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Mediation analysis shows that a decline in self-efficacy mediates the increase in fatigue severity following an initial positive response to cognitive behavioural therapy in Q fever fatigue syndrome

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ABSTRACT

Objective: Q fever fatigue syndrome (QFS) is characterized by chronic fatigue following acute Q fever. Previously, it was shown that cognitive behavioural therapy (CBT), and not doxycycline, was significantly more effective than placebo in reducing fatigue severity in QFS patients. However, this effect was not maintained after one year. The aim of this study is to elucidate the cognitive and behavioural variables which mediate the positive effect of CBT on fatigue during the treatment and the relapse of fatigue after completion of CBT, by using multiple mediation analysis.

Methods: Additional analyses were performed on data of a randomized controlled trial that investigated the efficacy of CBT and antibiotics compared to placebo for QFS [1]. Only those patients in the CBT group who completed the allocated CBT treatment, and those patients in the medication group who did not follow additional CBT during follow-up, were included in this study. Two mediation models were tested, using respectively assessments at baseline and end-of-treatment (EOT), and EOT and follow-up, comparing the CBT group (n = 43) with the medication group (n = 89).

Results: During treatment, the decrease in fatigue brought on by CBT was completely mediated by an increase in self-efficacy with respect to fatigue. A reduction in self-efficacy partly mediated the increase in fatigue at follow-up in the CBT group.

Conclusions: Given the decline in self efficacy, booster sessions focussing on restoration and maintenance of self-efficacy with respect to fatigue, may lead to elongation of the initial positive effects of CBT for QFS.

1. Introduction

Q fever, a zoonosis that occurs worldwide, is caused by the bacterium *Coxiella burnetii* [2,3]. From 2007 until 2011, the Netherlands faced the largest Q fever outbreak described to date, with over 4000 reported cases of symptomatic acute Q fever [4]. Persistent fatigue following acute Q fever, known as Q fever fatigue syndrome (QFS), is the most common sequela of a symptomatic Q fever infection [5]. Although most patients recover from fatigue in the first 6 to 12 months following an acute Q fever infection, around 20% of patients develop QFS in which symptoms may persist for up to 20 years or even longer [5]. Many QFS patients meet the criteria of case definitions of chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS), as symptoms partly overlap [6]. According to the Dutch consensus guideline on QFS [7], QFS is defined as severe fatigue after an acute Q fever infection, persisting for at least six months, and causing significant disabilities in daily life. Furthermore, fatigue should be absent before the acute Q fever infection or be significantly increased ever since, and other somatic or psychiatric causes of fatigue need to be excluded [7]. This debilitating fatigue syndrome has detrimental effects on daily

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functioning [5,8–12]. Following the Dutch Q fever outbreak, QFS accounted for the majority of Q fever-related economical consequences due to a loss of quality of life and health-related absenteeism at work [13,14]. A recent study showed that the reduced quality of life and social functioning of QFS patients was mediated by fatigue severity [15].

Cognitive behavioural therapy (CBT), aimed at changing fatigue-related cognitions and behaviours, has been proven effective in reducing fatigue in ME/CFS [16] [17,18], and other chronic medical conditions [19–21]. The cognitive-behavioural model on which CBT is based assumes that beliefs about the chronic condition and fatigue, and behaviours like the sleep-wake pattern or changes in the level of activity can maintain fatigue. Although different treatment protocols have been developed for chronic fatigue in different medical conditions there is considerable overlap in the fatigue maintaining factors as a recent study in various chronic medical conditions showed [22]. Additionally, a comparison of patients with CFS/ME and QFS showed, despite stronger somatic attributions and a less strong relation between fatigue-related beliefs and fatigue in QFS patients [23], a striking overlap in symptoms and cognitive-behavioural variables known to perpetuate fatigue. On the basis of aforementioned, CBT based on the cognitive-behavioural model of chronic fatigue was introduced as a possible treatment modality for QFS. The efficacy was subsequently evaluated in a randomized controlled clinical trial (RCT), comparing the efficacy of CBT and long-term doxycycline treatment with a placebo on fatigue severity in QFS patients [24]. CBT led to a larger decrease of fatigue following treatment. The effects of long-term doxycycline did not differ significantly from placebo. But, in contrast to the long-term results of CBT in ME/CFS showing maintenance of treatment effects, up to at least one and a half year post treatment with substantial maintenance of effect in the period thereafter [25,26], the initial positive effect of CBT for fatigue was not sustained at one year follow-up in QFS patients [27]. However, as antibiotics proved ineffective and no other treatment modalities have been investigated, the current treatment standard in the Netherlands is to still consider CBT for the treatment of patients with QFS [28].

Mediation analysis can help to elucidate the mechanisms behind the initial positive effect of CBT in reducing fatigue severity, and the relapse after completion of treatment. Previous mediation analysis of treatment studies testing the efficacy of CBT and mediation analysis of the effect of graded exercise therapy (GET) for ME/CFS showed that increased sense of control over fatigue [29], less focus on fatigue [29–31], increased perceived activity and physical functioning [29,32], a reduction of fear avoidance beliefs [33], and a decreased tendency to catastrophize in response to fatigue [33,34] were mediators of the treatment response. There has been one mediation analysis studying possible mechanisms behind relapse following CBT for fatigue. A randomized controlled trial testing the efficacy for CBT for fatigue in in multiple sclerosis (MS) showed that after an initial improvement in fatigue, patients relapsed. The increase in fatigue following CBT was mediated by reduced self-reported level physical activity, reduced concentration, and increased sleep problems [35]. At present, the mechanisms of change of CBT in QFS and the processes underlying the relapse in fatigue severity at long-term follow-up are unknown. In this study we investigated the mediators of the initial positive effect of CBT on fatigue severity in QFS and the mediators of the relapse in fatigue at follow-up. Based on the aforementioned studies and the variables addressed in our CBT program for ME/CFS, we included the following cognitive-behavioural variables as possible mediators [29–33,36–38]: catastrophizing beliefs in response to fatigue, focusing on bodily symptoms, self-efficacy with respect to fatigue and to performing activities, damaging beliefs, fear avoidance beliefs, resting/avoidance, all-or-nothing behaviour, problems with sleeping/resting, and the objective physical activity level. This study assesses whether cognitive-behavioural variables mediate the initial treatment response to CBT in QFS patients and the relapse of fatigue after completion of treatment.

2. Methods

2.1. Study design and participants

Data collected in a randomized controlled trial, the Qure study [24], were used in the present study. The Qure study protocol was published previously [1][]. In the original trial, 156 adults, diagnosed with QFS according to the Dutch consensus guideline [1,7], were recruited from the Radboud Expertise Centre for Q fever of the Radboud university medical center (Radboudumc), and randomized with a 2:1 ratio between oral study medication and CBT for 24 weeks. Patients allocated to the medication arm were randomized again with a 1:1 ratio to doxycycline or placebo medication. A total of 154 patients (98.7% of all included patients) completed the baseline, end-of-treatment (EOT) and follow-up (FU) assessments and were therefore included in the final analysis of the RCT; CBT (n = 50), doxycycline (n = 52), placebo (n = 52).

According to the Qure study, doxycycline was not more effective in reducing fatigue severity compared to placebo [27]. Therefore, to increase power while studying the mediation of the CBT effect, the doxycycline and placebo group were combined as control group (n = 89), henceforth referred to as 'medication group'. Based on a per-protocol method, only those patients in the CBT group who completed the allocated CBT treatment, and those patients in the medication group who did not follow additional CBT during follow-up, were included in this study.

In the original trial, questionnaires were filled out before randomization (baseline assessment), at 8 weeks, 26 weeks (EOT assessment), and 52 weeks (FU assessment). Assessments of the level of physical activity were only done at baseline and EOT. In this study, two mediation models were tested. The first mediation model described mediation *during* treatment, including data at baseline and at EOT assessment. The second mediation model uses data at EOT assessment and FU assessment, describing mediation of the relapse of fatigue *after completion of* CBT treatment. Baseline characteristics of patients can be found in Table 1.

2.2. Intervention

CBT consisted of individual sessions [1,39]. These face-to-face sessions, spread over a period of 24 weeks, were delivered by trained and supervised cognitive behavioural therapists. First, the model of perpetuation of fatigue was explained, describing the way through which thoughts and behaviours can lead to the persistence of fatigue. Second, at start of treatment, patients formulated their goals in behavioural terms (i.e. resumption of work or hobbies). Sessions focused on the development of healthy sleep-wake patterns, regulation of activity and a graded activity program, and challenging dysfunctional beliefs with respect to fatigue [1].

Table 1
Characteristics at baseline assessment [24] of all patients included in per-protocol analysis.

Characteristics	CBT (n = 43)	Medication (n = 89)
Female sex, No. (%)	21 (49)	42 (46)
Age, y, mean ± SD	43.7 ± 14.2	44.5 ± 10.9
Duration of symptoms, months ± SD	41.8 ± 20.5	39.3 ± 18.4
CIS 'subscale fatigue severity' score at baseline, mean ± SD	49.7 ± 4.5	50.7 ± 4.9

Abbreviations: CBT, cognitive behavioural therapy; SD, standard deviation; CIS, Checklist Individual Strength.
Sex is depicted as percentage of female participants. Age, duration of symptoms, an CIS, subscale on fatigue severity' scores are depicted as mean ± SD.

2.3. Outcome measures

2.3.1. Primary outcome

Fatigue severity, the primary outcome measure, was assessed with the subscale fatigue severity of the Checklist Individual Strength (CIS). This subscale, consisting of eight items, measures the level of fatigue experienced in the previous two weeks. All items are measured on a 7-point Likert-scale ranging from 'Yes, that is true' to 'No, that is not true'. The sum score ranges between 8 and 56, with higher scores indicating a higher level of fatigue severity. Patients with a cut-off score ≥ 35 are classified as severely fatigued. Cronbach's alpha ranges from 0.83 to 0.92 [40–42].

2.3.2. Potential mediators

At the design stage of the original trial a mediation analysis of the expected treatment effect was incorporated and described in the protocol paper [1]. Possible mediators were assessed at baseline, 8 weeks after the start of treatment and at EOT. After the start of the study it was decided to also perform a mediation analysis of the course of fatigue from EOT up to follow-up. A small set of questionnaires was selected, in order to limit patient burden and improve response rates. Consequently, some of the cognitive-behavioural variables were not measured at follow-up and could not be used in our mediation analysis. Potential mediators were fatigue-related cognitions and behaviours, except from objective physical activity, all measured with questionnaires (Table 2). The cognitive variables were catastrophizing beliefs in response to fatigue, focusing on bodily symptoms, self-efficacy with respect to fatigue, self-efficacy with respect to performing activities, damaging beliefs, and fear avoidance beliefs. The behavioural variables are resting/avoidance, all-or-nothing behaviour, sleeping/resting, and physical activity level.

2.4. Instruments

2.4.1. Cognitive and Behavioural responses to Symptoms Questionnaire (CBSQ)

The CBSQ measures different aspects of the response to symptoms. In this study two behavioural subscales and three cognitive subscales are used. The behavioural subscales are resting/avoidance (eight items) and all-or-nothing (five items). The cognitive subscales assessed catastrophizing beliefs (four items), damaging beliefs (five items), and fear avoidance beliefs (six items). All items are scored on a 5-point frequency scale ranging from never to all the time. Higher scores indicate more unhelpful responses. The Cronbach's alpha ranges between 0.72 and 0.88 [43].

2.4.2. Illness Management Questionnaire (IMQ)

Focusing on symptoms was assessed with the subscale focusing on symptoms of the IMQ. The subscale consists of nine items, which are all scored on a 6-point Likert-scale ranging from never to always. The sum score ranges from 9 to 54. Higher scores indicate more focus on symptoms. The Cronbach's alpha is 0.88 [29,44].

2.4.3. Self-Efficacy Scale (SES28)

Sense of control over fatigue was measured with the SES28, consisting of seven items. All items are scored on a 4-point Likert scale. Item scores are added from each subscale to obtain a total score, ranging between 7 and 28. Higher scores indicate more sense of control over fatigue. The Cronbach's alpha ranges from 0.68 to 0.77 [29,41].

2.4.4. Sickness Impact Profile (SIP)

Sleeping/resting behaviour was measured with the subscale sleeping/resting of the SIP questionnaire. This questionnaire consisting of seven items, measures the level of functional impairment of a patient due to health problems. The scores on the items are weighed and the total score ranges from 0 to 499. Higher scores indicate more limitations in sleeping/resting. It is a reliable instrument with a Cronbach's alpha of 0.91 [45].

2.4.5. Physical Activity Rating Scale (PARS)

Level of self-efficacy with respect to performing activities was measured with the subscale trust of the PARS questionnaire, consisting of sixteen specified daily activities (e.g. walking or cycling for 30 min, watching television for 1 h). All items are rated on a 5-point Likert-scale. Higher scores indicate a higher level of confidence in their ability to perform certain activities. The Cronbach's alpha is 0.94.

2.4.6. Physical activity

The level of physical activity was measured using an actometer, a small motion-sensing device worn at the ankle day and night during a period of twelve consecutive days [46]. A general activity score was calculated over these 12 days. Higher scores indicate a higher level of physical activity. The actometer is a reliable and valid instrument for the assessment of physical activity [47].

Table 2
Differences between the CBT and medication groups in changes in cognitive-behavioural variables from baseline to the end of treatment.

	Difference between CBT and medication group (mean 95% CI)	*P* value [a] CBT vs medication	Effect size [c]
Cognitive variables			
IMQ focusing on bodily symptoms	−1.96 (−4.83 to −0.92)	0.18	0.19
CBSQ catastrophizing beliefs in response to fatigue	−1.13 (−2.08 to −0.17)	0.02 [b]	0.34
CBSQ damaging beliefs	−1.28 (−2.58 to 0.014	0.05	0.30
CBSQ fear avoidance beliefs	−1.55 (−3.20 to 0.10)	0.07	0.29
SES28 self-efficacy with respect to fatigue	2.01 (0.84 to 3.18)	< 0.001 [b]	0.52
PARS self-efficacy with respect to performing activities	2.62 (−1.77 to 7.01)	0.24	0.18
Behavioural variables			
Physical activity level (actometer)	0.77 (−4.01 to 5.55)	0.75	0.04
CBSQ resting/avoidance	−1.43 (−2.85 to 0.00)	0.05 [b]	0.32
CBSQ all-or-nothing behaviour	−1.05 (−2.32 to 0.21)	0.11	0.27
SIP sleeping/resting	−25.12 (−48.52 to −1.71)	0.04 [b]	0.38

Abbreviations: CBT, cognitive behavioural therapy; CI, confidence interval; CBSQ, Cognitive and Behavioural Responses to Symptoms Questionnaire; IMQ, Illness Management Questionnaire; SES28, Self-Efficacy Scale; PARS, Physical Activity Rating Scale; SIP, Sickness Impact Profile.

[a] *P* values were based on analysis of covariance between CBT and medication group. End-of-treatment scores of variable (dependent factor) are adjusted for baseline scores of variable (covariate). Treatment strategy was used as fixed factor.

[b] Variable significantly differs between CBT and medication groups ($P \leq 0.05$), and is therefore included in mediation analysis.

[c] Calculated as the mean difference between CBT and medication at the end-of-treatment adjusted for the baseline measurement and divided by the pooled standard deviation at baseline.

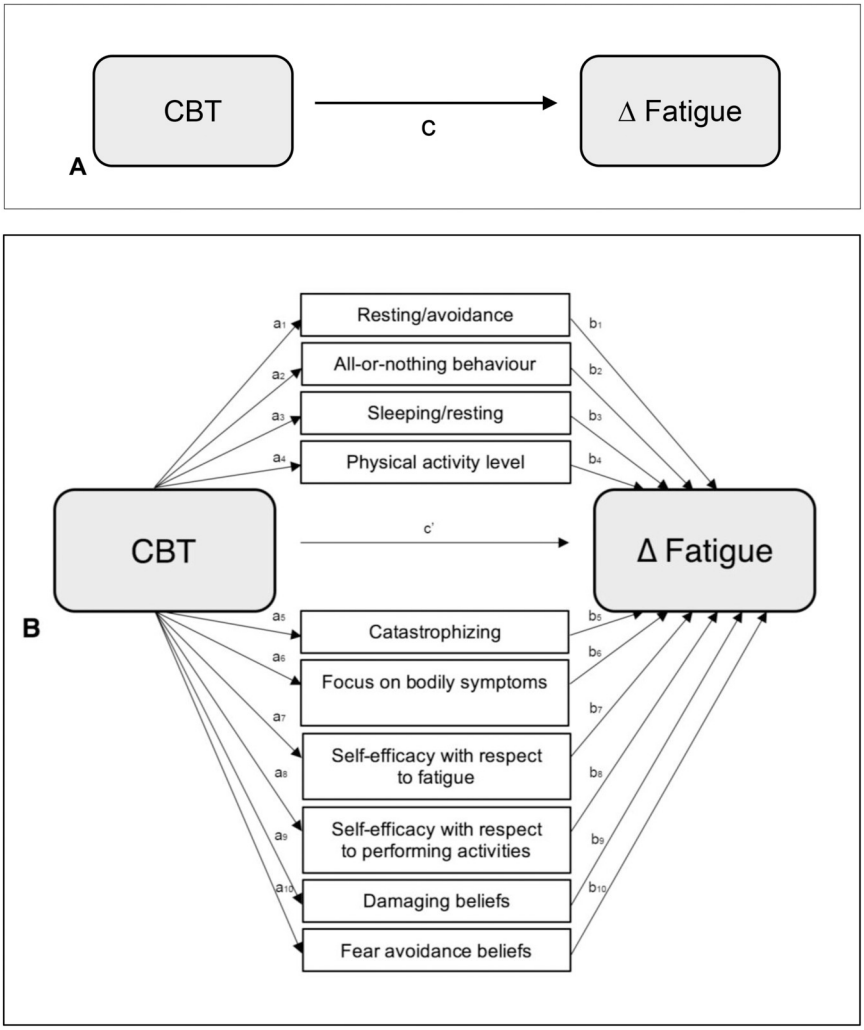

Fig. 1. (A) The total effect of CBT on fatigue severity (path c). Abbreviations: CBT, cognitive behavioural therapy. (B) The direct effect of CBT on fatigue severity (path c') and the indirect effect, mediated by a change in cognitive-behavioural variables (path ab). Abbreviations: CBT, cognitive behavioural therapy.

2.5. Mediation analysis

Mediation analysis explores the mechanisms by which an independent variable, in this case CBT, influences a dependent variable, i.e., fatigue severity, via intermediate variables called mediators. Possible mediators are the cognitive-behavioural variables that perpetuate fatigue and are addressed in CBT. As is the case here, the mediators of interest are often the general aspects that the treatment is targeting. Fig. 1A and B illustrate the parallel multiple mediation model of interest. The total effect of CBT on fatigue severity (path c) can be divided into a direct effect (path c') and an indirect effect mediated by a change in one (or more) mediator(s) (path ab), as depicted in Fig. 1B. Path c depicts the total effect of the causal variable, i.e., CBT, on the outcome variable, i.e., fatigue severity. Path a depicts the association between the causal variable, i.e., CBT, and the possible mediator(s), i.e., in the cognitive behavioural variables. Path b depicts the association between the possible mediator(s) and the outcome, i.e., fatigue severity, when controlling for the causal variable, i.e., CBT. Path c' depicts the direct effect of the causal variable, i.e. CBT, on the outcome variable, i.e., fatigue severity, when controlling for the possible mediator(s), i.e., the cognitive behavioural variables [48]. To identify which cognitive and behavioural variables mediate the positive effect of CBT on fatigue severity in QFS during treatment and relapse after completion of treatment, we constructed two parallel multiple mediation models [48]. The first model describes mediation of the reduction of fatigue *during* treatment, while the second model describes mediation of the increase in fatigue severity *after completion of* treatment.

2.6. Statistical analysis

Statistical analyses based on a per-protocol method, were performed using SPSS version 22.0.01 (SPSS Inc., Chicago, IL).

2.6.1. Preliminary analysis

To limit the number of potential mediators, which was necessary due to the limited sample size, we only included those cognitive-behavioural variables which showed a significant difference in change between the CBT and medication group at week 8. This was investigated with analyses of covariance with the 8-week score of the variable as dependent variable, baseline score of the variable included as co-variate and treatment group included as fixed factor. Significance was assumed at a P value of ≤ 0.05. We assessed the impact of potential mediators that yielded P values $< .10$ in a sensitivity analysis. If no significant differences were found when using the 8-week scores, analyses of covariance using the 26-week scores (EOT assessment) were used to assess potential mediators. Eight-week measurements were not available for 'physical activity level' and 'sleeping/resting'. Therefore, these variables were only included in the statistical analysis when 26-week scores were used for the preliminary analysis. We expressed the magnitude of the difference in the potential mediators between the two

groups in effect sizes by dividing the mean difference between the CBT and medication group at week 8 or week 26 adjusted for the baseline score by the pooled standard deviation.

2.6.2. Multiple mediation analysis

The first parallel mediation model described mediation of the reduction of fatigue during treatment, while the second parallel mediation model described mediation of the increase in fatigue severity after completion of treatment. In the first mediation model, scores on the primary outcome measure at 8 or 26 weeks (depending on results of the preliminary analysis) adjusted for the baseline measurement were used for the potential mediators. For fatigue severity, the 26 weeks measurement was used adjusted for the baseline measurement. In the second mediation model, change scores from 26 weeks to follow-up were used for the potential mediators as well as fatigue severity. We used change scores for this second mediation model because after completion of treatment the two groups were no longer comparable and change score are more appropriate for assessing change in non-equivalent groups [49]. Mediation analyses were performed using a macro expansion for SPSS introduced by Preacher & Hayes [50].

We investigated whether a possible relationship between CBT and fatigue reduction (model 1) or relapse in fatigue (model 2) was mediated by the cognitive-behavioural variables. We therefore established the association between: (Fig. 1A) CBT and fatigue reduction (model 1) or fatigue relapse (model 2) (c path) and the indirect path of CBT and fatigue reduction via the cognitive-behavioural variables (path a*b; Fig. 1B, model 1) or the indirect path of CBT and fatigue relapse (a*b path, model 2). In the third step, we established if the association between CBT and fatigue reduction (model 1) and fatigue relapse (model 2) was attenuated, indicating partial mediation, or disappeared, indicating complete mediation, after controlling for the cognitive and behavioural mediators (c' path). We investigated the statistical significance of the mediation effect using bootstrapping to calculate the 95% confidence intervals of this effect using the macro expansion for SPSS introduced by Preacher & Hayes [50]. If the 95% confidence interval did not include zero, the mediation effect was statistically significant at $P \leq .05$.

2.7. Ethical approval

The Medical Ethical Review Committee region Arnhem-Nijmegen (2011/069, NL35755.091.11) approved the study protocol of the Qure study, which included the mediation analysis [1].

3. Results

3.1. Study population and baseline characteristics

The flowchart in Fig. 2 depicts the selection process of study participants. Eight patients allocated to CBT who did not fully complete treatment were excluded. Of these, one patient withdrew informed consent, the other seven patients discontinued treatment because they could not adhere to the therapy for various reasons. The mean number of CBT sessions for these excluded patients was 3.88 (SD 3.0). Fifteen patients from the medication group who received additional CBT during follow-up (doxycycline $n = 8$ and placebo $n = 7$) were also excluded, leaving 132 included patients (CBT $n = 43$; medication $n = 89$, with doxycycline $n = 44$ and placebo $n = 45$).

The proportion of females was 49% in the CBT group and 46% in the medication group. The mean age of participants was 43.7 (SD 14.2) years in the CBT group and 44.5 (SD 10.9) in the medication group. Mean symptom duration was 41.8 months (SD 20.5) in de CBT group versus 39.3 months (SD 18.4) in the medication group. There were no significant differences in these baseline characteristics between the groups (Table 1). Also, no significant differences were found between baseline scores of included ($n = 132$) and excluded subjects ($n = 22$) (Appendix A), except from 'focusing on symptoms' which was significantly lower among the included patients (mean difference − 5.58 [95%CI, −9.97 to −1.18]; $P = .01$).

3.2. Selection of possible mediators

At 8 weeks after start of treatment, none of the potential variables showed a significant difference between the CBT and the medication group (Appendix B). Hence, the scores on the potential mediator variables at EOT (26 weeks) were used. ANCOVA with scores at 26 weeks adjusted for the baseline scores showed that the change in the CBT group compared to the medication group, was significantly greater for the following variables: 'catastrophizing beliefs in response to fatigue' ($P = .02$), 'self-efficacy with respect to fatigue' ($P < .001$), 'resting/avoidance' ($P = .05$), and 'sleeping/resting' ($P = .04$) (Table 2). These potential mediators were entered in the mediation analysis. Damaging beliefs and fear avoidance beliefs were additionally included as potential mediators in a sensitivity analysis, as their P-values were < 0.10.

3.3. Mediation analyses

The results of the parallel multiple mediation analyses, including the mediation during treatment (model 1) and mediation after completion of treatment (model 2), are given in Table 3. An increase in 'self-efficacy with respect to fatigue' mediated the decrease in fatigue severity at EOT, mediation effect −2.17 [95% CI -4.51 to −0.55] (Table 3 and Fig. 3A). The confidence interval of the direct effect of CBT on fatigue severity included zero, indicating non-significance when correcting for these mediators (path c'), which represents complete mediation (Table 3). Only a decrease in 'self-efficacy with respect to fatigue' significantly mediated the increase in fatigue severity at EOT, mediation effect 1.47 [95% CI 0.06 to 3.26] (Table 3 and Fig. 3B). This was partial mediation, as the increase in fatigue severity in the CBT group at follow-up did not include zero, and thus remained statistically significant after correcting for the increase in fatigue mediated by changes in 'self-efficacy with respect to fatigue' (path c') (Table 3). The sensitivity analyses revealed that neither damaging beliefs (mediation effect 0.55, 95% CI: −0.08 to 1.17) nor fear avoidance beliefs (mediation effect 0.45, 95% CI: −0.07 to 0.98) were significant mediators of reduction of fatigue during treatment. Sensitivity analysis also revealed that neither damaging beliefs (mediation effect 0.20 95% CI: −0.87 to 1.29) nor fear avoidance beliefs (mediation effect 0.05 95% CI: −0.92 to 1.25) were significant mediators of relapse in fatigue after treatment.

4. Discussion

This study set out to elucidate the cognitive-behavioural variables mediating the decrease in fatigue severity during CBT for QFS, and the subsequent relapse in fatigue following completion of treatment. We found that the decrease in fatigue severity in QFS brought on by CBT was mediated by an increase in self-efficacy with respect to fatigue. Although catastrophizing in response to fatigue, resting-avoidance and sleep problems significantly decreased during CBT, these changes did not significantly contribute to the mediation of the decrease in fatigue severity during CBT. The decrease in self-efficacy following end of treatment partially mediated the relapse in fatigue severity after cessation of CBT.

An increase in self-efficacy, has also been found to play an important role in the reduction of fatigue brought on by CBT in ME/CFS, although significant relapse-rates in CFS are not seen so shortly after end of CBT as is the case for QFS [29,32,51]. An increase in self-efficacy during CBT also mediated the reduction of fatigue associated with chronic disease like MS and diabetes [51,52].

All these findings strengthen the recently proposed transdiagnostic approach for the management of chronic fatigue in chronic conditions a

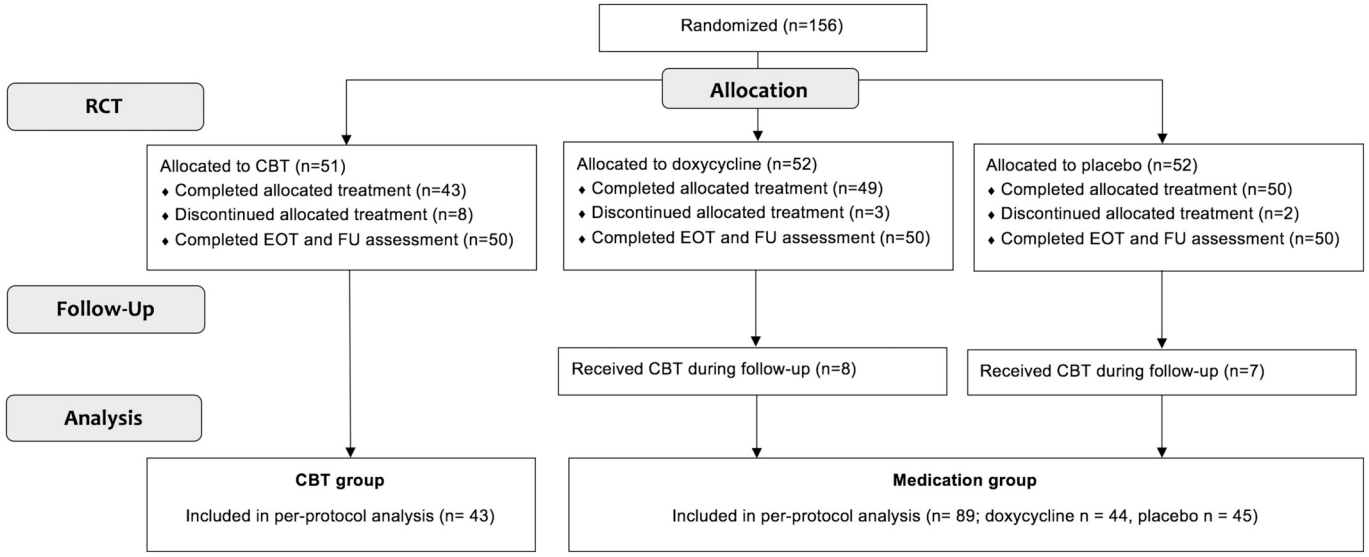

Fig. 2. Flow chart of the selection of study participants.
Abbreviations: CBT, cognitive behavioural therapy; EOT, end-of-treatment; FU, follow-up.
Analyses were based on a per-protocol method and included the data of 132 patients. Patients in the CBT group who completed the allocated treatment, and patients in the medication group who did not follow additional CBT during follow-up, were included.

suggested by Menting et al., [22]. They found that over conditions the same factors are associated with fatigue and assumed that the same intervention addressing the factors, like a low self-efficacy, can reduce fatigue in different medical conditions.

There are indeed many similarities, when looking at the mediators of CBT for chronic fatigue in several diseases (i.e. diabetes, MS, ME/CFS, cancer and QFS). However, also differences exist between mediators encountered in these diseases. In contrast to our study, several studies found that fewer or a lessening of fear-avoidance beliefs in CFS [33,36], diabetes [52] and MS [35,51], mediated a reduction in fatigue severity. Previous studies also showed that a decrease in catastrophizing beliefs in CFS mediated a reduced level of fatigue [33,34], whereas in our study catastrophizing was not found to be a mediator. These dissimilarities may be due to differences in the instruments used to assess the mediators, the use of small sample sizes, but may also point to differences or variations in perpetuating factors among medical conditions which are relevant for the development of intervention for specific subgroups.

A decrease in self-efficacy with respect to fatigue was found to be the only mediator of the relapse of fatigue after completion of treatment. CBT aims at improving self-efficacy with respect to fatigue. This goal is reached during treatment but following CBT, a period in which there is no longer active support from the therapist, patients seem to fall back in their old beliefs of not having control over their fatigue. The mediating effect of self-efficacy was partial, indicating that other mediators, not assessed in our model, also contributed to the relapse of fatigue severity during follow-up. The relapse in lack of self-efficacy might partly be due to the repetitive media attention to Q fever in the Netherlands, in which patients are frequently reminded of fatigue being caused by Q fever, and of the chronicity of the symptom. For example, a lawsuit in which the Dutch government was sued for negligence during the Dutch Q fever outbreak in 2007, was still pending during follow-up of the original trial. Patients were asked to supply attorneys with proof of the presence, persistence and debilitating nature of the fatigue due to QFS. It could well be that the emphasis on fatigue as a long-term sequela of Q fever also strengthens pre-existing somatic attributions, and consequently lowers the sense of control over the fatigue.

A potential approach to improve the long-term effectiveness of CBT in patients with QFS, would be to provide additional booster sessions

Table 3
Total-, direct- and mediated effects of CBT on fatigue using the bootstrap approach.

Mediator	Mediation during treatment (baseline – EOT)		Mediation after completion of treatment (EOT – follow-up)	
	Mediation effect (ab path)	95% CI	Mediation effect (ab path)	95% CI
Catastrophizing beliefs (CBSQ)	−1.40	−3.26 to 0.14	0.89	−0.21 to 2.60
Self-efficacy (SES28)	−2.17[a]	−4.51 to −0.55	1.47 [a]	0.08 to 3.34
Resting/avoidance (CBSQ)	- 0.18	−1.03 to 0.40	0.05	−0.86 to 0.79
Sleeping/resting (SIP)	- 1.04 [a]	−2.43 to 0.09	0.72	−0.20 to 2.03
Total effect of CBT on fatigue (path c in Fig. 1A)	c path −7.29	−11.74 to −2.84	c path 7.62	3.32 to 11.93
Direct effect of CBT on fatigue (path c' in Fig. 1B)	c' path −2.49	−5.74 to 0.76	c' path 4.49	0.83 to 8.16
Proportion of the effect of CBT on fatigue mediated by self-efficacy	ab/c.30%		ab/c 19%	

Abbreviations: EOT, end-of-treatment; CI, confidence interval; CBSQ, Cognitive and Behavioural Responses to Symptoms Questionnaire; SES28, Self-Efficacy Scale; SIP, Sickness Impact Profile.
Number of bootstrap samples = 5.000.
[a] The mediation effect is statistically significant at the 95% CI, when the CI does not include 0.

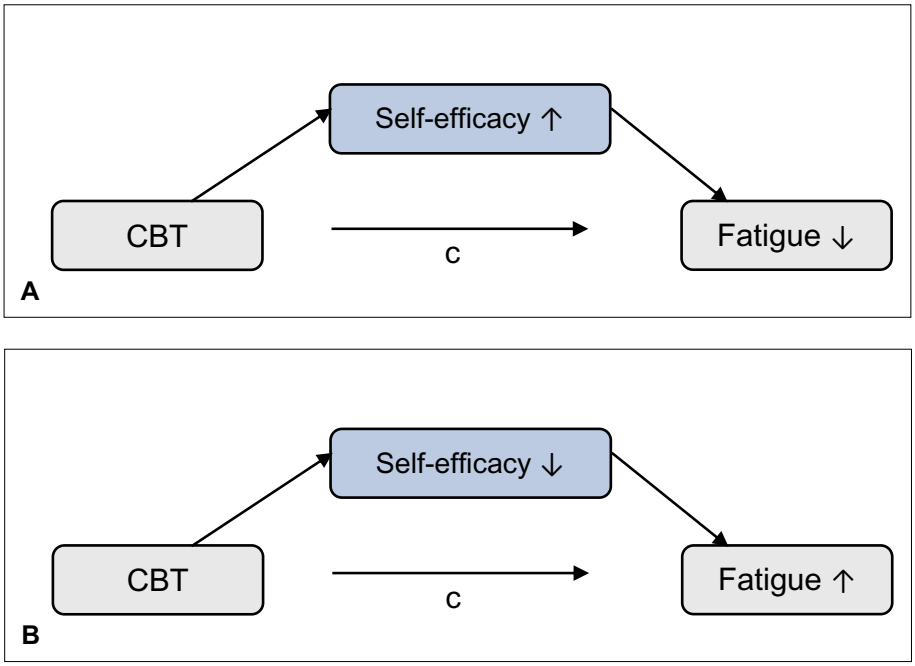

Fig. 3. The indirect effect of CBT on fatigue severity with mediators, (A) during treatment (B) after completion of treatment.
Abbreviations: CBT, cognitive behavioural therapy.
A. Mediation model 1 results in complete mediation: Mediation effect 'self-efficacy with respect to fatigue' -2.17 [95% CI -4.51 to −0.55];
B. Mediation model 2 results in partial mediation: Mediation effect 'self-efficacy with respect to fatigue' 1.47 [95% CI 0.08 to 3.34].

after completion of treatment, aimed at sustaining the positive effects of CBT by strengthening the self-efficacy of patients. Booster sessions have been shown to be effective in mood disorders that are known for their high relapse rate [53]. Our findings suggest that these additional CBT sessions should focus on long-term improvement of self-efficacy with respect to fatigue. As we found evidence of partial mediation, other mediators not assessed in our model are likely to contribute to the relapse in fatigue severity during follow-up, e.g., somatic attributions [23], depression, changes in illness cognitions, or changes in coping styles [35]. Further research is needed to elucidate these additional mediators in order to further refine and improve CBT for fatigue in QFS.

The main strength of this study is the analysis of the mediators of relapse after an initial positive effect during CBT, which can aid in the development of treatment strategies that enable patients to sustain the positive effects of CBT following treatment, e.g., booster sessions [53]. Moreover, this is the first study analysing mediation of the effect of CBT on fatigue, using an inactive medication group (i.e. doxycycline and placebo group) as comparison, instead of a waiting-list [19] or active comparators like specialist medical care, adaptive pacing therapy, and graded exercise therapy [33]. The original study showed that patients already reported a substantial reduction of fatigue following placebo medication [24]. By comparing the additional effect of CBT to the placebo effect of receiving treatment, our mediation model assesses the specific contribution of CBT to the reduction of fatigue.

One limitation of this study is the fact that the cognitive-behavioural variables and fatigue severity were measured at the same time. Since changes in potential mediators between baseline and 8-week assessments were not significantly different between the CBT and medication group, changes between baseline and 26-week assessment were used. Therefore, both the primary outcome measure (fatigue severity) and possible mediators were assessed at the same time point (baseline to EOT assessment). Including assessments of mediators during treatment, prior to the assessment of the primary outcome measure, would strengthen insights on a possible cause-and-effect relationship between the change in mediators and the change in fatigue severity. The relationship between mediating cognitive-behavioural variables and fatigue severity is more likely to be a complex feedback process, than a simple cause-effect relationship [29,51,54].

Another limitation is that patients in the CBT group were non-blinded as masking for CBT is not possible. Concerning the major burden for QFS patients and the limited number of eligible patients at the time, using another comparison arm than placebo, e.g., waiting-list, was not optional. We therefore chose to compare CBT to placebo plus usual care. By comparing the additional effect of CBT to the placebo effect of receiving treatment, our mediation model assesses the specific contribution of CBT to the reduction of fatigue.

It should be noted that a difference in dropout rate was observed between CBT, doxycycline, and placebo groups of respectively 15%, 6% and 4%. In the CBT group, a total of 8 patients discontinued treatment prematurely. One of them withdrew informed consent. Although the other 7 patients discontinued treatment because they could not adhere to the therapy for various reasons, this was not because of absence of improvement or worsening of complaints [1].

Although catastrophizing beliefs about fatigue, sleep problems and resting-avoidance of activity significantly decreased during CBT, these changes did not contribute to the mediation of the decrease in fatigue severity during CBT as the effects of these potential mediators on the difference in fatigue severity were not significant. This remarkable finding could possibly be explained by the limited power of this study. However, given the fact that the Q fever outbreak in the Netherlands has come to an end, the possibility to include a substantially larger number of patients did not exist. Moreover, the exclusion of subjects due to the per-protocol analysis could theoretically have introduced bias. However, comparison of baseline characteristics of included and excluded subjects did not indicate selection bias to be likely (Appendix A).

In order to limit patient burden and to improve response rate, only a small set of questionnaires was selected and could therefore be used as potential mediators. Because of this, not all relevant variables could be measured that might mediate the effect of CBT. An example of a possible mediator we did not assess is somatic attributions with respect to fatigue [55], which was only assessed at baseline and EOT. As QFS patients have strong somatic attributions [23], it would be interesting to determine if a change in attributions contributed to the treatment response or relapse.

In conclusion, an increased sense of control over fatigue is a key mechanism of the decrease in fatigue severity in QFS brought on by CBT. Failure of maintenance of the initial improvement of self-efficacy, plays an important role in the relapse in fatigue severity after cessation of CBT. An approach to improve the long-term effectiveness of CBT in

patients with QFS, could be providing booster sessions after completion of treatment aimed at a durable change of dysfunctional fatigue beliefs. Further research is needed to identify additional mediators that may contribute to a relapse in fatigue severity after completion of CBT.

Declaration of Competing Interest

We have no conflicts of interest to disclose, and all authors have approved of the submission of the manuscript to the Journal of Psychosomatic Research.

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Appendix A. Comparison of mean baseline scores (SD) between included and excluded subjects

	All subjects (CBT + medication group)		
	Included (n = 132)	Excluded (n = 22)	P value [a]
CIS fatigue	50.3 (4.8)	50.8 (4.8)	0.67
IMQ focusing on symptoms	28.7 (9.4)	34.3 (11.0)	0.01
CBSQ catastrophizing beliefs in response to fatigue	5.2 (3.2)	6.6 (4.1)	0.08
CBSQ damaging beliefs	9.9 (3.4)	10.7 (4.0)	0.31
CBSQ fear avoidance beliefs	12.5 (4.3)	13.0 (5.6)	0.70
SES28 self-efficacy with respect to fatigue	17.5 (3.3)	16.4 (3.1)	0.17
PARS self-efficacy with respect to performing activities	56.2 (13.9)	50.0 (14.4)	0.06
Physical activity (actometer)	75.5 (17.6)	68.5 (20.9)	0.10
CBSQ resting/avoidance	11.1 (4.7)	11.9 (5.3)	0.45
CBSQ all-or-nothing behaviour	9.2 (4.3)	8.0 (3.7)	0.23
SIP sleeping/resting	118.0 (75.7)	152.3 (78.7)	0.05

Abbreviations: SD, standard deviation; CBT, Cognitive al Therapy; CIS; Checklist Individual Strength; CBSQ, Cognitive and Behavioural Responses to Symptoms Questionnaire; IMQ, Illness Management Questionnaire; SES28, Self-Efficacy Scale; PARS, Physical Activity Rating Scale; SIP, Sickness Impact Profile.

[a] P values were calculated by Student's t-test

Appendix B. Differences between the CBT and medication groups in changes in cognitive-behavioural variables from baseline to 8 weeks

	Mean difference (95% CI)	P value [a] CBT vs medication
Cognitive variables		
IMQ focusing on bodily symptoms	−0.46 (−2.77–1.85)	0.70
CBSQ catastrophizing beliefs in response to fatigue	0.42 (−0.35–1.19)	0.28
CBSQ damaging beliefs	0.20 (−0.78–1.18)	0.69
CBSQ fear avoidance beliefs	0.20 (−1.10–1.49)	0.76
SES28 self-efficacy with respect to fatigue	−0.88 (−1.85–0.10)	0.08
PARS self-efficacy with respect to performing activities	2.53 (−0.79–5.85)	0.13
Behavioural variables		
Physical activity level (actometer) [b]		
CBSQ resting/avoidance	0.51 (−0.89–1.91)	0.47
CBSQ all-or-nothing	−0.02 (−1.19–1.16)	0.98
SIP sleeping/resting [b]		

Abbreviations: CBT, cognitive al therapy; CI, confidence interval; CBSQ, Cognitive and al Responses to Symptoms Questionnaire; IMQ, Illness Management Questionnaire; SES28, Self-Efficacy Scale; PARS, Physical Activity Rating Scale; SIP, Sickness Impact Profile.

[a] P values were based on analysis of covariance between CBT and medication group. 8-week scores of variable (dependent factor) are adjusted for baseline scores of variable (covariate). Treatment strategy was used as fixed factor.

[b] 8-week measurements not available for this variable.

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