

# 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 <sup>1</sup>, Elena Dragioti <sup>1</sup>, Marcelo Rivano Fischer<sup>2,3</sup>, Åsa Ringqvist<sup>2</sup>

<sup>1</sup>Pain and Rehabilitation Centre, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; <sup>2</sup>Department of Neurosurgery and Pain Rehabilitation, Skåne University Hospital, Lund, Sweden; <sup>3</sup>Department of Health Sciences, Faculty of Medicine, Lund University, Lund, Sweden

Correspondence: Björn Gerdle, Email [bjorn.gerdle@liu.se](mailto: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 ( $\beta$ :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 ( $\beta$ : 0.177–0.233; all  $P<0.001$ ) and changes in fear-avoidance ( $\beta$ : -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

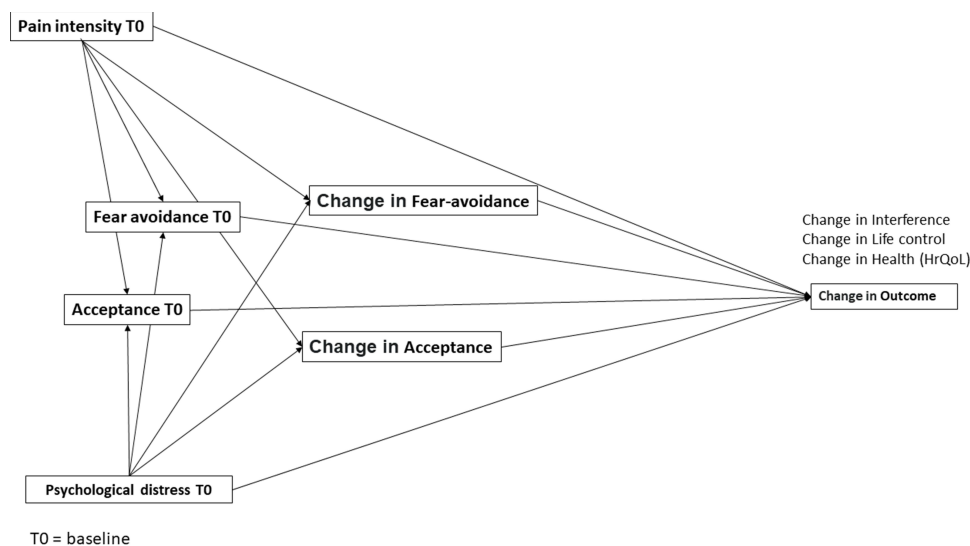
Interdisciplinary pain rehabilitation program (IPRP; also labelled as multimodal rehabilitation, multidisciplinary rehabilitation, biopsychosocial pain rehabilitation, pain management program) is an interdisciplinary treatment (with physical, occupational, psychological, social, and educational components) 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<sup>1</sup> and concepts such as patient-centeredness and strengthening of empowerment, there is no overarching theory that describes the mechanisms of

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.<sup>2</sup> Systematic reviews report significant efficacy for IPRP outcomes,<sup>2</sup> and real-world evidence supports the conclusion that IPRP is an effective intervention.<sup>3–7</sup> IPRP is generally described as an intervention based on Cognitive behavioural therapy (CBT), including Acceptance and commitment therapy (ACT).<sup>8–11</sup> Also, monotherapy with CBT and ACT for chronic pain are associated with significant treatment effects for important clinical variables.<sup>12–18</sup> Some authors conclude that IPRP can be sorted under the same general rubric of CBT for chronic pain.<sup>19</sup> This classification can be questioned since other major components of IPRP (physical activity/exercise and pain education)<sup>2</sup> are also associated with significant treatment effects.<sup>20–24</sup> 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.<sup>25–28</sup> 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.<sup>13,29</sup> In contrast, such studies are rare for IPRP and relatively small.<sup>19,30</sup> 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)<sup>31,32</sup> and the Validation and Application of a patient-relevant core set of outcome domains to assess multimodal PAIN therapy (VAPAIN) initiatives.<sup>33</sup> 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,<sup>5,34</sup> 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.<sup>26,28,35,36</sup> 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.<sup>4,5,34,37</sup> Moreover, a recent systematic review concluded that higher pain intensity and longer pain duration were associated with larger effect sizes for several IPRP outcomes.<sup>38</sup> 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.<sup>13,29,39</sup> CBT has been extended with the fear-avoidance model;<sup>40,41</sup> 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.<sup>29</sup> 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.<sup>42</sup> Catastrophic cognitions may lead to avoidance and hypervigilance for bodily sensations including pain.<sup>42–45</sup> This in turn can lead to heightened pain sensitivity, psychological distress, disuse, and disability.<sup>42</sup> 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.<sup>34,43–46</sup> 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.<sup>1,45,47–56</sup>

ACT is a development in CBT<sup>13</sup> and it focuses on improving psychological flexibility as a process of change to produce outcomes.<sup>57</sup> The ACT theory is based upon the psychological flexibility model which has six intercorrelated facets including an acceptance facet.<sup>13,58</sup> ACT emphasizes awareness and non-judgmental acceptance of pain while identifying valued life directions and teaching skills to support values-based goal setting.<sup>29</sup> Acceptance is essentially an act of allowing according to McCracken.<sup>58</sup> Hence, ACT aims at increasing psychological flexibility in the presence of pain to improve the physical function of the patient.<sup>59–62</sup> Pain acceptance has been defined as living with pain without reacting to, judging or attempting to reduce or avoid it.<sup>63–66</sup> It is an active willingness to engage in meaningful activities despite living with pain.<sup>67</sup> 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.<sup>66,68–73</sup>

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.<sup>13,19,29</sup> 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;<sup>29</sup> similar results have been reported in other studies.<sup>74</sup> Moreover, increased acceptance and psychological flexibility mediated effects of ACT on disability and/or functioning.<sup>29,75</sup> 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.<sup>5,76</sup> There are some reports indicating that women report a more severe clinical presentation<sup>77</sup> while other studies have not described an overall more severe clinical presentation in women.<sup>78</sup> A recent systematic review concluded that no sex/gender differences were found for four outcome variables of IPRP.<sup>79</sup> However, the literature is not in total consensus and several studies report sex/gender differences in IPRP outcomes<sup>77,78,80–82</sup>. Partially different mediators in men and women for the relationships between psychological and demographic variables with chronic pain and physical function have been reported.<sup>83</sup> 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<sup>84</sup> (for a detailed description of SQRP, see<sup>2</sup>). Adult patients (ie,  $\geq 18$  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.<sup>2,85</sup> As mentioned above these programs are often described as based on CBT models including ACT and are administered over several weeks or months.<sup>8–11</sup> 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.<sup>8–11</sup> Since IPRP is a complex intervention, the goals of IPRP are broad and multifactorial and include the patient's goals.<sup>33</sup> Hence, IPRP is evaluated using many outcomes.<sup>9,86,87</sup> 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.<sup>2–5</sup>

## 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;<sup>4,78,88,89</sup> 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

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

(Continued)

**Table 1** (Continued).

<b>Change in Acceptance</b>	Differences in (pre – post): CPAQ8-AE and CPAQ8-PW* Differences in (pre – 12m fu): CPAQ8-AE and CPAQ8-PW* Or Differences in (pre – post): CPAQ8-tot Differences in (pre – 12m fu): CPAQ8-tot
<b>Outcomes</b>	<b>Indicators</b>
<b>Change in Life control</b>	Differences (12m fu -pre) in: MPI-Control SF36-social function
<b>Change in Interference</b>	Differences in: MPI-Pain interference (pre – 12m fu), SF36-physical function (12m fu -pre), SF36-role physical (12m fu -pre)*
<b>Change in HRQoL</b>	Differences (12m fu -pre) in: EQ5D-index EQ-VAS Sf-36-general health
<b>Moderator</b>	<b>Indicator</b>
<b>Sex</b>	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.<sup>90–92</sup> 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).<sup>46,51,52,93</sup> 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).<sup>94</sup> 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.<sup>68</sup> 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.<sup>95–97</sup> 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  $\pm$  one standard deviation ( $\pm 1$  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  $\geq 0.80$ .<sup>98</sup>

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<sup>99</sup>); 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.<sup>100</sup> We followed Hair et al's recommendations for PLS-SEM analyses and presentation of results.<sup>100</sup> 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  $\leq 0.40$  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.<sup>100</sup> Path coefficients (ie, standardized regression coefficients  $\beta$  displaying direct effects) were determined. Using bootstrapping mean  $\pm$  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  $\geq 0.35$  = large effect. For mediating effect sizes, we used Chua's guidelines<sup>101</sup> (ie,  $\beta$ :  $0.01-0.08$  = small effect;  $0.09-0.24$  = medium effect; and  $\geq 0.25$  = large effect).

Multigroup analysis (MGA) was made to analyze moderator effects.<sup>100</sup>

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



## 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,<sup>29</sup> 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		
PR1*	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; CPAQ8-PW PA, pain willingness subscale of CPAQ; physical activity level; PR1, 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

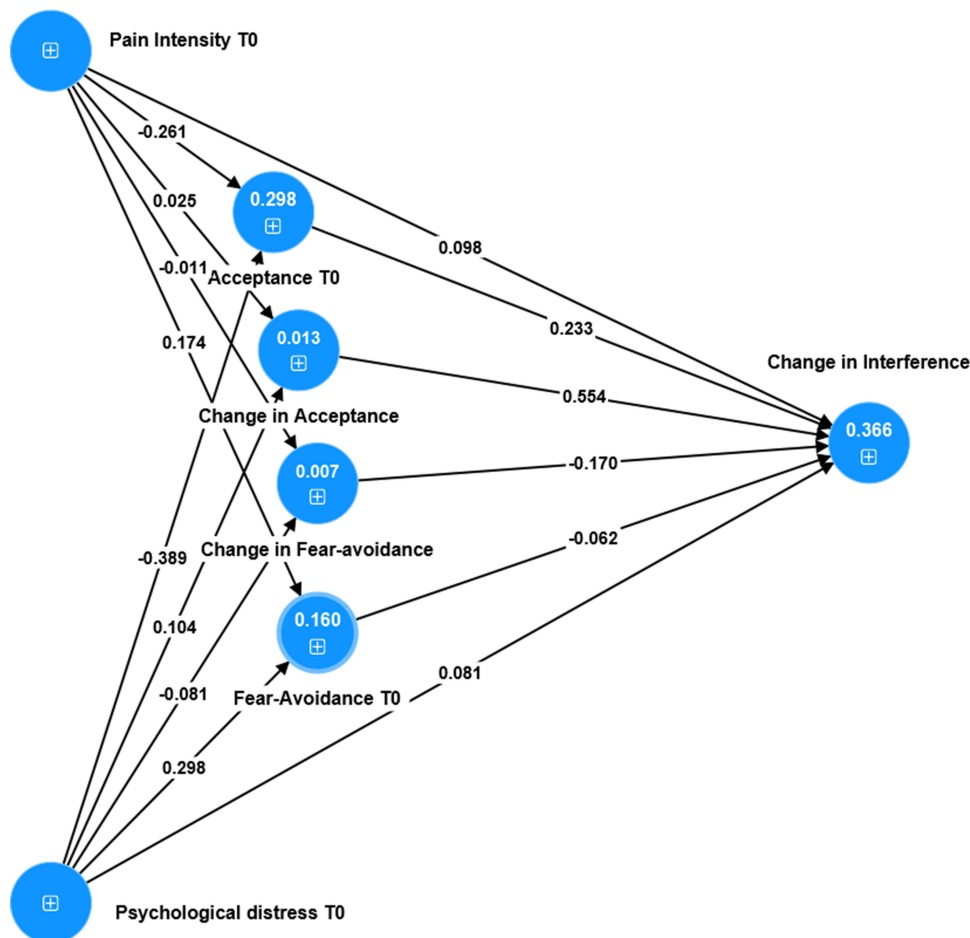
We checked for the possible influence of sex/gender, age, education level and region of birth upon the final indicators of the three latent outcome variables. No indications were found that these variables acted as confounders (VIPpred: 0.00–0.43 and  $|p(\text{corr})|$ : 0.02–0.15 (Supplementary Tables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

## PLS SEM

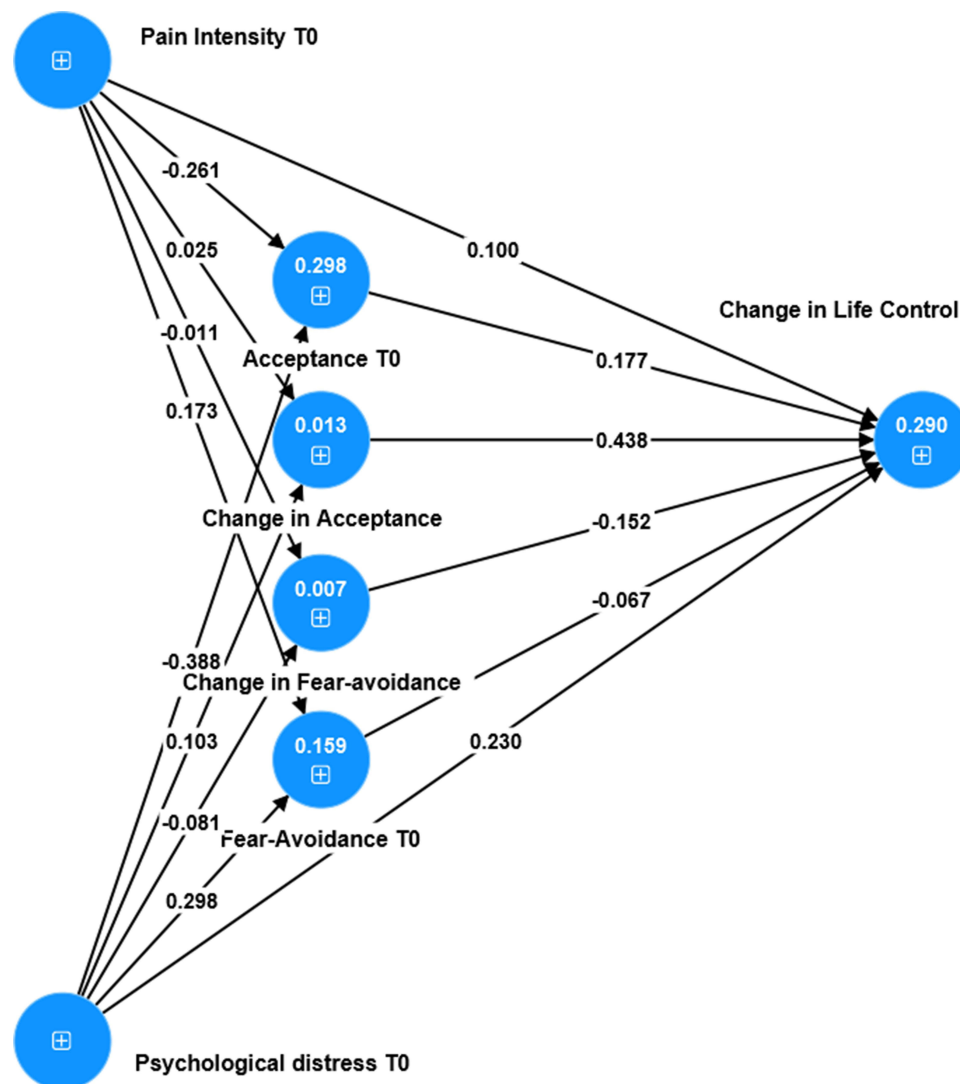
PLS-SEM analyses, guided by the overall hypothesis (Figure 1), explored three models differing in their outcome latent variable: Change in Interference, Life control, or Health-Related Quality of Life (HRQoL). The models achieved robust outcomes, as depicted in Figures 2–4. Table 1 lists the included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

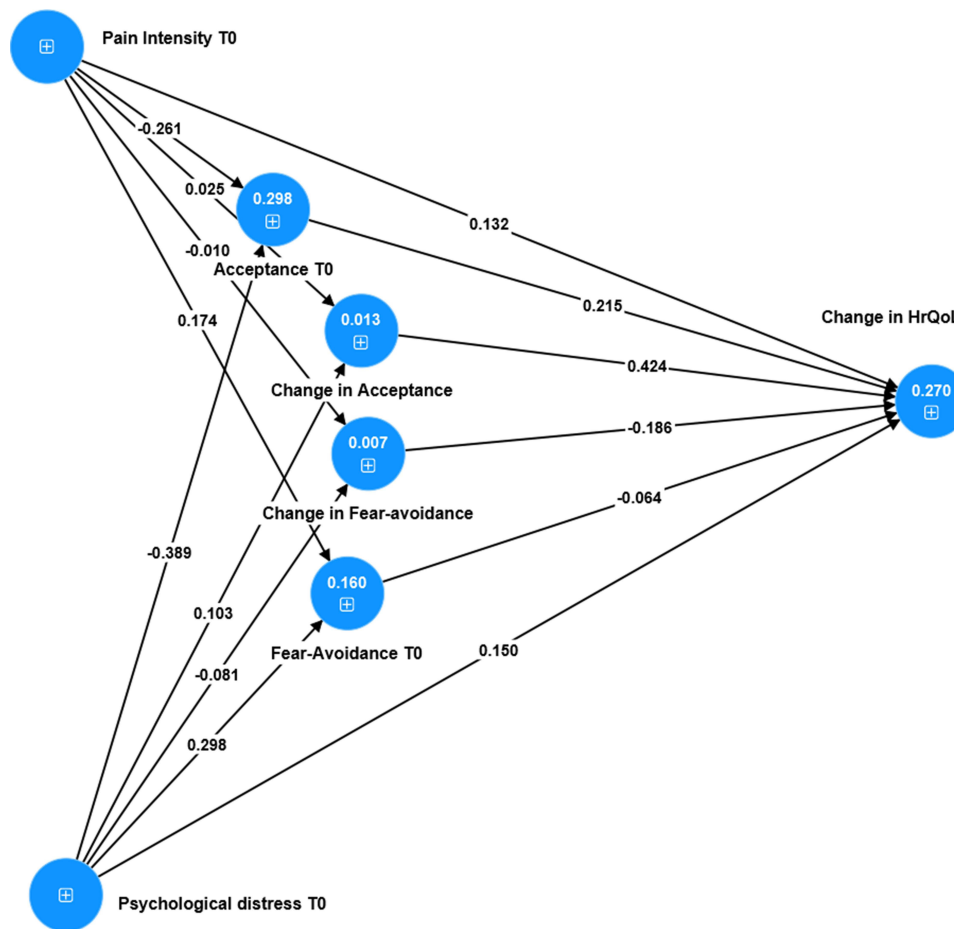
### The Associations Between the Latent Variables (ie, the Inner Models)

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  $\beta$  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 ( $\beta$ :0.424–0.553; all  $P<0.001$ ; small to medium effect sizes) than Change in Fear-Avoidance ( $\beta$ :  $-0.152$ – $-0.186$ ; 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 ( $\beta$ : 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 ( $\beta$ :  $-0.063$  –  $-0.064$ ;  $P$ :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 ( $\beta$ :0.09–0.132; all:  $P<0.001$ ), and Psychological distress T0 ( $\beta$ : 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 ( $\beta$ )

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
<b>Change in Life control</b>						
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
<b>Change in HrQoL</b>						
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;  $\beta$ ) for 8 Mediating Paths in the Three Analyses

Change in Interference	Mean	SD	T Statistics	P values	95% CI	
					Lower	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
<b>Change in Life control</b>						
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
<b>Change in HrQoL</b>						
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  $\rightarrow$  Acceptance T0  $\rightarrow$  Change in outcome (Interference, Life control, and HRQoL) ( $\beta$ :  $-0.069$  –  $-0.091$ ; all  $P < 0.001$ ; small to medium effect sizes). The second most important was Pain intensity T0  $\rightarrow$  Acceptance T0  $\rightarrow$  Change in outcome (Interference, Life control, and HRQoL) ( $\beta$ :  $-0.046$  –  $-0.061$ ; all  $P < 0.001$ ; all small effect sizes). The third significant mediating path was Psychological distress T0  $\rightarrow$  Change in Acceptance  $\rightarrow$  Change in outcome (Interference, Life control, and HRQoL) ( $\beta$ :  $0.044$ – $0.057$ ; 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.<sup>25–28,103</sup> 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 ( $\beta$ :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;<sup>85</sup> 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.<sup>104</sup> 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.<sup>19,30</sup> Like our study, that study found that acceptance and other measures of psychological flexibility were mediators of the outcome pain interference.<sup>19,30</sup> However, our results contrast with results reported in a study investigating the effect of a 10-week ACT-based IPRP.<sup>105</sup> 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.<sup>105</sup> 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.<sup>29</sup> Consistent with this, another systematic review and meta analysis reported that fear was a mediator between pain and disability in longitudinal studies.<sup>106</sup> Furthermore, enhancing pain acceptance and psychological flexibility mediated ACT effects on disability;<sup>29</sup> 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.<sup>13</sup>

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.<sup>30</sup> 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.<sup>12</sup> 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.<sup>4</sup> 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 ( $R^2 = 0.05–0.20$ ).<sup>27</sup> 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.<sup>4,5,34,37,88</sup> Against our theoretical model (Figure 1) it can be argued that psychological distress is a common comorbidity in chronic pain<sup>107,108</sup> 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.<sup>40,107,109–121</sup> Moreover, the intercorrelations between Pain intensity aspects and Psychological distress levels are generally low.<sup>5,122–124</sup> 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.<sup>55</sup> However, a more recent systematic review of longitudinal studies (n=4) from 2021 concluded that baseline fear of movement predict disability.<sup>125</sup> There are strong cross-sectional associations between the components of the fear-avoidance model and disability, pain intensity and psychological distress.<sup>56</sup> 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.<sup>47</sup>

Treatment mechanisms are characterized as specific or non-specific.<sup>29</sup> 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.<sup>126–128</sup> 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).<sup>129–133</sup> 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.<sup>29</sup> 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.<sup>134</sup> 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.<sup>29</sup> Also, intensity, duration, and consistency of the components of IPRP may for various reasons differ between the practice settings and therapists.<sup>2,85,135</sup> 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.<sup>136,137</sup> There are six components in the psychological flexibility model, but the present study was only able to investigate acceptance,<sup>138</sup> 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.<sup>139</sup> 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.

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