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Mechanisms of change in cognitive functional therapy: A longitudinal mediation analysis of the RESTORE clinical trial for disabling chronic low back pain

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ABSTRACT

Chronic low back pain (CLBP) is an urgent global health priority given its high prevalence and impact as the leading cause of disability. While several efficacious treatments exist, most have modest effects. Improving outcomes requires a better understanding of treatment mechanisms to enable optimisation. This study explored the mechanisms of cognitive functional therapy (CFT), a biopsychosocial intervention with large, durable effects for adults with disabling CLBP. A longitudinal mediation analysis was performed on data from the RESTORE multisite clinical trial comparing CFT (n = 327) to usual care (n = 165). Mediators (self-efficacy, fear, catastrophising, and pain intensity) were specified based on behavioural theories underlying CFT and previous research. The joint mediation of treatment effects on disability (Roland Morris Disability Questionnaire) and pain intensity (numerical rating scale), were examined using a counterfactual framework for mediation analysis. As hypothesised, earlier changes in self-efficacy, fear, catastrophising, and pain intensity mediated improvements in disability at the end of treatment and at 12-month follow-up, explaining up to 61 % of the effect. Similarly, self-efficacy, fear, and catastrophising mediated the effect of CFT on pain intensity, explaining up to 62 % of the effect. Results are consistent with previous CLBP mediation research highlighting self-efficacy, fear, and catastrophising as likely common mechanisms among effective biopsychosocial treatments. CFT demonstrates large, durable, and clinically important effects on these mechanisms. Findings shed light for clinicians and researchers on how CFT works, although the role of other mechanisms such as movement changes requires further exploration, along with research analysing how different treatment components activate these mechanisms.

1. Introduction

Improving the treatment of people with chronic low back pain (CLBP) is an urgent global health priority, given its high prevalence and impact as the leading cause of disability (Buchbinder et al., 2020). An obvious, yet challenging, task is to implement more high value care, while decreasing low value guideline inconsistent care, which still proliferates (Foster et al., 2018; Hartvigsen et al., 2022). Another challenge is to improve the effectiveness of existing treatments, since the large evidence base for physical (Hayden et al., 2021), psychological (Williams et al., 2020), pharmacological (Cashin, Wand, et al., 2023) and multidisciplinary interventions (Kamper et al., 2014) still reveals

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mostly modest effect sizes for guideline based care.

Boosting effect sizes requires a better understanding of how treatments for CLBP work, enabling optimal targeting of their active components. Mediation studies explore treatment mechanisms by breaking down the causal impact of a treatment exposure (e.g. exercise) on an outcome (e.g. disability) into the direct effects of the exposure and its indirect effects via a theoretically plausible mediator (e.g. self-efficacy) (Mittinty & Vansteelandt, 2020). Mediation research on CLBP treatments has yielded mixed findings; however, there is evidence that improvements in pain self-efficacy, pain catastrophising, and pain-related fear (described subsequently as self-efficacy, catastrophising, and fear) mediate the effects of non-pharmacological interventions on pain and disability (Alaiti et al., 2022; Murillo et al., 2022). It is possible that these could be common factors, or shared mechanisms by which all effective biopsychosocial pain treatments work. Yet most mediation research is marred by methodological weaknesses, including the widespread use of cross-sectional designs, underpowered samples, and uncontrolled confounders, prompting calls for well-designed longitudinal mediation studies to better investigate treatment mechanisms (Cashin, McAuley, et al., 2023; Lee et al., 2016; Murillo et al., 2022).

One CLBP treatment that warrants well-designed mechanistic research is cognitive functional therapy (CFT), given its recently demonstrated large, clinically important, durable, and cost-efficient effects in reducing disability, pain, and distress in people with CLBP (Kent et al., 2023; Thiveos et al., 2024). This physiotherapist led treatment has three core components – making sense of pain, exposure with pain control, and lifestyle change (O'Sullivan et al., 2018). The biopsychosocial theoretical framework underlying CFT is an integration of behavioural psychology, pain neuroscience, and physical therapy functional rehabilitation, which has been elaborated previously (Caneiro et al., 2022; O'Sullivan et al., 2018). It draws strongly on the fear-avoidance (Vlaeyen & Linton, 2012) and common sense (Bunzli et al., 2017) models to propose that when people are empowered to reconceptualise their pain and confront feared/avoided movements/activities within an individualised experiential learning framework, they relinquish pain-provocative safety behaviours, thereby reducing pain and disability. Based on this framework, hypothesised mechanisms leading to reduced disability during CFT include improvements in self-efficacy (e.g. confidence gained through re-engaging with movement/activity and understanding pain), catastrophising (e.g. pain makes sense and is reconceptualised as less threatening), fear (e.g. confronting feared movements promotes habituation and disconfirmation of threat predictions), and pain (e.g. relinquishing trunk bracing and breath-holding reduces pain associated with tension/loading).

Supporting this hypothesis, ideographic studies using qualitative and single case designs suggest these four mediators are important process variables in CFT, although they may operate differently across individuals (Bunzli et al., 2016; Caneiro et al., 2017, 2019; Wernli et al., 2022). While a previous CFT mediation study (N = 206) found self-efficacy was the only significant mediator out of seven investigated, interpretation was limited by missing data (33–59 %) and the assessment of mediators at the same timepoint, rather than preceding the outcomes, highlighting the need for a CFT mediation study that overcomes these limitations (O'Neill et al., 2020).

The present study aimed to respond to this call and investigate whether CFT works in a way that is consistent with its behavioural science underpinnings, using a counterfactual approach for mediation that accounts for temporal ordering, confounding and interrelated variables. We hypothesised that self-efficacy, catastrophising, and fear would jointly mediate the effect of CFT on pain intensity. We also expected these variables, plus pain intensity, to jointly mediate the effect of CFT on disability.

2. Methods

2.1. Study registration and ethical approval

The RESTORE trial was approved by Curtin University Human Research Ethics Committee (HRE2018-0062, Feb 6, 2018) and prospectively registered in the Australian New Zealand Clinical Trials Registry, ACTRN12618001396213. All participants provided informed consent before study entry. The RESTORE published trial protocol (Kent et al., 2019) included the prospective plans for investigation of the role of pain-related cognitions and emotions in mediating the treatment effect on disability. As shown in Table A.1, this study is reported in accordance with the AGReMA guideline for reporting mediation analyses of randomised trials (Lee et al., 2021).

2.2. Design

The RESTORE trial investigated CFT with or without biofeedback compared to usual care for the treatment of CLBP and included 492 patients in 20 primary care clinics in Perth and Sydney, Australia (Kent et al., 2023). Participants were randomly allocated to one of three groups (1:1:1 allocation ratio): usual care, CFT only, or CFT plus biofeedback. However, for the purposes of this study the CFT and CFT plus biofeedback groups were combined to maximise precision and simplify the analysis, as there were neither statistically nor clinically meaningful difference between the two CFT groups on the primary and secondary outcomes (Kent et al., 2023), or on lifting or bending kinematics (Au et al., 2025b; Chang et al., 2024). We adopted the counterfactual framework to strengthen causal interpretation (Vanderweele, 2015), as recommended in recent reviews of the mediation literature in pain (Murillo et al., 2022).

2.3. Participants

The RESTORE trial included adults (aged ≥18 years) with CLBP lasting more than 3 months, who had sought care from a primary care clinician at least 6 weeks previously, had an average back pain intensity of at least 4 on a 0–10 numerical pain rating scale, and had at least moderate pain-related interference with normal work or daily activities, measured by item 8 of the 36-item Short Form Health Survey (Ware et al., 2000). Exclusion criteria were serious spinal pathology (e.g., fracture, infection, or cancer), any medical condition that prevented being physically active, being pregnant or having given birth within the previous 3 months, inadequate English literacy for the study's questionnaires and instructions, a skin allergy to hypoallergenic tape adhesives, surgery scheduled within 3 months, or an unwillingness to travel to trial sites. All participants in the RESTORE trial were included in the current study.

2.4. Intervention and control

Participants in the usual care group received treatment that their health providers recommended, or the participant chose, with 38 % receiving care from a health-care practitioner (Kent et al., 2023). Examples of usual care included physiotherapy, massage, chiropractic care, medicines, injections, or surgical interventions. Participants were informed that "If you are allocated to the usual care group, your treatment options can be any of those offered by the health-care professionals you would normally choose to see in the community. In other words, you will choose your treatment, but it is not determined by the study or funded by it." Only usual care participants were paid a small reimbursement (AU$30–110) for their time completing key follow-up questionnaires. Complete details of all treatment that control participants reported receiving is available in appendix (p.14) of the published trial paper (Kent et al., 2023). It was not possible to blind participants to group allocation (CFT vs usual care).

Participants in the two CFT groups received up to seven treatment sessions over 12 weeks plus a booster session at 26 weeks from a physiotherapist trained to a competency standard for CFT. A flexible clinical-reasoning approach was used to identify movements, postures, pain-related cognitions, emotions, and lifestyle factors contributing to each individual's ongoing pain and disability. This approach informed an individualised treatment plan orientated to the patient's goals, with three broad components (O'Sullivan et al., 2018). The first component was making sense of pain. This involved a reflective process drawing from the patient's own story and examination findings to help them reconceptualise their low back pain from a biopsychosocial perspective that reduced its threat value. The second component was exposure with control, a process of functional behavioural change and pain control through graded exposure to movements and activities nominated as painful, feared, or avoided. The third component was lifestyle change. When relevant, this included coaching to develop healthy lifestyle behaviours such as paced physical activity based on preference, adopting healthy sleep and dietary habits, stress management, and social engagement. Physiotherapists in the CFT plus biofeedback group may have used movement sensor data for assessment, movement retraining, and for providing biofeedback**.** A more detailed description of the CFT and CFT plus biofeedback interventions with example cases can be found in the appendix (pp.2-9) of the published trial paper (Kent et al., 2023) and previous publications (O'Sullivan et al., 2018).

2.5. Measurements

Outcomes were collected using participant-reported outcome measures rather than blinded outcome assessors, at baseline, 3, 6, 13, 26, 40 and 52 weeks using online data capture, with the exception of fear which was not collected at 6 weeks per the trial protocol (Kent et al., 2019). Only data collected at baseline, 6, 13 and 52 weeks were used in this study because they were relevant to the mediation models of interest, which are described below and depicted in Fig. 1.

2.5.1. Outcomes

The two outcomes considered in this study were i) disability, measured as pain-related activity limitation using the Roland Morris Disability Questionnaire (RMDQ) (Roland & Morris, 1983), and ii) pain intensity (mean of three numeric rating scales – *now*, *most severe during past 14 days*, and *average during past 14 days*, on a 0–10 scale). While the pre-planned analysis only included disability as an outcome, we repeated the analysis with pain intensity as an outcome given its importance to patients (Hush et al., 2009). The mediation of the treatment exposure on each outcome was evaluated at i) 13 weeks, and ii) 52 weeks after randomisation.

2.5.2. Mediators

The pain-related cognitions and emotions pre-specified as potential mediators were pain catastrophising (Pain Catastrophising Scale short form (Darnall et al., 2017), 3-item 0–12 scale, measured at baseline, 6 and 13 weeks), pain self-efficacy (Pain Self-Efficacy Questionnaire (Nicholas, 2007), 0–60 scale, measured at baseline, 6 and 13 weeks) and fear of movement (physical activity subscale of the Fear Avoidance Beliefs Questionnaire (Waddell et al., 1993), 0–24 scale, measured at baseline and 13 weeks; note, this was not measured at 6 weeks). Pain intensity (average during past 14 days, 0–10 scale, measured at baseline, 6 and 13 weeks) was also evaluated as a potential mediator of the treatment effect for disability. All instruments used to measure these mediators are well-validated for use in CLBP (Darnall et al., 2017; Farrar et al., 2001; Nicholas, 2007; Waddell et al., 1993), with excellent psychometric properties exceeding recommended thresholds for mediation analysis (e.g. Cronbach's alpha and test-retest reliability >0.60) (Mansell et al., 2013).

2.5.3. Confounders

We selected potential confounders of the mediator-outcome association from measures available using the disjunctive clause criterion (VanderWeele & Shpitser, 2011). Potential confounders of the mediator-outcome association controlled for in statistical analyses included: sex (Bartley & Fillingim, 2013), age (Underwood et al., 2007), Body Mass Index (Heuch et al., 2024), university education (yes/no) (Underwood et al., 2007), duration of care-seeking (weeks) (Chen et al., 2018), length of current episode (weeks) (Bondesson et al., 2023), and use of pain medications (yes/no) (Shahidi et al., 2021).

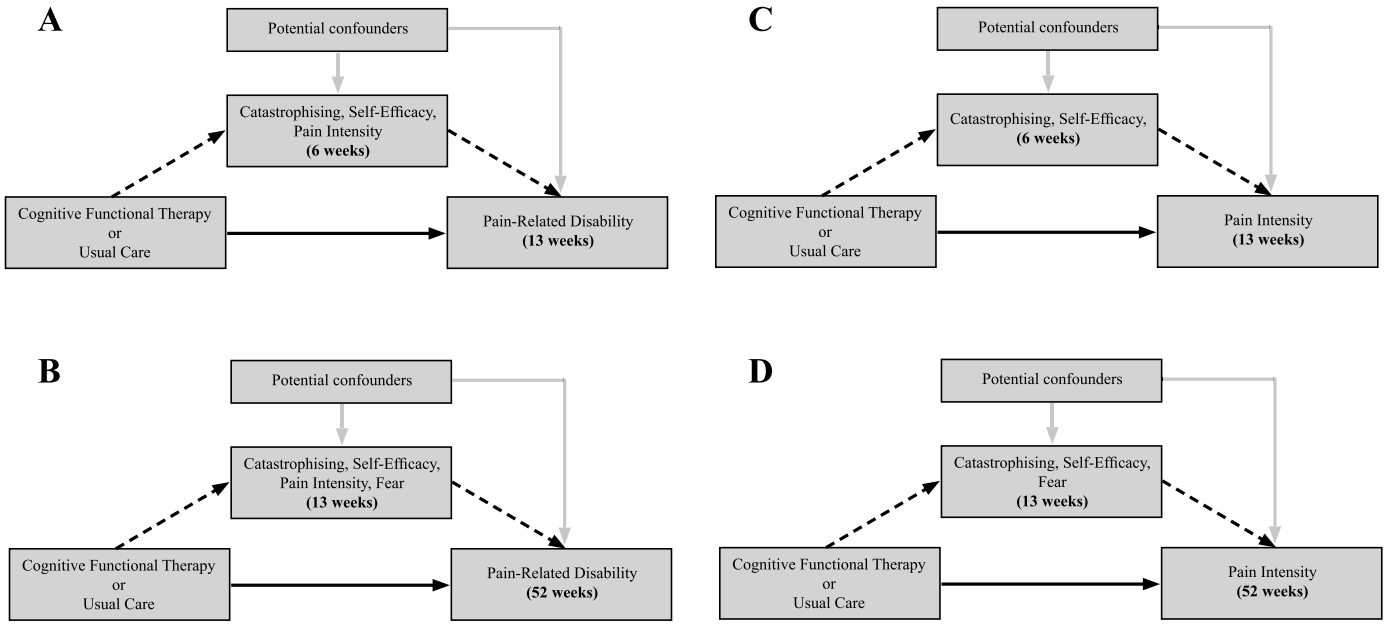

Fig. 1. Diagram of assumed causal relations between Cognitive Functional Therapy or Usual Care on pain-related disability and pain intensity through potential mediators at 13 weeks (A and C) and 52 weeks (B and D) after randomisation. Potential confounders are sex, age, Body Mass Index, university education, duration of care-seeking, length of current episode, taking medication for LBP.

2.6. Causal model and assumptions

Fig. 1 displays the assumed causal models and effects of interest for the longitudinal mediation analyses in this study. Mediation analysis decomposes the total effect of the intervention on a given outcome into an indirect effect (exerted through the mediator(s)) and a direct effect (effect exerted through mechanisms other than the mediator(s)). Mediation of the treatment effect of CFT compared to usual care on i) pain-related disability and ii) pain intensity was evaluated immediately post-intervention (13 weeks) via mediators measured at 6 weeks, and at longer term (52 weeks) by mediators measured at 13 weeks. We evaluated mediators jointly for each outcome at both 13 and 52 weeks, but also evaluated single-mediator models, whilst acknowledging that omission of other mediators in single mediator models will overestimate the indirect effect of that single mediator. In total, 16 mediation analyses were performed. We performed sensitivity analyses for unmeasured confounding, as detailed below.

2.7. Statistical analysis

All statistical analyses were performed in R version 4.3.0 (The R Foundation) and CMAverse (version 0.1.0) (Shi et al., 2021) for mediation analysis. Analytical code is provided in Table A.2. We estimated the intervention–mediator and mediator–outcome effects and corresponding uncertainty estimates for each of the potential mediators using two linear regression models: the mediator model and the outcome model. Both the mediator and the outcome model included baseline values of the outcome and mediator(s) (Landau et al., 2018) in addition to confounders, and a treatment group*mediator interaction term in outcome models.

Herein, we used the regression-based counterfactual framework (Valeri & Vanderweele, 2013; VanderWeele & Vansteelandt, 2014) for mediation analysis, whereby causal effects were estimated via counterfactual imputation (described below), and the standard errors of the causal effects estimands were estimated using bootstrapping (n = 1000). We were interested in the following causal effects: the total effect (TE), composed of the total natural indirect effect (TNIE) plus the pure natural direct effect (PNDE), and the percentage mediation, calculated as $\frac{TNIE}{TNIE+PNDE} \times 100$. For the percentage mediation, a value of 0 % means no mediation, whilst 100 % means complete mediation. The point estimate along with the 95 % confidence interval (CI) was estimated considering each mediator individually, and jointly as parallel mediators.

Since CMAverse does not handle missing data, we used mice (version 3.16.0) (van Buuren & Groothuis-Oudshoorn, 2011) for multiple imputation of missing data. We used chained equations to generate 20 separate imputed data sets for analysis, utilising all variables in each model, then pooling the results. Statistical significance of the causal effects was determined by a non-zero crossing of the 95 % CI.

Lastly, we conducted sensitivity analyses to understand if our TNIE estimates were likely to be biased by unmeasured confounding variables to the mediator-outcome relationship. We assumed no confounding of the intervention-mediator and intervention-outcome effects as the intervention was randomly allocated. We used the mediational E value (Mathur et al., 2018; Smith & VanderWeele, 2019; VanderWeele & Ding, 2017) to assess the minimum magnitude of association between an unmeasured confounder and the mediator, conditional on the current included set of confounding variables, that would shift the TNIE value to zero. E values were considered small (risk ratio <1.25), medium (risk ratio 1.25 to <2), and large (risk ratio ≥2) (Cashin, Lee, et al., 2023). A greater E value magnitude implies stronger confounder associations must be present to explain away the effect and hence, a greater E value magnitude implies less likelihood of there being an unmeasured confounding.

3. Results

Four hundred and ninety-two participants were recruited to the RESTORE trial and provided baseline data for this study, with 165 randomly assigned to usual care and 327 to the two CFT arms. The mean age of participants was 47.3 years (SD 15.2, range 19–87), and 292 (59 %) were female. Participants had high levels of pain-related disability (mean RMDQ 13.5 [SD 5.2]), pain intensity (mean of three NRS scales 6.2 [SD 1.6]), fear of movement (mean FABQ-PA 14.8 [SD 5.6]), and catastrophising (mean PCS 13-item version 24.6 [SD 12.5]) and moderate levels of self-efficacy (mean PSEQ 34.8 [SD 13.8]). Four hundred and five participants (82 %) provided data at the 6-week follow-up, 418 (85 %) provided data at the 13-week follow-up and 397 (81 %) provided data at the 52-week follow-up. The proportion of cases with an incomplete data set for mediation models ranged from 26 % to 29 % over the 16 mediation models tested. Descriptive statistics for all measures used in this study are reported in Table 1.

3.1. Mediation analysis

The decomposition of the causal effects of CFT compared with usual care on pain and disability outcomes at 13 and 52 weeks are reported in Table 2.

Table 1
Descriptive statistics for outcomes, mediators and confounders.

	Usual Care (n=165)	CFT (n=327)
	Mean (SD) [missing]	Mean (SD) [missing]
Outcomes		
Pain-related disability (RMDQ)		
Baseline	13.5 (5.4)	13.6 (5.1)
13 weeks	11.9 (6.2) [14.5 %]	7.3 (6.3) [15.3 %]
52 weeks	11.3 (6.8) [23.0 %]	6.3 (6.5) [17.4 %]
Pain intensity (NRS: mean of 3 scales)		
Baseline	6.3 (1.5)	6.1 (1.6)
13 weeks	5.9 (2.0) [15.2 %]	4.3 (2.2) [15.6 %]
52 weeks	5.6 (2.1) [23.6 %]	3.9 (2.5) [17.4 %]
Mediators		
Pain Catastrophising (PCS - 3 item)		
Baseline	5.9 (3.2)	6.1 (3.1)
6 weeks	5.8 (2.7) [20.6 %]	4.5 (2.7) [16.2 %]
13 weeks	5.8 (3.2) [16.4 %]	3.7 (2.6) [16.5 %]
Pain self-efficacy (PSEQ)		
Baseline	36.4 (13.5)	34.0 (13.9)
6 weeks	35.5 (14.6) [24.2 %]	42.0 (13.8) [21.4 %]
13 weeks	37.2 (14.0) [18.2 %]	45.8 (13.0) [16.5 %]
Fear of movement (FABQ-PA)		
Baseline	14.9 (5.6)	14.7 (5.6)
13 weeks	14.4 (5.9) [16.4 %]	8.2 (6.1) [16.5 %]
6 weeks	NA	NA
Pain intensity (NRS: last 14 days)		
Baseline	5.8 (1.5)	5.8 (1.7)
6 weeks	5.9 (1.9) [20.6 %]	4.6 (2.2) [16.2 %]
13 weeks	5.5 (2.1) [15.2 %]	3.8 (2.2) [15.6 %]
Potential Confounders measured at baseline		
	Mean (SD) {range}<%>	Mean (SD) {range}<%>
Female Sex	n=98 <59.4>	n=194 <59.3>
Age, years	47.7 (16.3)	47.1 (14.6)
Body Mass Index	28.3 (6.1)	28.9 (6.6)
University education	89 <54.3>	154 <47.5>
Duration of care-seeking, years	4.0 {1.3 – 10.0}	4.0 {1.0 – 11.0}
Length of current episode, years	5.0 {1.8 – 10.0}	5.0 {1.4 - 11.0}
Taking any LBP medication	91 <55.8>	207 <64.9>

Note. CFT = cognitive functional therapy. FABQ-PA=Fear Avoidance Beliefs Questionnaire physical activity subscale. LBP = low back pain. NRS = numeric rating scale. PCS=Pain Catastrophising Scale. PSEQ=Pain Self-Efficacy Questionnaire. RMDQ = Roland Morris Disability Questionnaire. SD=Standard deviation. NA=Not available since FABQ-PA was not administered at 6 weeks.

Table 2
Causal effects decomposition of effects of cognitive functional therapy compared with usual care on pain and disability outcomes at 13 and 52 weeks.

Outcomes	Mediators[a]	Intervention-mediator effect (95 %CI)	Mediator - outcome effect (95 %CI)	Total effect[b] (95 %CI)	Total natural indirect effect[c] (95 %CI)	Pure natural direct effect[d] (95 %CI)
Disability at 13 weeks[e]	Pain 6 weeks	−1.22 (−1.59, −0.85)	0.64 (0.18, 1.09)	−5.04 (−5.88, −4.08)	−1.04 (−1.65, −0.57)	−4 (−4.94, −2.95)
	Catastrophising 6 weeks	−1.57[f] (−2.03, −1.11)	0.68 (0.4, 0.96)	−5.19 (−5.9, −4.1)	−1.27 (−1.8, −0.71)	−3.91 (−4.71, −2.79)
	Self-efficacy 6 weeks	7.42[f] (5.07, 9.77)	−0.19 (−0.25, −0.14)	−4.9 (−5.95, −4.1)	−1.93 (−2.51, −1.23)	−2.97 (−4.15, −2.28)
	Joint effect 6 weeks	**NA**	**NA**	**−5.04 (-5.98, -4.17)**	**−2.34 (-2.99, -1.53)**	**−2.69 (-3.79, -1.86)**
Disability at 52 weeks[g]	Pain 13 weeks	−1.73 (−2.13, −1.32)	1.33 (0.84, 1.81)	−5.45 (−6.7, −4.52)	−2.12 (−2.85, −1.43)	−3.33 (−4.7, −2.35)
	Catastrophising 13 weeks	−2.19[h] (−2.66, −1.72)	0.65 (0.32, 0.99)	−5.53 (−6.67, −4.49)	−1.63 (−2.49, −1.01)	−3.9 (−5.18, −2.6)
	Fear 13 weeks	−6.3[h] (−7.55, −5.05)	0.39 (0.24, 0.54)	−5.59 (−6.65, −4.43)	−2.58 (−3.41, −1.79)	−3.01 (−4.26, −1.65)
	Self-efficacy 13 weeks	9.48[h] (7.42, 11.54)	−0.24 (−0.31, −0.17)	−5.69 (−6.69, −4.57)	−2.63 (−3.5, −2)	−3.06 (−4.01, −1.81)
	Joint effect 13 weeks	**NA**	**NA**	**−5.35 (-6.63, -4.38)**	**−3.27 (-4.17, -2.43)**	**−2.08 (-3.49, -0.97)**
Pain intensity at 13 weeks[e]	Catastrophising 6 weeks	−1.53[f] (−2.11, −0.95)	0.25 (0.11, 0.38)	−1.67 (−2.07, −1.29)	−0.46 (−0.69, −0.28)	−1.21 (−1.58, −0.82)
	Self-efficacy 6 weeks	7.54[f] (5.5, 9.57)	−0.05 (−0.08, −0.03)	−1.62 (−2.03, −1.3)	−0.59 (−0.85, −0.39)	−1.03 (−1.44, −0.63)
	Joint effect 6 weeks	**NA**	**NA**	**−1.69 (-1.99, -1.29)**	**−0.73 (-0.99, -0.51)**	**−0.96 (-1.28, -0.53)**
Pain intensity at 52 weeks[g]	Catastrophising 13 weeks	−2.26[h] (−2.73, −1.79)	0.21 (0.07, 0.36)	−1.72 (−2.16, −1.27)	−0.64 (−0.98, −0.31)	−1.08 (−1.63, −0.58)
	Fear 13 weeks	−6.43[h] (−7.46, −5.39)	0.1 (0.04, 0.16)	−1.72 (−2.12, −1.26)	−1.01 (−1.3, −0.64)	−0.71 (−1.18, −0.23)
	Self-efficacy 13 weeks	9.44[h] (7.06, 11.81)	−0.07 (−0.09, −0.04)	−1.68 (−2.21, −1.39)	−0.89 (−1.27, −0.63)	−0.79 (−1.32, −0.43)
	Joint effect 13 weeks	**NA**	**NA**	**−1.77 (-2.13, -1.33)**	**−1.09 (-1.51, -0.74)**	**−0.68 (-1.12, -0.14)**

Note. All effects are unstandardised.
[a] Mediation effects at 13 weeks did not include Fear as a mediator, since this was not measured at 6 weeks.
[b] Total effect = Total natural indirect effect + Pure natural direct effect.
[c] Total natural indirect effect is the indirect effect evaluated at the level of the treatment group (as outcome models include a treatment group*mediator interaction), i.e. the effect of treatment on the outcome when the level of the mediator is changed due to treatment, assuming that participants were in the treatment group when they were evaluated on the outcome.
[d] Pure natural direct effect is the direct effect of treatment if the participants had the mediator level under the control condition.
[e] Observed data n = 355 for 13 week outcome models.
[f] Slight differences in Intervention-mediator effects across mediation models for 13-week outcomes are because of the differences in imputation values and bootstrapped samples used for calculating the point estimates and the 95 %CI.
[g] Observed data n = 359 for 52 week outcome models.
[h] Slight differences in Intervention-mediator effects across mediation models for 52-week outcomes are because of the differences in imputation values and bootstrapped samples used for calculating the point estimates and the 95 %CI.

3.1.1. Effect of intervention on the mediators

When compared to usual care, CFT was more effective at improving pain intensity, catastrophising, and self-efficacy at 6 weeks. Specifically, CFT reduced pain intensity more than usual care by −1.22 (95 % CI -1.59, −0.85) points, reduced catastrophising by up to −1.57 (95 % CI -2.03, −1.11) points, and increased self-efficacy by up to 7.54 (95 % CI 5.5, 9.57) points (Table 2).

CFT was more effective than usual care at improving pain intensity, catastrophising, fear, and self-efficacy at 13 weeks. Specifically, CFT reduced pain intensity more than usual care by −1.73 (95 % CI -2.13, −1.32) points, reduced catastrophising by up to −2.26 (95 % CI -2.73, −1.79) points, reduced fear by up to −6.43 (95 % CI -7.46, −5.39) points, and increased self-efficacy by up to 9.48 (95 % CI 7.42, 11.54) points (Table 2).

3.1.2. Effect of mediators on the outcomes

All mediators at 6 weeks were significantly associated with disability and pain intensity outcomes at 13 weeks. Similarly, all mediators at 13 weeks were significantly associated with disability and pain intensity outcomes at 52 weeks (Table 2).

3.1.3. Indirect effects

For disability, the indirect effects of all mediators measured were statistically significant, jointly and individually, as estimated in separate models (Fig. 2, Table 2). The proportion of the total effect of CFT on disability at 13 weeks explained jointly by all 3 mediators measured at 6 weeks was 46.5 % (95 % CI 30.5 %, 59.3 %). The proportion of the total effect of CFT on disability at 52 weeks explained jointly by all 4 mediators measured at 13 weeks was 61.1 % (95 %CI 43.4 %, 79.7 %).

For pain intensity, the indirect effects of all mediators measured were also statistically significant, jointly and individually, as estimated in separate models (Fig. 2, Table 2). The proportion of the total effect of CFT on pain intensity at 13 weeks explained jointly by both mediators measured at 6 weeks was 43.3 % (95 %CI 31.0 %, 62.8 %). The proportion of the total effect of CFT on pain intensity at 52 weeks explained jointly by all 3 mediators measured at 13 weeks was 61.6 % (95 %CI 42.1 %, 90.9 %).

3.1.4. Sensitivity analysis

Fig. 3 reports the mediational E values of our sensitivity analyses performed for the indirect effects reported presently. The mediational E values for the TNIEs for the outcome of disability ranged from 1.57 to

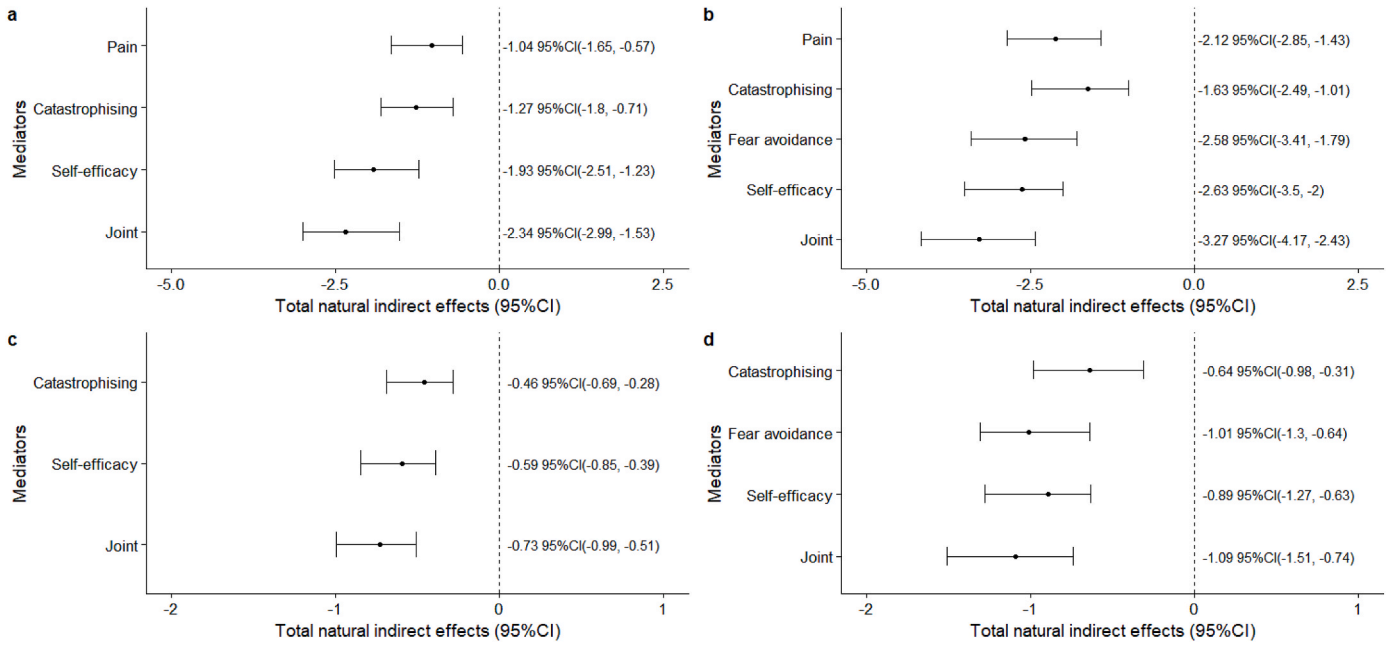

Fig. 2. Point estimate with error bars as 95 % confidence intervals of the total natural indirect effects, for the outcomes of (a) disability at 13 weeks, (b) disability at 52 weeks, (c) pain intensity at 13 weeks, and (d) pain intensity at 52 weeks, derived from separate models for individual and joint mediation.

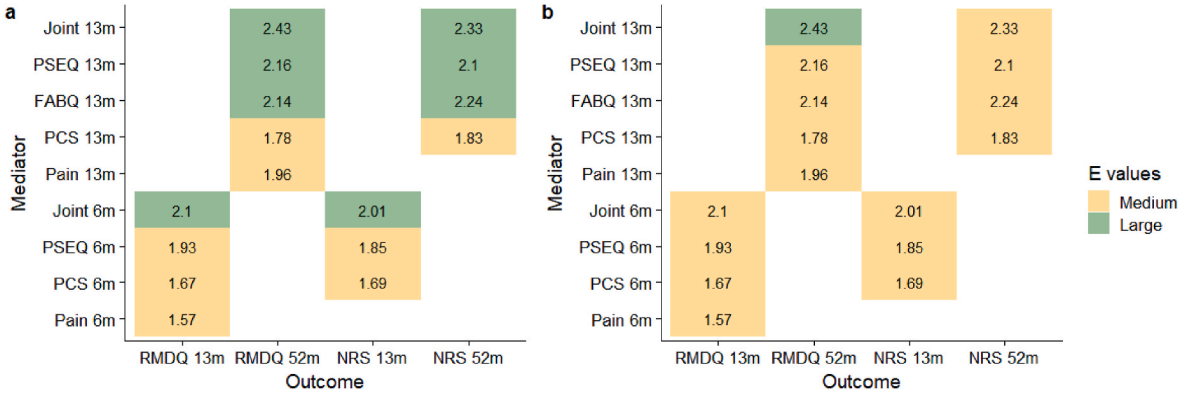

Fig. 3. Mediation E values for the total natural indirect effect on the risk ratio scale for the (a) point estimate and (b) the lower bound of the 95 % confidence interval.

2.43. The E values for the TNIEs for the outcome of pain ranged from 1.69 to 2.33. Since these are medium to large, our results suggest that the statistically significant indirect effects reported here were robust against potential confounding by unmeasured variables on the mediator-outcome relationship.

4. Discussion

This study aimed to elucidate possible treatment mechanisms of CFT for CLBP using longitudinal mediation analysis within the RESTORE clinical trial. Understanding how CFT and other biopsychosocial interventions work is important for improving their efficacy and implementation. We hypothesised that earlier treatment-related improvements in pain, self-efficacy, catastrophising, and fear would mediate improvements in disability because these mediators are consistent with the theoretical underpinnings of CFT and many other biopsychosocial interventions. Similarly, we expected earlier improvements in self-efficacy, catastrophising, and fear to mediate improvements in pain intensity. The results confirmed these hypotheses, with significant indirect temporal effects for all mediators when considered both individually and jointly. Therefore, these proposed mediators seem to have important causal effects in improving pain and disability immediately after CFT treatment and at one-year follow-up.

These results provide further support for the putative therapeutic mechanisms underlying CFT, which focuses on empowering individuals to self-manage their back pain by making sense of it and confronting feared/avoided movements to engage with valued activities (Caneiro et al., 2022; O'Sullivan et al., 2018). This is consistent with previous studies that, taken together, have found evidence for improvements in these mediators being important process variables in CFT, using experimental (Caneiro et al., 2017, 2019), qualitative (Bunzli et al., 2016; Klem et al., 2024), and clinical trial (O'Neill et al., 2020) designs. This study provides stronger evidence of these mechanisms since it is embedded within a high quality multisite clinical trial with large effects (Kent et al., 2023), and measured mediators at timepoints prior to outcomes (O'Neill et al., 2020).

Together, these mediators accounted for 47 % and 61 % of improvements in disability in the short and long term, and 43 % and 62 % of improvements in pain intensity in the short and long term, respectively. Non-specific factors such as expectancy, therapeutic alliance, and

various clinician/patient/setting characteristics, common across all biopsychosocial treatments for CLBP, may account for some of the remaining effects as they exert influence on clinical outcomes that are difficult to quantify and are often operationalised as placebo/nocebo effects in pain research (Miller et al., 2021; Rossettini et al., 2018). They are also the subject of a longstanding debate in psychological research about whether intervention effects stem from these common factors or features unique to specific interventions (Cuijpers et al., 2019; Mulder et al., 2017). A limitation of this study is the omission of these variables from the mediation models due to a large number of missing values for expectancy and inability to measure therapeutic alliance in the usual care control since care seeking was not ubiquitous in this arm of the trial.

Our findings echo previous mediation research in CLBP and musculoskeletal pain more broadly. Systematic reviews show that the dominant mediators of reduced disability in various biopsychosocial treatments – including exercise, psychological therapies, mind-body interventions, and multimodal therapies – are improvements in self-efficacy, catastrophising, and fear (Alaiti et al., 2022; Lee et al., 2016; Mansell et al., 2013; Murillo et al., 2022). As noted by others (Burns, 2016; Burns et al., 2023), one interpretation of this is that these are common factors (e.g. similar to therapeutic alliance and expectancy) by which all effective biopsychosocial CLBP treatments work, although other unmeasured specific factors may explain further variance. Notwithstanding this, the present study is the first to provide robust causal evidence of these mechanisms in CFT, which is a requirement for advancing treatment mechanism research in CLBP and more generally (Cuijpers et al., 2019; Mansell et al., 2014; Murillo et al., 2022).

Further research (e.g. component studies) is needed to explore which CFT intervention components modify these mediator variables and how. Existing qualitative and replicated single case studies of CFT have highlighted the likely importance of experiential learning in improving these mediators, particularly self-efficacy (Bunzli et al., 2016; Caneiro et al., 2019; Wernli et al., 2022). For example, CFT's use of movement based behavioural experiments to test and reconceptualise patients' pain beliefs, provides a powerful vehicle for gaining confidence to move and re-engage with valued activities (Caneiro et al., 2019). The integration of changes in cognition (e.g. 'bending is safe', 'my pain makes sense', 'I'm in control'), emotion (e.g. less fear of bending), and behaviour (e.g. decreased muscle guarding and increased engagement with rewarding activities involving bending) is consistent with the fear avoidance (Vlaeyen & Linton, 2012) and common sense (Bunzli et al., 2017) models underpinning CFT. Patients have described this experiential learning as empowering and motivating (Bunzli et al., 2016; Klem et al., 2024; Wernli et al., 2022), which may partly explain the durable effects of CFT given the importance of self-discovery and empowerment in facilitating chronic pain recovery (Devan et al., 2018; Toye et al., 2020). Again, this is speculative and would require further research using dismantling or additive trial designs (Kazdin, 2007); for example, comparing variants of CFT with and without hypothesised active components such as behavioural experiments, lifestyle advice, or reflective pain reconceptualisation dialogue.

Different intervention components are also likely to influence multiple mechanisms, some of which were not explored in this study. For example, beyond influencing psychological variables, components of CFT such as behavioural experiments (exposure with control) are likely to have resulted in changes in movement behaviours. Previous idiographic studies have found that restoring natural non-protective movements is related to positive clinical outcomes in CFT (Wernli et al., 2020, 2022). This suggests movement change might account for some of the total effect not explained here, although there is covariance between movement change and some of the psychological mediators we measured (Au, Smith, O'Sullivan, et al., 2025; Chang et al., 2025). We were not able to test this in RESTORE because movement data were only collected for CFT participants. However, improvements in forward bending velocity were strongly related to improvements in pain and disability at the within-person level in CFT participants (Chang et al., 2024). Therefore, exploring whether movement behaviours mediate CFT effects would be a valuable future step in exploring its mechanisms.

Addressing these unresolved questions has important clinical implications for what is prioritised in treatment and how therapeutic mechanisms are best targeted. For example, is catastrophising best reduced through pain education or exposure? An enduring challenge in answering such questions is the likely reciprocal effect between mediators and outcomes (Burns et al., 2023). Our study did not examine reciprocal effects, although RESTORE clinicians qualitatively report such impressions (Simpson, Holopainen, Schütze, O'Sullivan, Kent, et al., 2024). In contrast to a gradual upward spiral of reciprocal effects, an experimental CFT study found rapid, concurrent change in mediators and outcomes for some people (Caneiro et al., 2019). Meanwhile, a longitudinal qualitative study of RESTORE participants suggested heterogeneity in patients' journeys towards self-management (Klem et al., 2024). These findings point towards multiple possible recovery pathways through CFT, although this cannot be discerned from the current nomothetic (group-level) mediation study. Clinically, the heterogeneity of recovery pathways is assumed in CFT, as reflected in its individualised, person-centred approach using a multidimensional clinical reasoning framework to tailor treatment. This is highlighted in previous case studies (Caneiro et al., 2019; Kent et al., 2023; O'Sullivan et al., 2018).

It is noteworthy that pain mediated CFT's effect on disability in the current study. This finding is comparatively rare (Alaiti et al., 2022; Lee et al., 2016; Murillo et al., 2022), notwithstanding isolated previous examples (Mansell et al., 2016; Wicksell et al., 2010). One explanation for this could be the explicit targeting of pain control strategies during exposure tasks in CFT, using body relaxation, movement control, and elimination of pain-provocative safety-seeking behaviours. Another unique finding was the mediating effect of self-efficacy, catastrophising, and fear on pain reduction. Systematic reviews have not generally found these to be mechanisms for pain reduction (Alaiti et al., 2022; Lee et al., 2016; Murillo et al., 2022). Our significant finding for pain intensity is likely related to the comparatively large effects observed across most outcomes, including pain, in the RESTORE data.

This investigation was designed to meet reporting guidelines and used a longitudinal design with a counterfactual framework for analysis. The RESTORE trial was *a priori* powered to detect clinically important treatment group differences in the primary outcome (Kent et al., 2023), although no formal sample size calculation was performed for this mediation study. We attempted to minimise potential bias due to missing data by use of multiple imputation, but results may be biased due to missingness that is dependent on mechanisms unrelated to the variables used in our models.

The analysis considered joint mediation, mediator-outcome confounding, and assessed sensitivity to unmeasured confounding. However, the temporal separation of nine months between mediators and outcomes heightens the possibility that the mediator-outcome relationships may have been influenced by other factors, and our models did not differentiate the treatment effect occurring after treatment versus that occurring during treatment. Furthermore, the use of an analytic approach prioritising joint mediation precluded accurate estimation of single mediator effects, which should be interpreted cautiously, as omission of other mediators increases the risk of Type I error. Further research is needed using recently developed techniques that disentangle the indirect effects of correlated multiple mediators (Loh et al., 2022). Another limitation is that jointly the mediators in this study did not completely explain the treatment effects observed in the RESTORE trial. This suggests further research is needed to understand how CFT works by testing other plausible mediators, such as changes in movement behaviours, physical activity, stress, anxiety, mood and sleep, which are all targeted in CFT. Exploring the meditating effect of beliefs about back pain consequences is also recommended, given the targeting of these beliefs in CFT and their strong mediation effects in another recent biopsychosocial intervention (Cashin, Lee, et al., 2023). Furthermore, the

conditionality of mediation effects found here should be tested with moderated-mediation studies. For example, we recently reported that baseline disability moderates the effect of CFT (Hancock et al., 2024). Therefore, it is possible that such baseline characteristics may impact the indirect effect of mediators described here.

Addressing these questions will help refine the CFT intervention and its wider implementation. This includes optimising the training of physiotherapists to deliver it (Simpson, Holopainen, Schütze, O'Sullivan, Smith, et al., 2024), and the integration of this physiotherapist-led treatment into interdisciplinary CLBP care (Vaegter et al., 2021). This study is an important step in this process as it elucidates some of CFT's treatment mechanisms, which are shared with many other biopsychosocial interventions. The strength with which CFT influences these common pathways suggests further exploration of this intervention may yield insights that can improve back pain treatments more broadly.

CRediT authorship contribution statement

Robert Schütze: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Bernard Liew:** Writing – original draft, Methodology, Formal analysis, Data curation. **J.P. Caneiro:** Writing – review & editing, Supervision, Conceptualization. **Peter O'Sullivan:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Peter Kent:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Mark Hancock:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Jan Hartvigsen:** Writing – review & editing, Conceptualization. **Kieran O'Sullivan:** Writing – review & editing, Investigation, Conceptualization. **Alison McGregor:** Writing – review & editing, Conceptualization. **Amity Campbell:** Writing – review & editing, Funding acquisition, Conceptualization. **Stephanie Attwell:** Writing – review & editing, Investigation. **Anne Smith:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing interest

Peter O'Sullivan, JP Caneiro, Mark Hancock, Robert Schütze, and Kieran O'Sullivan have received speaker fees for lectures or workshops on the biopsychosocial management of pain, including on CFT, from special interest physiotherapy groups and multi-disciplinary audiences of clinicians and researchers.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2025.104853.

Data availability

De-identified individual participant data and the data dictionary can be made available by request to the corresponding author. Access will require submission of a protocol, approval by our review committee, and the signing of a data access agreement. Potential access will be for the period beginning 9 months and ending 36 months following publication of this article. Analytical code is provided in Table A.2. This research was preregistered with an analysis plan in the Australian New Zealand Clinical Trials Registry, ACTRN12618001396213.

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