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Do maladaptive beliefs delay whiplash associated disorders (WAD): A systematic review

Erika Gabriela Macias, Vasileios Georgopoulos, Alan Taylor

ABSTRACT

The purpose of the study is to try to establish if maladaptive beliefs effect recovery times and poor outcomes in whiplash associated disorders (WAD). In May 2017 the following databases were searched from their inception until June 2017: SPORT Discuss, CINAHL, PsycINFO, MEDLINE, Ovid MEDLINE, Cochrane, AMED, Embase. A combination of sensitive search strategies was used for locating articles on maladaptive beliefs and WAD. Hand-searching of relevant journals and citation tracking were used to maximise the identified study pool. A total of 189 references were retrieved and an additional three studies were identified through different sources, 178 remained after the removal of duplicates. For 43 references, the full text was assessed, and 7 studies were included. The methodological quality was assessed independently by two assessors. Data extraction was carried out using a standardised data extraction form. Most articles scored a high overall quality and fourteen percent (14%) of articles (1 out of 7) were rated with moderate overall quality. Meta-analysis was not undertaken due to the heterogeneity of prognostic factors, outcome measures and methods used. Four out of the seven studies presented a correlation between catastrophising and disability in at least one follow-up time point (3, 6 or 12 months) whilst three studies found a correlation between fear-avoidance and disability. Four of the studies showed an association between maladaptive beliefs (catastrophising or fear avoidance) and pain and two found a negative effect. Our findings show that outcomes, such as pain and disability, were found to be associated with maladaptive beliefs (catastrophising and fear avoidance).

Keywords: Catastrophising, Fear avoidance, Whiplash

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INTRODUCTION

Whiplash injury due to a road traffic collision is considered common as it composes 75% of all road

traffic collision injuries [1]. The incidence of whiplash associated disorders (WAD) has been increasing over the past 30 years [2]. WAD has become an important burden to healthcare systems, insurance organisations and economies of industrialised countries [3]. In the UK, whiplash effects the economy with an added cost of approximately £3 billion per annum [4]. The Quebec Task Force (QTF) defines the term "whiplash" as an acceleration-deceleration mechanism that results in injury to the neck [5]. This may lead to soft tissue damage, hence resulting in clinical manifestations such as neck pain. The term "whiplash associated disorder" is given to the symptoms presented following a whiplash-related injury and to differentiate it from the acceleration-deceleration mechanism of injury [5]. Around 83% of individuals, who are affected by a motor vehicle collision (MVC), develop WAD [6]. Recovering from WAD can be an extended process that involves significant use of health resources.

Challenges persist in management, prediction of prognosis and functional recovery for patients with WAD. Many patients recover within a normal time frame (less than three months), although a considerable proportion (40–60%) develop chronic and disabling symptoms [7]. Additionally, there appear to be no meaningful changes in the recovery of pain and disability beyond three months following the injury [8]. A challenge that clinicians often encounter is the difficulty to predict the prognosis of functional recovery for patients with WAD. If the prognosis appears to be favourable, clinicians have the option of selecting less-intensive interventions, such as advice and education [9]. On the contrary, if the prognosis seems to be unfavourable, the clinicians should have the ability to recognise and opt for specific, more targeted interventions [9].

The most consistent risk factors for poor recovery are initial elevated levels of pain and disability [1, 10]. Contemporary studies have included psychological factors as prognostic factors. These include pain catastrophising, presence and symptoms of depression, anxiety, fear avoidance and posttraumatic stress symptoms [10, 11]. Low expectations of recovery have also been found to predict outcome in WAD [1, 12]. Maladaptive beliefs, such as fear avoidance beliefs and pain catastrophising, are described as unhelpful evaluative cognitions related to the self in the domain of interpersonal interactions [13]. Screening for maladaptive beliefs incorporates key elements of the biopsychosocial model into clinical practice [14, 15]. The biopsychosocial model attributes injury outcomes to the complex interaction of biological, psychological and social factors [16]. Literature tends to agree that psychological factors such as post-traumatic stress symptoms, pain catastrophising and fear avoidance are common in patients with WAD [17].

Interventions related to cognitive behavioural therapy, propose that beliefs influence pain perception and adjustment to pain. Therefore, it is hypothesised that individuals who present maladaptive beliefs about pain have a higher risk of poor outcomes and impediment to their recovery [18]. Poor treatment outcomes include maintained distress, pain and disability [19, 20].

The aim of this review was to establish if maladaptive beliefs affect recovery times and poor outcomes in WAD and to discuss whether these results have a clinical application.

METHODS

Data sources and searches

The identification of relevant studies was performed through a systematic literature search of SPORTDiscuss, CINAHL, PsycINFO, MEDLINE, Cochrane, AMED and Embase, from database inception until June 2017. The synthesis of maladaptive belief-sensitive searches adapted for this study has been used in the past by similar systematic reviews [8, 17]. However, considering the lack of an accepted and standardised search strategy relevant to WAD, a robust search scheme was needed. The Cochrane Back Group (CBG) [21] proposed a search method for WAD studies. The suggested strategy by the CBG was incorporated by adding recommended keywords to establish the final search plan (Appendix 1).

The search included various terms identified in the literature for maladaptive beliefs (eg, catastophising, catastrophization, maladaptive beliefs, fear of movement) with different combinations and subject headings. Additionally, the reviewers screened bibliographies of all included studies and retrieved review articles by hand to assure the completeness of the literature search and possibly add appropriate references not retrieved by the systematic search. All potential related articles, were included in the full-text review. The inclusion and exclusion criteria also applied to these studies.

A total of 189 references were retrieved, additionally 3 more studies were identified through different sources and 178 remained after the removal of duplicates. For 43 references, the full text was assessed, and 7 studies were included.

Inclusion criteria

Articles were included if they satisfied the following criteria; Adults with WAD, a prospective study design that provided a baseline measure of at least one maladaptive belief variable, such as pain, disability, depression and/or anxiety and were published as full papers in English or with a translation available. No limitations were applied on the type or predictor variables (history, physical examination, imaging, etc.) nor on the clinical setting and the type of patients with WAD.

All relevant literature collected from various databases were downloaded into EndNote – Web were duplicates were removed.

One independent reviewer was assigned to execute the first and second stage of the screening process. The first-stage consisted of the evaluation of titles and abstracts based on the eligibility criteria stated above. All studies allocated for inclusion to the systematic review proceeded to the second-stage along with the studies that were identified through citation tracking or hand searching.

Exclusion criteria

Studies were excluded if they presented the following criteria; Not a primary research study, conference abstracts, PhD thesis, unpublished dissertations and books, did not include at least one maladaptive belief measure, did not present pain and/or disability as an outcome measure and if neck pain was not related with a whiplash injury.

Data extraction and quality assessment

A standardised tool for data extraction was used by two independent reviewers. The data extracted was (a) setting, (b) method of diagnosis, (c) sample selection (d) study population: number of participants and patient characteristics (age, gender, body mass index), (e) study design, (f) duration of study (g) Pain and disability measurements (h) maladaptive belief measure.

Following independent data extraction, the completed forms were compared by two independent reviewers. Disagreement between examiners was resolved by consensus or if needed, by a third party.

Similarly, the quality assessment for the 7 eligible studies was also carried out by 2 reviewers who assessed the studies independently using a quality assessment tool based on clearly defined methodological standards for Randomised control trials (RCTS) and cohort studies. The Quality in Prognosis tool (QUIPS) [22] was used to assess cohort studies whilst the PEDro scale [23] was used to assess the RCT for this review.

Data synthesis

Studies included for this review were expected to manifest elevated levels of heterogeneity, therefore no statistical pooling was attempted for result analysis. This article was composed under the guidelines of the Preferred reporting items of systematic reviews and meta-analysis (PRISMA) [24].

Maladaptive beliefs

Maladaptive beliefs associated with outcomes were extracted from all 6 cohort studies and 1 RCT. A correlation value was considered statistically significant if the reported p-value was less than 0.05, if the article reported that the association was significant, or if the 95% confidence intervals around a rate ratio or similar statistic did not cross 1. Where a maladaptive belief was assessed with respect to the outcome at several time-points in one cohort, data was extracted for a short-term follow-up (less than 6 months) and for long term follow-up (the longest follow-up point greater than or equal to six months).

RESULTS

Study selection

An overview of the search results is presented in Figure 1. Overall, 189 articles were identified. Three additional studies were collected and added to the study pool via hand searching of scientific journals and citation tracking. After duplicates were removed, 178 studies were screened through title and abstract assessment. 43 records were found eligible to progress to the next screening stage where the full-text copies were retrieved for careful examination. Following the application of eligibility criteria and detailed evaluation, 7 studies were included in this review

Characteristics of included studies

The seven studies involved 1 RCT and 6 cohort studies. Three of these studies originated from Australia [25–27], one from Switzerland [28], one from Denmark [29], one from Canada [30] and one from the Netherlands [31]. The RCT by Jull [25] aimed to identify whether multidisciplinary treatments for individuals with acute whiplash had an ability to reduce the incidence of chronicity. Although this study did not specifically try to examine an association between maladaptive beliefs

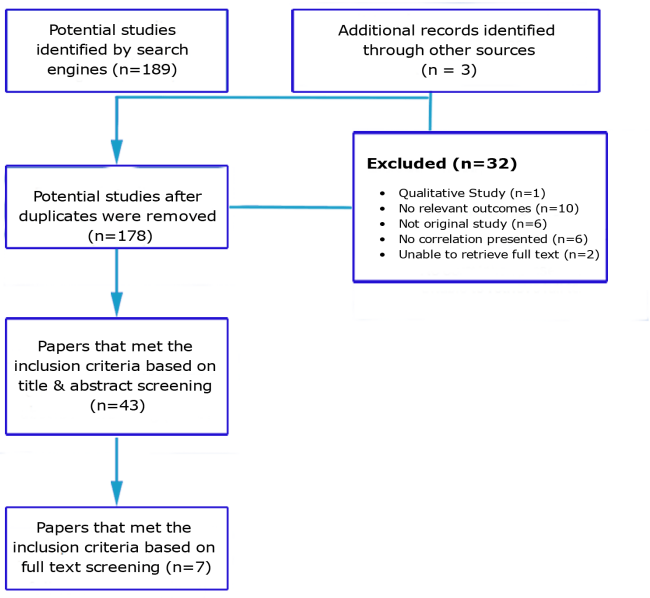

Figure 1: PRISMA flow diagram for search results and study selection.

and disability, the information was provided. The study by Angst [28] focused on finding factors that predicted pain relief, improved physical function and improved working capacity by examining the association between catastrophising and pain. A limitation of the study is the patients' high drop-out rate at baseline as this may indicate attrition bias. Andersen [29] researched pain-catastrophising and fear-avoidance beliefs as mediators to pain as well as post-traumatic stress symptoms by assessing the association between maladaptive beliefs (catastrophising, fear avoidance) and outcome. This study was presented with a short-follow up period and an elevated percentage of individual withdrawal. This should be contemplated when analysing the outcome of the sample size. The cohort study by Buithenhuis [31] inspected the role of catastrophising and causal beliefs with severe persisting neck disorders after a MVC. To assess individual's causal beliefs of post-traumatic neck complaints, the authors used the newly developed Causal Beliefs Questionnaire for Whiplash (CBQ-W). However, the validity and reliability of the CBQ-W has not been formally established. This should be considered when interpreting the results due to the exclusive development of the tool for the purposes of that study. The cohort study by Pedler [27] attempted to examine a model for the maintenance of pain and disability in WAD patients, including PTSD, sensory hypersensitivity, and fear avoidance model factors. The study also assessed the association between catastrophising, kinesiophobia and disability. Bostick [30] studied the predictive capacity of pain beliefs and catastrophising in WAD. Participants were invited to complete maladaptive belief and disability measures at baseline as well as at 3 and 6 months post-injury. Subsequently, using multiple linear regression modelling, baseline belief and catastrophising scores were examined for their association with prospective pain and disability. Findings of the study, must be interpreted with discretion due to the relatively small sample size (n=72). Additionally, Casey [26] intended to determine recovery trajectories based on disability, pain catastrophising and mental health. This study also attempted to investigate linkages between these trajectories, finding a correlation between catastrophising and disability. However, previous history such as trauma, comorbidities or pre-existing physical and mental health were not considered for this study. Appendix 2 includes specific study details.

Qualitative appraisal of included studies

Each study was independently examined by two reviewers. The 6 cohort studies were assessed using the Quality in Prognosis Studies (QUIPS) tool [32]. The QUIPS tool has an interrater agreement (κ statistic) range from 0.56 to 0.82 (median, 0.75). The RCT in this study was assessed using the PEDro scale [23]. The reliability of the PEDro score is described as "fair" to "good", ICC for the total score was 0.56 (95% CI = 0.47 to 0.65).

For this review, there were only four episodes of disagreement in quality assessment, which was resolved by discussion. No disagreements were referred to a third party for settlement. An overall quality score was assigned to each article. Although most articles scored a high overall quality, fourteen percent (14%) of articles (1 out of 7) were rated as a moderate overall quality. The score was due to a lack of adequate description regarding the study participation (place of recruitment not specified), study attrition (differences between participants who completed the study and those who did not) and clear specification of outcome measures. Table 1 displays the quality appraisal scoring for each study.

OUTCOME MEASURES

Pain beliefs

Pain beliefs for catastrophising and fear of movement were measured with various tools. The two most consistent tools used where the pain catastrophising scale (PCS) and the pictorial fear of activities scale - cervical spine (PFActS-C).

The assessment of pain catastrophising for the studies presented in this systematic review were obtained using PCS and the Coping Strategies Questionnaire (CSQ) [33]. The PCS assesses three domains specific for catastrophising (helplessness, rumination and magnification), while the CSQ assesses helplessness and pessimism in the context of pain. The PCS may be considered a wider assessment tool of catastrophising than CSQ. The PCS has been previously found to correlate with outcomes such as pain intensity in conditions such as WAD [34, 35]. Additionally, PCS has been found to have adequate psychometric properties, with acceptable internal consistency (Cronbach's α= 0.66–0.87) [34] and good temporal stability (Pearson's r^2=0.92) in both acute and chronic pain populations [36]. The PCS was used in 4 of the 7 studies [26, 29–31].

Two of the seven studies used the PRActS-C [25, 27].

Table 1: Quality appraisal score for each study

Studies	PEDro	QUIPS
Buitenhuis et al., (2008)		Low
Bostick et al., (2012)		Low
Jull et al., (2013)	7	
Angst et al., (2014)		Moderate
Andersen et al., (2015)		Low
Casey et al., (2015)		Low
Pedler et al., (2016)		Low

QUIPS: Quality in Prognostic Studies tool

This tool assesses fear specifically related to neck pain, it has an acceptable internal consistency of 0.978, a temporal stability (r=0.749, p <0.001) and ICC (0.856, 95% CI: 0.74–0.92) [37]. Other questionnaires used to assess WAD-related pain beliefs were the Survey of Pain Attitudes (SOPA-35) [30], the Pain Beliefs and Perceptions Inventory (PBPI) [30], the Causal Beliefs Questionnnaire (CBQ-W) [31] and the Orebro Musculoskeletal Pain Screening Questionnaire [29].

Pain and disability

The outcome measures for pain and disability were the Neck Disability Index (NDI), Functional Rating Index (FRI), Whiplash Disability Questionnaire (WDQ), Visual Analogue Scale (VAS), 11-point numerical rating scale, the Short Form-36 (SF-36) and the Posttraumatic Stress Diagnostic Scale (PDS). Three studies measured both pain and disability [25, 27, 30] whilst two measured only disability [26, 31] and two others only assessed pain [28, 29]. Three out of seven articles measured disability with the NDI. The NDI has been used extensively in patients with WAD and it has been shown to be reliable, valid and with high internal consistency [38]. One cohort study [26] used the FRI to measure disability. The FRI has shown to have excellent responsiveness, reliability and validity and internal consistency (Cronbach's α=0.92) [39]. The WDQ was also used to assess disability in other studies [21]. It has been shown to have psychometric properties that demonstrate high internal consistency (Cronbach's α=0.96), excellent reproducibility, short-term test-retest reliability and receptiveness in a physiotherapy setting for individuals with acute and chronic WAD [40, 41]. The VAS for pain [95% CI = 0.96 to 0.98] [42] was used by two studies [25, 27], the 11-point numerical rating scale [43] was also used by two studies for its high test-retest reliability (r = 0.96 and 0.95) [29, 30] and one used the SF-36 (Cronbach's α = 0.59) [44]. The PDS was only used by one study [26]. The alpha rating for PDS has been shown to be 0.92 with a test-retest reliability of (r=-0.74) [45].

SUMMARY OF EVIDENCE

Based on the evidence retrieved for this review, only two maladaptive beliefs were reported, fear-avoidance beliefs and catastrophising. Various baseline maladaptive belief measurements were assessed with outcome measurements such as pain and disability, at long-term follow-up (6 to 12 months) and one at short term follow-up (less than 6 months). Results have been summarised in Table 2.

Three [26, 30, 31] out of the seven studies presented an association between baseline catastrophising and disability in at least one follow-up time point (3, 6 or 12 months). In a multiple logistic regression model by Buitenhuis [31] findings demonstrated a slight positive association between baseline catastrophising (PCS) and disability (NDI) at three months (β=0.34, p<0.001) and 12 months (β=0.19, p= 0.035). Causal beliefs at baseline were also found to have an important association with post-whiplash syndrome at 6 months (β=3.00, p<0.001) and 12 months (β=2.39, p=0.002). The study by Bostick et al., (2012) found a significant association between baseline catastrophising (PCS) and disability (WDQ) (β=0.08, p<0.05) at 3 months. Findings on the cohort by Casey et al., [26] demonstrated an association between baseline catastrophising (PCS) and disability (FRI) (β=0.05, p=0.02) following 24 months (Table 3). However, the outcome measure (FRI) was used to examine both pain and function. Using specific measures for each outcome may have provided more precise results. Additionally, the study found an association between baseline catastrophising (PCS) and mental health (SF36 MCS) (β=0.04, p=0.01) at a 12-month follow-up (Table 4).

There were only four studies [25, 26, 30, 31] that found an association between fear-avoidance and disability (Table 3).These studies agreed that higher initial scores for beliefs had an impact on initial and follow-up disability scores. The study by Buitenhuis [31] presented a multiple logistic regression model, using the persistence of post-whiplash syndrome at 6 and 12 months as a dependent variable. Findings demonstrated that causal beliefs regarding whiplash (CBQ-W) can contribute to concurrent disability (NDI) at a 6 (β=3.00, p<0.001) and 12-month follow-up (β=2.39, p=0.002). In accordance to these findings, the RCT by Jull [25] introduced a univariate logistic regression analysis of recovery demonstrating that fear of movement (PFActS-C) had asignificant impact (β=2.54, p<0.001) at 6 months (β=2.54, p<0.001) at 12 months. Bostick [30] carried out a multiple linear regression analysis to examine the capacity of baseline beliefs to predict 3 and 6 months pain intensity and self-reported disability. Baseline patient beliefs (PBPI) about pain were demonstrated to be significantly correlated to disability at 3 months (β=0.18, p<0.05) and 6 months (β=0.14, p<0.05).

The longitudinal study by Pedler [27] demonstrated a nonsignificant association between baseline (6 weeks) and disability (NDI) at 3 months (β=0.18, ns). Additionally, the association between kinesiophobia (TSK) at baseline and NDI did not reach significance (β=0.27, p=0.056) at 3 months.

Findings in five [26–30] of the studies agreed on an association between baseline maladaptive beliefs (catastrophising or fear avoidance) and pain (Table 5). Pain was measured using the 11-point numerical rating scale (NRS), subjective VAS scores and by The North American Spine Society (NASS) questionnaire. In the final regression model by Andersen et al., [29] findings demonstrated an association between post-traumatic stress syndrome (PTSS) and pain intensityfollowing

Table 2: Study Cohorts displaying an association between maladaptive beliefs and treatment outcomes

Cohort Study	Author	Study Design	Sample Size	Was maladaptive beliefs vs Outcome the primary research question?	Diagnosis	Site of Pathology	Baseline Maladaptive Beliefs Measurement	Outcome Variable	Outcome Measure	Statistical Analysis Measurement	Correlation Analysis Findings	Regression Analysis Findings
1	**Angst et al., 2014**	Prospective Cohort Study	185	No	Whiplash	Neck	CSQ	Pain	SF-36, NASS	Regression Analysis		CSQ to Pain (NASS)(6mo): β= 0.348; CSQ to Pain (SF-36 bodily pain) (6 mo): β=0.445
2	**Andersen et al., 2015**	Longitudinal Cohort	198	Yes	Whiplash	Neck	PCS	Pain	11-point Likert Scale	Regression Analysis		Adjusted Estimates: PTTS-PCS to Pain (11-point Likert Scale) (6mo): β= 0.02; PTSS-FA to Pain (11-point Likert Scale) (6mo): β= -0.0004
3	**Bostick et al., 2012**	Prospective Cohort Study	72	Yes	Whiplash	Neck	SOPA-35, PBPI, PCS	Pain and disability	11 point numerical rating scale, WDQ	Regression Analysis		PCS to Pain (NRS)(3mo): β=0.09; PCS to Pain (NRS) (6mo): β=0.10; PBPI Permanence to Pain (NRS) (3mo): β=0.17; PBPI Permanence to Pain (NRS) (6mo): β=0.25; SOPA(mc) to Pain (NRS) (6mo): -0.28. SOPA(mc) to Disability (WDQ) (6mo): β=-0.19; PBPI Mystery to WDQ (6mo): β=0.18; PBPI Permanence to WDQ (3mo): β=0.18; PBPI Permanence to WDQ (6mo): β=0.14; PCS to WDQ (3mo): β=0.08
4	**Buitenhuis et al., 2008**	Prospective Cohort Study	140	No	Whiplash	Neck	PSC, CBQ-W	Disability	NDI	Regression Analysis		PCS to Disability (NDI) (6mo): β=0.34; PCS to Disability (NDI) (12mo):β=019; CBQ-W whiplash to Disability (NDI) (6mo): β=3.00; CBQ-W whiplash to Disability (NDI) (12mo): β=2.39
5	**Casey et al., 2015**	Cohort	197	Yes	Whiplash	Neck	PCS, SF36MCS	Disability	FRI	Regression Analysis		**Moderate disability**: PCS to Disability (FRI) (12mo): β= 0.05;**Severe Disability:** PCS to disability(FRI)(12mo):β=0.12;**Moderate disability:** PCS to mental heatlh (SF36 MCS) (12mo): β=0.04; **Severe disability:** PCS to mental health (SF36 MCS)(12mo): β=0.07; **Moderate-low catastrophising:** PCS to Pain (FRI)(12mo)= β=0.04
6	**Jull et al., 2013**	RCT	101	No	Whiplash	Neck	PFActS-C	Disability	NDI	Regression Analysis		PFActS-C to Disability (NDI)(6mo):β=2.54; PFActS-C to disability (NDI)(12mo): β=2.54
7	**Pedler et al., 2016**	Longitudinal Cohort	91	No	Whiplash	Neck	TSK, PFActs-C, CSQ, PDS	Pain and disability	VAS, NDI	Regression Analysis	TSK to NDI: r= 0.681; PFActS-C to NDI: r= -0.627; CSQ-C to NDI: r=0.619; CSQ-C to Pain: r=0.444; TSK to Pain: r=0.522; PFActS-C to Pain: r=0.426	TSK to Disability (NDI) (3mo): β=0.27; CSQ-C to Disabilitiy (NDI) (3mo): β=0.97; PFActS-C to Disability (NDI) (3mo):β=0.18; PDS to Disability (NDI) (3mo): β=0.15; PDS to Pain (VAS)(3mo): β=-0.01; TSK to Pain (VAS) (3mo): β=0.03; PFActS-C to Pain (VAS)(3mo): β=-0.03

PCS: Pain Catastrophising Scale; CBQ-W: Causal Beliefs Questionnaire Whiplash; NDI: Neck Disability Index; SOPA-35: Survey of Pain and Attitudes; PBPI: Pain Beliefs and Perceptions Inventory; WDQ: Whiplash Disability Questionnaire; RCT: Randomised Control Trial; PFActS-C: Pictorial Fear of Activity Scale; CSQ: Coping Strategy Questionnaire; SF-36: Short Form 36; NASS: The North American American Spine Society questionnaire; SF36-MCS: SF 36 Mental Component Score; FRI: Functional Rating Index; TSK: Tampa Scale of Kinesiophobia; PDS: PDS:Posttraumatic Stress Diagnostic Scale; VAS: Visual analogue scale

Table 3: Identified association between maladaptive beliefs and disability

Study Cohort	Authors	Study Design	Sample Size	Was maladaptive beliefs vs Outcome the primary question?	Diagnosis	Site of Pathology	Baseline Maladaptive Belief Predictor	Outcome Variable	Outcome Measures	Statystical Analyisis Measure	Association Modalities	(r) / (β) values	p-values	OR	95% CI Lower Limit	95% CI Higher Limit	SE	t-value
1	**Bostick et al., 2012**	Prospective Cohort Study	72	No	Whiplash	Neck	SOPA Medical Cure	Disability	WDQ	Regressional analysis	SOPA Medical Cure to Disability (6mo)	-0.19	<0.05		-0.35	-0.03		
							PBPI Permanence	Disability	WDQ	Regressional analysis	PBPI Permanence to Disability (3mo)	0.18	<0.05		0.05	0.32		
							PBPI Permanence	Disability	WDQ	Regressional analysis	PBPI Permanence to Disability (6mo)	0.14	<0.05		0.07	0.21		
							PCS	Disability	WDQ	Regressional analysis	PCS to Disability (3mo)	0.08	<0.05		0.01	0.16		
2	**Buitenhuis et al., 2008**	Prospective Cohort	140	No	Whiplash	Neck	CBQ-W	Disability	NDI	Regressional analysis	CBQ-W to Disability (6mo)	3.00	<0.001		-1.69	4.31	0.66	4.558
							CBQ-W	Disability	NDI	Regressional analysis	CBQ-W to Disability (12mo)	2.39	0.002		0.92	3.86	0.73	3.260
							PCS	Disability	NDI	Regressional analysis	PCS to Disability (3mo)	0.34	<0.001		0.21	0.47	0.17	5.216
							PCS	Disability	NDI	Regressional analysis	PCS to Disability (12 mo)	0.19	0.035		0.01	0.36	0.09	2.159
3	**Casey et al., 2015**	Cohort	197	Yes	Whiplash	Neck	PCS	Disability	FRI	Regressional analysis	PCS to Disability (24 mo- Moderate Disability)	0.05	0.02	1.05	1.01	1.10	0.02	
							PCS	Disability	FRI	Regressional analysis	PCS to Disability (24mo-severe disability)	0.12	≤0.01	1.11	1.06	1.17	0.03	
4	**Jull et al., 2013**	RCT	101	No	Whiplash	Neck	PFActS-C	Disability	NDI	Regressional analysis	PFActS-C to Disability (6mo)	2.54	<0.001				0.45	
							PFActS-C	Disability	NDI	Regressional analysis	PFActS-C to Disability (12mo)	2.54	<0.001				0.45	
5	**Pedler et al., 2016**	Longitudinal cohort	91	No	Whiplash	Neck	PFActS-C	Disability	NDI	Regressional analysis	PFActS-C to NDI (3mo)	0.18	ns		-0.77	1.1		
							TSK	Disability	NDI	Regressional analysis	TSK to NDI (3mo)	0.27	ns		-0.01	0.54		

SOPA: Survey of Pain Attituedes; PBPI: Pain beliefs and perceptions inventory; WDQ: Whiplash Disability Questionnaire; PCS:Pain Catastrophising Scale; CBQ-W: Causal Beliefs Questionnaire Whiplash; NDI: Neck Disability Index; PFActS-C: Pictorial Fear of Activity Scale; TSK: Tampa Scale of Kinesiophobia

Table 4: Identified association between maladaptive beliefs and mental health/PTSS

Study Cohort	Author	Study Design	Sample Size	Was maladaptive belief vs Outcome the primary question?	Diagnosis	Site of Pathology	Baseline maladaptive belief Predictor	Outcome Variable	Outcome Measure	Statistical Analysis Method	Association Modalities	(r) / (β) values	p-values	OR	95% CI Lower Limit	95% CI Higher Limit	SE
1	**Casey et al., 2015**	Cohort	197	Yes	Whiplash	Neck	PCS	Mental Health	SF36 MCS	Regression analysis	PCS to SF36MCS (moderate low levels)	0.04	0.01	1.04	1.01	1.08	0.02
							PCS	Mental Health	SF36 MCS	Regression analysis	PCS to SF36MCS (severe low levels)	0.070	≤0.01	1.07	1.03	1.12	0.02

PTSS: Post Traumatic Stress Symptoms; PCS: Pain Catastrophising Scale; SF36-MCS: SF 36 Mental Component Score; PDS: Posttraumatic Stress Diagnostic Scale; NDI: Neck Disability Index; VAS: visual analogue scale

Table 5: Identified association between maladaptive beliefs and pain

Study Cohort	Author	Study Design	Sample Size	Was maladaptive beliefs vs Outcome the primary question?	Diagnosis	Site of Pathology	Baseline maladaptive belief Predictor	Outcome Variable	Outcome Measure	Statystical Analyisis Measure	Association Modalities	(r) / (β) values	p-values	R² value	OR	95% CI Lower Limit	95% CI Higher Limit	SE
1	**Angst et al., 2014**	Prospectiv Cohort Study	185	No	Whiplash	Neck	CSQ	Pain	NASS pain	Regressional analysis	CSQ to Pain (6mo)	0.348	0.039					
							CSQ	Pain	SF-36	Regressional analysis	CSQ to Pain (6mo)	0.445	<0.001					
2	**Andersen et al., 2015**	Longitudinal Cohort	198	Yes	Whiplash	Neck	PTSS-PCS	Pain	11 point numerical rating scale	Regressionalanalysis	PTSS-PCS to Pain (6mo)	0.02	0.016			0.01	0.03	
							PTSS-FA (Baseline)	Pain (6 months)	11 point numerical rating scale	Regressional analysis	PTSS-FA to Pain (6mo)	-0.0004	0.890			-0.01	0.004	
3	**Bostick et al., 2012**	Prospective Cohort Study	140	No	Whiplash	Neck	PBPI Permanence	Pain	11 point numerical rating scale	Regressional analysis	PBPIPermanence to Pain (3mo)	0.17	<0.05			0.03	0.3	
							PBPI Permanence	Pain	11 point numerical rating scale	Regressional analysis	PBPI Permanence to Pain (6mo)	0.25	<0.05			0.09	0.41	
							SOPA Medical Cure	Pain	11 point numerical rating scale	Regressional analysis	SOPA Medical Cure to Pain (6mo)	-0.28	<0.05			-0.47	-0.10	
							PCS	Pain	11 point numerical rating scale	Regressional analysis	PCS to Pain (3mo)	0.09	<0.05			0.03	0.16	
							PCS	Pain	11 point numerical rating scale	Regressional analysis	PCS to Pain (6mo)	0.10	<0.05			0	0.18	
4	**Casey et al. 2015**	Cohort	197	Yes	Whiplash	Neck	PCS	Pain	FRI	Regressional analysis	PCS to Pain (12mo)	0.04	≤0.01		1.05	1.01	1.08	
5	**Pedler et al., 2016**	Longitudinal Cohort	91	No	Whiplash	Neck	TSK	Pain	VAS	Correlation analysis	TSK-C to Pain	0.03	0.259					
							PFActS-C	Pain	VAS	Correlation analysis	PFActS-C to Pain	-0.03	0.643					

PBPI: Pain beliefs and perceptions inventory; PCS: Pain Catastrophising Scale; CSQ: Coping strategies Questionnaire; NASS: The North American Spine Society questionnaire; SF-36: Short Form 36; PTSS: Post-traumatic stress symptoms; PCS: Pain-catastrophising; FA: Fear-avoidance beliefs; TSK: Tampa Scale of Kinesiophobia; VAS: Visual analogue scale; PFActS-C: Pictorial Fear of Activity Scale

6 months, which were mediated by baseline pain-catastrophising (PTSS-PCS) (β=0.02, p=0.016) and fear-avoidance beliefs (β=-0.0004, p=0.890). In the study by Bostick [30] the association between baseline catastrophising (PCS) and pain was significant at 3 (β=0.09, p<0.05) and 6 months (β=0.10, p<0.05) follow up. Additionally, patient beliefs about pain at baseline were demonstrated to be significantly associated with pain at 3 (β=0.53, p<0.05) and 6 months (β=0.25, p<0.05). In the prospective cohort study by Angst [28] findings showed that reduction of catastrophising were associated with improvements in three dependent variables (pain, function, working capacity). Catastrophising was associated to disability and a greater display of pain behaviour. Catastrophising (CSQ) at baseline presented an association with pain (NASS) at a 6-month follow-up (β=0.348, p=0.039). However, the study uses two outcome measures that are not specific for pain, which challenges the validity of the results, due to inadequate pain evaluation. The SF-36 measures physical function, social function and comprehensive bodily pain whilst the NASS questionnaire assess physical function, neurogenic symptoms and cervical spine-specific pain. The interactive effects of pain with kinesiophobia (TSK) (β=0.03, p=0.259), and pain with fear of activities (PFActS-C) (β=-0.03, p=0.643) was non-significant according to results found by Pedler et al., (2016). Conversely, the study by Casey [26] demonstrated an association between baseline catastrophising (PCS) and pain (FRI) (β=0.04, p≤0.01).

DISCUSSION

Over the last decade there has been a significant increase in physiotherapy studies related to maladaptive beliefs. This movement in healthcare displays an eagerness for advanced clinical decision-making and the acquisition to cost-effective medical management.

Models such as the fear-avoidance model were originally designed for LBP [46]. Those models have attempted to analyse precise beliefs that impact LBP-related outcomes [46]. Pain beliefs related to WAD are less well understood [47].

To the author's knowledge, there is no other review that systematically attempted to appraise and establish the effects of maladaptive beliefs on WAD recovery. Up until now, studies addressing maladaptive beliefs have primarily focused on WAD management and the use of cognitive behavioural therapy. However, there is an existing systematic review that has attempted to assess the prognostic importance of catastrophising as a coping strategy in patients with low back pain (LBP) [48]. Results found in this systematic review [48] supports the findings of this study. In the review [48] catastrophising was also found to be associated with disability and pain after follow-up for patients presenting LBP in an acute, subacute and chronic stage. Another study [49] published in 2014, reviewed fear avoidance beliefs as a prognostic factor for patients with nonspecific LBP. This systematic review, assessed fear avoidance with the Fear Avoidance Beliefs Questionnaire (FABQ) and the Tampa Scale of Kinesiophobia. The research included in this current analysis have been published after 2006, similar to our studies. The findings found in this systematic review [49], are in line with the findings of our study that suggests that fear avoidance beliefs may be an indicator of a poor prognosis for patients with subacute LBP.

Additionally, another systematic review by Williamson [17] examined the effect of psychological factors and the development of late whiplash syndrome. Although this review considered maladaptive beliefs (catastrophising and fear avoidance) as psychological factors, these variables were not considered primary predictors of outcome. Additionally, maladaptive belief barriers were mediated by pain severity [17]. Nonetheless, it is important to also consider additional nonsystematic reviews that focus on the development of chronic pain due to the influence of psychological factors [50, 51].

The evidence presented in this review suggests that beliefs relevant to causation, fear-avoidance and self-efficacy correlate with WAD pain and disability. The fear avoidance model leads to the development of maladaptive beliefs (e.g. catastrophising) and such beliefs have the capacity to negatively influence pain and disability. While the hypotheses of these correlations require clarification, there is existing evidence that suggests there is an effect on cognitive factors as well.

STUDY LIMITATIONS

Meta-analysis was impossible due to the heterogeneity of outcome measures and the various maladaptive belief variables. Results from meta-analysis may have demonstrated more precise results.

CONCLUSIONS

This study is the first to systematically identify and evaluate the correlation of maladaptive beliefs to recovery in WAD. The data provided in this systematic review, demonstrates a moderate to strong association between maladaptive beliefs (catastrophising and fear avoidance) and pain and disability. Although, there is a compelling amount of research studying maladaptive beliefs, the approach for evaluating and reporting correlations between maladaptive beliefs and outcome measures is identified as an obstacle for the interpretation of relevant literature. There is a need to compare baseline characteristics of study populations who present maladaptive beliefs in comparison with those who do not and identify plausible reasons why maladaptive beliefs are associated with pain and disability. Even though these findings suggest a plausible association between

pain, disability, catastrophising and fear-avoidance, we are unable to fully establish if maladaptive beliefs are important in delaying WAD outcome and further research is required.

REFERENCES

1. Carroll LJ, Holm LW, Hogg-Johnson S, et al. Course and prognostic factors for neck pain in whiplash-associated disorders (WAD): Results of the Bone and Joint Decade 2000–2010 task force on neck pain and its associated disorders. J Manipulative Physiol Ther 2009 Feb;32(2 Suppl):S97–S107.
2. Holm LW, Carroll LJ, Cassidy JD, et al. The burden and determinants of neck pain in whiplash-associated disorders after traffic collisions: Results of the bone and Joint decade 2000–2010 task force on neck pain and its associated disorders. J Manipulative Physiol Ther 2009 Feb;32(2 Suppl):S61–9.
3. Hendriks EJ, Scholten-Peeters GG, van der Windt DA, Neeleman-van der Steen CW, Oostendorp RA, Verhagen AP. Prognostic factors for poor recovery in acute whiplash patients. Pain 2005 Apr;114(3):408–16.
4. Crouch R, Whitewick R, Clancy M, Wright P, Thomas P. Whiplash associated disorder: Incidence and natural history over the first month for patients presenting to a UK emergency department. Emerg Med J 2006 Feb;23(2):114–8.
5. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E. Scientific monograph of the Quebec task force on whiplash-associated disorders: Redefining “whiplash” and its management. Spine (Phila Pa 1976) 1995 Apr 15;20(8 Suppl):1S–73S.
6. van der Velde G, Yu H, Paulden M, et al. Which interventions are cost-effective for the management of whiplash-associated and neck pain-associated disorders? A systematic review of the health economic literature by the Ontario protocol for traffic injury management (OPTIMa) collaboration. Spine J 2016 Dec;16(12):1582–97.
7. Bogduk N. An overview of the International Congress on whiplash associated disorders. Pain Res Manag 2003;8(2):103–6.
8. Kamper SJ, Rebbeck TJ, Maher CG, McAuley JH, Sterling M. Course and prognostic factors of whiplash: A systematic review and meta-analysis. Pain 2008 Sep 15;138(3):617–29.
9. Jull G, Moore A, Falla D, Lewis J, McCarthy C, Sterling M. Grieves’s modern musculoskeletal physiotherapy. London, United Kingdom: Elsevier; 2015.
10. Walton DM, Pretty J, MacDermid JC, et al. Teasell RW. Risk factors for persistent problems following whiplash injury: Results of a systematic review and meta-analysis. J Orthop Sports Phys Ther 2009 May;39(5):334–50.
11. Sterling M, Hendrikz J, Kenardy J, et al. Assessment and validation of prognostic models for poor functional recovery 12 months after whiplash injury: A multicentre inception cohort study. Pain 2012 Aug;153(8):1727–34.
12. Holm LW, Carroll LJ, Cassidy JD, Skillgate E, Ahlbom A. Expectations for recovery important in the prognosis of whiplash injuries. LoS Med 2008 May 13;5(5):e105.
13. Boden MT, John OP, Goldin PR, Werner K, Heimberg RG, Gross JJ. The role of maladaptive beliefs in cognitive-behavioral therapy: Evidence from social anxiety disorder. Behav Res Ther 2012 May;50(5):287–91.
14. Frantsve LM, Kerns RD. Patient-provider interactions in the management of chronic pain: Current findings within the context of shared medical decision making. Pain Med 2007 Jan–Feb;8(1):25–35.
15. Pincus T, Foster NE, Vogel S, Santos R, Breen A, Underwood M. Attitudes to back pain amongst musculoskeletal practitioners: A comparison of professional groups and practice settings using the ABS-mp. Man Ther 2007 May;12(2):167–75.
16. Rice FP. Human development: A Life-Span Approach. Upper Saddle River, NJ: Prentice Hall; 1998.
17. Williamson E, Williams M, Gates S, Lamb SE. A systematic literature review of psychological factors and the development of late whiplash syndrome. Pain 2008 Mar;135(1–2):20–30.
18. Pincus T, McCracken LM. Psychological factors and treatment opportunities in low back pain. Best Pract Res Clin Rheumatol 2013 Oct;27(5):625–35.
19. Main CJ, Foster N, Buchbinder R. How important are back pain beliefs and expectations for satisfactory recovery from back pain? Best Pract Res Clin Rheumatol 2010 Apr;24(2):205–17.
20. Furlan AD, Malmivaara A, Chou R, et al. 2015 updated method guideline for systematic reviews in the Cochrane back and neck group. Spine (Phila Pa 1976) 2015 Nov;40(21):1660–73.
21. Pincus T, Vogel S, Burton AK, Santos R, Field AP. Fear avoidance and prognosis in back pain: A systematic review and synthesis of current evidence. Arthritis Rheum 2006 Dec;54(12):3999–4010.
22. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013 Feb 19;158(4):280–6.
23. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther 2003 Aug;83(8):713–21.
24. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 1;4:1.
25. Jull G, Kenardy J, Hendrikz J, Cohen M, Sterling M. Management of acute whiplash: A randomized controlled trial of multidisciplinary stratified treatments. Pain 2013 Sep;154(9):1798–806.
26. Casey PP, Feyer AM, Cameron ID. Course of recovery for whiplash associated disorders in a compensation setting. Injury 2015 Nov;46(11):2118–29.
27. Pedler A, Kamper SJ, Sterling M. Addition of posttraumatic stress and sensory hypersensitivity more accurately estimates disability and pain than fear avoidance measures alone after whiplash injury. Pain 2016 Aug;157(8):1645–54.

28. Angst F, Gantenbein AR, Lehmann S, et al. Multidimensional associative factors for improvement in pain, function, and working capacity after rehabilitation of whiplash associated disorder: A prognostic, prospective outcome study. BMC Musculoskelet Disord 2014 Apr 16;15:130.
29. Andersen TE, Karstoft KI, Brink O, Elklit A. Pain-catastrophizing and fear-avoidance beliefs as mediators between post-traumatic stress symptoms and pain following whiplash injury - A prospective cohort study. Eur J Pain 2016 Sep;20(8):1241–52.
30. Bostick GP, Carroll LJ, Brown CA, Harley D, Gross DP. Predictive capacity of pain beliefs and catastrophizing in whiplash associated disorder. Injury 2013 Nov;44(11):1465–71.
31. Buitenhuis J, de Jong PJ, Jaspers JP, Groothoff JW. Catastrophizing and causal beliefs in whiplash. Spine (Phila Pa 1976) 2008 Oct 15;33(22):2427–33.
32. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006 Mar 21;144(6):427–37.
33. Rosenstiel AK, Keefe FJ. The use of coping strategies in chronic low back pain patients: Relationship to patient characteristics and current adjustment. Pain 1983 Sep;17(1):33–44.
34. Sullivan MJ, Thorn B, Haythornthwaite JA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain 2001 Mar;17(1):52–64.
35. Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: A critical review. Expert Rev Neurother 2009 May;9(5):745–58.
36. Crombez G, Vlaeyen JW, Heuts PH, Lysens R. Pain-related fear is more disabling than pain itself: Evidence on the role of pain-related fear in chronic back pain disability. Pain 1999 Mar;80(1–2):329–39.
37. Turk DC, Robinson JP, Sherman JJ, Burwinkle T, Swanson K. Assessing fear in patients with cervical pain: Development and validation of the pictorial fear of activity scale-cervical (PFActS-C). Pain 2008 Sep 30;139(1):55–62.
38. Vernon H, Mior S. The neck disability index: A study of reliability and validity. J Manipulative Physiol Ther 1991 Sep;14(7):409–15.
39. Feise RJ, Michael Menke J. Functional rating index: A new valid and reliable instrument to measure the magnitude of clinical change in spinal conditions. Spine (Phila Pa 1976) 2001 Jan 1;26(1):78–86.
40. Pinfold M, Niere KR, O'Leary EF, Hoving JL, Green S, Buchbinder R. Validity and internal consistency of a whiplash-specific disability measure. Spine (Phila Pa 1976) 2004 Feb 1;29(3):263–8.
41. Willis C, Niere KR, Hoving JL, Green S, O'Leary EF, Buchbinder R. Reproducibility and responsiveness of the whiplash disability questionnaire. Pain 2004 Aug;110(3):681–8.
42. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med 2001 Dec;8(12):1153–7.
43. Bijur PE, Latimer CT, Gallagher EJ. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. Acad Emerg Med 2003 Apr;10(4):390–2.
44. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (VAS pain), numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). Arthritis Care Res (Hoboken) 2011 Nov;63 Suppl 11:S240–52.
45. Foa EB. Posttraumatic stress diagnostic scale (PDS). Minneapolis: National Computer Systems; 1995.
46. Lethem J, Slade PD, Troup JD, Bentley G. Outline of a fear-avoidance model of exaggerated pain perception—I. Behav Res Ther 1983;21(4):401–8.
47. Nieto R, Miró J, Huguet A. The fear-avoidance model in whiplash injuries. Eur J Pain 2009 May;13(5):518–23.
48. Wertli MM, Eugster R, Held U, Steurer J, Kofmehl R, Weiser S. Catastrophizing-a prognostic factor for outcome in patients with low back pain: A systematic review. Spine J 2014 Nov 1;14(11):2639–57.
49. Wertli MM, Rasmussen-Barr E, Weiser S, Bachmann LM, Brunner F. The role of fear avoidance beliefs as a prognostic factor for outcome in patients with nonspecific low back pain: A systematic review. Spine J 2014 May 1;14(5):816–36.e4.
50. Vlaeyen JW, Morley S. Cognitive-behavioral treatments for chronic pain: What works for whom? Clin J Pain 2005 Jan–Feb;21(1):1–8.
51. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol 2011 Apr;7(4):216–24.

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Erika Gabriela Macias – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published
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Consent Statement

Written informed consent was obtained from the patient for publication of this study.

Conflict of Interest

Authors declare no conflict of interest.

APPENDIX 1

Appendix 1: Database Search Strategy

	Medline via OVID (1946-June 2017)
1	Neck Pain.mp.
2	Whiplash Injuries.mp.
3	whiplash associated disorder$.mp.
4	Neck Injuries.mp.
5	Whiplash Injuries.mp.
6	post-whiplash syndrome.mp.
7	WAD.mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	Culture.mp.
10	illness beliefs.mp.
11	whiplash culture.mp.
12	pain catastrophi$.mp.
13	Catastrophi$.mp.
14	9 or 10 or 11 or 12 or 13
15	(fear of movement or kinesiophobia).mp.
16	pain-related fear.mp.
17	maladaptive beliefs.mp.
18	fear avoidance.mp.
19	15 or 16 or 17 or 18
20	14 or 19
21	8 and 20
22	randomi$ control trial.mp.
23	controlled clinical trial.mp.
24	randomi$ control trials.mp.
25	random allocation.mp.
26	22 or 23 or 24 or 25
27	cohort study.mp.
28	cohort.mp.
29	27 or 28
30	26 or 29
31	21 and 30
32	remove duplicates from 31
33	limit 32 to english language
34	limit 33 to humans