Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

# Acceptance and Fear-Avoidance Mediate Outcomes of Interdisciplinary Pain Rehabilitation Programs at 12-Month Follow-Up: A Clinical Registry-Based Longitudinal Cohort Study from the Swedish Quality Registry for Pain Rehabilitation (SQRP)

Björn Gerdle[1], Elena Dragioti[1], Marcelo Rivano Fischer[2,3], Åsa Ringqvist[2]

[1]Pain and Rehabilitation Centre, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; [2]Department of Neurosurgery and Pain Rehabilitation, Skåne University Hospital, Lund, Sweden; [3]Department of Health Sciences, Faculty of Medicine, Lund University, Lund, Sweden

Correspondence: Björn Gerdle, Email bjorn.gerdle@liu.se



**Background:** Factors that influence outcomes of interdisciplinary pain rehabilitation programs (IPRP) are poorly known. It is unclear how outcomes are influenced by pain intensity, psychological distress, and coping strategies.

**Aim:** This clinical registry-based longitudinal cohort study has three aims: 1) to determine the relative importance of pain intensity, psychological distress, acceptance, and fear-avoidance for changes in three outcomes of IPRP at 12-month follow-up; 2) to investigate whether the effects of pain intensity and psychological distress on the three outcomes are mediated via acceptance and fear-avoidance; and 3) to determine whether sex is a moderator.

**Methods:** This study uses Patient-Reported Outcome Measures (PROMs) from specialist units reporting data (2008–2016) to the Swedish Quality Registry for Pain Rehabilitation (SQRP). Adult chronic pain patients (N = 1991) answered the PROMs (background, pain, psychological distress, coping, participation, and health-related quality of life (HRQoL)). Partial Least Squares Structural Equation Modelling (PLS-SEM) was used to explore the aims.

**Results:** Changes in acceptance (β:0.424–0.553; all P<0.001) were the strongest predictor of the three outcomes (changes in life control, interference, and HRQoL) at 12-month follow-up. The next strongest predictor was baseline acceptance (β: 0.177–0.233; all P<0.001) and changes in fear-avoidance (β: −0.152– −0.186; all P<0.001). Baseline pain intensity and psychological distress showed weak positive associations. Their effects on the three outcomes were mediated via acceptance aspects. Sex was not a moderator.

**Discussion and Conclusion:** Acceptance aspects (baseline and changes) were important predictors of IPRP outcomes. Changes in fear-avoidance were also important although to a lesser degree. Some of the effects of pain intensity and psychological distress on outcomes were mediated via acceptance at baseline. Future PLS-SEM analysis of real-world IPRP should include more potential mediators (eg, catastrophizing and more facets of psychological flexibility and fear-avoidance) and the components of IPRP.

**Keywords:** anxiety, chronic pain, coping strategies, depression, health, pain management

## Introduction

Interdisciplinary pain rehabilitation program (IPRP; also labelled as multimodal rehabilitation, multidisciplinary rehabilitation, biopsychosocial pain rehabilitation, pain management program) is an interdisciplinary treatment (with physical, occupational, psychological, social, and educational components) according to the International Association for the Study of Pain (IASP). This complex intervention is provided by a multidisciplinary team collaborating in assessment and treatment using a shared biopsychosocial approach and goals. Apart from a biopsychosocial view[1] and concepts such as patient-centeredness and strengthening of empowerment, there is no overarching theory that describes the mechanisms of

Received: 26 September 2023
Accepted: 19 December 2023
Published: 5 January 2024

changes during IPRP. Instead, IPRP is based on several different components, each of which is associated with one or more theories for positive change. The components are expected to have synergistic positive effects on IPRP outcomes. Thus, IPRP is currently to be perceived as an eclectic and pragmatically developed complex intervention.

Swedish guidelines, which have been approved by several authorities and professional organizations, recommend that IPRP is offered to chronic pain patients with complex clinical presentations including insufficient coping strategies and when monodisciplinary interventions have not been effective.[2] Systematic reviews report significant efficacy for IPRP outcomes,[2] and real-world evidence supports the conclusion that IPRP is an effective intervention.[3–7] IPRP is generally described as an intervention based on Cognitive behavioural therapy (CBT), including Acceptance and commitment therapy (ACT).[8–11] Also, monotherapy with CBT and ACT for chronic pain are associated with significant treatment effects for important clinical variables.[12–18] Some authors conclude that IPRP can be sorted under the same general rubric of CBT for chronic pain.[19] This classification can be questioned since other major components of IPRP (physical activity/exercise and pain education)[2] are also associated with significant treatment effects.[20–24] For improving the small to medium effect sizes of IPRP we need to understand which variables predict (eg, baseline situation) outcomes where conflicting or unclear results are reported.[25–28] Several studies including systematic reviews of CBT/ACT have examined mediating factors (eg, pain-related fear, catastrophizing, pain acceptance and psychological flexibility) for changes in various important treatment outcomes.[13,29] In contrast, such studies are rare for IPRP and relatively small.[19,30] Several of the important processes of CBT/ACT for changes in outcomes may also be relevant for IPRP. That is, for IPRP it is unclear how treatment outcomes are influenced by pain intensity, psychological distress, and coping strategies eg, pain acceptance and fear-avoidance. This study addresses this knowledge gap by employing advanced path analysis to explore how variables such as pain intensity, psychological distress, and coping strategies, including pain acceptance and fear-avoidance, influence IPRP outcomes at a 12-month follow-up. This research aims to contribute valuable insights to optimize the effectiveness of IPRP in managing chronic pain.

## Our Path Model – Overall Hypothesis

When performing advanced path analysis, it is important to do this based on a model ie, an overall hypothesis (Figure 1). Two well-known initiatives to bring consensus into the areas of evaluating clinical trials including IPRP are The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[31,32] and the Validation and Application of a patient-relevant core set of outcome domains to assess multimodal PAIN therapy (VAPAIN) initiatives.[33] These

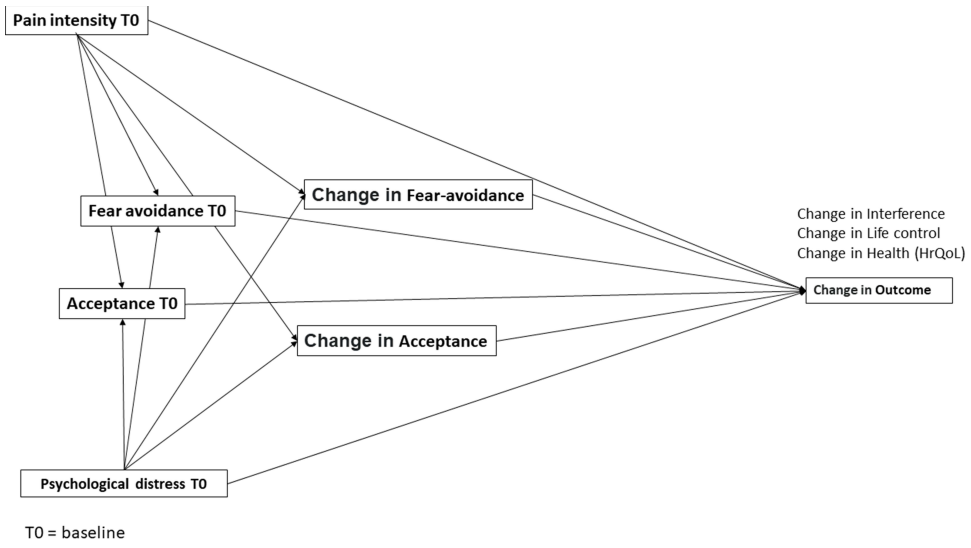


**Figure 1** The path model (overall hypothesis). Latent variables (constructs) are shown together with the paths including directions according to our overall hypothesis (see Introduction). First, the importance (direct paths) of baseline latent variables together and changes in Acceptance and Fear avoidance (mediators) for changes in outcomes are investigated. Second, mediating paths to changes in three different outcomes are explored ie, four parallel from Pain Intensity and four parallel from Psychological distress via 1) Fear avoidance T0, 2) Acceptance T0, 3) Change in Fear avoidance, and 4) Change in Acceptance.

initiatives emphasize the need to use several outcomes when evaluating eg, IPRP. Important outcomes for many patients – and in agreement with the two initiatives - are the ability to live socially and physically active and meaningful lives in the presence of pain and restore health-related quality of life (HRQoL). Hence, as outcomes of IPRP in the present study, we focus on three changes: 1) Change in life control – ie, the ability to live socially meaningful lives; 2) Change in interference – ie, the ability to live physically active and meaningful lives; and 3) Change in health-related quality of life (HRQoL) – ie, the ability to improve perceived physical and emotional health.

Important aspects of clinical severity are pain intensity and psychological distress,[5,34] which we assume would significantly affect the three selected outcomes of IPRP. It may appear reasonable that patients with a severe clinical picture at assessment show less improvements after IPRP and some studies support such an assumption.[26,28,35,36] However, as recently reported from different studies of IPRP including a large pain registry study, the most prominent changes occur in patients with the most severe clinical presentation.[4,5,34,37] Moreover, a recent systematic review concluded that higher pain intensity and longer pain duration were associated with larger effect sizes for several IPRP outcomes.[38] As this study examines real-world data and as previous real-world studies have shown that a more severe clinical picture is associated with better results, we hypothesize that the baseline values of pain intensity and psychological distress would show positive associations with the three outcomes (Figure 1).

As described above, IPRP consists of several components. The psychological component of IPRP mainly consists of CBT including ACT. CBT interventions target maladaptive pain-related cognitions and behaviors through reconceptualizing catastrophizing belief, addressing avoidance, training coping skills and promoting graded return to activity.[13,29,39] CBT has been extended with the fear-avoidance model;[40,41] treatment methods such as challenging negative expectations that lead to avoidance behaviors and exposure to feared movements/activities have been incorporated to reduce pain-related disability.[29] A negative cycle of fear, avoidance and increased sensitivity to pain are important components of the fear-avoidance model, which is one of the most influential behavioral pain models. When pain is perceived as threatening and the subject catastrophize pain-related fear can evolve.[42] Catastrophic cognitions may lead to avoidance and hypervigilance for bodily sensations including pain.[42–45] This in turn can lead to heightened pain sensitivity, psychological distress, disuse, and disability.[42] Hence, Fear-avoidance is avoidance of physical and social activities of daily living due to fear of increased pain and/or fear of injury or reinjury.[34,43–46] Hence, actions such as avoiding painful activities or seeking medical interventions are perceived as the relevant actions. Fear-avoidance is associated with increased risk for development of chronic pain, higher pain intensity, increased psychological distress, disability facets, and poor treatment outcomes.[1,45,47–56]

ACT is a development in CBT[13] and it focuses on improving psychological flexibility as a process of change to produce outcomes.[57] The ACT theory is based upon the psychological flexibility model which has six intercorrelated facets including an acceptance facet.[13,58] ACT emphasizes awareness and non-judgmental acceptance of pain while identifying valued life directions and teaching skills to support values-based goal setting.[29] Acceptance is essentially an act of allowing according to McCracken.[58] Hence, ACT aims at increasing psychological flexibility in the presence of pain to improve the physical function of the patient.[59–62] Pain acceptance has been defined as living with pain without reacting to, judging or attempting to reduce or avoid it.[63–66] It is an active willingness to engage in meaningful activities despite living with pain.[67] Low acceptance is characterized by a non-constructive inner struggle with the pain experience, including attempts to avoid pain. Higher pain intensity, depressive symptoms, suffering, lower functioning, insufficient coping with chronic pain and poor treatment outcomes are found in patients reporting low pain acceptance.[66,68–73]

Hence, we anticipated that the baseline values of acceptance (positively) and fear avoidance (negatively) directly influenced the IPRP outcomes (Figure 1).

One of IPRP's - as well as CBT/ACT's - aims is to improve how patients manage and cope with their overall situation. Therefore, it is reasonable to also investigate whether changes in acceptance and fear-avoidance during and immediately after IPRP lead to improvements in outcomes. There are several indications that changes in acceptance and fear-avoidance act as treatment mediators in pain interventions.[13,19,29] A recent systematic review concluded that reductions in pain-related fear (as well as reduction in catastrophizing and increases in self-efficacy) mediated effects of CBT on disability;[29] similar results have been reported in other studies.[74] Moreover, increased acceptance and psychological flexibility mediated effects of ACT on disability and/or functioning.[29,75] Hence, we hypothesize that changes in acceptance and in fear-avoidance are significant mediators of changes in the three outcomes (Figure 1).

In addition to the suggested direct positive effects of pain intensity and psychological distress on IPRP outcomes, we assume there are indirect (mediating) effects via acceptance and fear-avoidance aspects (Figure 1).

In Sweden, women are overrepresented in specialist clinics compared to the community prevalence.[5,76] There are some reports indicating that women report a more severe clinical presentation[77] while other studies have not described an overall more severe clinical presentation in women.[78] A recent systematic review concluded that no sex/gender differences were found for four outcome variables of IPRP.[79] However, the literature is not in total consensus and several studies report sex/gender differences in IPRP outcomes[77,78,80–82]. Partially different mediators in men and women for the relationships between psychological and demographic variables with chronic pain and physical function have been reported.[83] Hence, sex/gender may be a treatment moderator.

## Aims

This clinical registry-based longitudinal cohort study, which uses advanced path analysis, has three main aims:

1. To determine the relative importance of baseline pain intensity, psychological distress, acceptance, and fear-avoidance aspects as well as changes in acceptance, and fear-avoidance during IPRP for changes in outcomes (changes in life control, interference, and HRQoL) at the 12-month IPRP follow-up.
2. To investigate if some of the effects of pain intensity and psychological distress on the three outcome variables are mediated via acceptance and fear-avoidance aspects; and
3. To determine whether sex is a treatment moderator.

Achieving these aims will be potentially important from several aspects. This study endeavours to provide a comprehensive understanding of the factors influencing the effectiveness of IPRPs, exploring the roles of pain intensity, psychological distress, acceptance, and fear-avoidance. Through mediation analyses, the study aims to uncover the psychological pathways through which pain and distress impact IPRP outcomes. Additionally, by considering sex as a potential treatment moderator, the research aims to contribute insights that may inform more personalized and effective approaches to interdisciplinary pain rehabilitation.

## Subjects and Methods

### Subjects and the Swedish Quality Registry for Pain Rehabilitation (SQRP)

The Swedish Quality Registry for Pain Rehabilitation (SQRP) registers Patient-Reported Outcome Measures data (PROMs) from a majority of the Swedish specialist chronic pain departments[84] (for a detailed description of SQRP, see[2]). Adult patients (ie, ≥18 years) with chronic pain registered in the SQRP between 2008 and 2016 were eligible. Patient data in the SQRP include patients with complex pain conditions for instance with respect to comorbidities, not adequate or ineffective coping strategies, prolonged sick leave, and/or unresponsiveness to unimodal interventions. However, no strict inclusion criteria exist. General exclusion criteria in this clinical registry are drug or alcohol abuse, severe psychiatric disease, cancer, medical conditions that do not allow physical exercise, and red flag pain conditions (ie, other treatments are available).

The SQRP includes the Tampa Scale for Kinesiophobia (TSK) and the Chronic Pain Acceptance Questionnaire (CPAQ), but these instruments are not mandatory for the participating specialist clinical departments. Each clinical department determines whether non-mandatory variables are to be included. In the present study, the hypothesis requires that these two instruments be used, so we identified patients who had answered these instruments both at baseline and at the 12-month IPRP follow-up. Thus, the investigated cohort included 1991 patients; a flow chart is given in Supplementary Figure 1. The proportion of missing data was low for all variables included ie, <0.7%.

### Brief Description of Interdisciplinary Pain Rehabilitation Programs (IPRPs)

Patients in the investigated cohort participated in Interdisciplinary Pain Rehabilitation Programs (IPRPs) for chronic pain patients. IPRP is an interdisciplinary treatment according to the International Association for the Study of Pain (IASP). For

detailed descriptions of IPRP, see.[2,85] As mentioned above these programs are often described as based on CBT models including ACT and are administered over several weeks or months.[8–11] The Swedish programs generally include group activities such as supervised physical activity, pain education, training in simulated environments, and CBT/ACT coordinated by an interdisciplinary team based on a biopsychosocial model of chronic pain.[8–11] Since IPRP is a complex intervention, the goals of IPRP are broad and multifactorial and include the patient's goals.[33] Hence, IPRP is evaluated using many outcomes.[9,86,87] Systematic reviews and large real-world registry studies generally report higher efficacy both on a general level and for specific outcomes of IPRP compared with single-treatment or treatment-as-usual interventions.[2–5]

## Patient-Reported Outcome Measures (PROMs)

The PROMs of SQRP include background, pain facets, psychological aspects, pain-cognitions, activity/participation, and HRQoL variables. PROMs are completed by patients on up to three occasions: before the first visit (baseline assessment), immediately after treatment for those who participated in interdisciplinary pain rehabilitation programs (IPRP), and at a 12-month follow-up (12m fu). The present study uses baseline data and 12-month follow-up data. The PROMs included in SQRP have been described in detail, including psychometry, elsewhere;[4,78,88,89] only brief descriptions for the variables are given here.

## Background Variables

The following variables were used to characterize the cohort: age (years); sex; education level (university education vs without university education); country of birth (born in vs outside of Europe); pain duration (days); and spatial extent of pain (Pain Region Index (PRI) – ie, number of painful areas from a list of 36 predefined anatomical regions).

## Brief Descriptions of the Variables Included in the Path Analyses

Several indicators are generally used to define a latent variable (construct), which is an advantage from a measurement error point of view. Table 1 lists the latent variables (constructs) and their potential and final indicators together with the moderator included in the path analyses. The hypothesized relationships between the latent variables are shown in Figure 1. Throughout the text, we capitalize the initial letter of latent variables eg, Pain intensity and Fear-avoidance.

Pain intensity aspects at baseline: Pain intensity at baseline (T0) was measured using three scales or subscales: the mean pain intensity over the past week (NRS-7 days) scale, which uses a numerical rating (0 = no pain to 10 = worst possible pain); the Multidimensional Pain Inventory-Pain (MPI-Pain) subscale, which is based on questions about present

**Table 1** Summary of Latent Variables (Constructs) and Potential and Final Indicators and Moderators Included in the PLS-SEM Analyses

| *Latent Variable* | *Indicators* |
|---|---|
| **Pain intensity T0** | NRS-7d T0<br>MPI-Pain severity T0<br>SF36-bodily pain-rev T0 |
| **Psychological distress T0** | HAD-tot T0<br>MPI-Distress T0<br>SF36-mental health-rev T0<br>SF36-role emotional-rev T0 |
| **Fear avoidance T0** | TSK T0 |
| **Change in Fear-avoidance** | Difference (pre-post) in TSK<br>Difference (pre – 12m fu) in TSK |
| **Acceptance T0** | CPAQ8-AE T0<br>CPAQ-PW T0 |

(*Continued*)

**Table 1** (Continued).

| | |
|---|---|
| **Change in Acceptance** | Differences in (pre – post):<br>CPAQ8-AE and CPAQ8-PW*<br>Differences in (pre – 12m fu):<br>CPAQ8-AE and CPAQ8-PW*<br>Or<br>Differences in (pre – post):<br>CPAQ8-tot<br>Differences in (pre – 12m fu):<br>CPAQ8-tot |
| ***Outcomes*** | ***Indicators*** |
| **Change in Life control** | Differences (12m fu -pre) in:<br>MPI-Control<br>SF36-social function |
| **Change in Interference** | Differences in:<br>MPI-Pain interference (pre – 12m fu),<br>SF36-physical function (12m fu -pre),<br>SF36-role physical (12m fu -pre)* |
| **Change in HRQoL** | Differences (12m fu -pre) in:<br>EQ5D-index<br>EQ-VAS<br>Sf-36-general health |
| ***Moderator*** | ***Indicator*** |
| **Sex** | Sex |

**Note**: *Not included in the final analyses.
**Abbreviations**: T0, baseline; -rev, variable revised to indicate a troublesome situation; fu, follow-up; NRS-7d, Pain intensity according to a numeric rating scale; HAD, The Hospital Anxiety and Depression Scale; HAD-tot, sum of the two subscales of HAD; MPI=Multidimensional Pain Inventory; HRQoL, health-related quality of life; EQ-5Dindex, European Quality of Life instrument – index; EQ-VAS, health scale of European Quality of Life instrument; SF36, The Short Form Health Survey; TSK, The Tampa Scale for Kinesiophobia; CPAQ8, Chronic Pain Acceptance Questionnaire- 8 items version; CPAQ8-AE, Activity Engagement Scale of CPAQ8; CPAQ8-PW, Pain Willingness Scale of CPAQ8.

pain, pain during last week; and suffering due to pain; and the Short-Form Health Survey-bodily pain (SF36-bodily pain) subscale, which measures bodily pain.

Psychological distress aspects at T0: Two subscales of the Hospital Anxiety and Depression Scale (HAD), HAD-tot, capture signs of depression and anxiety and are summed.[90–92] MPI-Affective distress, an MPI subscale, is based on items concerning mood, irritation, and anxiety. SF36-mental health is a subscale that captures anxiety, depression, loss of behavioural/emotional control, and psychological well-being. SF36-role emotional is a subscale that covers role limitations due to emotional problems.

Fear-avoidance aspects at T0 and change during IPRP: The Tampa Scale for Kinesiophobia (TSK; score range: 17–68) measures fear-avoidance (ie, fear of movement/(re)injury).[46,51,52,93] In the models, both baseline value (T0) and the change in TSK (ie, differences pre-post IPRP and pre-12m fu) are included.

Pain acceptance aspects at T0 and change during IPRP: To indicate pain acceptance aspects at baseline, we used an 8-item version of the Chronic Pain Acceptance Questionnaire (CPAQ 8).[94] CPAQ 8 consists of two subscales: the Activity Engagement Scale (CPAQ8-AE) and the Pain Willingness Scale (CPAQ8-PW). CPAQ8-AE captures behavioural components, including the pursuit of life activities despite pain, and the CPAQ8-PW captures attitudinal components of acceptance, including the recognition of the uncontrollability of pain.[68] Sometimes the total score of

CPAQ8 is used as a single measure (CPAQ8-tot). In the model, we also include the change of CPAQ8 as mediators – ie, differences (pre-post IPRP and pre-12m fu) – for CPAQ8-AE and CPAQ8-PW or CPAQ8-tot.

### The Three Outcome Latent Variables and Their Potential Indicators

Change in Interference: Differences in MPI-Pain interference (pre-12m fu), SF36-physical function (pre-12m fu), and SF36-role physical (pre-12m fu) are included as potential indicators. The MPI-Pain Interference subscale covers disturbances due to pain in daily activities, work capacity, leisure activities, general reductions in activities, and the ability to socialize and have relations with family and friends. The SF36-physical function subscale measures physical limitation/ability in a range of activities from self-care to exercise. The SF36-role physical measures role limitations related to physical functioning, including work and daily activities.

Change in Life control: Differences (pre-12m fu) in MPI-Control and in SF36-social function are considered potential indicators. The MPI-Control subscale concerns the ability to manage daily life problems, pain, and stressful situations. The SF36-social function subscale covers the impact of physical and mental health on social functioning.

Change in Health-related quality of life aspects (HRQoL): Differences (pre-12m fu) in EQ5D-index, EQ-VAS, and SF36-general health are included as potential indicators. The European Quality of Life instrument (EQ-5D) measures generic HRQoL.[95–97] The first part of the instrument presents an index based on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (three alternatives for each dimension). The EQ-5D is based on representative data from the general population. The second part of the EQ-5D measures present health on a vertical thermometer-like 100-point scale (EQ-VAS) with defined end points (high values indicate good health and low values indicate poor health). The SF36-general health subscale concerns self-related health.

### Moderator

Sex was chosen as moderator in the present study.

## Strategy of Analyses and Presentation of Results

The analyses are presented as follows:

1) The predictors of the three outcome latent variables. The direct effects of Pain intensity T0, Psychological distress T0, the two Acceptance latent variables and the two Fear-avoidance latent variables on the three outcomes (Changes in Interference, Life control, and HRQoL). Change in Acceptance and Change in Fear-avoidance indicate changes during IPRP and are thus mediators in this context.
2) When analysing whether some of the effects of Pain intensity and Psychological distress on the three outcome variables are mediated via Acceptance and Fear-avoidance aspects, we used parallel mediation analyses. Thus, we investigate the importance of the following eight mediating paths:
   - Pain Intensity T0 → Acceptance T0 → Change in Outcome
   - Psychological distress T0 → Acceptance T0 → Change in Outcome
   - Pain Intensity T0 → Change in Fear-avoidance → Change in Outcome
   - Psychological distress T0 → Change in Fear-avoidance → Change in Outcome
   - Pain Intensity T0 → Fear-avoidance T0 → Change in Outcome
   - Psychological distress T0 → Fear-avoidance T0 → Change in Outcome
   - Pain Intensity T0 → Change in Acceptance → Change in Outcome
   - Psychological distress T0 → Change in Acceptance → Change in Outcome
3) The moderator effect of sex on the explored paths in the three models (Changes in Interference, Life control, and HRQoL).

## Statistics

We used IBM SPSS Statistics (version 28.0; IBM Corporation, Route 100 Somers, New York, USA), SIMCA-P+ (version 17.0; Sartorius Stedim Biotech, Umeå, Sweden) and Smart-PLS version 4 (Ringle, Christian M., Wende, Sven,

and Becker, Jan-Michael. (2022). SmartPLS 4. Boenningstedt: SmartPLS. Retrieved from https://www.smartpls.com). We report mean value ± one standard deviation (± 1 SD) of continuous variables and percentages (%) for categorical variables. The retrieved SQRP data included missing data (Table 1). The few data that were missing data were replaced with mean for variables with missing data. Treatment effects for the outcome variables/indicators were tested using Related-Samples Wilcoxon Signed Rank Test and effect sizes (Cohen's d). The absolute effect size was considered clinically insignificant if <0.20, small if 0.20–0.49, moderate if 0.50–0.79, and large if ≥0.80.[98]

Orthogonal Partial Least Square Regressions (OPLS) in SIMCA-P+ was used for the multivariate regression analyses of the indicators of the three latent outcome variables (for detailed descriptions see[99]); this was done to check for the possible influence of sex/gender, age, education level (University education or not) and region of birth (in or outside Europe). The Variable Influence on Projection predictive (VIPpred) indicates the relevance of each X–variable pooled over all dimensions and Y-variables – ie, the group of variables that best explains Y. P(corr) was used to note the direction of the relationship (positive or negative) – ie, the loading of each variable was scaled as a correlation coefficient and therefore standardized the range from −1 to +1. Variables with VIPpred > 1.0 and $|p(corr)|$ >0.40 were considered significant.

We used SMART-PLS version 4 for the non-parametric Partial Least Squares Structural Equation Modelling (PLS-SEM). This method analyses complex relationships among several (dependent and independent) variables based on a hypothesis; for details about this method, see.[100] We followed Hair et al's recommendations for PLS-SEM analyses and presentation of results.[100] However, note that this type of analysis necessarily produces many results. In the article, only the most important coefficients (ie, direct and indirect path coefficients) are presented. For reasons of research transparency, other results associated with the analyses are found in the supplementary material. To facilitate the understanding of the results from the PLS-SEM analyses the first sentence/s of each result section summarize the results followed by more in-depth results.

Evaluation of the outer model: Several indicators are generally used to define a latent variable (construct) (Table 1), which is an advantage from a measurement error point of view. The outer model shows the relationships (loadings) between indicators and their latent variable; a reflective relationship was assumed for all relationships of latent variable versus indicators (not relevant for single indicator constructs). The indicators of a certain component cannot be negatively intercorrelated and some variables/indicators are therefore reversed. Good indicator reliability, internal consistency reliability, convergent validity, and discriminant validity for the outer model are some of the prerequisites for performing the path analyses (ie, interpreting the inner model; see below).

More in detail, we evaluated the outer model to check that the individual variables (indicators) are good fit for our latent variables. The first check is that all variables (indicators) should load on the latent variables with absolute loadings >0.708 (range: −1 to 1). Variables with absolute loadings ≤0.40 are excluded. Indicators with absolute loading between 0.40 and 0.708 are excluded if internal consistency or convergent validity increased. Reliability was checked in several ways. For internal consistency reliability, we used the composite reliability coefficient ($rho_c$; range: 0–1); >0.50). To indicate convergent validity, the Average Variance Extracted (AVE; range: 0–1; >0.50 required) was applied. Discriminant validity was measured using the Heterotrait-monotrait ratio (HTMT) (values <0.90, preferably <0.85, are required).

Evaluation of the inner model: The inner model displays the associations (paths) between the latent variables and is the focus of the present study. Collinearity is a consistent risk in multivariate modelling and risk giving false-positive results. We checked this using variance inflation factor (VIF); <5 was acceptable.[100] Path coefficients (ie, standardized regression coefficients β displaying direct effects) were determined. Using bootstrapping mean ± SD, t-values, p-values, and 95% confidence intervals (95% CI) of path coefficients, total effects, indirect effects, and specific indirect effects was obtained (bootstrapping options: 10,000 samples, complete bootstrapping, percentile boot strap, two-tailed, p=0.05). Explanatory power was determined from coefficient of determination ($R^2$; range: 0–1) as well as effect size $f^2$. We used the following guidelines to determine effect size: <0.02 = no measurable effect; 0.02–0.14 = small effect; 0.15–0.34 = medium effect; and ≥0.35 = large effect. For mediating effect sizes, we used Chua's guidelines[101] (ie, β: 0.01–0.08 = small effect; 0.09–0.24 = medium effect; and ≥0.25 = large effect).

Multigroup analysis (MGA) was made to analyze moderator effects.[100]

This exploratory study does not focus on predictive power. However, we determined $Q^2_{predictive}$ values (>0 indicates predictive relevance). The greater the $Q^2$, the greater predictability of the model.[102]

# Results

## Patient Characteristics

Most patients were women (80.3%). A minority had university education (27.3%) and 8.8% were born outside Europe. Descriptive data for the continuous variables are shown in Table 2. For example, pain intensity was relatively high and psychological distress was evident in the cohort. The average pain duration was 8.6 years.

Although mediation analysis does not require that treatment effects be significant,[29] we analysed this for the potential indicators of the three outcome latent variables. Notably, all potential indicators of the three outcome latent variables

**Table 2** Descriptive Data: Mean, One Standard Deviation (SD) and Percentage % Missing for the Cohort Investigated (N=1991)

| *Variable* | *Mean* | *SD* | *% Missing* | | |
|---|---|---|---|---|---|
| Age (years)* | 42.45 | 10.48 | 0.00 | | |
| PRI* | 15.47 | 8.39 | 0.00 | | |
| Pain duration (days)* | 3101 | 3312 | 0.66 | | |
| NRS-7d T0 | 6.84 | 1.63 | 0.23 | | |
| MPI-Pain severity T0 | 4.42 | 0.86 | 0.02 | | |
| SF36-bodily pain-rev T0 | 76.04 | 13.63 | 0.05 | | |
| HAD-tot T0 | 17.68 | 7.92 | 0.05 | | |
| MPI-Distress T0 | 3.51 | 1.19 | 0.02 | | |
| SF36-mental health-rev T0 | 44.86 | 20.17 | 0.02 | | |
| SF36-role emotional-rev T0 | 55.29 | 42.31 | 0.25 | | |
| CPAQ8-AE T0 | 26.22 | 11.35 | 0.00 | | |
| CPAQ8-PW T0 | 21.80 | 8.43 | 0.00 | | |
| CPAQ8-tot T0* | 48.02 | 16.61 | 0.00 | | |
| TSK T0 | 38.13 | 8.69 | 0.00 | | |
| Change in CPAQ8-AE-pre vs post* | 6.19 | 10.71 | 0.00 | | |
| Change in CPAQ8-PW-pre vs post* | 4.13 | 8.27 | 0.00 | | |
| Change in CPAQ8-AE-pre vs 12m* | 7.83 | 11.52 | 0.00 | | |
| Change in CPAQ8-PW- pre vs 12m* | 5.86 | 8.69 | 0.00 | | |
| Change in CPAQ8-tot- pre vs post | 10.42 | 15.66 | 0.00 | | |
| Change in CPAQ8-tot- pre vs 12m | 13.68 | 16.98 | 0.00 | | |
| Change in TSK- pre vs post | −4.19 | 7.01 | 0.00 | | |
| Change in TSK- pre vs 12m | −4.12 | 7.40 | 0.00 | | |
| ***Variable*** | ***Mean*** | ***SD*** | ***% Missing*** | ***P-value T0 vs 12-m fu*** | ***Effect size*** |
| Change in MPI-Pain interference | 0.63 | 1.09 | 0.22 | <0.001 | 0.57 |
| Change in SF36-physical function | 6.34 | 17.93 | 0.21 | <0.001 | 0.35 |
| Change in SF36-role physical* | 12.05 | 35.68 | 0.40 | <0.001 | 0.33 |
| Change in MPI-Control | 0.50 | 1.26 | 0.14 | <0.001 | 0.40 |
| Change in SF36-social function | 8.98 | 27.04 | 0.16 | <0.001 | 0.33 |
| Change in EQ5Dindex | 0.13 | 0.34 | 0.52 | <0.001 | 0.39 |
| Change in EQ-VAS | 8.58 | 22.94 | 0.65 | <0.001 | 0.37 |
| Change in SF36-general health | 5.42 | 18.66 | 0.33 | <0.001 | 0.29 |

**Notes**: In the lower part of the table is shown the changes (differences baseline (T0) versus 12-month follow-up) for the potential indicators of the three outcome latent variables, P-values for these comparisons and absolute effect sizes (Cohen's d). *Not included in the final analyses.

**Abbreviations**: T0, baseline; -rev, variable revised to indicate a troublesome situation; For details of calculation of changes (see Table 1); 12m, 12-month follow-up; NRS-7d, Pain intensity according to a numeric rating scale; HAD, The Hospital Anxiety and Depression Scale; HAD-tot, sum of the two subscales of HAD; MPI, Multidimensional Pain Inventory; SF36, Short Form Health Survey (SF36): the following scales were included – physical function, role physical, social function, mental health, and role emotional; TSK, Tampa Scale for Kinesiophobia; CPAQ, Chronic Pain Acceptance Questionnaire 8-item version; CPAQ8-AE, activity engagement subscale of CPAQ; CPAQ-PW PA, pain willingness subscale of CPAQ; physical activity level; PRI, Pain region Index; EQ-5Dindex, European Quality of Life instrument – index; EQ-VAS, health scale of European Quality of Life instrument.

exhibited significant differences (all P < 0.001) pre-IPRP versus 12-month IPRP follow-up (Table 2), indicating impactful changes over the course of the intervention. The small to medium effect sizes signify meaningful alterations in the cohort's outcomes.

## OPLS Regressions

We checked for the possible influence of sex/gender, age, education level and region of birth upon the final indicators of the three latent outcome variables. No indications were found that these variables acted as confounders (VIPpred: 0.00–0.43 and |p(corr)|: 0.02–0.15 (Supplementary Tables 1a–c)), strengthening the reliability of subsequent analyses. Thus, these variables were consequently excluded from not the subsequent PLS-SEM analyses.

## PLS SEM

PLS-SEM analyses, guided by the overall hypothesis (Figure 1), explored three models differing in their outcome latent variable: Change in Interference, Life control, or Health-Related Quality of Life (HRQoL). The models achieved robust outcomes, as depicted in Figures 2–4. Table 1 lists the included latent variables and final indicators in the PLS-SEM analyses. The models achieved robust outcomes, as depicted in Figures 2–4.

### The Relationships Between Indicators and Their Latent Variables (ie, the Outer Models)

The final outer models were associated with good indicator reliability, internal consistency reliability, convergent validity, and discriminant validity, meeting the prerequisites for un-biased path analyses in the inner models. Details about the

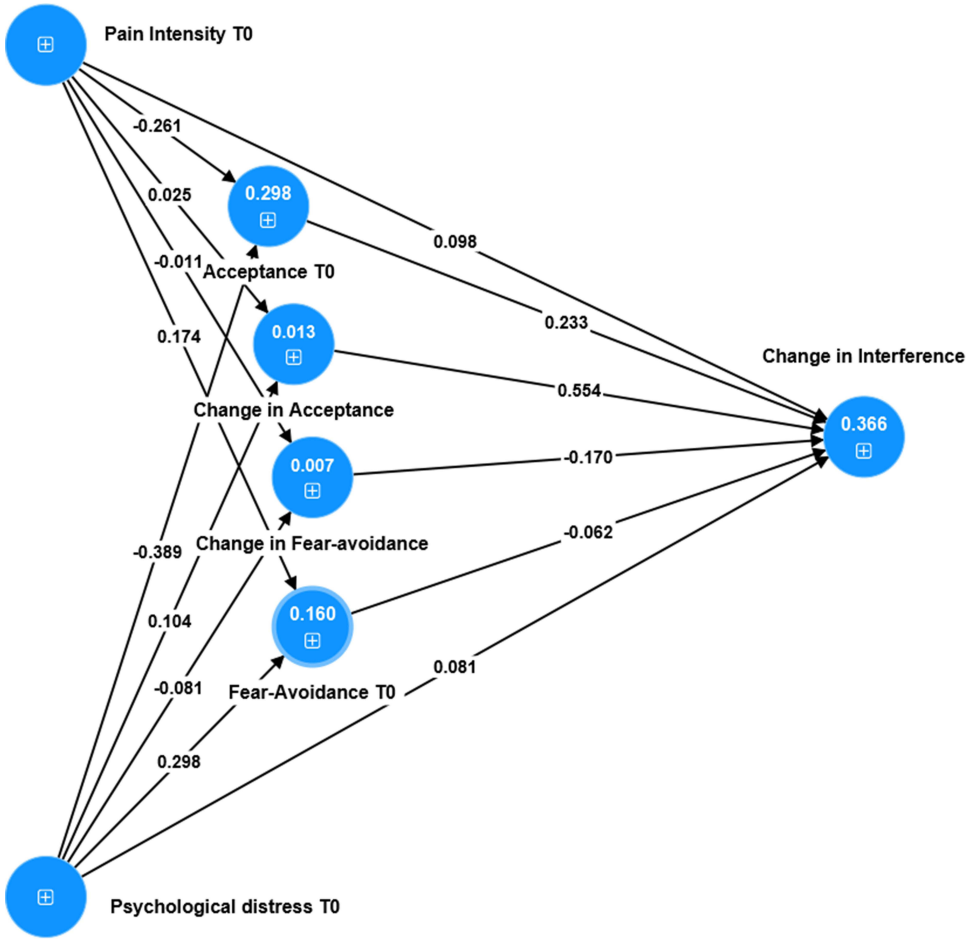


**Figure 2** Model of Change in Interference. The blue circles show the latent variables (constructs). Loadings for the indicators are shown in Table 3. The standardized path coefficient β for each path are shown (P-values are reported in Table 3). The explained variance ($R^2$) is reported within the relevant latent variables.

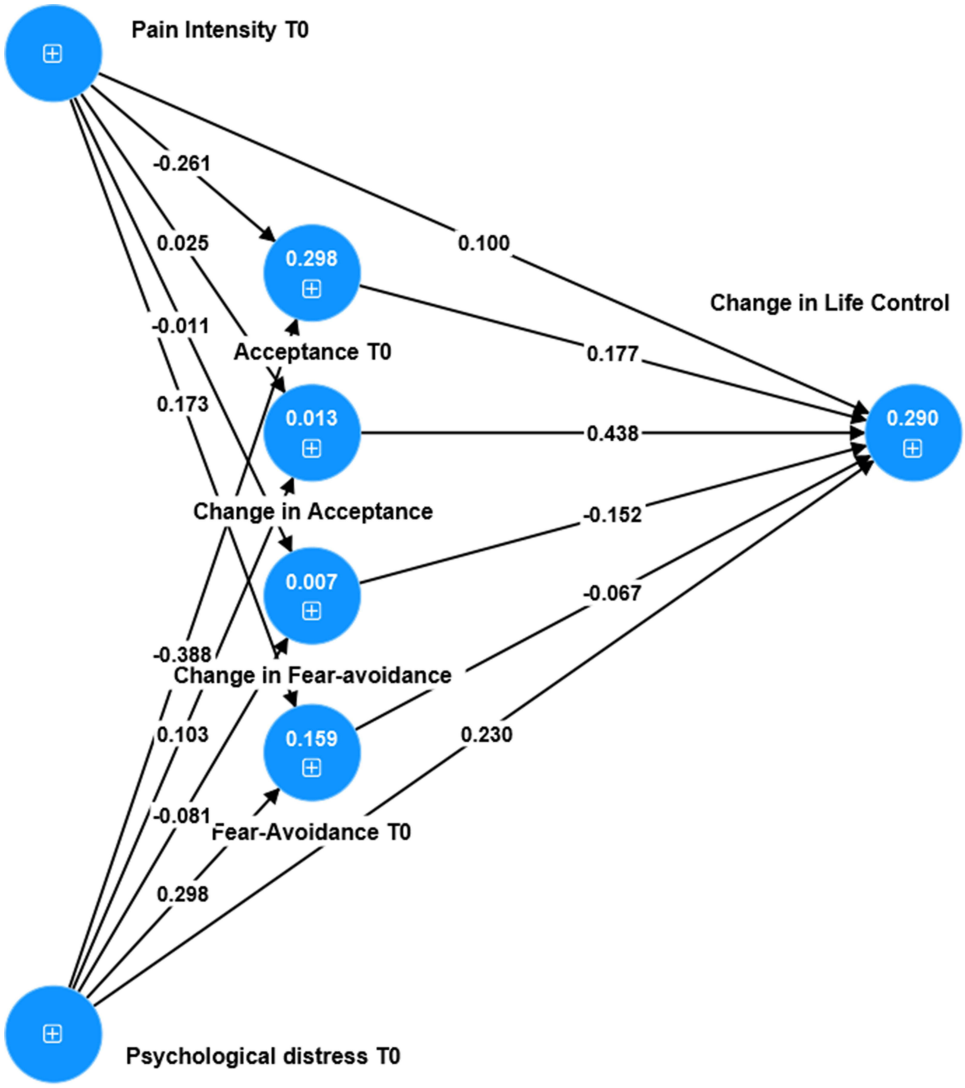


**Figure 3** Model of Change in Life control. The blue circles show the latent variables (constructs). Loadings for the indicators are shown in Table 3. The standardized path coefficient β for each path are shown (P-values are reported in Table 3). The explained variance ($R^2$) is reported within the relevant latent variables.

selection of indicators together with loadings, reliability and validity results are given in Supplementary Material 1 and Supplementary Tables 2–4.

## The Associations Between the Latent Variables (ie, the Inner Models)

The inner model revealed associations (paths) between the latent variables, providing key insights into our study's aims (Table 3, Figures 2–4).

The explained variation (coefficients of determination; $R^2$) for the outcome latent variables were highest for Change in Interference ($R^2$=0.368) and lowest for Change in HRQoL ($R^2$=0.272) and with Change in Life control intermediary ($R^2$=0.292) (Figures 2–4, Supplementary Table 5). The prediction power of the three outcome latent variables was satisfactory (Supplementary Table 6).

### Predictors of Outcomes – Direct Effects

To summarize, Change in Acceptance and Acceptance T0 were strongest (and positively) associated with the three outcome latent variables with Change in Fear-avoidance being either the third or fourth strongest (negatively associated). Hence, these analyses highlighted the significance of both mediators (Change in Acceptance and Change in Fear-avoidance) and

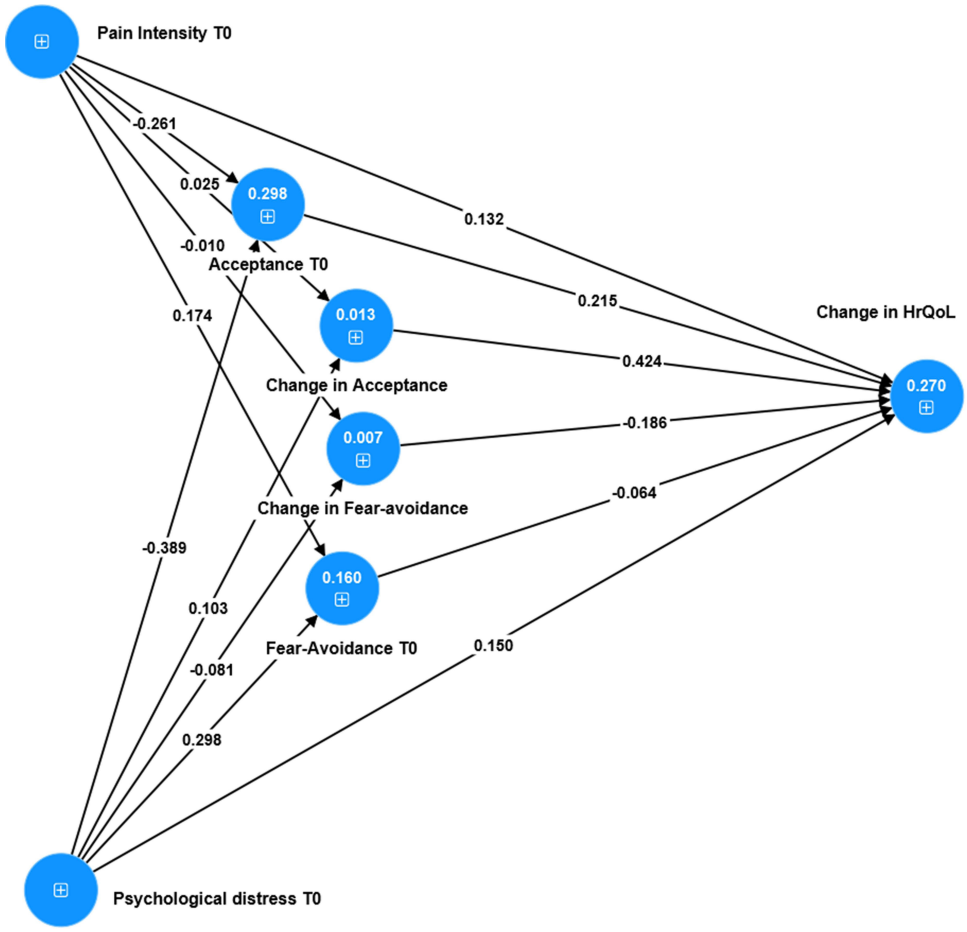


**Figure 4** Model of Change in HRQoL. The blue circles show the latent variables (constructs). Loadings for the indicators are shown in Table 3. The standardized path coefficient β for each path are shown (P-values are reported in Table 3). The explained variance ($R^2$) is reported within the relevant latent variables.

certain baseline variables in predicting the three outcomes investigated. Comparing the two mediators, Change in Acceptance exhibited markedly stronger absolute direct effects (β:0.424–0.553; all P<0.001; small to medium effect sizes) than Change in Fear-Avoidance (β: −0.152–−0.186; all P<0.001; no measurable effect to small effect size) upon the Change in outcomes (Interference, Life control, and HRQoL) (Table 3, Supplementary Table 7).

The baseline aspects Acceptance T0 (β: 0.177–0.233; all P<0.001; all: small effect sizes) showed stronger absolute associations with Changes in outcome (Interference, Life control, and HRQoL) than Fear-avoidance T0 (β: −0.063 – −0.064; P:0.014–0.016; all: no measurable effect) (Table 3, Supplementary Table 7). In fact, Fear-avoidance T0 had the lowest absolute coefficients of the predictors.

Pain intensity and Psychological distress showed significant positive associations with the three outcome latent variables; effect sizes were small at best. Thus, high pain intensity and high psychological distress were positively associated with improvements in the three outcome latent variables. More in detail, Pain intensity T0 (β:0.09–0.132; all: P<0.001), and Psychological distress T0 (β: 0.081–0.229; all: P<0.001) had significant positive direct paths with the three outcome latent variables (Table 3; Figures 2–4). In two of the analyses (Change in Life control model and Change in HRQoL), Psychological distress had somewhat stronger direct effects than Pain intensity. Although all these paths were highly significant (P<0.001), the effect sizes were not impressive. Thus, both paths in the Interference model were associated with no measurable effect, one in the Life control model (the path starting with Psychological distress had a small effect size while the path starting with pain intensity had no measurable effect), and both paths had small effect sizes in the HRQoL model (Supplementary Table 7).

**Table 3** Direct Standardized Path Coefficients (β)

| Change in Interference | Mean | SD | T Statistics | P values | 95% CI Low | 95% CI High |
|---|---|---|---|---|---|---|
| Pain Intensity T0 -> Change in Interference | 0.098 | 0.021 | 4.671 | <0.001 | 0.056 | 0.139 |
| Psychological distress T0 -> Change in Interference | 0.081 | 0.022 | 3.620 | <0.001 | 0.037 | 0.125 |
| Acceptance T0 -> Change in Interference | 0.233 | 0.028 | 8.434 | <0.001 | 0.178 | 0.288 |
| Fear-avoidance T0 -> Change in Interference | −0.063 | 0.026 | 2.408 | 0.016 | −0.114 | −0.012 |
| Change in Acceptance -> Change in Interference | 0.553 | 0.023 | 24.544 | <0.001 | 0.509 | 0.597 |
| Change in Fear-avoidance -> Change in Interference | −0.171 | 0.025 | 6.941 | <0.001 | −0.218 | −0.122 |
| Pain Intensity T0 -> Acceptance T0 | −0.262 | 0.020 | 13.340 | <0.001 | −0.301 | −0.224 |
| Psychological distress T0 -> Acceptance T0 | −0.389 | 0.020 | 19.587 | <0.001 | −0.427 | −0.349 |
| Pain Intensity T0 -> Change in Acceptance | 0.026 | 0.024 | 1.063 | 0.288 | −0.020 | 0.073 |
| Psychological distress T0 -> Change in Acceptance | 0.104 | 0.025 | 4.185 | <0.001 | 0.054 | 0.151 |
| Pain Intensity T0 -> Fear-Avoidance T0 | 0.174 | 0.022 | 8.019 | <0.001 | 0.133 | 0.217 |
| Psychological distress T0 -> Fear-avoidance T0 | 0.298 | 0.022 | 13.773 | <0.001 | 0.255 | 0.340 |
| Pain Intensity T0 -> Change in Fear avoidance | −0.011 | 0.024 | 0.437 | 0.662 | −0.057 | 0.036 |
| Psychological distress T0 -> Change in Fear-avoidance | −0.081 | 0.025 | 3.279 | 0.001 | −0.131 | −0.033 |
| **Change in Life control** | | | | | | |
| Pain Intensity T0 -> Change in Life Control | 0.100 | 0.022 | 4.463 | <0.001 | 0.056 | 0.144 |
| Psychological distress T0 -> Change in Life Control | 0.229 | 0.023 | 10.085 | <0.001 | 0.184 | 0.273 |
| Acceptance T0 -> Change in Life Control | 0.177 | 0.029 | 5.995 | <0.001 | 0.118 | 0.234 |
| Fear-Avoidance T0 -> Change in Life Control | −0.067 | 0.027 | 2.468 | 0.014 | −0.122 | −0.015 |
| Change in Acceptance -> Change in Life Control | 0.439 | 0.025 | 17.257 | <0.001 | 0.388 | 0.488 |
| Change in Fear-avoidance -> Change in Life Control | −0.152 | 0.027 | 5.598 | <0.001 | −0.206 | −0.099 |
| Pain Intensity T0 -> Acceptance T0 | −0.262 | 0.020 | 13.306 | <0.001 | −0.301 | −0.223 |
| Psychological distress T0 -> Acceptance T0 | −0.388 | 0.020 | 19.485 | <0.001 | −0.427 | −0.348 |
| Pain Intensity T0 -> Change in Acceptance | 0.026 | 0.024 | 1.054 | 0.292 | −0.021 | 0.073 |
| Psychological distress T0 -> Change in Acceptance | 0.103 | 0.025 | 4.145 | <0.001 | 0.053 | 0.151 |
| Pain Intensity T0 -> Fear-avoidance T0 | 0.174 | 0.022 | 7.982 | <0.001 | 0.133 | 0.216 |
| Psychological distress T0 -> Fear-avoidance T0 | 0.297 | 0.022 | 13.706 | <0.001 | 0.254 | 0.339 |
| Pain Intensity T0 -> Change in Fear-avoidance | −0.011 | 0.024 | 0.440 | 0.660 | −0.058 | 0.036 |
| Psychological distress T0 -> Change in Fear-avoidance | −0.081 | 0.025 | 3.260 | 0.001 | −0.131 | −0.033 |
| **Change in HrQoL** | | | | | | |
| Pain Intensity T0 -> Change in HrQoL | 0.132 | 0.022 | 5.971 | <0.001 | 0.087 | 0.176 |
| Psychological distress T0 -> Change in HrQoL | 0.149 | 0.023 | 6.622 | <0.001 | 0.105 | 0.193 |
| Acceptance T0 -> Change in HrQoL | 0.215 | 0.029 | 7.320 | <0.001 | 0.157 | 0.272 |
| Fear-Avoidance T0 -> Change in HrQoL | −0.064 | 0.028 | 2.329 | 0.020 | −0.119 | −0.009 |
| Change in Acceptance -> Change in HrQoL | 0.424 | 0.025 | 16.711 | <0.001 | 0.374 | 0.475 |
| Change in Fear-avoidance -> Change in HrQoL | −0.186 | 0.027 | 6.885 | <0.001 | −0.239 | −0.134 |
| Pain Intensity T0 -> Acceptance T0 | −0.262 | 0.020 | 13.327 | <0.001 | −0.301 | −0.224 |
| Psychological distress T0 -> Acceptance T0 | −0.388 | 0.020 | 19.573 | <0.001 | −0.427 | −0.349 |
| Pain Intensity T0 -> Change in Acceptance | 0.025 | 0.024 | 1.036 | 0.300 | −0.021 | 0.073 |
| Psychological distress T0 -> Change in Acceptance | 0.103 | 0.025 | 4.142 | <0.001 | 0.053 | 0.151 |
| Pain Intensity T0 -> Fear-avoidance T0 | 0.174 | 0.022 | 8.006 | <0.001 | 0.133 | 0.216 |
| Psychological distress T0 -> Fear-avoidance T0 | 0.298 | 0.022 | 13.767 | <0.001 | 0.255 | 0.340 |
| Pain Intensity T0 -> Change in Fear-avoidance | −0.011 | 0.024 | 0.436 | 0.663 | −0.057 | 0.036 |
| Psychological distress T0 -> Change in Fear-avoidance | −0.081 | 0.025 | 3.272 | 0.001 | −0.132 | −0.033 |

**Abbreviations**: T0, baseline; HRQoL, health-related quality of life.

### Are Pain Intensity and Psychological Distress Effects on Outcomes Mediated via Acceptance and Fear-Avoidance Aspects?

Intriguingly, mediation analyses explored whether Pain intensity and Psychological distress effects on outcomes were mediated via Acceptance and Fear-avoidance aspects.

**Table 4** Specific Indirect Standardized Effects (ie, Mediating Effects; β) for 8 Mediating Paths in the Three Analyses

| Change in Interference | Mean | SD | T Statistics | P values | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|
| Pain Intensity T0 -> Acceptance T0 -> Change in Interference | −0.061 | 0.009 | 7.067 | <0.001 | −0.079 | −0.045 |
| Psychological distress T0 -> Acceptance T0 -> Change in Interference | −0.091 | 0.012 | 7.757 | <0.001 | −0.114 | −0.068 |
| Pain Intensity T0 -> Change in Acceptance -> Change in Interference | 0.014 | 0.013 | 1.062 | 0.288 | −0.011 | 0.040 |
| Psychological distress T0 -> Change in Acceptance -> Change in Interference | 0.057 | 0.014 | 4.137 | <0.001 | 0.030 | 0.084 |
| Pain Intensity T0 -> Fear-avoidance T0 -> Change in Interference | −0.011 | 0.005 | 2.262 | 0.024 | −0.021 | −0.002 |
| Psychological distress T0 -> Fear-avoidance T0 -> Change in Interference | −0.019 | 0.008 | 2.376 | 0.018 | −0.035 | −0.004 |
| Pain Intensity T0 -> Change in Fear-avoidance -> Change in Interference | 0.002 | 0.004 | 0.430 | 0.667 | −0.006 | 0.010 |
| Psychological distress T0 -> Change in Fear-avoidance -> Change in Interference | 0.014 | 0.005 | 2.976 | 0.003 | 0.005 | 0.024 |
| **Change in Life control** | | | | | | |
| Pain Intensity T0 -> Acceptance T0 -> Change in Life Control | −0.046 | 0.008 | 5.472 | <0.001 | −0.063 | −0.030 |
| Psychological distress T0 -> Acceptance T0 -> Change in Life Control | −0.069 | 0.012 | 5.760 | <0.001 | −0.092 | −0.045 |
| Pain Intensity T0 -> Change in Acceptance -> Change in Life Control | 0.011 | 0.011 | 1.050 | 0.294 | −0.009 | 0.032 |
| Psychological distress T0 -> Change in Acceptance -> Change in Life Control | 0.045 | 0.011 | 4.050 | <0.001 | 0.023 | 0.067 |
| Pain Intensity T0 -> Fear-avoidance T0 -> Change in Life Control | −0.012 | 0.005 | 2.334 | 0.020 | −0.022 | −0.003 |
| Psychological distress T0 -> Fear-avoidance T0 -> Change in Life Control | −0.020 | 0.008 | 2.407 | 0.016 | −0.037 | −0.005 |
| Pain Intensity T0 -> Change in Fear avoidance -> Change in Life Control | 0.002 | 0.004 | 0.428 | 0.669 | −0.005 | 0.009 |
| Psychological distress T0 -> Change in Fear-avoidance -> Change in Life Control | 0.012 | 0.004 | 2.867 | 0.004 | 0.005 | 0.021 |
| **Change in HrQoL** | | | | | | |
| Pain Intensity T0 -> Acceptance T0 -> Change in HRQoL | −0.056 | 0.009 | 6.448 | <0.001 | −0.074 | −0.040 |
| Psychological distress T0 -> Acceptance T0 -> Change in HRQoL | −0.084 | 0.012 | 6.717 | <0.001 | −0.109 | −0.060 |
| Pain Intensity T0 -> Change in Acceptance -> Change in HrQoL | 0.011 | 0.010 | 1.032 | 0.302 | −0.009 | 0.031 |
| Psychological distress T0 -> Change in Acceptance -> Change in HrQoL | 0.044 | 0.011 | 4.022 | <0.001 | 0.022 | 0.065 |
| Pain Intensity T0 -> Fear-avoidance T0 -> Change in HRQoL | −0.011 | 0.005 | 2.206 | 0.027 | −0.022 | −0.002 |
| Psychological distress T0 -> Fear-avoidance T0 -> Change in HRQoL | −0.019 | 0.008 | 2.306 | 0.021 | −0.036 | −0.003 |
| Pain Intensity T0 -> Change in Fear-avoidance -> Change in HRQoL | 0.002 | 0.005 | 0.430 | 0.667 | −0.007 | 0.011 |
| Psychological distress T0 -> Change in Fear-avoidance -> Change in HRQoL | 0.015 | 0.005 | 2.929 | 0.003 | 0.006 | 0.026 |

**Abbreviations**: T0, baseline; HRQoL, health-related quality of life.

Specifically, three of eight mediating paths – all related to Acceptance aspects – were significant (p<0.001) in the three models (Table 4). This underscores the role of Acceptance as a mediator in the relationship between baseline Pain intensity and Psychological distress with changes in outcomes. The strongest mediating path was Psychological distress T0 → Acceptance T0 → Change in outcome (Interference, Life control, and HRQoL) (β: −0.069 – −0.091; all P<0.001; small to medium effect sizes). The second most important was Pain intensity T0 → Acceptance T0 → Change in outcome (Interference, Life control, and HRQoL) (β: −0.046 – −0.061; all P<0.001; all small effect sizes). The third significant mediating path was Psychological distress T0 → Change in Acceptance → Change in outcome (Interference, Life control, and HRQoL) (β: 0.044–0.057; all P<0.001; all small effect sizes).

### Is Sex a Moderator of the Paths in the Investigated Models?

MGA analyses of all paths in the three models did not reveal significant sex differences. This implies that the interrelationships between predictors, mediators, and outcomes did not differ between men and women.

## Discussion

This real-world longitudinal observational study produced several important findings. Significant predictors/mediators of the three outcome latent variables were identified. The two latent Acceptance variables (Change in Acceptance and Acceptance T0) with Change in Fear-avoidance being the third or fourth were most important with respect to strongest

associations. Pain Intensity and Psychological distress at baseline showed weak positive associations. Pain intensity and Psychological distress effects were to some extent mediated via Acceptance aspects. Sex was not a moderator.

## Baseline Variables and Mediators as Predictors of the Three Outcome Latent Variables

The literature has addressed the importance of understanding predictors (baseline variables and/or mediators) of treatment outcomes.[25–28,103] The importance of changes in Acceptance and Fear-avoidance for the three outcomes is encouraging and may indicate that these aspects are targeted during IPRP. Thus, these two latent variables capturing changes throughout IPRP (ie, mediators) were significant predictors of outcomes. In fact, Change in Acceptance was the strongest predictor among all latent variables (β:0.424–0.553; all P<0.001; small to medium effect sizes). Change in Fear-avoidance was also significantly associated (small effects for two of the models) with the outcomes, indicating that this aspect also had some importance. In addition to CBT, Swedish teams have also included central ACT components such as Acceptance;[85] this clinical focus may reflect the stronger effects for Change in Acceptance than for Change in Fear-avoidance. Increased focus on decreasing fear-avoidance beliefs might increase the importance of changes in Fear-avoidance for outcomes of IPRP and increase $R^2$ for the outcomes. Catastrophizing is considered a key driver in the fear-avoidance model of pain.[104] Unfortunately, no measures of catastrophizing were available for this cohort.

Our study could be considered a continuation and extension of an IPRP study from a single specialist clinic in Sweden.[19,30] Like our study, that study found that acceptance and other measures of psychological flexibility were mediators of the outcome pain interference.[19,30] However, our results contrast with results reported in a study investigating the effect of a 10-week ACT-based IPRP.[105] Here, change in acceptance was found to be a mediator for change in depressed mood, whereas change in catastrophizing mediated pain interference, pain intensity, and depressed mood.[105] Our results concerning Change in Acceptance and Change in Fear-avoidance are mainly consistent with recent systematic reviews of CBT/ACT. The systematic review and meta-analysis of Murillo et al in several aspects confirmed the relevance of the fear-avoidance model; reductions in pain-related fear and catastrophizing as well as increases in self-efficacy mediated effects of CBT on disability but not on pain intensity.[29] Consistent with this, another systematic review and meta analysis reported that fear was a mediator between pain and disability in longitudinal studies.[106] Furthermore, enhancing pain acceptance and psychological flexibility mediated ACT effects on disability;[29] psychological flexibility mediated a greater proportion than acceptance. Another review, which included six RCTs with mediation analyses, concluded that processes of change in psychological flexibility were important for outcomes of disability, life satisfaction, pain interference, emotional distress, and physical functioning.[13]

Acceptance T0 was the strongest baseline predictor in two of three models. Hence, relatively higher levels of Acceptance at baseline indicated larger improvement in the investigated outcomes (Figures 2–4). However, another IPRP study reported that baseline values of the psychological inflexibility in pain scale (PIPS) predicted outcome but not baseline values of acceptance.[30] In a review of studies, McCracken concluded that pain intensity and aspects of psychological flexibility were not consistent predictors of CBT outcomes and produced conflicting results for depression.[12] In contrast to these conclusions, we not only report that Acceptance T0 is a predictor but also that the baseline variables Psychological distress T0 and Pain Intensity T0 are significant positive predictors (ie, have significant direct effects; p>0.001) of the three outcome latent variables (Table 4). In a large evaluation of IPRP in Sweden, a blend of baseline variables, including psychological distress aspects, pain intensity, interference, and life control, were significant predictors of overall outcome post IPRP and at the 12-month IPRP follow-up.[4] However, another study also found the explained variations to be low ($R^2$=0.08 both analyses) as well as regressing changes in physical function and changes in health aspects ($R^2$=0.05–0.20).[27] The positive significant associations for Pain intensity and Psychological distress with the changes in the three outcomes are consistent with other studies including large SQRP studies; patients with high pain intensity, psychological distress, and interference show the most prominent positive changes in outcome for IPRP.[4,5,34,37,88] Against our theoretical model (Figure 1) it can be argued that psychological distress is a common comorbidity in chronic pain[107,108] and that Pain intensity and Psychological distress are intercorrelated. Bidirectional complex interactions and cohort heterogeneity between pain and psychological distress have been found in different types of studies.[40,107,109–121] Moreover, the intercorrelations between Pain intensity aspects and Psychological distress levels are generally low.[5,122–124] Since our study focuses on outcomes of IPRP, we let them "compete" in relation to each

other and in relation to the other latent variables. Psychological distress was somewhat more strongly associated with the three outcome latent variables. However, the clinical importance of this finding is limited (ie, at best small effect sizes).

Fear-avoidance T0 was not a significant direct predictor of the three outcome latent variables. A systematic review from 2019 reported inconsistent results in the longitudinal perspective for disability and pain.[55] However, a more recent systematic review of longitudinal studies (n=4) from 2021 concluded that baseline fear of movement predict disability.[125] There are strong cross-sectional associations between the components of the fear-avoidance model and disability, pain intensity and psychological distress.[56] The lower and non-significant coefficients for Fear-avoidance T0 both for direct and indirect effects with the three latent outcome variables may be due to the focus of the instrument used (ie, TSK), which measures fear only in the context of injury or reinjury.[47]

Treatment mechanisms are characterized as specific or non-specific.[29] Specific effects are actively targeted by the intervention. Non-specific factors include contextual factors (eg, therapeutic alliance, patient satisfaction, or natural disease fluctuations) and reflect common mechanisms across different types of intervention. To some extent CBT, ACT, mindfulness-based interventions, as well as exercise-based interventions share behavioral and cognitive mechanisms.[126–128] As expected, on the basis of this study, it can be concluded that IPRP also belongs to this group of interventions.

Although most latent variables showed significant associations with the three outcome latent variables, the explained variances were low ($R^2$: 0.270–0.366). Thus, we have an incomplete understanding of the factors determining IPRP outcomes. In future studies, PLS-SEM analyses could obtain a better understanding of the factors that determine outcomes and thereby a better explanation for the variances ($R^2$) by including processes of change relevant for exercise and pain education (ie, other important IPRP components) as well as readiness for change and motivation (these are currently not registered in SQRP). Another cause for the low $R^2$ may be that predictors/mediators are sought at least partially at the wrong level. Chronic pain and common comorbidities as well as IPRP and their individual components are associated with molecular alterations (eg, at the immune level).[129–133] Hence, future research may also have to include molecular processes to expand our knowledge about the mechanisms determining IPRP outcomes.

## Mediating Paths for Pain Intensity and Psychological Distress on Outcomes

We also investigated whether the effect of Pain intensity and Psychological distress on the three outcome latent variables was mediated via the two Acceptance and the two Fear-avoidance aspects. Two notable mediating paths involving Acceptance T0 were identified. Both Pain intensity and Psychological distress effects were mediated through Acceptance T0. Strikingly, these mediating paths exhibited negative indirect paths, suggesting that, counterintuitively, higher levels of Pain intensity and Psychological distress at baseline, when mediated through Acceptance T0, were associated with diminished changes in the outcome latent variables (Table 4). This paradoxical finding underscores the intricate dynamics between baseline characteristics and their mediating effects on rehabilitation outcomes. Our results illuminated the complex roles of Psychological distress and Pain intensity, as the direct effects were positive while the indirect effects were negative. This paradox prompts the need for more in-depth investigations into the roles of Psychological distress and Pain intensity at baseline compared to their potential roles as mediators. Unravelling the dual nature of these variables is crucial for refining our understanding of their contributions to the rehabilitation process.

Furthermore, the analysis unveiled an additional layer of complexity in the relationship between Psychological distress and outcomes. Psychological distress demonstrated a significant positive mediating path via Change in Acceptance. This suggests that higher levels of Psychological distress, when channelled through the process of Change in Acceptance, enhanced the outcome latent variables. This intriguing finding highlights the potential adaptability and resilience individuals with high Psychological distress may exhibit when they engage in processes that lead to increased Acceptance during the rehabilitation journey.

## Sex Was Not a Moderator

In treatment studies, moderation, which concerns heterogeneity, may reflect whom benefits most. We hypothesised that sex would be influential, but we were unable to confirm such a heterogeneity. Hence, it is possible that men and women in the study employed similar coping mechanisms or responded similarly to the interventions provided in the interdisciplinary pain rehabilitation program (IPRP).

## Strength and Limitations

A strength of this study is its relatively large real-world longitudinal cohort of chronic pain patients with nation-wide representation who participated in IPRP with a 12-month follow-up. Our results are relevant for patients referred to specialist care, which represents the most complex chronic pain patients. Since we assumed that the effects operated through several mechanisms, we applied multiple parallel mediator analysis.[29] Several of the latent variables had various indicators, which is an advantage from a measurement error point of view.

There are also limitations that must be mentioned. Most of the evidence concerning mediators is based upon RCTs but also cohort studies can be important.[134] Because this is a single-group design without a control group, time effects are not necessarily due to IPRP. The patients included had long pain durations (on average 8.5 years), so it is less likely that the changes reflect improvements that would appear spontaneously. We were unable to investigate which of the IPRP components were most important for the outcome latent variables.[29] Also, intensity, duration, and consistency of the components of IPRP may for various reasons differ between the practice settings and therapists.[2,85,135] Another possible limitation is that we did not include diagnoses in our examined models. Whether common chronic pain diagnoses are associated with different IPRP outcomes is currently unclear.[136,137] There are six components in the psychological flexibility model, but the present study was only able to investigate acceptance;[138] a broader coverage may be more adequate for identifying important mediators. Another limitation is that aspects of catastrophizing could not be included in the models. In our models, we used the changes in acceptance and fear-avoidance (eg, differences between pre and post), which is a common procedure used in the literature. However, this procedure has been criticized and it has been suggested that both the pre and post values should be included in the models.[139] However, this generally leads to more complex models and potentially more complex interpretations. In future methodological SQRP studies, it is important to investigate whether this leads to decisive differences in the interpretation of the results from PLS-SEM analyses. Moderators other than sex may be present. We did not perform sensitivity analysis but on the other hand the percentage missing was less than 0.7% for all variables (indicators) included. Thus, it is highly unlikely that missing data would have biased our results. It is also important to point out that our analyses are based on a specific overarching hypothesis and more studies – which may be based on other hypotheses – may be needed to validate the results. Another limitation concerns the complexity of the models in terms of the number of covariates. There are many potential covariates in chronic pain (especially from a biopsychosocial perspective) and a trade-off between the number of covariates and the complexity of the model must be done. Future research including more covariates will determine whether our results are robust. Finally, it can be argued that this study is limited by the variables included in the registry. Other aspects that might be important for the analyses – eg, motivation, readiness for change and individual goals – are not measured and therefore not available in the registry.

## Conclusions

In this longitudinal cohort study of IPRP outcomes using advanced path analysis, we found that changes in Acceptance had the greatest influence on chronic pain patients' abilities to lead socially and physically active and meaningful lives in the presence of pain and restore health-related quality of life. Yet again Acceptance aspects have been identified as important predictors of IPRP outcomes, which support a focus on addressing and improving Acceptance processes both in the clinic and as a research topic. Our results also suggest fear-avoidance beliefs as an important aspect that might be better targeted during IPRP.

Future PLS-SEM analyses of IPRP need to have a broader coverage of possible mediators (eg, catastrophizing) and more facets of psychological flexibility and fear-avoidance. A combination of advanced cluster analysis for the identification of different subgroups and PLS-SEM could enable an increased understanding of how the severity of the total clinical presentation affects the outcome measures. By systematically evaluating the Fear Avoidance Models and Pain Acceptance Models into IPRP, the goal is to create a holistic and synergistic approach that addresses the complex interplay between psychological and biological aspects of chronic pain. Finally, future studies should analyze the importance of the different components of IPRP.

## Data Sharing Statement

The datasets generated and/or analysed in this study will be available upon reasonable request from the corresponding author or from SQRP.

## Ethics Approval and Consent to Participate

The study was conducted in accordance with the Helsinki Declaration and was approved by the Ethical Review Board in Linköping (Dnr: 2015/108-31). All the participants received written information about the study and gave their written consent.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

No specific funding for this study.

## Disclosure

The authors report no conflicts of interest. The funders had no role in the design of the study or in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

## References

1. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. 2007;133(4):581. doi:10.1037/0033-2909.133.4.581
2. Gerdle B, Rivano Fischer M, Ringqvist Å. Interdisciplinary pain rehabilitation programs: evidence and clinical real-world results. In: Witney A, editor. *Pain Management - From Pain Mechanisms to Patient Care [Working Title]*. London: IntechOpen; 2022.
3. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain management: past, present, and future. *Am Psychol*. 2014;69(2):119–130. doi:10.1037/a0035514
4. Ringqvist Å, Dragioti E, Björk M, Larsson B, Gerdle B. Moderate and stable pain reductions as a result of Interdisciplinary Pain Rehabilitation – a cohort study from the Swedish Quality Registry for Pain Rehabilitation (SQRP). *J Clin Med*. 2019;8(6):905. doi:10.3390/jcm8060905
5. Gerdle B, Akerblom S, Brodda Jansen G, et al. Who benefits from multimodal rehabilitation - an exploration of pain, psychological distress, and life impacts in over 35,000 chronic pain patients identified in the Swedish Quality Registry for Pain Rehabilitation. *J Pain Res*. 2019;12:891–908. doi:10.2147/JPR.S190003
6. Vaegter HB, Christoffersen LO, Enggaard TP, et al. Socio-demographics, pain characteristics, quality of life and treatment values before and after specialized interdisciplinary pain treatment: results from the Danish Clinical Pain Registry (PainData). *J Pain Res*. 2021;14:1215–1230. doi:10.2147/JPR.S306504
7. Elbers S, Wittink H, Konings S, et al. Longitudinal outcome evaluations of Interdisciplinary Multimodal Pain Treatment programmes for patients with chronic primary musculoskeletal pain: a systematic review and meta-analysis. *Eur J Pain*. 2022;26(2):310–335. doi:10.1002/ejp.1875
8. Bennett M, Closs S. Methodological issues in non pharmacological trials for chronic pain. *Pain Clin Updates*. 2010;18(2):1–6.
9. SBU. *Methods for Treatment of Chronic Pain a Systematic Review of the Literature (In Swedish: Metoder För Behandling Av Långvarig Smärta: En Systematisk Litteraturöversikt)*. Vol. 177. Stockholm: SBU – Swedish Council on Health Technology Assessment; 2006:1–2.
10. SBU. *Rehabilitation of Chronic Pain [In Swedish: Rehabilitering Vid Långvarig Smärta. En Systematisk Litteraturöversikt]*. Stockholm: SBU – Swedish Council on Health Technology Assessment; 2010.
11. Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. *Rheumatology*. 2008;47(5):670–678. doi:10.1093/rheumatology/ken021
12. McCracken LM. Personalized pain management: is it time for process-based therapy for particular people with chronic pain? *Eur J Pain*. 2023;27(9):1044–1055. doi:10.1002/ejp.2091
13. McCracken LM, Yu L, Vowles KE. New generation psychological treatments in chronic pain. *BMJ*. 2022;376:e057212.
14. Trindade IA, Guiomar R, Carvalho SA, et al. Efficacy of online-based acceptance and commitment therapy for chronic pain: a systematic review and meta-analysis. *J Pain*. 2021;22(11):1328–1342. doi:10.1016/j.jpain.2021.04.003
15. Ma TW, Yuen AS, Yang Z. The efficacy of acceptance and commitment therapy for chronic pain: a systematic review and meta-analysis. *Clin J Pain*. 2023;39(3):147–157. doi:10.1097/AJP.0000000000001096
16. Fordham B, Sugavanam T, Edwards K, et al. Cognitive-behavioural therapy for a variety of conditions: an overview of systematic reviews and panoramic meta-analysis. *Health Technol Assess*. 2021;25(9):1–378. doi:10.3310/hta25090
17. Hughes LS, Clark J, Colclough JA, Dale E, McMillan D. Acceptance and Commitment Therapy (ACT) for chronic pain: a systematic review and meta-analyses. *Clin J Pain*. 2017;33(6):552–568. doi:10.1097/AJP.0000000000000425

18. Lai L, Liu Y, McCracken LM, Li Y, Ren Z. The efficacy of acceptance and commitment therapy for chronic pain: a three-level meta-analysis and a trial sequential analysis of randomized controlled trials. *Behav Res Ther*. 2023;165:104308. doi:10.1016/j.brat.2023.104308
19. Akerblom S, Perrin S, Rivano Fischer M, McCracken LM. The mediating role of acceptance in multidisciplinary cognitive-behavioral therapy for chronic pain. *J Pain*. 2015;16(7):606–615. doi:10.1016/j.jpain.2015.03.007
20. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017;4:CD011279.
21. Owen PJ, Miller CT, Mundell NL, et al. Which specific modes of exercise training are most effective for treating low back pain? Network meta-analysis. *Br J Sports Med*. 2020;54(21):1279–1287. doi:10.1136/bjsports-2019-100886
22. Searle A, Spink M, Ho A, Chuter V. Exercise interventions for the treatment of chronic low back pain: a systematic review and meta-analysis of randomised controlled trials. *Clin Rehabil*. 2015;29(12):1155–1167. doi:10.1177/0269215515570379
23. Louw A, Zimney K, Puentedura EJ, Diener I. The efficacy of pain neuroscience education on musculoskeletal pain: a systematic review of the literature. *Physiother Theory Pract*. 2016;32(5):332–355. doi:10.1080/09593985.2016.1194646
24. Tegner H, Frederiksen P, Esbensen BA, Juhl C. Neurophysiological pain education for patients with chronic low back pain: a systematic review and meta-analysis. *Clin J Pain*. 2018;34(8):778–786. doi:10.1097/AJP.0000000000000594
25. Liechti S, Tseli E, Taeymans J, Grooten W. Prognostic factors for quality of life after interdisciplinary pain rehabilitation in patients with chronic pain-a systematic review. *Pain Med*. 2023;24(1):52–70. doi:10.1093/pm/pnac098
26. Tseli E, Boersma K, Stalnacke BM, et al. Prognostic factors for physical functioning after multidisciplinary rehabilitation in patients with chronic musculoskeletal pain: a systematic review and meta-analysis. *Clin J Pain*. 2019;35(2):148–173. doi:10.1097/AJP.0000000000000669
27. Gerdle B, Molander P, Stenberg G, Stalnacke BM, Enthoven P. Weak outcome predictors of multimodal rehabilitation at one-year follow-up in patients with chronic pain-A practice based evidence study from two SQRP centres. *BMC Musculoskelet Disord*. 2016;17(1):490. doi:10.1186/s12891-016-1346-7
28. Tseli E, Vixner L, LoMartire R, Grooten WJA, Gerdle B, Ang BO. Prognostic factors for improved physical and emotional functioning one year after interdisciplinary rehabilitation in patients with chronic pain: results from a national quality registry in Sweden. *J Rehabil Med*. 2020. doi:10.2340/16501977-2648
29. Murillo C, Vo TT, Vansteelandt S, et al. How do psychologically based interventions for chronic musculoskeletal pain work? A systematic review and meta-analysis of specific moderators and mediators of treatment. *Clin Psychol Rev*. 2022;94:102160. doi:10.1016/j.cpr.2022.102160
30. Akerblom S, Perrin S, Rivano Fischer M, McCracken LM. Predictors and mediators of outcome in cognitive behavioral therapy for chronic pain: the contributions of psychological flexibility. *J Behav Med*. 2021;44(1):111–122. doi:10.1007/s10865-020-00168-9
31. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1–2):9–19. doi:10.1016/j.pain.2004.09.012
32. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003;106(3):337–345. doi:10.1016/j.pain.2003.08.001
33. Kaiser U, Kopkow C, Deckert S, et al. Developing a core outcome-domain set to assessing effectiveness of interdisciplinary multimodal pain therapy: the VAPAIN consensus statement on core outcome-domains. *Pain*. 2018;159(4):673–683. doi:10.1097/j.pain.0000000000001129
34. Gerdle B, Åkerblom S, Stålnacke B-M, et al. The importance of emotional distress, cognitive behavioural factors and pain for life impact at baseline and for outcomes after rehabilitation – a SQRP study of more than 20 000 chronic pain patients. *Scand J Pain*. 2019;19(4):693–711. doi:10.1515/sjpain-2019-0016
35. de Rooij A, Roorda LD, Otten RHJ, van der Leeden M, Dekker J, Steultjens MPM. Predictors of multidisciplinary treatment outcome in fibromyalgia: a systematic review. *Disabil Rehabil*. 2013;35(6):437–449. doi:10.3109/09638288.2012.699582
36. Craner JR, Flegge LG, Lake ES, Perra AEA. Patients with clinically elevated depressive symptoms report improvements in mood, pain, and functioning following participation in interdisciplinary pain rehabilitation. *Pain Med*. 2022;23(2):362–374. doi:10.1093/pm/pnab242
37. Oliveira DS, Velia Ferreira Mendonca L, Sofia Monteiro Sampaio R, Manuel Pereira Dias de castro-lopes J, Ribeiro de Azevedo LF. The impact of anxiety and depression on the outcomes of chronic low back pain multidisciplinary pain management-a multicenter prospective cohort study in pain clinics with one-year follow-up. *Pain Med*. 2019;20(4):736–746. doi:10.1093/pm/pny128
38. Lewis GN, Bean DJ. What influences outcomes from inpatient multidisciplinary pain management programs? A systematic review and meta-analysis. *Clin J Pain*. 2021;37(7):504–523. doi:10.1097/AJP.0000000000000941
39. Fordham B, Sugavanam T, Hopewell S, et al. Effectiveness of cognitive-behavioural therapy: a protocol for an overview of systematic reviews and meta-analyses. *BMJ open*. 2018;8(12):e025761. doi:10.1136/bmjopen-2018-025761
40. Vlaeyen JW, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain*. 2012;153(6):1144–1147. doi:10.1016/j.pain.2011.12.009
41. Vlaeyen JWS, Crombez G, Linton SJ. The fear-avoidance model of pain. *Pain*. 2016;157(8):1588–1589. doi:10.1097/j.pain.0000000000000574
42. Gatchel RJ, Neblett R, Kishino N, Ray CT. Fear-avoidance beliefs and chronic pain. *J Orthop Sports Phys Ther*. 2016;46(2):38–43. doi:10.2519/jospt.2016.0601
43. Asmundson GJ, Norton PJ, Norton GR. Beyond pain: the role of fear and avoidance in chronicity. *Clin Psychol Rev*. 1999;19(1):97–119. doi:10.1016/S0272-7358(98)00034-8
44. Norton PJ, Asmundson GJG. Amending the fear-avoidance model of chronic pain: what is the role of physiological arousal? *Behavior Ther*. 2003;34(1):17–30. doi:10.1016/S0005-7894(03)80019-9
45. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. 2000;85(3):317–332. doi:10.1016/S0304-3959(99)00242-0
46. Vlaeyen J, Kole-Snijders A, Boeren R, van Eek H. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain*. 1995;62:363–372. doi:10.1016/0304-3959(94)00279-N
47. Neblett R, Mayer TG, Williams MJ, et al. The Fear-Avoidance Components Scale (FACS): responsiveness to functional restoration treatment in a Chronic Musculoskeletal Pain Disorder (CMPD) Population. *Clin J Pain*. 2017;33(12):1088–1099. doi:10.1097/AJP.0000000000000501
48. Zale EL, Ditre JW. Pain-related fear, disability, and the fear-avoidance model of chronic pain. *Curr Opin Psychol*. 2015;5:24–30. doi:10.1016/j.copsyc.2015.03.014

49. Wertli MM, Rasmussen-Barr E, Held U, Weiser S, Bachmann LM, Brunner F. Fear-avoidance beliefs-A moderator of treatment efficacy in patients with low back pain: a systematic review. *Spine J*. 2014;14(11):2658–2678. doi:10.1016/j.spinee.2014.02.033
50. Krismer M, van Tulder M; Low Back Pain Group of the B, Joint Health Strategies for Europe P. Strategies for prevention and management of musculoskeletal conditions. Low back pain (non-specific). *Best Pract Res Clin Rheumatol*. 2007;21(1):77–91. doi:10.1016/j.berh.2006.08.004
51. Leeuw M, Goossens ME, van Breukelen GJ, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. *Pain*. 2008;138(1):192–207. doi:10.1016/j.pain.2007.12.009
52. Lundberg M, Larsson M, Ostlund H, Styf J. Kinesiophobia among patients with musculoskeletal pain in primary healthcare. *J Rehabil Med*. 2006;38(1):37–43. doi:10.1080/16501970510041253
53. Wertli MM, Rasmussen-Barr E, Weiser S, Bachmann LM, Brunner F. The role of fear avoidance beliefs as a prognostic factor for outcome in patients with nonspecific low back pain: a systematic review. *Spine J*. 2014;14(5):816–836 e814. doi:10.1016/j.spinee.2013.09.036
54. Kroska EB. A meta-analysis of fear-avoidance and pain intensity: the paradox of chronic pain. *Scand J Pain*. 2016;13(1):43–58. doi:10.1016/j.sjpain.2016.06.011
55. Martinez-Calderon J, Flores-Cortes M, Morales-Asencio JM, Luque-Suarez A. Pain-related fear, pain intensity and function in individuals with chronic musculoskeletal pain: a systematic review and meta-analysis. *J Pain*. 2019;20(12):1394–1415. doi:10.1016/j.jpain.2019.04.009
56. Rogers AH, Farris SG. A meta-analysis of the associations of elements of the fear-avoidance model of chronic pain with negative affect, depression, anxiety, pain-related disability and pain intensity. *Eur J Pain*. 2022;26(8):1611–1635. doi:10.1002/ejp.1994
57. Hayes SB, Strosahl K, Wilson K. *Acceptance and Commitment Therapy: The Process and Practice of Mindful Change*. 2nd ed. New York: Guilford Press; 2012.
58. McCracken LM. Psychological flexibility, chronic pain, and health. *Annual Review of Psychology*. 2023. doi:10.1146/annurev-psych-020223-124335
59. McCracken LM, Vowles KE. Acceptance and commitment therapy and mindfulness for chronic pain: model, process, and progress. *Am Psychol*. 2014;69(2):178–187. doi:10.1037/a0035623
60. Hayes SC, Levin ME, Plumb-Vilardaga J, Villatte JL, Pistorello J. Acceptance and commitment therapy and contextual behavioral science: examining the progress of a distinctive model of behavioral and cognitive therapy. *Behav Ther*. 2013;44(2):180–198. doi:10.1016/j.beth.2009.08.002
61. Asghari A, Nicholas MK. Personality and pain-related beliefs/coping strategies: a prospective study. *Clin J Pain*. 2006;22(1):10–18. doi:10.1097/01.ajp.0000146218.31780.0b
62. Esteve R, Ramirez-Maestre C, Lopez-Marinez AE. Adjustment to chronic pain: the role of pain acceptance, coping strategies, and pain-related cognitions. *Ann Behav Med*. 2007;33(2):179–188. doi:10.1007/BF02879899
63. Hayes S, Jacobson N, Follette V, Dougher M. *Acceptance and Change: Content and Context in Psychotherapy*. Reno: Context Press; 1994.
64. McCracken L. Commentary: toward understanding acceptance and psychological flexibility in chronic pain. *Pain*. 2010;149(3):420–421. doi:10.1016/j.pain.2010.02.036
65. Scott W, McCracken L. Psychological flexibility, acceptance and commitment therapy, and chronic pain. *Curr Opin Psychol*. 2015;2:91–96. doi:10.1016/j.copsyc.2014.12.013
66. McCracken LM. Learning to live with the pain: acceptance of pain predicts adjustment in persons with chronic pain. *Pain*. 1998;74(1):21–27. doi:10.1016/S0304-3959(97)00146-2
67. Cederberg JT, Cernvall M, Dahl J, von Essen L, Ljungman G. Acceptance as a mediator for change in acceptance and commitment therapy for persons with chronic pain? *Int J Behav Med*. 2016;23(1):21–29. doi:10.1007/s12529-015-9494-y
68. Kranz D, Bollinger A, Nilges P. Chronic pain acceptance and affective well-being: a coping perspective. *Eur J Pain*. 2010;14(10):1021–1025. doi:10.1016/j.ejpain.2010.03.010
69. McCracken LM, Eccleston C. A prospective study of acceptance of pain and patient functioning with chronic pain. *Pain*. 2005;118(1–2):164–169. doi:10.1016/j.pain.2005.08.015
70. Viane I, Crombez G, Eccleston C, Devulder J, De Corte W. Acceptance of the unpleasant reality of chronic pain: effects upon attention to pain and engagement with daily activities. *Pain*. 2004;112(3):282–288. doi:10.1016/j.pain.2004.09.008
71. McCracken LM, Spertus IL, Janeck AS, Sinclair D, Wetzel FT. Behavioral dimensions of adjustment in persons with chronic pain: pain-related anxiety and acceptance. *Pain*. 1999;80(1–2):283–289. doi:10.1016/S0304-3959(98)00219-X
72. Viane I, Crombez G, Eccleston C, et al. Acceptance of pain is an independent predictor of mental well-being in patients with chronic pain: empirical evidence and reappraisal. *Pain*. 2003;106(1–2):65–72. doi:10.1016/S0304-3959(03)00291-4
73. Karayannis N, Sturgeon J, Kemani M, et al. Pain acceptance and psychological inflexibility predict pain interference outcomes for persons with chronic pain receiving pain psychology. *Scand J Pain*. 2023;23(3):464–475. doi:10.1515/sjpain-2022-0107
74. 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(17):E1031–E1039. doi:10.1097/BRS.0000000000002066
75. Stockton D, Kellett S, Berrios R, Sirois F, Wilkinson N, Miles G. Identifying the underlying mechanisms of change during Acceptance and Commitment Therapy (ACT): a systematic review of contemporary mediation studies. *Behav Cogn Psychother*. 2019;47(3):332–362. doi:10.1017/S1352465818000553
76. Svanberg M, Stalnacke BM, Enthoven P, Brodda-Jansen G, Gerdle B, Boersma K. Impact of emotional distress and pain-related fear on patients with chronic pain: subgroup analysis of patients referred to multimodal rehabilitation. *J Rehabil Med*. 2017;49(4):354–361. doi:10.2340/16501977-2212
77. Pester BD, Crouch TB, Christon L, et al. Gender differences in multidisciplinary pain rehabilitation: the mediating role of pain acceptance. *J Context Behav Sci*. 2022;23:117–124. doi:10.1016/j.jcbs.2022.01.002
78. Gerdle B, Boersma K, Asenlof P, Stalnacke BM, Larsson B, Ringqvist A. Influences of sex, education, and country of birth on clinical presentations and overall outcomes of interdisciplinary pain rehabilitation in chronic pain patients: a cohort study from the Swedish Quality Registry for Pain Rehabilitation (SQRP). *J Clin Med*. 2020;9(8):2374. doi:10.3390/jcm9082374
79. Flegge LG, Lake E, Truesdale C, Craner JR. Sex differences in interdisciplinary pain rehabilitation outcomes: a systematic review. *Scand J Pain*. 2022;22(2):218–231. doi:10.1515/sjpain-2021-0188

80. Krogstad BS, Jokstad A, Dahl BL, Vassend O. The reporting of pain, somatic complaints, and anxiety in a group of patients with TMD before and 2 years after treatment: sex differences. *J Orofac Pain*. 1996;10(3):263–269.
81. Spinord L, Kassberg AC, Stenberg G, Lundqvist R, Stalnacke BM. Comparison of two multimodal pain rehabilitation programmes, in relation to sex and age. *J Rehabil Med*. 2018;50(7):619–628. doi:10.2340/16501977-2352
82. Murphy JL, Phillips KM, Rafie S. Sex differences between Veterans participating in interdisciplinary chronic pain rehabilitation. *J Rehabil Res Dev*. 2016;53(1):83–94. doi:10.1682/JRRD.2014.10.0250
83. Danielsson L, Kvarstein G, Bergvik S. Mediators of pain and physical function in female and male patients with chronic pain. *J Pain Res*. 2020;13:1059–1071. doi:10.2147/JPR.S233501
84. Bromley Milton M, Borsbo B, Rovner G, Lundgren-Nilsson A, Stibrant-Sunnerhagen K, Gerdle B. Is pain intensity really that important to assess in chronic pain patients? A study based on the Swedish Quality Registry for Pain Rehabilitation (SQRP). *PLoS One*. 2013;8(6):e65483. doi:10.1371/journal.pone.0065483
85. Rivano Fischer M, Schults M, Stålnacke B, Ekholm J, Persson E, Löfgren M. Variability in patient characteristics and service provision of interdisciplinary pain rehabilitation: a study using the Swedish national quality registry for pain rehabilitation. *J Rehabil Med*. 2020;52(11): jrm00128.
86. Shiell A, Hawe P, Gold L. Complex interventions or complex systems? Implications for health economic evaluation. *BMJ*. 2008;336 (7656):1281–1283. doi:10.1136/bmj.39569.510521.AD
87. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337:a1655.
88. Gerdle B, Cervin M, Rivano Fischer M, Ringqvist A. Outcomes of interdisciplinary pain rehabilitation across subgroups of the multidimensional pain inventory - a study from the Swedish Quality Registry for Pain Rehabilitation. *Pain Pract*. 2021;21(6):662–679. doi:10.1111/papr.13007
89. Gerdle B, Rivano Fischer M, Cervin M, Ringqvist Å. Spreading of pain in patients with chronic pain is related to pain duration and clinical presentation and weakly associated with outcomes of interdisciplinary pain rehabilitation: a cohort study from the Swedish Quality Registry for Pain Rehabilitation (SQRP). *J Pain Res*. 2021;14:173–187. doi:10.2147/JPR.S288638
90. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67(6):361–370. doi:10.1111/j.1600-0447.1983.tb09716.x
91. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*. 2002;52(2):69–77.
92. LoMartire R, Ang BO, Gerdle B, Vixner L. Psychometric properties of Short Form-36 Health Survey, EuroQol 5-dimensions, and Hospital Anxiety and Depression Scale in patients with chronic pain. *Pain*. 2020;161(1):83–95. doi:10.1097/j.pain.0000000000001700
93. Roelofs J, Sluiter J, Frings-Dresen M, et al. Fear of movement and (re)injury in chronic musculoskeletal pain: evidence for an invariant two-factor model of the Tampa Scale for Kinesiophobia across pain diagnoses and Dutch, Swedish, and Canadian samples. *Pain*. 2007;131 (1):181–190. doi:10.1016/j.pain.2007.01.008
94. Rovner GS, Arestedt K, Gerdle B, Borsbo B, McCracken LM. Psychometric properties of the 8-item Chronic Pain Acceptance Questionnaire (CPAQ-8) in a Swedish chronic pain cohort. *J Rehabil Med*. 2014;46(1):73–80. doi:10.2340/16501977-1227
95. EuroQol. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199–208. doi:10.1016/0168-8510(90)90421-9
96. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53–72. doi:10.1016/0168-8510(96)00822-6
97. Dolan P, Sutton M. Mapping visual analogue scale health state valuations onto standard gamble and time trade-off values. *Soc Sci Med*. 1997;44 (10):1519–1530. doi:10.1016/S0277-9536(96)00271-7
98. Bäckryd E, Persson EB, Larsson AI, Fischer MR, Gerdle B. Chronic pain patients can be classified into four groups: clustering-based discriminant analysis of psychometric data from 4665 patients referred to a multidisciplinary pain centre (a SQRP study). *PLoS One*. 2018;13(2):e0192623. doi:10.1371/journal.pone.0192623
99. Eriksson L, Byrne T, Johansson E, Trygg J, Vikström C. *Multi- and Megavariate Data Analysis: Basic Principles and Applications*. Third revised edition ed. Malmö: MKS Umetrics AB; 2013.
100. Hair JJ, Hult G, Ringle C, Sarstedt M. *A Primer on Partial Least Squares Structural Equation Modelling (PLS-SEM)*. Third ed. SAGE; 2022.
101. Chua Y. *A Step-By-Step Guide: PLS-SEM Data Analysis Using SmartPLS 4*. Kuala Lumpur: Researchtree Education; 2023.
102. Sheko A, Braimllari A. Information technology inhibitors and information quality in supply chain management: a PLS-SEM analysis. *Acad J Interdiscip Stud*. 2018;7(3):125–138. doi:10.2478/ajis-2018-0064
103. Heelas L, Soni A, Barker K. Do baseline patient reported outcome measures predict changes in self-reported function, following a chronic pain rehabilitation programme? *Br J Pain*. 2023;17(6):532–545. doi:10.1177/20494637231190190
104. Martinez-Calderon J, Jensen MP, Morales-Asencio JM, Luque-Suarez A. Pain catastrophizing and function in individuals with chronic musculoskeletal pain: a systematic review and meta-analysis. *Clin J Pain*. 2019;35(3):279–293. doi:10.1097/AJP.0000000000000676
105. Craner JR, Lake ES, Bancroft KA, George LL. Treatment outcomes and mechanisms for an ACT-based 10-week interdisciplinary chronic pain rehabilitation program. *Pain Pract*. 2020;20(1):44–54. doi:10.1111/papr.12824
106. Lee H, Hubscher M, Moseley GL, et al. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *Pain*. 2015;156(6):988–997. doi:10.1097/j.pain.0000000000000146
107. Hooten W. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. *Mayo Clin Proc*. 2016;91 (7):955–970. doi:10.1016/j.mayocp.2016.04.029
108. Armbrecht E, Shah A, Schepman P, et al. Economic and humanistic burden associated with noncommunicable diseases among adults with depression and anxiety in the United States. *J Med Econ*. 2020;23(9):1032–1042. doi:10.1080/13696998.2020.1776297
109. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003;163(20):2433–2445. doi:10.1001/archinte.163.20.2433
110. Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *Clin J Pain*. 1997;13(2):116–137. doi:10.1097/00002508-199706000-00006
111. May A. Chronic pain may change the structure of the brain. *Pain*. 2008;137(1):7–15. doi:10.1016/j.pain.2008.02.034

112. Romano JM, Turner JA. Chronic pain and depression: does the evidence support a relationship? *Psychol Bull*. 1985;97(1):18–34. doi:10.1037/0033-2909.97.1.18
113. Stubbs B, Koyanagi A, Thompson T, et al. The epidemiology of back pain and its relationship with depression, psychosis, anxiety, sleep disturbances, and stress sensitivity: data from 43 low- and middle-income countries. *Gen Hosp Psychiatry*. 2016;43:63–70. doi:10.1016/j.genhosppsych.2016.09.008
114. Bisgaard TH, Allin KH, Keefer L, Ananthakrishnan AN, Jess T. Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment. *Nat Rev Gastroenterol Hepatol*. 2022;19(11):717–726. doi:10.1038/s41575-022-00634-6
115. Angst F, Benz T, Lehmann S, et al. Extended overview of the longitudinal pain-depression association: a comparison of six cohorts treated for specific chronic pain conditions. *J Affect Disord*. 2020;273:508–516. doi:10.1016/j.jad.2020.05.044
116. Qiu Y, Ma Y, Huang X. Bidirectional relationship between body pain and depressive symptoms: a pooled analysis of two national aging cohort studies. *Front Psychiatry*. 2022;13:881779. doi:10.3389/fpsyt.2022.881779
117. Zhu Z, Galatzer-Levy IR, Bonanno GA. Heterogeneous depression responses to chronic pain onset among middle-aged adults: a prospective study. *Psychiatry Res*. 2014;217(1–2):60–66. doi:10.1016/j.psychres.2014.03.004
118. Leino-Arjas P, Rajaleid K, Mekuria G, Nummi T, Virtanen P, Hammarstrom A. Trajectories of musculoskeletal pain from adolescence to middle age: the role of early depressive symptoms, a 27-year follow-up of the Northern Swedish Cohort. *Pain*. 2018;159(1):67–74. doi:10.1097/j.pain.0000000000001065
119. Schneider S, Junghaenel DU, Keefe FJ, Schwartz JE, Stone AA, Broderick JE. Individual differences in the day-to-day variability of pain, fatigue, and well-being in patients with rheumatic disease: associations with psychological variables. *Pain*. 2012;153(4):813–822. doi:10.1016/j.pain.2012.01.001
120. Page MG, Gauvin L, Sylvestre MP, Nitulescu R, Dyachenko A, Choiniere M. An ecological momentary assessment study of pain intensity variability: ascertaining extent, predictors, and associations with quality of life, interference and health care utilization among individuals living with chronic low back pain. *J Pain*. 2022;23(7):1151–1166. doi:10.1016/j.jpain.2022.01.001
121. Bondesson E, Larrosa Pardo F, Stigmar K, et al. Comorbidity between pain and mental illness – evidence of a bidirectional relationship. *Eur J Pain*. 2018;22(7):1304–1311. doi:10.1002/ejp.1218
122. Akerblom S, Cervin M, Perrin S, Rivano Fischer M, Gerdle B, McCracken LM. A network analysis of clinical variables in chronic pain: a study from the Swedish Quality Registry for Pain Rehabilitation (SQRP). *Pain Med*. 2021;22(7):1591–1602. doi:10.1093/pm/pnaa473
123. Zhao X, Boersma K, Gerdle B, Molander P, Hesser H. Fear network and pain extent: interplays among psychological constructs related to the fear-avoidance model. *J Psychosom Res*. 2023;167:111176. doi:10.1016/j.jpsychores.2023.111176
124. Gerdle B, Dragioti E, Rivano Fischer M, Ringqvist A. Pain intensity and psychological distress show different associations with interference and lack of life control: a clinical registry-based cohort study of >40,000 chronic pain patients from SQRP. *Front Pain Res*. 2023;4:1093002. doi:10.3389/fpain.2023.1093002
125. Alhowimel AS, Alotaibi MA, Alenazi AM, et al. Psychosocial predictors of pain and disability outcomes in people with chronic low back pain treated conservatively by guideline-based intervention: a systematic review. *J Multidiscipl Healthc*. 2021;14:3549–3559. doi:10.2147/JMDH.S343494
126. Jensen MP. Psychosocial approaches to pain management: an organizational framework. *Pain*. 2011;152(4):717–725. doi:10.1016/j.pain.2010.09.002
127. Windgassen S, Goldsmith K, Moss-Morris R, Chalder T. Establishing how psychological therapies work: the importance of mediation analysis. *J Ment Health*. 2016;25(2):93–99. doi:10.3109/09638237.2015.1124400
128. Alaiti RK, Castro J, Lee H, et al. What are the mechanisms of action of cognitive-behavioral, mind-body, and exercise-based interventions for pain and disability in people with chronic primary musculoskeletal pain? A systematic review of mediation studies from randomized controlled trials. *Clin J Pain*. 2022;38(7):502–509. doi:10.1097/AJP.0000000000001047
129. Shields GS, Spahr CM, Slavich GM. Psychosocial interventions and immune system function: a systematic review and meta-analysis of randomized clinical trials. *JAMA psychiatry*. 2020;77(10):1031–1043. doi:10.1001/jamapsychiatry.2020.0431
130. Kuna K, Szewczyk K, Gabryelska A, et al. Potential role of sleep deficiency in inducing immune dysfunction. *Biomedicines*. 2022;10(9):2159. doi:10.3390/biomedicines10092159
131. Scheffer DDL, Latini A. Exercise-induced immune system response: anti-inflammatory status on peripheral and central organs. *Biochim Biophys Acta Mol Basis Dis*. 2020;1866(10):165823. doi:10.1016/j.bbadis.2020.165823
132. Hysing EB, Smith L, Thulin M, Karlsten R, Bothelius K, Gordh T. Detection of systemic inflammation in severely impaired chronic pain patients and effects of a multimodal pain rehabilitation program. *Scand J Pain*. 2019;19(2):235–244. doi:10.1515/sjpain-2018-0340
133. Wåhlen K, Yan H, Welinder C, et al. Proteomic investigation in plasma from women with fibromyalgia in response to a 15-wk resistance exercise intervention. *Med Sci Sports Exerc*. 2022;54(2):232–246. doi:10.1249/MSS.0000000000002790
134. Maric M, Wiers RW, Prins PJ. Ten ways to improve the use of statistical mediation analysis in the practice of child and adolescent treatment research. *Clinical Child and Family Psychology Review*. 2012;15(3):177–191. doi:10.1007/s10567-012-0114-y
135. Waller G, Turner H. Therapist drift redux: why well-meaning clinicians fail to deliver evidence-based therapy, and how to get back on track. *Behav Res Ther*. 2016;77:129–137. doi:10.1016/j.brat.2015.12.005
136. Angst F, Lehmann S, Sandor PS, Benz T. Catastrophizing as a prognostic factor for pain and physical function in the multidisciplinary rehabilitation of fibromyalgia and low back pain. *Eur J Pain*. 2022;26(7):1569–1580. doi:10.1002/ejp.1983
137. Ghafouri N, Backryd E, Dragioti E, Rivano Fischer M, Ringqvist A, Gerdle B. Effects of interdisciplinary pain rehabilitation programs on neuropathic and non-neuropathic chronic pain conditions - A registry-based cohort study from Swedish Quality Registry for Pain Rehabilitation (SQRP). *BMC Musculoskelet Disord*. 2023;24(1):357. doi:10.1186/s12891-023-06462-2
138. Gilpin HR, Stahl DR, McCracken LM. A theoretically guided approach to identifying predictors of treatment outcome in Contextual Cognitive Behavioural Therapy for chronic pain. *Eur J Pain*. 2019;23(2):354–366. doi:10.1002/ejp.1310
139. Hayes AF, Rockwood NJ. Regression-based statistical mediation and moderation analysis in clinical research: observations, recommendations, and implementation. *Behav Res Ther*. 2017;98:39–57. doi:10.1016/j.brat.2016.11.001