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Transdiagnostic therapy for persistent physical symptoms: A mediation analysis of the PRINCE secondary trial

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A B S T R A C T

The PRINCE secondary trial did not find any evidence that transdiagnostic cognitive behavioural therapy (TDT-CBT) plus standard medical care (SMC) was more efficacious than SMC for patients with Persistent Physical Symptoms (PPS) for the primary outcome Work and Social Adjustment Scale (WSAS) at final follow-up (52 weeks). There was a significant treatment effect for TDT-CBT plus CBT compared with SMC for two secondary outcomes: WSAS at the end of active treatment (20 weeks) and symptom severity (Patient Health Questionnaire, PHQ-15) at 52 weeks.

To understand mechanisms that lead to effects of TDT-CBT plus SMC versus SMC we performed a planned secondary mediation analysis. We investigated whether TDT-CBT treatment effects on these two secondary outcomes at the end of the treatment could be explained by effects on variables that were targeted by TDT-CBT during the initial phase of treatment. We pre-specified mediator variables measured at mid-treatment (9 weeks).

Reductions in catastrophising and symptom focusing were the strongest mediators of TDT-CBT treatment effects on WSAS at the end of treatment. Improvements in symptom focusing also mediated the effect of TDT-CBT on PHQ-15.

Future developments of the TDT-CBT intervention could benefit from targeting these mediators.

1. Introduction

Persistent physical symptoms (PPS) otherwise known as medically unexplained symptoms (MUS) are associated with psychological distress, disability and increased health care costs (Bermingham et al., 2010; Nimnuan et al., 2001; Poloni et al., 2018). We carried out a randomised controlled trial, PRINCE Secondary (Persistent physical symptoms Reduction Intervention: a system Change and Evaluation) in secondary care that compared therapist delivered transdiagnostic cognitive behavioural therapy (TDT-CBT) plus standard medical care (SMC) versus SMC alone for patients with PPS (Chalder et al., 2021). Follow-up assessments were conducted mid treatment (9 weeks), at the end of treatment (20 weeks), 40 and, 52 weeks post randomisation with the primary outcome being the Work and Social Adjustment Scale (WSAS) at 52 weeks. In addition, we assessed a range of secondary outcomes at 52 weeks which included symptom severity, depression, and anxiety.

Our trial intervention adopted a transdiagnostic approach which was flexible enough to address disorder specific issues (Chalder & Willis, 2017). The case for a transdiagnostic approach for PPS is based on three factors. Firstly, there are a wide range of PPS's, resulting in health care professionals potentially being faced with many specific treatment protocols for each symptom/syndrome. Secondly, there is evidence to suggest that there is considerable overlap between different PPS (Aaron & Buchwald, 2001). For example more than 50% of patients with one syndrome such as fibromyalgia fulfil the criteria for at least one other syndrome such as irritable bowel syndrome (Nimnuan et al., 2001) Thirdly, people with different PPS share some cognitive and behavioural responses to symptoms, including catastrophising, symptom focusing, fear avoidance beliefs, avoidance behaviour and lack of acceptance (Deary, Chalder, & Sharpe, 2007). Targeting these processes across symptoms/syndromes may be an efficient way of providing health care.

Our primary trial analysis found no evidence that TDT-CBT plus SMC was more efficacious than SMC alone at 52 weeks at changing our primary outcome WSAS. However, we found statistically significant beneficial treatment effects of TDT-CBT for WSAS assessed at the end of

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therapy at 20 weeks, as well as for the PHQ-15, a measure of symptom severity at 52 weeks.

Although these results provide valuable insight into whether our intervention affected our primary and secondary trial outcomes, they do not explain how the treatment effects came about. An understanding of the mechanisms that lead to the treatment effects can help us clarify the extent to which TDT-CBT improved outcomes by changing key processes targeted by the therapy. Understanding mechanisms of change can also guide further intervention development (Windgassen et al., 2016). We measured putative mediators as part of our original trial design (Chalder et al., 2019) so that we could empirically assess these mechanisms of change.

We assessed mediator variables at baseline, 9, 20, 40 and 52 weeks. Based on our transdiagnostic model (Deary et al.; Chalder & Willis, 2017; Chalder et al., 2019) we hypothesised that unhelpful cognitive and behavioural responses such as fearful avoidance beliefs (e.g., 'I am afraid that I will make my symptoms worse if I exercise'), catastrophising (e.g. 'I will never feel right again'), embarrassment avoidance (e.g. 'I worry that people will think badly of me because of my symptoms'), damage beliefs (e.g. 'The severity of my symptoms must mean there is something serious going on in my body'), symptom focusing (e.g. 'I think a great deal about my symptoms'), avoidance resting (e.g. 'I stay in bed to control my symptoms') and lack of acceptance would mediate the treatment effect (Kratz et al., 2007). Given the high prevalence of anxiety and depression in people with PPS (van Exk van der Sluijs et al., 2015) and the fact that the transdiagnostic variables targeted are key in reducing anxiety and depression we also hypothesised that anxiety and depression would mediate the treatment effect.

In this paper we carry out a planned secondary mediation analysis to understand how TDT-CBT effects are brought about. We investigate whether TDT-CBT treatment effects on the two important secondary outcomes WSAS and PHQ-15 could be explained by effects on variables that were targeted by TDT-CBT. More specifically, we empirically assess the ability of our hypothesised set of mediator variables measured at mid-treatment (9 weeks) to explain the TDT-CBT effect on outcome variables at the end of active treatment (20 weeks).

In this instance all the variables featuring as putative mediator or outcome variables are continuous variables. In the case of continuous variables, we can carry out a causal mediation analysis and assess the mechanisms of change by assessing three crucial paths: The action effect, also referred to as the "a path" for continuous mediators, the conceptual effect ("b path") and the indirect effect ("ab path") (Mackinnon et al., 2013). The a path shows the effect of the intervention on each of the putative mediators and can be referred to as the action path as this is the point of the mediation process that the interventions can act upon. If there is evidence to support that the intervention has successfully induced change in the mediators, then the treatment can be considered to be effectively targeting what was intended in the development of that treatment. The b path looks at associations between the mediator and the outcome and can be referred to as the conceptual path as the relationship between the mediators and the outcome is hypothesised based on substantive theory and prior evidence. If there is evidence to support that change in the mediator is associated with improvements in outcome, then the conceptual mechanism of change holds. The indirect (or mediated) effect is the part of the total treatment effect that operates by changing the putative mediator variable, and for continuous variables can be calculated by multiplying a by b. The size of the indirect effect indicates the amount of mediation that is present. Formal assessment of these paths form the objectives of this secondary data analysis.

The specific objectives are:

1. To describe the effect of TDT-CBT on the putative mediator variables when compared to SMC at 9 (mid treatment), 20 (end of active treatment) as well as 40 and 52 weeks (follow ups).
2. To formally assess whether the effect of TDT-CBT on the WSAS and PHQ-15 at the end of active treatment (20 weeks) is mediated by change in the hypothesised mediators at mid treatment (9 weeks). To achieve this objective, we will answer the following three questions:
   a. Does TDT-CBT affect the proposed mediators at mid treatment when compared to SMC (i.e., is there a significant a path/evidence for the action path)?
   b. Which of the putative mediators at 9 weeks affected improvements in outcome at end of active treatment (i.e., is there a significant b path/evidence for the conceptual path)?
   c. How much of the total effect on outcomes at 20 weeks is transmitted by the respective mediator singly (i.e., how large is the ab or indirect effect).
   d. Do identified mediators have an independent mediation effect on outcomes at 20 weeks?

2. Methods

This is a planned secondary mediation analysis using the secondary outcome measures and putative mediator measures recorded as part of the PRINCE Secondary trial comparing TDT-CBT plus SMC to SMC alone for patients with PPS.

2.1. Study design and participants

The trial protocol (Chalder et al., 2019) describing the trial design and study interventions, and main trial results (Chalder et al., 2021) have been published. Here we will provide a brief overview. Between August 2015 and Jan 2018, 324 participants with PPS aged between 18 and 70 years were recruited from the UK National Health Service. We approached a variety of secondary care clinics including rheumatology, cardiology, respiratory, gastroenterology and neurology and therefore the patient cohort was diverse in terms of the symptoms present. Recruitment into the study was undertaken by the research team. If eligible, the study was discussed with the patient and those who agreed were asked to complete a consent form.161 participants were randomised to the intervention (TDT-CBT plus SMC) of which 135 (83.9%) participants were deemed adherent to the intervention (attended more than 3 sessions). 163 participants were randomly allocated to the control trial arm (SMC). The mean age of the participants was 43.1 (SD = 12.6) years and 83% of patients were female.

2.1.1. Transdiagnostic-CBT

Our transdiagnostic intervention, which consisted of 8 sessions, was manualised to maximise therapy integrity. Therapists received regular supervision. The hypothesised mechanisms of change i.e. catastrophising and avoidance were targeted by behaviour change techniques, such as goal setting, self-monitoring, activity scheduling, as well as refocussing attention and challenging unhelpful thoughts.

Fidelity outcomes, rated by two independent clinicians, suggested that therapy was delivered as intended. Patients attended on average 6.7 sessions out of 8. The trial was deemed safe as there were no differences in adverse events or serious adverse events between the two groups.

2.2. Ethics

The PRINCE Secondary trial was approved by Camberwell St Giles Research Ethics Committee REC 15/LO/0058. The trial was registered in April 2015 with ClinicalTrials.gov NCT02426788.

2.3. Description of the mediation model

Fig. 1 shows our mediation model in relation to the PRINCE Secondary study. We have illustrated the pathways between our intervention, the putative mediators (M) that we evaluated and our two outcomes (O) of interest which are the WSAS and the PHQ-15 (symptom

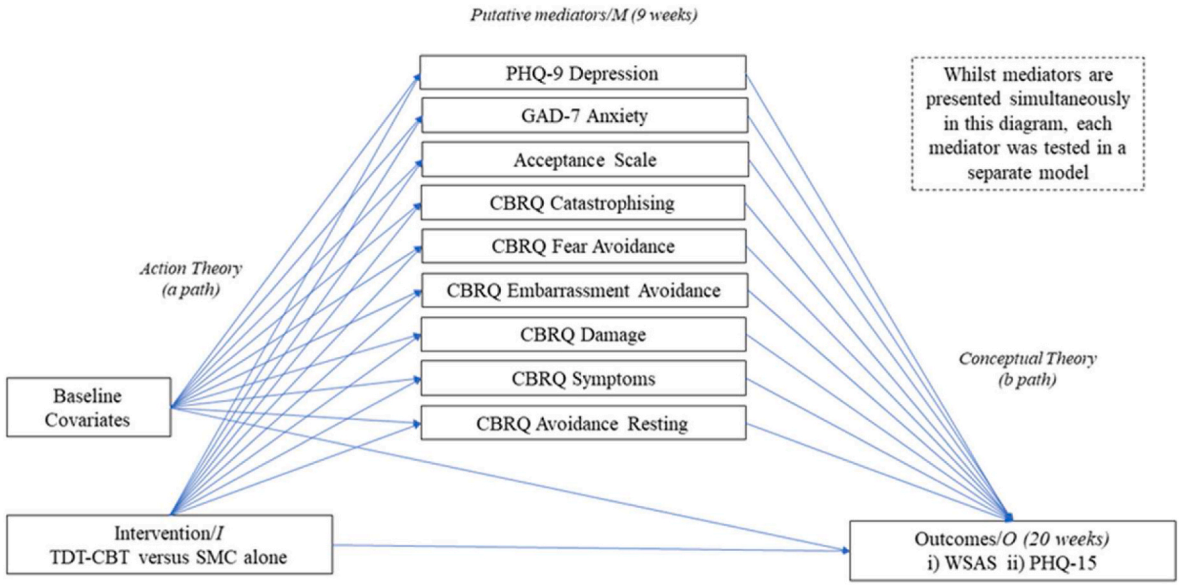

Fig. 1. Illustration of mediation model in relation to the PRINCE Secondary trial. PHQ-9, Patient Health Questionnaire – 9 item Scale; GAD-7, Generalised Anxiety Disorder – 7 item Scale; CBRQ, Cognitive Behavioural Responses Questionnaire; WSAS, Work and Social Adjustment Scale, PHQ-15, Patient Health Questionnaire – 15 item Scale; TDT-CBT, Transdiagnostic Cognitive Behavioural Therapy; SMC, Standard Medical Care.

severity).

2.4. Measures

All outcome and mediator variables were measured at each of the trial time points; baseline, 9-, 20-, 40- and 52-weeks post randomisation with measures being completed by the participant and returned to the research team.

2.5. Outcome measures

Two secondary outcomes from the trial were subject to mediation analysis. The WSAS (Mundt et al., 2002) and the PHQ-15 (Kroenke et al., 2010). The Work and Social Adjustment Scale (WSAS) is a widely used measure of functional impairment. Patients were asked to report using a 8-point Likert scale to what extent their PPS impacted their daily lives in terms of work, home management, relationships, and leisure activities. This 5-item measure is a simple tool to administer and is valid and reliable. The total score can range from 0 to 40 where a higher score indicates increased functional impairment (Mundt et al., 2002). It has been used as an outcome measure in a number of PPS related CBT studies (Kennedy et al., 2006; White et al., 2011).

The PHQ-15 is a measure of symptom severity and is rated on a 3-point Likert scale. This brief validated measure looks at a range of symptoms and asks patients to report to what extent their symptoms bothered them in the past four weeks. The PHQ-15 contains 15 items and the total score can range from 0 to 30 where a higher score indicates greater symptom severity (Kroenke et al., 2010). The items include several related to pain, (stomach pain, back pain, pain in arms and legs or other joints, headaches, chest pain), fatigue, as well as other symptoms related to the different systems of the body i.e. shortness of breath, dizziness, bowel symptoms.

2.6. Potential mediators

Table 1 outlines the measures considered putative mediator variables. Variables measured at the mid-treatment treatment time point (9 weeks) were considered mediators based on theoretical grounds. Variables listed in Table 1 are targeted during the initial phase of TDT-CBT therapy in order to bring about improvements in outcome variables measured at the end of therapy (20 weeks). We measured these variables as part of the original trial design to enable a secondary mediation analysis. All measures have good psychometric properties. The CBRQ and acceptance subscales were pre-specified as potential mediators in the trial protocol (Chalder et al., 2019). The PHQ-9 and GAD-7 were added to the putative mediator list as we thought it possible that they would mediate outcome.

2.7. Statistical analysis

To deal with missing values in questionnaire items outcome and mediator scales were pro-rated when fewer than 20% of items were missing. For modelling purposes follow up outcome and mediator variables were standardised to baseline by subtracting the respective mean at baseline and then dividing by the baseline standard deviation (SD). Hence treatment effect estimates are shown in baseline SD units of the respective outcome measure.

The formal analyses can be separated out into two parts based on our two objectives. For objective 1 (quantification of effects of TDT-CBT on variables considered as mediators measured at any time point in the trial) the analysis approach was kept consistent with that used for the main analysis of the trial data (Chalder et al., 2021). Regression models were used to look at the treatment effect at each time point separately with the mediator as the dependent variable and with baseline mediator values, dummy variables for randomisation stratifiers clinic and disability, therapist (3 levels), and treatment as explanatory variables. As we previously found that compliance with the intervention predicted missingness of the primary trial outcome we used multiple imputation by chained equations (MICE) to deal with missingness in the mediator and outcome variables. We also found that criteria one on the fibromyalgia assessment titled 'Pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist' was associated with missingness of the primary outcome so this was also included in the imputation step of our approach as described in our primary publication. Respective imputation models further contained all variables of the analysis models, all predictors of missingness of the primary outcome, all measures of the mediator at all time-points and demographic variables age and sex as the latter might be predictors of both mediator and outcome (see below). These analyses are for descriptive purposes to look at patterns of therapy effects over time and

Table 1
List of putative mediation measures used to assess any mechanisms of change in response to the TDT-CBT plus SMC intervention.

Mediation Measure	How this measure relates to PPS	Psychometric Properties
PHQ-9 (Kroenke et al., 2010)	Measures the severity of depression in patients with PPS.	- Scale length 9 items - Item scoring 3- point Likert scale - Scale definition higher score indicates greater depressive severity - Scale scoring/range sum items/0 - 27
GAD-7 (Löwe et al., 2008)	Measures the severity of generalised anxiety in patients with PPS.	- Scale length 7 items - Item scoring 4- point Likert scale - Scale definition higher score indicates greater anxiety - Scale scoring/range sum items/0 - 21
Acceptance Scale (McCracken et al., 2004)	Measures to what extent patients were willing to accept their symptoms. This measure was adapted using the Chronic Pain and Acceptance questionnaire to ask about symptom rather than pain, only the acceptance subscale was used.	- Scale length 9 items - Item scoring 7- point Likert scale - Scale definition higher score indicates greater acceptance - Scale scoring/range sum items/0 - 42
[a]**CBRQ Catastrophising**	Measures the negative cognitions that relate to catastrophic consequences of a symptom	- Subscale length 4 items - Item Scoring 5- point Likert scale - Scale definition higher score indicates the worse possible outcome for their symptoms - Subscale scoring sum items/0 - 20
[a]**CBRQ Fear Avoidance**	Measures whether patients with PPS are likely to avoid certain behaviours to avoid symptoms and related distress.	- Subscale length 6 items - Item scoring 5- point Likert scale - Scale definition higher score indicates greater avoidance - Subscale scoring sum items/0 - 30
[a]**CBRQ Embarrassment Avoidance**	Measures whether patients with PPS are likely to avoid certain situations to avoid embarrassment.	- Subscale length 6 items - Item scoring 5- point Likert scale - Scale definition higher score indicates increased likelihood to withdraw from activities - Subscale scoring sum items/0 - 30
[a]**CBRQ Damage**	Measures whether patients with PPS have a tendency to believe their symptoms cause continuous harm to their body.	- *Subscale length* 5 items - *Item scoring* 5- point Likert scale - *Scale definition* higher score indicates that the presence of symptoms are a sign of harm being caused. - *Subscale scoring* sum items/0 - 25
[a]**CBRQ Symptom focusing**	Measures whether patients with PPS are likely to be preoccupied with their symptoms and consequently use unhelpful coping strategies.	- Subscale length 6 items - Item scoring 5- point Likert scale - Scale definition higher score indicates increased attention to symptoms - Subscale scoring sum items/0 - 30
[a]**CBRQ Avoidance Resting**	Measures whether patients with PPS are likely to engage in maladaptive coping strategies in response to their symptoms.	- Subscale length 6 items - Item scoring 5- point Likert scale - Scale definition higher score indicates increased likelihood to avoid activities due to the symptoms present - *Subscale scoring* sum items/0 - 30

PHQ-9, Patient Health Questionnaire – 9 item Scale; GAD-7, Generalised Anxiety Disorder – 7 item Scale; CBRQ, Cognitive Behavioural Responses Questionnaire.
[a] This is a subscale of the CBRQ which has a total scale length of 40 items (Ryan et al., 2018).

were carried out in Stata.

For objective 2 we performed a formal causal mediation analysis that remains valid in the presence of missing values in the respective mediator or outcome variables provided data were missing at random (MAR). We assumed parametric regression models for the continuous mediator and outcome variables, and further assumed that there was no interaction between the mediator and the treatment. Causal mediation modelling that allows for multiple imputation to handle missing values under the MAR assumption was carried out using parametric regression modelling via quasi-Bayesian Monte Carlo simulation in R (mediation package Imai et al., 2010 in conjunction with wrapper functions amelidiate and mediations). Single mediator models fitted considered each combination of 9-week mediator variable and 20-week outcome variable. Each causal mediation analysis provides an estimate (and confidence interval) of the a path, b path and the natural indirect effect (the ab path).

We proceeded as follows: The regression (analysis) model for the mediator variable included dummy variables for clinic, disability, therapist and treatment, age and sex as potential observed confounders of the mediator outcome path and baseline values of both the mediator and the outcome variable (Landau et al., 2018).The regression model for the outcome included dummy variables for clinic, disability, therapist and treatment, age and sex, the mediator variable and baseline values of both the mediator and the outcome variable (Landau et al., 2018). For each mediator and outcome variable combination further datasets were imputed with respective imputation models also including all measures of the outcome at each trial time-point. Imputations were carried out in Stata, 100 imputed datasets were saved. Then causal mediation analysis was carried out in R using the amelidiate and mediations commands with 2000 simulations. The steps of the Quasi-Bayesian simulation approach on the imputed datasets are as follows. Step 1: Fit regression models for the observed outcome and mediator variables. Step 2: Simulate model parameters from their sampling distribution. Step 3: Repeat the following three steps for each draw of model parameters; (i) Simulate the potential values of the mediator under each treatment, (ii) Simulate the potential outcomes given the simulated values of the mediator, (iii) Compute quantities of interest. Then combine simulated distributions of quantities of interest across imputations. And finally step 4: Compute summary statistics such as point estimates and confidence intervals for the a, b and ab path (objectives 2a, 2b and 2c) from respective distributions.

This modelling approach relies on the sequential ignorability assumptions which states that conditional on covariates that are included in the models there is no unmeasured confounding of the treatment-mediator, treatment-outcome or mediator-outcome relationships (Imai et al., 2010). As treatment is randomised, we can be sure that this is satisfied for the treatment-mediator and treatment-outcome relationships, but we cannot be certain that there is no unmeasured confounding of the mediator-outcome relationship. We have included age and sex

which were deemed clinically as potential confounders to try and make these assumptions more realistic. The action effect estimates from these models will be similar to results reported for objective 1 but will be slightly different due to differences in the covariates that are included in the models such as baseline measures of both the mediator and outcome.

In order to assess our final objective (2d) all mediators that were found to be significant (95% confidence interval does not include 0) in the individual mediator models were included in a parallel model for each outcome. First, an imputation step was performed including all measures of the outcome at each trial time-point and all measures of each of the significant mediators. A sequence of models was then built by first including the mediator with the largest indirect effect and then adding in each significant mediator in order of magnitude. Adding each mediator to the model in this way will mean that we can see how much extra information on the mediated effect is provided from each mediator.

3. Results

Of the 324 randomised participants 259 (80%) provided WSAS data at 20 weeks and 258 (80%) provided PHQ-15 data. Completion rates of the putative mediators at 9 weeks post randomisation ranged from 75% to 81%. Summary statistics for the mediator and outcome variables are shown in Figs. 2 and 3 with the unadjusted means plotted over all trial timepoints split by treatment arm. Baseline characteristics of those participants included in the mediation analysis are shown in Table 2.

3.1. Question 1 – how large is the effect of TDT-CBT when compared to SMC at 9, 20, 40 or 52 weeks?

Fig. 2 shows mean summaries of the two outcome measures that we considered in this study – WSAS and PHQ-15. Fig. 3, and Table 1 in the appendix shows mean summaries for all the putative mediators at all trial time points. For all mediators a decrease in score represents a clinically beneficial change. Fig. 4 presents a forest plot of estimated standardised treatment effects of TDT-CBT. These effect size estimates are derived from our modelling for Objective 1 and are adjusted for missing data biases. The general trend is that for each mediator the largest treatment effect can be seen at 20 weeks, immediately after the completion of the intervention, with exception of the acceptance and fear avoidance scales which show the largest treatment effects at 40 weeks post randomisation respectively. The largest effects at 20 weeks can be seen for symptom focusing (−0.37, 95% CI: −0.58, −0.16) and avoidance resting (−0.38, 95% CI: −0.58, −0.18) followed by catastrophising (−0.30, 95% CI: −0.49, −0.11), with symptom focusing and catastrophising already achieving small to moderate treatment effects at the mid-treatment time point 9 weeks.

Fig. 2. WSAS, Work and Social Adjustment Scale; PHQ-15, Patient Health Questionnaire – 15 item Scale; TDT-CBT, Transdiagnostic Cognitive Behavioural Therapy; SMC, Standard Medical Care.

Fig. 3. PHQ-9, Patient Health Questionnaire – 9 item Scale; GAD-7, Generalised Anxiety Disorder – 7 item Scale; CBRQ, Cognitive Behavioural Responses Questionnaire; TDT-CBT, Transdiagnostic Cognitive Behavioural Therapy; SMC, Standard Medical Care.

3.2. Question 2: is the total effect of TDT-CBT on end of treatment outcome transmitted via the hypothesised mediators at mid treatment?

3.2.1. 2a. Does TDT-CBT have an effect on the putative mediators of change when compared to SMC (action paths/a path)?

Fig. 5 provides estimates of the sizes of the action paths derived from our mediation modelling. When looking at the effect of TDT-CBT plus SMC as compared to SMC on the mediators at 9 weeks catastrophising was significantly lower/better when assessed within the mediation model with WSAS at 20 weeks as the outcome (−0.30, CI: −0.59, −0.01) with a similar size of effect when assessing PHQ-15 at 20 weeks as the outcome (−0.29, CI: −0.61, 0.03). Although not all reaching statistical significance, we can see treatment effect estimates of similar magnitude for symptom focusing (−0.28, CI: −0.59, 0.02) and embarrassment avoidance (−0.23, CI: −0.47, 0.01) at 9 weeks within the model for WSAS at 20 weeks and for symptom focusing (−0.32, CI: −0.64, 0.00) and damage (−0.28, CI: −0.60, 0.04) within the model for PHQ-15 at 20 weeks. No apparent change could be seen for the other putative mediators. The standardised action effect sizes are akin to Cohen's d effect sizes with all values in range 0.2–0.44 considered small to moderate (Cohen, 1988).

3.2.2. 2b. Which of the putative mediators at 9 weeks affect improvements in outcome at 20 weeks (i.e., is there evidence for the conceptual path)?

Fig. 6 provides estimates of the effects of each of the putative mediator variables on each of the two outcome variables, i.e., of the link between intermediate variables and outcome. There were significant conceptual effects for all mediators except for damage and avoidance resting. For functional impairment (WSAS) the largest conceptual effects were estimated for embarrassment avoidance (0.42, CI: 0.24, 0.60), acceptance (0.38, CI: 0.24, 0.52), catastrophising (0.38, CI: 0.22, 0.53) and depression (PHQ-9) (0.35, CI: 0.19, 0.51). For symptom severity (PHQ-15) the largest effects were seen for depression (0.39, CI: 0.26, 0.51) and catastrophising (0.28, CI: 0.15, 0.41). The standardised conceptual effect sizes shown in Fig. 6 are akin to correlation coefficients, with positive effect size estimates indicating that change in the mediator is linked to change in the outcome in the same direction, and coefficients in the range 0.3–0.5 considered moderate to large (Cohen, 1988). So, for example, for every baseline SD unit decrease in embarrassment avoidance we estimate that it would lead to a 0.42 baseline SD decrease in functional impairment. All the conceptual effects listed above would be considered moderately strong showing that for WSAS there are number of mechanisms that can lead to outcome improvements while for symptom severity only PHQ-9 presents a strong mechanism to induce change in the outcome (see Fig. 7).

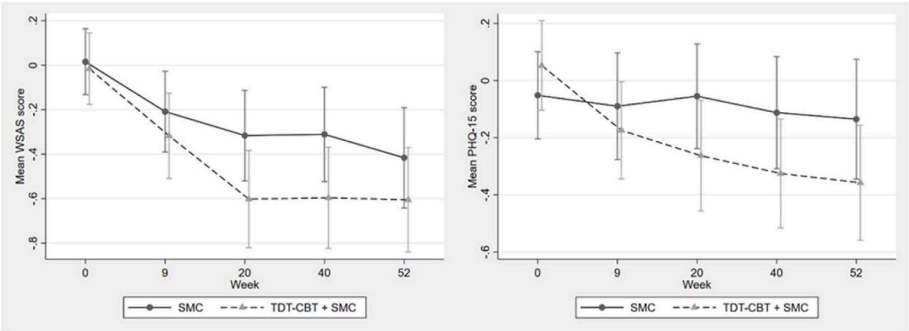

Fig. 2. Summaries of outcome measures by trial arms and time point (plus 95% CIs).

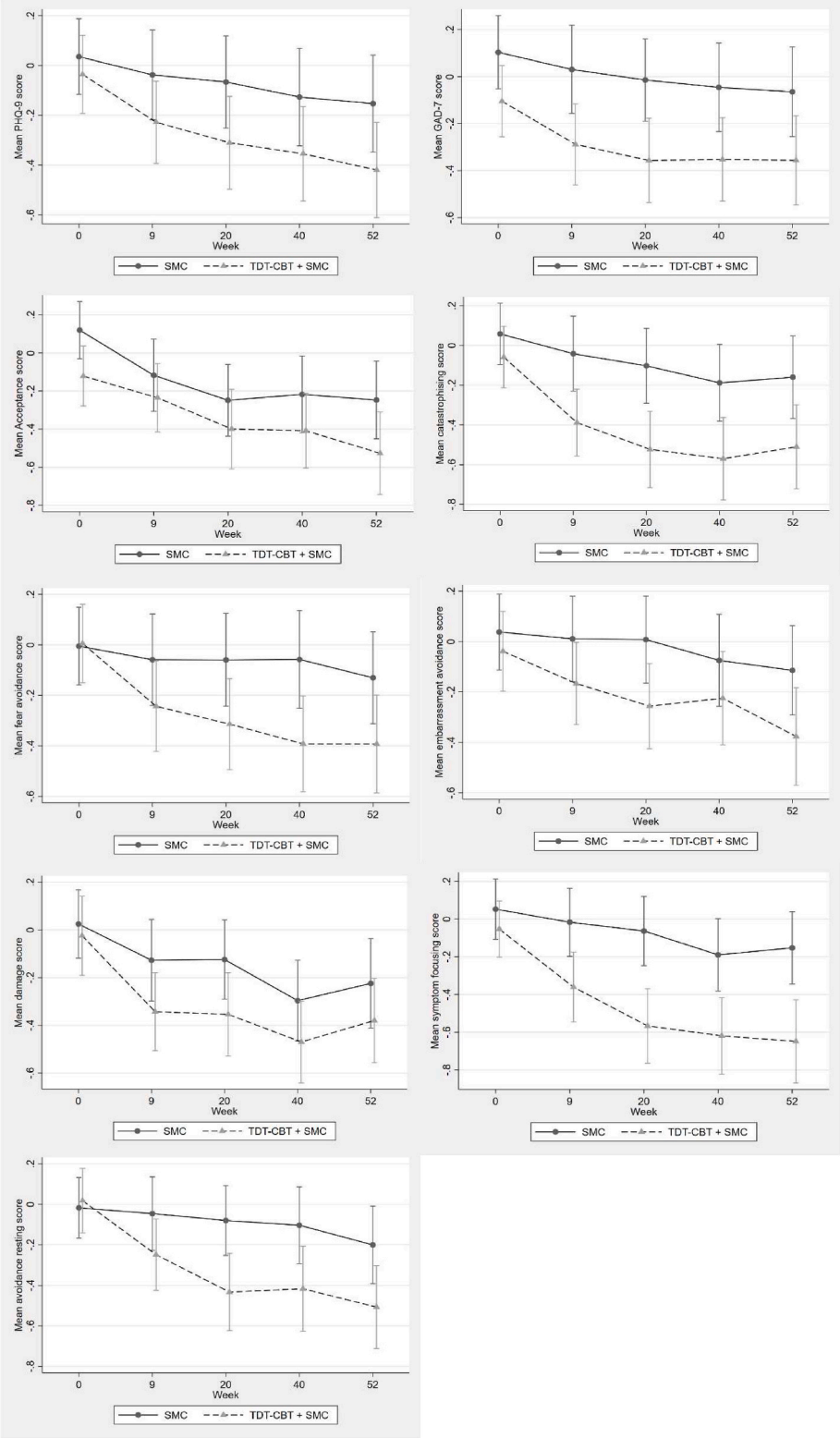

Fig. 3. Summaries for putative mediators by trial arms and time point (plus 95% CIs).

3.2.3. 2c. How much of the total effect on outcomes at 20 weeks was transmitted by the respective individual mediator (i.e., how large is the indirect effect)?

The standardised total effect of TDT-CBT on the functional impairment (WSAS) outcome at 20 weeks was −0.29 and for the symptom severity (PHQ-15) outcome was −0.24 (Chalder et al., 2021). According to Cohen the standardised differences for functional impairment and symptom severity can be considered small/moderate.

The mediated effect of TDT-CBT on the functional impairment outcome at 20 weeks was significant for catastrophising (−0.11, CI: −0.25, 0.00) and symptom focusing (−0.07, CI: −0.18, 0.00) at the approximate 5% level. Proportion mediated was 37.9% for catastrophising and 24.1% for symptom focusing (appendix Table 2a). These results imply that for catastrophising for example, of the total effect of

Table 2
Baseline demographics.

Baseline demographics		SMC N = 163	TDT-CBT plus SMC N = 161	Overall N = 324
Age mean (SD)		42.5 (12.9)	43.7 (12.3)	43.1 (12.6)
Gender *n (%)*	Female	133 (81.6)	136 (84.5)	269 (83.0)
Ethnic Background *n (%)*	White	117 (71.8)	117 (72.7)	234 (72.2)
	Black, Asian and Minority Ethnic	35 (21.5)	33 (20.5)	68 (21.0)
	Other/Missing	11 (6.7)	11 (6.8)	22 (6.8)
First Language *n (%)*	English	140 (85.9)	134 (83.2)	274 (84.6)
	Other	23 (14.1)	27 (16.8)	50 (15.4)
Marital Status *n (%)*	Single	71 (43.6)	65 (40.4)	136 (42.0)
	Married/living together	71 (43.6)	70 (43.5)	141 (43.5)
	Separated/ divorced	18 (11.0)	24 (14.9)	42 (13.0)
	Widowed	3 (1.8)	1 (0.6)	4 (1.2)
	Missing	0 (0.0)	1 (0.6)	1 (0.3)
Currently Live with *n (%)*	Steady partner	43 (26.4)	37 (23.0)	80 (24.7)
	Partner and children	23 (14.1)	35 (21.7)	58 (17.9)
	Parents	20 (12.3)	18 (11.2)	38 (11.7)
	Children	18 (11.0)	19 (11.8)	37 (11.4)
	Alone	36 (22.1)	34 (21.1)	70 (21.6)
	Other	22 (13.5)	18 (11.2)	40 (12.3)
	Missing	1 (0.6)	0 (0.0)	1 (0.3)
Have Children *n (%)*	Yes	83 (50.9)	96 (59.6)	179 (55.2)
Have Elderly Relatives *n (%)*	Yes	19 (11.7)	17 (10.6)	36 (11.1)
Place of residence *n (%)*	Owner occupied	61 (37.4)	59 (36.6)	120 (37.0)
	Private renting	40 (24.5)	39 (24.2)	79 (24.4)
	Authority renting	51 (31.3)	55 (34.2)	106 (32.7)
	Other i.e., flat share	11 (6.7)	8 (5.0)	19 (5.9)
Educational Level *n (%)*	None	15 (9.2)	13 (8.1)	28 (8.6)
	GCSE or equivalent	42 (25.8)	31 (19.3)	73 (22.5)
	A level or equivalent	31 (19.0)	27 (16.8)	58 (17.9)
	Degree	45 (27.6)	53 (32.9)	98 (30.2)
	Postgraduate	18 (11.0)	25 (15.5)	43 (13.3)
	Other	12 (7.4)	12 (7.5)	24 (7.4)
Member of self-help group or national patient organisation *n (%)*	Yes	9 (5.5)	5 (3.1)	14 (4.3)
Had Cognitive Behavioural Therapy (CBT) *n (%)*	Yes	45 (27.6)	47 (29.2)	92 (28.4)
Had Physiotherapy *n (%)*	Yes	108 (66.3)	119 (73.9)	227 (70.1)
Had Other Therapy *n (%)*	Yes	69 (42.3)	84 (52.2)	153 (47.2)
Clinic *n (%)*	Neurology		16 (9.9)	
		17 (10.4)		33 (10.2)
	Cardiology	12 (7.4)	11 (6.8)	23 (7.1)
	Rheumatology	80 (49.1)	79 (49.1)	159 (49.1)
	Gastroenterology	36 (22.1)	36 (22.4)	72 (22.2)
	Respiratory	15 (9.2)	15 (9.3)	30 (9.3)
	Pain	3 (1.8)	3 (1.9)	6 (1.9)
	OH	0 (0.0)	1 (0.6)	1 (0.3)
Meets all criteria for fibromyalgia assessment n (%)	N	163	159	322
	Met	88 (54)	86 (54.1)	174 (54)

0.29 baseline SD units on WSAS, 0.11 baseline SD of the difference in catastrophising for TDT-CBT versus SMC decrease was transmitted via this mediator.

The mediated effect of TDT-CBT on symptom severity outcome at 20 weeks via the mediators was significant for symptom focusing (−0.06, CI: −0.15, 0.00) and proportion mediated was 25.0% (appendix Table 2b).

The small/moderate treatment effect of TDT-CBT when assessing WSAS as the outcome was singly mediated by catastrophising and symptom focusing. The small/moderate total treatment effect on PHQ-15 was only shown to be mediated by symptom focusing.

3.2.4. 2d. Do identified mediators have an independent mediation effect on outcomes at 20 weeks (parallel model?

For the functional impairment outcome, we included the mediators, catastrophising and symptom focusing in the parallel model. Mediators were added sequentially by magnitude with the first model including only catastrophising as a mediator and the second also including embarrassment avoidance as an additional mediator. Adding mediators sequentially did not lead to an increase in the mediated effect suggesting that we were gaining no new information from the addition of symptom focusing when already accounting for catastrophising.

For the symptom severity outcome, we only saw one mediator so did not conduct any further modelling.

4. Discussion

4.1. Summary of findings

In the PRINCE-secondary trial (Chalder, 2021) there was a statistically significant ($p < 0.05$) small to moderate sized (total) treatment effect at the end of treatment (20 weeks). In this study we used mediation models to explore whether TDT-CBT acted via selected key cognitive behavioural responses which were targeted in treatment and measured at 9 weeks. The current study also further investigated symptom severity (PHQ-15) which showed a small sized but non-significant (total) treatment effect at 20 weeks. Our intervention significantly changed several mechanisms. This provides some evidence for our theoretical model. We found that some of our putative mediator variables did indeed mediate the TDT-CBT effect on WSAS (catastrophising and symptom focusing) or the effect on PHQ-15 (symptom focusing). However, even for the strongest mediators the associated indirect effect only accounted for less than half the treatment effect (the largest proportion mediated of 37.9% was found for catastrophising on WSAS). Furthermore, the size of the indirect effect could not be increased by considering the detected mediators jointly in a multiple mediator model for the WSAS, suggesting that these variables may have

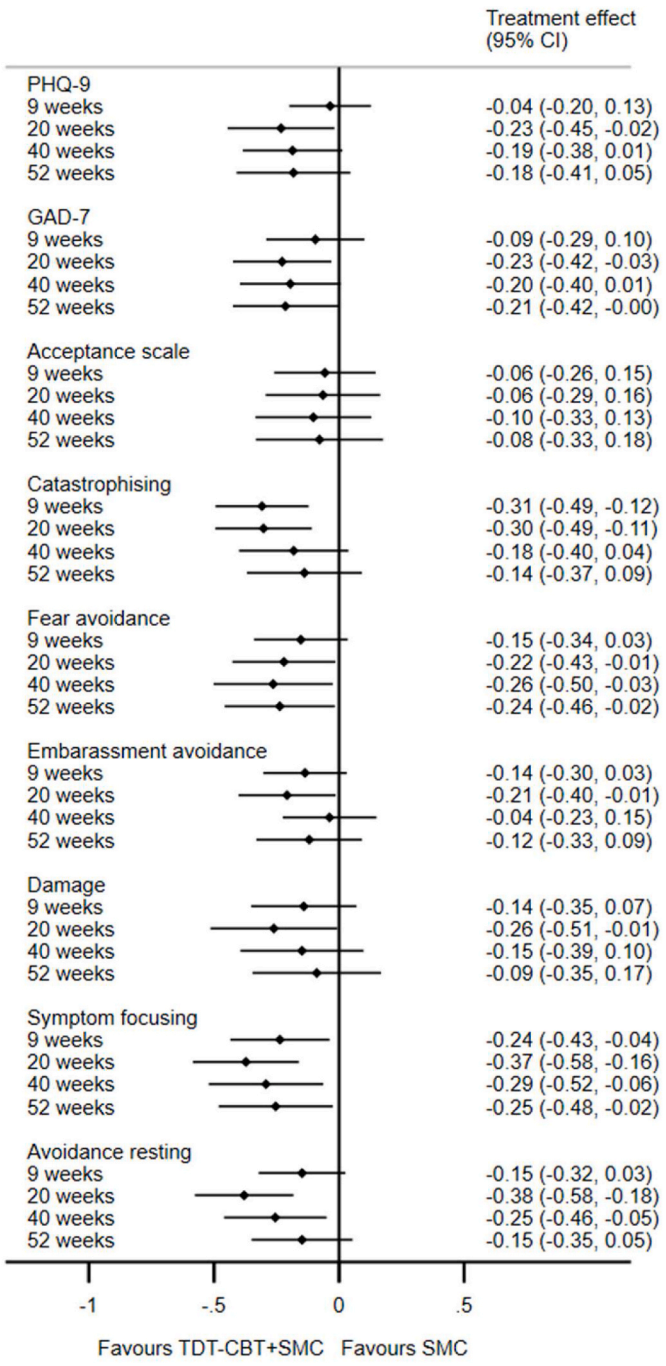

Fig. 4. Estimated effects of TDT-CBT plus SMC compared with SMC alone derived by multiple imputation (100 imputations, estimated differences, CIs).

some shared variance. The relatively large sizes of the remaining direct effects (for details see appendix Tables 2a and 2b) suggest that the treatment effects were partly brought about by changing variables not captured in this study. Consideration of the a path showed that the action effect might have worked for a few of the hypothesised mediator variables (for WSAS catastrophising showed a significant action path, symptom focusing achieved similar small to moderate effect sizes) but not for the majority (4 were estimated to have effect sizes <0.2). Consideration of the b path showed that our conceptual theory of how TDT-CBT brings about improvements in outcome was empirically supported with all putative mediator variables but two (damage and avoidance resting) being statistically significant and of moderate to large b effect sizes in the hypothesised direction. It also suggests that the lack of empirical support for mediation for some of the hypothesised variables is due to TDT-CBT failing to induce sufficient change in these variables.

Half of our sample met criteria for fibromyalgia. Research has previously shown that changes in catastrophising mediated the reduction in depression and pain behaviour following CBT (Spinhoven et al., 2004). Catastrophising is well recognised as modulating pain related outcomes (Petrini & Arendt-Nielsen, 2020) and is defined as a cognitive-affective response to anticipated or actual pain and is associated with pain related outcomes. The items on the scale we used included items largely commensurate with future directed thinking. Such items include "I worry that I may become permanently bedridden because of my symptoms, I think that if my symptoms get too severe, they may never decrease, and I will never feel right again". In Becks model of cognitive distortions where catastrophising is seen as a cognitive error it is viewed as a signal of danger and impending disaster. Three out of four items on our scale relate to future oriented threat, described by some as an anxiety emotional response rather than a fear emotional response (Asmundson & Katz, 2009). Given the future threat nature of the items coupled with the fact that we found that anxiety mediated the treatment effect on symptom severity it seems reasonable to assume that our intervention was changing symptom related anxiety as suggested by Asmundson and Katz (2009).

The ongoing nature of symptoms understandably generates an awareness of the body and symptom focusing becomes a perpetuating factor in symptom persistence and this symptom focusing is difficult to move away from. Our intervention included several ways of helping participants to do just that. Participants were encouraged to regularise their activity, increase enjoyable activities as well as to use re-focusing techniques and relaxation (Chalder et al., 2019). Although we cannot know which element of the intervention was particularly potent our results suggest that future trials should target catastrophising and symptom focusing in particular.

Our complex intervention involved a relatively small number of sessions. While future interventions should continue to target these processes, the effect may well be potentiated by additional sessions. In addition, the multi-modal intervention could be fine-tuned so that any link between symptoms or anxiety and responses such as catastrophising and symptom focusing could be linked more explicitly. Because of the relatively short number of sessions and the diverse number of symptoms described it is likely that there was insufficient time to address all the possible processes in a way that was fully understood by participants.

It is highly likely that additional change mechanisms were not measured. It is possible that changes in other emotional regulation strategies such as emotional avoidance would bring about a change in outcomes. Although there were a number of emotion-focused strategies included in our TDT-CBT, a specific emotion-focused therapy (EFT) may be warranted for persistent physical symptoms. The prevalence of anxiety and depression in PPS certainly suggests this may be a possible avenue for future research particularly given that EFT was developed as a transdiagnostic approach (Greenberg & Korman, 1993) and is now being evaluated as such (Timulak et al., 2020).

4.2. *Strengths and limitations*

This RCT is the first to evaluate a transdiagnostic approach to PPS and therefore the first to carry out a planned secondary mediation analysis. Our model and interventions were coherent and based on the a priori theoretical model which assumed that cognitive behavioural and affective processes maintain symptoms and disability across conditions (Chalder et al., 2019). Accordingly, the putative mediators we chose to investigate were theoretically informed. Our outcome measures were chosen as they are valid and reliable. However, there may have been better outcome measures which were more comprehensive. Our analyses were set out to infer causality under clearly specified assumptions. Our statistical models controlled for potential confounders such as age

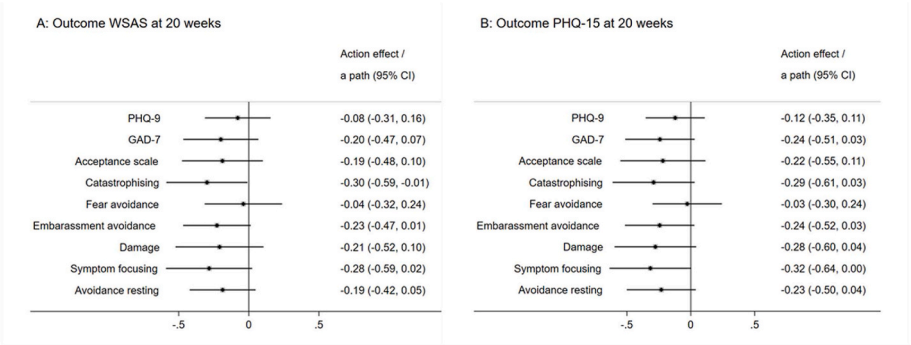

Fig. 5. Estimated standardised action effects (a path) for all mediators at 9 weeks by multiple imputation (100 imputations). (Estimates can vary between outcome models due to differences in respective imputation models.)

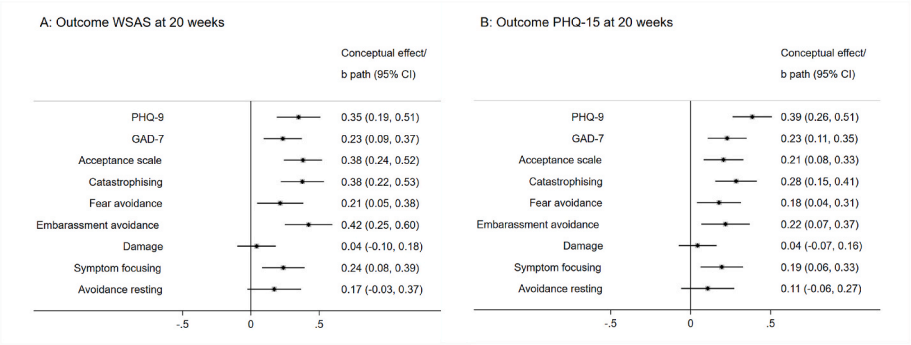

Fig. 6. Estimated standardised conceptual effects (b path) for all mediators at 9 weeks and outcomes at 20 weeks derived by multiple imputation (100 imputations).

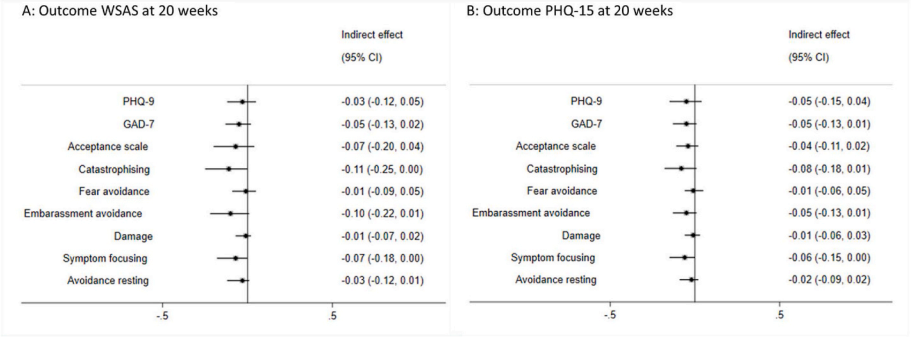

Fig. 7. Estimated standardised indirect effects (ab path) for all mediators at 9 weeks and outcomes at 20 weeks derived by multiple imputation (100 imputations).

and sex and temporal ordering of the variables makes causal inferences about the mechanisms of action plausible. We had some missing data and therefore used a method for mediation analysis that avoided biases provided that the missing values were missing at random. However, due to the missingness pattern, depending on the particular combinations of mediators and outcomes considered, effect estimates of the a path or c path depended on the outcome and mediators respectively. Although our sample was reasonably large and the outcome study was sufficiently powered to test whether one intervention was superior to the other, the study was not powered to detect an indirect effect (mediation). Ideally, mediators would be assessed at every session. By doing this a more nuanced understanding of mechanisms of change would be possible. Notwithstanding this, we were able to measure and assess all the change mechanisms that we previously described in our LOGIC model (Chalder et al., 2019).

4.3. Conclusions

We developed a transdiagnostic treatment that targeted certain cognitive behavioural mechanisms. We did indeed change the mechanisms which led to change in disability and symptom burden. Future evaluations might include more treatment sessions to potentially increase effect sizes. Understanding mechanisms will help facilitate the development of new interventions or help refine the ones we have. Given the emotional nature of the mediators (catastrophising and symptom focusing) it is possible that interventions that teach patients emotional regulation strategies could improve outcomes. Although our intervention included strategies to help regulate emotion, future studies should explore this further.

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CRediT authorship contribution statement

Kirsty James: Formal analysis, drafted the manuscript. **Meenal Patel:** drafted the manuscript. **Kimberley Goldsmith:** All authors contributed to the final draft. **Rona Moss-Morris:** All authors contributed to the final draft. **Mark Ashworth:** All authors contributed to the final draft. **Sabine Landau:** Formal analysis, drafted the manuscript, All authors contributed to the final draft. **Trudie Chalder:** was the Chief investigator, drafted the manuscript.

Declaration of competing interest

TC received ad hoc payments for conducting workshops on evidence-based treatments for persistent physical symptoms. TC has received grants from NIHR programme grants, HTA, RfPB, Guy's and St Thomas Charity, King's Challenge Fund. Personal financial interests: TC is the author of several self-help books on chronic fatigue and received royalties in the past. TC received expenses for workshops on evidence-based treatments for persistent physical symptoms for BABCP and IAPT services (travel and accommodation). RMM reports grants from NIHR programme grants, grants from MS Society UK, grants from Crohn's and Colitis UK, grants from Breast Cancer Now, grants from National MS society, grants from NIHR HTA grants, personal fees from National Advisor to NHS England for Increasing Access to Psychological Therapies (IAPT) for People with Long-Term Conditions from 2011 to 2016, personal fees from Ad hoc payments for workshop training, personal fees from Consultancy payments from Mahana Therapeutics, other from travel expenses to present invited talks to conferences WBCBT, ICBM, ECTRIMS, EHPS, ARPH, outside the submitted work; and King's College London has signed a license agreement with Mahana Therapeutics for a digital version of CBT for Irritable Bowel Syndrome that was developed by RMM and colleagues at Southampton and TC at King's College London. RMM and other inventors are beneficiaries of this license through contracts with their respective universities. SL has received grants from NIHR, MRC, ESRC, Wellcome Trust, Stanley Medical Research, MND and ALS Associations, Parkinson Disease Society, Psychiatry Research Trust, KCL Translational Research, PPP Healthcare Medical Trust and Johnson and Johnson.

Data availability

Data will be made available on request.

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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.2022.104224.

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