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Investigating the causal mechanisms of symptom recovery in chronic whiplash associated disorders using Bayesian Networks

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Abstract

Objectives: The present study's objective is to understand the causal mechanisms underpinning the recovery of individuals with whiplash-associated disorders (WAD). We applied Bayesian Networks (BN) to answer two study aims: 1) to identify the causal mechanism(s) of recovery underpinning neck-specific exercise, and 2) quantify if the cyclical pathway of the fear avoidance model (FAM) is supported by the present data.

Methods: We analysed a prospective cohort dataset of 216 individuals with chronic WAD. Fifteen variables were used to build a BN model: treatment group (neck-specific exercise with or without a behavioural approach, or general physical activity), muscle endurance, range of motion, hand strength, neck proprioception, pain catastrophizing, fear, anxiety, depression, self-efficacy, perceived work ability, disability, pain intensity, sex, and follow-up time.

Results: The BN model showed that neck pain reduction rate was greater after neck-specific exercise compared to physical activity prescription ($\beta = 0.59$ points/month [$P < 0.001$]) only in the presence of two mediators: global neck muscle endurance and perceived work ability. We also found the following pathway of variables that constituted the FAM: anxiety, followed by depressive symptoms, fear, catastrophizing, self-efficacy, and consequently pain

Conclusion: We uncovered two mediators which explained the mechanisms of effect behind neck-specific exercise, and proposed an alternative FAM pathway. The present study is the first to apply BN modelling to understand the causal mechanisms of recovery in WAD. In doing so, it is anticipated that such analytical methods could increase the precision of treatment in individuals with chronic WAD.

Keywords: Whiplash, Pain, Mediation analysis, Bayesian networks, Fear avoidance model

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Introduction

Neck pain is a global problem with an estimated point prevalence of up to 20% [1]. Neck pain incurred after a traumatic event such as a motor vehicle accident is often collectively referred to as whiplash associated disorders (WAD) [2]. Exercise-based interventions are commonly prescribed to individuals with WAD [3-6], and can be broadly categorized into neck-specific exercise or general physical activity (e.g. walking). In a recent randomized controlled trial, neck-specific exercise reduced neck pain-related disability more than general physical activity [7], although the mechanisms behind why one treatment is superior than the other remains unclear. It is possible that neck-specific exercise operates by improving cervical muscular function, which is known to be affected in individuals with WAD [8-11]. Previous research, which undertook a mediation analysis, reported that exercise- and cognitive-based interventions improve disability by reducing pain catastrophizing [12], reducing fear avoidance and increasing self-efficacy in individuals with low back pain [13-16]. A causal understanding behind the mechanisms by which different exercise-based interventions work is critical for clinicians to better manage a heterogeneous disorder such as WAD.

Fear avoidance, which is typically understood within the context of the Fear-Avoidance Model (FAM) [17, 18], has been found to mediate the recovery from a whiplash injury [19-21]. Although there are multiple variants of the FAM [22], the present study specifically refers to the FAM conceptualized by Vlaeyen et al. [18] and updated by Leeuw et al. [17], unless otherwise stated. The FAM describes a cyclical relationship whereby the initial pain experience triggers pain catastrophizing, fear avoidance, depression, eventually resulting in disability [17]. The FAM provides clinicians and researchers with a set of potentially modifiable mediators to intervene, to prevent an initial pain episode from progressing to persistent disability. For example, treatments targeted at minimizing pain

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catastrophizing would minimize pain related disability in the presence of pain [23, 24]. Research has provided supportive evidence of associations between some variables within the FAM. For example, studies have reported significant associations between pain catastrophizing and fear [18, 25]; and between fear and disability [26]. However, current investigations in individuals with musculoskeletal pain have not provided evidence in support of the entire sequential pathway of the FAM [27-29]. Current FAM pathway analysis studies [27-29] have not focused on uncovering alternative FAM pathways; a critical step, not least because it allows researchers to test the validity of competing pathways, and design alternative treatment approaches to prevent the onset of persistent pain-related disability.

Exercise-based interventions can have mechanisms of action via both physical (e.g. muscle endurance) and psychosocial pathways (e.g. fear) [30]. Contemporary prognostic studies in WAD have not focused on uncovering the causal mechanisms of recovery from WAD [31-35], especially after exercise-based interventions. Hence, the first aim of the present study was to identify the causal mechanism(s) which might explain the differing clinical effectiveness of neck-specific exercise and general physical activity. The second aim was to examine if the cyclical pathway of the FAM is supported empirically by the present cohort of individuals with chronic WAD; and if the evidence does not support the FAM pathway, generate an alternative pathway. To fulfil these aims, we used Bayesian Networks (BN) to "learn" and quantify from data, the relationships between multiple biopsychosocial prognostic variables [36].

Materials and Methods

Participants

The study consisted of 142 women and 74 men with a mean age of 40.4 years (SD = 11.4). Participants included in the present study had to fulfil the following criteria: aged 18 to

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63 years old, WAD classification of grade 2 or 3, experienced a whiplash injury in the past 6-36 months, and having a Neck Disability Index (NDI) score of > 20% and/or an average pain of > 20 mm on a 100 mm Visual Analogue Scale (VAS) [4].

Participants who were excluded from the study had a whiplash injury with associated signs of traumatic brain injury, reported persistent symptoms from a previous neck trauma, myelopathy, had a history of having a neck surgery, spinal infection or tumour, > 1 month of work absence preceding the whiplash injury due to neck pain, more dominant pain in other body regions, and insufficient competence of the Swedish language. The study was conducted in accordance to the Declaration of Helsinki and was approved by the Ethics Committee of Linköping University, Linköping, Sweden.

Study design

The present analysis was undertaken on a prospective cohort dataset collected as part of a randomized controlled trial [4]. The methodological details of the original study has been previously reported [4, 37], and will be briefly summarized in the present study. Participants were randomly allocated into one of three intervention groups: 1) physiotherapist supervised neck-specific exercise (NSE); 2) NSE coupled with a behavioural approach (NSEB); or 3) prescription of physical activity (PPA). All three interventions lasted for 12 weeks and the detailed description of the program has been previously reported [4, 38]. The behavioural component of NSEB was designed around the concepts of operant conditioning and graded activity [39], which briefly included strategies such as: encouraging participants to focus on the success of exercise progression rather than on transient increases in pain; management and problem-solving strategies during symptom relapse; and physiotherapist-led education of the biopsychosocial nature of pain [4].

Approach to sample selection

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All continuous variables (i.e. variables 1 to 12 above) were assessed at baseline, 3, 6, and 12 months follow-up, with the exception of the Hospital Anxiety and Depression Scale anxiety sub-score (HAD_A), Hospital Anxiety and Depression Scale depression sub-score (HAD-D), and Tampa Scale for Kinesiophobia (TSK) which were not measured at 3 months [40]. The maximum proportion of missing data was at 39.4% for the WAI data at 12 months follow-up. The number of participants with complete missing data of variables 1 to 12 at baseline, 3 months, 6 months, and 12 months follow-up were zero, 24, 45, and 45, respectively. Reasons for the missing data can be found in two other reports of the study [4, 37].

Outcome measures

The following 15 variables were used to form a BN:

1. Total neck endurance: cervical extensor and flexor timed endurance were measured in the prone and supine position respectively [38]. Total endurance (seconds) was calculated by adding extensor and flexor endurance.
2. Total hand strength: a Jamar hand dynamometer was used to measure isometric grip strength bilaterally [38]. Total hand strength (kg) was calculated by combining left and right hand strength.
3. Total range of motion (ROM): active cervical ROM in all three cardinal planes were measured with a cervical ROM device in a seated position [38]. The total ROM (°) was calculated by adding ROM from all six directions.
4. Average neck proprioception: a measure of the ability to return the head to a neutral head posture from 30° of cervical rotation with the eyes closed. Neck proprioception was tested across four repetitions, twice following both right and left cervical rotation. Proprioception (°) was averaged across the four repetitions.

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5. Pain Catastrophizing Scale (PCS): measures the magnitude of pain catastrophizing. Score ranges from 0 (no catastrophizing) to 52 (maximal catastrophizing)[41].
6. TSK short form (TSK-11): measures fear of movement and (re)injury. Score ranges from 11 (no fear) to 44 (maximal fear) [42].
7. HAD_A: measures anxiety in a general medical population. Total score ranges from 0 (absent anxiety) to 21 (maximal anxiety) [43].
8. HAD_D: measures depression in a general medical population. Total score ranges from 0 (absent depression) to 21 (maximal depression) [43].
9. Self-Efficacy Scale (SES): a measure of self-efficacy. Score ranges from 0 to 200, with higher scores indicating greater self-efficacy [44].
10. Work Ability Index (WAI): a measure of self-reported work ability. Score ranges from 7 to 49, with higher scores indicating better work ability [45].
11. Neck Disability Index (NDI): a measure to quantify disability attributed to neck pain. Score ranges from 0 (no activity limitations) to 50 (maximal activity limitations) [46].
12. Cervical pain: a self-reported measure of current neck pain on the visual analogue scale (VAS). Score ranges from 0 (no pain) to 100 (worst imaginable pain).
13. Sex: men or women
14. Time: follow-up time of 3, 6, and 12 months
15. Treatment: the randomized allocation into the three intervention arms (NSE, NSEB, PPA).

Approach to data analysis

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Differential equation model. We modelled the nonlinear rates of change of the physical and psychosocial variables, to understand the response to treatment over time. We prefixed (with "d") the variables which are modelled as rates of change (e.g. "dNDI"). We do so by taking the difference for each variable $\Delta Y = Y_{T2} - Y_{T1}$, where T_1 is the baseline and T_2 represents the three follow-up time points of 3, 6, and 12 months. The linear rate of change of each variable, $\frac{\Delta Y}{\Delta T}$, was derived where $\Delta T = T_2 - T_1$. The nonlinear trend in $\frac{\Delta Y}{\Delta T}$, where the rates of change depends on the time itself, can be modelled using the form:

$$\frac{\Delta Y}{\Delta T} = \mu + \frac{\Delta X_1}{\Delta T}\beta_1 + \Delta T\beta_2 \ldots + \frac{\varepsilon_{\Delta Y}}{\Delta T} \ldots (1)$$

where $\frac{\varepsilon_{\Delta Y}}{\Delta T} \sim N(0, \frac{\sigma^2_{\Delta Y}}{\Delta T})$.

Bayesian network analysis. Causal analysis has been studied using structured equations modelling (SEM) [14, 16, 47, 48] and linear regression models [49, 50]. Both methods can be seen as particular cases of Bayesian Networks (BN) [51], a causal modelling approach used increasingly in the medical field [52-55] (see supplementary material for a detailed explanation of the BN methodology, Supplemental Digital Content 1, http://links.lww.com/CJP/A580). BN emphasizes learning pathways directly from data, as opposed to considering problems with a fixed structure like SEM; and they are foundations upon which counterfactual causal inference was built [56]. Crucially, BN are able to handle missing data [57], which makes them practical in settings where patient records are often incomplete.

All analyses were performed in R software [58] using the bnlearn package [59]. Authors may send a request to the corresponding author, Bernard Liew, to obtain a detailed report of the statistical analysis, codes, and results. BN model the relationships among a set of variables $\mathbf{X} = \{X_1, \ldots, X_N\}$*, where N is the number of different variables, using a directed

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acyclic graph (DAG) in which each variable is associated with a node. Learning BN from data involves first identifying which arcs are present in the DAG (structure learning), and then estimating the parameters that regulate the strength and the direction of the corresponding relationships (parameter learning).

We made use of blacklisting and model averaging to reduce the number of arcs that are incorrectly included in the BN. A blacklist is simply a set of relationships that we know do not exist (based on existing literature and clinical experience) and are ignored during structure learning. We blacklisted the arcs from all physical and psychosocial variables to the variables of treatment, time, and sex – given that the former do not determine the latter variables. Model averaging consists of resampling the data multiple times ($B = 200$) using bootstrap and performing structure learning on each of the resulting sample using Expectation-Maximization (EM) [57]. We computed an "average" consensus DAG by selecting those arcs that have a frequency of > 50% in the bootstrapped samples [60].

BN can easily incorporate prior knowledge available from the literature and expert opinions into the models, by encoding prior knowledge in sets of whitelisted arcs. We built a second BN model using the same blacklists as the first model but added the sequential path of the FAM as whitelist (see whitelisted arcs in Table 1). The second BN model was used to compare its predictive correlation with the first model (without whitelist). If the empirical data supported the sequential pathway of the FAM, then the predictive correlation of the second model would be superior to first model.

We randomly split the data into a training set (90%) and a testing set (10%), and performed structural and parameter learning on the training dataset. We used the BN model learned from the training set to perform validation on the testing set by computing the correlation coefficient between the predicted and observed values of each continuous

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variable. The strength of correlation was categorized as negligible ($|r| \leq 0.30$), low ($|r| = 0.31$ to 0.50), moderate ($|r| = 0.51$ to 0.70), high ($|r| = 0.71$ to 0.90) and very high ($|r| = 0.91$ to 1) [61].

Missing data imputation. We used the averaged BN of the first model to impute missing data present in the change values of variables 1 to 12 on the original incomplete dataset. The mean (SD) of change values for each of the 12 variables for both the observed (incomplete) and imputed dataset was calculated and compared, to judge the quality of data imputation.

Conditional probability queries. The derived averaged BN was used to answer the two questions posed in the Introduction. We did so using a technique known as belief updating, a technique used to estimate the posterior probability of an event happening based on the knowledge of the available evidence on the values of certain variables. In particular, we adopted a specific method of belief updating known as logic sampling [51].

Results

The mean and SD of the rate of change scores of the observed and imputed data is shown in Figure 1. The averaged BN consensus model learnt from 200 networks constructed from the data, with arcs appearing at least in 50% of the networks kept, is shown in Figure 2. The predictive correlations for the physical variables were absent and psychosocial variables were at moderate to strong (Table 2).

Mediators of neck-specific exercise and neck pain intensity

Treatment appears to alter dPain via two mediators: dNeckEndr and dWAI (Figure 2). This implies that NSE and NSEB, in comparison with PPA, differentially altered neck pain dynamics because of its differential effects on neck muscle endurance and WAI dynamics.

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We verified this interpretation in several steps. When dNeckEndr and dWAI improvements were greater than the 75th percentile of the group's change scores, the probability of being classified as improved was greater in NSEB (0.52) and NSE (0.50), compared to PPA (0.46). Using simple linear regression, NSEB reduced neck pain at a rate of $\beta = 0.81$ points/month ($t = -6.21$, $P < 0.001$), and NSE reduced neck pain at a rate of $\beta = 0.59$ points/month more than PPA ($t = -4.47$, $P < 0.001$). Next, we removed the Treatment-dNeckEndr and Treatment-dWAI arcs, by fixing the value of the dNeckEndr and dWAI regression coefficients in the local distributions to zero. This means that dNeckEndr and dWAI do not depend on treatment. When both arcs were removed, the rate of neck pain reduction was not significantly different between groups (NSEB vs PPA: $t = -1.45$, $P = 0.14$; NSE vs PPA: $t = -1.78$, $P = 0.08$).

Sequential pathway analysis of the FAM

The averaged BN consensus model learnt from the data, revealed that an increase in dHAD_D resulted in an increase dTSK ($t = 148.6$, $P < 0.001$) (Figure 3); an increase in dTSK resulted in an increase in dPCS ($t = 170.0$, $P < 0.001$) (Figure 4); an increase in dPCS reduced dSES ($t = -104.6$, $P < 0.001$) (Figure 5); and a greater increase in dSES resulted in a greater rate of neck pain reduction ($t = -87.16$, $P < 0.001$) (Figure 6). We built a second BN model using the same blacklists as the first model (Figure 7), but added the sequential path of the FAM as whitelist. This meant that the structure of the BN contained prior knowledge of the relationships between variables. The predictive correlation values of the second model was comparable to the first model (Table 2), the implications of which is discussed below.

Discussion

In the present study, we used a Bayesian Networks approach to understand the causal mechanisms underpinning the differential response to different exercise interventions; as well

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as elucidating the cyclical relationship of the FAM in the present cohort of individuals with chronic WAD. A causal understanding can help in the development of new and better matched interventions, but such research has rarely been performed in the area of WAD. In addition, clinicians often desire to seek a causal understanding behind a treatment's clinical efficacy prior to clinical implementation.

In the present study, neck muscle endurance but not cervical proprioception and ROM, mediated the relationship between neck-specific exercise and neck pain dynamics. It is likely that this was because the neck-specific exercise program was designed to facilitate the recruitment of the deep cervical muscles, and ultimately train the endurance of the cervical flexor and extensor muscles [4]. The mediating effect of neck muscle endurance supported previous studies that used association-based analysis to investigate the relationship between neck muscle endurance and neck pain [8, 62-64]. Interestingly, a systematic review reported that changes to the physiological features of the transversus abdominis were largely unrelated to improvements in low back pain intensity and disability after exercise [65]. A limitation of the review was that it did not include studies which used statistical methods to study mediation [65]. Alternatively, findings from the present study suggests that global (multi-muscle), rather than local (single muscle), physiological measures are more important mediators of pain recovery in exercise-based interventions. Muscles typically work in functional groups and the individual functioning of a muscle can be compensated by synergistic muscles [66].

The results of the present study also revealed that perceived work ability mediated the relationship between neck-specific exercise and neck pain dynamics. This finding was surprising given that the neck-specific exercise program was not designed specifically to facilitate return to work. The WAI questionnaire evaluates an individual's return to work expectations, as well as their work ability relative to the work's physical demands (see

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questions six and two of WAI). A previous study on sub-acute WAD reported that return to work expectations mediated the relationship between variables of perceived injustice, fear of movement, pain catastrophizing and the return-to-work status [67, 68]. In addition, perceived physical exertion in the workplace, mediated the relationship between a multi-faceted workplace rehabilitation program and low back pain intensity [69]. It is plausible that neck-specific exercise was better at improving perceived physical capacity, and more optimistic return to work expectations, than a general physical activity program.

Similar to previous studies [28, 29], the sequential pathway of the FAM [17] was not observed in the BN model learnt purely from the data. The pathway connecting variables of the FAM learnt using BN was as follows: anxiety, followed by depressive symptoms, fear, catastrophizing, self-efficacy, and consequently pain. A benefit of using BN is that the predictive validity of competing pathway models can be tested. BN can be used to build pathways that vary from being completely data-driven to completely informed by prior knowledge (e.g. theory, literature, expert opinion). Although there are other FAM variants [22], we only compared our data-driven model to another model informed by a single FAM [17], as it is the most widely used in musculoskeletal pain research. Despite the capacity to build completely data-driven pathways, factors such as a relatively small sample size (see range of sample sizes in [22]), presence of missing data, and the plausibility of pathology specific FAM pathways [17, 22]; which means that we remain cautious when interpreting our data-driven model and generalizing it to other patient cohorts.

The most surprising findings of the present study were that depressive symptoms preceded fear, and fear preceded pain catastrophizing. Both of the present findings stand in contrast to the FAM [17], but had empirical support from the literature [70, 71]. In a study of general musculoskeletal pain, Thompson et al. [71] reported that more depression was positively correlated with more fear, although their analysis cannot determine if depression

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preceded or proceeded fear. Depressive symptoms were found to have a substantial direct influence on fear in individuals with low back pain [48]. Even when investigating other FAM pathway variants, allowing negative affectivity (a measure of depressive feelings) to directly affect fear increased the fit of the statistical model, compared to a model without negative affectivity [47]. The importance of depressive symptoms early in the FAM pathway prior to fear, has also been previously proposed within the "Depression pathway model" of Pincus et al. [72]. Depressive symptoms can be conceptualized as a dispositional trait which gives rise to behavioural withdrawal and general tiredness, which leads to greater fear [73]. Greater fear may heighten the cognitive mechanisms that result in selective attention to threatening stimuli (catastrophizing) [70], which from an evolutionary perspective, confer the organism greater survival benefits [70].

Greater pain catastrophizing either directly decreased the rate of neck pain reduction, or it worsened self-efficacy which decreased the rate of neck pain reduction. This finding supports an increasing body of research identifying self-efficacy as an important mediator of recovery in painful musculoskeletal disorders [14, 19, 74]. A person with a higher sense of self-efficacy may be more likely to utilize adaptive coping strategies and adhere to treatment, compared to those with a lower sense of self-efficacy [75]. In contrast to previous studies [19, 74], we observed that self-efficacy mediated the disability leading to pain relationship, rather than the pain leading to disability relationship. An important distinction between previous studies and the present study, was that prior research tested the mediating effect of self-efficacy with the assumption that more pain leads to more disability [19, 74].The NDI was used to provide a self-reported measure of physical activity levels, which may not correspond to objective measures such as accelerometry [29]. A greater amount of physical activity can improve pain by improving a person's self-efficacy [76], but also potentially by exercise-induced hypoalgesic effects [77].

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Findings of the present study have several clinical implications. First, a causal understanding behind how different exercises work can help clinicians prioritize therapeutic efforts to the most important impairments that determine recovery. Second, therapeutic interventions based on the FAM pathway of Leeuw et al [17], which focused on fear reduction, have not had convincing results [78]. The present finding proposes an alternative FAM pathway, from which new interventions can be developed and its efficacy tested. Third, knowing the sequential pathway between the initial pain episodes to long term disability/recovery means that a clinician can select the modifiable impairments easiest to treat in an individual. For example, an individual with WAD who has a high level of depression, may benefit from interventions which targets reducing depressive symptoms, and/or interventions aimed at reducing fear – since fear lies on the pathway from depression to pain.

The findings of the present study must be interpreted in light of the limitations of the investigation. First, building a BN model that captures the full causal mechanisms of recovery in complex musculoskeletal disorders using "noisy" epidemiological data is challenging. Causal mechanisms of recovery may be specific to pathologies, stage of recovery, and even subject-specific depending on an individual's comorbidities. Future research could augment BN modelling by combining expert knowledge with empirical data. Second, most of the variables included in the BN were self-reported, and whether self-reported questionnaires reflect the true underlying construct of the phenomenon being assessed could be questioned. Third, the physical measures used in the present study largely reflected what could be reasonably performed clinically. It is anticipated that the structure of the BN model may change when anatomical (e.g. cross-sectional area of a muscle) and physiological measures (e.g. muscle synergies) used in research, are included in the analysis.

Conclusions

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The present study is the first to apply BN modelling to understand the causal mechanisms of recovery in WAD. We found that neck muscle endurance and perceived work ability were the two mediating factors underlying the superiority of neck specific exercise over physical activity prescription in the mediation of neck pain dynamics. In addition, the BN model did not support the full sequential pathway of the FAM. We observed the following pathway: anxiety, followed by depressive symptoms, fear, catastrophizing, self-efficacy, and consequently pain. The present study provides several candidate modifiable mediators that could be the target of future intervention trials. In so doing, BN models could increase the precision of treatment and outcome assessment of individuals with chronic WAD, as well as increase the predictability of improving this costly condition.

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Figure captions

Figure 1. Mean and standard deviation of observed and imputed values for change scores on continuous outcome variables. Abbreviation: d – prefix to indicate change values; HAD_A: Hospital Anxiety and Depression Scale– anxiety sub-score; HAD_D - Hospital Anxiety and Depression Scale depression sub-score; HandStr – Total hand strength; NeckEndr – Total neck muscle endurance; PCS – Pain Catastrophizing Scale; Propr – Averaged neck proprioception; SES - Self-Efficacy Scale; ROM – Total range of motion; TSK - Tampa Scale for Kinesiophobia; WAI – Work Ability Index

Figure 2. The directed acyclic graph (DAG) underlying the consensus Bayesian Network of the first model learned from the variables across 216 participants. The thickness of the arcs is in proportion to their strength. Only arcs with strength > 0.5 are included in the consensus network. Abbreviation: d – prefix to indicate change values; HAD_A: Hospital Anxiety and Depression Scale– anxiety sub-score; HAD_D - Hospital Anxiety and Depression Scale depression sub-score; HandStr – Total hand strength; NeckEndr – Total neck muscle endurance; PCS – Pain Catastrophizing Scale; Propr – Averaged neck proprioception; SES - Self-Efficacy Scale; ROM – Total range of motion; TSK - Tampa Scale for Kinesiophobia; WAI – Work Ability Index

Figure 3. Values simulated from the consensus Bayesian Network for dTSK and dHAD_D. The black line represents the regression line of dTSK against dHAD_D. Its positive slope confirms that as dHAD_D increases (more depression) dTSK increases (more fear)

Figure 4. Values simulated from the consensus Bayesian Network for dPCS and dTSK. The black line represents the regression line of dPCS against dTSK. Its positive slope confirms that as dTSK increases (more fear) dPCS increases (more catastrophizing)

Figure 5. Values simulated from the consensus Bayesian Network for dSES and dPCS. The black line represents the regression line of dSES against dPCS. Its negative slope confirms that as dPCS increases (more catastrophizing) dSES reduces (less self-efficacy)

Figure 6. Values simulated from the consensus Bayesian Network for dPain and dSES. The black line represents the regression line of dPain against dSES. Its negative slope confirms that as dSES increases (more catastrophizing) neck pain reduction increases.

Figure 7. The directed acyclic graph (DAG) underlying the consensus Bayesian Network of the second model learned from the variables across 216 participants. Arcs in red are enforced to be present in the network by the whitelist. The thickness of the arcs is in proportion to their strength. Only arcs with strength > 0.5 are included in the consensus network. Abbreviation: d – prefix to indicate change values; HAD_A: Hospital Anxiety and Depression Scale– anxiety sub-score; HAD_D - Hospital Anxiety and Depression Scale depression sub-score; HandStr – Total hand strength; NeckEndr – Total neck muscle endurance; PCS – Pain Catastrophizing Scale; Propr – Averaged neck proprioception; SES - Self-Efficacy Scale; ROM – Total range of motion; TSK - Tampa Scale for Kinesiophobia; WAI – Work Ability Index

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References

[1] Hoy DG, Protani M, De R, Buchbinder R. The epidemiology of neck pain. Best Pract Res Clin 2010;24:783-92.

[2] Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, et al. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining "whiplash" and its management. Spine 1995;20:1s-73s.

[3] Michaleff ZA, Maher CG, Lin CW, Rebbeck T, Jull G, Latimer J, et al. Comprehensive physiotherapy exercise programme or advice for chronic whiplash (PROMISE): a pragmatic randomised controlled trial. Lancet (London, England) 2014;384:133-41.

[4] Ludvigsson ML, Peterson G, O'Leary S, Dedering A, Peolsson A. The effect of neck-specific exercise with, or without a behavioral approach, on pain, disability, and self-efficacy in chronic whiplash-associated disorders: a randomized clinical trial. Clin J Pain 2015;31:294-303.

[5] Griffin A, Leaver A, Moloney N. General Exercise Does Not Improve Long-Term Pain and Disability in Individuals With Whiplash-Associated Disorders: A Systematic Review. J Orthop Sports Phys Ther 2017;47:472-80.

[6] Rushton A, Wright C, Heneghan N, Eveleigh G, Calvert M, Freemantle N. Physiotherapy rehabilitation for whiplash associated disorder II: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2011;1:e000265.

ACCEPTED

[7] Ludvigsson ML, Peterson G, Dedering A, Falla D, Peolsson A. Factors associated with pain and disability reduction following exercise interventions in chronic whiplash. Eur J Pain 2016;20:307-15.

[8] Krogh S, Kasch H. Whiplash injury results in sustained impairments of cervical muscle function: A one-year prospective, controlled study. J Rehabil Med 2018;50:548-55.

[9] De Pauw R, Coppieters I, Kregel J, De Meulemeester K, Danneels L, Cagnie B. Does muscle morphology change in chronic neck pain patients? - A systematic review. Man Ther 2016;22:42-9.

[10] Peterson G, Nilsson D, Trygg J, Falla D, Dedering A, Wallman T, et al. Novel insights into the interplay between ventral neck muscles in individuals with whiplash-associated disorders. Sci Rep 2015;5:15289.

[11] Falla D, Bilenkij G, Jull G. Patients with chronic neck pain demonstrate altered patterns of muscle activation during performance of a functional upper limb task. Spine 2004;29:1436-40.

[12] Hall AM, Kamper SJ, Emsley R, Maher CG. Does pain-catastrophising mediate the effect of tai chi on treatment outcomes for people with low back pain? Complement Ther Med 2016;25:61-6.

[13] Spinhoven P, ter Kuile M, Kole-Snijders AMJ, Hutten Mansfeld M, den Ouden D-J, Vlaeyen JWS. Catastrophizing and internal pain control as mediators of outcome in the multidisciplinary treatment of chronic low back pain. Eur J Pain 2004;8:211-9.

ACCEPTED

[14] Fordham B, Ji C, Hansen Z, Lall R, Lamb SE. Explaining How Cognitive Behavioral Approaches Work for Low Back Pain: Mediation Analysis of the Back Skills Training Trial. Spine 2017;42:E1031-e9.

[15] Whittle R, Mansell G, Jellema P, van der Windt D. Applying causal mediation methods to clinical trial data: What can we learn about why our interventions (don't) work? Eur J Pain 2017;21:614-22.

[16] 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.

[17] Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. J Behav Med 2007;30:77-94.

[18] Vlaeyen JWS, Kole-Snijders AMJ, Boeren RGB, van Eek H. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. Pain 1995;62:363-72.

[19] Söderlund A, Åsenlöf P. The mediating role of self-efficacy expectations and fear of movement and (re)injury beliefs in two samples of acute pain. Disabil Rehabil 2010;32:2118-26.

[20] Nieto R, Miro J, Huguet A. The fear-avoidance model in whiplash injuries. Eur J Pain 2009;13:518-23.

ACCEPTED

[21] Andersen TE, Karstoft K-I, 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;20:1241-52.

[22] Holla JFM, Sanchez-Ramirez DC, van der Leeden M, Ket JCF, Roorda LD, Lems WF, et al. The avoidance model in knee and hip osteoarthritis: a systematic review of the evidence. J Behav Med 2014;37:1226-41.

[23] Vlaeyen JW, de Jong J, Geilen M, Heuts PH, van Breukelen G. The treatment of fear of movement/(re)injury in chronic low back pain: further evidence on the effectiveness of exposure in vivo. Clin J Pain 2002;18:251-61.

[24] Woods MP, Asmundson GJ. Evaluating the efficacy of graded in vivo exposure for the treatment of fear in patients with chronic back pain: a randomized controlled clinical trial. Pain 2008;136:271-80.

[25] Goubert L, Crombez G, Van Damme S. The role of neuroticism, pain catastrophizing and pain-related fear in vigilance to pain: a structural equations approach. Pain 2004;107:234-41.

[26] Peters ML, Vlaeyen JW, Weber WE. The joint contribution of physical pathology, pain-related fear and catastrophizing to chronic back pain disability. Pain 2005;113:45-50.

[27] Gheldof ELM, Crombez G, Van den Bussche E, Vinck J, Van Nieuwenhuyse A, Moens G, et al. Pain-related fear predicts disability, but not pain severity: A path analytic approach of the fear-avoidance model. Eur J Pain 2010;14:870.e1-e9.

ACCEPTED

[28] Wideman TH, Adams H, Sullivan MJL. A prospective sequential analysis of the fear-avoidance model of pain. Pain 2009;145:45-51.

[29] Pedler JA, Kamper JS, Maujean JA, Sterling JM. Investigating the Fear Avoidance Model in People With Whiplash: The Association Between Fear of Movement and In Vivo Activity. Clin J Pain 2018;34:130-7.

[30] Sluka KA, Frey-Law L, Hoeger Bement M. Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation. Pain 2018;159 Suppl 1:S91-s7.

[31] Carstensen TB. The influence of psychosocial factors on recovery following acute whiplash trauma. Dan Med J 2012;59:B4560.

[32] Daenen L, Nijs J, Raadsen B, Roussel N, Cras P, Dankaerts W. Cervical motor dysfunction and its predictive value for long-term recovery in patients with acute whiplash-associated disorders: a systematic review. J Rehabil Med 2013;45:113-22.

[33] Ritchie C, Sterling M. Recovery Pathways and Prognosis After Whiplash Injury. J Orthop Sports Phys Ther 2016;46:851-61.

[34] Sarrami P, Armstrong E, Naylor JM, Harris IA. Factors predicting outcome in whiplash injury: a systematic meta-review of prognostic factors. J Orthop Traumatol 2017;18:9-16.

[35] Walton DM, Macdermid JC, Giorgianni AA, Mascarenhas JC, West SC, Zammit CA. Risk factors for persistent problems following acute whiplash injury: update of a systematic review and meta-analysis. J Orthop Sports Phys Ther 2013;43:31-43.

ACCEPTED

[36] Scutari M, Auconi P, Caldarelli G, Franchi L. Bayesian Networks Analysis of Malocclusion Data. Sci Rep 2017;7:15236.

[37] Ludvigsson ML, Peterson G, Dedering A, Peolsson A. One- and two-year follow-up of a randomized trial of neck-specific exercise with or without a behavioural approach compared with prescription of physical activity in chronic whiplash disorder. J Rehabil Med 2016;48:56-64.

[38] Peolsson A, Landen Ludvigsson M, Overmeer T, Dedering A, Bernfort L, Johansson G, et al. Effects of neck-specific exercise with or without a behavioural approach in addition to prescribed physical activity for individuals with chronic whiplash-associated disorders: a prospective randomised study. BMC Musculoskelet Disord 2013;14:311.

[39] Leeuw M, Goossens ME, van Breukelen GJ, de Jong JR, Heuts PH, Smeets RJ, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. Pain 2008;138:192-207.

[40] Ludvigsson ML, Peterson G, Peolsson A. The effect of three exercise approaches on health-related quality of life, and factors associated with its improvement in chronic whiplash-associated disorders: analysis of a randomized controlled trial. Qual Life Res 2018.

[41] Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychol Assess 1995;7:524-32.

[42] Miller RP, Kori S, Todd D. The Tampa Scale for Kinesiophobia. Unpublished report 1991.

ACCEPTED

[43] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.

[44] Altmaier EM, Russell DW, Kao CF, Lehmann TR, Weinstein JN. Role of self-efficacy in rehabilitation outcome among chronic low back pain patients. J Couns Psychol 1993;40:335-9.

[45] Ilmarinen J. The Work Ability Index (WAI). Occup Med 2007;57:160-.

[46] Vernon H. The Neck Disability Index: state-of-the-art, 1991-2008. J Manipulative Physiol Ther 2008;31:491-502.

[47] Holla JF, van der Leeden M, Knol DL, Peter WF, Roorda LD, Lems WF, et al. Avoidance of activities in early symptomatic knee osteoarthritis: results from the CHECK cohort. Ann Behav Med 2012;44:33-42.

[48] Seekatz B, Meng K, Bengel J, Faller H. Is there a role of depressive symptoms in the fear-avoidance model? A structural equation approach. Psychol Health Med 2016;21:663-74.

[49] Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods 2013;18:137-50.

[50] Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. Stat Methods Med Res 2010;19:237-70.

ACCEPTED

[51] Nagarajan R, Scutari M, Lèbre S. Bayesian networks in R with applications in systems biology. Verlag, New York: Springer; 2013.

[52] Farmer N. An update and further testing of a knowledge-based diagnostic clinical decision support system for musculoskeletal disorders of the shoulder for use in a primary care setting. J Eval Clin Pract 2014;20:589-95.

[53] Takenaka S, Aono H. Prediction of Postoperative Clinical Recovery of Drop Foot Attributable to Lumbar Degenerative Diseases, via a Bayesian Network. Clin Orthop Relat Res 2017;475:872-80.

[54] Zhang Y, Zhang T, Zhang C, Tang F, Zhong N, Li H, et al. Identification of reciprocal causality between non-alcoholic fatty liver disease and metabolic syndrome by a simplified Bayesian network in a Chinese population. BMJ Open 2015;5:e008204.

[55] Sesen MB, Nicholson AE, Banares-Alcantara R, Kadir T, Brady M. Bayesian networks for clinical decision support in lung cancer care. PloS one 2013;8:e82349.

[56] Pearl J. Causality. 2 ed. New York: Cambridge University Press; 2009.

[57] Friedman N. Learning Belief Networks in the Presence of Missing Values and Hidden Variables. Proceedings of the Fourteenth International Conference on Machine Learning: Morgan Kaufmann Publishers Inc.; 1997. p. 125-33.

[58] R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing URL http://wwwR-projectorg/.

ACCEPTED

[59] Scutari M. Learning Bayesian Networks with the bnlearn R Package. J Stat Softw 2010;35:22.

[60] Scutari M, Nagarajan R. Identifying significant edges in graphical models of molecular networks. Artif Intell Med 2013;57:207-17.

[61] Hinkle D, Wiersma W, Jurs S. Applied Statistics for the Behavioral Sciences. 5 ed. Boston: Houghton Mifflin; 2003.

[62] Lee H, Nicholson LL, Adams RD. Neck Muscle Endurance, Self-Report, and Range of Motion Data From Subjects With Treated and Untreated Neck Pain. J Manipulative Physiol Ther 2005;28:25-32.

[63] O'Leary S, Jull G, Kim M, Vicenzino B. Cranio-cervical flexor muscle impairment at maximal, moderate, and low loads is a feature of neck pain. Man Ther 2007;12:34-9.

[64] Jull GA. Considerations in the physical rehabilitation of patients with whiplash-associated disorders. Spine 2011;36:S286-91.

[65] Wong AY, Parent EC, Funabashi M, Kawchuk GN. Do changes in transversus abdominis and lumbar multifidus during conservative treatment explain changes in clinical outcomes related to nonspecific low back pain? A systematic review. J Pain 2014;15:377.e1-35.

[66] Liew BXW, Del Vecchio A, Falla D. The influence of musculoskeletal pain disorders on muscle synergies—A systematic review. PloS one 2018;13:e0206885.

ACCEPTED

[67] Carriere JS, Thibault P, Adams H, Milioto M, Ditto B, Sullivan MJL. Expectancies mediate the relationship between perceived injustice and return to work following whiplash injury: A 1-year prospective study. Eur J Pain 2017;21:1234-42.

[68] Carriere JS, Thibault P, Milioto M, Sullivan MJL. Expectancies Mediate the Relations Among Pain Catastrophizing, Fear of Movement, and Return to Work Outcomes After Whiplash Injury. J Pain 2015;16:1280-7.

[69] Stevens ML, Boyle E, Hartvigsen J, Mansell G, Søgaard K, Jørgensen MB, et al. Mechanisms for reducing low back pain: a mediation analysis of a multifaceted intervention in workers in elderly care. Int Arch Occup Environ Health 2018.

[70] Sullivan JLM, Thorn CB, Rodgers CW, Ward CL. Path Model of Psychological Antecedents to Pain Experience: Experimental and Clinical Findings. Clin J Pain 2004;20:164-73.

[71] Thompson EL, Broadbent J, Fuller-Tyszkiewicz M, Bertino MD, Staiger PK. A Network Analysis of the Links Between Chronic Pain Symptoms and Affective Disorder Symptoms. Int J Behav Med 2018.

[72] Pincus T, Smeets RJ, Simmonds MJ, Sullivan MJ. The fear avoidance model disentangled: improving the clinical utility of the fear avoidance model. Clin J Pain 2010;26:739-46.

ACCEPTED

[73] Asmundson GJ, Parkerson HA, Petter M, Noel M. What is the role of fear and escape/avoidance in chronic pain? Models, structural analysis and future directions. Pain Manag 2012;2:295-303.

[74] Costa Lda C, Maher CG, McAuley JH, Hancock MJ, Smeets RJ. Self-efficacy is more important than fear of movement in mediating the relationship between pain and disability in chronic low back pain. Eur J Pain 2011;15:213-9.

[75] Thompson LE, Broadbent DJ, Bertino KM, Staiger KP. Do Pain-related Beliefs Influence Adherence to Multidisciplinary Rehabilitation?: A Systematic Review. Clin J Pain 2016;32:164-78.

[76] Quicke JG, Foster NE, Ogollah RO, Croft PR, Holden MA. Relationship Between Attitudes and Beliefs and Physical Activity in Older Adults With Knee Pain: Secondary Analysis of a Randomized Controlled Trial. Arthritis Care Res 2017;69:1192-200.

[77] Naugle KM, Fillingim RB, Riley JL, 3rd. A meta-analytic review of the hypoalgesic effects of exercise. J Pain 2012;13:1139-50.

[78] Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev 2012;11:Cd007407.

ACCEPTED

Table 1. Whitelist arcs used in second BN model (using knowledge from [1, 2])

From	To	Explanation
dPain	dPCS	Pain experience → pain catastrophizing
dHAD_A	dPCS	Anxiety → Pain catastrophizing
dPCS	dTSK	Pain catastrophizing → pain related fear
dTSK	dSES	Pain related fear → low self-efficacy (resulting in avoidance)
dSES	dHAD_D	Low self-efficacy (resulting in avoidance)→ depression
dHAD_D	dNDI	Depression → disability

Abbreviation: d – prefix to indicate change values; PCS – Pain Catastrophizing Scale; HAD_A: Hospital Anxiety and Depression Scale– anxiety sub-score; TSK - Tampa Scale for Kinesiophobia; SES - Self-Efficacy Scale; HAD_D - Hospital Anxiety and Depression Scale depression sub-score

References:

[1] Woby SR, Urmston M, Watson PJ. Self-efficacy mediates the relation between pain-related fear and outcome in chronic low back pain patients. Eur J Pain 2007;11:711-8.

[2] Norton PJ, Asmundson GJG. Amending the fear-avoidance model of chronci pain: What is the role of physiological arousal? Behavior Therapy 2003;34:17-30.

ACCEPTED

Table 2. Correlation values between observed and predicted variables in the testing subset of data

Variables	**Model 1 (no whitelist)**	**Model 2 (whitelist)**
	r	r
dHAD_A	0.87	0.88
dHAD_D	0.79	0.87
dHandStr	0.25	0.05
dNDI	0.79	0.69
dNeckEndr	0.41	0.32
dPCS	0.88	0.93
dPropr	-0.04	0.05
dSES	0.76	0.67
dROM	0.27	0.28
dTSK	0.89	0.93
dPain	0.72	0.66
dWAI	0.56	0.52

Abbreviation: d – prefix to indicate change values; HAD_A: Hospital Anxiety and Depression Scale– anxiety sub-score; HAD_D - Hospital Anxiety and Depression Scale depression sub-score; HandStr – Total hand strength; NeckEndr – Total neck muscle endurance; PCS – Pain Catastrophizing Scale; Propr – Averaged neck proprioception; SES - Self-Efficacy Scale; ROM – Total range of motion; TSK - Tampa Scale for Kinesiophobia; WAI – Work Ability Index

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Rationale for whitelist arcs

Variables	Rationale
Total neck endurance	Individuals with WAD have lower values than health controls [1]. A total value was calculated to reduce the number of variables in the Bayesian Network model, and increase the simplicity of interpreting the model.
Total hand strength	Individuals with WAD have lower values than health controls [1]. A total value was calculated to reduce the number of variables in the Bayesian Network model, and increase the simplicity of interpreting the model.
Total range of motion	Individuals with WAD have lower values than health controls [1]. A total value was calculated to reduce the number of variables in the Bayesian Network model, and increase the simplicity of interpreting the model.
Average neck proprioception	Reduced cervical proprioception has been documented in individuals with WAD [2]. An average value was calculated to reduce the number of variables in the Bayesian Network model, and increase the simplicity of interpreting the model.
Pain Catastrophizing Scale (PCS)	Construct used in a mediation study in WAD [3].
Tampa Scale for Kinesiophobia	Construct used in a mediation study in WAD [3].
Hospital Anxiety and Depression Scale – anxiety sub-score	Construct associated with poorer recovery in WAD [4]
Hospital Anxiety and Depression Scale – depression sub-score	Construct used in a mediation study in WAD [5].
Self-Efficacy Scale	Construct used in a mediation study in low back pain [6]
Work Ability Index	An important outcome used in WAD [7]
Neck Disability Index	Core outcome measure in WAD [8]
Cervical pain	Core outcome measure in WAD

Detailed report of Bayesian network analysis

BN model the relationships among a set of variables $\mathbf{X} = \{X_1, \ldots, X_N\}$*, where N is the number of different variables, using a directed acyclic graph (DAG) in which each variable is associated with a node. Direct effects are represented as arcs; and those arcs can be given causal interpretation under the assumptions discussed by Pearl [9] for counterfactual inference. Indirect effects that are mediated by other variables can then be read as paths

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between the nodes. The joint distribution of the variables **X** then decomposes into the local distributions of the individual variables X_i as

$$f(\mathbf{X}) = \sum_{i=1}^{N} f(X_i \mid Pa(X_i)) \dots (2)$$

where $Pa(X_i)$ are the variables that correspond to the parents of X_i in the DAG (i.e. the nodes with an arc pointing towards X_i). Learning BN from data involves first identifying which arcs are present in the DAG (structure learning), and then estimating the parameters that regulate the strength and the direction of the corresponding relationships (parameter learning). In contrast, SEM models and approaches based on linear equations assume a known fixed DAG and only perform parameter learning (e.g. in [30, 31]).

BN can accommodate both categorical and continuous variables in what are called conditional linear Gaussian BN [10]. The local distribution of categorical variables are only allowed to have other categorical variables as parents; and are estimated with the probabilities of each of their values x_i for each combination z_i of the values of the respective parents,

$$f(X_i \mid Pa(X_i)) = P(X_i = x_i \mid Pa(X_i) = z_i) \dots (3)$$

which is equivalent to fitting a multinomial logistic regression of X_i against its parents $Pa(X_i)$. Continuous variables are modelled using linear regressions, and can have both categorical and continuous variables as parents. Their local distributions are estimated using a separate linear regression of X_i against its continuous parents for each combination z_i of the values of the discrete parents,

$$f(X_i \mid Pa(X_i)) = \mu_{X_i,z_i} + Pa_{continuous}(X_i)\boldsymbol{\beta}_{\boldsymbol{z_i}} + \varepsilon_{X_i,z_i} \dots (4)$$

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The errors are assumed to be normally distributed. Again, SEM and approaches based on sets of linear equations such as those in [30, 31] are a particular case of this model in which there are only continuous or categorical variables, but otherwise make the same assumptions on the distributions of the variables. In this paper we identify the structure of the model as the DAG that maximizes the Bayesian Information Criterion [11]; and we estimate the parameters using their maximum likelihood estimates for consistency with the SEM literature.

In order to improve the accuracy of structure learning we also make use of blacklisting and model averaging, to reduce the number of arcs that are incorrectly included in the BN. A blacklist is simply a set of relationships that we know do not exist (based on existing literature and clinical experience); hence we do not consider BN containing the corresponding arcs during structure learning. In the case of longitudinal data this includes all relationships whose direction goes against the arrow of time, following Granger causality [12] as well as Pearl's counterfactual theory of causality. In addition, we blacklisted the arcs from all physical and psychosocial variables to the variables of treatment, time, and sex – given that the former do not determine the latter variables.

BN can easily incorporate prior knowledge available from the literature and expert opinions into the models, by encoding prior knowledge in sets of whitelisted arcs. These whitelisted arcs represent real dependent relationships between variables and are forced to be present in the model. We built a second BN model using the same blacklists as the first model, but added the sequential path of the FAM as whitelist (see whitelisted arcs in Table 1). This meant that the structure of the BN contained prior knowledge of the relationships between variables contained within the FAM [13]. The second BN model was used to compare its predictive correlation with the first model (without whitelist). If the empirical

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data supported the sequential pathway of the FAM, than the predictive correlation of the second model would be superior to first model.

Model averaging consists of resampling the data multiple times (*B = 200*) using bootstrap [14] and performing structure learning on each of the resulting sample using Expectation-Maximization (EM). The EM algorithm allows structural learning of BN models in the presence of missing data [15]. We then compute the frequency with which each arc appears in those 200 DAGs. This allows us to compute an "average" consensus DAG by selecting those arcs that have a frequency above a certain threshold (the frequency was set at 50% in the present study) [16]. The resulting averaged BN has a number of favourable statistical properties; in particular, it is less sensitive to "noisy" data and it produces more accurate predictions for new observations. Intuitively, we can imagine that adding or removing a few observations from the data may result in learning different arcs, in turn leading to different conclusions; selecting only those arcs that appear consistently despite perturbing the data, reduces the uncertainty in model selection.

We randomly split the data into a training set (90%) and a testing set (10%), and performed structural and parameter learning on the training dataset. We used the BN model learned from the training set to perform validation on the testing set by computing the correlation coefficient between the predicted and observed values of each continuous variable. The strength of correlation was categorized as negligible ($|r| \leq 0.30$), low ($|r| = 0.31$ to 0.50), moderate ($|r| = 0.51$ to 0.70), high ($|r| = 0.71$ to 0.90) and very high ($|r| = 0.91$ to 1) [17].

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References

1.Peolsson A, Ludvigsson ML, Wibault J, Dedering A, Peterson G. Function in patients with cervical radiculopathy or chronic whiplash-associated disorders compared with healthy volunteers. J Manipulative Physiol Ther. 2014;37(4):211-8.

2.Treleaven J. Dizziness, Unsteadiness, Visual Disturbances, and Sensorimotor Control in Traumatic Neck Pain. J Orthop Sports Phys Ther. 2017;47(7):492-502.

3.Pedler JA, Kamper JS, Maujean JA, Sterling JM. Investigating the Fear Avoidance Model in People With Whiplash: The Association Between Fear of Movement and In Vivo Activity. The Clinical Journal of Pain. 2018;34(2):130-7.

4.Sarrami P, Armstrong E, Naylor JM, Harris IA. Factors predicting outcome in whiplash injury: a systematic meta-review of prognostic factors. Journal of Orthopaedics and Traumatology. 2017;18(1):9-16.

5.Andersen TE, Karstoft K-I, 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;20(8):1241-52.

6.Costa Lda C, Maher CG, McAuley JH, Hancock MJ, Smeets RJ. Self-efficacy is more important than fear of movement in mediating the relationship between pain and disability in chronic low back pain. Eur J Pain. 2011;15(2):213-9.

7.Carriere JS, Thibault P, Adams H, Milioto M, Ditto B, Sullivan MJL. Expectancies mediate the relationship between perceived injustice and return to work following whiplash injury: A 1-year prospective study. Eur J Pain. 2017;21(7):1234-42.

8.Rebbeck TJ, Refshauge KM, Maher CG, Stewart M. Evaluation of the core outcome measure in whiplash. Spine (Phila Pa 1976). 2007;32(6):696-702.

9.Pearl J. Causality. 2 ed. New York: Cambridge University Press; 2009.

10.Lauritzen SL, Wermuth N. Graphical Models for Associations between Variables, some of which are Qualitative and some Quantitative. Ann Statist. 1989;17(1):31-57.

11.Schwarz G. Estimating the Dimension of a Model. Ann Statist. 1978;6(2):461-4.

12.Granger CWJ. Investigating Causal Relations by Econometric Models and Cross-spectral Methods. Econometrica. 1969;37(3):424-38.

ACCEPTED

13.Woby SR, Urmston M, Watson PJ. Self-efficacy mediates the relation between pain-related fear and outcome in chronic low back pain patients. Eur J Pain. 2007;11(7):711-8.

14.Efron B, Tibshirani R. An introduction to the bootstrap: Chapman & Hall/CRC; 1993.

15.Friedman N. Learning Belief Networks in the Presence of Missing Values and Hidden Variables. Proceedings of the Fourteenth International Conference on Machine Learning. 657145: Morgan Kaufmann Publishers Inc.; 1997. p. 125-33.

16.Scutari M, Nagarajan R. Identifying significant edges in graphical models of molecular networks. Artificial Intelligence in Medicine. 2013;57(3):207-17.

17.Hinkle D, Wiersma W, Jurs S. Applied Statistics for the Behavioral Sciences. 5 ed. Boston: Houghton Mifflin; 2003.

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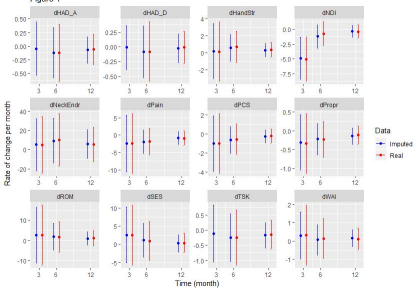
Figure 1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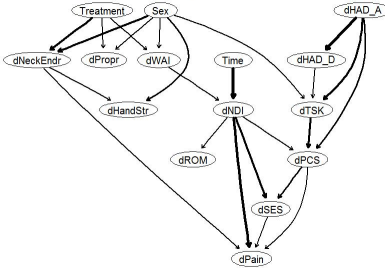
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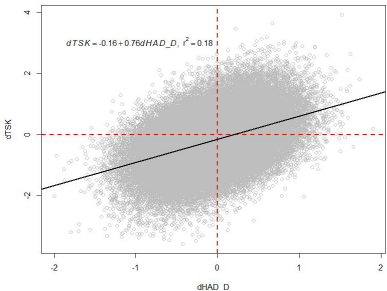

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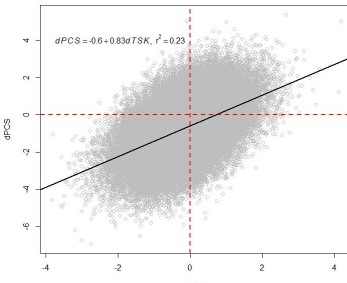

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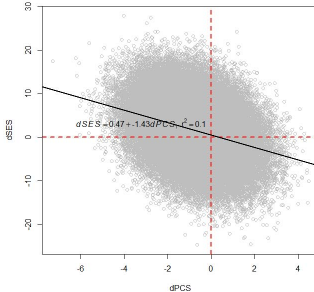

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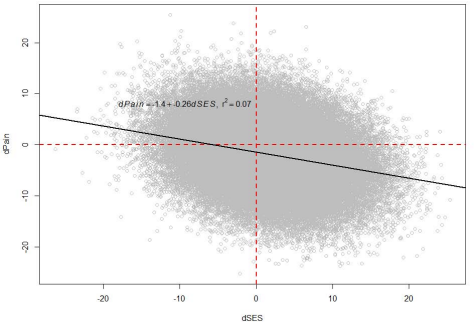

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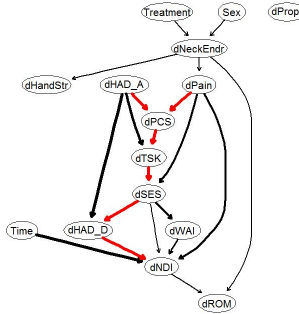

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