

Investigating the Causal Mechanisms of Symptom Recovery in Chronic Whiplash-associated Disorders Using Bayesian Networks

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1 **Title:** Investigating the causal mechanisms of symptom recovery in chronic whiplash
2 associated disorders using Bayesian Networks

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27 **Abstract**

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

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

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

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

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

50 Introduction

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

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

75 catastrophizing would minimize pain related disability in the presence of pain [23, 24].
76 Research has provided supportive evidence of associations between some variables within the
77 FAM. For example, studies have reported significant associations between pain
78 catastrophizing and fear [18, 25]; and between fear and disability [26]. However, current
79 investigations in individuals with musculoskeletal pain have not provided evidence in support
80 of the entire sequential pathway of the FAM [27-29]. Current FAM pathway analysis studies
81 [27-29] have not focused on uncovering alternative FAM pathways; a critical step, not least
82 because it allows researchers to test the validity of competing pathways, and design
83 alternative treatment approaches to prevent the onset of persistent pain-related disability.

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

95 **Materials and Methods**

96 **Participants**

97 The study consisted of 142 women and 74 men with a mean age of 40.4 years (SD =
98 11.4). Participants included in the present study had to fulfil the following criteria: aged 18 to

99 63 years old, WAD classification of grade 2 or 3, experienced a whiplash injury in the past 6-
100 36 months, and having a Neck Disability Index (NDI) score of > 20% and/or an average pain
101 of > 20 mm on a 100 mm Visual Analogue Scale (VAS) [4].

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

109 **Study design**

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

122 **Approach to sample selection**

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

131 **Outcome measures**

132 The following 15 variables were used to form a BN:

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

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

166 **Approach to data analysis**

167 **Differential equation model.** We modelled the nonlinear rates of change of the
168 physical and psychosocial variables, to understand the response to treatment over time. We
169 prefixed (with “d”) the variables which are modelled as rates of change (e.g. “dNDI”). We do
170 so by taking the difference for each variable $\Delta Y = Y_{T_2} - Y_{T_1}$, where T_1 is the baseline and T_2
171 represents the three follow-up time points of 3, 6, and 12 months. The linear rate of change of
172 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
173 rates of change depends on the time itself, can be modelled using the form:

$$174 \quad \frac{\Delta Y}{\Delta T} = \mu + \frac{\Delta X_1}{\Delta T} \beta_1 + \Delta T \beta_2 \dots + \frac{\varepsilon_{\Delta Y}}{\Delta T} \dots (1)$$

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

176 **Bayesian network analysis.** Causal analysis has been studied using structured
177 equations modelling (SEM) [14, 16, 47, 48] and linear regression models [49, 50]. Both
178 methods can be seen as particular cases of Bayesian Networks (BN) [51], a causal modelling
179 approach used increasingly in the medical field [52-55]. BN emphasizes learning pathways
180 directly from data, as opposed to considering problems with a fixed structure like SEM; and
181 they are foundations upon which counterfactual causal inference was built [56]. Crucially,
182 BN are able to handle missing data [57], which makes them practical in settings where patient
183 records are often incomplete.

184 All analyses were performed in R software [58] using the bnlearn package [59]. The
185 statistical codes and results can be found in a public repository [60]. A detailed report of the
186 statistical analysis, codes, and the results are presented as supplementary material. BN model
187 the relationships among a set of variables $\mathbf{X} = \{X_1, \dots, X_N\}^*$, where N is the number of
188 different variables, using a directed acyclic graph (DAG) in which each variable is associated
189 with a node. Learning BN from data involves first identifying which arcs are present in the

190 DAG (structure learning), and then estimating the parameters that regulate the strength and
191 the direction of the corresponding relationships (parameter learning).

192 We made use of blacklisting and model averaging to reduce the number of arcs that
193 are incorrectly included in the BN. A blacklist is simply a set of relationships that we know
194 do not exist (based on existing literature and clinical experience) and are ignored during
195 structure learning. We blacklisted the arcs from all physical and psychosocial variables to the
196 variables of treatment, time, and sex – given that the former do not determine the latter
197 variables. Model averaging consists of resampling the data multiple times ($B = 200$) using
198 bootstrap and performing structure learning on each of the resulting sample using
199 Expectation-Maximization (EM) [57]. We computed an “average” consensus DAG by
200 selecting those arcs that have a frequency of $> 50\%$ in the bootstrapped samples [61].

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

208 We randomly split the data into a training set (90%) and a testing set (10%), and
209 performed structural and parameter learning on the training dataset. We used the BN model
210 learned from the training set to perform validation on the testing set by computing the
211 correlation coefficient between the predicted and observed values of each continuous
212 variable. The strength of correlation was categorized as negligible ($|r| \leq 0.30$), low ($|r| = 0.31$

213 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)
214 [62].

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

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

225 **Results**

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

231 **Mediators of neck-specific exercise and neck pain intensity**

232 Treatment appears to alter dPain via two mediators: dNeckEndr and dWAI (Figure 2).
233 This implies that NSE and NSEB, in comparison with PPA, differentially altered neck pain
234 dynamics because of its differential effects on neck muscle endurance and WAI dynamics.
235 We verified this interpretation in several steps. When dNeckEndr and dWAI improvements

236 were greater than the 75th percentile of the group's change scores, the probability of being
237 classified as improved was greater in NSEB (0.52) and NSE (0.50), compared to PPA (0.46).
238 Using simple linear regression, NSEB reduced neck pain at a rate of $\beta = 0.81$ points/month (t
239 $= -6.21$, $P < 0.001$), and NSE reduced neck pain at a rate of $\beta = 0.59$ points/month more than
240 PPA ($t = -4.47$, $P < 0.001$). Next, we removed the Treatment-dNeckEndr and Treatment-
241 dWAI arcs, by fixing the value of the dNeckEndr and dWAI regression coefficients in the
242 local distributions to zero. This means that dNeckEndr and dWAI do not depend on
243 treatment. When both arcs were removed, the rate of neck pain reduction was not
244 significantly different between groups (NSEB vs PPA: $t = -1.45$, $P = 0.14$; NSE vs PPA: $t = -$
245 1.78 , $P = 0.08$).

246 **Sequential pathway analysis of the FAM**

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

256 **Discussion**

257 In the present study, we used a Bayesian Networks approach to understand the causal
258 mechanisms underpinning the differential response to different exercise interventions; as well
259 as elucidating the cyclical relationship of the FAM in the present cohort of individuals with

260 chronic WAD. A causal understanding can help in the development of new and better
261 matched interventions, but such research has rarely been performed in the area of WAD. In
262 addition, clinicians often desire to seek a causal understanding behind a treatment's clinical
263 efficacy prior to clinical implementation.

264 In the present study, neck muscle endurance but not cervical proprioception and
265 ROM, mediated the relationship between neck-specific exercise and neck pain dynamics. It is
266 likely that this was because the neck-specific exercise program was designed to facilitate the
267 recruitment of the deep cervical muscles, and ultimately train the endurance of the cervical
268 flexor and extensor muscles [4]. The mediating effect of neck muscle endurance supported
269 previous studies that used association-based analysis to investigate the relationship between
270 neck muscle endurance and neck pain [8, 63-65]. Interestingly, a systematic review reported
271 that changes to the physiological features of the transversus abdominis were largely unrelated
272 to improvements in low back pain intensity and disability after exercise [66]. A limitation of
273 the review was that it did not include studies which used statistical methods to study
274 mediation [66]. Alternatively, findings from the present study suggests that global (multi-
275 muscle), rather than local (single muscle), physiological measures are more important
276 mediators of pain recovery in exercise-based interventions. Muscles typically work in
277 functional groups and the individual functioning of a muscle can be compensated by
278 synergistic muscles [67].

279 The results of the present study also revealed that perceived work ability mediated the
280 relationship between neck-specific exercise and neck pain dynamics. This finding was
281 surprising given that the neck-specific exercise program was not designed specifically to
282 facilitate return to work. The WAI questionnaire evaluates an individual's return to work
283 expectations, as well as their work ability relative to the work's physical demands (see
284 questions six and two of WAI). A previous study on sub-acute WAD reported that return to

285 work expectations mediated the relationship between variables of perceived injustice, fear of
286 movement, pain catastrophizing and the return-to-work status [68, 69]. In addition, perceived
287 physical exertion in the workplace, mediated the relationship between a multi-faceted
288 workplace rehabilitation program and low back pain intensity [70]. It is plausible that neck-
289 specific exercise was better at improving perceived physical capacity, and more optimistic
290 return to work expectations, than a general physical activity program.

291 Similar to previous studies [28, 29], the sequential pathway of the FAM [17] was not
292 observed in the BN model learnt purely from the data. The pathway connecting variables of
293 the FAM learnt using BN was as follows: anxiety, followed by depressive symptoms, fear,
294 catastrophizing, self-efficacy, and consequently pain. A benefit of using BN is that the
295 predictive validity of competing pathway models can be tested. BN can be used to build
296 pathways that vary from being completely data-driven to completely informed by prior
297 knowledge (e.g. theory, literature, expert opinion). Although there are other FAM variants
298 [22], we only compared our data-driven model to another model informed by a single FAM
299 [17], as it is the most widely used in musculoskeletal pain research. Despite the capacity to
300 build completely data-driven pathways, factors such as a relatively small sample size (see
301 range of sample sizes in [22]), presence of missing data, and the plausibility of pathology
302 specific FAM pathways [17, 22]; which means that we remain cautious when interpreting our
303 data-driven model and generalizing it to other patient cohorts.

304 The most surprising findings of the present study were that depressive symptoms
305 preceded fear, and fear preceded pain catastrophizing. Both of the present findings stand in
306 contrast to the FAM [17], but had empirical support from the literature [71, 72]. In a study of
307 general musculoskeletal pain, Thompson et al. [72] reported that more depression was
308 positively correlated with more fear, although their analysis cannot determine if depression
309 preceded or proceeded fear. Depressive symptoms were found to have a substantial direct

310 influence on fear in individuals with low back pain [48]. Even when investigating other FAM
311 pathway variants, allowing negative affectivity (a measure of depressive feelings) to directly
312 affect fear increased the fit of the statistical model, compared to a model without negative
313 affectivity [47]. The importance of depressive symptoms early in the FAM pathway prior to
314 fear, has also been previously proposed within the “Depression pathway model” of Pincus et
315 al. [73]. Depressive symptoms can be conceptualized as a dispositional trait which gives rise
316 to behavioural withdrawal and general tiredness, which leads to greater fear [74]. Greater fear
317 may heighten the cognitive mechanisms that result in selective attention to threatening stimuli
318 (catastrophizing) [71], which from an evolutionary perspective, confer the organism greater
319 survival benefits [71].

320 **Greater pain catastrophizing either directly decreased the rate of neck pain reduction,**
321 **or it worsened self-efficacy which decreased the rate of neck pain reduction.** This finding
322 supports an increasing body of research identifying self-efficacy as an important mediator of
323 recovery in painful musculoskeletal disorders [14, 19, 75]. A person with a higher sense of
324 self-efficacy may be more likely to utilize adaptive coping strategies and adhere to treatment,
325 compared to those with a lower sense of self-efficacy [76]. In contrast to previous studies [19,
326 75], we observed that self-efficacy mediated the disability leading to pain relationship, rather
327 than the pain leading to disability relationship. An important distinction between previous
328 studies and the present study, was that prior research tested the mediating effect of self-
329 efficacy with the assumption that more pain leads to more disability [19, 75]. The NDI was
330 used to provide a self-reported measure of physical activity levels, which may not correspond
331 to objective measures such as accelerometry [29]. A greater amount of physical activity can
332 improve pain by improving a person’s self-efficacy [77], but also potentially by exercise-
333 induced hypoalgesic effects [78].

334 Findings of the present study have several clinical implications. First, a causal
335 understanding behind how different exercises work can help clinicians prioritize therapeutic
336 efforts to the most important impairments that determine recovery. Second, therapeutic
337 interventions based on the FAM pathway of Leeuw et al [17], which focused on fear
338 reduction, have not had convincing results [79]. The present finding proposes an alternative
339 FAM pathway, from which new interventions can be developed and its efficacy tested. Third,
340 knowing the sequential pathway between the initial pain episodes to long term
341 disability/recovery means that a clinician can select the modifiable impairments easiest to
342 treat in an individual. For example, an individual with WAD who has a high level of
343 depression, may benefit from interventions which targets reducing depressive symptoms,
344 and/or interventions aimed at reducing fear – since fear lies on the pathway from depression
345 to pain.

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

358 **Conclusions**

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

369

370

371

Figure captions

372

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

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

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

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

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

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

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

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