**Abstract**

Cognitive Functional Therapy (CFT) is a physiotherapist-led individualised intervention for people with people with non-specific chronic low back pain (CLBP), involving biopsychosocial pain education, graded movement exposure and lifestyle coaching. A multicentre randomised controlled trial (RCT), including 206 participants with CLBP in Ireland, supported CFT's effectiveness for reducing disability, but not pain, compared to a group exercise and education intervention. In this study, causal mediation analysis was used to determine whether the effect of CFT on disability and the lack of effect on pain (relative to a group exercise and education intervention) is mediated by certain psychological and lifestyle factors. Hypothesised mediators measured were pain self-efficacy, stress, fear of physical activity, coping, depression, anxiety, and sleep, at 6 months. The outcomes measured were functional disability and pain intensity at 12 months. This causal mediation study shows that the majority of benefit of CFT (relative to a group exercise and education intervention) for disability is due to increasing pain self-efficacy. CFT did not improve the majority of the hypothesised mediators (stress, fear of physical activity, coping, depression, anxiety and sleep) and these mediators were not associated with either disability or pain. Unfortunately, the proportion of missing data in this study is substantial and these findings can only be considered hypothesis-generating. Therefore, future research should examine replicating the results of this study to verify the role of self-efficacy and other proposed mediators (e.g. stress, coping, sleep, fear) on clinical outcomes.



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# Examining what factors mediate treatment effect in chronic low back pain: a mediation analysis of a Cognitive Functional Therapy clinical trial

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**Statement of Significance**

- An exploration of seven potential mediators was undertaken to determine the effect of Cognitive Functional Therapy (CFT) on disability and pain intensity in individuals with chronic low back pain compared to a group exercise and education intervention.
- CFT improved pain self-efficacy, which was associated with disability and pain outcomes. CFT did not improve the other six potential mediators (stress, fear of physical activity, coping, depression, anxiety and sleep) and these were not associated with disability or pain.
- The proportion of missing data in this study is substantial and these findings should be considered hypothesis-generating only.

## 1. Introduction

Cognitive Functional Therapy (CFT) is an individualised multidimensional approach involving biopsychosocial pain education, graded movement exposure and lifestyle coaching. [29] CFT was designed to help physiotherapists individualise the management of people with non-specific chronic low back pain (CLBP). [29] The aim of CFT is to build self-efficacy to break the cycle of pain and disability, to help individuals self-manage their CLBP. [29] However, since it is a multi-component intervention, several different variables have been hypothesised to underlie how CFT may exert its potential effect on pain and disability.

There is clinical trial evidence to support the effectiveness of CFT for improving clinical outcomes in individuals with CLBP. [27; 39; 40] The first randomised clinical trial (RCT) [39; 40] demonstrated superior effects for CFT on pain and disability over physiotherapist-led manual therapy and exercise in individuals with CLBP at 3 and 12 months, and on disability but not pain at 36 months follow-up. The second RCT [27] demonstrated a superior effect for CFT on disability compared to a group exercise and education intervention at 6 and 12 months follow-up, but did not to show a superior effect on pain at any of these time points. Evaluating the mechanisms underlying the effect of CFT could provide important information. Where CFT is effective, a mechanism evaluation could reveal whether a hypothesised mediator (e.g. self-efficacy) explained much of the effect. Where CFT is ineffective, a mechanistic evaluation would reveal where the hypothesised mechanism broke down [14; 19], and potentially where the intervention needs to be strengthened.

Causal mediation analysis is one method to identify and quantify the mechanisms that underlie the effects of interventions. [17; 19; 24] A mediation analysis quantifies causal mechanisms by dividing the causal effect of the intervention on the outcome into the indirect effect (the effect which acts through a hypothesised mediator) and direct effect (total effect minus the indirect effect). [17] Available mediation analyses have shown that interventions including exercise [34], graded exposure, graded activity [21], cognitive behavioural therapy [34], the STarT back approach, [23] and multidisciplinary treatment, [35] can reduce disability and pain in individuals with CLBP, through changes in catastrophising [11; 21; 23; 34; 35], pain-self-efficacy, pain-related stress and pain intensity. [23; 34; 35] While a number

of mediation trials for CLBP have been conducted, [20] none have specifically involved the analysis of CFT.

For the second RCT [27] examining the efficacy of CFT, a causal mediation analysis was proposed, with pain self-efficacy, stress, fear of physical activity, coping, depression, anxiety, and sleep identified as hypothesised mediators. A mediation analysis of this trial can inform us on why the intervention may have been more effective for disability, but not for pain intensity.

The aim of this study was to determine whether the effect of CFT (relative to a group exercise and education intervention) on disability and pain intensity was mediated by pain self-efficacy, stress, fear of physical activity, coping, depression, anxiety, and sleep.

## 2. Methods

### 2.1. Study Design and Data Source

Causal mediation analysis of a multicentre RCT in Ireland. This trial [27; 28] (NCT02145728) was a two-group, pragmatic RCT in which 206 people with CLBP were recruited from three sites (one public hospital and two primary care centres) in Ireland with follow-up at post intervention, 6 months post randomisation, and 12 months post randomisation. A total of three physiotherapists (one in each setting) were chosen to deliver both the CFT intervention and the group exercise and education intervention in this trial. 206 participants with CLBP for 6 months duration or more were randomised to receive CFT (experimental arm) or a group education and exercise intervention (control arm). The trial methods and interventions have been described in detail in the published protocol [28], and the accompanying RCT [27].

### 2.2 Measures

#### 2.2.1. Hypothesised Mediators

The hypothesised mediators measured were pain self-efficacy, stress, fear of physical activity, coping, depression, anxiety, and sleep measured at 6 month follow-up. Due to the pragmatic nature of the CFT intervention, the treatment period varied, such that the post intervention measures for the CFT and group intervention were conducted at different time points.[27] Therefore, the 6 month mediator data, rather than the post intervention data, were included in the analysis to reduce the potential for detection bias.

- Pain self-efficacy (scale 0-60) was measured using the 10-item Pain Self-Efficacy Questionnaire (PSEQ). [6]
- Stress (scale 0-42) was measured using the seven-item stress subscale of the Depression, Anxiety and Stress Scale (DASS). [22]
- Fear of physical activity (scale 0-24) was measured using the four-item physical activity subscale of the Fear-Avoidance Beliefs Questionnaire (FABQ). [41]
- Coping (scale 0-30) was measured using the five-item coping subscale of the Coping Strategies Questionnaire (CSQ). [12]
- Sleep, depression and anxiety (scale 0-3 for each item) were measured using the single item questions regarding these variables in the Subjective Health Complaints

Inventory (SHCI). [7] These data were recoded to binary variables, where a score of 0 indicated no depression/anxiety/sleep issue and a score of 1, 2, or 3 indicated some issue with depression, anxiety, or sleep [3; 30].

### 2.2.2. Outcomes

- Functional disability was measured using the Oswestry Disability Index (ODI) (0-100) [8] at 12 month follow-up.
- Pain intensity was measured using the Numeric Rating Scale (0-10) at 12 month follow-up. [16] Participants were asked to rate their pain on average during the past week; 0 representing no pain and 10 representing pain as bad as you can imagine.

### 2.2.3. Potential Confounders

We controlled for potential pretreatment confounders by including baseline data for self-efficacy, stress, fear of physical activity, coping, depression, anxiety, sleep, functional disability, pain intensity as covariates.

## 2.3.Data analysis

Causal mediation analysis was used to analyse the data, using the 'mediation' package in R. [37] This deviates from our protocol proposal to use the approach by Baron and Kenny. [2] Our decision to change our method of analysis was based on methodological advances in mediation analyses. [17; 18] While, the Baron and Kenny approach can successfully quantify the mediating effect, it works under more restricted conditions, when mediators and outcomes are continuous and no exposure-mediator interactions are present. Causal mediation relies on defining causal estimates and simulating unobserved potential outcomes through modelling procedures to indirectly estimate point estimates. The causal mediation package in R supports both continuous and binary mediators and was therefore considered more appropriate for this study. [37]

We constructed independent single mediator models for each hypothesised mediator (pain self-efficacy, stress, fear of physical activity, coping, depression, anxiety, and sleep) for functional disability and pain intensity. Adjusted mediator models were fitted to control for measured confounders, with the directed acyclic graph (DAG) for these adjusted models shown in Figure 1. These DAGs were not planned a priori.

The average causal mediation effect (ACME), the average direct effect (ADE), the average total effect (ATE) and the proportion mediated were estimated for each model. The ACME is the effect of the intervention (i.e. CFT) on the outcome (functional disability/pain) exerted through the mediator. The ADE is the remaining effect of the intervention (i.e. CFT) on the outcome (functional disability/pain) that is not exerted through the mediator of interest. The sum of the ACME and the ADE is equal to the ATE. The proportion mediated is the fraction of ATE that is explained by the ACME.

The analysis of the causal model involved fitting two linear regression models: the mediator model and the outcome model. The mediator model was constructed with the allocated intervention status (i.e. CFT) as the independent variable and the hypothesised mediator (e.g. pain self-efficacy) as the dependent variable. In the case where the mediator was binary (e.g. sleep, depression, and anxiety), a binomial probit regression model was fit. The outcome model was constructed with the treatment status, the mediator as the independent variable and the outcome as the dependent variable. In the outcome model, we accounted for the possibility of an intervention-mediator interaction by including the product of the intervention allocation and selected mediator into the regression models. A set of observed baseline confounders were included in the adjusted models as covariates. The 'mediates' function was used to obtain unstandardised point estimates of the ACME, ADE, ATE and the proportion mediated, and 1000 bootstrap simulations were performed.[37]

Sensitivity analysis:

In a mediator model, we cannot assume that the mediator-outcome effect is not confounded, as the mediator is not randomised. Therefore a sensitivity analysis was conducted to determine the robustness of the ACME, in the adjusted mediator models which control for measured confounders, to the influence of the sequential ignorability assumption. Sequential ignorability assumes that there are no unmeasured confounders for the intervention to mediator pathway and the mediator to outcome pathway. The level of residual confounding is represented by the correlation between the residuals from the mediator model and residuals from the outcome model, and is represented by $\rho$, where $\rho$ represents hypothetical levels of unmeasured and unknown confounding. A $\rho$ of 0 would suggest no unmeasured confounding. The 'medsens' function [37] was used to estimate $\rho$ and examine how varying levels of $\rho$, between the extremes of -1 and +1, influences the ACME. The output provides the values of

ρ at which the confidence intervals for the ACME include 0 (a non-significant ACME ie. no mediating effect). This estimates how strong the effect of unmeasured confounding needs to be to invalidate the ACME.

We examined violations in the assumption of normality for the linear regression models via visual inspections of the residual histogram and normal quantile (Q-Q) plots. If normality was violated, the variables were transformed using a square or square root transformation as appropriate. [13] A sensitivity analysis was then conducted to compare the results from the mediation analysis using transformed variables against the results from the original analysis.

The three categorical variables (depression, anxiety and sleep) were recoded as binary variables to be included in the regression models. This dichotomisation may lead to reduced statistical power and inflate false positive probabilities. Further, the cut-offs are arbitrary and may not reflect the true underlying cut-off. [1] Therefore a sensitivity analysis, considering these three mediators as continuous variables, was also conducted.

The primary analysis was conducted on complete cases. However as over 32% of the data for functional disability and 31% of the data for pain intensity were missing at 12 month follow-up, a post hoc sensitivity analysis using Multiple Imputation by Chained Equations (MICE) was conducted to assess the possible impact of missing data. Twenty datasets, with 50 iterations, were imputed and the bootstrap method was used to estimate standard errors. Continuous variables were imputed by predictive mean matching and logistic regression was used to impute the binary variables. All seven hypothesised mediators, treatment and outcome variables were included in the imputation model. The estimates and standard errors were pooled using Rubin's rule and 95% CIs were calculated.

## 4. Results

### 4.1.Descriptive Statistics

At baseline the sample included 206 individuals, of which 106 were randomly assigned to the CFT intervention and 100 were randomly assigned to the group exercise and education intervention. The descriptive statistics for the outcome and mediator variables are presented in Table 1.

**Table 1: Descriptive statistics of outcome and mediator variables**

| **Outcome Variables** | **Baseline** | **Follow-up at 12 Months[1]** |
|---|---|---|

| | **Mean (SD)** [1] | **Mean (SD)** |
|---|---|---|
| Functional Disability (ODI) (0-100) (n=140) [2] | 32.76 (12.57) | 24.64 (15.22) |
| Pain Intensity (NRS) (0-10) (n=142) [2] | 5.94 (2.21) | 4.58 (2.63) |
| | | |
| **Mediator Variables** | **Baseline** | **Follow-up at 6 Months** |
| Self-efficacy (PSEQ) (0-60) (n=142) [2] | 34.06 (12.28) | 42.38 (14.25) |
| Stress (DASS) (0-42) (n=135) [2] | 15.81 (10.86) | 14.95 (10.91) |
| Fear (FABQ) (0-24) (n=130) [2] | 15.09 (5.67) | 10.15 (6.84) |
| Coping (CSQ) (0-30) (n=134) [2] | 16.58 (6.51) | 18.51 (6.25) |
| Depression[3] | | |
| - Not depressed | 95 (51.91) | 67 (48.55) |
| - Depressive symptoms | 88 (48.09) | 71 (51.45) |
| Anxiety[3] | | |
| - Not anxious | 87 (48.07) | 61 (44.20) |
| - Anxiety symptoms | 94 (51.93) | 77 (55.80) |
| Sleep[3] | | |
| - No sleep issues | 31 (16.67) | 40 (28.78) |
| - Issues with sleep | 155 (83.33) | 98 (71.01) |

ODI: Oswestry Disability Index; NRS: Numeric Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; DASS: Depression, Anxiety and Stress Scale; FABQ: Fear-Avoidance Beliefs Questionnaire; CSQ: Coping Strategies Questionnaire.

[1]Analysis of complete cases.

[2]Sample size presented for data at follow-up.

[3]Count (%) presented.

### 4.2. Mediation Analysis

CFT significantly reduced disability, but not pain intensity, when compared to group exercise and education at 6 and 12 month follow-ups.[27]

Our adjusted findings show that CFT caused a significant change in self-efficacy (5.82, 95% CI = 1.58, 10.05), and self-efficacy was associated with both disability (-0.41, 95% CI = -0.66, -0.16) and pain intensity (-0.07 (-0.13, -0.02). In the adjusted mediation analysis of CFT on disability, this causal pathway is further highlighted by the significant AMCE and proportion mediated (Table 2).

Our adjusted model found that CFT did not improve the remaining six hypothesised mediators (stress, fear of physical activity, coping, depression, anxiety and sleep), and these mediators were not associated with either disability or pain (Table 2).

**Table 2: Effect decomposition for self-efficacy, stress, fear, coping, depression, anxiety and sleep as hypothesised mediators measured at 6 months, controlling for measured confounders (adjusted model[1])**

| Mediator | Intervention-mediator effect | Mediator-outcome effect | ATE | ADE | ACME | Proportion Mediated (%) |
|---|---|---|---|---|---|---|
| **Functional Disability (ODI) at 12 months** | | | | | | |
| Self-efficacy (PSEQ, 0-60) (n=91) | 5.82 (1.58, 10.05)* | -0.41 (-0.66, -0.16)* | -6.33 (-11.17, -1.69)* | -3.28 (-7.58, 1.09) | -3.04 (-6.33, -0.64)* | 0.48* |
| Stress (DASS, 0-42) (n=88) | -1.41 (-35.12, 13.63) | 0.33 (-0.00, 0.66) | -7.28 (-11.52, -2.00)* | -7.02 (-11.25, -1.86)* | -0.26 (-2.11, 1.36) | 0.04 |
| Fear (FABQ, 0-24) (n=86) | 0.76 (-3.51, 1.41) | 0.38 (-0.22, 0.98) | -6.94 (-11.36, -1.67)* | -6.28 (-10.64, -1.38)* | -0.56 (-2.16, 0.45) | 0.08 |
| Coping (CSQ, 0-30) (n=88) | 1.07 (-0.97, 3.10) | -0.59 (-1.19, 0.00) | -6.66 (-11.34, -1.79)* | -5.98 (-10.56, -1.40)* | -0.68 (-2.29, 0.52) | 0.10 |
| Depression (SHCI) (n=90) | -0.28 (-0.81, 0.25)[2] | -1.34 (-8.14, 5.46) | -7.27 (-11.85, -1.94)* | -7.10 (-11.28, --1.96)* | -0.17 (-1.81, 0.68) | 0.02 |
| Anxiety (SHCI) (n=90) | -0.35 (-0.96, 0.24)[2] | 3.62 (-4.05, 11.29) | -6.64 (-11.22, -2.00)* | -6.26 (-10.77, -1.79)* | -0.38 (-2.14, 0.67) | 0.06 |
| Sleep (SHCI) (n=117) | -0.21 (-0.81, 0.38)[2] | 3.50 (-4.36, 11.37) | -6.51 (-11.34, -1.85)* | -6.26 (-10.51, -1.17)* | -0.26 (-2.11, 0.46) | 0.04 |
| **Pain Intensity (NRS) at 12 months** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Self-efficacy (PSEQ, 0-60) (n=91) | 5.82 (1.58, 10.05)* | -0.07 (-0.13, -0.02)* | -0.57 (-1.68, 0.06) | 0.01 9-1.01, 1.23) | -0.58 (-1.30, -0.11)* | 1.02 |
| Stress (DASS, 0-42) (n=90) | -1.41 (-35.12, 13.63) | 0.04 (-0.03, 0.11) | -0.79 (-1.97, 0.16) | -0.74 (-1.92, 0.23) | -0.05 (-0.42, 0.27) | 0.06 |
| Fear (FABQ, 0-24) (n=86) | 0.76 (-3.51, 1.41) | 0.05 (-0.08, 0.19) | -0.80 (-1.88, 0.43) | -0.75 (-1.85, 0.48) | -0.05 (-0.36, 0.15) | 0.06 |
| Coping (CSQ, 0-30) (n=88) | 1.07 (-0.97, 3.10) | -0.11 (-0.25, 0.03) | -0.58 (-1.78, 0.56) | -0.54 (-1.73, 0.61) | -0.05 (-0.29, 0.09) | 0.08 |
| Depression (SHCI) (n=90) | -0.28 (-0.81, 0.25) [2] | -0.38 (-1.94, 1.18) | -0.73 (-1.94, 0.40) | -0.66 (-1.89, 0.42) | -0.07 (-0.31, 0.14) | 0.10 |
| Anxiety (SHCI) (n=90) | -0.35 (-0.96, 0.24) [2] | -0.72 (-0.66, 2.80) | -0.66 (-173, 0.58) | -0.55 (-1.71, 0.64) | -0.11 (-0.48, 0.18) | 0.16 |
| Sleep (SHCI) (n=90) | -0.12 (-0.81, 0.38) [2] | 1.49 (-0.23, 3.21) | -0.69 (-1.82, 0.55) | -0.52 (-1.56, 0.63) | -0.17 (-0.63, 0.18) | 0.25 |

All effects unstandardized with their 95% confidence intervals, unless otherwise stated.[1] Controlling for all baseline outcomes and mediators.

[2] Binary models are presented as odds ratios.

ATE: average total effect; ADE: average direct effect; ACME: average causal mediation effect; ODI: Oswestry Disability Index; NRS: Numeric Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; DASS: Depression, Anxiety and Stress Scale; FABQ: Fear-Avoidance Beliefs Questionnaire; CSQ: Coping Strategies Questionnaire.

*$p < 0.05$,

### 4.3 Missing Data

Unfortunately, there were substantial missing data in this study. The first column in Table 1, presents the sample size included in each mediator model. At best, a sample of 117 (57%) was included in the mediation analysis, and at worst a sample of 85 (41%) was included. A mediation analysis of imputed data was investigated in the sensitivity analysis section, to support the results presented in Table 1. However, as suggested by Jakobsen et al. [15], missingness over 40% must be interpreted with caution and should be considered hypothesis-generating.

### 4.4 Sensitivity Analysis

The sensitivity analyses for the sequential ignorability assumption indicated that the ACME estimates were robust. All the ACMEs remained relatively stable across low to high levels of unknown and unmeasured confounding (Appendix 1).We observed violations of normality in the linear regression models assessing the following mediators: pain self-efficacy, stress and fear of physical activity. To overcome violations of normality, we transformed these three mediator variables and conducted sensitivity analyses of the mediation models using the transformed variables. We did not observe extreme deviations in the estimates from the sensitivity analyses when compared with the original analyses. The results of the sensitivity analyses are presented in Appendix 2.

The sensitivity analysis to investigate the effect of dichotomising depression, anxiety and sleep (Appendix 3)was similar to the results presented in Table 2.

The pooled estimates obtained from the imputed datasets were compared. Pain self-efficacy still accounted for the largest proportion of the effect of CFT on functional disability. Results from the imputed analysis for self-efficacy found proportions mediated of 37% for the adjusted model, compared to 48% for the full-case analysis. The results are presented in Appendix 4.

## 5. Discussion

In this causal mediation analysis, we tested the extent to which seven hypothesised mediators explained the effect of a CFT intervention (relative to a group exercise and education intervention) on reductions in disability, and the lack of effect on pain intensity, in individuals with CLBP. We found that CFT, based on adjusted analyses, did not improve six of our hypothesised mediators (stress, fear of physical activity, coping, depression, anxiety

and sleep), and these mediators were not associated with disability or pain. We found that CFT did improve pain self-efficacy, and self-efficacy was associated with disability and pain intensity. 48% of the total effect of CFT on disability was explained by increased pain self-efficacy, for the adjusted mediation model.

Previous mediation analyses of interventions for back pain have examined the effect of a range of mediators on disability and pain. [20] Our findings on the mediating effect of self-efficacy on disability broadly align with previous CLBP RCTs. [9; 10; 32; 33; 43] These studies examined a range of different interventions: yoga and stretching, [33] exercise therapy, dietary weight loss and a combined approach, [9] exercise therapy alone, [32] acceptance and commitment therapy, [43] and advice with cognitive behavioural therapy. [10] Four of the five studies did not provide the necessary data to reliably compare effect sizes with our self-efficacy findings. However, one study [33] found that 35.7% and 23.3% of the effect of yoga and stretching, respectively, on disability, was mediated through self-efficacy. Studies reveal mixed results for the mediating effect of fear [10; 21; 23; 42] on clinical outcomes. Our negative findings for pain coping align with two previous RCTs examining the effect of behavioural therapy [26] and behavioural therapy combined with cognitive coping skills [35]; though another RCT examining the effect of cognitive behavioural therapy found improved coping was associated with better clinical outcomes. [38] To our knowledge, some of our hypothesised mediators (e.g. sleep, anxiety, depression) have not been examined previously. Conversely, some mediators we did not examine have been found to be associated with back pain clinical outcomes. For example, reductions in pain catastrophising have been associated with improvements in pain and disability in several studies [11; 21; 34; 35; 38] examining a range of exercise (e.g. tai chi, general exercise) and psychological treatments (e.g. exposure therapy, CBT), while both psychological flexibility [43] and distress [23] have been found to be associated with clinical outcomes in one RCT, respectively. It is possible that the effect of various interventions on outcomes could work via shared mechanisms. [4; 5] Variation in the results of mediation analyses might also be partially explained by the use of different outcome measures, testing of different interventions, and outcome measurement at varying timepoints.

CFT did not change most of the hypothesised mediators in our study. Yet, some mediators (e.g. sleep, stress, coping and fear) were still associated with clinical outcomes in others studies, suggesting their potential importance. CFT may not be targeting these factors explicitly enough, or a higher dose of treatment may be needed to improve some factors. In

this RCT [27] an average of five sessions were provided to patients with CLBP. In contrast, the first trial [39] examining the effect of CFT (relative to a manual therapy and exercise intervention) observed changes in fear after an average of eight sessions. Improving some factors (e.g. depression) may require integrating CFT with other health care professionals (i.e. general practitioners, psychologists, or social workers) and over a longer period.

**Strengths and limitations**

We examined a broad range of hypothesised mediators in this study. The data source for this study is a pragmatic RCT which examined the effect of a individualised behaviourally orientated intervention on pain and disability in people with CLBP compared to a group exercise and education intervention. The trial had an a priori published protocol, [28] using concealed allocation, and intention to treat analysis.

However, our mediation analysis has limitations. While we had pre-planned a mediation analysis, [28] we did not specify our analysis plan a priori. For example, we changed our method from what was mentioned in the protocol, [28] and we did not create our direct acyclic graphs at the planning stage. We had to handle a significant amount of missing data in our sensitivity analysis; 37% of randomised participants in the RCT did not start or complete treatment, 72% completed the six-month follow-up, and 69% of participants completed the 12-month follow-up. Within the mediation models, missingness ranged from 41% to 57% and while imputed results provide some reassurance, Jakobsen et al. [15] suggests that anything over 40% missing warrants caution and should be considered as hypothesis-generating. We made a number of deviations from our trial protocol. In our protocol we had specified back pain beliefs as a potential mediator to examine but we removed the back beliefs questionnaire based on pilot testing, to reduce participant burden.

While we incorporated measured confounders into our mediator models and completed a sensitivity analysis as part of our causal mediation analysis, we cannot rule out the role of unmeasured confounding and its potential biasing effects on estimates of indirect and direct effects in our study. There is also potential that multiple mediator models would provide further insights into how intervention, mediators and outcomes interact over time.

The interpretation of our results is limited by the timing of the measurements for both mediators and outcomes. We are unable to establish evidence of temporality (the order in

which change occurred) as all data were measured at the same time point. Thus the direction of the relationship between all mediators and disability is unclear.

For depression, anxiety, and sleep, we used a single-item question on the SHCI. [7] We did this to reduce participant burden by reducing the number of questionnaires. A cross-sectional study [31] found that depression and stress, but not anxiety, mediated the relationship between pain and disability in people with hand or wrist fractures. The DASS-21 questionnaire was used [31] to measure these variables, and may be more of an appropriate measure of anxiety and depression to use in future mediation analyses. Depression, anxiety and sleep, which are scored on a scale from 0 to 3, were dichotomised to be included in the mediation analysis. This may lead to loss of information, or a reduction in statistical power.

**Clinical implications**

Due to the level of missing data in this study, our findings are hypothesis-generating and therefore we are unable to provide any strong clinical implications. Nevertheless, this study may be an important contribution to our understanding of the mechanisms underlying the positive effect of CFT on disability and the lack of an effect on pain, when compared to group exercise and education. Examining mechanisms of intervention effects, as well as lack of effects, may have important implications for clinical practice through identifying the key factors that lead to improved outcomes, and may help design better interventions by providing information on the parts of treatment that are both effective and ineffective.

**Future Research**

Replication of the results of this hypothesis-generating study is needed to verify the role of pain-self efficacy on outcomes, as well as verify that the remaining mediators are not associated with pain or disability in this population (as indicated by our adjusted analysis). If pain self-efficacy is verified as important, research could examine which component(s) of CFT may be most important in increasing pain self-efficacy. This could potentially be aided through the use of an adaptive trial design, with repeated measures at earlier timepoints to allow modifications or the addition of extra components to CFT based on interim data. [36] Qualitative studies to examine what may underpin self-efficacy changes may also inform our understanding. Studies should also examine if CFT can better target other potential mediators (e.g. depression, sleep, fear). This may involve examining the effect of adding boosters of

continued care, to allow for flareups to be identified, and the involvement of integrated co-care.

Future studies should attempt to build on the limitations of current mediation analyses by performing regular assessments of mediators (e.g. pain self-efficacy) and outcomes (e.g. disability) over time so that we can better understand this relationship. [11; 24]

The proportion mediated estimated by the causal mediation package in R [37], is not bounded between 0 and 1. Future studies should explore advancing this package to ensure the proportion is in the 0 to 1 range.

## 6. Conclusion

In a recent RCT, CFT reduced disability, but did not reduce pain, compared to a group exercise and education intervention. This causal mediation study shows that the majority of benefit of CFT (relative to a group exercise and education intervention) for disability is due to increasing pain self-efficacy. However, CFT did not improve the majority of hypothesised mediators (stress, fear of physical activity, coping, depression, anxiety and sleep). Unfortunately, the proportion of missing data in this study is substantial and these findings can only be considered hypothesis-generating. Therefore, future research should examine replicating the results of this study to verify the role of self-efficacy and other proposed mediators (e.g. stress, coping, sleep, fear) on clinical outcomes.

## Conflict of interest statement

Two authors (K.O. and P.O.) provide continuing education on Cognitive Functional Therapy for physiotherapists for the management of chronic low back pain. The remaining authors have no conflict of interest to declare.

**Ethics approval:** Ethics approval was obtained from Mayo General Hospital research ethics committee (MGH-14-UL).

## References:

[1] Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006;332(7549):1080.

[2] Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of Personality and Social Psychology 1986;51(6):1173.

[3] Bjørnstad S, Patil GG, Raanaas RK. Nature contact and organizational support during office working hours: benefits relating to stress reduction, subjective health complaints, and sick leave. Work 2016;53(1):9-20.

[4] Burns JW. Mechanisms, mechanisms, mechanisms: it really does all boil down to mechanisms. Pain 2016;157(11):2393.

[5] Burns JW, Nielson WR, Jensen MP, Heapy A, Czlapinski R, Kerns RD. Specific and general therapeutic mechanisms in cognitive behavioral treatment of chronic pain. Journal of consulting and clinical psychology 2015;83(1):1.

[6] Di Pietro F, Catley MJ, McAuley JH, Parkitny L, Maher CG, Costa LdCM, Macedo LG, Williams CM, Moseley GL. Rasch analysis supports the use of the Pain Self-Efficacy Questionnaire. Physical Therapy 2014;94(1):91-100.

[7] Eriksen HR, Ihlebæk C, Ursin H. A scoring system for subjective health complaints (SHC). Scandinavian Journal of Public Health 1999;27(1):63-72.

[8] Fairbank JC, Pynsent PB. The Oswestry disability index. Spine 2000;25(22):2940-2953.

[9] Focht BC, Rejeski WJ, Ambrosius WT, Katula JA, Messier SP. Exercise, self-efficacy, and mobility performance in overweight and obese older adults with knee osteoarthritis. Arthritis Care & Research 2005;53(5):659-665.

[10] Fordham B, Ji C, Hansen Z, Lall R, Lamb SE. Explaining How Cognitive Behavioral Approaches Work for Low Back Pain. Spine 2017;42(17):E1031-E1039.

[11] Hall AM, Kamper SJ, Emsley R, Maher CG. Does pain-catastrophising mediate the effect of tai chi on treatment outcomes for people with low back pain? Complementary Therapies in Medicine 2016;25:61-66.

[12] Harland NJ, Georgieff K. Development of the Coping Strategies Questionnaire 24, a Clinically Utilitarian Version of the Coping Strategies Questionnaire. Rehabilitation Psychology 2003;48(4):296.

[13] Hoyle M. Transformations: An introduction and a bibliography. International Statistical Review/Revue Internationale de Statistique 1973:203-223.

[14] Imai K, Keele L, Tingley D, Yamamoto T. Unpacking the black box of causality: Learning about causal mechanisms from experimental and observational studies. American Political Science Review 2011;105(4):765-789.

[15] Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials–a practical guide with flowcharts. BMC medical research methodology 2017;17(1):162.

[16] Jensen MP, Turner JA, Romano JM, Fisher LD. Comparative reliability and validity of chronic pain intensity measures. Pain 1999;83(2):157-162.

[17] Lee H, Herbert RD, McAuley JH. Mediation analysis. JAMA 2019;321(7):697-698.

[18] Lee H, Hübscher M, McAuley JH. Importance of quantifying indirect effects from mediation analyses. Pain 2015;156(12):2634-2635.

[19] Lee H, Lamb SE. Advancing physical therapist interventions by investigating causal mechanisms. Physical Therapy 2017;97(12):1119-1121.

[20] Lee H, Mansell G, McAuley J, Kamper S, Hübscher M, Moseley G, Wolfenden L, Hodder R, Williams C. Causal mechanisms in the clinical course and treatment of back pain. Best Practice & Research Clinical Rheumatology 2016;30(6):1074-1083.

[21] Leeuw M, Goossens ME, van Breukelen GJ, de Jong JR, Heuts PH, Smeets RJ, Köke AJ, Vlaeyen JW. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. Pain 2008;138(1):192-207.

[22] Lovibond SH, Lovibond PF. Manual for the depression anxiety stress scales: Psychology Foundation of Australia, 1996.

[23] Mansell G, Hill JC, Main C, Vowles KE, Van Der Windt D. Exploring what factors mediate treatment effect: example of the STarT back study high-risk intervention. The Journal of Pain 2016;17(11):1237-1245.

[24] Mansell G, Kamper SJ, Kent P. Why and how back pain interventions work: what can we do to find out? Best Practice & Research Clinical Rheumatology 2013;27(5):685-697.

[25] Marshall GN, Hays RD. The patient satisfaction questionnaire short-form (PSQ-18): Rand Santa Monica, CA, 1994.

[26] Nicassio P, Radojevic V, Weisman M, Schuman C, Kim J, Schoenfeld-Smith K, Krall T. A comparison of behavioral and educational interventions for fibromyalgia. The Journal of Rheumatology 1997;24(10):2000-2007.

[27] O'Keeffe M, O'Sullivan P, Purtill H, Bargary N, O'Sullivan K. Cognitive functional therapy compared with a group-based exercise and education intervention for chronic low back pain: a multicentre randomised controlled trial (RCT). British Journal of Sports Medicine 2019:bjsports-2019-100780.

[28] O'Keeffe M, Purtill H, Kennedy N, O'Sullivan P, Dankaerts W, Tighe A, Allworthy L, Dolan L, Bargary N, O'Sullivan K. Individualised cognitive functional therapy compared with a

combined exercise and pain education class for patients with non-specific chronic low back pain: study protocol for a multicentre randomised controlled trial. BMJ Open 2015;5(6):e007156.

[29] O'Sullivan PB, Caneiro J, O'Keeffe M, Smith A, Dankaerts W, Fersum K, O'Sullivan K. Cognitive functional therapy: an integrated behavioral approach for the targeted management of disabling low back pain. Physical Therapy 2018;98(5):408-423.

[30] Poulsen OM, Persson R, Kristiansen J, Andersen LL, Villadsen E, Ørbæk P. Distribution of subjective health complaints, and their association with register based sickness absence in the Danish working population. Scandinavian Journal of Public Health 2013;41(2):150-157.

[31] Ross C, Juraskova I, Lee H, Parkitny L, Stanton TR, Moseley GL, McAuley JH. Psychological distress mediates the relationship between pain and disability in hand or wrist fractures. The Journal of Pain 2015;16(9):836-843.

[32] Seymour RB, Hughes SL, Campbell RT, Huber GM, Desai P. Comparison of two methods of conducting the Fit and Strong! program. Arthritis Care & Research 2009;61(7):876-884.

[33] Sherman KJ, Wellman RD, Cook AJ, Cherkin DC, Ceballos RM. Mediators of yoga and stretching for chronic low back pain. Evidence-based Complementary and Alternative Medicine 2013;2013.

[34] Smeets RJ, Vlaeyen JW, Kester AD, Knottnerus JA. Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. The Journal of Pain 2006;7(4):261-271.

[35] Spinhoven P, Ter Kuile M, Kole-Snijders AM, Mansfeld MH, den Ouden DJ, Vlaeyen JW. Catastrophizing and internal pain control as mediators of outcome in the multidisciplinary treatment of chronic low back pain. European Journal of Pain 2004;8(3):211-219.

[36] Thorlund K, Haggstrom J, Park JJ, Mills EJ. Key design considerations for adaptive clinical trials: a primer for clinicians. BMJ 2018;360:k698.

[37] Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R Package for Causal Mediation Analysis. Journal of Statistical Software 2014;59:1-38.

[38] Turner JA, Holtzman S, Mancl L. Mediators, moderators, and predictors of therapeutic change in cognitive–behavioral therapy for chronic pain. Pain 2007;127(3):276-286.

[39] Vibe Fersum K, O'Sullivan P, Skouen J, Smith A, Kvåle A. Efficacy of classification-based cognitive functional therapy in patients with non-specific chronic low back pain: A randomized controlled trial. European Journal of Pain 2013;17(6):916-928.

[40] Vibe Fersum K, Smith A, Kvåle A, Skouen JS, O'Sullivan P. Cognitive functional therapy in patients with non-specific chronic low back pain—a randomized controlled trial 3-year follow-up. European Journal of Pain 2019.

[41] Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. Pain 1993;52(2):157-168.

[42] Whittle R, Mansell G, Jellema P, Van Der Windt D. Applying causal mediation methods to clinical trial data: What can we learn about why our interventions (don't) work? European Journal of Pain 2017;21(4):614-622.

[43] Wicksell RK, Olsson GL, Hayes SC. Psychological flexibility as a mediator of improvement in Acceptance and Commitment Therapy for patients with chronic pain following whiplash. European Journal of Pain 2010;14(10):1059. e1051-1059. e1011.

**Figure 1:** Directed acyclic graph of hypothesised mediators. The dashed blue arrows represent the average causal mediation effect (ACME), the solid green arrow represents the average direct effect (ADE), the dotted red arrows represet possible effects that could induce confounding for indirect and direct effects.

**Supplementary Figure (Appendix 1):** Sensitivity plots for each adjusted mediator model with functional disability (1) and pain intensity (2) as the outcomes and self-efficacy (A), stress (B), fear (C), coping (D), depression (E), anxiety (F), and sleep (G) as the mediators for the group intervention (left panel) and CFT intervention (right panel), respectively. The average mediation effects are plotted as a function of the sensitivity parameter (magnitude of residual confounding). The correlation between the error terms in the mediator and outcome regression models ($\rho$) is plotted against the average causal mediation effect (ACME). A sensitivity parameter of 0 represents null hypothesised levels of residual confounding and the extremes of $-1$ and 1 represent maximum hypothesised levels of residual confounding. The estimated ACME (assuming sequential ignorability) is the dashed line and the 95% confidence intervals are represented by the shaded regions.