Jull G, Kenardy J, Hendrikz J, Cohen M, Sterling M. Management of acute whiplash: a randomized controlled trial of multidisciplinary stratified treatments. PAIN 2013;154:1798–806.
[16] Kamper SJ, Rebbeck TJ, Maher CG, McAuley JH, Sterling M. Course and prognostic factors of whiplash: a systematic review and meta-analysis. PAIN 2008;138:617–29.
[17] Kongsted A, Bendix T, Qerama E, Kasch H, Bach FW, Korsholm L, Jensen TS. Acute stress response and recovery after whiplash injuries. A one-year prospective study. Eur J Pain 2008;12:455–63.
[18] Lamb SE, Gates S, Williams MA, Williamson EM, Mt-Isa S, Withers EJ, Castelnuovo E, Smith J, Ashby D, Cooke MW, Petrou S, Underwood MR. Emergency department treatments and physiotherapy for acute whiplash: a pragmatic, two-step, randomised controlled trial. Lancet 2013;381:546–56.
[19] Lazaridou A, Edwards RR. Getting personal: the role of individual patient preferences and characteristics in shaping pain treatment outcomes. PAIN 2016;157:1–2.
[20] Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer, 1984.
[21] Lin J, Klatt LI, McCracken LM, Baumeister H. Psychological flexibility mediates the effect of an online-based acceptance and commitment therapy for chronic pain: an investigation of change processes. PAIN 2018;159:663–72.
[22] Lovibond SH, Lovibond PF. Manual for the depression anxiety stress scales. Sydney, Australia: Psychology Foundation of Australia, 1995.
[23] Mansell G, Hill JC, Main C, Vowles KE, van der Windt D. Exploring what factors mediate treatment effect: example of the STarT Back study high-risk intervention. J Pain 2016;17:1237–45.
[24] Marsh HW, Hau KT, Wen Z. In Search of golden rules: comment on hypothesis-testing approaches to setting cutoff values for fit indexes and dangers in overgeneralizing Hu and Bentler's (1999) findings. Structural Equation Modeling: A Multidisciplinary Journal. 2004;11:320–341.
[25] Martinez-Calderon J, Flores-Cortes M, Morales-Asencio JM, Luque-Suarez A. Pain-related fear, pain intensity and function in individuals with chronic musculoskeletal pain: a systematic review and meta-analysis. J Pain 2019;20:1394–1415.
[26] Muthén LK, Muthén BO. Mplus user's guide. 8th ed. Los Angeles: Muthén & Muthén, 2017.
[27] Nicholas MK, Costa DSJ, Linton SJ, Main CJ, Shaw WS, Pearce G, Gleeson M, Pinto RZ, Blyth FM, McAuley JH, Smeets RJEM, McGarity A. Implementation of early intervention protocol in Australia for high risk injured workers is associated with fewer lost work days over 2 years than usual (stepped) Care. J Occup Rehabil 2020;30:93–104.
[28] Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. 2007;11:153–63.
[29] Ritchie C, Kenardy J, Smeets R, Sterling M. StressModEx—physiotherapist-led stress inoculation training integrated with exercise for acute whiplash injury: study protocol for a randomised controlled trial. J Physiother 2015;61:157.
[30] Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low back pain patients: relationship to patient characteristics and current adjustment. PAIN 1983;17:33–44.
[31] Shrout PE, Bolger N. Mediation in experimental and nonexperimental studies: new procedures and recommendations. Psychol Methods 2002;7:422–45.
[32] Smeets RJ, Vlaeyen JW, Kester AD, Knottnerus JA. Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. J Pain 2006;7:261–71.
[33] Southerst D, Nordin MC, Côté P, Shearer HM, Varatharajan S, Yu H, Wong JJ, Sutton DA, Randhawa KA, van der Velde GM, Mior SA, Carroll LJ, Jacobs CL, Taylor-Vaisey AL. Is exercise effective for the management of neck pain and associated disorders or whiplash-associated disorders? A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Spine J 2016;16:1503–23.
[34] State Insurance Regulatory Authority. Guidelines for the management of acute whiplash associated disorders for health professionals. Sydney, Australia: State Insurance Regulatory Authority, 2014.
[35] 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.
[36] Sterling M, Smeets R, Keijzers G, Warren J, Kenardy J. Physiotherapist-delivered stress inoculation training integrated with exercise versus physiotherapy exercise alone for acute whiplash-associated disorder (StressModex): a randomised controlled trial of a combined psychological/physical intervention. Br J Sports Med 2019;53:1240–1247.
[37] Teasell RW, McClure JA, Walton D, Pretty J, Salter K, Meyer M, Sequeira K, Death B. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): part 2—interventions for acute WAD. Pain Res Manag 2010;15:295–304.
[38] Turner JA, Holtzman S, Mancl L. Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain. PAIN 2007;127:276–86.
[39] Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J Manipulative Physiol Ther 1991;14:409–15.
[40] Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, Carter A, Casey DC, Charlson FJ, Chen AZ, Coggeshall M, Cornaby L, Dandona L, Dicker DJ, Dilegge T, Erskine HE, Ferrari AJ, Fitzmaurice C, Fleming T, Forouzanfar MH, Fullman N, Gething PW, Goldberg EM, Graetz N, Haagsma JA, Hay SI, Johnson CO, Kassebaum NJ, Kawashima T, Kemmer L, Khalil IA, Kinfu Y, Kyu HH, Leung J, Liang X, Lim SS, Lopez AD, Lozano R, Marczak L, Mensah GA, Mokdad AH, Naghavi M, Nguyen G, Nsoesie E, Olsen H, Pigott DM, Pinho C, Rankin Z, Reinig N, Salomon JA, Sandar L, Smith A, Stanaway J, Steiner C, Teeple S, Thomas BA, Troeger C, Wagner JA, Wang H, Wanga V, Whiteford HA, Zoeckler L, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abraham B, Abubakar I, Abu-Raddad LJ, Abu-Rmeileh NME, Ackerman IN, Adebiyi AO, Ademi Z, Adou AK, Afanvi KA, Agardh EE, Agarwal A, Kiadaliri AA, Ahmadieh H, Ajala ON, Akinyemi RO, Akseer N, Al-Aly Z, Alam K, Alam NKM, Aldhahri SF, Alegretti MA, Alemu ZA, Alexander LT, Alhabib S, Ali R, Alkerwi AA, Alla F, Allebeck P, Al-Raddadi R, Alsharif U, Altirkawi KA, Alvis-Guzman N, Amare AT, Amberbir A, Amini H, Ammar W, Amrock SM, Andersen HH, Anderson GM, Anderson BO, Antonio CAT, Aregay AF, Ärnlöv J, Artaman A, Asayesh H, Assadi R, Atique S, Avokpaho EFGA, Awasthi A, Quintanilla BPA, Azzopardi P, Bacha U, Badawi A, Balakrishnan K, Banerjee A, Barac A, Barker-Collo SL, Bärnighausen T, Barregard L, Barrero LH, Basu A, Bazargan-Hejazi S, Beghi E, Bell B, Bell ML, Bennett DA, Bensenor IM, Benzian H, Berhane A, Bernabé E, Betsu BD, Beyene AS, Bhala N, Bhatt S, Biadgilign S, Bienhoff K, Bikbov B, Biryukov S, Bisanzio D, Bjertness E, Blore J, Borschmann R, Boufous S, Brainin M, Brazinova A, Breitborde NJK, Brown J, Buchbinder R, Buckle GC, Butt ZA, Calabria B, Campos-Nonato IR, Campuzano JC, Carabin H, Cárdenas R, Carpenter DO, Carrero JJ, Castañeda-Orjuela CA, Rivas JC, Catalá-López F, Chang JC, Chiang PPC, Chibueze CE, Chisumpa VH, Choi JYJ, Chowdhury R, Christensen H, Christopher DJ, Ciobanu LG, Cirillo M, Coates MM, Colquhoun SM, Cooper C, Cortinovis M, Crump JA, Damtew SA, Dandona R, Daoud F, Dargan PI, das Neves J, Davey G, Davis AC, Leo DD, Degenhardt L, Gobbo LCD, Dellavalle RP, Deribe K, Deribew A, Derrett S, Jarlais DCD, Dharmaratne SD, Dhillon PK, Diaz-Torné C, Ding EL, Driscoll TR, Duan L, Dubey M, Duncan BB, Ebrahimi H, Ellenbogen RG, Elyazar I, Endres M, Endries AY, Ermakov SP, Eshrati B, Estep K, Farid TA, Farinha CSeS, Faro A, Farvid MS, Farzadfar F, Feigin VL, Felson DT, Fereshtehnejad SM, Fernandes JG, Fernandes JC, Fischer F, Fitchett JRA, Foreman K, Fowkes FGR, Fox J, Franklin RC, Friedman J, Frostad J, Fürst T, Futran ND, Gabbe B, Ganguly P, Gankpé FG, Gebre T, Gebrehiwot TT, Gebremedhin AT, Geleijnse JM, Gessner BD, Gibney KB, Ginawi IAM, Giref AZ, Giroud M, Gishu MD, Giussani G, Glaser E, Godwin WW, Gomez-Dantes H, Gona P, Goodridge A, Gopalani SV, Gotay CC, Goto A, Gouda HN, Grainger R, Greaves F, Guillemin F, Guo Y, Gupta R, Gupta R, Gupta V, Gutiérrez RA, Haile D, Hailu AD, Hailu GB, Halasa YA, Hamadeh RR, Hamidi S, Hammami M, Hancock J, Handal AJ, Hankey GJ, Hao Y, Harb HL, Harikrishnan S, Haro JM, Havmoeller R, Hay RJ, Heredia-Pi IB, Heydarpour P, Hoek HW, Horino M, Horita N, Hosgood HD, Hoy DG, Htet AS, Huang H, Huang JJ, Huynh C, Iannarone M, Iburg KM, Innos K, Inoue M, Iyer VJ, Jacobsen KH, Jahanmehr N, Jakovljevic MB, Javanbakht M, Jayaraman SP, Jayatilleke AU, Jee SH, Jeemon P, Jensen PN, Jiang Y, Jibat T, Jimenez-Corona A, Jin Y, Jonas JB, Kabir Z, Kalkonde Y, Kamal R, Kan H, Karch A, Karema CK, Karimkhani C, Kasaeian A, Kaul A, Kawakami N, Keiyoro PN, Kemp AH, Keren A, Kesavachandran CN, Khader YS, Khan AR, Khan EA, Khang YH, Khera S, Khoja TAM, Khubchandani J, Kieling C, Kim P, Kim C-i, Kim D, Kim YJ, Kissoon N, Knibbs LD, Knudsen AK, Kokubo Y, Kolte D, Kopec JA, Kosen S, Kotsakis GA, Koul PA, Koyanagi A, Kravchenko M, Defo BK, Bicer BK, Kudom AA, Kuipers EJ, Kumar GA, Kutz M, Kwan GF, Lal A, Lalloo R, Lallukka T, Lam H, Lam JO, Langan SM, Larsson A, Lavados PM, Leasher JL, Leigh J, Leung R, Levi M, Li Y, Li Y, Liang J, Liu S, Liu Y, Lloyd BK, Lo WD, Logroscino G, Looker KJ, Lotufo PA, Lunevicius R, Lyons RA, Mackay MT, Magdy M, Razek AE, Mahdavi M, Majdan M, Majeed A, Malekzadeh R, Marcenes W, Margolis DJ, Martinez-Raga J, Masiye F, Massano J, McGarvey ST, McGrath JJ, McKee M, McMahon BJ, Meaney PA, Mehari A, Mejia-Rodriguez F, Mekonnen AB, Melaku YA, Memiah P, Memish ZA, Mendoza W, Meretoja A, Meretoja TJ, Mhimbira FA, Millear A, Miller TR, Mills EJ, Mirarefin M, Mitchell PB, Mock CN, Mohammadi A, Mohammed S, Monasta L,

Hernandez JCM, Montico M, Mooney MD, Moradi-Lakeh M, Morawska L, Mueller UO, Mullany E, Mumford JE, Murdoch ME, Nachega JB, Nagel G, Naheed A, Naldi L, Nangia V, Newton JN, Ng M, Ngalesoni FN, Nguyen QL, Nisar MI, Pete PMN, Nolla JM, Norheim OF, Norman RE, Norrving B, Nunes BP, Ogbo FA, Oh IH, Ohkubo T, Olivares PR, Olusanya BO, Olusanya JO, Ortiz A, Osman M, Ota E, Pa M, Park E-K, Parsaeian M, de Azeredo Passos VM, Caicedo AJP, Patten SB, Patton GC, Pereira DM, Perez-Padilla R, Perico N, Pesudovs K, Petzold M, Phillips MR, Piel FB, Pillay JD, Pishgar F, Plass D, Platts-Mills JA, Polinder S, Pond CD, Popova S, Poulton RG, Pourmalek F, Prabhakaran D, Prasad NM, Qorbani M, Rabiee RHS, Radfar A, Rafay A, Rahimi K, Rahimi-Movaghar V, Rahman M, Rahman MHU, Rahman SU, Rai RK, Rajsic S, Ram U, Rao P, Refaat AH, Reitsma MB, Remuzzi G, Resnikoff S, Reynolds A, Ribeiro AL, Blancas MJR, Roba HS, Rojas-Rueda D, Ronfani L, Roshandel G, Roth GA, Rothenbacher D, Roy A, Sagar R, Sahathevan R, Sanabria JR, Sanchez-Niño MD, Santos IS, Santos JV, Sarmiento-Suarez R, Sartorius B, Satpathy M, Savic M, Sawhney M, Schaub MP, Schmidt MI, Schneider IJC, Schöttker B, Schwebel DC, Scott JG, Seedat S, Sepanlou SG, Servan-Mori EE, Shackelford KA, Shaheen A, Shaikh MA, Sharma R, Sharma U, Shen J, Shepard DS, Sheth KN, Shibuya K, Shin M-J, Shiri R, Shiue I, Shrime MG, Sigfusdottir ID, Silva DAS, Silveira DGA, Singh A, Singh JA, Singh OP, Singh PK, Sivonda A, Skirbekk V, Skogen JC, Sligar A, Sliwa K, Soljak M, Søreide K, Sorensen RJD, Soriano JB, Sposato LA, Sreeramareddy CT, Stathopoulou V, Steel N, Stein DJ, Steiner TJ, Steinke S, Stovner L, Stroumpoulis K, Sunguya BF, Sur P, Swaminathan S, Sykes BL, Szoeke CEI, Tabarés-Seisdedos R, Takala JS, Tandon N, Tanne D, Tavakkoli M, Taye B, Taylor HR, Ao BJT, Tedla BA, Terkawi AS, Thomson AJ, Thorne-Lyman AL, Thrift AG, Thurston GD, Tobe-Gai R, Tonelli M, Topor-Madry R, Topouzis F, Tran BX, Truelsen T, Dimbuene ZT, Tsilimbaris M, Tura AK, Tuzcu EM, Tyrovolas S, Ukwaja KN, Undurraga EA, Uneke CJ, Uthman OA, van Gool CH, Varakin YY, Vasankari T, Venketasubramanian N, Verma RK, Violante FS, Vladimirov SK, Vlassov VV, Vollset SE, Wagner GR, Waller SG, Wang L, Watkins DA, Weichenthal S, Weiderpass E, Weintraub RG, Werdecker A, Westerman R, White RA, Williams HC, Wiysonge CS, Wolfe CDA, Won S, Woodbrook R, Wubshet M, Xavier D, Xu G, Yadav AK, Yan LL, Yano Y, Yaseri M, Ye P, Yebyo HG, Yip P, Yonemoto N, Yoon SJ, Younis MZ, Yu C, Zaidi Z, Zaki MES, Zeeb H, Zhou M, Zodpey S, Zuhlke LJ, Murray CJL. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;388:1545–602.