

Factors related to pain and disability outcomes after an internet-delivered or physiotherapist-led exercise programme for individuals with chronic whiplash symptoms: secondary analysis of a randomized controlled study

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Table of Contents

Original Manuscript.....	5
Supplementary Files.....	38
0.....	38
Figures.....	39
Figure 4.....	43
Multimedia Appendixes.....	44
Multimedia Appendix 1.....	45
Multimedia Appendix 2.....	45
CONSORT (or other) checklists.....	46
CONSORT (or other) checklist 0.....	46
CONSORT (or other) checklist 0.....	46

Factors related to pain and disability outcomes after an internet-delivered or physiotherapist-led exercise programme for individuals with chronic whiplash symptoms: secondary analysis of a randomized controlled study

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Abstract

Background: A neck-specific exercise program has shown sustained clinically important changes in pain and disability for approximately 50% of individuals with chronic whiplash-associated disorders (WAD). However, there is limited information about factors related to treatment response.

Objective: This study aimed to identify factors related to change in pain and disability after a neck-specific exercise program delivered in two different ways for individuals with persistent whiplash-associated disorders (WAD) grade II or III.

Methods: This is a secondary analysis, based on a prospective randomized controlled multicenter study (RCT). Participants (n = 140) with persistent (? 6 months and ? 5 years from injury) WAD grade II or III were randomized into a 12-week internet-supported neck-specific exercise program (NSEIT) with four physiotherapy visits or the same exercise program (NSE) supervised by a physiotherapist twice a week for 12 weeks. Multivariate data analyses were used to investigate factors related to change in the dependent variables: neck pain measured with the Visual Analogue Scale, and neck-related disability measured with the Neck Disability Index and the Patient Specific Functional Scale. Outcomes were measured at baseline, 3- and 15-month follow-up.

Results: There were no significant differences between the groups. In both NSEIT and NSE, improvements in the following factors were related to improvements in pain and disability at three- and 15-month follow-up: anxiety, depression, cognitive failure, pain catastrophizing, self-efficacy, fear avoidance beliefs, cervical range of motion, headache, and symptom satisfaction ($R^2 = 0.31\text{--}0.37$; $Q^2 = 0.25\text{--}0.30$; CV-ANOVA $P < 0.001$). No significant models could be built to separate clinically improved versus non-improved patients in terms of pain or disability, based on baseline factors.

Conclusions: Improvements in both psychological and physical factors were related to improvements in pain and disability after 12 weeks of NSEIT or NSE. The results indicate that these factors are interrelated and can be improved both with NSEIT and with NSE. No baseline factors could predict clinically improved versus non-improved in the present study. Already known risk factors for poor outcomes of neck disability in chronic WAD such as low self-efficacy, fear avoidance beliefs, depressive symptoms, and catastrophizing were improved after NSEIT and NSE. Therefore, we need to identify other factors not included in the present study that can identify those who are non-improved after NSEIT or NSE. Clinical Trial: ClinicalTrials.gov (NCT03022812); <https://clinicaltrials.gov/ct2/show/NCT03022812>

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Original Manuscript

INTRODUCTION

Whiplash-associated disorders (WAD) are indirect trauma to the neck, commonly related to a car crash [1], and approximately half of those injured develop chronic disability and pain [1,2]. Chronic WAD will have extensive consequences for the individual living with persistent pain, leading to a burden for the individual and high costs for society [3,4]. Depression, low levels of life satisfaction and post-traumatic stress have been observed five years after whiplash injury [5]. Costs increase as many individuals with chronic WAD are consumers of multiple health services and experience reduced work ability [4,6]. Although the evidence is moderate at best, exercise and patient education are recommended treatments in chronic WAD [7].

Approximately 50% of the included participants in a neck-specific exercise programme (NSE), conducted by two of the authors in the present study (G.P. and A.P.), with chronic WAD grades II (neck pain and musculoskeletal findings during a physical examination) and III (as grade II but with additional neurological findings) had a sustained clinically important change in pain and disability [8,9]. Despite these promising results, about half of the participants were not clinically improved, demonstrating that chronic moderate-to-severe WAD is difficult to treat successfully. Consequently, there is a need to identify factors related to improvement in disability and pain in order to optimize treatment, discriminating them from factors that may contribute to sustained problems.

An earlier study found that depression, low self-efficacy and higher disability were associated with a larger pain area in women with chronic WAD [14]. In another study, self-efficacy mediated the association between pain intensity and pain-related disability, and kinesiophobia mediated the association between self-efficacy and pain catastrophizing in acute and subacute WAD [16], which can lead to chronic disability. However, that study did not investigate factors related to improvements after rehabilitation. In studies where interventions included acceptance and commitment therapy or cognitive behavioural therapy, psychological factors had a mediating or predictive effect on pain and/or disability outcome for individuals with chronic WAD [17,18]. Another study found that

participation in a neck-specific exercise programme was the only significant factor associated with neck pain reduction at 12-month follow-up [19], and neck muscle endurance and perceived work ability were mediators for reduction in pain [20] in chronic WAD. The treatment of chronic non-malignant pain is influenced by biological, psychological and sociological factors [21]. Numerous studies have found factors such as anxiety, catastrophizing and severe pain to be related to poor treatment outcomes after acute whiplash injury [22].

However, to our knowledge, there is very limited information about factors related to treatment response in chronic WAD, or about the optimization of a neck-specific exercise programme delivered via internet. Internet-based exercise interventions with fewer visits to physiotherapists can increase availability, shorten waiting times and reduce costs. Internet-based treatment may also strengthen the patient's own resources for greater autonomy and the ability to conduct long-term self-care [23]. Factors associated with improvements in an internet-based neck-specific exercise programme (NSEIT) may differ compared to regular visits to a physiotherapist (NSE) and need to be investigated. Moreover, the ability to predict those who will not recover after NSEIT and NSE is highly relevant to improving treatment in chronic WAD.

The aims of the study were: a) to investigate factors related to change in neck pain and disability after NSEIT or the same exercise programme supervised by a physiotherapist (NSE) for individuals with chronic WAD grade II or III, and: b) to investigate whether other factors could predict those with clinically improved versus not improved pain and disability after three months of NSEIT or NSE.

METHODS

The recruitment of participants and the exercise interventions were reported earlier [9] and are briefly described below.

This is psychological factors [9]. Data were collected from 6 April, 2017, until 15 September, 2020,

and the main outcome data have been published [9]. The participants were recruited from 10 county councils in Sweden.

Participants

Individuals with chronic (between 6 months and 5 years from injury) WAD grades II–III [24] with neck symptoms within the first week after a whiplash injury in a four-wheeled motor vehicle crash were eligible for inclusion. Symptoms emanating from the neck were verified through medical history and a physical clinical examination. For additional inclusion and exclusion criteria, see Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
• Average neck pain last week ≥ 20 mm on a 0–100 mm visual analogue scale • Neck disability ≥ 20 % • Age 18–63 years • Daily access to a computer / tablet / smartphone and the internet • Sufficient time and motivation to follow the treatment programme	• Signs of head injury • Serious physical pathology • Surgery on the cervical column • Generalized or more dominant pain elsewhere in the body • Previous fractures or dislocation of the cervical column • Other illness or injury that may prevent full participation in the study and/or for which exercises are contraindicated • Previous severe neck problems that resulted in sick leave for more than one month in the year before the current whiplash injury • Lack of knowledge of the Swedish language • Diagnosed severe mental illness • Current alcohol and/or drug abuse

Reason for exclusion criteria were: a) NSEIT/NSE could lead to increased illness or potentially negatively influence other important treatments, b) other illness/disease made it impossible to perform NSEIT/NSE and/or follow the programme for 3 months, c) when exercises were contraindicated, d) participants were unable to understand the information and/or the exercises.

Ethical considerations

The study was approved by the regional ethical review board (approval nos. 2016/135–31; 2016/526–32; 2017/45–32). The study was registered in ClinicalTrials.gov (Protocol ID: NCT03022812, initial release 12/20/2016) and the study protocol was published prior to data collection [24]. The original written and informed consent allowed for this secondary analysis without requiring additional consent, and no new data was collected for the present study. De-identification was employed to prevent the identification of individuals. The key code is securely stored according to the regulations from the ethics committee and the Swedish Authority for Privacy Protection (IMY). The results are presented at the group level, ensuring no connection to individual participants. Participants were not compensated for their involvement in the study, except for travelling cost compensation in accordance with national ethical regulations.

Recruitment

Information about the study was provided via healthcare personnel and advertising. Interested participants completed a short survey on the Linköping University website. The patient's medical history was compiled and a physical examination was carried out before inclusion. Once the study criteria had been met, the participants were included after giving written and oral informed consent. The test leaders were blinded to group allocation. The participants were blinded to group allocation when baseline data were collected [24].

Randomization

Participants (n = 140) were randomized into two groups (n = 70 in each group) using a computerized block randomization list stratified by sex. After randomization, the treating physiotherapist was contacted by the research team and called the patient to the first appointment.

Before study start, all treating physiotherapists received oral and written information and a day of practical training from the project leaders. A detailed prescription of the NSEIT and NSE exercise programme has been published [9].

NSEIT group: Neck-specific exercise with an internet-based programme

In the NSEIT group, the participants underwent a 12-week exercise programme with four visits to the physiotherapist (at weeks 1, 2, 3 and 7) to be introduced to the exercises, to progress the exercises and for follow-up to ensure correct performance. The patient had access to the internet-based programme on a website. The programme included photos and videos of the exercises, information about the musculoskeletal anatomy of the neck and about neurophysiological and neurobiological pain, and strategies for dealing with neck pain relapse. The exercises were initially targeted to activate the deep neck muscles and increase postural control, continuing with an individually tailored progression of neck muscle endurance exercises [9,24]. At the end of the treatment period, the participants were encouraged to continue doing the exercises two to three times a week and to include neck-specific exercise; for details see [9].

NSE group: Neck-specific exercise group at a physiotherapy clinic twice a week

In the NSE group, participants received the same information and exercises as the NSEIT group, but in visits to the physiotherapy clinic twice a week (a maximum of 24 sessions) [9,24].

Patient and public involvement

Patients were involved in developing the questionnaires before recruitment to the study started. The questionnaires were tested by three patients to ensure the inclusion of relevant questions and readability. Patient satisfaction with the exercises, information, tests and intervention (NSEIT or NSE) were measured post intervention.

Adverse events could be reported to the project leaders directly by participants, the test leaders or the treating physiotherapists; for details see [9].

Predictor variables and outcome measures used in multivariate modelling

Measurements were collected via questionnaires at baseline, and at 3-month and 15-month follow-ups. The following variables were used in the multivariate modelling.

Background variables

The following variables were only collected at baseline: *age* (years); *sex* (male/female); *smoking* (yes/no); *level of education*; *pain duration* (months since injury); *WAD grade II and III* according to the Quebec Task Force (QTF) classification [25]; *expectations of the intervention* on a 0 to 10 scale (with higher scores indicating stronger belief that the treatment would help) [26].

Dependent factors

Neck Disability Index (NDI) measures self-perceived disability in everyday life because of neck pain, including ten items of neck-related disability, which are summed and transformed into a percentage (0% = no disability; 100% = highest score for disability) [27].

Neck pain now was measured on a visual analogue scale (VAS) from 0–100 mm, where 0 = no pain and 100 = worst imaginable pain intensity) [28].

The Patient-Specific Functional Scale (PSFS) measured level of physical function, graded from 0 (unable to do the activity) to 10 (functional level equal to pre-injury status) regarding self-perceived physical activity, leisure time and work [29].

Independent factors

Measures of factors considered as potentially related to change in pain and disability were selected based on a review of the literature and on clinical experience of two specialist physiotherapists with over 15 years' experience managing patients following a whiplash injury.

Self-reported pain medication ("Do you take pain medication?", yes/no).

Symptom satisfaction was measured on a seven-point scale from 1 = happy about symptoms to 7 = unhappy about symptoms [30].

Exercise level rating daily activities and sports (from 1 = inactivity to 4 = high activity level) [31].

Dizziness at rest and during motion, and *unsteadiness* and *headache intensity* were measured on VAS scales from 0 mm = no dizziness/unsteadiness or headache to 100 mm = extreme dizziness/unsteadiness or headache [28, 32].

Post-Traumatic Stress Disorder (PTSD) Checklist, the specific trauma version (PCL-S), measures post-traumatic stress reactions and consists of four subscales (re-experience, avoidance, negative alterations in cognition and mood and hyper-arousal), with a total score ranging from 0 = no stress reaction to 80 = extreme stress [33].

Fear Avoidance Beliefs Questionnaire (FABQ) measures the individual's fear of pain and consequent avoidance of physical activity because of their fear. It consists of two subscales (Physical Activity subscale (four items) and Work subscale (seven items)), with a total score ranging from 0 to 66, where higher scores indicate higher fear avoidance beliefs [34].

Hospital Anxiety and Depression Scale (HAD) gives an anxiety score (from 0 = no anxiety to 21 = maximal anxiety) and a depression score (from 0 = absent depression to 21 = maximal depression) [35].

Pain Catastrophizing Scale (PCS) measures the extent of catastrophizing according to the three subscales (rumination, magnification and helplessness) with a total score range of 0–52, with higher scores indicating higher pain catastrophizing [36].

Self-Efficacy Scale (SES) measures self-perceived performance of 20 everyday functional tasks in spite of pain, with total scores ranging from 0 to 200, where higher scores indicate higher perceived self-efficacy [37].

Cognitive Failures Questionnaire (CFQ) measures behavioural problems associated with attentiveness and memory in everyday life, with total score ranging from 0 to 100, where a higher score indicates a greater frequency of cognitive failures [38].

EQ-5D-3L and *EQ VAS* measure health-related quality of life. EQ-5D-3L scores range from –0.624

to 1 and EQ VAS scores range from 0 to 100 mm, with higher values indicating better health-related quality of life [39].

The following physiological measures were collected by the test leader at baseline, 3-month and 15-month follow-up.

Dynamic hand strength was measured in kilograms using the Jamar dynamometer [40].

Ventral and dorsal neck muscle endurance (NME) was registered in seconds [41].

Active range of cervical motion in sagittal, lateral and frontal planes was recorded in degrees using the cervical range-of-motion (CROM) device [42].

The *Cranio-Cervical Flexion test (CCFT)* measures the action of the deep cervical flexor muscles, registered in mmHg [43].

Balance test: standing on one leg with eyes closed (SOLEC) was measured in seconds [32].

Statistical and multivariate data analysis

Multivariate data analysis was used to investigate the relationships between the variables, using (SIMCA software v.18.0.0.372 Sartorius Stedim Data Analytics AB, Göttingen, Germany). For this, orthogonal partial least squares (OPLS) and OPLS discriminant analysis (OPLS-DA) were utilized. In general terms, these methods are linear regression methods that model the association between predictors (X) and response (Y) variables. They do this by summarizing the information in the original variables into a few virtual variables (components) that are selected to maximize the covariance between the X and Y variables. This allows the identification of the association between many X and Y variables simultaneously. The methods also separate variation in predictors that are either predictive for the response variables or not (orthogonal). This minimizes the issue of collinearity seen with classical regression models.

First, the differences between patients randomized to either NSEIT or the same exercises and information at a physiotherapy clinic (NSE) [9] were investigated by studying the changes (change

scores) of variables between the three time points (baseline to 3 months, baseline to 15 months, and 3 months to 15 months) using OPLS-DA. Both the dependent factors disability (NDI), neck pain (VAS), and physical function (PSFS) and the independent factors (defined above) were included as X variables to investigate which of the variables may explain differences between NSE and NSEIT.

Secondly, OPLS models were used to investigate the relationship between changes for the dependent and independent factors at the three time points (baseline to 3 months, baseline to 15 months, and 3 months to 15 months). Y variables were set to the change scores for the dependent factors NDI, neck pain and PSFS (using the average of the three PSFS components Physical activity, Leisure time and Work). X variables included all independent factors and all background variables detailed above. A positive change score indicates improvement (for example, a higher change score in neck pain indicates less pain) and a negative change score indicates deterioration. To identify which of the X variables (independent factors) were most important for the changes in the Y variables (dependent factors; NDI, neck pain and PSFS), those independent factors in a first model that had a variable influence on projection (VIP) value of at least 1.0 and a VIP value greater than the standard error were included in a second OPLS model with one predictive and one orthogonal component.

Thirdly, multivariate models using OPLS-DA were used to investigate whether background variables and baseline measurements of any of the independent factors could predict clinically significant improvement in the dependent factors NDI, neck pain and PSFS. Individuals with clinically improved NDI, neck pain and PSFS (value change NDI ≥ 7 , neck pain $\geq 50\%$ improvement, PSFS ≥ 2 -point improvement) [27,28,44] were compared to individuals with no improvement or deteriorated values on these outcome measures.

All multivariate models were assessed using the fit of the data to the model (R^2) and the predictability of the model fit on new data (Q^2); the significance of group separation was assessed using cross-validated analysis of variance (CV-ANOVA) [45]. The maximum value for each (R^2 and Q^2) is 1.0 and symbolizes a perfect model. The loadings (weights representing the variables) were

used for interpretation of the association between the X (independent factors) and Y (dependent factors) variables.

Sample size and power calculations were calculated based on the primary outcome measure (NDI) in the previous randomized controlled study [8]. To detect a between-group noninferiority margin of 7% with 1-sided $\alpha = .025$ and $\beta = .8$, a total of 47 participants were needed in each group. To account for dropouts, 70 participants were included in each of the two groups (140 in total) [9]. Compliance with the exercise programme (NSEIT, NSE) was defined as at least 50% self-reported completion of the exercises.

RESULTS

Baseline characteristics of the participants are shown in Table 2. In the NSEIT group, 63 (90%) and 56 (80%) participants completed the 3-month and 15-month questionnaires, respectively. In the NSE group, 64 (91%) and 58 (83%) completed the 3-month and 15-month questionnaires, respectively (Supplementary file 1).

During the 12-week intervention period, the participants' self-reported compliance with the exercise programme was higher in the NSE group ($n = 59$, 94%) than in the NSEIT group ($n = 46$, 75%, $P = .006$). No adverse events were reported.

Table 2. Baseline characteristics of participants with whiplash associated disorders (WAD) grade II and III, by treatment group

	NSEIT (n = 70)	NSE (n = 70)
Age , mean (SD)	40.4 ± 11.6	40.5 ± 11.4
Sex , female, n (%)	55 (79%)	55 (79%)
Months since injury , mean (SD)	27.4 ± 21.0	25.2 ± 15.5
Whiplash-associated disorders , n (%)		
Grade II ^a	46 (66%)	43 (61%)
Grade III ^b	24 (34%)	27 (39%)
Educational level , n (%)		

Elementary school	1 (1%)	0 (0%)
Upper secondary school	30 (43%)	39 (57%)
University	35 (50%)	27 (39%)
Other	4 (6%)	3 (4%)
Marital status , married or cohabiting, n (%)	52 (74%)	53 (76%)
Previous treatment , yes, n (%)	62 (89%)	66 (94%)
Use of analgesic drugs , n (%)		
Yes	57 (81%)	60 (86%)
No	12 (17%)	10 (14%)
Sick leave , n (%)		
No	61 (87%)	62 (89%)
Sick leave, part-time	6 (9%)	5 (7%)
Sick leave, full time	3 (4%)	3 (4%)
Disability , mean (SD)		
Neck Disability Index (NDI) (0–100%)	39.4 ± 12.2	36.6 ± 10.8
Neck pain intensity , mean (SD)		
Neck pain now, VAS (0–100 mm)	34.6 (21.4)	39.7 (22.4)
Neck pain average previous week, VAS (0–100 mm)	44.9 ± 20.6	47.6 ± 21.7
Patient-Specific Functional Scale (PSFS) , mean (SD)		
PSFS Work (0–10)	3.9 ± 2.1	3.6 ± 2.3
PSFS Leisure time (0–10)	3.7 ± 2.1	3.6 ± 2.3
PSFS Activity (0–10)	3.2 ± 2.5	3.5 ± 2.8

^aWhiplash-associated disorders grade II: neck pain and musculoskeletal findings during a physical examination); ^bgrade III: as grade II but with additional neurological findings. (NSEIT, neck-specific exercises with internet support; NSE, neck-specific exercises at physiotherapy clinic; SD, standard deviation; VAS, visual analogue scale.)

Between-group differences

No significant OPLS-DA models could be built to separate patients receiving NSEIT from those receiving NSE, (baseline to 3 months: $R^2 = 0.22$, $Q^2 = -0.12$; baseline to 15 months: $R^2 = 0.22$, $Q^2 = 0.01$; 3 months to 15 months: $R^2 = 0.17$, $Q^2 = -0.10$, all models CV-ANOVA $P=1.0$). Neither were there any differences between the NSEIT and NSE groups regarding independent factors associated with improvements in the dependent factors NDI, neck pain and PSFS (Supplementary file 2, Figs.

1–3).

Factors related to improvements in disability, neck pain and physical function

No background factors were found to be associated with improvements in NDI, neck pain or PSFS in any of the multivariate models.

Improvement from baseline to 3-month follow-up

At 3 months compared to baseline, 20 independent factors were identified as associated with improvements in NDI, neck pain or PSFS (Fig. 1), ($R^2 = 0.31$, $Q^2 = 0.25$, CV-ANOVA $P < .001$).



Fig. 1. OPLS model depicting changes in independent factors from baseline to 3 months. **A:** Score plot of the participating patients. The colour corresponds to grouping in either NSE (blue squares) or NSEIT (green circles). There were no differences between the NSEIT and NSE groups. **B:** Loading plot of analysed variables, showing the contribution of each independent factors to the OPLS component underlying the participant separation in the score plot A. The x-axis depicts the most important predictive component for separating participants based on improvements in NDI, neck pain and PSFS (blue circles) in both the NSEIT and NSE groups ($R^2 = 0.31$, $Q^2 = 0.25$, CV-ANOVA $P < .001$). NDI, Neck Disability Index; PSFS_Avg, Patient-Specific Functional Scale average (the average of the three PSFS components Physical activity, Leisure time and Work); CROM, cervical range of motion; FABQ, Fear Avoidance Beliefs Questionnaire; EQ5D, EuroQOL health-related quality-of-life scale; EQVAS, EuroQOL visual analogue scale; PCS, Pain Catastrophizing Scale.

Improvement from baseline to 15-month follow-up

At 15 months compared to baseline, 16 independent factors were identified as associated with improvements in NDI, neck pain and PSFS; ($R^2 = 0.37$, $Q^2 = 0.30$, CV-ANOVA $P < .001$ for NDI and neck pain, and $P < .01$ for PSFS) (Fig. 2).

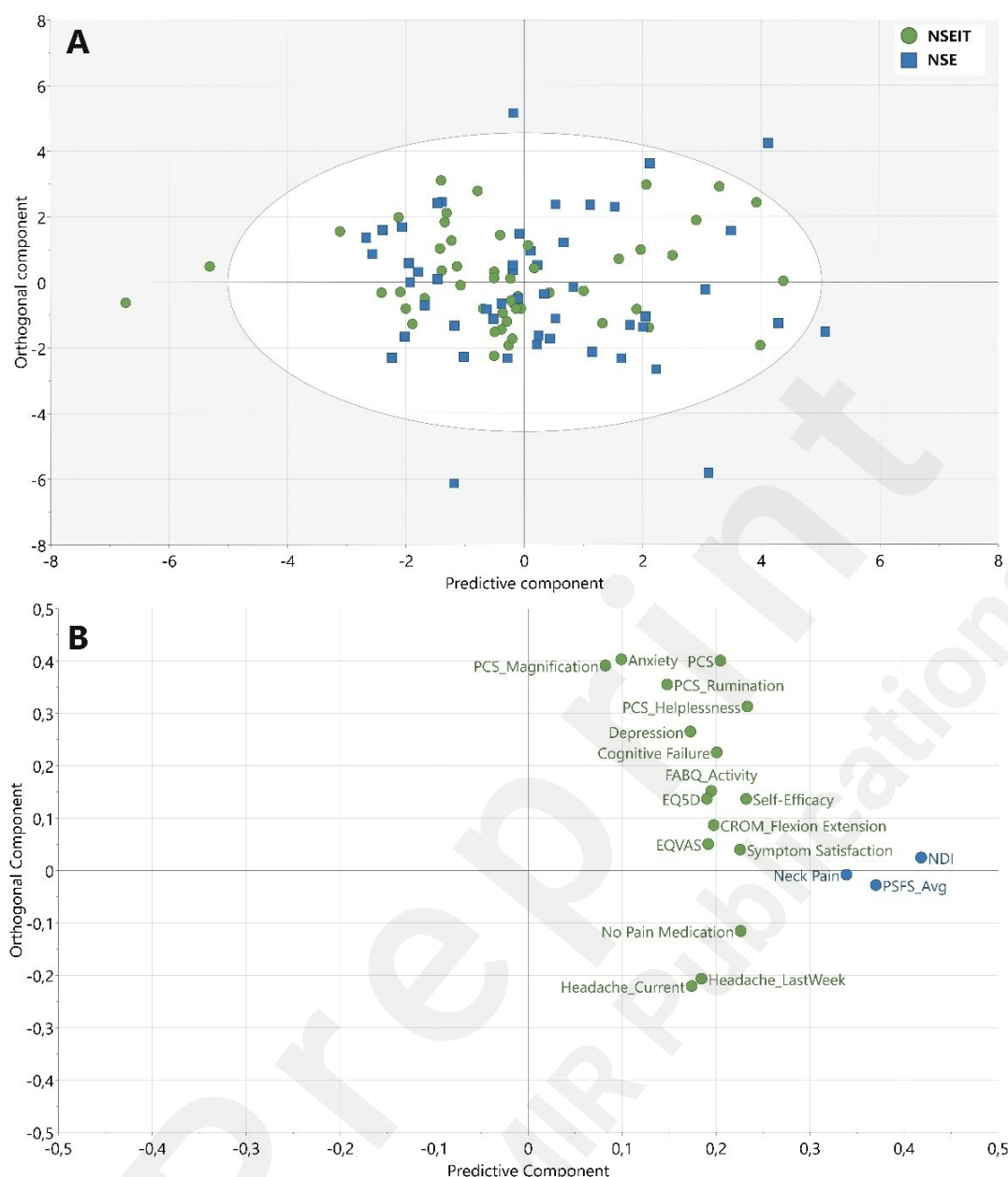


Fig. 2. OPLS model depicting changes in independent factors from baseline to 15 months. **A:** Score plot of the participating patients. The colour corresponds to grouping in either NSE (blue squares) or NSEIT (green circles). There were no differences between the NSEIT and NSE groups. **B:** Loading plot of analysed variables, showing the contribution of each independent factors to the OPLS component underlying the participant separation in the score plot A. The x-axis depicts the most important predictive component for separating participants based on improvements in the primary outcomes NDI, neck pain and PSFS (blue circles) ($R^2 = 0.37$, $Q^2 = 0.30$, CV-ANOVA $P < .001$ for NDI and neck pain, and $P < .01$ for PSFS). NDI, Neck Disability Index; PSFS_Avg, Patient-Specific Functional Scale average (the average of the three PSFS components Physical activity, Leisure time and Work); CROM, cervical range of motion; FABQ, Fear Avoidance Beliefs Questionnaire; EQ5D, EuroQOL health-related quality-of-life scale; EQVAS, EuroQOL visual analogue scale; PCS, Pain Catastrophizing Scale.

Improvement from 3-month to 15-month follow-up

At 15 months compared to 3 months, 18 independent factors were identified to be associated with improvements in NDI, neck pain and PSFS), $R^2 = 0.34$, $Q^2 = 0.28$, CV-ANOVA $P < .001$ (Fig. 3).

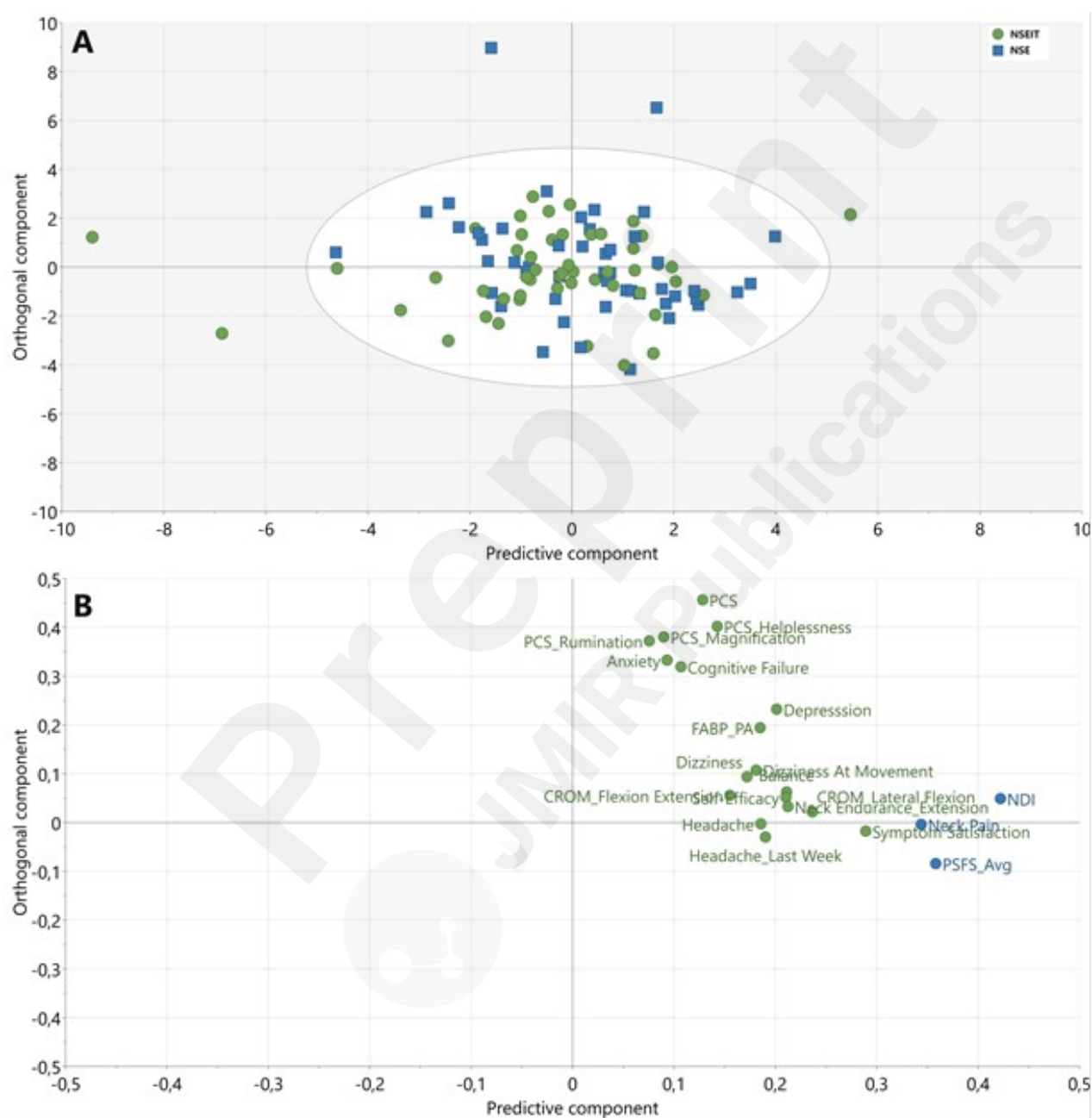


Fig. 3. OPLS model depicting changes in independent factors from 3 months to 15 months. **A:** Score plot of participating patients. The colour corresponds to grouping in either NSE (blue squares) and NSEIT (green circles). There were no differences between the NSEIT and NSE groups. **B:** Loading plot of analysed variables, showing the contribution of each independent factors to the OPLS component underlying the participant separation in the score plot A. The x-axis depicts the most important predictive component for separating participants based on improvements in the primary outcomes NDI, neck pain and PSFS (blue circles). $R^2 = 0.34$, $Q^2 = 0.28$, CV-ANOVA $P < .001$. NDI, Neck Disability Index; PSFS_Avg, Patient-Specific Functional Scale average (the average of the three PSFS components Physical activity, Leisure time and Work); CROM, cervical range of motion; FABQ, Fear Avoidance Beliefs Questionnaire; EQ5D, EuroQoL health-related quality-of-life scale; EQVAS, EuroQoL visual analogue scale; PCS, Pain Catastrophizing Scale.

Variable loadings for the three models

The contribution of each variable (loadings) to the predictive component (x-axis) for the three models (Fig. 1–3) are visualized in Fig. 4. Thirteen of the 23 identified independent factors were common for all three models and included both psychological and physiological factors. The most important factors, as determined by a higher loading, that were related to improvements in NDI, neck pain and PSFS were as follows: anxiety and depression, cognitive failure, pain catastrophizing, self-efficacy, fear avoidance beliefs, cervical range of motion, headache last week, current headache and symptom satisfaction. Factors only found in one or two models were: fear avoidance beliefs subscale Work, balance (standing on one leg), cervical motion (lateral flexion and rotation), neck muscle endurance (extension), taking no pain medication, dizziness at rest and at movement, and health-related quality of life (Fig. 4).

The five most important independent factors related to changes in NDI, neck pain and PSFS between baseline and 3-month follow-up were improvement in cervical range of motion (flexion/extension), symptom satisfaction, depression, cognitive failure and self-efficacy (Fig. 4 A).

The five most important independent factors related to changes in NDI, neck pain and PSFS between baseline and 15-month follow-up were improvement in pain catastrophizing (helplessness), self-efficacy, taking no pain medication, symptom satisfaction and pain catastrophizing (total score) (Fig.

4 B).

The five most important independent factors related to changes in NDI, neck pain and PSFS between 3-month and 15-month follow-up were improvement in symptom satisfaction, cervical range of motion (lateral flexion), NME (extension), balance and self-efficacy (Fig. 4 C).

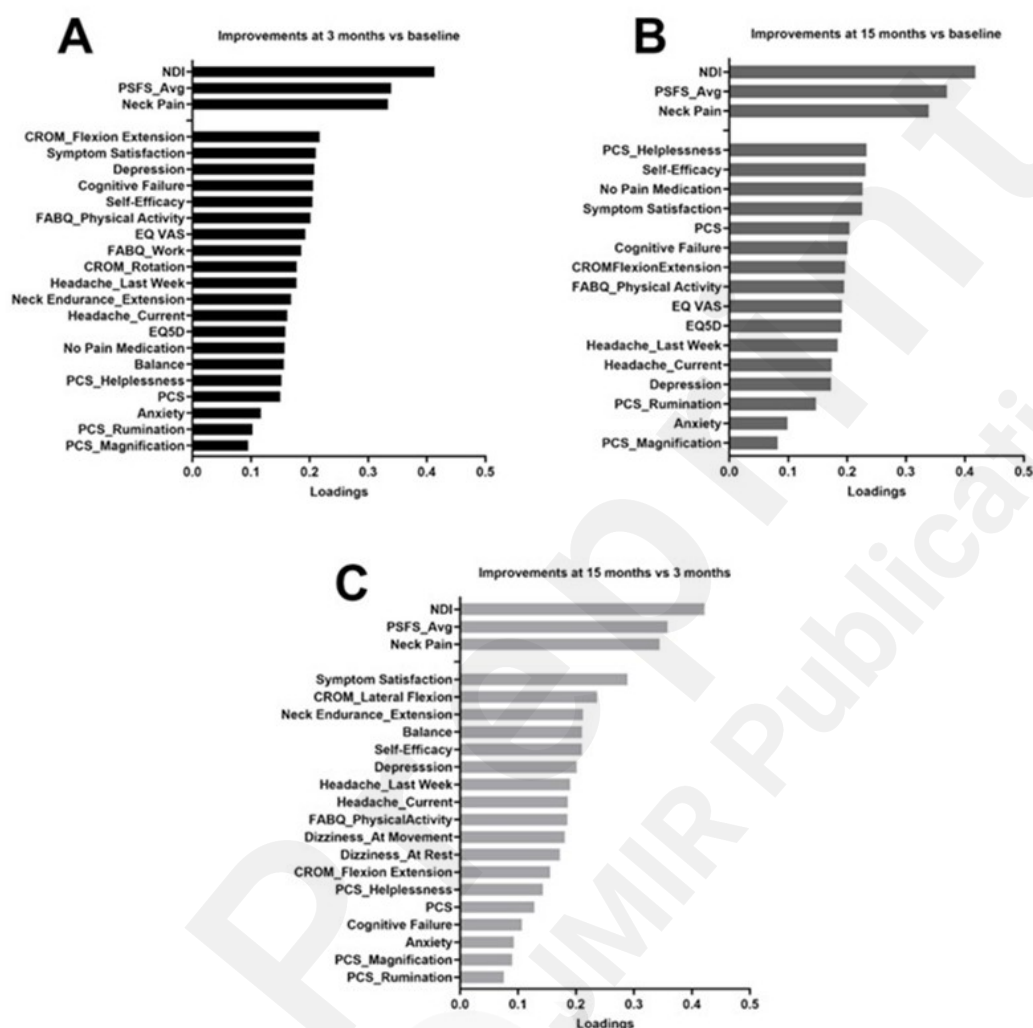


Fig. 4. Loadings (contribution of each independent factors) obtained through OPLS after selecting outcome measures with variable influence on projection (VIP) greater than 1.0. The three models (A-C) showing association between independent factors for improvements in NDI, neck pain and PSFS at different time points. **A:** Improvements between baseline and 3-month follow-up. **B:** Improvements between baseline and 15-month follow-up. **C:** Improvements between 3-month and 15-month follow-up. A higher value for the loadings indicates it is more important in the models. NDI, Neck Disability Index; PSFS_Avg, Patient-Specific Functional Scale (the average of the three PSFS components Physical activity, Leisure time and Work); CROM, cervical range of motion; FABQ, Fear Avoidance Beliefs Questionnaire; EQ5D, EuroQoL health-related quality of life scale; EQVAS, EuroQoL visual analogue scale; PCS, Pain Catastrophizing Scale.

Baseline factors determining clinically improved versus non-improved patients in disability, neck pain and physical function

Using OPLS-DA modelling, no significant models could be built to separate those patients whose NDI, neck pain or PSFS was clinically improved from those with no improvement or showing deterioration based on background variables and baseline measurements of any of the independent factors (Supplementary file 2, figures 4–9).

DISCUSSION

Principal findings

This secondary analysis of a prospective randomized study investigated factors related to change in neck pain and disability (including functional ability) after a NSEIT or NSE exercise programme for individuals with chronic WAD grade II or III.

The multivariate OPLS-DA models showed no significant differences between NSEIT and NSE. Thus, factors related to changes in pain and disability were the same in both groups independently of how the exercise programme was delivered. On the other hand, the multivariate OPLS models of improvements in neck pain and disability between the three time points (baseline to 3 months, baseline to 15 months and 3 months to 15 months) indicated a number of related factors in both NSEIT and NSE. In total, 23 factors were identified and 13 of them featured in all three time points. However, neither the baseline factors nor changes in the independent factors could predict which patients had improved versus non-improved in pain and disability.

Improvements in psychological and physiological factors were associated with improvement in disability, pain and physical function in both groups (NSEIT and NSE). It seems reasonable to assume that the effect may be related to the neck-specific exercise intervention itself, regardless of internet-based or physiotherapist-supervised, because the neck-specific exercise and information programme were identical in NSEIT and NSE. The four face-to-face visits in NSEIT included examination, an introduction to performing the exercises, progression of exercises and follow-up. A possible explanation is that four visits to the physiotherapist combined with the internet-based programme enabled these patients to feel confident and skilled enough to perform the exercises to the same extent as participants in the NSE group, who had many more visits to the physiotherapist.

In our study, participants in both groups described having increased knowledge regarding WAD, a stronger neck and fewer symptoms [46]. Moreover, no significant differences were seen between NSEIT and NSE for primary or secondary outcomes [9, 47].

The interpretation of the multivariate OPLS models was based on the weights (loadings) reflecting the relationship between dependent factors (NDI, neck pain, PSFS) and independent factors. Thus, independent factors with higher loadings were more closely related to improvements in NDI, neck pain, PSFS compared to outcomes with lower loadings in the same model (Fig. 4). Improvements in self-efficacy and symptom satisfaction were prominent in all three models (baseline to 3 months, baseline to 15 months and 3 months to 15 months). Neck-specific exercises have been shown to improve neck-related function [47] and, in combination with the patient education in our NSEIT/NSE programme, the exercises may lead to enhanced ability to perform everyday functional activities, as the improvements in NDI and PSFS indicate [9].

Comparison to prior work

Psychological factors such as low self-efficacy, fear avoidance beliefs, depressive symptoms and catastrophizing have earlier been shown to be predictors of poor outcome of neck disability in chronic WAD [10-13, 15], but they are also shown to be improved after 3 months of neck-specific exercise [48]. One of the most important factors to improve self-efficacy is personal mastery experiences: the ability to successfully perform a task [49]. When individuals in the NSEIT and NSE groups could perform activities with less pain, their self-efficacy and symptom satisfaction increased. A painful stimulus, such as neck pain, can trigger catastrophic thinking, fear-avoidance beliefs and avoidance behaviours, resulting in more pain and depression and leading to chronic disability as described by Vlaeyen and Linton in their fear-avoidance model [50]. Our neck-specific exercise programme included information on whiplash injury, outlining why pain can persist even after potential injuries to muscles and/or ligaments have healed, and highlighting the importance of exercising the neck muscles. The exercises should not exacerbate neck pain but should be progressed over time, leading to the activity level recommended by WHO, as described in detail previously [9].

Physical activities and exercises are highly effective for improving symptoms of depression [51]. This may explain the association between improvements in NDI and PSFS (physical function) and depressive symptoms in the present study. A speculative explanation is that the effect of our neck-specific exercise programme is related to mutually positive associations. Physical function and self-efficacy increased, pain, fear avoidance and depression decreased, as a result of the exercise programme. Anxiety and pain catastrophizing were included in the three models but had a lower influence on the dependent factors, neck pain and disability. Improvement in cognitive failures was also related to improvement in pain and disability in all three models. Previous studies have shown that cognitive failures and attention problems are common and disabling when living with pain [52], a finding that is not limited to subjective reports, as these patients also fail in standardized cognitive tests [53]. However, another study found the relationship between chronic pain and cognitive tests in whiplash inconclusive [54]. Coexisting brain injury due to the whiplash trauma may be another reason for cognitive failures independent of pain [53], although individuals with brain injury were excluded in the present study. Our results indicate that improvement in pain and disability after NSEIT or NSE were to some extent related to improvement in anxiety, pain catastrophizing and cognitive failures. A causal relationship cannot be established in the present study, but the findings may be of importance for improved rehabilitation in chronic WAD.

Background variables and baseline values of the independent factors in our study could not separate individuals with clinical improvement versus non-improvement in disability, neck pain and physical function. Moreover, no background variables were found to be associated with improvements in NDI, neck pain or PSFS. A possible reason is that we failed to include the most relevant factors in the analyses despite the inclusion of many variables in the OPLS and OPLS-DA models. However, we included background variables and independent factors that were previously reported in the

literature to be important in predicting and relating to disability and pain in WAD and chronic pain [10,11,13-16,19,55-57]. Nonetheless, there are conflicting results in earlier studies regarding the importance of some of the background variables and baseline values of the independent factors to pain intensity in chronic pain [55]. In chronic WAD, female gender, older age and WAD grade III were related to non-recovery in one study [56], while another study found that pain-related catastrophizing explained the variance in disability in patients with chronic WAD [11]. In contrast, we have previously found that no background variables were predictive of pain reduction in chronic WAD at one-year follow-up [19]. However, higher baseline NDI score, absence of dizziness and higher patient expectations, but not psychological factors, were associated with disability reduction [19]. We have also previously found that neck muscle endurance and perceived work ability were mediators for reduction in pain [20] in chronic WAD, and we identified a lack of improvement in ventral NME as a factor for ongoing dizziness in WAD after an exercise intervention [57]. The participants in the present study had higher neck muscle endurance at baseline [47] compared to earlier results [58] and they improved more at the 3-month follow-up [47,58]. Higher neck muscle endurance may reduce disability and pain, which in turn can influence other factors and may explain the discrepancy between the present results and other studies [11,17,56].

We have recently reported that between 47% and 74% of participants with chronic WAD grade II and III demonstrated sustained improvement in disability, pain and physical function after 3 months of NSEIT or NSE [9], but we failed to identify factors associated with responders and non-responders. Differences in analysis methods may explain the discrepancy between the present results and other studies [11,17,56]. An interesting result in the present study was that neither psychological factors such as low self-efficacy, depression and fear avoidance, nor background characteristics such as older age, low disability level or WAD grade III could predict non-responders. Further studies should include factors related to possible tissue damage or altered function in chronic WAD, but one problem is that there is still a lack of reliable and effective diagnostic tools.

The results indicate that we need to go further to be able to improve our understanding of chronic WAD and to optimize treatment. Biomedical and/or psychosocial factors not investigated in the present study are likely to be important for identifying non-responders to NSEIT and NSE in chronic WAD.



Strengths and limitations

This is the first study investigating factors related to pain and disability after an internet-based exercise programme for chronic WAD grade II and III patients, and, to our knowledge, factors related to the outcome of PSFS have not previously been reported for chronic WAD.

The strengths of multivariate OPLS analysis are the ability to include many variables and observations and the fact that several response variables (dependent factors) can be modelled together. OPLS can also cope with multicollinearity and missing values, which is a major advantage compared with traditional regression models. OPLS models use latent variables to model the data; these latent variables, which are linear combinations of the original variables, reduce the dimensions and minimize the issue of multicollinearity. Furthermore, OPLS separates the predictive variation (related to the response variable) from the orthogonal variation (unrelated to the response variable), thus focusing on the most relevant information, which simplifies the model and improves interpretability [59,60,61]. Moreover, the benefits of using multivariate statistics in this analysis are that variables can be scaled and centred on the mean, implying that each variable will have the same potential to affect the model, and that a patient or cluster of patients can be related to a variable profile rather than a single variable.

There are several limitations in the present study. Firstly, in the OPLS analyses, all three models (baseline to 3 months, baseline to 15 months, and 3 months to 15 months) showed relatively low explained variance, with the highest explanation level for the baseline to 15-month follow-up, $R^2 = 0.37$, $Q^2 = 0.30$. The goodness of fit of a model varies depending on the type of data and the specific application. For example, spectroscopic calibration models require values close to 1.0. However, while high R^2 and Q^2 values are desirable, they must be interpreted in the context of the specific application and data type [62]. Lower values indicate a less robust fit and predictive ability but might be acceptable, for example, in OPLS models that include self-reported psychological symptoms. Secondly, the present study results are only generalizable to those individuals who fulfil the study criteria and are motivated to participate in exercise, but not to all individuals with WAD. Moreover, long-term effects can be influenced by various factors. For example, consistently measuring outcomes over time can introduce bias and affect the reliability of the results due to changes in the patient's life situation. Additionally, dropouts commonly increase over time. Thirdly, only individuals who understood the Swedish language were included, and the age range was limited to 18–63 years. Thus, the study excluding minorities from a different background who did not understand Swedish and the results cannot be generalised to those aged under 18 or over 63 years.

Conclusions

After three months of NSEIT or NSE, improvements in neck pain and disability were related to improvements in 23 other physical and psychological factors. However, the findings should be interpreted with caution, as the results showed relatively low explained variance. No recommendations can be given for which individuals will benefit from NSEIT or NSE, due to the study's inability to distinguish between clinically improved and non-improved participants regarding neck pain and disability. Further research is warranted to improve our understanding of those who

are improved or not improved after three months of NSE or NSEIT.

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Author Contributions

G.P. and A.P. designed, formulated and created the study; G.P., AP. and S.L. analyzed and interpreted the data; G.P., A.P. and S.L. wrote the manuscript; G.P., A.P. and S.L. reviewed and approved the final manuscript, **G.P., A.P. responsible for presentation of the published work.**

Project administration

G.P and AP, were responsible for management and coordination for the research study.

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Data availability

The data sets generated during this study are available from the corresponding author on reasonable request and after ethical approval.

Declaration of interests

The authors declare no conflict of interest associated with any financial organization regarding the material discussed in this study.

Abbreviations

CCFT: Cranio-Cervical Flexion Test

CFQ: Cognitive Failures Questionnaire

EQ-5D-3L: EuroQoL quality-of-life instrument version with 5 dimensions and 3 response levels

EQ-VAS; EuroQoL health-related quality of life measure using a visual analogue scale

CROM: cervical range of motion

FABQ: Fear Avoidance Beliefs Questionnaire

HAD: Hospital Anxiety and Depression Scale

NDI: Neck Disability Index

NME: neck muscle endurance

NSE: neck-specific exercise programme supervised by a physiotherapist

NSEIT: neck-specific exercise programme via internet

PSFS: Patient-Specific Functional Scale

PTSD: post-traumatic stress disorder

PCS: Pain Catastrophizing Scale

SES: Self-Efficacy Scale

SOLEC: standing on one leg with eyes closed (balance test)

VAS: visual analogue scale

WAD: whiplash-associated disorders

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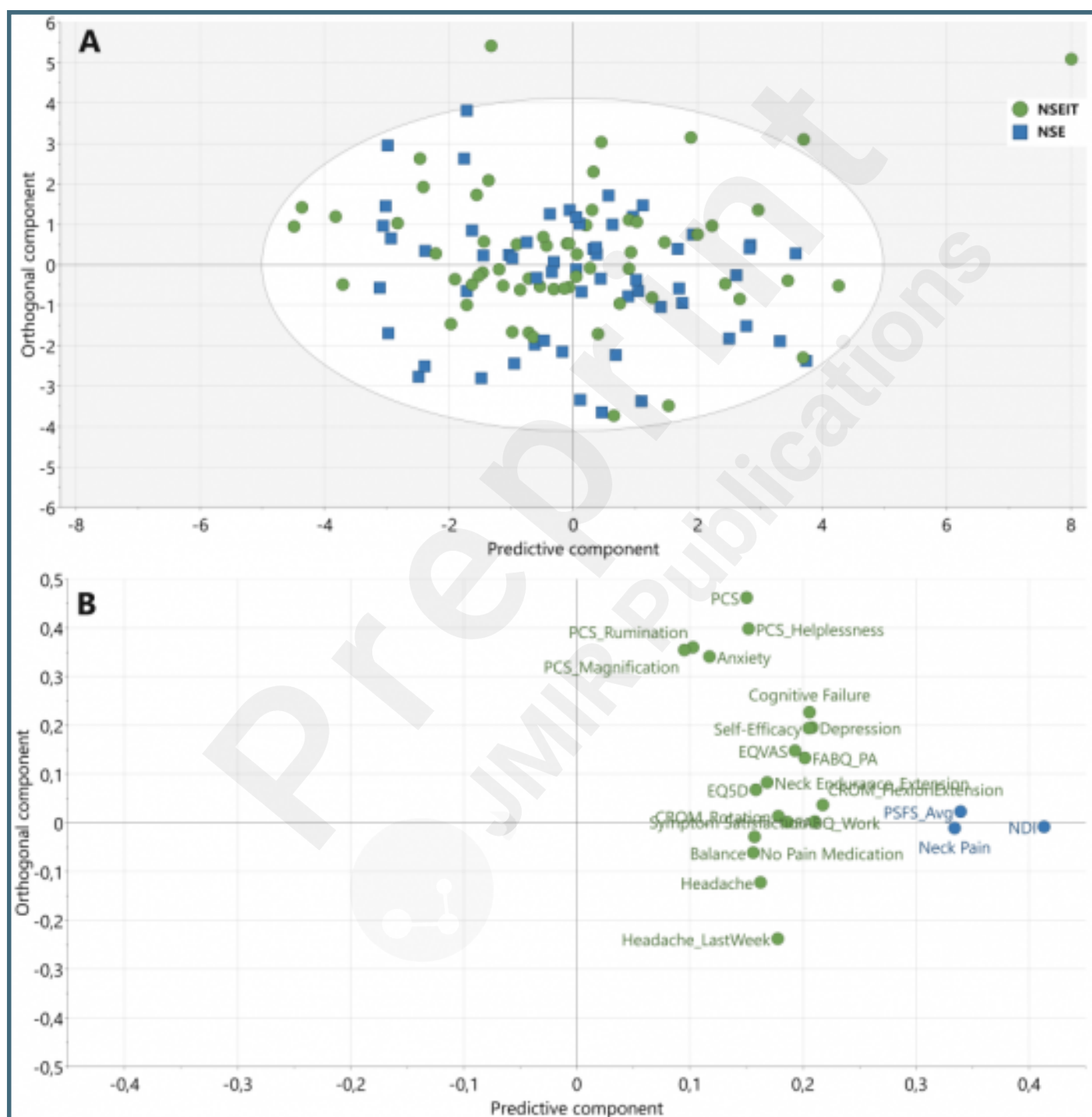
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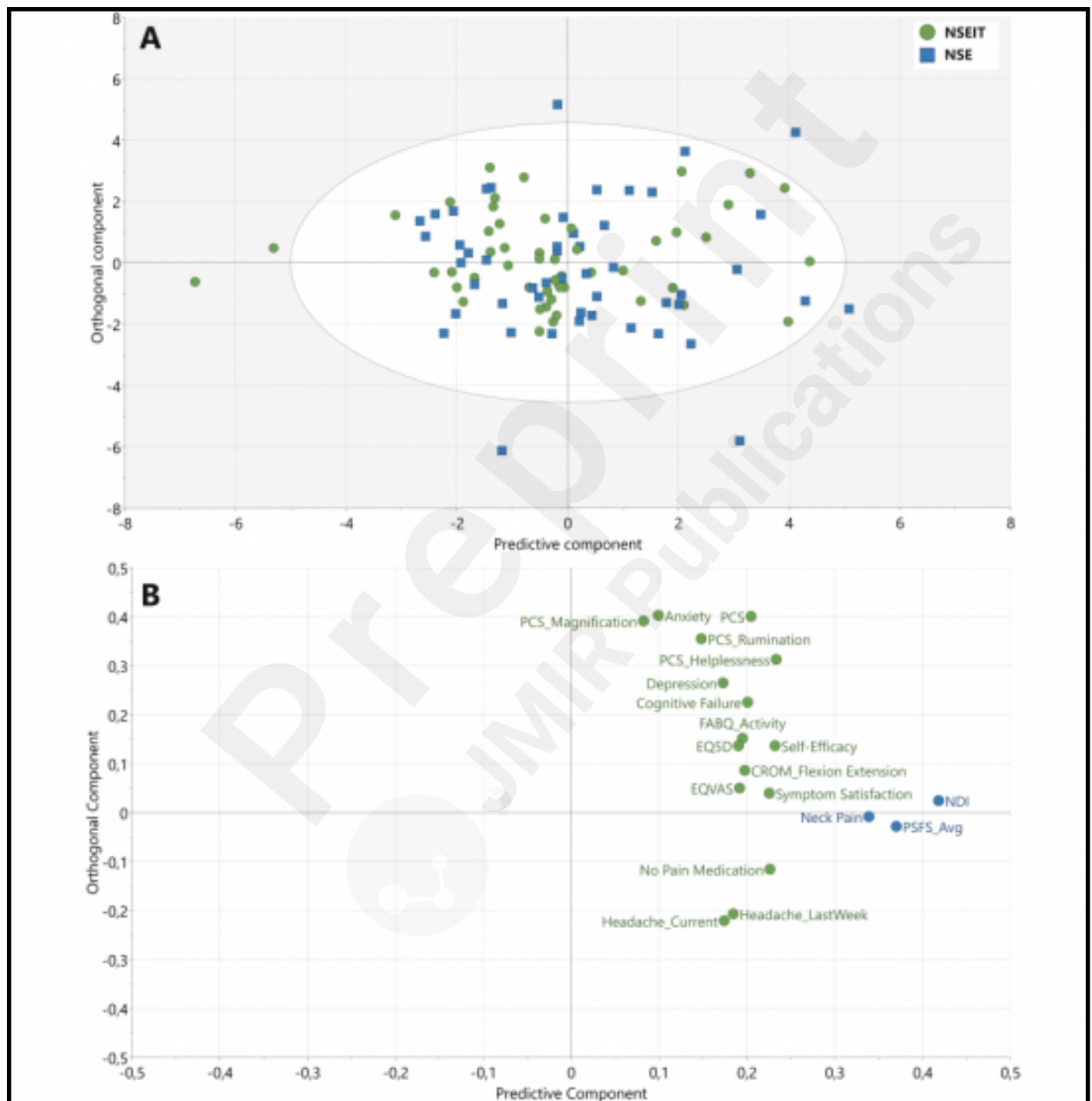
Supplementary Files

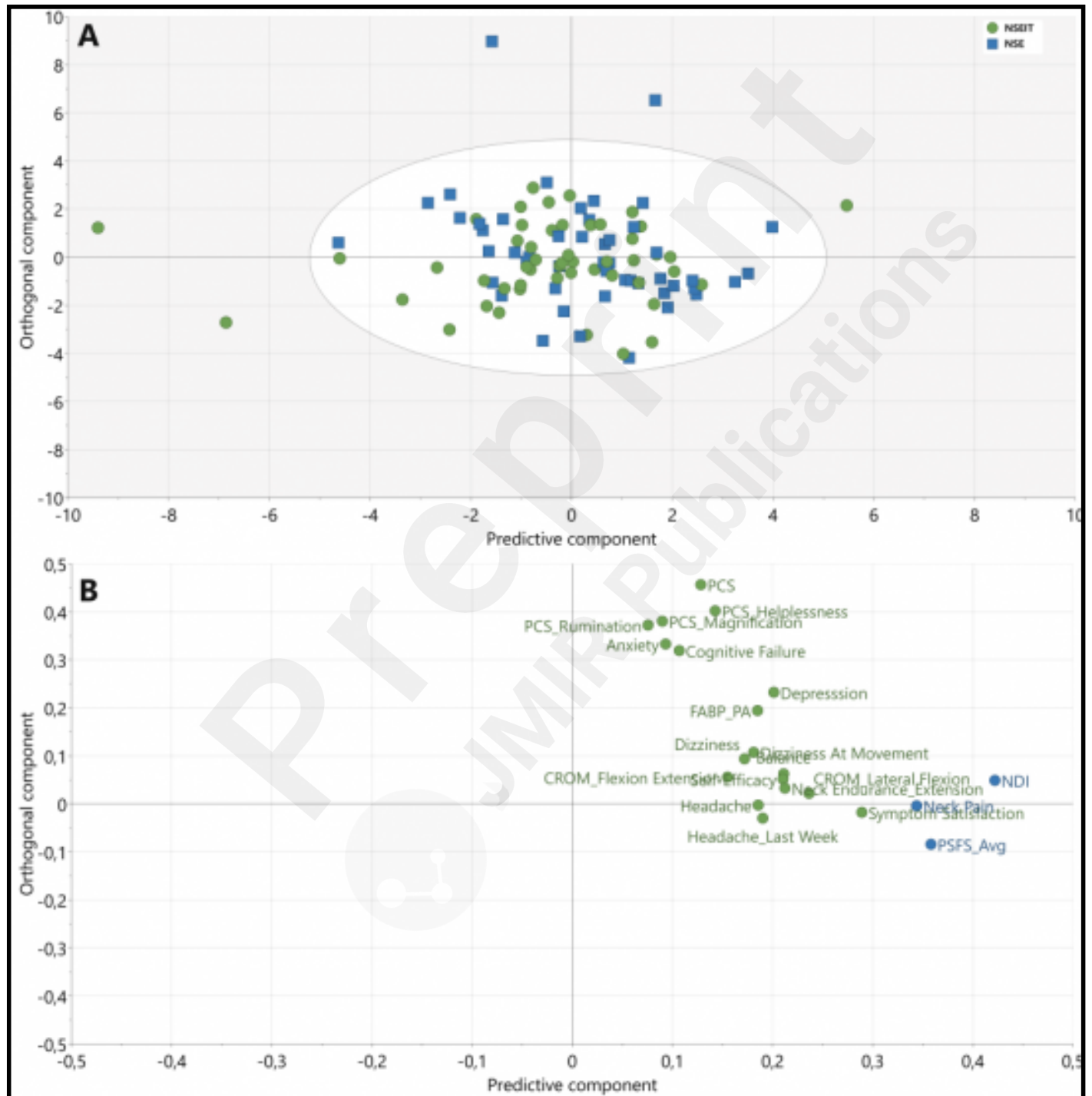
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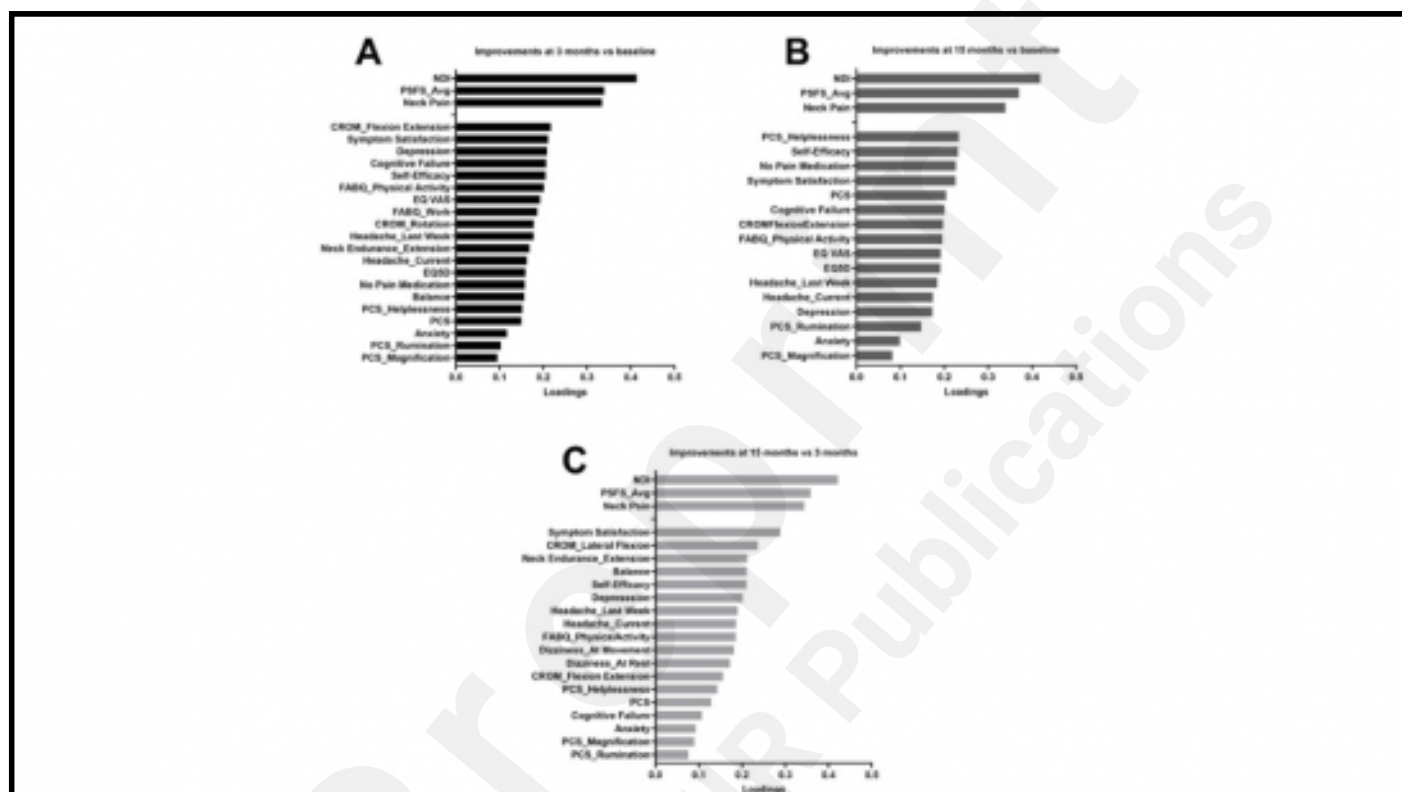
Figures







Loadings (contribution of each independent factors) obtained through OPLS after selecting outcome measures with variable influence on projection (VIP) greater than 1.0. The three models (A-C) showing association between independent factors for improvements in NDI, neck pain and PSFS at different time points. A: Improvements between baseline and 3-month follow-up. B: Improvements between baseline and 15-month follow-up. C: Improvements between 3-month and 15-month follow-up. A higher value for the loadings indicates it is more important in the models. NDI, Neck Disability Index; PSFS_Avg, Patient-Specific Functional Scale (the average of the three PSFS components Physical activity, Leisure time and Work); CROM, cervical range of motion; FABQ, Fear Avoidance Beliefs Questionnaire; EQ5D, EuroQoL health-related quality of life scale; EQVAS, EuroQoL visual analogue scale; PCS, Pain Catastrophizing Scale.



Multimedia Appendixes

Flow chart.

URL: <http://asset.jmir.pub/assets/78fc745ac20fb03c4d62bedba0fc0f03.pdf>

OPLS models.

URL: <http://asset.jmir.pub/assets/f0c5d4c2eb354cd4305323da3024549c.pdf>



CONSORT (or other) checklists

CONSORT 2010 checklist.

URL: <http://asset.jmir.pub/assets/638ff2bd76c8d63c5ca5b756d83198a7.pdf>

TIDier checklist.

URL: <http://asset.jmir.pub/assets/3aba63ea347dc0ddae94efaf85b7330c.pdf>