# Anxiety, disability, and pain predict outcomes of Complex Regional Pain Syndrome: An 8-year follow-up of a prospective cohort

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**Abstract**

Factors contributing to the varied outcomes of complex regional pain syndrome (CRPS) are not well known. This study aimed to determine whether baseline psychological factors, pain, and disability influence long-term CRPS outcomes. We conducted an 8-year follow-up from a previous prospective study of CRPS outcomes. Sixty-six people diagnosed with acute CRPS were previously assessed at baseline, 6 months, and 12 months and in the current study, 45 were followed up after 8 years. At each timepoint, we measured: signs and symptoms of CRPS, pain, disability, and psychological factors. Mixed-model repeated measures were used to identify baseline predictors of CRPS severity, pain, and disability at 8 years. Predictors of greater CRPS severity at 8 years were female sex, greater baseline disability, and greater baseline pain. Predictors of greater pain at 8 years were greater baseline anxiety and disability. The only predictor of greater disability at 8 years was greater baseline pain. Findings suggest CRPS is best understood from a biopsychosocial perspective, and baseline anxiety, pain and disability may influence the trajectory of CRPS outcomes as far as 8 years later. These variables could be used to identify those at risk of poor outcomes or form targets for early interventions.

Perspective: This paper presents the findings of the first study to prospectively investigate predictors of CRPS outcomes over 8 years. Baseline anxiety, pain, and disability predicted greater CRPS severity, pain, and disability over 8 years. These factors could identify those at risk of poor outcomes or form targets for early interventions.

Complex regional pain syndrome (CRPS) is a condition characterised by persistent pain and a range of sensory, vasomotor, sudomotor, and motor/trophic symptoms [23]. CRPS outcomes are reported to vary substantially across those who develop the condition. Some early studies suggest people make a rapid and spontaneous recovery within 12 months of symptom onset [60,75] while others suggest a chronic disabling condition develops [7,14]. It is not yet well understood why this variation in outcomes occurs, though it is likely that there are factors that differ between people with CRPS that influence the condition [4,71]. Identifying factors that predict CRPS outcomes could make it possible to identify those at risk of worse outcomes, provide insight into the mechanisms that maintain CRPS over time, and (for modifiable risk factors) may form the basis of targeted treatments that could prevent long-term pain and disability.

Although psychological factors do not *cause* CRPS [40], it is proposed in the CRPS literature that they may influence the outcomes of the condition [20]. This proposition arises partly from the well-evidenced influence of psychological factors on other chronic pain conditions [38] and from conceptualisations of pain as a biopsychosocial experience. Further support for the role of psychological factors in CRPS comes from the understanding that CRPS is maintained by physiological protective mechanisms (i.e., inflammation, autonomic arousal, behavioural avoidance and neuroplasticity) [45]. This has led to the hypothesis that the condition represents an aberrant protective response to perceived threat of tissue damage [45,49]. Thus, psychological factors associated with threat perception (i.e., anxiety) could plausibly influence the pathophysiological mechanisms of CRPS and maintain the condition over time.

The few studies investigating prognostic psychological factors in CRPS provide evidence that psychological factors influence CRPS outcomes. For example, early post-operative increases in anxiety and depression scores have been associated with greater CRPS severity at 6 and 12

months [21], while it was previously documented in the present study's cohort that anxiety, pain-related fear, pain, and disability were associated with worse CRPS outcomes over 12 months [4]. Research has not yet prospectively investigated prognostic psychological factors in CRPS beyond 1 year.

This study aimed to determine whether individual differences in psychological factors and modifiable risk factors (pain and disability) were associated with the trajectory of change in pain-relevant outcomes approximately 8 years following CRPS diagnosis.

## Materials and Methods

### Participants

Participants were people with previous CRPS diagnoses who were recruited for an earlier 12-month prospective study. The inclusion criteria for the original study were as follows:

1. Met the 1994 IASP criteria for CRPS [48]; incidentally, 89% of the original cohort and 96% of those who completed the 8-year follow-up also met the Budapest research criteria [20]
2. Had CRPS signs/symptoms for less than 12 weeks
3. Had CRPS Type 1 (symptoms were not attributable to nerve injury)
4. Aged 18 years or over
5. Able to communicate in English
6. Had no previous history of CRPS.

### Procedure

The study was approved by the New Zealand Ministry of Health Northern B Health and Disability Ethics Committee and the Auckland District Health Board (20/NTB/313).

Participants from the original study were contacted and invited to participate in the follow-up between March-September 2021 and informed consent was obtained for each participant. This was a single long-term follow-up that occurred between 7.2 and 9.3 years (mean 8.6 years) following CRPS diagnosis. The sample size was determined by the previous study's cohort [3]. Each participant was sent a questionnaire to complete online or on paper, measuring pain, disability, pain-related fear, pain catastrophising, depression, anxiety, stress, and perceived ownership of the affected limb. Participants were also scheduled for a single 30-minute clinical assessment to conduct a physical examination, assess the signs and symptoms of CRPS and measure body perception disturbance. This occurred in various clinical locations around Auckland, New Zealand, or participants' homes. Participants were given an NZ $20 gift voucher upon completion.

**Measures**

The following measures were collected at the 3 original study time points (baseline, 6 months, and 12 months) and in the 8-year follow-up:

*CRPS Severity*

The presence or absence of the signs and symptoms of CRPS were assessed using the CRPS Severity Score [21]. During the clinical assessment, participants were asked to report whether they experience any of the following CRPS symptoms: colour asymmetry, hair or nail asymmetry, sweating asymmetry, temperature asymmetry, swelling, range of motion asymmetry, motor changes, and allodynia. The primary researcher then assessed each participant's affected and unaffected limbs for the CRPS signs listed above and hyperpathia. A CRPS severity score was calculated by summing the number of symptoms reported by the participant (out of 8) and the number of signs observed by the primary researcher (out of 9) to produce a total score out of 17, with higher scores indicating more severe CRPS. This scale

discriminates between people with and without CRPS and provides greater sensitivity to change compared to measuring CRPS as either present or absent [21]. A reduction of ≥4.9 points is considered the minimal clinically important difference (MCID) in CRPS Severity Scores [22].

*Pain: Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2)*

This 22-item scale asks participants to rate their experience of a range of pain descriptors on a scale from 0 (none) to 10 (worst possible) [15]. Responses across the 22 items are summed and averaged to give a final score between 0 (minimum pain) to 10 (maximum pain). This scale has good convergent validity and excellent internal reliability [15,41]. In the present study, Cronbach's $\alpha$ ranged from .93-.97 across the four time points, indicating that internal consistency was in the 'excellent' range.

*Disability: Pain Disability Index (PDI)*

This 7-item scale asks participants to rate their level of disability across 7 life domains from 0 (no disability) to 10 (total disability) [58]. Scores from each item are summed, with total scores ranging from 0-70, with higher scores representing greater disability. This scale has adequate construct validity and internal reliability [64]. In the present study, Cronbach's $\alpha$ ranged from .80-.95 across the four time points, indicating internal consistency between the 'good' and 'excellent' ranges. A reduction of 7 points for those in the lowest baseline quartile (≤27 points) and 20 points for those in the highest baseline quartile (≥43) is considered the MCID for PDI scores [6].

*Pain-Related Fear: Tampa Scale for Kinesiophobia (TSK-11)*

This 11-item scale asks participants to rate their level of agreement with statements assessing pain-related fear, with items scored from 1 (highly disagree) to 4 (highly agree) [72]. Scores for

the 11 items are summed, and total scores range from 11 (no fear of movement) to 44 (high fear of movement). For the present study, 0 (not applicable) was added to the scale for ease of interpretation for participants no longer experiencing pain. Scores endorsed as not applicable (0) were re-scored as highly disagree (1) for the analyses. This scale has good concurrent and predictive validity and internal reliability [72]. In the present study, Cronbach's $\alpha$ ranged from .83-.92 across the four time points, indicating internal consistency between the 'good' and 'excellent' ranges.

*Pain Catastrophising: Pain Catastrophising Scale (PCS)*

This 13-item scale asks participants to indicate the frequency to which they think about their pain in an anxiety-provoking manner on a scale from 0 (not at all) to 4 (all the time) [63]. Scores from each item are summed, and total scores range between 0 and 52, with higher scores indicating greater catastrophising. This scale has good concurrent validity [53] and good internal reliability [63]. In the present study, Cronbach's $\alpha$ ranged from .96 - .97 across the four time points, indicating that internal consistency was in the 'excellent' range.

*Depression, Anxiety & Stress Scale 21 (DASS-21)*

This 21-item scale comprises three subscales of 7 items that assess depression, anxiety, and stress [42]. Each item ranges from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time). A total score for each subscale is calculated by summing the 7 items with scores ranging from 0 to 21, with higher scores indicating greater distress on that subscale. This scale has good convergent and discriminant validity and good internal reliability [42]. In the present study, Cronbach's $\alpha$ ranged from .83 - .94 for the depression subscale, .84 - .88 for the anxiety subscale, and .90 - .94 for the stress subscale across the four time points, indicating that internal consistency was between the 'good' and 'excellent' range.

*Bath CRPS Body Perception Disturbance Scale*

This 11-item scale asks participants to rate their connection to, and awareness of, their affected limb [36]. Four items assess discrepancies between sensory and visual experiences associated with the affected limb, two assess the desire to amputate the affected limb, and one assesses the participant's mental image of their affected and unaffected limbs. A total score for this scale is calculated by summing all items, with total scores ranging from 0-57 and higher scores indicating greater body perception disturbance. This scale has adequate psychometric properties [37]. A recent study showed that internal consistency improves when item 3 ("how much attention do you pay to your limb in terms of looking at it and thinking about it") is omitted [66]. This was true for the present study, so item three was omitted. The total score for this scale subsequently ranged from 0-47, with higher scores representing greater body perception disturbance. In the present study, Cronbach's $\alpha$ was .61 at baseline, .72 at 6 months, .81 at 12 months, and .41 at 8 years. This provides low confidence in the internal reliability of the 8-year scores but acceptable confidence in the internal reliability of the score at baseline, which was used in the predictor analysis.

*Perceived Ownership of the Affected Limb*

This single-item scale asks participants to score on a 100mm visual analogue scale the degree to which they perceive ownership over the affected limb [50]. The scale is anchored at the left end with "very weak – I feel like the limb doesn't belong to me at all" and at the right end "normal – the same as all my other limbs." The further the participant scored on the scale to the right, the greater the perceived ownership of their affected limb.

*Demographic and Clinical Variables*

The following variables were collected in the original study. They are included in the present analyses to describe the population where appropriate:

1. Demographic characteristics (age, sex, and ethnicity)
2. Affected limb (upper/lower)
3. Duration of CRPS at baseline
4. Treatment use (paracetamol, anti-inflammatories, tricyclic antidepressants, gabapentin, codeine, tramadol, other opioids, prednisone, clonidine patches, vitamin C, interventional procedures (e.g., nerve blocks, infusions), and any of the following interventions: hand therapy/ physiotherapy/occupational therapy, splinting, exercises, mirror therapy, graded motor imagery, psychological therapy, or multi-disciplinary pain management)
5. CRPS "trigger" – coded as either:
    a. Major injury (fracture/crush/other) requiring surgical repair
    b. Fracture not requiring surgical repair
    c. Minor surgical procedure (such as carpal tunnel release)
    d. Soft tissue injury
    e. Minor incident/no known tissue injury.
6. Comorbidities ("please list any current health conditions you experience"), calculated as the number of comorbidities.

**Data Analysis**

Statistical analyses were conducted in SAS SAS/STAT software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). Tests comparing participant demographics and clinical characteristics at baseline between those who did and did not take part in the 8-year follow-up were conducted to determine any biases in the current sample. Independent samples *t*-tests were used to compare the two groups on continuous variables, and Pearson's chi-square tests were used for categorical variables.

Mixed-effects models for repeated measures (MMRM) were used to identify independent variables associated with each of the three outcome variables assessed at the four time points. The outcome variables were: CRPS severity (measured by CRPS scores), pain (measured by the Short-Form McGill Pain Questionnaire 2), and disability (measured by the Pain Disability Index). The PROC MIXED procedure was used. Analyses assumed a random intercept and slope, allowing for individual differences at baseline and recovery trajectory. The within-subject errors were modelled using a first-order autoregressive (co)variance structure. The first-order Kenward-Roger method estimated the denominator degrees of freedom for fixed effects. A restricted maximum likelihood estimation method was selected to use all available data.

For each outcome variable, the following process was used to build each model:

1. Step 1: To determine which independent variables to include in our models, correlations, *t*-tests or analyses of variance were conducted between the independent variables at baseline and the three outcome variables at 8 years. The independent variables tested included age, sex, ethnicity, CRPS trigger, number of comorbidities, and baseline scores for CRPS severity, pain (SF-MPQ-2), disability (PDI), pain-related fear (TSK-11), pain catastrophising (PCS), depression, anxiety, and stress (DASS-21), body perception disturbance, and perceived limb ownership.
2. Step 2: The initial models were built, including the combinations of independent variables that were significant in Step 1. Those variables whose effects did not remain significant once combined were dropped from the model until a parsimonious model was reached. Age and sex were included in the model regardless of statistical significance as recognised covariates.

3. Step 3: The final model is a random intercept and slope model with fixed effects of time and those independent variables that had significant effects on the outcome of interest in Step 2.

We also conducted a sensitivity analysis where the analyses were repeated but included only the individuals who completed the 8 year follow-up ($N = 45$).

Mixed models for repeated measures method is a recommended statistical method for analysing longitudinal data with missing values. One advantage of MMRM is that the models use all available data to analyse correlations between repeated measures within each subject and variance between subjects, including data from subjects with missing observations at some time points. This means the method can handle unbalanced data and the number of observations per subject can vary across time points. This advantage makes MMRM a powerful and efficient tool for analysing longitudinal data and results in more accurate estimation of the effects [25,33,39,70]. Missing data: MMRM assumes missing data at random,[34,62] and assumes the participants' missing data followed the trend of the rest of the group. MMRM analysis uses all observed data at every time point and does not explicitly impute any missing values.

Restricted maximum likelihood (REML) method is a common method used for estimating the variance components in MMRM analysis. REML is often the preferred method over maximum likelihood (ML) because REML provides unbiased estimation of the fixed effects and therefore more accurate estimates of the variance components. Another advantage of REML is that the fixed effects are estimated from the same data used to estimate the variance components and makes it very useful for small-sample settings [29,47,55].

## Results

## Participants

There were 66 people who met the inclusion criteria and completed the baseline assessment. Of these, 64 participants completed the 6-month follow-up, 63 completed the 12-month follow-up, and 45 completed the 8-year follow-up, with 21 participants lost to follow-up (see Figure 1). The principal reason for loss to follow-up across all 3 follow-up time points was the inability to contact the participant via phone, email, or mail. The only missing data was for CRPS Severity Scores, which were missing for 10 participants at the 8-year follow-up as these participants had either left Auckland or were unavailable for an in-person appointment, so the physical examination could not be completed. The demographic and clinical characteristics of the sample are displayed in Table 1. The mean time since CRPS diagnosis was 8.6 years (range 7.2 to 9.3 years).

Analyses compared the baseline characteristics between those who did and did not complete the 8-year follow-up. Chi-square and independent samples *t*-tests showed no significant differences between the two groups on demographics, pain, disability, or psychological functioning. An independent samples *t*-test showed that participants who took part in the present study had greater baseline CRPS severity scores (M = 12.60, SD = 2.17) than those who did not (M = 11.29, SD = 2.69), $t$ (64) = -2.12, $p$ = .038.

## Improvements Over 8 Years

Table 2 displays the mean scores for all variables measured across the four time points. This table shows a general trajectory for improvement over time, with mean scores for CRPS severity, pain, disability, and all psychological factors improving from baseline to 8 years.

## Variables Associated with CRPS Outcomes Over 8 Years

Mixed-effects models for repeated measures were conducted to identify baseline variables associated with the three outcome variables - CRPS severity, pain, and disability - over 8 years. Age and sex were included in all final models as covariates.

**Variables Associated with CRPS Severity**

Based on univariate correlations and previous findings from the same cohort, baseline pain, catastrophising, disability, and body perception disturbance were included in the initial model to predict CRPS severity over 8 years (along with age and gender). The final multivariate model retained the variables that continued to display significant effects when combined and showed that time, sex, pain, and disability significantly predicted CRPS severity. Specifically, CRPS severity reduced with time, while females and those with higher pain and disability scores at baseline had worse CRPS severity scores over the 8 years. The final model is displayed in Table 3, and the effects of pain and disability on CRPS severity are shown graphically in Figure 2a. This figure shows that those in the lowest quartile for baseline pain and disability showed continued improvements in CRPS severity over the 8-year follow-up. In contrast, those in the highest quartile for baseline pain and disability showed a relative plateau of CRPS severity scores after 6 months. Over 8 years, mean reductions in CRPS severity scores indicate that those with low baseline pain met thresholds for minimal clinically important differences (MCID) in CRPS severity (≥4.9 points), while those with high baseline pain never met this threshold [22]. Similarly, over 8 years those with low baseline disability met MCID thresholds for CRPS severity scores while those with high baseline disability did not. Sensitivity analyses including only the individuals who completed the 8-year follow-up demonstrated similar effects though the effects of gender ($p$=0.07) and disability ($p$=0.11) were no longer statistically significant (see Supplementary Table 1).

**Variables Associated with Pain**

Based on univariate correlations and previous findings from the same cohort, baseline CRPS severity, anxiety, disability, and body perception disturbance were entered into initial models (along with age and gender). The final multivariate model retained variables that displayed significant effects when combined and showed that time, anxiety, and disability significantly predicted pain (Table 3). Specifically, pain improved over time, while those with higher anxiety and disability scores at baseline had greater pain over the 8 years. The effect of anxiety and disability on pain are shown in Figure 2b. This shows that those with lower baseline anxiety and disability showed lower levels of pain at baseline and improvements to minimal pain scores over time. In contrast, those with higher baseline anxiety and disability showed a relative plateau in pain scores after 6 months. Sensitivity analyses including only the individuals who completed the 8-year follow-up demonstrated similar effects though the effect of disability ($p$=0.16) was no longer statistically significant (see Supplementary Table 1).

**Variables Associated with Disability**

Based on univariate correlations and previous findings from the same cohort, baseline CRPS severity, pain, pain-related fear, and body perception disturbance were entered into the initial multivariate model. The final model retained variables that displayed significant effects when combined and showed that time and pain significantly predicted disability (Table 3). Specifically, disability reduced over time, while those with higher baseline pain scores were more disabled at 8 years. A non-significant trend was found for an effect of baseline CRPS severity on disability at 8 years, suggesting that those with greater baseline CRPS severity may be more disabled over time. The effect of pain on disability is depicted in Figure 2c. This shows that those in the lowest quartile for baseline pain showed continued improvements in disability over time, to negligible scores by 8 years. In contrast, those in the

highest quartile for baseline pain showed a relative plateau of disability scores after 6 months. Both those with high and low baseline pain met the threshold for a MCID for disability over the 8 years (7 points for lowest quartile and 20 points for highest quartile) [6]. Those with low baseline pain experienced continued reduction in disability so they also met the threshold for a MCID for disability between 6 months and 8 years, while those with high baseline pain did not. Sensitivity analyses including only the individuals who completed the 8-year follow-up demonstrated the same significant effects (see Supplementary Table 1).

## Discussion

This study found that amongst people with CRPS, females and those who were more anxious, disabled, or had greater pain at baseline had worse outcomes over 8 years than those who were less anxious, disabled, or experienced less pain.

Baseline anxiety predicted pain over 8 years. This is consistent with previous research reporting a positive association between anxiety and pain in people with CRPS [5,12,69], and the previous findings from this cohort [4]. Several factors could explain this finding. Anxiety could exacerbate the pro-inflammatory immune response associated with CRPS [30,59], and this may cause peripheral sensitisation and increase pain [10]. Anxiety could also increase levels of circulating catecholamines [74], which may influence pain through peripheral sensitisation or sympathetic-afferent coupling [28]. Anxiety may also impact neuroplasticity, resulting in changes in the grey matter of pain-related brain areas with associated increases in pain [2,56] or central sensitisation and increased pain [31]. Finally, anxiety may be associated with greater pain perception [57]. Anxious individuals show attentional and reasoning biases towards threat-related stimuli, of which pain is one [3,68]. These biases likely direct attention toward pain disproportionately, resulting in greater anxiety levels, leading to an overestimation of the pain

experienced [61]. This influence of anxiety in CRPS supports the hypothesis that the condition represents an aberrant protective response to perceived threat of tissue damage, as psychological factors associated with threat perception influenced CRPS outcomes.

Baseline disability predicted CRPS severity and pain over 8 years. This is consistent with the previously published 12-month outcomes from the same cohort [4]. This finding could result from several factors. Reported disability could reflect immobilisation of the limb [46], as limb immobilisation can generate pain, hyperalgesia, trophic and vascular changes, and temperature abnormalities [54,67]. It is also possible that people who immobilise their limb develop maladaptive cortical changes in the area of representation of the CRPS-affected limb within the somatosensory and motor cortices [32,44] with changes in these brain regions correlating with pain and CRPS symptoms [43,44]. It may also be that the association between disability and future CRPS severity and pain is attributable to a person's perceptions of their condition. CRPS is often not well understood by those who develop it [17], possibly leading to negative perceptions of the condition that could be reflected in the severity of disability ratings. Negative illness perceptions are associated with greater pain in people with CRPS [1] and other pain conditions [19,27]. The influence of disability on CRPS outcomes suggests that the value of intervening early to prevent disability is worthy of exploration.

Baseline pain predicted disability and CRPS severity over 8 years, consistent with the 12-month outcomes of the present cohort [4]. Previous studies predicting CRPS development show that pain is the best predictor of the condition's development [7,11,51], suggesting that pain itself might be a key driver for CRPS. Greater baseline pain is also associated with the development of broader chronic pain conditions [16]. Greater baseline pain may reflect the process of early central sensitisation, a key mechanism in the transition from acute to chronic pain [52], and could contribute to the maintenance and severity of CRPS over time [73]. Pain may

also influence CRPS symptoms via its influence on neurogenic inflammation or autonomic arousal, resulting in swelling and temperature changes. [63] It could also be that pain motivates the behavioural response pattern termed experiential avoidance [24], whereby an individual seeks to avoid pain by immobilising and protecting their painful limb, which could maintain the symptoms of CRPS over time [54,67]. Finally, [46,58] greater baseline pain has been associated with future disability in people with CRPS [5,13]. Possible reasons for this could be explained by Leventhal's self-regulatory model of illness perceptions [9,35], whereby greater pain causes a person to perceive their condition as more severe, resulting in them reporting greater disability. Previous studies have shown that illness perceptions are associated with disability in people with CRPS [1] and other pain conditions [8].

Females experienced greater CRPS severity over 8 years. This is consistent with the previous outcomes within this cohort and broader research suggesting that females are less likely to recover from CRPS [18] and have consistently worse outcomes for all chronic pain conditions [65].

In terms of magnitude of effects, the threshold for MCIDs for the outcome variables of interest, specifically CRPS severity and disability, were met for those lower on the baseline predictor variables while they were not met for those scoring highly on those variables. As MCIDs reflect a threshold at which a change is experienced as relevant by an individual [26], our findings reflect a magnitude of effects that is clinically meaningful. We cannot report whether the criteria for an MCID for pain occurred over time as there are no published MCIDs for the SF-MPQ-2, but we do note those who were higher on the baseline predictor variables had pain scores that were 2-3 points (out of 10) higher at 8 years.

In contrast to the 12-month outcomes of this study [4] and other previous research [5] we did not find a relationship between pain-related fear and CRPS outcomes, specifically pain and disability, at 8 years. It is possible that pain-related fear changed over 8 years due to exposure to activities or specific treatment so that baseline pain-related fear was no longer associated with disability at 8 years. Further, other factors, such as life events, employment status or comorbidities, may influence 8-year disability scores. Additionally, the TSK-11 may not be the ideal tool for CRPS research. Previous research showed that a pictorial measure of pain-related fear aligned better with CRPS outcomes than the TSK-11 [13], so future research should carefully consider the measurement of pain-related fear in the CRPS population.

This research has several implications. First, risk factors influencing CRPS outcomes could be used to identify those in the acute phase of the condition at risk of worse outcomes. These factors may be good targets for intervention as they are modifiable through psychologically informed practice. Such interventions could focus on reducing anxiety, increasing understanding of CRPS, facilitating early mobilisation, and reducing pain. Future research should investigate the efficacy of such an approach. Second, our findings contribute to the understanding of CRPS, supporting the conceptualisation of CRPS as a biopsychosocial condition and the hypothesis that CRPS represents an aberrant protective response to perceived threat of tissues damage, as psychological factors associated with threat detection may contribute to maintaining the condition. Ongoing research to determine the possible mechanisms contributing to this response could elucidate this theory further.

The study has several limitations. Our observational design precludes the determination of cause-and-effect associations between baseline and outcome measures, such associations could be related to a third set of unmeasured variables, such as autonomic activity or inflammation, which would be worth further investigation. It is possible bidirectional effects

between psychological factors and CRPS symptoms occurred by the time of recruitment (up to 12 weeks following symptom onset), which could influence the associations documented. Our sample was small, reducing statistical power to determine the effect of baseline measures on outcome measures. The IASP-Orlando criteria were used to maximise recruitment because this was still in common use at the time of study design, though 96% of the 8-year sample met the stricter IASP-Budapest criteria. Future work would be enhanced by utilising the IASP-Budapest criteria from the beginning to ensure the relevance of findings to modern CRPS samples. It is also a limitation of this study that only 45 of the original 66 participants completed the 8-year follow-up. Analyses showed no differences in demographics, pain, disability or psychological functioning between those who did and did not complete the 8-year follow-up but revealed that those who dropped out had lower CRPS severity scores at baseline than those who did complete the follow-up. On average, non-completers had 1.3 fewer signs or symptoms of CRPS at baseline. Therefore the findings may apply more to those with more severe CRPS. The original sample also might not represent all people with CRPS; for example, we had an under-representation of lower limb CRPS for whom different factors may influence outcomes. It may also be that people with milder symptoms or whose symptoms resolved rapidly did not seek medical care and attain a CRPS diagnosis, preventing their inclusion in the study. However, our findings likely represent those with CRPS who would benefit most from early intervention to avoid worse outcomes. Finally, we did not measure the treatments received by participants after 12 months and did not control statistically for treatments received by each participant during the analyses, as at the 12-month follow-up, no treatments were associated with better outcomes in this cohort [4].

To our knowledge, this is the first study to investigate prognostic psychological factors in a prospective sample of people with CRPS over 8 years. Our findings point towards a pattern

of anxiety, pain, and disability that perpetuates CRPS over time. Such factors could influence physiological processes like inflammation, autonomic activity or neuroplasticity, or operate through behavioural or psychological mechanisms such as immobilisation, beliefs, or attention. These findings support the theory that CRPS represents an aberrant response to perceived threat of tissue damage, as anxiety, which likely primes people to perceive greater threat, was associated with the condition's duration over time. Finally, these findings suggest that interventions targeting anxiety, pain, and disability are worth exploring in future work.

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**Figure Legends**

**Figure 1.**

Flow chart depicting participant recruitment and retention across the four time points (nb data from all 66 participants were included in mixed model analyses).

**Figure 2.**

Line Graphs Demonstrating Associations Between Baseline and Outcome Variables.

*Note.* Figure 2(a) displays the observed mean CRPS severity scores for those with high and low baseline pain and disability scores. Figure 2(b) displays the observed mean pain scores for those with high and low baseline anxiety and disability scores. Figure 2(c) displays the observed mean disability scores for those with high and low pain scores. High scores represent the top quartile, and low scores the bottom quartile. T1 = time 1 (baseline); T2 = time 2 (6 months); T3 = time 3 (12 months); T4 = time 4 (8 years). All figures display means for participants who completed each follow-up: T1 (*N*=66); T2 (*N*=64); T3 (*N*=63); T4 (*N*=45).

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**Table 1.** Demographic and clinical characteristics (N = 66).

| | **M (SD) or N (%)** |
|---|---|
| Age (years) | 47.1 (14.3) |
| Female | 48 (72.7%) |
| Ethnicity/Race | |
| European | 47 (61.8%) |
| Māori | 6 (7.9%) |
| Pacific Islander | 3 (3.9%) |
| Asian | 9 (11.8%) |
| Other | 1 (1.3%) |
| Upper limb affected | 60 (90.9%) |
| CRPS duration at baseline (days) | 62.4 (24.4) |
| Circumstance of CRPS onset | |
| Major injury (fracture/crush/other) with surgery | 16 (24.2%) |
| Fracture without surgery | 20 (30.3%) |
| Minor surgical procedure | 20 (30.3%) |
| Soft tissue injury | 4 (6.1%) |
| Minor incident/no known tissue injury | 6 (9.1%) |

*Note.* CRPS = complex regional pain syndrome.

**Table 2.** Mean (SD) scores for all variables at baseline, 6 months, 12 months, and 8 years.

| | **T1 (N = 66)** | **T2 (N = 64)** | **T3 (N = 63)** | **T4 (N = 45)** |
|---|---|---|---|---|
| CRPS severity | 12.6 (2.7) | 8.8 (3.3) | 6.5 (4.2) | 6.1 (4.4) |
| Pain | 4.1 (2.2) | 2.4 (2.2) | 1.8 (2.2) | 1.5 (1.9) |
| Disability | 36.5 (15.9) | 19.2 (14.8) | 16.5 (16.3) | 14.2 (16.9) |
| Depression | 6.4 (5.5) | 4.8 (6.0) | 4.9 (6.1) | 4.4 (5.2) |
| Anxiety | 5.6 (5.5) | 3.8 (5.0) | 4.3 (5.5) | 4.4 (4.7) |
| Stress | 9.7 (6.5) | 6.6 (6.0) | 6.6 (6.2) | 5.7 (5.7) |
| Catastrophising | 21.0 (15.0) | 13.8 (14.1) | 13.0 (14.9) | 11.5 (13.2) |
| Pain-related fear | 28.6 (7.4) | 23.8 (7.6) | 22.9 (9.0) | 19.8 (7.1) |
| Body perception disturbance | 14.5 (8.2) | 12.5 (9.9) | 10.0 (12.8) | 11.8 (7.3) |
| Perceived limb ownership | 63.6 (30.9) | 74.2 (28.6) | 77.9 (30.6) | 74.0 (30.9) |

*Note.* CRPS = complex regional pain syndrome. T1 = time 1 (baseline); T2 = time 2 (6 months); T3 = time 3 (12 months); T4 = time 4 (8 years).

**Table 3.** Results of mixed models for repeated-measures analyses to identify baseline variables associated with CRPS severity, pain, and disability over 8 years.

| | CRPS Severity | | | Pain | | | Disability | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Est** | **95%CI** | **Pr>F** | **Est** | **95%CI** | **Pr>F** | **Est** | **95%CI** | **Pr>F** |
| Follow-up visit (ref=T4) | | | <.001** | | | <.001** | | | <.001** |
| T1 (baseline) | 6.07 | 4.95-7.19 | | 2.72 | 2.19-3.26 | | 23.39 | 18.99-27.80 | |
| T2 (6 months) | 2.43 | 1.31-3.55 | | 0.89 | 0.34-1.42 | | 4.48 | 0.10-8.86 | |
| T3 (12 months) | 0.63 | -.05-1.78 | | 0.29 | -0.27-0.84 | | 0.98 | -3.68-5.63 | |
| Age at onset (years) | 0.03 | -.01-0.06 | .183 | -0.01 | -0.03-0.02 | .657 | 0.08 | -0.09-0.25 | .349 |
| Sex (female vs male) | 1.21 | 0.01-2.40 | .047* | 0.44 | -.32-1.19 | .250 | 1.25 | -4.22-6.73 | .649 |
| Pain at T1 | 0.35 | 0.35-0.66 | .030* | | Not included | | 3.02 | 1.89-4.16 | <.001** |
| Disability at T1 | 0.06 | 0.01-0.11 | .011* | 0.04 | 0.1-0.06 | .007** | | Not included | |
| Anxiety at T1 | | Not included | | 0.13 | 0.06-0.21 | <.001** | | Not included | |
| CRPS severity at T1 | | Not included | | | Not included | | 0.91 | -0.14-1.97 | 0.088 |

*Note.* T = Time; DV = dependent variable; Est = parameter estimate; 95%CI=95% confidence interval; Pr>F = probability of F statistic; CRPS = complex regional pain syndrome; *$p$<.05; **$p$<.01. Predictor variables that were not included in the final model for the listed outcome variable are labelled not included.

**Figure 1.**

Flow chart depicting participant recruitment and retention across the four time points (nb data from all 66 participants were included in mixed model analyses).

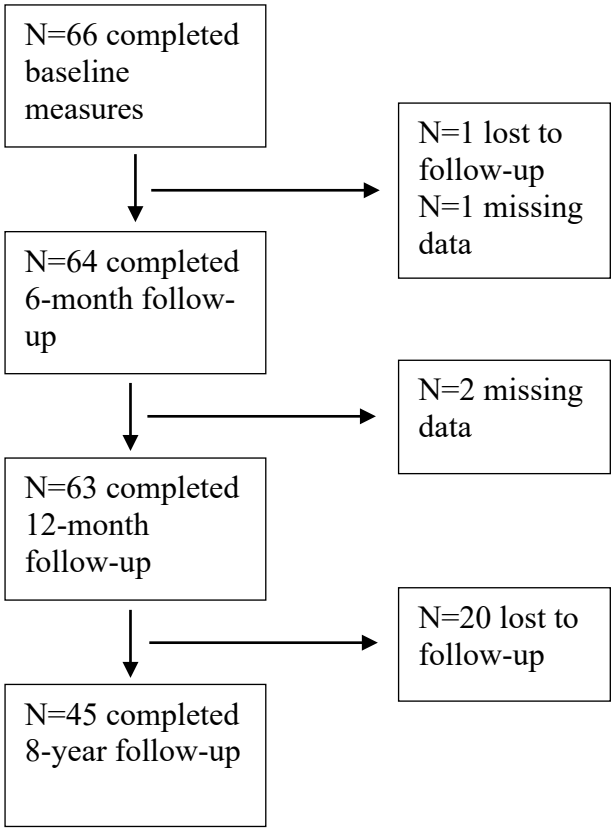
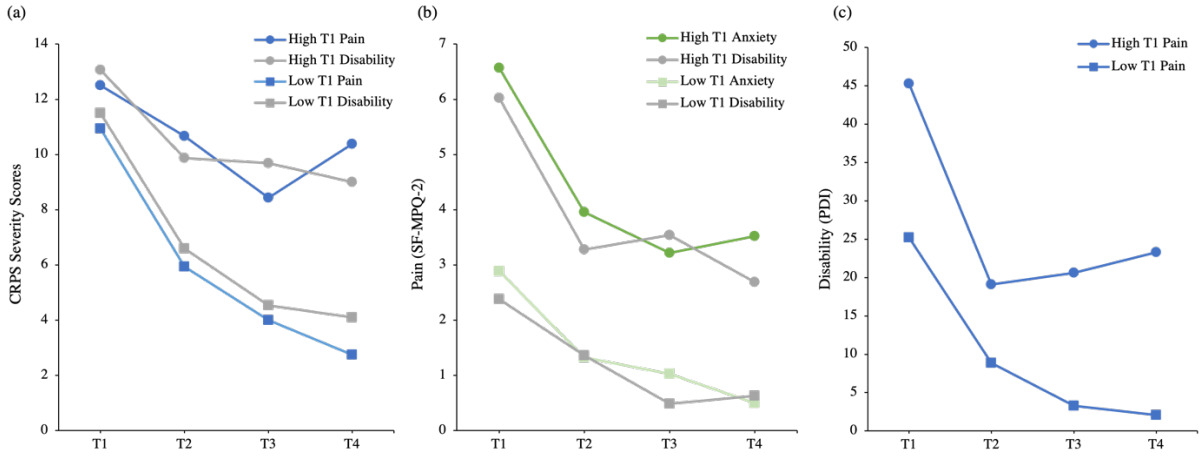


**Figure 2.**

Line Graphs Demonstrating Associations Between Baseline and Outcome Variables.



**Supplementary Table 1.** Results of sensitivity analyses: Mixed models for repeated-measures analyses to identify baseline variables associated with CRPS severity, pain, and disability over 8 years for the N=45 participants who completed the 8 year follow-up.

| | CRPS Severity | | | Pain | | | Disability | | |
|---|---|---|---|---|---|---|---|---|---|
| | Est | 95% CI | Pr > F | Est | 95% CI | Pr > F | Est | 95% CI | Pr > F |
| Follow up visit (ref=4) | | | <.001* | | | <.001* | | | <.001* |
| Visit 1 | 6.40 | 5.25-7.55 | | 2.60 | 2.05-3.16 | | 22.30 | 17.54-27.05 | |
| Visit 2 | 2.69 | 1.56-3.82 | | 0.97 | 0.41-1.52 | | 5.24 | 0.45-10.02 | |
| Visit 3 | 0.29 | -0.93-1.51 | | 0.34 | -0.21-0.88 | | 2.26 | -2.58-7.11 | |
| Age at onset | 0.02 | -0.03-0.07 | 0.41 | <0.001 | -0.04-0.03 | 0.88 | 0.11 | -0.11-0.32 | 0.33 |
| Gender (female vs male) | 1.31 | -0.11-2.72 | 0.07† | 0.40 | -0.57-1.37 | 0.41 | 4.32 | -2.46-11.10 | 0.21 |
| Baseline Pain | 0.54 | 0.16-0.92 | 0.01* | | Not included | | 3.72 | 2.25-5.19 | <.001* |
| Baseline Disability | 0.04 | -0.01-0.10 | 0.11 | 0.02 | -0.01-0.06 | 0.16 | | Not included | |
| Baseline Anxiety | | Not included | | 0.16 | 0.06-0.26 | <0.001* | | Not included | |
| Baseline CRPS Severity | | Not included | | | Not included | | 0.40 | -1.20-2.01 | 0.61 |

*Note.* T = Time; DV = dependent variable; Est = parameter estimate; 95%CI=95% confidence interval; Pr>F = probability of F statistic; CRPS = complex regional pain syndrome; *p<.05; **p<.01. Predictor variables that were not included in the final model for the listed outcome variable are labelled “not included”.