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# Are the effects of cognitive behavior therapy for severe fatigue in cancer survivors sustained up to 14 years after therapy?

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## Abstract

**Purpose** Cognitive behavior therapy (CBT) reduces cancer-related fatigue (CRF) in cancer survivors in the short term. We examined fatigue levels up to 14 years after CBT.

**Methods** Eligible participants of two randomized controlled trials who had completed CBT for CRF and a post-treatment assessment were contacted ( $n = 81$ ). Fatigue was assessed with the subscale “fatigue severity” of the Checklist Individual Strength (CIS-fatigue). The course of fatigue over time was examined with linear mixed model analyses. Fatigue levels of participants were compared to matched population controls at long-term follow-up. We tested with multiple regression analysis if fatigue at follow-up was predicted by the patients’ fatigue level and fatigue-perpetuating factors directly after CBT (post-CBT).

**Results** Seventy-eight persons completed a follow-up assessment (response rate = 96%, mean time after CBT = 10 years). The mean level of fatigue increased from 23.7 (SD = 11.1) at post-CBT to 34.4 (SD = 12.4) at follow-up ( $p < 0.001$ ). Population controls ( $M = 23.9$ , SD = 11.4) reported lower fatigue levels than participants. Half of the patients (52%) who were recovered from severe fatigue at post-CBT (CIS-fatigue < 35) were still recovered at long-term follow-up. Patients with lower fatigue levels at post-CBT were less likely to show relapse.

**Conclusion** Despite initial improvement after CBT, levels of fatigue deteriorated over time. Half of the patients who were recovered from severe fatigue after CBT still scored within normal ranges of fatigue at long-term follow-up.

**Implications for Cancer Survivors** It should be explored how to help patients with a relapse of severe fatigue following an initially successful CBT. They may profit from CBT again, or another evidence-based intervention for fatigue (like mindfulness or exercise therapy). Future research to gain insight into reasons for relapse is warranted.

**Keywords** Cognitive-behavioral therapy · Cancer-related fatigue · Cancer survivors · Long-term follow-up

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## Introduction

Fatigue is one of the most common and distressing consequences of cancer and cancer treatment. Cancer-related fatigue (CRF), defined by the National Comprehensive Cancer network (NCCN) as “a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning, arises over a continuum, ranging from tiredness to exhaustion. When compared to the tiredness felt by a healthy individual, cancer-related fatigue is perceived of greater magnitude, disproportionate to activity and exertion, and not completely relieved by rest [1].” CRF has negative effects on the patients’ quality of life. Prevalence rates of CRF vary, approximately 25–30% of the cancer survivors report persistent fatigue after cancer treatment [2, 3].

The cognitive-behavioral model of CRF makes a distinction between precipitating and perpetuating factors of fatigue. It is assumed that cancer and its treatment trigger fatigue, but that cognitive and behavioral factors perpetuate it. Six perpetuating factors are distinguished: (1) insufficient coping with the experience of cancer, (2) excessive fear of disease recurrence, (3) dysfunctional cognitions concerning fatigue, (4) deregulation of the sleep-wake pattern, (5) deregulation of activity or low activity, and (6) perceived lack of social support and negative social interactions [4].

Cognitive behavior therapy (CBT) for CRF is aimed at these fatigue-perpetuating cognitions and behaviors. The efficacy of CBT for CRF has been tested in several randomized controlled trials (RCT’s) [4–6]. It was found that CBT led to significant reduction of fatigue and functional impairment in severely fatigued cancer survivors. Positive effects of CBT were maintained up to 2 years after completion of CBT [7], with the majority of patients reporting a level of fatigue within normal range following treatment.

It is unclear if treatment effects are maintained in the long-term; there are no studies on CBT in cancer survivors that expanded the scope of the follow-up beyond the aforementioned period of 2 years. Studies on the long-term effect of CBT for fatigue in other patient populations have shown that sustainment of treatment effect is not self-evident.

For example, Janse et al. [8] recently reported on the long-term effect of CBT for chronic fatigue syndrome (CFS). Patients with CFS suffer from medically unexplained severe fatigue. The long-term outcome was assessed in 583 participants of four previously published studies reporting on the effects of CBT for CFS. Positive effects of CBT were sustained up to 18 months after CBT. At long-term follow-up, up to 10 years after end of treatment, fatigue severity had significantly increased. The percentage participants with a fatigue score in the normal range was substantially lower compared to the short-term follow-up. Similar results were found

by Van Akker et al. in patients with multiple sclerosis [9]. Their study showed a positive effect of CBT on fatigue following treatment, which was also not sustained at follow-up.

The main objective of this study was to determine whether the positive effect of CBT on fatigue severity in cancer survivors was sustained at long-term follow-up. The second objective of this study was to determine predictors of fatigue severity at long-term follow-up. Knowledge on which patients are vulnerable for a relapse of severe fatigue and whether relapse is related to the presence of fatigue-perpetuating factors at post-treatment would be valuable to optimize the intervention.

## Material and methods

### Study design and participants

In our study, we defined long-term follow-up as more than 2 years after finishing CBT for CRF. Participants were derived from two previous RCTs of Gielissen et al. [4] and Prinsen et al. [5]:

- In the RCT of Gielissen et al. [4], a total of 112 patients were randomized to either CBT or waiting list condition. Patients from both conditions received CBT, either directly after randomization or after the waiting list period. Of the 112 patients, 98 started CBT and 70 completed the post-treatment assessment. These 70 patients were invited to participate in the current follow-up study.
- In the RCT of Prinsen et al. [5], 50 patients were randomized to either CBT or a waiting list. At second assessment, the CBT of a number of patients was still ongoing. Although the CBT continued, the study was stopped and these patients had no post-CBT assessment. Only 23 randomized patients from the intervention condition were included in the analyses to determine the efficacy of CBT [5]. We invited these 23 patients to participate in the follow-up study.

A total of 93 patients (70 from the Gielissen study and 23 from the Prinsen study) were invited to participate in the study. The initial RCTs had the following inclusion criteria: (1) being severely fatigued at baseline (operationalized as a score of 35 or higher on the fatigue subscale of the Checklist Individual Strength (CIS), (2) no known somatic cause for the fatigue, (3) completion of curative treatment for cancer at least 1 year ago, (4) a minimal age at disease onset of 18 years, (5) no evidence of disease recurrence, and (6) not being older than 65 years [4, 5]. In the current follow-up study, we excluded patients who had metastatic cancer and/or received treatment for cancer in the 6 months prior to the follow-up assessment. Patients were treated for mixed cancer diagnosis.

Because general population surveys have shown that fatigue increases with advancing age [10], we examined if fatigue levels of our participants at long term follow-up differed from the level of fatigue in an age-matched control group that represented the general Dutch population. We assessed whether patients treated with CBT for CRF experienced a comparable level of fatigue. A sample of general population controls was derived from a research panel of CentERdata, a research institute at Tilburg University. CentERdata has access to a large panel of participants for surveys. The panel reflects the distribution of the Dutch population with respect to age, sex, education level, and socioeconomic status. For each participant in our study, three controls were derived from the research panel. The control group was matched to our study population based on age and gender with the procedure Coarsened Exact Matching (CEM) using STATA/SE12.1.

## Intervention

CBT for CRF is protocolized and aimed at the aforementioned fatigue-perpetuating factors [4]. CBT starts with educating patients about the cognitive-behavioral model of CRF. Treatment is tailored: the relevant perpetuating factors are assessed through use of specific questionnaires. The patient formulates treatment goals and then starts with regulating the sleep-wake pattern. This is followed by reformulating fatigue-related beliefs and a graded activity program. Low active patients gradually increase their level of physical activity; relatively active patients first learn to divide their activities more evenly before the start of the graded activity program. If indicated, excessive fear of cancer recurrence, insufficient coping with cancer, and cancer treatment are addressed. It is also discussed how to deal with a perceived lack of support with respect to fatigue and how to reduce negative interactions. During therapy, patients realize their goals step by step followed by an evaluation of the treatment. The mean number of therapy sessions during the 6-month period was 12.5 (SD 4.7) in the intervention condition and 12.4 (SD 4.6) in the waiting list condition in the Gielissen study [4] and 12.0 (SD 5.0) in the Prinsen study [5]. A detailed description of the conditions and followed procedures concerning both studies can be found in the original published papers [4, 5].

## Procedures

The municipal registration was consulted in case of unknown address and for the purpose of preventing approaching the family of deceased participants. An invitation letter and follow-up questionnaires were sent by mail. Patients who did not respond within a timeframe of 2 weeks received the questionnaires again and were contacted by phone simultaneously. Non-responders that could not be reached by phone were sent a reminder by mail up to five

times. When patients did not want to fill in questionnaires, they were asked to complete only the primary outcome measure, the subscale Fatigue Severity of the Checklist Individual Strength (CIS-fatigue) by phone. The local medical ethical committee Arnhem-Nijmegen approved the study (registration number: 2015-2048).

## Assessment

### Patient characteristics

Sociodemographic and medical data were collected by a self-report questionnaire. Data on work status and recent life events were gathered. Patients were asked if they were currently treated for fatigue, received treatment by a psychologist or psychiatrist, had seen a specialist for a somatic comorbidity other than cancer, had a recurrence of cancer since their treatment with CBT for CRF, and/or were treated for cancer in the past 6 months.

*Fatigue severity* was assessed with the subscale Fatigue Severity of the Checklist Individual Strength (CIS-fatigue), indicating the level of fatigue in the previous 2 weeks, measured with eight items on a seven-point scale (range 8–56). A score of 35 or higher indicates severe fatigue. The CIS is found to be a reliable and valid instrument with a high internal consistency: Cronbach's alpha ranges from 0.92 to 0.95 in cancer survivors [11].

*Physical functioning, mental health, and bodily pain* were assessed with the respective subscales of the Short Form-36 (SF-36) [12]. Physical functioning at follow-up was measured, because the negative effect of fatigue on physical functioning is well known and CBT had a positive effect on physical functioning in the two RCTs [4, 5]. Mental health and pain were measured as potential confounders of the long-term effect of CBT on fatigue severity. Weighted subscale scores range from 0 to 100, with higher scores indicating a better health status. The SF-36 is a valid and reliable instrument for different patient populations [13].

### Perpetuating factors of fatigue directly after CBT

The model of CBT for CRF comprises six perpetuating factors. During CBT, each of the relevant perpetuating factors is targeted with a specific treatment module. We examined whether the level of fatigue at long-term follow-up could be predicted by the fatigue-perpetuating factors and the patients' level of fatigue directly after CBT. The dataset we used did not include a consistent useable measure of "fear of cancer recurrence," one of the six perpetuating factors, that was used in both studies. Therefore, this perpetuating factor was left out of our analyses. We included the other five perpetuating factors of fatigue, measured post-CBT, as possible predictors of fatigue at long-term follow-up:

- *Deregulated activities*: self-reported activity level was measured with the activity subscale of the CIS.
- *Coping with the experience of cancer* (i.e., the extent to which a subject is currently occupied with the coping process after cancer and its treatment) was measured with the Dutch version of the Impact of Event Scale (IES) [14].
- *Dysfunctional cognitions*: self-efficacy with respect to fatigue (i.e., confidence in one's own ability to cope with fatigue) was measured with the Self-Efficacy Scale (SES) [15].
- *Deregulated sleep-wake cycle*: sleep disturbances were measured with the sleep/rest subscale of the Sickness Impact Profile-8 (SIP-8) [16].
- *A perceived lack of social support*: discrepancies between amount of received and desired amount of social support were measured with the subscale “discrepancies” (i.e., discrepancies between amount and desired amount of social support) of the van Sonderen Social Support Inventory (SSL-D) [17].

### Statistical analyses

Data analyses were performed using SPSS (version 22). The threshold for significance was  $p < 0.05$  (two tailed). Sample characteristics were analyzed using frequencies, percentages, and mean scores.

Each participant had data of three measurement points: baseline, post-CBT, and long-term follow-up. Analyses were conducted for both fatigue and physical functioning as continuous variables and for fatigue as a dichotomous variable (within normal range  $< 35$ , outside normal range 35 or higher).

### Sustainment of effects of CBT on fatigue severity and physical functioning

We used linear mixed model analyses to examine the course of fatigue and physical functioning over time with three assessments clustered within each participant. Time was included as a categorical variable (using dummy variables) to compare scores at long-term follow-up assessment with the scores at the baseline and post-CBT assessments. Because of the extensive span of the follow-up period, it was important to take into account that besides cancer and its treatment, many other factors can cause and perpetuate fatigue. For both outcomes, additional analyses were conducted to assess the influence of the following covariates on the development of fatigue over time: somatic comorbidities (yes/no), cancer recurrence (yes/no), significant life events (yes/no), pain (subscale SF-36), and mental health (subscale SF-36). A recent review by Abrahams et al. [18] has shown these factors to be of importance in CRF.

The same analyses (with and without covariates) were conducted with fatigue as a dichotomous outcome (i.e., within or

outside normal ranges) using logistic generalized estimating equations (GEE). It was not possible to calculate the time effect between baseline and follow-up, as only severely fatigued patients (CIS-fatigue  $\geq 35$ ) were eligible to participate in the trials. All patients were severely fatigued at baseline, i.e., had a score of one. This lack of variance made it impossible to estimate proper regression coefficients.

### Comparison of fatigue level of participants with the general population

The fatigue level of the participants at long-term follow-up was compared with the fatigue level of general population controls using a  $t$  test for independent samples.

### Determining predictors of fatigue severity at long-term follow-up

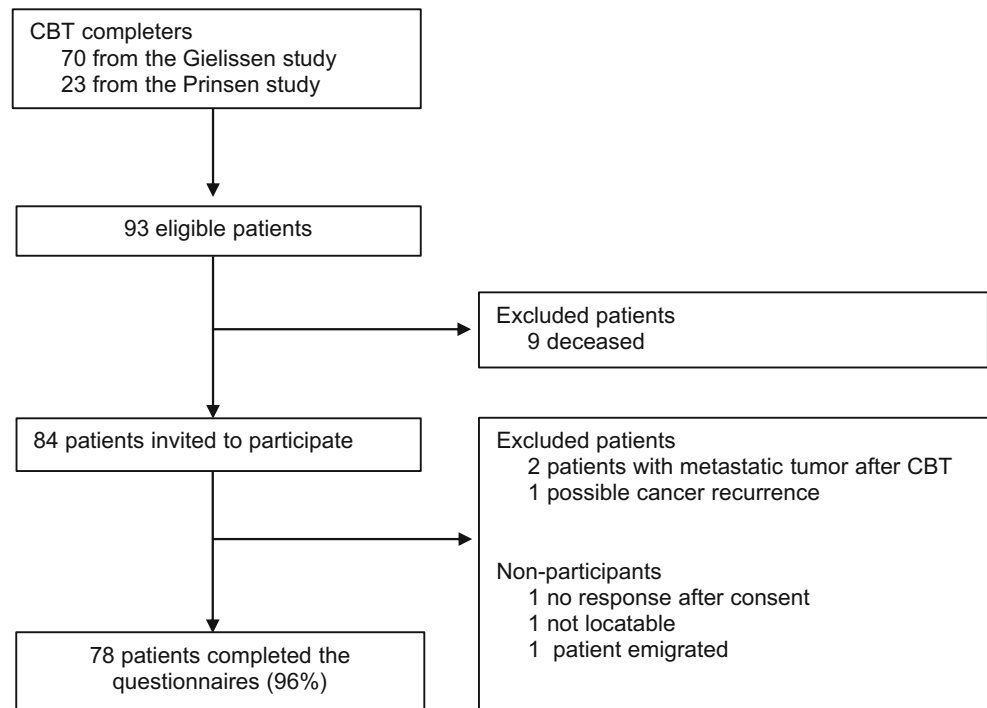
We performed multiple regression analyses (method enter) to determine whether fatigue severity at long-term follow-up (dependent variable) was predicted by fatigue severity (block 1) and/or the fatigue-perpetuating factors measured at post-CBT (poor coping with cancer/treatment, activity regulation, dysregulation of sleep, dysfunctional cognitions, a perceived lack of social support, and fatigue severity) (block 2).

In a post hoc analysis, we used the mean CIS-fatigue score of the population control group ( $M = 24$ ,  $SD = 11$ ) as a reference point to divide our participants in the following two groups: a low fatigue group (CIS-fatigue  $< 24$ ) and a high fatigue group (CIS-fatigue  $\geq 24$ ). By performing a chi-squared test, we determined if patients in the low fatigue group were less likely to relapse (CIS-fatigue  $\geq 35$  at long-term follow-up) than patients in the high fatigue group.

## Results

Of the 93 eligible patients, nine had died. We invited 84 patients to participate and excluded three participants: two patients were excluded because they reported to have received cancer treatment in the 6 months prior to follow-up and one patient was in the process of medical diagnostics because of possible cancer recurrence. In addition, three patients did not participate: one patient did not respond, and for two patients no contact details were available. A total of 78 patients participated in the study (78/81; response rate 96%) (see Fig. 1 for the flowchart of patient inclusion).

Mean age at long-term follow-up was 55.1 years ( $SD = 10.1$ ), 38 participants were female (49%), and the majority of our participants were married or living together (76%). Of the total group, 24 participants (31%) had experienced a significant life event in the 3 months prior to the study and 32

**Fig. 1** Flowchart of patient inclusion

participants (41%) reported the presence of a somatic comorbidity (see also Table 1).

### Sustainment of effects of CBT on fatigue severity and physical functioning

Linear mixed model analyses showed that fatigue levels had increased at long-term follow-up compared with post-CBT assessment (mean change = 10.7 points,  $p < 0.001$ ). This time effect remained significant when the covariates were added. Lower mental health and higher pain scores predicted higher fatigue levels over time (Table 3). Fatigue levels at long-term follow-up were still lower compared the baseline assessment (see also Table 2, mean change = -12.5 points,  $p < 0.001$ ) after adding the covariates to the model. Results were largely similar when comparing severely and non-severely fatigued patients in logistic GEE analyses. Time effects were comparable, but only pain was a significant covariate in this analysis. Higher pain levels predicted higher levels of fatigue over time (supplementary Table 1). In the previous two RCTs, 65 of 78 participants (83%) were recovered from severe fatigue (CIS-fatigue < 35) directly after CBT. A total of 34 of these 65 participants (52%) were still recovered at long-term follow-up. Of the 13 participants (17%) that did not recover from severe fatigue directly after CBT, 11 participants were still severely fatigued at long-term follow-up whereas 2 participants (15%) were recovered.

Physical functioning scores at long-term follow-up were improved compared to the baseline assessment (SF-36 mean change = 9.1 points,  $p < 0.001$ ). However, the level of

physical functioning (SF-36) was decreased at long-term follow-up compared with post-CBT assessment (SF-36 mean change = -9.7 points,  $p < 0.001$ ). After controlling for covariates, there was no significant reduction in levels of physical functioning between post-CBT assessment and follow-up anymore. Pain and somatic comorbidities predicted physical functioning over time (Table 3).

### Comparison of fatigue level of participants with the general population

The participants' fatigue scores at long-term follow-up were significantly higher than fatigue scores in the sample of the general population matched on age and gender (resp. CIS-fatigue severity  $M = 34.4$  SD = 12.4 vs.  $M = 23.9$ , SD = 11.4,  $p = 0.01$ ).

### Determining predictors of fatigue severity at long-term follow-up

The blockwise linear regression analysis showed that fatigue at long-term follow-up was predicted by the level of fatigue directly after CBT (Table 4). None of the perpetuating factors at post-CBT assessment predicted fatigue severity at long-term follow-up.

When comparing the low and high fatigue group at follow-up, patients in the low fatigue group at post-CBT assessment were less likely to be severely fatigued at follow-up ( $p < 0.05$ ).

**Table 1** Patient characteristics at long-term follow-up assessment ( $N = 78$ )

	Number (%)
<b>Marital status</b>	
Married, living together	59 (76)
Divorced	11 (14)
Widowed	3 (4)
Living alone	5 (6)
<b>Gender</b>	
Female	38 (49)
Male	40 (51)
<b>Having paid work</b>	
Yes	32 (41)
No	46 (59)
<b>Self-reported somatic comorbidity</b>	
Yes	32 (41)
No	46 (59)
<b>Significant life events during past 3 months</b>	
Yes	24 (31)
No	54 (69)
<b>Treatment by psychologist/psychiatrist during past 6 months</b>	
Yes	11 (14)
No	67 (86)
<b>Current treatment for fatigue complaints</b>	
Yes	3 (4)
No	74 (95)
Unknown	1 (1)
<b>Cancer recurrence (currently no treatment, no metastatic cancer)</b>	
Yes	9 (12)
No	69 (88)

## Discussion

This study was the first to investigate the long-term effects of CBT for CRF in cancer survivors. Although the significant improvement in fatigue levels following CBT were sustained up to 2 years after therapy, fatigue levels again increased over a longer time period. At long-term follow-up up to 14 years after therapy, fatigue levels had deteriorated and were higher

than in general population controls. This deterioration could not be explained by cancer recurrence, significant life events, somatic comorbidities, pain, or a reduced mental health. Nevertheless, at long-term follow-up, positive effects of CBT on fatigue were sustained in a substantial subgroup. Half of the patients (51%) who were recovered from severe fatigue at post-CBT were still recovered at long-term follow-up. Patients with a lower fatigue level at post-CBT were less likely to show relapse.

Just like the levels of fatigue, levels of physical functioning also showed deterioration between post-CBT assessment and follow-up. However, this time effect was no longer significant after correction for covariates, with pain and comorbidities predicting physical functioning over time. We think that these results indicate that the positive effects of CBT for CRF on physical functioning are maintained at long-term follow-up. As previous studies have shown that higher levels of fatigue are associated with a reduced physical functioning [18], it is remarkable that the deterioration of fatigue levels over time did not go together with a worsening of the patients' level of physical functioning.

The significant relationship between fatigue severity directly after CBT and fatigue levels at long-term follow-up needs to be replicated, but could have clinical implications. Reducing fatigue severity as much as possible during therapy may improve the long-term effectiveness of CBT. This suggests that it may be beneficial to continue treatment with CBT as long as the fatigue level decreases. A maximum reduction of the fatigue level is not a treatment goal in itself in the current treatment protocol for CBT for CRF.

The finding that there is relapse in a subgroup of patients at long-term follow-up of CBT has been previously found in several studies and in a variety of conditions. Our results show similarities with the study of Janse et al. on the long-term effects of CBT for patients with chronic fatigue syndrome (i.e., medically unexplained severe fatigue) [8].

Understanding factors and mechanisms that determine the long-term effect of CBT is crucial for the improvement of the existing treatment protocol and for identifying patients at risk for a relapse of CRF. After correction for covariates, fatigue still deteriorated over time. It is poorly understood why fatigue levels increased. To understand the reasons for relapse, longitudinal studies incorporating qualitative research methods are

**Table 2** Fatigue and physical functioning at the three measurement points

	Baseline assessment	Post-CBT assessment	Long-term follow-up
Fatigue severity	46.9 (6.6, 78)	23.7 (11.0)	34.4 (12.4)
Mean (SD)			
Physical functioning	66.0 (19.5)	84.7 (15.8)	75.4 (22.5)*
Mean (SD)			

\* $N = 75$

**Table 3** Levels of fatigue and physical functioning over time

	Level of fatigue			Level of physical functioning		
	$\beta$	95% CI	<i>p</i>	$\beta$	95% CI	<i>p</i>
Crude model						
Time baseline_FU	12.47	9.75 to 15.20	0.0000000000000006	-9.06	-14.05 to -4.08	0.0004
Time post_FU	-10.71	-13.43 to -7.98	0.0000000000000001	9.72	4.73 to 14.70	0.0001
Model with covariates						
Time baseline_FU	14.66	11.66 to 17.66	0.00000000000000007	-15.36	-21.22 to -9.51	0.0000006
Time post_FU	-4.65	-7.70 to -1.60	0.003	0.42	-5.47 to 6.30	0.889
Mental health	-0.24	-0.31 to -0.16	0.000000002	0.10	-0.04 to 0.24	0.168
Pain	-0.09	-0.15 to -0.03	0.004	0.34	0.23 to 0.45	0.000000007
Cancer recurrence	3.73	-2.32 to 9.77	0.225	-0.61	-12.14 to 10.91	0.916
Self-reported comorbidities	2.58	-1.53 to 6.70	0.217	-9.99	-17.94 to -2.03	0.014
Significant life events	2.43	-1.81 to 6.66	0.260	-4.52	-12.68 to 3.65	0.277

Notes. Linear mixed model analyses. *Time baseline\_FU* = time between baseline and follow-up assessment; *time post\_FU* = time between post-CBT and follow-up assessment

needed to assess the course of fatigue, stressors, and possible fatigue-perpetuating factors.

There are several possible explanations for the deterioration after successful treatment of CRF: it is possible that patients who developed CRF after being treated for cancer had a pre-existent vulnerability for developing fatigue in response to a stressor, i.e., a serious somatic illness like cancer. According to the cognitive-behavioral model of CRF, cancer and its treatment trigger the fatigue but the fatigue perpetuates due to cognitive-behavioral factors. Perhaps patients remain vulnerable for developing fatigue in response to stressors. The likelihood to encounter one or more serious stressors will increase over time, this may explain the partial relapse at long-term follow-up with sustained treatment effects at the follow-up 2 years post-treatment. This vulnerability could also be caused by cancer and its treatment; up to date, it is largely unclear how biological processes influence the mechanisms underlying CRF and its persistence. It could be that CBT for CRF

addresses the fatigue but does not change an underlying somatic vulnerability which makes cancer survivors prone to develop severe fatigue. An alternative explanation is that patients relapse into dysfunctional coping in response to “everyday” fatigue, and dysfunctional behaviors and cognitions eventually lead to severe and persistent fatigue. Our outcome measure at long-term follow-up was restricted to fatigue severity. Measurement of scores on fatigue-perpetuating factors would have been valuable as well. Insight in these factors at long-term follow-up would enable us to test whether deterioration of fatigue scores is associated with changes in the perpetuating factors over time.

The strengths of this study are the long follow-up period and the high response rate. A limitation of our study is that the primary outcome variable, the level of fatigue, was measured only once at long-term follow-up. Patients were only asked about their level of fatigue in the previous 2 weeks. Therefore, it remains unclear whether severe fatigue at

**Table 4** Multiple regression analysis to predict changes in fatigue severity between post-CBT and long-term follow-up (*n* = 78)

Predictors	Block 1			Block 2		
	$\beta$	SE $\beta$	<i>p</i>	$\beta$	SE $\beta$	<i>p</i>
Fatigue severity (CIS-fatigue)	0.351	0.123	0.005	0.103	0.174	0.557
Poor coping with cancer/treatment (IES)	-	-	-	-0.096	0.143	0.504
Activity regulation (CIS-activity)	-	-	-	0.573	0.410	0.211
Dysregulation of sleep (SIP sleep/rest)	-	-	-	0.029	0.030	0.333
Dysfunctional cognitions (SES)	-	-	-	-0.149	0.475	0.755
Discrepancies in social support (SSL-D)	-	-	-	0.387	0.423	0.363

CIS-activity Checklist Individual Strength, subscale activity, CIS-fatigue Checklist Individual Strength, subscale fatigue severity, IES Impact of Events Scale, SES Self-Efficacy Scale, SIP Sickness Impact Profile, SSL-D = van Sonderen Social Support – Discrepancies



long-term follow-up was present longer than 2 weeks. Other limitations are the relatively small sample size and the fact that we excluded patients who did not complete CBT. The course of fatigue in this group may be different from the completers. The exclusion of patients who did not complete CBT and this assessment may bias our results and could have caused an overestimation of long-term treatment effects.

Relapse prevention is an important topic in the field of psychotherapy. Various interventions with the aim of preventing relapse have been developed, especially for depression. Examples of these are booster sessions, mindfulness, or metacognitive therapy for depression [19]. The fact that the relapse following CBT for CRF occurred only after a period of more than 2 years post-CBT makes it less likely that interventions aimed at relapse prevention given shortly after termination of the CBT for CRF will be successful. It seems more practical and efficient to develop interventions for patients who are referred again after a relapse of fatigue has occurred. It should be determined whether patients who have a relapse of severe fatigue following an initially successful CBT can profit from booster sessions of CBT again or whether another evidence-based intervention for fatigue (like mindfulness or exercise therapy) should be given.

In summary, we found that significant deterioration of fatigue over time occurred, but positive effects of CBT on fatigue severity were sustained in about half of the participants at long-term follow-up. Future research should study the underlying mechanisms of CRF and aim for optimizing the long-term treatment results of CBT for CRF.

**Author contributions** Lidewij D. van Gessel: conceptualization, methodology, data curation, formal analysis, investigation, project administration, visualization, writing—original draft, and writing—review and editing.

Harriët J.G. Abrahams: conceptualization, methodology, data curation, formal analysis, investigation, supervision, project administration, visualization, writing—original draft, and writing—review and editing.

Hetty Prinsen: writing—review and editing.

Gijs Bleijenberg: conceptualization, writing—review, and editing.

Marianne Heins: formal analysis, writing—review, and editing.

Jos Twisk: formal analysis, methodology, writing—review, and editing.

Hanneke van Laarhoven: writing—review and editing.

Stans A.H.H.V.M. Verhagen: writing—review and editing.

Marieke F.M. Gielissen: conceptualization, methodology, writing—review, and editing.

Hans Knoop: conceptualization, methodology, supervision, visualization, writing—review, and editing.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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## References

- Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet*. 2003;362(9384):640–50. [https://doi.org/10.1016/s0140-6736\(03\)14186-4](https://doi.org/10.1016/s0140-6736(03)14186-4).
- Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*. 2014;32(17):1840–50. <https://doi.org/10.1200/jco.2013.53.4495>.
- Abrahams HJG, Gielissen MFM, Schmits IC, Verhagen CAHHVM, Rovers MM, Knoop H. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. *Ann Oncol*. 2016;27(6):965–74. <https://doi.org/10.1093/annonc/mdw099>.
- Gielissen MF, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol*. 2006;24(30):4882–7. <https://doi.org/10.1200/jco.2006.06.8270>.
- Prinsen H, Bleijenberg G, Heijmen L, Zwarts MJ, Leer JWH, Heerschap A, et al. The role of physical activity and physical fitness in postcancer fatigue: a randomized controlled trial. *Support Care Cancer*. 2013;21(8):2279–88. <https://doi.org/10.1007/s00520-013-1784-9>.
- Abrahams HJ, Gielissen MF, Donders RR, et al. The efficacy of Internet-based cognitive behavioral therapy for severely fatigued survivors of breast cancer compared with care as usual: a randomized controlled trial. *Cancer*. 2017;123(19):3825–34. <https://doi.org/10.1002/cncr.30815>.
- MFM G, Verhagen CAHHVM, Bleijenberg G. Cognitive behaviour therapy for fatigued cancer survivors: long-term follow-up. *Br J Cancer*. 2007;97(5):612–8. <https://doi.org/10.1038/sj.bjc.6603899>.
- Janse A, Nikolaus S, Wiborg JF, Heins M, van der Meer JWM, Bleijenberg G, et al. Long-term follow-up after cognitive behaviour therapy for chronic fatigue syndrome. *J Psychosom Res*. 2017;97:45–51. <https://doi.org/10.1016/j.jpsychores.2017.03.016>.
- Akker LEVD, Beckerman H, Collette EH, et al. Cognitive behavioral therapy positively affects fatigue in patients with multiple sclerosis: Results of a randomized controlled trial. *Mult Scler J*. 2017;23(11):1542–53. <https://doi.org/10.1177/1352458517709361>.
- Vestergaard S, Nayfield SG, Patel KV, Eldadah B, Cesari M, Ferrucci L, et al. Fatigue in a representative population of older persons and its association with functional impairment, functional limitation, and disability. *J Gerontol Ser A Biol Med Sci*. 2009;64A(1):76–82. <https://doi.org/10.1093/gerona/gln017>.
- Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven HWM, van Engelen BGM, van Riel P, et al. The assessment of fatigue: psychometric qualities and norms for the Checklist individual strength. *J Psychosom Res*. 2017;98:40–6. <https://doi.org/10.1016/j.jpsychores.2017.05.007>.
- Ware JE, Sherbourne CD. MOS 36-item short-form health survey. *PsychTESTS Dataset*. 1992. <https://doi.org/10.1037/t06708-000>.

13. Stewart AL, Hays RD, Ware JE. The MOS short-form general health survey: reliability and validity in a patient population. *Med Care*. 1988;26:724–35.
14. Ploeg EVD, Mooren TTM, Kleber RJ, Velden PGVD, Brom D. Construct validation of the Dutch version of the impact of event scale. *Psychol Assess*. 2004;16(1):16–26. <https://doi.org/10.1037/1040-3590.16.1.16>.
15. Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet*. 2001;357(9259):841–7. [https://doi.org/10.1016/s0140-6736\(00\)04198-2](https://doi.org/10.1016/s0140-6736(00)04198-2).
16. Jacobs HM, Luttik A, Touw-Otten FW, de Melker RA. The sickness impact profile; results of an evaluation study of the Dutch version. *Ned Tijdschr Geneesk*. 1990;40:1950–4.
17. Van Sonderen E. Sociale Steun Lijst-Interacties (SSL-I) en Sociale Steun Lijst Discrepanties (SLL-D). Noorderlijk Centrum voor Gezondheidsvraagstukken: Rijksuniversiteit Groningen; 1993.
18. Abrahams H J G, Gielissen M F M, Verhagen C A H H V M, Knoop H. The relationship of fatigue with quality of life and psychological factors in breast cancer survivors: a systematic review. Submitted for publication.
19. Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, et al. The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse/recurrence: results of a randomized controlled trial (the PREVENT study). *Health Technol Assess*. 2015;19(73):1–124. <https://doi.org/10.3310/hta19730>.

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