Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial

Trudie Chalder*, Kimberley A Goldsmith*, Peter D White, Michael Sharpe, Andrew R Pickles

Summary

Background Cognitive behaviour therapy (CBT) added to specialist medical care (SMC), or graded exercise therapy (GET) added to SMC, are more effective in reducing fatigue and improving physical function than both adaptive pacing therapy (APT) plus SMC and SMC alone for chronic fatigue syndrome. We investigate putative treatment mechanisms.

Methods We did a planned secondary mediation analysis of the PACE trial comparing SMC alone or SMC plus APT with SMC plus CBT and SMC plus GET for patients with chronic fatigue syndrome. 641 participants were recruited from six specialist chronic fatigue syndrome clinics in the UK National Health Service between March 18, 2005, and Nov 28, 2008. We assessed mediation using the product of coefficients method with the 12 week measure of the mediators and the 52 week measure of the outcomes. The primary outcomes were fatigue measured by the Chalder fatigue scale and physical function measured by the physical function subscale of the SF-36. We included confounder covariates and used treatment by mediator interaction terms to examine differences in mediator–outcome relations by treatment group.

Findings The largest mediated effect for both CBT and GET and both primary outcomes was through fear avoidance beliefs with an effect of larger magnitude for GET (standardised effects ×10, CBT *vs* APT, fatigue –1·22, 95% CI –0·52 to –1·97, physical function 1·54, 0·86 to 2·31; GET *vs* APT, fatigue –1·86, –0·80 to –2·89, physical function 2·35, 1·35 to 3·39). Increase in exercise tolerance (6 min walk distance) was a potent mediator of the effect of GET (*vs* APT, fatigue –1·37, 95% CI –0·76 to –2·21, physical function 1·90, 1·10 to 2·91), but not CBT.

Interpretation Our main finding was that fear avoidance beliefs were the strongest mediator for both CBT and GET. Changes in both beliefs and behaviour mediated the effects of both CBT and GET, but more so for GET. The results support a treatment model in which both beliefs and behaviour play a part in perpetuating fatigue and disability in chronic fatigue syndrome.

Funding UK Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions, National Institute for Health Research (NIHR), NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust, and Institute of Psychiatry, Psychology, and Neuroscience, King's College London.

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For more on the **PACE trial** see www.pacetrial.org

Introduction

Chronic fatigue syndrome, sometimes referred to as myalgic encephalomyelitis, is associated with profound disability.[1,2] Our multicentred randomised controlled trial, PACE (adaptive Pacing, graded Activity and Cognitive behaviour therapy; a randomised Evaluation),[3,4] compared specialist medical care (SMC) alone versus SMC with adaptive pacing therapy (APT), cognitive behaviour therapy (CBT), or graded exercise therapy (GET) for chronic fatigue syndrome.

We standardised treatments by the provision of manuals for doctors, therapists, and participants. At least three sessions of SMC were offered over 52 weeks and 14 hourly therapy sessions were offered weekly, then fortnightly, up to 24 weeks. A booster therapy session was given at 36 weeks. Specialist doctors gave participants general advice about managing the illness. It was suggested that extremes of activity and rest should be avoided, self-help books were suggested, and specific pharmacotherapy could be offered for insomnia, pain, or mood problems.

CBT involves enabling individuals to develop a consistent approach to activity, and is followed by gradual increases in activity. CBT also encourages people to develop healthy sleep patterns and enables them to identify and challenge unhelpful cognitions[5] with the primary aims of reducing fatigue and improving physical function. It is based on a theoretical model, which supposes that unhelpful interpretations of symptoms, fearful beliefs about engaging in activity, and excessive focus on symptoms are central in driving disability and symptom severity.[5] These cognitive responses are associated with unhelpful behavioural patterns, including avoidance of activity or all-or-nothing behaviour—a pattern of excessive resting alternating with pushing too hard or being overactive when well.

GET for chronic fatigue syndrome involves establishing a baseline of consistent activity and regular sleep–wake cycle, then encouraging mutually negotiated increments in the time spent physically active (most commonly walking) followed by an incremental increase in the intensity of exercise to a target of 30 min of physical exercise five times a week. It is based on a model of both de-conditioning (loss of muscle strength and reduced exercise capacity) and avoidance of activity.[6] Both these

factors are thought to maintain fatigue and disability.[7–9] Systematic reviews have suggested that patients with chronic fatigue syndrome are less physically active and have less isometric muscle strength and reduced exercise capacity than healthy controls.[10,11]

CBT and GET in the context of this trial had much in common, but could be differentiated. Both involved agreeing an achievable and consistent baseline of activity and then increasing activity, although GET specifically focused on physical exercise. CBT addressed unhelpful thoughts but GET did not. CBT and GET were clearly distinguished by independent raters who rated treatment integrity and were masked to the treatment group.[3]

APT for chronic fatigue syndrome involved the encouragement of participants to plan activity with a view to avoiding increases in symptoms, and restricting demands and stress. It included specific advice not to undertake activities that demanded more than 70% of participants' perceived energy envelopes to establish a baseline of achievable activity, and then increasing as able.[3] It was based on the envelope theory of chronic fatigue syndrome in which the illness is assumed to be entirely physical, with fixed energy levels.[12]

We found that, when added to SMC, CBT and GET had greater success in reducing fatigue and physical disability than did APT or SMC alone.[3] The number of therapy sessions received was similar across groups. However, the SMC-alone group received a median of two more SMC sessions than the therapy supplemented treatment groups. Antidepressant and hypnotic use did not differ significantly between groups, either at baseline or at follow-up. The interval between baseline and follow-up was the same for all treatments. There were no important differences in safety outcomes between treatment options. Mean differences between groups on primary outcomes almost always exceeded predefined clinically useful differences for CBT and GET when compared with APT and SMC. In all comparisons of the proportions of participants who had either improved or were within normal ranges for these outcomes, CBT and GET were superior to APT or SMC alone.[3] Improvements were moderate in size and therefore outcomes need to be improved further. Identification of the mechanisms of change might explain how effective treatments can be further developed, improved, or optimised. The study of mediation might also provide information about the utility of the model on which treatment is based.

We designed the PACE trial to gain perspective on the mechanisms of change through the identification of mediators. To this end, the trial measured a range of putative mediators and outcomes. We aimed to explore whether specific putative mediators measured at 0, 12, 24, and 52 weeks changed to a different extent between treatment groups, and to examine whether these factors mediated differences in fatigue and physical function in CBT and GET compared with APT and SMC. Based on

models of chronic fatigue syndrome and previous findings we postulated that fearful beliefs, in particular fear avoidance beliefs (eg, "I am afraid that I will make my symptoms worse if I exercise"), symptom focusing (eg, "I think a great deal about my symptoms"), catastrophising (eg, "I will never feel right again"), and avoidance behaviour (eg, "I stay in bed to control my symptoms") would mediate change in fatigue and physical function in both CBT and GET. We also postulated that timed walking distance as a measure of exercise tolerance, but also as a more objective measure of activity engagement, would mediate change in both outcomes for CBT and GET. Based on the fact that embarrassment avoidance, damage beliefs, self-efficacy, perception of effort, and unhelpful sleep routines are targeted in CBT, these additional processes were also examined. Some empirical evidence exists to support their inclusion. Embarrassment avoidance (eg, "I am embarrassed about my symptoms") and damage beliefs (eg, "Symptoms are a signal that I am damaging myself") have been shown to change with routine CBT and an exploratory latent trait model suggested that the observed partial mediation model generalised to illness-related cognitive traits.[13] There is evidence that self-efficacy might be an important transdiagnostic mechanism of change.[14,15] Perception of effort with exercise is increased in people with chronic fatigue syndrome and we believed it was likely to change with rehabilitative treatments such as CBT and GET.[16] A poor sleep routine is commonplace in people with chronic fatigue syndrome,[17] and establishing a sleep routine is a focus of CBT and therefore might improve fatigue and disability. Finally, on the basis of previous trials we predicted that anxiety, depression, all-or-nothing behaviour, and fitness would not mediate treatment outcome either in CBT or GET.

Methods

Study design and participants

Between March 18, 2005, and Nov 28, 2008, 641 participants aged 18 years or older were recruited from consecutive new outpatients attending six specialist chronic fatigue syndrome clinics in the UK National Health Service. Participants fulfilled the Oxford criteria for chronic fatigue syndrome,[2] which requires fatigue to be the principal symptom. All participants were medically assessed by the specialist clinic doctors to exclude alternative diagnoses.[4] The West Midlands Multicentre Research Ethics Committee (MREC 02/7/89) approved the original PACE study.

The main results of the trial have been reported elsewhere;[3] 561 (88%) received an adequate dose of treatment and ten (2%) were completely lost to follow-up. We did a planned secondary mediation analysis of the PACE trial comparing SMC alone or SMC plus APT with SMC plus CBT and SMC plus GET for patients with chronic fatigue syndrome.[3,4]

Description of the generic mediation model

Mediation is a hypothesised causal chain in which a baseline variable R affects a post-baseline mediating variable M, which in turn affects an outcome variable Y.[18] In the case of a trial such as PACE, R is treatment group, for example CBT compared with APT, and an example mediator and outcome might be fear avoidance and physical function (figure 1). If the intervening variable M explains the relation between R and Y (the relation between R and Y is no longer statistically significant when adjusting for M in the model and the estimate for R is essentially equal to zero), then M is a mediator and we have a full mediational model.[19,20] If the intervening variable only partially explains the relation between R and Y (the M effect is statistically significant but R is not equal to zero or still has a significant effect on Y after including M in the model) the model is consistent with partial but not full mediation.[19,20]

Procedures

The measures, which are described in more detail in the appendix, were all assessed at 0, 12, 24, and 52 weeks after randomisation, and these were described with unadjusted mean profile plots. For the mediation analysis, we used the 52 week measure of the outcome and the 12 week measure of the putative mediator. The exception was the walk test where the 24 week measure was used as the mediator; the walk test was not done at 12 weeks owing to the anticipated burden for participants. The 12 week measure of the mediator was used to capture change as early as possible and have the maximum possible separation between mediator and outcome measurements. This temporal separation between the variables was employed to meet the implicit mediation model assumption of ordering of the variables in the causal chain.[18] This ordering is important for rendering causal mediation inferences more plausible.

The primary outcomes were fatigue measured by the Chalder fatigue scale and physical function measured by the physical function subscale of the SF-36. We measured several of the putative mediators using the Cognitive Behavioural Responses Questionnaire (CBRQ); these were five cognitive measures: catastrophising, fear avoidance beliefs, damage beliefs, symptom focusing, and embarrassment avoidance beliefs, and two behavioural measures: all-or-nothing behaviour and avoidance or resting behaviour. Other putative mediators were: self-efficacy, sleep measured using the Jenkins Sleep Scale, anxiety and depression measured using the Hospital Anxiety and Depression Scale (HADS), fitness and perceived exertion measured using a step test, and walking distance measured using the 6 min walk test.

Statistical analysis

The main outcomes were pro-rated only when there were at most two items missing from the scale. We calculated the mean value of complete item scores and used them in place of missing item values. The mediators were not pro-rated since most with missing data were missing all items. We restricted the main analyses, including regression models, to participants with complete records for all variables considered. We summarised mediators using the mean, SD, and 95% CI for the mean.

We assessed mediation from regressions with the product of coefficients method (POC),[18] shown in both equation (below) and path diagram form (figure 1), where Y is the outcome, M is the mediator, R is the randomised treatment group, and ε is an error term (other covariates are not shown for simplicity):

$$Y_i = \alpha_1 + \beta_1 R_{i} + \varepsilon_{i1} \qquad \text{(Model 1)}$$
$$M_i = \alpha_2 + \beta_2 R_{i} + \varepsilon_{i2} \qquad \text{(Model 2)}$$
$$Y_i = \alpha_3 + \beta_3 R_{i} + \gamma M_{i} + \varepsilon_{i3} \qquad \text{(Model 3)}$$

The β_1 parameter is the overall effect of the treatment on the outcome, referred to as the c pathway in the mediation literature. The mediated (indirect) effect is then β_2 multiplied by γ, or a multiplied by b from figure 1. The direct effect of R on Y in the presence of M is given by β_3 and is called the c' pathway. In addition to the temporal ordering assumption, the usual assumptions are associated with the regressions used in the POC method, including: accurate measurement, linearity, normally distributed residuals, and no omitted variables.[18] The latter assumption has received a great deal of attention in mediation, particularly in clinical trials where, despite randomisation, there could still be confounding of the non-randomised relation between the mediator and outcome (U in figure 1).[18,20,21] If there are unmeasured variables that affect both mediator and outcome, the estimate obtained for this relation might be biased. Although unmeasured confounding cannot
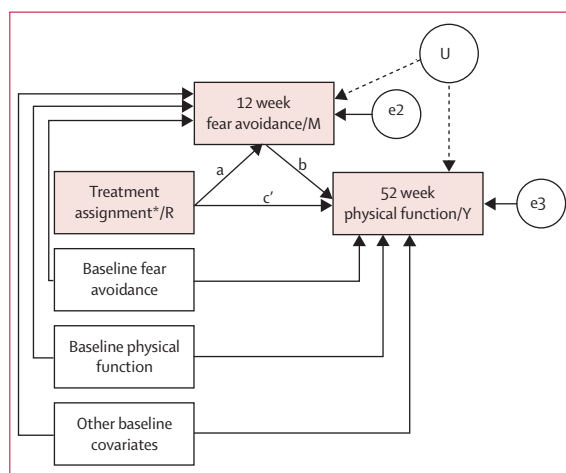
Figure 1: **Example of a PACE mediation model**
R=randomised treatment. M=mediator. Y=outcome. U=unmeasured confounders. a=a path (treatment to mediator). b=b path (mediator to outcome). c'=c' path (direct effect of treatment on outcome accounting for mediator). e2=error term in mediator model. e3=error term in outcome model. *For example, cognitive behaviour therapy versus adaptive pacing therapy.

be ruled out, adding baseline variables that might be confounders makes a causal interpretation more plausible; further covariates were included in the models to address this.[18,21] For example, if these variables were confounders, including them will have provided an adjusted and hopefully more accurate estimate, and if they were proxies for unmeasured confounders they might have partially adjusted for the omitted variables as well. The variables were selected for inclusion in models because they were thought to be potential predictors of mediators and outcomes. Age and sex could also be proxies for other variables that were not measured. The original trial stratification factors were included to respect the trial design. The included baseline variables were: centre, Standardised Clinical Interview for DSM-IV (SCID) depression status,[22] London criteria for myalgic encephalomyelitis status,[23] International Criteria for chronic fatigue syndrome status,[1] baseline measure of mediator, baseline measures of both outcomes, baseline work and social adjustment scale,[24] any anxiety disorder as determined using the SCID, age, sex, chronic fatigue syndrome patient group membership, receipt of financial benefits, being in dispute regarding financial benefits, physical illness attribution, fibromyalgia status,[25] illness duration, Jenkins Sleep Score, employment status, body-mass index, and physical symptoms (Patient Health Questionnaire-15) score.[26] All these variables were included in all models, except where they were likely to be collinear with the baseline measure of the mediator (ie, SCID depression was omitted in the HADS depression model, and likewise for anxiety). Medication use variables were available, but were not used because these were not theorised to be likely confounders in the context of the large number of other confounders included.

The POC method shares some similarities with two other methods commonly applied to the study of mediation, the Baron-Judd-Kenny causal steps approach and the use of the structural equation model framework.[18–20] The causal steps approach requires the overall treatment effect, or the effect of β_1 in model 1, to be significant before proceeding. Similar to others[18,21] we do not believe this to be necessary. Rather, we suggest examining whether there is an absence of a treatment effect on the mediator, an absence of a mediator effect on the outcome, or the occurrence of opposing direct and indirect effects. The structural equation modelling framework requires some additional assumptions such as multivariate normality.

The mediator models (model 2) had the 12 week post-randomisation measurement of each of the putative mediators as the dependent variable (except for the 6 min walking distance where the 24 week measure was used) and both treatment group (as a three-level dummy variable with either APT or SMC as the reference category) and the potential confounders as covariates. The outcome models had the 52 week post-randomisation

measure of each of the outcomes as the dependent variable, with treatment group, the 12 week measure of the putative mediator, and the potential confounders as covariates (model 3). Tests of interaction between treatment and mediator on outcome were all non-significant, allowing a coefficient b to be estimated that was common to all treatments (figure 1), improving efficiency and model stability. We used the statistical significance and magnitude of the model parameters associated with the c and c' pathways to assess whether mediation was partial or full.

All continuous variables were standardised (each value had the mean of the variable subtracted and was divided by the SD of the variable) so that parameters represented changes in SD units. Results from the mediator models are therefore in SD units of the mediator; results from the outcome models are in SD units of the outcome. The a multiplied by b mediation effect here therefore constituted the recommended standardised mediation effect in SD units of the outcome,[18] with a bias-corrected bootstrap 95% CI. This allowed for asymmetry of the interval, obtained using bootstrapping with 1000 repetitions.[18,27] Bootstrap CIs can have incorrect endpoints; the bias-corrected bootstrap adjusts the interval endpoints by a constant quantifying the approximate median bias of the bootstrap estimate in units of the standard normal distribution.[27] All mediated effects were multiplied by 10 to decrease the number of decimal places in figures and tables for visualisation purposes. Mediated effects have also been expressed as the proportion of the overall effect of the treatment on the outcome, in other words $(ab / c) \times 100$. Note that the percent mediated would not be expected to add up to 100% within a given comparison as the mediators have been studied individually and any overlapping effects have not yet been examined. Both CBT and GET were compared with APT and SMC. Some mediated effects have been compared between CBT and GET using Wald tests of the equality of the two parameter estimates in the mediator models (model 2). The statistical analyses were done using Stata, version 10.

Role of the funding source

Results
The appendix shows information about data completeness, balance of baseline variables between treatment groups in the mediation analysis data subset, and differences between the people with and without complete data for the mediation analysis. Unadjusted
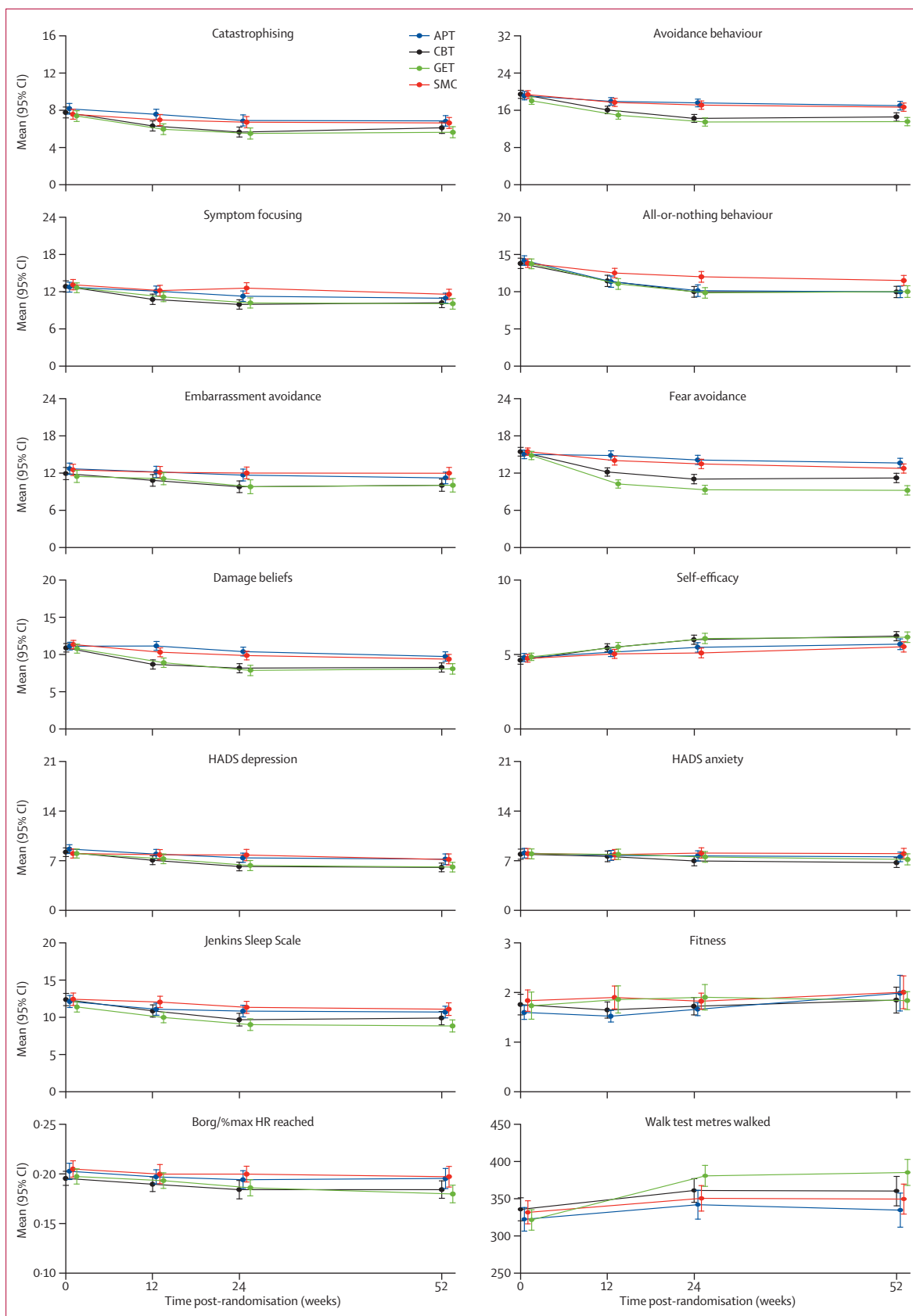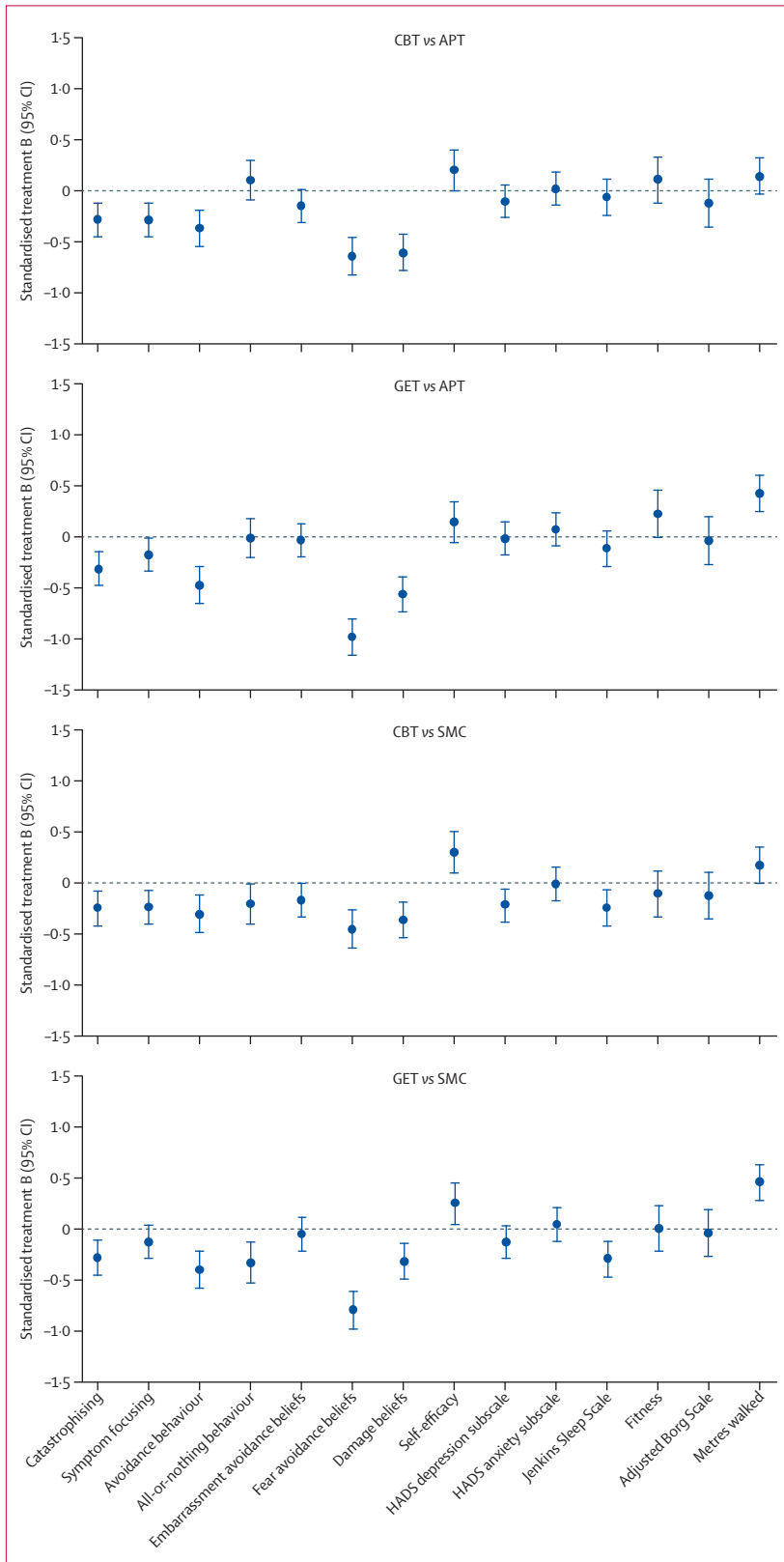
Figure 2: **Unadjusted mean (95% CI) of putative mediator measures over time**
For mediation analysis, baseline measurements were used as covariates and 12-week measurements were used as mediators. APT=adaptive pacing therapy. CBT=cognitive behaviour therapy. GET=graded exercise therapy. SMC=specialist medical care. HADS=Hospital Anxiety and Depression Scale. HR=heart rate.

Figure 3: Standardised effects of treatments on putative mediators in SD units of the mediator
As well as treatment, models also included: centre, Standardised Clinical Interview for DSM-IV (SCID) depression status, London criteria for myalgic encephalomyelitis status, International Chronic Fatigue Syndrome (CFS) criteria, baseline measures of both outcome variables, baseline Work and Social Adjustment Scale, SCID anxiety disorder status, age, sex, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins sleep score, employment status, body-mass index, and physical symptoms (PHQ-15) score. APT=adaptive pacing therapy. B=standardised β parameter from model for mediator. CBT=cognitive behaviour therapy. GET=graded exercise therapy. HADS=Hospital Anxiety and Depression Scale. SMC=specialist medical care.

mean profile plots of the outcomes over time are also presented in the appendix.

Plots and summary statistics for the putative mediators (figure 2, appendix) show similar patterns to those of the outcomes with greater improvement with CBT and GET, the majority of change occurring during the treatment phase. There was little change between the end of treatment at 24 weeks and follow-up at 52 weeks. There were some exceptions to the general pattern; all-or-nothing behaviour decreased to a similar level for APT, CBT, and GET, and fear avoidance improved more in the GET group than for CBT.

Figure 3 shows the treatment effects of CBT and GET, as compared with APT and SMC, on the putative mediating variables. These effects equate to the *a* path shown in figure 1 and are differences in mediator SD units between compared treatments. Compared with APT and SMC, both CBT and GET significantly decreased catastrophising, avoidance behaviour, fear avoidance beliefs, and damage beliefs. The strongest effects were on fear avoidance beliefs (CBT *vs* APT −0·64, 95% CI −0·46 to −0·83, GET *vs* APT −0·98, −0·80 to −1·16), and damage beliefs (CBT *vs* APT −0·61, −0·43 to −0·78, GET *vs* APT −0·56, −0·39 to −0·73). GET had a larger effect on fear avoidance beliefs than did CBT (p=0·0004). Compared with APT, both CBT and GET decreased symptom focusing, and compared with SMC, the treatments significantly decreased all-or-nothing behaviour and sleep problems, and increased self-efficacy. Additionally, CBT also decreased symptom focusing, embarrassment avoidance, and HADS depression as compared with SMC. In both types of comparisons, GET significantly increased the number of metres walked, whereas CBT did not (GET *vs* APT 0·43, 95% CI 0·25–0·61; GET *vs* SMC 0·46, 0·28–0·63; CBT *vs* GET p=0·001). There were no effects on HADS anxiety, physical fitness, or the adjusted perception of effort measure (Borg scale).

Figure 4 shows the relation between the putative mediators and the outcomes. These effects equate to the *b* path shown in figure 1, and are differences in outcome SD units for a 1 SD unit change in the mediator. The models show that increases in catastrophising, all-or-nothing behaviour, embarrassment avoidance, fear avoidance beliefs, damage beliefs, HADS depression,

sleep problems, and adjusted Borg scores (=worsening) were associated with significantly worse fatigue, which means that when treatments reduced these variables, there was a reduction in fatigue. Increases in (=better) scores of self-efficacy and metres walked were associated with significant decreases in fatigue. The strongest effects on fatigue were for metres walked (–0·32, 95% CI –0·20 to –0·44) and embarrassment avoidance (0·27, 0·16–0·38). All of the mediators with the exception of the physical fitness measure were associated with physical function; and similar to fatigue, these were in the directions expected. The largest effects here were for metres walked (0·44, 0·34–0·55) and HADS depression (–0·33, –0·23 to –0·43). Self-efficacy also had reasonably strong effects on both outcomes.

Figures 5 and 6 show standardised mediation effects (×10) for all mediators and treatment comparisons studied (parameter estimates, CIs, and proportion mediated are shown in appendix). Fear avoidance beliefs had the largest mediated effect on both fatigue and physical function for both CBT (fatigue CBT *vs* APT –1·22, 95% CI –0·52 to –1·97; physical function CBT *vs* APT 1·54, 0·86 to 2·31) and GET (fatigue GET *vs* APT –1·86, –0·80 to –2·89; physical function GET *vs* APT 2·35, 1·35–3·39). This accounted for 51% of the overall effect on physical function for GET and 37% for CBT, as compared with APT. The proportions were 61% and 34% for the same comparisons for the fatigue outcome. Damage beliefs also mediated the effects of both treatments on both outcomes—the effects were the second largest in magnitude of the cognitive mediators for comparisons with APT (fatigue CBT *vs* APT –0·85, –0·23 to –1·68, GET *vs* APT –0·78, –0·24 to –1·58; physical function CBT *vs* APT 1·26, 0·61–2·13, GET *vs* APT 1·16, 0·57–2·02), with approximately 25–30% of the overall effect on both outcomes being accounted for by damage beliefs. Damage beliefs and self-efficacy were mediators of similar magnitude for the SMC comparisons. For comparisons with APT, self-efficacy was either a relatively weak or non-significant mediator because it did not change significantly more with either CBT or GET than with APT (figure 3). Catastrophising and avoidance behaviour were also significant mediators of treatments for all comparisons and both outcomes, albeit with effects of smaller magnitude as compared with fear avoidance (figures 5 and 6, appendix). For example, the largest proportion of the overall effect explained for catastrophising was 18% for CBT versus APT for the physical function outcome. The number of metres walked (exercise tolerance) was a strong mediator of the effect of GET on both outcomes, both for comparisons with APT (fatigue GET *vs* APT –1·37, –0·76 to –2·21; physical function GET *vs* APT 1·90, 1·10–2·91) and SMC (fatigue GET *vs* SMC –1·46, –0·75 to –2·34; physical function GET *vs* SMC 2·03, 1·16–2·99), with this accounting for approximately 33% of the overall effect for the comparisons with APT.
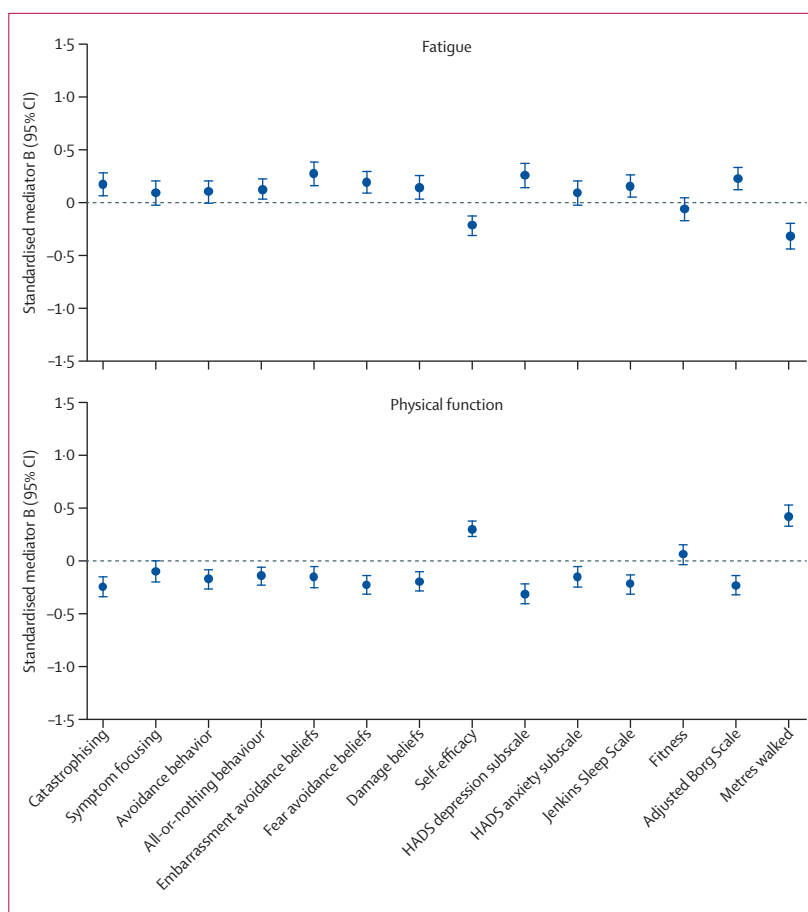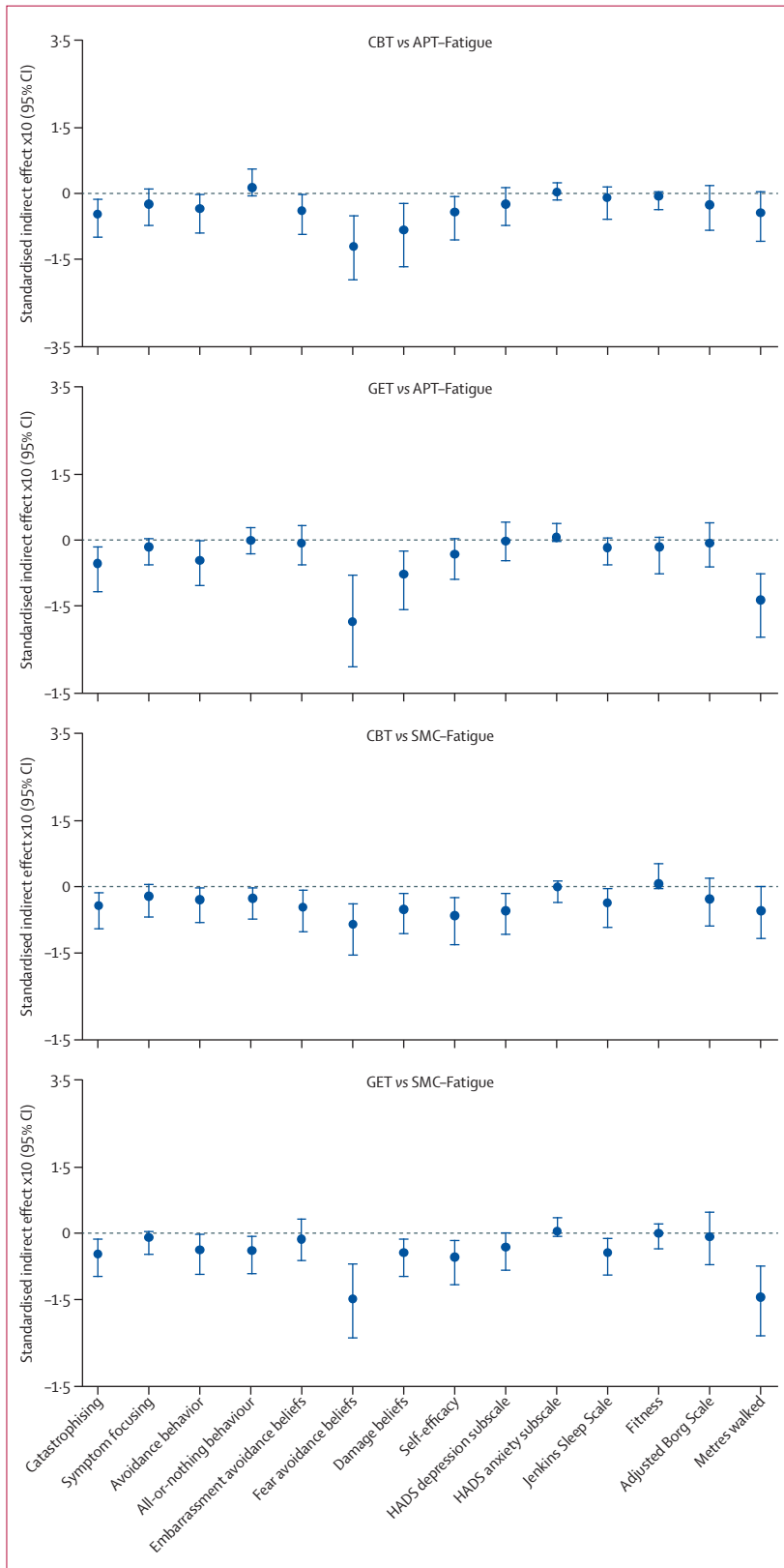

Figure 4: **Standardised effects of putative mediators on outcomes in SD units of the outcome**
As well as treatment, models also included: centre, Standardised Clinical Interview for DSM-IV (SCID) depression status, London criteria for myalgic encephalomyelitis status, International Chronic Fatigue Syndrome (CFS) criteria, baseline measures of both outcome variables, baseline Work and Social Adjustment Scale, SCID anxiety disorder status, age, sex, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins sleep score, employment status, body-mass index, and physical symptoms (PHQ-15) score. B=standardised beta parameter from model for outcome. HADS=Hospital Anxiety and Depression Scale.

Other mediated effects that were statistically significant for both outcomes were embarrassment avoidance for CBT for both comparisons, all-or-nothing behaviour and sleep problems for CBT and GET comparisons to SMC, and depression for CBT versus SMC only. One mediating effect was restricted to the outcome of physical function: symptom focusing was a mediator of CBT as compared with both APT and SMC. Figure 7 shows path diagrams for the fear avoidance beliefs mediator. Fear avoidance was a partial rather than a full mediator in both cases. This can be seen by looking at the *c'* path, or residual direct effect of treatment. This path was only non-significant for the GET versus APT comparison for the fatigue outcome, and even so it still differs substantially from zero.

The analysis was repeated using the full information maximum-likelihood structural equation modelling framework that required the weaker assumption of data

Figure 5: **Standardised mediation effects in SD units of the outcome (×10) of treatments on fatigue**

As well as treatment, models also include: centre, Standardised Clinical Interview for DSM-IV (SCID) depression status, London criteria for myalgic encephalomyelitis status, International Chronic Fatigue Syndrome (CFS) criteria, baseline measures of both outcome variables, baseline Work and Social Adjustment Scale, SCID anxiety disorder status, age, sex, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins sleep score, employment status, body-mass index, and physical symptoms (PHQ-15) score. APT=adaptive pacing therapy. CBT=cognitive behaviour therapy. GET=graded exercise therapy. HADS=Hospital Anxiety and Depression Scale. SMC=specialist medical care.

missing at random and allowed for loss selective on covariates and measured outcomes as described in the Methods.[28] The effective sample sizes were increased: 613 to 617 for questionnaire measures (up to 96% complete), 534 for fitness (83% complete), 535 for perceived exertion (Borg, 84% complete), and 595 for walking (93% complete). Results remained essentially unchanged, although some effects that were not significant but borderline in the original analysis became significant: walking for CBT versus SMC, symptom focusing for GET versus APT for physical function, and depression for GET versus SMC for fatigue.

Discussion

Our main finding was that fear avoidance beliefs were the strongest mediator for both CBT and GET. Fear avoidance beliefs are characterised by fears that activity or exercise will make symptoms worse. Damage beliefs were also important in comparison with APT. Exercise tolerance as measured by the number of metres walked in a fixed time was a strong mediator of GET alone. Other cognitive and behavioural measures, such as catastrophising and avoidance behaviour, had small but significant mediation effects for both of the effective treatments affecting both outcomes.

The results suggest that GET might be more specific in its effects than CBT, with two strong mediators, fear avoidance beliefs, and timed walking distance. The increase in exercise tolerance (walking distance) without an increase in exercise capacity (fitness) might have been facilitated by the mediating effect of reduced fear avoidance beliefs.

For CBT, several mediators were implicated with smaller effects of similar magnitude, including depression for comparisons to SMC. Although we are cautious about over interpreting the role of depression as a mediator, CBT is an evidence-based approach for depression that comprises a variety of different procedures including behavioural activation and cognitive restructuring not dissimilar to CBT for chronic fatigue syndrome.

Fear avoidance beliefs, the strongest mediator, accounted for up to 60% of the overall effect, providing evidence for partial mediation. Many of the mediators accounted for much smaller proportions of the overall effects, suggesting that in some cases the effects of treatment on outcomes might have been mediated
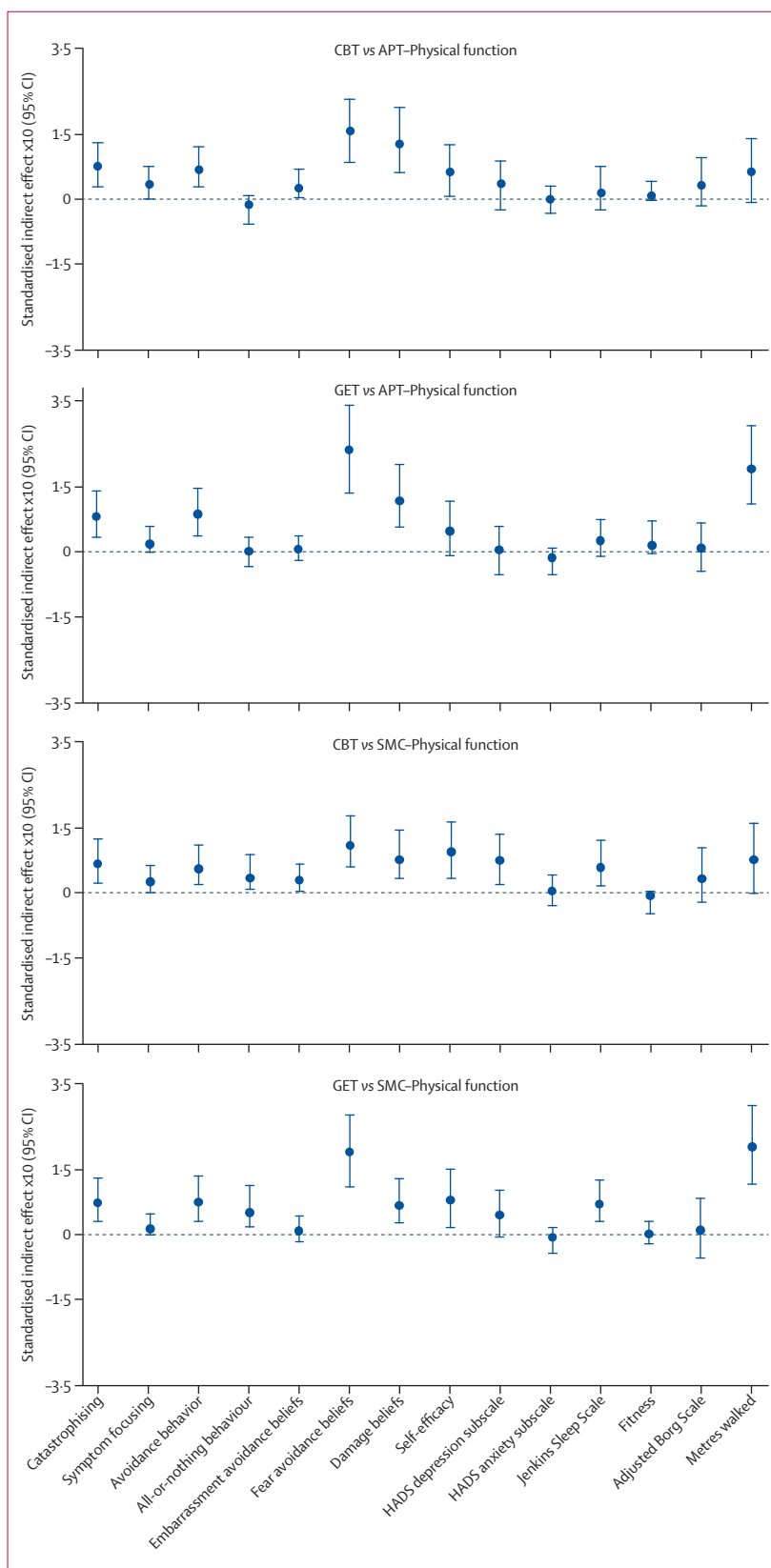
through several small effects and that some of the overall treatment effects were mediated through variables that were not measured.

These findings, which benefit from temporal separation in mediator and outcome measures, support the preliminary findings of previous studies[9,29–33] of treatment mechanisms in chronic fatigue syndrome (panel). In a trial of CBT compared with relaxation,[29] Deale and colleagues found that avoidance behaviour was a mediator of the effect of CBT on physical function cross-sectionally, and a reduction in fearful cognitions was associated with better outcomes. Wiborg and colleagues[30] found that a decrease in focusing on fatigue mediated the effect of CBT in one trial, whereas in another trial by the same investigators,[31] the effect of therapy was mediated by a decrease in perceived problems with activity and an increase in the sense of control over fatigue. These and other similar studies have relied on cross-sectional data.[6,8,9,29–31,33] Consequently, a temporal separation between the mediator and outcomes was missing, making it difficult to ascertain the direction of the causal relation. More recently, the Fatigue Intervention by Nurses Evaluation (FINE) trial compared pragmatic rehabilitation with supportive listening or treatment as usual in chronic fatigue syndrome. Pragmatic rehabilitation contained elements of CBT and GET. It involved regular sessions with a health professional, and included physiological explanations for symptoms with graded activity, but also ensured that the individual had appropriate rest and relaxation. It was delivered at home, over an 18 week period by specially trained general nurses. The mediation analysis of the FINE trial found that fear avoidance, embarrassment avoidance, all-or-nothing and avoidance behaviour were cross-sectional mediators of the treatment effect,[32] whereas catastrophising and avoidance behaviour measured after treatment (20 weeks after randomisation) were prospective mediators of the effect on fatigue at follow-up (70 weeks after randomisation).

Although symptom focusing was found to be a cross-sectional mediator of CBT and GET on fatigue in two previous studies,[9,30] it was not a mediator of the effect of the pragmatic rehabilitation treatment in the FINE trial.[32] Additionally, symptom focusing was only a weak mediator of the effect of CBT on physical function in our

Figure 6: Standardised mediation effects in SD units of the outcome (×10) of treatment on physical function
As well as treatment, models also include: centre, Standardised Clinical Interview for DSM-IV (SCID) depression status, London criteria for myalgic encephalomyelitis status, International Chronic Fatigue Syndrome (CFS) criteria, baseline measures of both outcome variables, baseline Work and Social Adjustment Scale, SCID anxiety disorder status, age, sex, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins sleep score, employment status, body-mass index, and physical symptoms (PHQ-15) score. APT=adaptive pacing therapy. CBT=cognitive behaviour therapy. GET=graded exercise therapy. HADS=Hospital Anxiety and Depression Scale. SMC=specialist medical care.
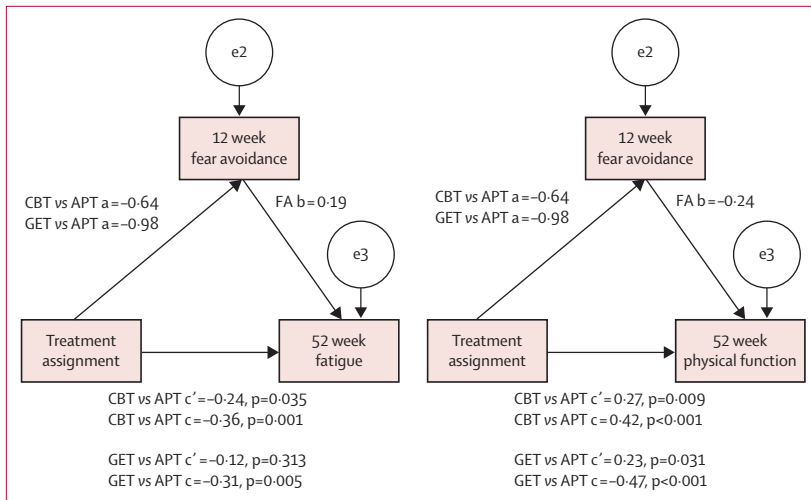
Figure 7: Standardised effects in mediation models through fear avoidance beliefs
As well as treatment, models also include: centre, Standardised Clinical Interview for DSM-IV (SCID) depression status, London criteria for myalgic encephalomyelitis status, International Chronic Fatigue Syndrome (CFS) criteria, baseline measures of both outcome variables, baseline Work and Social Adjustment Scale, SCID anxiety disorder status, age, sex, CFS group membership, receipt of benefits, benefits in dispute, physical illness attribution, fibromyalgia status, illness duration, Jenkins Sleep Score, employment status, body-mass index, and physical symptoms (PHQ-15) score. APT=adaptive pacing therapy. CBT=cognitive behaviour therapy. e2, e3=model error terms. FA=fear avoidance beliefs. GET=graded exercise therapy.

study. These dissimilar results could be explained by differences in the measurement of symptom focusing, and there might have been subtle but important differences in treatment protocols.

We found that fitness and perception of exertion did not appear to mediate treatment effects, but that timed walking distance, assessed for the first time in our study, mediated the effect of GET. This suggests that increasing tolerance of physical activity might produce benefit without improving physical fitness. These findings are consistent with those of previous studies.[8,9,32] A randomised controlled trial of GET for chronic fatigue syndrome[8,16] found that those who rated themselves as better were no fitter or stronger than the rest. A second trial of GET also suggested that physical reconditioning was not a mediator of the effect of treatment, but that a reduction in symptom focusing and increased exercise tolerance (as assessed by maximum heart rate achieved with exercise) mediated change in mental and physical fatigue.[9] It must be acknowledged, however, that the walking test might not reflect activity or exercise levels in everyday life and might provide an explanation for why Wiborg and colleagues[33] found no evidence that actometer-measured physical activity mediated the effect of CBT.

This mediational analysis strengthens the validity of our theoretical model of CBT and supports the idea that a similar model is valid for GET by confirming the role of fearful beliefs and avoidance behaviour. The review of beliefs in chronic fatigue syndrome and fibromyalgia[34] suggested that fear and avoidance of movement were related to poorer outcomes. Our results suggest that fearful beliefs can be changed by directly challenging

Panel: Research in context

Systematic review
For the adaptive Pacing, graded Activity and Cognitive behaviour therapy; a randomised Evaluation (PACE) trial, PubMed and Cochrane Library databases were searched to Nov 6, 2010, and the detailed findings of this are in the Research in context panel in the primary trial publication.[3] This review concluded that cognitive behaviour therapy (CBT) and graded exercise therapy (GET) were moderately effective treatments for chronic fatigue syndrome, and the results of the PACE trial agreed with this.[3] Few papers have been published on mediation of treatment effects in chronic fatigue syndrome, so these were found through pre-existing knowledge of publications, reference lists in these publications, and in the course of routine searches for publications in the field using PubMed up to May 28, 2014. There is an early paper formulating a general model for fatigue in a group of patients with chronic fatigue syndrome.[6] There are also several studies using cross-sectional mediator and outcome data to study either mediation or relations between mediators and outcomes for CBT[29–31,33] and for GET.[9,16] The recent mediation analysis of the FINE trial of pragmatic rehabilitation for chronic fatigue syndrome used longitudinal data to study mediation.[32] In cross-sectional studies, both CBT and GET were found to target cognitive measures such as fear of, and perceived problems with, activity, symptom focusing, and self-efficacy.[9,29–31] Fitness measures did not mediate the effects of the treatments.[9,33] The FINE trial showed both cognitive (catastrophising) and behavioural (avoidance behaviour) variables to be longitudinal mediators of the relation between pragmatic rehabilitation and fatigue.[32]

Interpretation
We confirm that fear avoidance beliefs partially mediate the effects of CBT and GET on physical function and fatigue outcomes, and that fitness measures do not appear to mediate the effects of either treatment. We have also shown that changes in behaviour (ie, increased walking distance and reduced avoidance behaviour) can transmit the effects of treatments to the outcomes, in particular walking distance for GET. We did not find much evidence for symptom focusing as a mediator in this study. These findings from longitudinal data respecting the hypothesised causal ordering of mediators and outcomes are likely more robust than those from past studies using cross-sectional data. Additionally, we identified mediators with strong relations with outcomes; self-efficacy, and walking distance. If treatments for chronic fatigue syndrome could be refined to target these mediators more accurately, they might lead to greater improvements in outcomes.

such beliefs (as in CBT) or by simple behaviour change with a graded approach to the avoided activity (as in GET).

Clinically, the results suggest that therapies focusing more on self-efficacy and physical activities could have

greater effects given that these mediators had strong effects on the outcomes. For example, therapists delivering CBT could encourage walking, which might enhance the effect of CBT and could be more acceptable to patients. Feedback from young people with chronic fatigue syndrome suggested that they liked the behavioural aspects of CBT, but did not like cognitive restructuring.[35]

This study has several strengths. The results originate from the largest trial of CBT and GET to date. The study had few drop-outs and adherence to treatment was high. The study of mediation was incorporated at the design stage of PACE, so mediators were measured at mid-treatment allowing the study of mediator measurements taken before those of the outcomes. Temporal ordering of variables and the inclusion of many potential confounding variables makes causal inferences about the mediated effects more plausible. Both self-report and objective measures were used, and both were found to mediate treatment effects, lending credence to the results.

Limitations include the issue of potential residual unmeasured confounding of the mediator to outcome path. However, given that adjustment was made for several potential confounders it seems unlikely that residual confounding could explain the mediation effects found, especially for the stronger effects. It is possible that variables were measured with error; however, this generally leads to the dampening of effects and so would have disguised a variable's mediating effect rather than leading to a variable being found to be a mediator in error. This was a complete case analysis, requiring an assumption of missing completely at random. This limitation was a greater concern for the step-test and walk-test mediators, where more data were missing, than for the questionnaire-based mediators. However, the results of the full information maximum-likelihood analysis did not differ greatly from the complete case analysis, suggesting serious missing data biases were unlikely.

In an ideal world, mediators would have been assessed at every session. Given the pattern of change in the mediators was similar to the pattern of change in the outcomes it is possible that the variables were affecting each other reciprocally and more measures might have helped clarify this. However, this was prohibitive in this trial because of cost and possible measurement fatigue on the patients' part. Results from longitudinal analyses incorporating all available mediator and outcome measurements will be discussed in future publications. Additionally, we were only able to assess walking at 24 weeks when most of the change in outcomes had occurred. It would have been more convincing as a mediator if walking had been assessed at 12 weeks mid treatment. We did not find evidence of differing *b* paths (relations between the mediators and outcomes) by treatment group, but we might have had limited power to test for these interactions. Given the number of mediators that have been considered it is possible that

some of the findings could be due to chance (ie, type 1 errors might have been made). This should be kept in mind when interpreting the findings, in particular for the more exploratory mediators. Finally, in this analysis we focused on single mediators and the effects of some of these variables are not likely to be independent. Our forthcoming analysis of multiple mediator effects will provide more information on this issue.

References
1   Reeves WC, Lloyd A, Vernon SD, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Serv Res* 2003; **3:** 25.
2   Sharpe MC, Archard LC, Banatvala JE, et al. A report—chronic fatigue syndrome: guidelines for research. *J R Soc Med* 1991; **84:** 118–21.
3   White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011; **377:** 823–36.
4   White PD, Sharpe MC, Chalder T, DeCesare JC, Walwyn R. Protocol for the PACE trial: a randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. *BMC Neurol* 2007; **7:** 6.
5   Burgess M, Andiappan M, Chalder T. Cognitive behaviour therapy for chronic fatigue syndrome in adults: face to face versus telephone treatment—a randomized controlled trial. *Behav Cogn Psychoth* 2012; **40:** 175–91.
6   Vercoulen JH, Swanink CM, Galama JM, et al. The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. *J Psychosom Res* 1998; **45:** 507–17.
7   Clark LV, White PD. The role of deconditioning and therapeutic exercises in chronic fatigue syndrome (CFS). *J Ment Health* 2005; **14:** 237–52.
8   Fulcher KY, White PD. Strength and physiological response to exercise in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* 2000; **69:** 302–07.

9   Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. *J Health Psychol* 2005; **10:** 245–59.

10   Nijs J, Aelbrecht S, Meeus M, Van Oosterwijck J, Zinzen E, Clarys P. Tired of being inactive: a systematic literature review of physical activity, physiological exercise capacity and muscle strength in patients with chronic fatigue syndrome. *Disabil Rehabil* 2011; **33:** 1493–500.

11   Evering RM, van Weering MG, Groothuis-Oudshoorn KC, Vollenbroek-Hutten MM. Daily physical activity of patients with the chronic fatigue syndrome: a systematic review. *Clin Rehabil* 2011; **25:** 112–33.

12   Pesek JR, Jason LA, Taylor RR. An empirical investigation of the envelope theory. *J Hum Behav Soc Environ* 2000; **3:** 59–77.

13   Stahl D, Rimes KA, Chalder T. Mechanisms of change underlying the efficacy of cognitive behaviour therapy for chronic fatigue syndrome in a specialist clinic: a mediation analysis. *Psychol Med* 2014; **44:** 1331–44.

14   Stanton AL, Luecken LJ, MacKinnon DP, Thompson EH. Mechanisms in psychosocial interventions for adults living with cancer: opportunity for integration of theory, research, and practice. *J Consult Clin Psychol* 2013; **81:** 318–35.

15   Turner JA, Holtzman S, Mancl L. Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain. *Pain* 2007; **127:** 276–86.

16   Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ* 1997; **314:** 1647–52.

17   Fossey M, Libman E, Bailes S, et al. Sleep quality and psychological adjustment in chronic fatigue syndrome. *J Behav Med* 2004; **27:** 581–605.

18   MacKinnon DP. Introduction to Statistical Mediation Analysis. Taylor and Francis: New York, 2008; 47–102, and 335.

19   Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; **51:** 1173–82.

20   Judd CM, Kenny DA. Process analysis—estimating mediation in treatment evaluations. *Evaluation Rev* 1981; **5:** 602–19.

21   Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Stat Methods Med Res* 2010; **19:** 237–70.

22   First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV-TR, research version, patient edition with psychotic screen. New York: Biometrics Research, New York State Psychiatric Institute, 2002.

23   National Task Force. Report on chronic fatigue syndrome (CFS), post viral fatigue syndrome (PVFS) and myalgic encephalomyelitis (ME). Bristol, UK: Westcare, 1994.

24   Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Brit J Psychiat* 2002; **180:** 461–64.

25   Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; **33:** 160–72.

26   Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosomat Med* 2002; **64:** 258–66.

27   Efron B, Tibshirani R. An Introduction to the Bootstrap. Boca Raton, FL: Chapman and Hall/CRC, 1993.

28   Enders CK, Bandalos DL. The relative performance of full information maximum likelihood estimation for missing data in structural equation models. *Struct Equ Modeling* 2001; **8:** 430–57.

29   Deale A, Chalder T, Wessely S. Illness beliefs and treatment outcome in chronic fatigue syndrome. *J Psychosom Res* 1998; **45:** 77–83.

30   Wiborg JF, Knoop H, Prins JB, Bleijenberg G. Does a decrease in avoidance behavior and focusing on fatigue mediate the effect of cognitive behavior therapy for chronic fatigue syndrome? *J Psychosom Res* 2011; **70:** 306–10.

31   Wiborg JF, Knoop H, Frank LE, Bleijenberg G. Towards an evidence-based treatment model for cognitive behavioral interventions focusing on chronic fatigue syndrome. *J Psychosom Res* 2012; **72:** 399–404.

32   Wearden AJ, Emsley R. Mediators of the effects on fatigue of pragmatic rehabilitation for chronic fatigue syndrome. *J Consult Clin Psychol* 2013: **81:** 831–88.

33   Wiborg JF, Knoop H, Stulemeijer M, Prins JB, Bleijenberg G. How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. *Psychol Med* 2010; **40:** 1281–87.

34   Nijs J, Roussel N, Van Oosterwijck J, et al. Fear of movement and avoidance behaviour toward physical activity in chronic-fatigue syndrome and fibromyalgia: state of the art and implications for clinical practice. *Clin Rheumatol* 2013; **32:** 1121–29.

35   Dennison L, Stanbrook R, Moss-Morris R, Yardley L, Chalder T. Cognitive behavioural therapy and psycho-education for chronic fatigue syndrome in young people: reflections from the families' perspective. *Br J Health Psychol* 2010; **15:** 167–83.