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Efficacy of Cognitive-Behavioral Therapy Targeting Severe Fatigue Following Coronavirus Disease 2019: Results of a Randomized Controlled Trial

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Background. Severe fatigue following coronavirus disease 2019 (COVID-19) is prevalent and debilitating. This study investigated the efficacy of cognitive-behavioral therapy (CBT) for severe fatigue following COVID-19.

Methods. A multicenter, 2-arm randomized controlled trial was conducted in the Netherlands with patients being severely fatigued 3–12 months following COVID-19. Patients (N = 114) were randomly assigned (1:1) to CBT or care as usual (CAU). CBT, targeting perpetuating factors of fatigue, was provided for 17 weeks. The primary outcome was the overall mean difference between CBT and CAU on the fatigue severity subscale of the Checklist Individual Strength, directly post-CBT or CAU (T1), and after 6 months (T2). Secondary outcomes were differences in proportions of patients meeting criteria for severe and/or chronic fatigue, differences in physical and social functioning, somatic symptoms, and problems concentrating between CBT and CAU.

Results. Patients were mainly nonhospitalized and self-referred. Patients who received CBT were significantly less severely fatigued across follow-up assessments than patients receiving CAU (−8.8 [95% confidence interval {CI}, −11.9 to −5.8]); $P < .001$), representing a medium Cohen's d effect size (0.69). The between-group difference in fatigue severity was present at T1 (−9.3 [95% CI, −13.3 to −5.3]) and T2 (−8.4 [95% CI, −13.1 to −3.7]). All secondary outcomes favored CBT. Eight adverse events were recorded during CBT, and 20 during CAU. No serious adverse events were recorded.

Conclusions. Among patients, who were mainly nonhospitalized and self-referred, CBT was effective in reducing fatigue. The positive effect was sustained at 6-month follow-up.

Clinical Trials Registration. Netherlands Trial Register NL8947.

Keywords. COVID-19; long COVID; fatigue; cognitive-behavioral therapy.

As the coronavirus disease 2019 (COVID-19) pandemic enters its fourth year, increasing attention is directed toward its long-term sequelae, referred to as long COVID or PASC (postacute sequelae of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) [1]. Fatigue is among the most prevalent symptoms of PASC and is common among patients being previously hospitalized and those not being hospitalized [2, 3]. The fatigue is often severe [4] and still reported by some up to 2 years after the acute phase of COVID-19, indicating a chronic course in a subset of patients [5]. As severe fatigue following COVID-19 and related disability affects millions worldwide, evidence-based interventions are urgently needed.

Persistent, severe fatigue is a common symptom following infectious diseases [6–8]. Cognitive-behavioral variables, such as a disrupted sleep–wake pattern, low or unevenly distributed level of activity, or unhelpful fatigue-related beliefs, are associated with the persistence of fatigue across several long-term

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medical conditions [9]. Cognitive-behavioral therapy (CBT) targeting these perpetuating cognitive-behavioral factors has been shown to be effective in reducing severe fatigue in patients with postinfectious fatigue and in long-term medical conditions directly posttreatment [10–12]. Furthermore, CBT targeting fatigue in other conditions not only led to a reduction of fatigue but also improved physical and/or social functioning [11]. Long-term outcomes of CBT for severe fatigue have been mixed: some studies have shown sustainment of treatment effects in the majority of patients while others have shown a substantial relapse [13, 14]. Until now, the efficacy of CBT has not been investigated in patients suffering from post–COVID-19 fatigue. We hypothesized that addressing cognitive-behavioral factors that can maintain fatigue may lead to a reduction of severe fatigue following COVID-19.

The ReCOVer study is a randomized controlled trial (RCT) designed to investigate the efficacy of CBT directly posttreatment and at 6-month follow-up for severe fatigue following COVID-19, as compared to care as usual (CAU), in patients being severely fatigued 3–12 months post–COVID-19.

METHODS

Study Design

ReCOVer is an investigator-initiated, 2-arm, multicenter RCT conducted in the Netherlands. The trial protocol has been previously published [15].

Participants

Eligible patients were diagnosed with a symptomatic, laboratory-confirmed SARS-CoV-2 infection; were severely fatigued, with fatigue starting or increasing substantially directly after the onset of symptoms of COVID-19; were functionally impaired; and were 3–12 months post–COVID-19. See Table 1 for all inclusion and exclusion criteria and their operationalization.

Patients were recruited by physicians of 6 participating hospitals in the Netherlands, by healthcare providers, and by self-referral. For clinician-referred patients, the physician or research nurse checked the medical eligibility criteria. The eligibility of self-referred patients was checked by contacting their general practitioner (GP) and requesting a copy of the positive SARS-CoV-2 test result. In case of doubt, the self-referred patient was seen by a physician of a participating hospital. After obtaining written informed consent, additional screening questionnaires were administered. The remaining inclusion and exclusion criteria were checked by the research assistant.

Randomization

Participants were randomly assigned in a 1:1 ratio to either CBT or CAU. Randomization was performed with Castor EDC [22], a web-based data capture system, using randomly selected block sizes (2, 4, or 6), and stratified according to (1) no admission to hospital, admitted to hospital, or admitted to intensive care unit (ICU) during hospitalization; and (2) dyspnea, based on the Medical Research Council [23] score (<3 vs ≥3). A research assistant blinded to the allocation sequence performed the randomization. Due to the nature of the intervention, research assistants, participants, and therapists were not blinded to randomization outcome. Data were analyzed by 2 statisticians independently (P. N., I. C.) using a file blinded for intervention allocation.

Procedures

Eligible participants completed the baseline questionnaires (T0) before they were randomized. For practical reasons, CBT with a planned duration of 17 weeks started approximately 2 weeks

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Diagnosed with symptomatic COVID-19, confirmed by a positive PCR for SARS-CoV-2 *or* another positive NAAT test (RT-PCR, LAMP, TMA, or mPOCT) *or* positive SARS-CoV-2 serology (in absence of or before vaccination) *or* a positive Antigen test *or* CORADS 4 or 5 on CT scan. • 3 months up to and including 12 months after being diagnosed with COVID-19 or after hospital discharge in case the patient was admitted[a]. • Severe fatigue, operationalized as a score ≥35 on the CIS-fatigue [16]. Fatigue started with or increased substantially directly after the onset of symptoms of COVID-19, as reported by patients and confirmed by their GP or treating consultant. • Limitations in physical functioning operationalized as a score of ≤65 on the physical functioning subscale of the SF-36 [17] and/or social functioning operationalized as a score of ≥10 on the WSAS [18]. • Age of 18 y or older. • Sufficient command of the Dutch language.	• Known psychiatric or somatic condition that can explain the fatigue. Screening for somatic condition was done by the referring physician or the patient's GP in case of self-referral. Participants were screened for the presence of PTSD with the PCL-5 [19] and for the presence of depressive disorder with the BDI-PC [20]. When the score on the BDI-PC was ≥4 or the score on the PCL-5 was ≥33, the MINI [21] was conducted to determine if patients met the criteria for PTSD or a depressive disorder. • Current participation in a multidisciplinary rehabilitation program aimed to ameliorate the consequences of COVID-19. • Objective hypoxemia at rest for which oxygen therapy at home was indicated.

Abbreviations: BDI-PC, Beck Depression Inventory for Primary Care; CIS-fatigue, fatigue severity subscale of the Checklist Individual Strength; CORADS, COVID-19 reporting and data system; COVID-19, coronavirus disease 2019; CT, computed tomography; GP, general practitioner; LAMP, loop-mediated isothermal amplification; MINI, Mini-International Neuropsychiatric Interview; mPOCT, molecular point-of-care test; NAAT, nucleic acid amplification test; PCL-5, posttraumatic stress disorder checklist for *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; PTSD, posttraumatic stress disorder; PCR, polymerase chain reaction; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SF-36, Short Form Health Survey; TMA, transcription-mediated amplification; WSAS, Work and Social Adjustment Scale.

[a]For patients hospitalized, the date of hospital discharge was taken as reference point, as patients might have been admitted for a long time period (weeks to months) and we wanted to allow enough time for physical recovery before starting a cognitive-behavioral intervention aimed at fatigue.

after randomization. After the CBT or CAU period, participants completed the T1 questionnaires (19 weeks postrandomization). Six months after T1, the follow-up assessment (T2) was completed. Questionnaires were completed online.

CBT for post–COVID-19 fatigue, called Fit after COVID, was developed by adapting existing CBT protocols for severe fatigue in long-term medical conditions [11, 14]. It is based on a cognitive-behavioral model of fatigue, which assumes that a disease (in this case, COVID-19) triggers fatigue while cognitive-behavioral variables can perpetuate it [9, 10]. The 7 perpetuating factors addressed are (1) a disrupted sleep–wake pattern; (2) unhelpful beliefs about fatigue; (3) a low or unevenly distributed activity level; (4) perceived low social support; (5) problems with psychological processing of COVID-19; (6) fears and worries regarding COVID-19; and (7) poor coping with pain. Fit after COVID is a blended intervention. For details on the content of the modules and tailoring of the intervention, see Supplementary Table 1. During development of the intervention, 3 patients suffering from fatigue following COVID-19 and recruited by the patient organization Lung Foundation Netherlands read the treatment protocol and tested the online modules. They evaluated the content and usability of the internet intervention positively.

Participants could access treatment modules on an online platform. During the COVID-19 pandemic, using an internet intervention ensured therapy continuation despite preventive public health measures, while face-to-face contact was also available for those patients who were unable or unwilling to use the internet-based format. All therapists were psychologists trained in the treatment protocol during a 4-day course and supervised biweekly by experienced clinical psychologists (H. K., T. A. K.) to ensure treatment integrity.

Participants randomized to CAU had no access to Fit after COVID but were not restricted in seeking care including psychological interventions for fatigue or other symptoms. There were no restrictions on care received by participants in the CBT group during CBT, other than multidisciplinary rehabilitation.

Outcomes

To investigate the effect of CBT directly posttreatment and at a follow-up 6 months later, the primary outcome was the difference in fatigue severity across follow-up assessments (T1 and T2) between the CBT group and the CAU group. Fatigue severity was assessed with the fatigue subscale of the 20-item Checklist Individual Strength (CIS-fatigue) [16]. The CIS-fatigue subscale consists of 8 items with a total score ranging from 8 to 56, with higher scores indicating more severe fatigue. The validated cutoff score for severe fatigue is ≥35 [16].

As secondary outcomes, we evaluated the difference in the proportion of patients between the CBT and the CAU group at T1 and T2 separately who were (1) no longer severely fatigued, operationalized as scoring <35 on the CIS-fatigue [16]; (2) no longer severely fatigued and reporting a reliable change in fatigue (ie, reliable change index [RCI] of >1.96 [24]); and (3) not chronically fatigued, with chronic fatigue operationalized as having severe fatigue with a self-reported duration of ≥6 months. In addition, we compared the CBT and CAU group across T1 and T2 regarding (4) physical functioning assessed with the physical functioning subscale of the Short Form Health Survey (SF-36) [17]; (5) social functioning, operationalized as the score on the Work and Social Adjustment Scale (WSAS) [18]; (6) somatic symptom severity, assessed with the Patient Health Questionnaire (PHQ-15) [25]; and (7) problems concentrating, assessed with the concentration problems subscale of the CIS.

Serious adverse events (SAEs) and adverse events (AEs) were recorded based on participants' self-report at T1 and observations by the study staff and therapists. Two physicians (C. B. R., S. P. K.), blinded to intervention allocation, independently rated the likelihood that the events could be attributed to CBT and discussed discrepancies until consensus was reached.

Statistical Analysis

The sample size calculation was based on testing the primary hypothesis that CBT leads to a significantly lower mean CIS-fatigue score across T1 and T2 as compared to CAU. A difference of 6 points on the CIS-fatigue score is considered clinically relevant [26]. Based on previous research, we assume a common standard deviation (SD) of 12 and correlation coefficients of 0.4 among CIS-fatigue scores assessed at T1 and T2. With a sample size of 45 in each group, a 2-sided test for the time-averaged difference between 2 means in a repeated-measures design with a .05 significance level has 80% power to detect a difference in means of 6 in a design with 2 repeated measurements. Assuming a dropout of 20%, 114 participants were randomized, 57 to each condition.

Primary and secondary outcomes were analyzed according to intention-to-treat. The primary outcome was analyzed using a mixed linear model, which included CIS-fatigue as the dependent variable; condition (CBT vs CAU), time (T1, T2), and condition-by-time interaction as fixed effects; and the CIS-fatigue score at baseline (T0) as covariate and in which the repeated measurements were nested within participants. Only when the main effect of condition was statistically significant, then the statistical significance of the between-group differences at T1 and T2 was separately interpreted. Cohen's d effect size was calculated by dividing the parameter estimate for the mean difference in CIS-fatigue scores between conditions from the mixed linear model by the pooled standard deviation at T2 of both conditions combined. Effect size magnitudes were interpreted as small (0.2–0.5), medium (0.5–0.8), and large (≥0.8) [27].

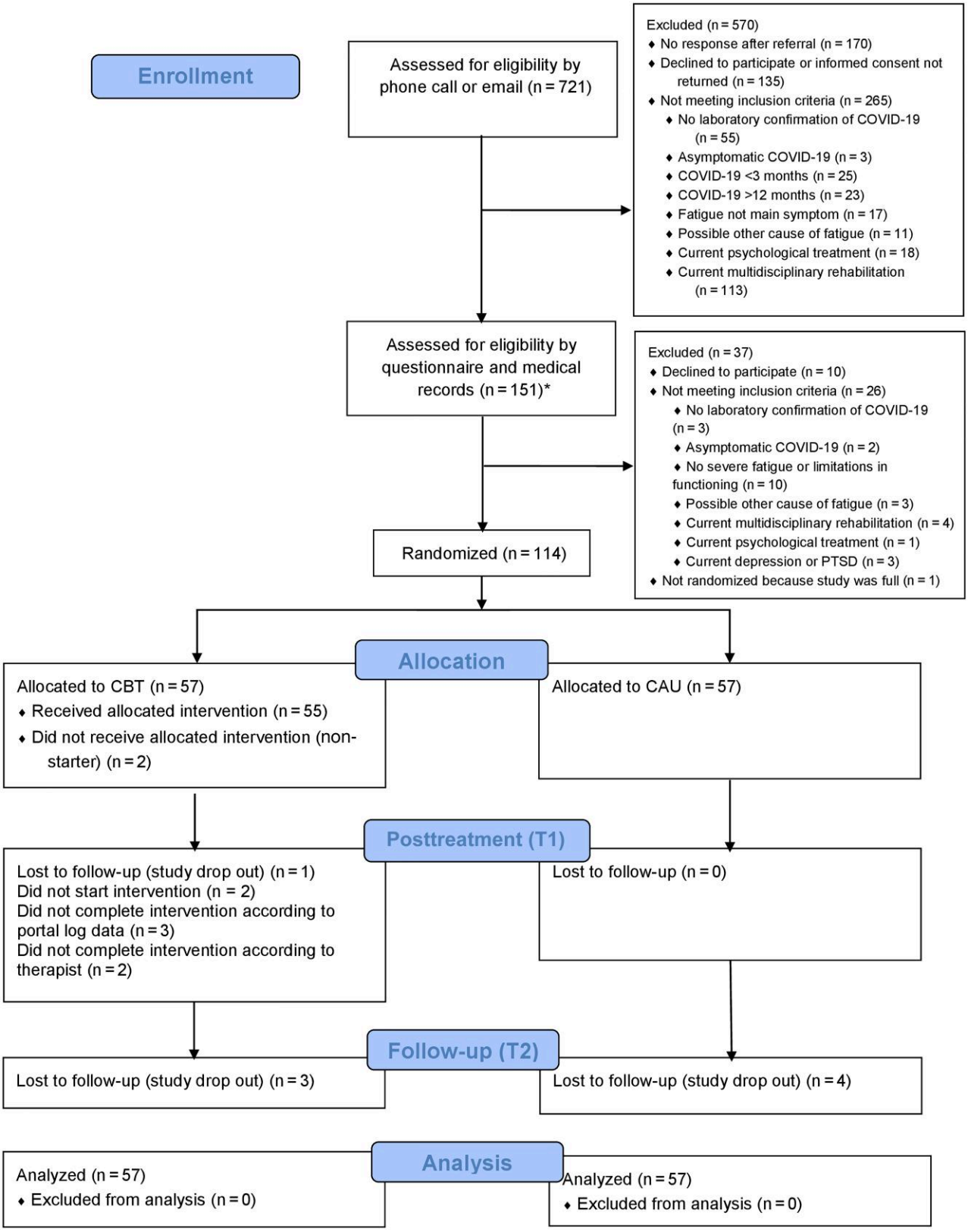

Figure 1. Flowchart of enrollment and randomization of patients. *One self-referred patient was screened for eligibility by a physician of a participating hospital. Abbreviations: CAU, care as usual; CBT, cognitive-behavioral therapy; COVID-19, coronavirus disease 2019; PTSD, posttraumatic stress disorder; T1, 19 weeks postrandomization; T2, 6 months after T1.

Dichotomous secondary outcomes were compared at T1 and T2 separately by calculating relative risks with 95% confidence intervals (CIs) of not being severely and/or chronically fatigued in the CBT versus the CAU group. The RCI was calculated as $RCI = (x_2 - x_1)/S_{diff}$, where x_1 is the CIS-fatigue score at baseline, x_2 the CIS-fatigue score at follow-up, and S_{diff} the standard error of the difference. S_{diff} was calculated with $S_{diff} = \sqrt{2(S_E)^2}$, where S_E is the standard error of the measurement. To calculate S_E, the average Cronbach α of the CIS-fatigue score from previous studies (0.89) was used [11, 16]. The continuous secondary outcomes were analyzed using mixed linear models as described for the primary outcome.

To explore the robustness of our findings from the primary analysis, 4 sensitivity analyses were conducted. The first comprised per protocol analyses with 2 operationalizations of treatment completion: (1) participants who have filled out the treatment goals and opened the 5 standard modules of the intervention (portal log data) and (2) participants who attended at least 3 sessions (therapist registration) face-to-face or via video consult. Second, the extent to which our results would change if based on a single time point was explored. Therefore a separate 1-way analysis of covariance (ANCOVA) was conducted with group allocation as a fixed factor, baseline CIS-fatigue score as covariate, and the CIS-fatigue score at either T1 or T2 as dependent variable. For each time point, Cohen's d was calculated. Third, we explored the extent to which dyspnea at T0, disease severity, operationalized as previously being hospitalized for COVID-19, time since diagnosis of COVID-19, age, and sex have an impact on the primary outcome, and whether this impact differs between CBT and CAU. Fourth, ANCOVAs of fatigue severity at T1 and T2 separately were reanalyzed replacing missing values with multiple imputation.

The statistical analysis was conducted using SPSS version 28. Cohen's d was calculated using R version 4.0.3.

Table 2. Characteristics of the Patients at Baseline

Characteristic	CBT (n = 57)	CAU (n = 57)
Demographics		
Age, y, mean (SD)	45.7 (12.4)	46.0 (12.9)
Female sex	45 (79)	38 (67)
BMI, kg/m^2, mean (SD)	26.9 (5.0)	27.2 (5.8)
Education level[a] (ISCE)		
Low	4 (7)	4 (7)
Middle	43 (75)	37 (65)
High	10 (18)	16 (28)
Clinical variables		
COVID-19 confirmation		
RT-PCR	49 (86)	51 (89)
Serology	8 (14)	6 (11)
Other	0 (0)	0 (0)
Hospital admission	6 (11)	7 (12)
Days since COVID-19 diagnosis or hospital discharge, mean (SD)	191.2 (75.8)	183.7 (75.5)
Referral		
Hospital outpatient clinic	11 (19)	17 (30)
Self-referral	39 (68)	36 (63)
Other healthcare provider	7 (12)	4 (7)
Self-reported comorbidities		
None	32 (56)	31 (54)
1	18 (32)	17 (30)
2 or more	7 (12)	9 (16)
Clinically relevant depressive symptoms[b]	12 (21)	15 (26)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, self-reported body mass index; CAU, care as usual; CBT, cognitive-behavioral therapy; COVID-19, coronavirus disease 2019; ISCE, International Standard Classification of Education; RT-PCR, reverse-transcription polymerase chain reaction; SD, standard deviation.

[a]Low indicates early childhood education, primary education, or lower secondary education; medium indicates upper secondary education or postsecondary nontertiary education; high indicates short cycle of tertiary education, bachelor's degree (or equivalent level), master's degree (or equivalent level), or doctoral degree (or equivalent level) [28].

[b]Operationalized as a score of ≥4 on the Beck Depression Inventory–Primary Care [20].

RESULTS

From 12 November 2020 to 21 September 2021, 721 patients were assessed for eligibility. Of this group, 114 patients, the target sample size, were randomized to CBT (n = 57) or to CAU (n = 57). The majority of the patients were self-referred (75/114 [66%]) and did not require hospitalization during their initial COVID-19 (101/114 [89%]). All patients but 1 were infected before being vaccinated. See Figure 1 for the flowchart and Table 2 for the baseline characteristics. At T1, data were missing for <1% of patients (1/114, CBT) for the primary outcome and <4% of patients (2 CBT, 2 CAU [4/114]) for secondary outcomes. At T2, data were missing for <6% of patients (3 CBT, 4 CAU [7/114]) for the primary outcome and <8% of patients (3 CBT, 6 CAU [9/114]) for secondary outcomes.

The mean duration of CBT was 18.7 (SD, 2.3) weeks. The mean number of interactions between the therapist and patient was 11.8 (SD, 3.5), consisting of 4.6 (SD, 4.2) interactions by email, 4.0 (SD, 3.8) video consults, 2.9 (SD, 3.0) face-to-face consults, and 0.3 (SD, 0.7) telephone consults. Of the 56 patients who followed the intervention, 55 followed the blended format. One patient (1/56 [2%]) had only face-to-face sessions without use of the internet intervention. For all details on the delivery of CBT, see Supplementary Table 2.

Figure 2 and Table 3 present the primary and secondary outcomes at the different time points. The overall between-group difference of the fatigue severity score was −8.8 (95% CI, −11.9 to −5.8; $P < .001$), favoring CBT and representing a medium effect size (Cohen's d = 0.69). The between-group difference in fatigue severity was present at T1 and T2. At T1, the estimated mean difference was −9.3 (95% CI, −13.3 to −5.3; $P < .001$), favoring CBT and representing a medium effect size (Cohen's d = 0.74). At T2, the estimated mean difference was −8.4 (95% CI, −13.1 to −3.7; $P < .001$), favoring CBT and also representing a medium effect size (Cohen's d = 0.65).

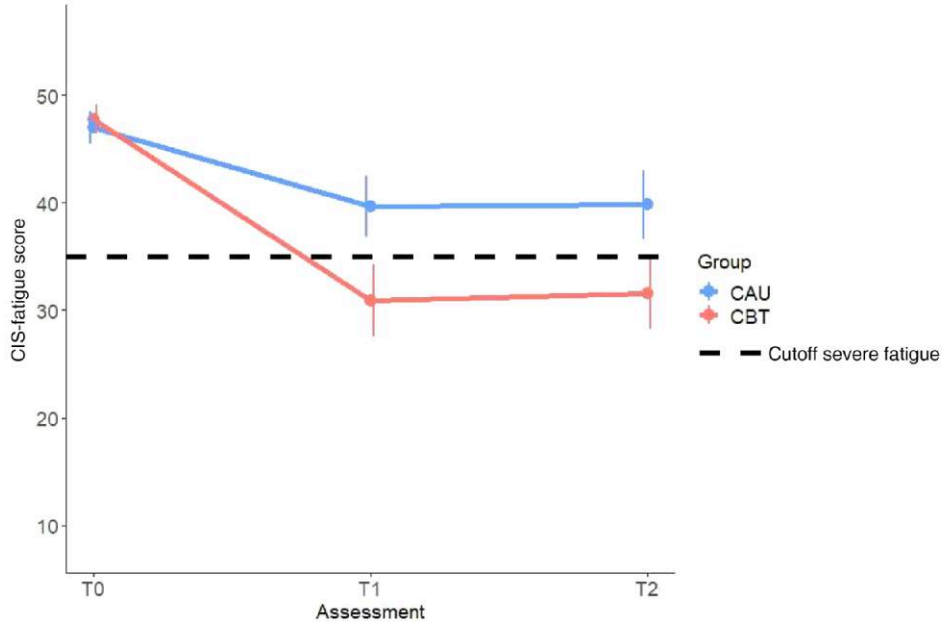

Figure 2. Checklist Individual Strength–fatigue scores and standard errors from baseline to the posttreatment assessment for the cognitive-behavioral therapy group and the care as usual group. Abbreviations: CAU, care as usual; CBT, cognitive-behavioral therapy; CIS, Checklist Individual Strength; T0, baseline; T1, 19 weeks postrandomization; T2, 6 months after T1.

All secondary outcomes were in favor of the CBT group. At T1 and T2, the majority of the patients in the CBT group were no longer severely fatigued, were no longer severely fatigued and reported a reliable change in fatigue, and were not chronically fatigued, as compared to a minority in the CAU group. See Figure 3 and Table 3 for all outcomes and relative risks. As can be derived from Figure 3, there was no indication of deterioration of fatigue following CBT. The overall between-group mean difference in the physical functioning score between the CBT and CAU group was 7.1 (95% CI, 2.9–11.3; $P = .001$), favoring CBT and representing a small effect of CBT (Cohen's $d = 0.34$). For social functioning, the mean difference in WSAS score was −6.6 (95% CI, −9.1 to −4.2;
$P < .001$), favoring CBT and representing a medium effect (Cohen's $d = 0.60$). The overall mean difference between both groups in somatic symptom severity was −2.0 (95% CI, −2.9 to −1.0; $P < .001$), favoring CBT and representing a small effect size (Cohen's $d = 0.43$). Last, the mean difference in scores indicating problems concentrating was −5.1 (95% CI, −6.9 to −3.4; $P < .001$), favoring CBT and representing a medium effect (Cohen's $d = 0.63$).

The sensitivity analyses (see Supplementary Table 3*A*–*D*) showed the same pattern of results as the primary analysis.

During the study period, 73% of patients (40/55) in the CBT group and 91% of patients (51/56) in the CAU group received care outside of the study with a mean number of consulted healthcare practitioners of 1.1 (SD, 1.0) and 2.4 (SD, 1.6), respectively. These were mainly the GP, a physician in an outpatient clinic, or a physical therapist, the latter most often for guided exercise. (Supplementary Table 4).

Eight AEs (Supplementary Table 5) occurred in 12% of patients (7/57) in the CBT group, of which 6 AEs were rated as possibly related to CBT. In the CAU group, 20 AEs occurred in 25% of patients (14/57). No SAEs were recorded.

DISCUSSION

This RCT showed that patients who reported severe fatigue 3–12 months following COVID-19 were significantly less severely fatigued after CBT than after CAU. Our findings are in line with previous studies investigating the efficacy of CBT for severe fatigue in other patient groups [10–12]. Moreover, positive effects of CBT were sustained for 6 months after the intervention. This is an important finding given mixed long-term outcomes of CBT in other studies [13, 14]. Furthermore, patients randomized to CBT were also less often severely and chronically fatigued and reported fewer concentration problems, less severe somatic symptoms, and improved physical and social functioning across follow-up assessments.

This study has several strengths. It was a multicenter RCT and entailed a follow-up assessment 6 months after CBT or CAU. The high number of self-referrals and low attrition rate suggest that CBT is an acceptable and feasible intervention for at least a group of post–COVID-19 patients. Furthermore, our preliminary data on AEs and the absence of deterioration of fatigue in

Table 3. Estimated Means and Linear Mixed Model Analyses for Primary and Secondary Outcomes Over Time

Outcome Measure	Study Arm	T0 (Baseline), Mean (SE)	T1, Estimated Mean (SE)	T2, Estimated Mean (SE)	Overall Between-Group Difference, Mean (95% CI)	*P* Value Overall Between-Group Difference	Cohen's d of the Overall Effect
Primary outcome							
Fatigue							
CIS-fatigue[a]	CBT	47.8 (0.7)	30.6 (1.4)	31.5 (1.7)	−8.8 (−11.9 to −5.8)	<.001	0.69
	CAU	47.0 (0.8)	39.9 (1.4)	39.9 (1.7)	…		
Secondary continuous outcomes							
Physical functioning							
SF-36[b]	CBT	64.7 (2.4)	80.3 (1.8)	77.2 (2.4)	7.1 (2.9–11.3)	.001	0.34
	CAU	62.5 (2.7)	70.9 (1.8)	72.3 (2.5)	…		
Social functioning							
WSAS[c]	CBT	24.5 (1.0)	11.9 (1.0)	11.7 (1.4)	−6.6 (−9.1 to −4.2)	<.001	0.60
	CAU	21.8 (1.0)	19.7 (1.0)	17.1 (1.4)	…		
Somatic symptoms							
PHQ-15[d]	CBT	11.4 (0.6)	7.8 (0.4)	8.5 (0.5)	−2.0 (−2.9 to −1.0)	<.001	0.43
	CAU	11.0 (0.5)	10.1 (0.4)	10.0 (0.5)	…		
Problems concentrating							
CIS-conc[e]	CBT	26.6 (0.7)	18.4 (0.7)	17.3 (1.0)	−5.1 (−6.9 to −3.4)	<.001	0.63
	CAU	24.6 (0.9)	23.6 (0.7)	22.5 (1.0)	…		
		T1	T1	T1	T2	T2	T2
		No. (%)	Relative Risk (95% CI)	*P* Value	No. (%)	Relative Risk (95% CI)	*P* Value
Secondary dichotomous outcomes							
CIS-fatigue <35	CBT	33 (59%)	2.24 (1.38–3.64)	.001	34 (63%)	2.38 (1.46–3.91)	<.001
	CAU	15 (26%)			14 (26%)		
CIS-fatigue <35 and reliable change[f]	CBT	33 (59%)	2.24 (1.38–3.64)	.001	34 (63%)	2.57 (1.53–4.30)	<.001
	CAU	15 (26%)	…		13 (25%)	…	
Not chronically fatigued	CBT	36 (64%)	2.12 (1.36–3.30)	<.001	39 (72%)	2.30 (1.49–3.57)	<.001
	CAU	17 (30%)	…		16 (31%)	…	

Abbreviations: CAU, care as usual; CBT, cognitive-behavioral therapy; CI, confidence interval; CIS-conc, concentration subscale of the Checklist Individual Strength; CIS-fatigue, fatigue severity subscale of the Checklist Individual Strength; PHQ-15, Patient Health Questionnaire; SE, standard error; SF-36, Short Form Health Survey; T0, baseline; T1, 19 weeks postrandomization; T2, 6 months after T1; WSAS, Work and Social Adjustment Scale.

[a]Scores on CIS-fatigue [16] range from 8 to 56, with higher scores indicating more severe fatigue; a score of ≥35 indicates severe fatigue.

[b]Scores on the physical functioning subscale of SF-36 [17] range from 0 to 100, with higher scores indicating better physical functioning.

[c]Scores on WSAS [18] range from 0 to 40, with a higher score indicating more social impairment. A score of ≥10 indicates significant impairment.

[d]Scores on PHQ-15 [25] range from 0 to 30, with higher scores indicating higher symptom severity.

[e]Scores on CIS-conc [16] range from 5 to 35, with higher scores indicating more problems concentrating.

[f]For a better comparison of the relative risks, this outcome has been reformulated relative to the protocol paper so that it is in the same direction as the other dichotomous secondary outcomes. The operationalization was not changed.

the CBT group indicate that CBT for severe post–COVID-19 is safe. The intervention, due to its online format, could be relatively swiftly implemented and reach a wide patient group.

This study has limitations. As in all studies testing the efficacy of behavioral/psychotherapeutic interventions, blinding is not possible because both patient and therapist are aware of the allocated treatment. Also, this is the first study testing the efficacy of CBT for post–COVID fatigue. Replication in other settings or regions is warranted to determine the generalizability of our results. Furthermore, the majority of included patients did not require hospitalization for COVID-19. Our results might therefore not generalize to patients with hospital or ICU admission. As there is no reliable biomarker of severe fatigue, we used a patient-reported outcome to assess fatigue severity.

Despite efforts to recruit patients consecutively, the majority of included patients were self-referred. This might have caused a selection bias—for example, this group may have been more motivated to undertake a behavioral intervention than patients routinely visiting an outpatient clinic [30]. However, self-referrals may better represent the target patient group for implementation of CBT in clinical practice.

A further limitation of this study is the use of CAU as comparison condition. A placebo condition matched with respect to the attention given and offering of a treatment rationale would have been preferable to rule out that the effects of

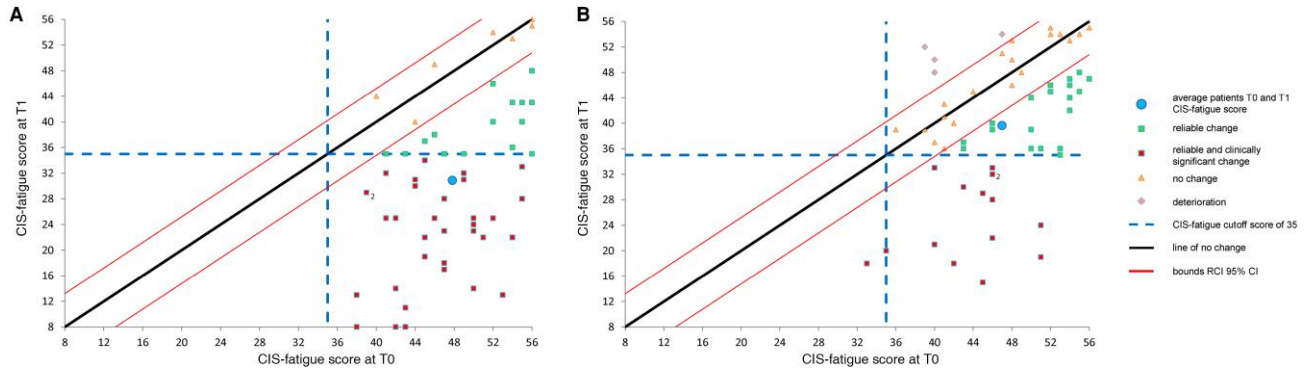

Figure 3. Changes in Checklist Individual Strength–fatigue scores from baseline to the posttreatment assessment for the cognitive-behavioral therapy group (*A*) and the care as usual group (*B*). The score of 1 patient in the care as usual group dropped below 35 between screening and baseline. [2]These points are double as 2 patients had the same scores. Figures were created using the Leeds reliable change index calculator [29]. Abbreviations: CI, confidence interval; CIS, Checklist Individual Strength; RCI, reliable change index; T0, baseline; T1, 19 weeks postrandomization.

CBT were (partly) nonspecific. However, most participants in the CAU group received care, including exercise, which has been found to be effective for post-COVID-19 sequelae [31]. A substantial number of patients in the CAU condition might therefore have received an intervention with a comparable amount of attention provided and which also offered a credible treatment rationale, but without the specific elements of CBT.

Finally, a limitation of our study is that a formal treatment integrity check was not performed. However, all therapists were trained and supervised to assure protocol adherence. Furthermore, the delivery of treatment modules was registered.

Of note, applying a cognitive-behavioral approach to the treatment of post-COVID-19 fatigue neither implies that its cause is psychological, nor does it negate a possible somatic cause. We encourage research into its underlying (neuro)biological mechanisms. Relatedly, while the majority of patients were no longer severely fatigued following CBT, a substantial group remained severely fatigued. Research into other treatment approaches is warranted.

This study provides first evidence for the positive effect of CBT in patients with severe post–COVID-19 fatigue.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Data sharing. The de-identified patient data set can be made available after publication. Any request to share the data of this RCT will be considered by the trial steering committee and will need to be approved by the ethics committee of the Amsterdam University Medical Center, location University of Amsterdam. The meta-dataset is available at https://COVID19initiatives.health-ri.nl/p/Project/27866022694497984. The informed consent form is published with the protocol paper: https://doi.org/10.1186/s13063-021-05569-y.

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References

1. Salamanna F, Veronesi F, Martini L, Landini MP, Fini M. Post-COVID-19 syndrome: the persistent symptoms at the post-viral stage of the disease. A systematic review of the current data. Front Med **2021**; 8:653516.
2. Ceban F, Ling S, Lui LMW, et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. Brain Behav Immun **2022**; 101:93–135.
3. Han Q, Zheng B, Daines L, Sheikh A. Long-term sequelae of COVID-19: a systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. Pathogens **2022**; 11:269.
4. Verveen A, Wynberg E, van Willigen HDG, et al. Severe fatigue in the first year following SARS-CoV-2 infection: a prospective cohort study. Open Forum Infect Dis **2022**; 9:ofac127.
5. Huang L, Li X, Gu X, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. Lancet Respir Med **2022**; 10:863–76.
6. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC Neurol **2011**; 11:37.
7. Lam MHB, Wing YK, Yu MWM, et al. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors long-term follow-up. Arch Intern Med **2009**; 169:2142–7.
8. Morroy G, Keijmel SP, Delsing CE, et al. Fatigue following acute Q-fever: a systematic literature review. PLoS One **2016**; 11:e0155884.
9. Hulme K, Hudson JL, Rojczyk P, Little P, Moss-Morris R. Biopsychosocial risk factors of persistent fatigue after acute infection: a systematic review to inform interventions. J Psychosom Res **2017**; 99:120–9.
10. Keijmel SP, Delsing CE, Bleijenberg G, et al. Effectiveness of long-term doxycycline treatment and cognitive-behavioral therapy on fatigue severity in patients with Q fever fatigue syndrome (Qure Study): a randomized controlled trial. Clin Infect Dis **2017**; 64:998–1005.
11. Menting J, Tack CJ, van Bon AC, et al. Web-based cognitive behavioural therapy blended with face-to-face sessions for chronic fatigue in type 1 diabetes: a multicentre randomised controlled trial. Lancet Diabetes Endocrinol **2017**; 5:448–56.
12. Okkersen K, Jimenez-Moreno C, Wenninger S, et al. Cognitive behavioural therapy with optional graded exercise therapy in patients with severe fatigue with myotonic dystrophy type 1: a multicentre, single-blind, randomised trial. Lancet Neurol **2018**; 17:671–80.
13. Raijmakers RPH, Keijmel SP, Breukers EMC, et al. Long-term effect of cognitive behavioural therapy and doxycycline treatment for patients with Q fever fatigue syndrome: one-year follow-up of the Qure study. J Psychosom Res **2019**; 116: 62–7.
14. Gielissen MFM, Verhagen CAHHVM, Bleijenberg G. Cognitive behaviour therapy for fatigued cancer survivors: long-term follow-up. Br J Cancer **2007**; 97: 612–8.
15. Kuut TA, Müller F, Aldenkamp A, et al. A randomised controlled trial testing the efficacy of Fit After COVID, a cognitive behavioural therapy targeting severe post-infectious fatigue following COVID-19 (ReCOVer): study protocol. Trials **2021**; 22:867.
16. Worm-Smeitink M, Gielissen M, Bloot L, et al. The assessment of fatigue: psychometric qualities and norms for the Checklist Individual Strength. J Psychosomatic Res **2017**; 98:40–6.
17. Aaronson NK, Muller M, Cohen PDA, et al. Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol **1998**; 51:1055–68.
18. Mundt JC, Marks IM, Shear MK, Greist JH. The work and social adjustment scale: a simple measure of impairment in functioning. Br J Psychiatry **2002**; 180:461–4.
19. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): development and initial psychometric evaluation. J Trauma Stress **2015**; 28:489–98.
20. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for primary care. Behav Res Ther **1997**; 35:785–91.
21. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and *ICD-10*. J Clin Psychiatry **1998**; 59(Suppl 20):22–33.
22. Castor. Castor electronic data capture system. Amsterdam, the Netherlands: Castor; **2019**.
23. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax **1999**; 54: 581–6.
24. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol **1991**; 59: 12–9.
25. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med **2002**; 64: 258–66.
26. Knoop H, Van Der Meer JWM, Bleijenberg G. Guided self-instructions for people with chronic fatigue syndrome: randomised controlled trial. Br J Psychiatry **2008**; 193:340–1.
27. Cohen J. A power primer. Psychol Bull **1992**; 112:155–9.
28. Institute for Statistics, United Nations Educational, Scientific and Cultural Organization (UNESCO). International standard classification of education. **2011**. Montreal, Canada: UNESCO Institute for Statistics, **2012**.
29. Morley S, Dowzer CN. Manual for the Leeds reliable change indicator: simple Excel applications for the analysis of individual patient and group data. Leeds, UK: University of Leeds, **2014**.
30. Thewes B, Rietjens JAC, van den Berg SW, et al. One way or another: the opportunities and pitfalls of self-referral and consecutive sampling as recruitment strategies for psycho-oncology intervention trials. Psycho-Oncology **2018**; 27: 2056–9.
31. Jimeno-Almazán A, Franco-López F, Buendía-Romero Á, et al. Rehabilitation for post-COVID-19 condition through a supervised exercise intervention: a randomized controlled trial. Scand J Med Sci Sports **2022**; 32:1791–801.