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Changes in sleep following internet-delivered cognitive-behavioral therapy for insomnia in women treated for breast cancer: A 3-year follow-up assessment

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ABSTRACT

Background: Sleep disturbances are common in women treated for breast cancer. We have previously shown that internet-delivered cognitive-behavioral therapy for insomnia (e-CBT-I) is an efficacious, low-cost treatment approach. Furthermore, research has shown that e-CBT-I can result in sustained improvements at 12 months post-treatment. However, given the complexity and long duration of post-treatment symptomatology in breast cancer patients, as well as the recommended use of anti-hormonal therapy for up to 10 years, it is relevant to investigate long-term (>12 months) changes in sleep following e-CBT-I in this population. In the present study, we report data from a 3-year long-term follow-up assessment after e-CBT-I.

Methods: Women treated for breast cancer with sleep disturbances (Pittsburg Sleep Quality Index [PSQI] global score >5) who had previously been enrolled in a randomized-controlled trial investigating the efficacy of e-CBT-I (n = 255), were invited to participate in a 3-year follow-up study. All women in the initial control group had also been granted access to e-CBT-I. Assessment included self-reported sleep quality (PSQI), insomnia severity (Insomnia Severity Index, ISI), cancer-related fatigue and symptoms of depression. Within-group changes in these outcomes from baseline to the 3-year long-term follow-up assessment were analyzed.

Results: A total of 131 women (51%) participated in the 3-year follow-up study of which 77 (59%) were from the initial intervention group and 54 (41%) from the initial control group. For the pooled sample, within-group improvements from baseline to the 3-year follow-up assessment corresponding to large effect sizes were observed in sleep quality (Cohen's d = 1.0 95% CI [0.78, 1.21]) and insomnia severity (Cohen's d = 1.36 CI 95% [1.12, 1.59]). Similar changes were observed in cancer-related fatigue (Cohen's d = 0.48 CI 95% [0.30, 0.66]) and symptoms of depression (Cohen's d = 0.80 CI 95%. [0.60, 0.99]). The proportion of patients with scores above established cut-offs on the PSQI and the ISI were 56.1% and 29.8%, respectively. Within the initial intervention group, 15.6% evidenced relapse at the 3-year assessment.

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Conclusion: Overall, these results indicate that long-term sleep quality and insomnia severity following the use of e-CBT-in women treated for breast cancer is significantly lower than the pre-treatment levels. However, a substantial proportion of participants still evidence sleep disturbances.

1. Introduction

Sleep disturbances are known to be significantly increased in cancer patients and survivors [1,2]. Compared with the general population, cancer patients are estimated to have up to three times higher rates of sleep disturbances [3]. Identified risk factors include lower socio-economic status, certain cancer treatment modalities (i.e., chemotherapy, antihormonal therapy), higher body-mass index (BMI), co-occurring psychological and physical distress symptoms (i.e., depression, fatigue, pain), as well as poorer self-reported pre-diagnosis sleep [4–7].

Irrespective of the exact underlying pathways leading to sleep disturbances after cancer treatment, chronically disturbed sleep (i.e., insomnia) is best understood and treated within the framework of the behavioral model originally proposed by Ref. [8]. According to this framework, chronic insomnia is often perpetuated by maladaptive behaviors that initially served as strategies to cope with acute sleep disturbances. In alignment with this model, the key aim of non-pharmacological interventions targeting insomnia is to rectify perpetuating and maladaptive behaviors as well as cognitions.

The recommended non-pharmacological treatment for insomnia is cognitive-behavioral therapy for insomnia (CBT-I) [9]. CBT-I is a multicomponent treatment approach that often includes a combination of several or all of the following cores: *stimulus-control therapy (SCT)*, *sleep restriction therapy (SRT)*, *relaxation therapy (RT)*, *cognitive therapy* (CT) and *sleep hygiene education (SHE)*. Briefly, SCT aims to re-establish and strengthen the bed and bedroom as discriminant cues for sleep by minimizing the time in bed when not sleeping. Adding to this component, SRT aims to increase sleep quality (i.e., sleep efficiency) by providing specific bed- and rise time schedules to ensure improved sleep consolidation; RT aims to improve the patient's ability to gear down both mentally and physically; CT aims to help the patient by addressing maladaptive and dysfunctional thoughts and beliefs about sleep; and finally, SH provides recommendations about habits and environmental factors to improve and maintain healthy sleep.

CBT-I has been shown efficacious in several meta-analyses (e.g. Ref. [10], including in insomnia patients with co-morbid psychiatric and medical conditions [11]. CBT-I has generally been shown to result in clinically significant sustained effects [12]. In cancer populations, including in breast cancer survivors, CBT-I has similarly been shown to be an efficacious treatment [13,14].

However, the availability of CBT-I is limited due to a general lack of trained therapists, inadequate geographical availability, and costs associated with face-to-face therapy. One option to overcome these challenges has been to provide CBT-I over the internet (e-CBT-I), which has been shown to produce rapid and long-term symptom reductions in adults with clinical insomnia [15,16]. In our own work with breast cancer patients, we have previously shown that e-CBT-I, delivered in a fully automated online program, is an efficacious treatment for sleep disturbances, as well as cancer-related fatigue [17]. Although the beneficial effects of e-CBT-I in breast cancer patients were maintained at 6 weeks post-intervention, it remains unclear to what degree they are sustained over longer durations.

Results of a recent meta-analysis showed that CBT-I in women treated for breast cancer, both when provided face-to-face and online, resulted in relatively swift, as well as sustained long-term positive effects on sleep at 12 months with effect sizes in the small to medium range [14]. Although the results provide some evidence of the sustained effects of e-CBT-I at 12 months, given the complexity and long duration of post-treatment symptomatology in breast cancer survivors and the recommended use of antihormonal therapy for up to 10 years, which may have a disruptive effect on sleep, it is highly relevant to investigate long-term outcomes beyond a 12-month period.

Thus, the main aim of the present study was to investigate the long-term (>12 months) changes in sleep following the completion of e-CBT-I in a sample of breast cancer survivors with sleep disturbances, as well as to examine possible associations between sleep outcomes and other co-occurring late-effects such as cancer-related fatigue and depressive symptoms.

2. Materials and methods

For detailed information about the present study, including participant characteristics, recruitment procedures, and study design, see Ref. [17]. In brief, 3206 women aged 18–75 years and treated for breast cancer between June 1, 2011, and December 31, 2013, according to national treatment guidelines were identified through the Danish Breast Cancer Group (DCBG) database. Invitation letters with study information including a link to an online version of the Pittsburg Sleep Quality Index (PSQI) [18] were mailed by post to potential participants. Women who completed the PSQI and exceeded the primary inclusion criteria of a global score >5, were contacted by phone by a research assistant who shared further details about the study and screened subjects for eligibility using a semi-structured interview, which included the Mini-international Neuropsychiatric Interview [19]. Exclusion criteria included recurrence of breast cancer, second cancer, severe psychological or physical comorbidity, other sleep disorders (sleep apnea, parasomnia, narcolepsy), and inability to read Danish. Eligible women who provided informed consents and who responded to a subsequent baseline questionnaire package were then randomized to e-CBT-I or a wait-list control group. Participants within the wait-list control group were informed that they would receive access to the intervention program after the trial period.

2.1. Initial intervention and randomization

Internet-delivered CBT-I (e-CBT-I) was offered using a fully automated and online program (Sleep Healthy Using The Internet, SHUTi) [20] consisting of six successively delivered learning modules covering the following: *treatment rationale*, *sleep restriction*, *stimulus control*, *cognitive restructuring*, *sleep hygiene*, and *relapse prevention*. Upon successful completion of each module, the subsequent module was automatically delivered after a week. Apart from technical support from research assistants, the participants had no interact with the research team. A total of 255 women were randomized to either an active intervention group (n = 133) or a wait-list control condition (n = 122). All participants were initially

assessed at three timepoints at baseline (T1, week 0), post-intervention (T2, week 6–9) and at a 6-weeks follow-up (T3, week 15). Shortly after the final assessment (T3), wait-list control participants were offered access to the program.

2.2. Long-term follow-up assessment

In 2017, ethical approval was granted by the regional ethical committee to contact all participants who had originally been included in the trial and to invite them to respond to an online long-term follow-up questionnaire regarding the status of their sleep and other prevalent late effect symptoms (e.g. cancer-related fatigue, depression). An e-mail was sent to all participants of the previous trial describing the aim of the long-term follow-up assessment with a link to the online questionnaire. Participants who did not respond to the first e-mail received reminders at two subsequent occasions. Data collection was undertaken between May 8–22, 2018. The online questionnaire was kept brief to maximize participant rates and included the PSQI [18], the Insomnia Severity Index (ISI) [21], FACIT-Fatigue (FACIT-F) [22], Beck Depression Inventory (BDI-II) [23], and single items regarding the patients' use of the program.

2.3. Statistical analysis

Group differences in relevant demographic, clinical, and sleep outcomes between 1) participants initially randomized to e-CBT-I and the wait-list control group, and 2) participants and non-participants of the long-term follow-up assessment were tested with independent-sample t-tests, Fisher's exact tests, or Chi-square tests. Changes in sleep outcomes were analyzed in two steps; first, for each group, mixed linear models (MLM) were used to investigate within-group changes on the ISI, PSQI and FACIT-fatigue across all four assessment time points from T1-T4 with subsequent Sidak-adjusted pairwise comparisons between the last assessment time point (T4) and all other previous time points. Second, pooled data from both groups collected at baseline (T1) and long-term follow-up (T4) were analyzed using repeated-measures ANOVA to investigate the long-term changes in sleep, fatigue, and depression. This was necessary, because e-CBT-I had been offered to the groups at different time points, and thus, data from T2 and T3 are not directly comparable (see Fig. 1). Clinical levels of sleep disturbances at follow-ups were determined using established cut-offs on the ISI (>10) [24] and the PSQI (>5) [18]. Relapse for each sleep outcome was defined as a score at T3 below the cut-off and a subsequent score at T4 exceeding the cut-off. The number of participants evidencing minimal clinically important differences (MCID) on the ISI and the PSQI from baseline to follow-ups was determined using an ISI change score of 7 or higher [24] and a PSQI change score of 3 or higher [25]. Non-responders were defined as participants with an ISI-score >10 at T2, T3, and T4. Finally, associations between sleep outcomes and fatigue/depression were analyzed using Pearson's correlation coefficient and regression models were used to explore predictors of changes in fatigue/depression from T1-T4. For each of these outcomes, two regression models were built, one for each of the sleep outcomes (ISI, PSQI). Predictor variables in each model included change scores from T1-T4 for each of the sleep outcomes, as well as the following variables: age, BMI, antihormone therapy, and time since surgery. All statistical analyses were performed using IBM SPSS Statistics, version 27.

2.4. Ethical approvals

The study was approved by the Regional Science Ethical Committees (Registration No. 1-10-72-553-12; amendment: 59222) and the Danish Data Protection Agency and preregistered at ClinicalTrials.gov (NCT02444026).

3. Results

3.1. Participants

Of the 255 participants who were initially randomized in the original trial [17], 131 (51.4%) responded to our invitation and participated in the long-term follow-up assessment. The average time between the baseline and long-term follow-up assessments was 2.8 (SD = 0.24) years. Demographic and clinical data for this group are presented in Table 1.

Of the 131 women who participated in the long-term follow-up assessment, 77 (58.8%) had originally been randomized to the intervention group, while 54 (41.2%) had been randomized to the wait-list control group indicating a slightly higher response rate in the former ($p = .03$, Fisher's exact test). More women in the initial intervention group (57.1%) compared with the control group (35.2%) had received antihormone therapy ($p = .01$), which had been initiated prior to the study inclusion. No further between-group differences in demographic or clinical characteristics were found (see Table 1). In addition, no between-group differences were

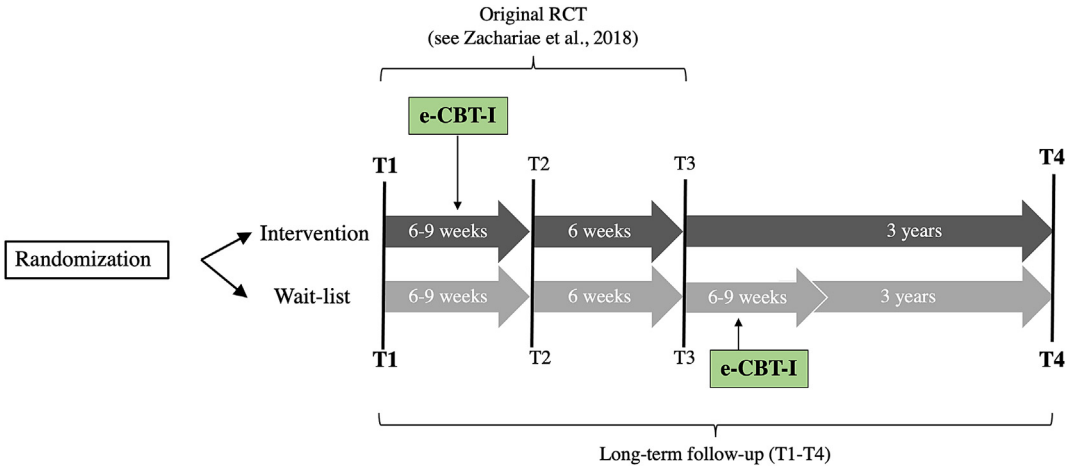

Fig. 1. Original study d*esign and long-term follow-up*.
Note: eCBT-I: Internet-delivered Cognitive Behavioral Therapy for Insomnia.

Table 1
Participant demographics and clinical characteristics at baseline.

	All	Initial Intervention Group	Initial Control Group
N (%)	131 (100)	77 (58.8)	54 (41.2)
Age, mean (SD)	53.7 (8.4)	53.5 (8.9)	54.0 (7.8)
BMI, mean (SD)	25.6 (4.9)	25.2 (3.7)	26.3 (6.2)
Smoker (%)	7 (5.3)	5 (6.5)	2 (3.7)
Alcohol (drinks/wk), mean (SD)	7.9 (5.8)	7.6 (5.8)	8.2 (5.8)
Married/cohabiting, N (%)	103 (78.6)	61 (79.2)	42 (77.8)
Working, N(%)	105 (80.2)	64 (83.1)	41 (75.9)
Tumor size (mm), mean, SD	19.4 (13.4)	21.1 (14.0)	16.8 (12.4)
Malignancy grade, N (%)			
- I	36 (30.8)	24 (33.8)	12 (26.1)
- II	47 (40.2)	25 (35.2)	22 (47.8)
- III	33 (28.2)	22 (31.0)	11 (23.9)
Chemotherapy, N (%)	67 (51.5)	37 (48.1)	30 (56.6)
Radiotherapy, N (%)	92 (91.1)	50 (90.1)	42 (91.3)
Antihormone therapy, N (%)	63 (48.1)	44 (57.1)	19 (35.2)
Insomnia duration (years), mean (SD)	3.7 (3.2)	3.6 (3.2)	3.8 (3.3)
rMEQ, mean (SD)	17.0 (3.3)	16.8 (3.2)	17.2 (3.4)
PSQI, mean (SD)	10.0 (3.4)	10.3 (3.7)	9.9 (3.0)
ISI, mean, (SD)	14.5 (4.8)	14.6 (5.0)	14.4 (4.5)
FACIT-F, mean (SD)	35.7 (9.2)	35.7 (9.3)	35.7 (9.2)
BDI-II, mean (SD)	12.3 (7.4)	11.6 (7.3)	13.4 (7.4)

N: Number of participants; SD: Standard deviation; BMI_ body-mass index; rMEQ: Reduced Morningness-Eveningness Questionnaire; PSQI: Pittsburg Sleep Quality Index; ISI: Insomnia Severity index; FACIT - Fatigue: The Functional Assessment of Chronic Illness Therapy – Fatigue; BDI-II: Beck Depression Inventory – II; Statistical significance (2-sided): *$p < .05$.

observed for the ISI or the PSQI at baseline (see Table 1). Overall, 127 (97%) participants had completed at least one treatment core and 106 (81%) had completed all six cores.

3.2. Differences between participants and non-participants of the long-term follow-up assessment

There were no statistically significant differences between participants (n = 131) and non-participants (n = 124) of the 3-year long-term follow-up assessment on any demographic or clinical variables (p's > .08). Furthermore, no baseline differences were observed between these groups on the PSQI, ISI, sleep diary outcomes, FACIT-F or BDI-II (p's > 0.25).

Within the initial intervention group, no statistically significant differences were observed between participants and non-participants of the long-term follow-up assessment in pre-to post-intervention changes on any of the sleep outcomes (p's > .14). Within the initial intervention group, we observed statistically significant mean differences between participants and non-participants of the long-term follow-up assessment on the number of completed treatment cores, mean = 5.3 (SD = 1.8) versus 2.5 (SD = 2.5), respectively, $p < .001$, and program logins, mean = 72.8 (SD = 47.4) versus 44.2 (SD = 53.0) respectively, $p < .01$).

3.3. Changes in sleep outcomes from baseline to long-term follow-up

MLMs revealed statistically significant changes across time in each of the randomization groups on both sleep outcomes ($ISI_{Intervention}$, F(3, 75.62) = 80.75, $p < .001$, and the $PSQI_{Intervention}$, F(3, 74.78) = 39.12, $p < .001$; $ISI_{Controls}$, F(3, 52.85) = 56.09, $p < .001$, and the $PSQI_{Controls}$, F(3, 53.20) = 26.57, $p < .001$) (See Fig. 2). In the intervention group, adjusted pairwise comparisons revealed that at T4, mean ISI and PSQI were significantly lower compared with T1 (both p's < 0.001). Compared with T3, T4 scores were significantly higher (p's < 0.05). No statistically significant differences were observed between T2 and T4. In the initial control group, pairwise comparisons indicated that mean scores on ISI and PSQI at T4 were significantly lower than all other time points (all p's < 0.001) with the largest reduction occurring from T3 to T4.

Repeated-measures ANOVAs revealed statistically significant main effects of time from T1 to T4 on both the PSQI, F(1,129) = 235.32, $p > .001$, and ISI, F (1,121) = 119.96, $p < .001$, corresponding to large effect sizes (See Table 2). No main effects of group or interaction effects (group × time) were observed (p's > .51) for any of the sleep outcomes. Adjustment for antihormone therapy did not alter these results, however we did detect significant time × antihormone therapy interactions for the overall group on both the ISI, F(1, 129) = 4.24, $p = .04$, and the PSQI, F(1, 121) = 4.28, $p = .04$ indicating that sleep improvement across time was smaller for women on antihormone therapy ($\eta^2 = 0.03$). The proportion of women who experienced improvements corresponding to MCIDs from T1-T4 on the ISI and PSQI was 64.9% (n = 85) and 56.9% (n = 70), respectively. Comparing the frequency of MCID in women receiving antihormone therapy (47.5%, n = 28) with those who did not (65.6%, n = 42), revealed a statistically significant difference for the PSQI ($p = .04$), but not the ISI ($p = .24$). Of the 131 participants in the present study, 7.6% (n = 10) evidenced a worsening of their ISI scores at long-term follow-up compared with their baseline scores, while 9.9% (n = 13) were defined as non-responders (ISI>10 at T2, T3, and T4). The proportion of patients who had scores above the established cut-offs on the ISI and the PSQI at T4 were 29.8% (n = 39) and 56.1% (n = 69), respectively.

Within the initial intervention group, remission rates based on the PSQI (≤ 5) at T3 and T4 were 50.7% (n = 38) and 42.3% (n = 30), respectively. Using the ISI (≤ 10) remission rates at T3 and T4 were 84.0% (n = 63) and 70.1% (n = 54), respectively. MCIDs within the intervention group from T1-T3 and T1-T4 on the PSQI were 64.0% (n = 48) and 52.1% (n = 37), respectively. MCIDs on ISI from T1-T3 and T1-T4 were 61.3% (n = 46) and 41.6% (n = 32). Within the initial intervention group, 5.2% (n = 4) were categorized as non-responders with an ISI > 10 at T2, T3, and T4. Relapse on both the ISI and PSQI from T3 to T4 within this group was 15.6% (n = 12).

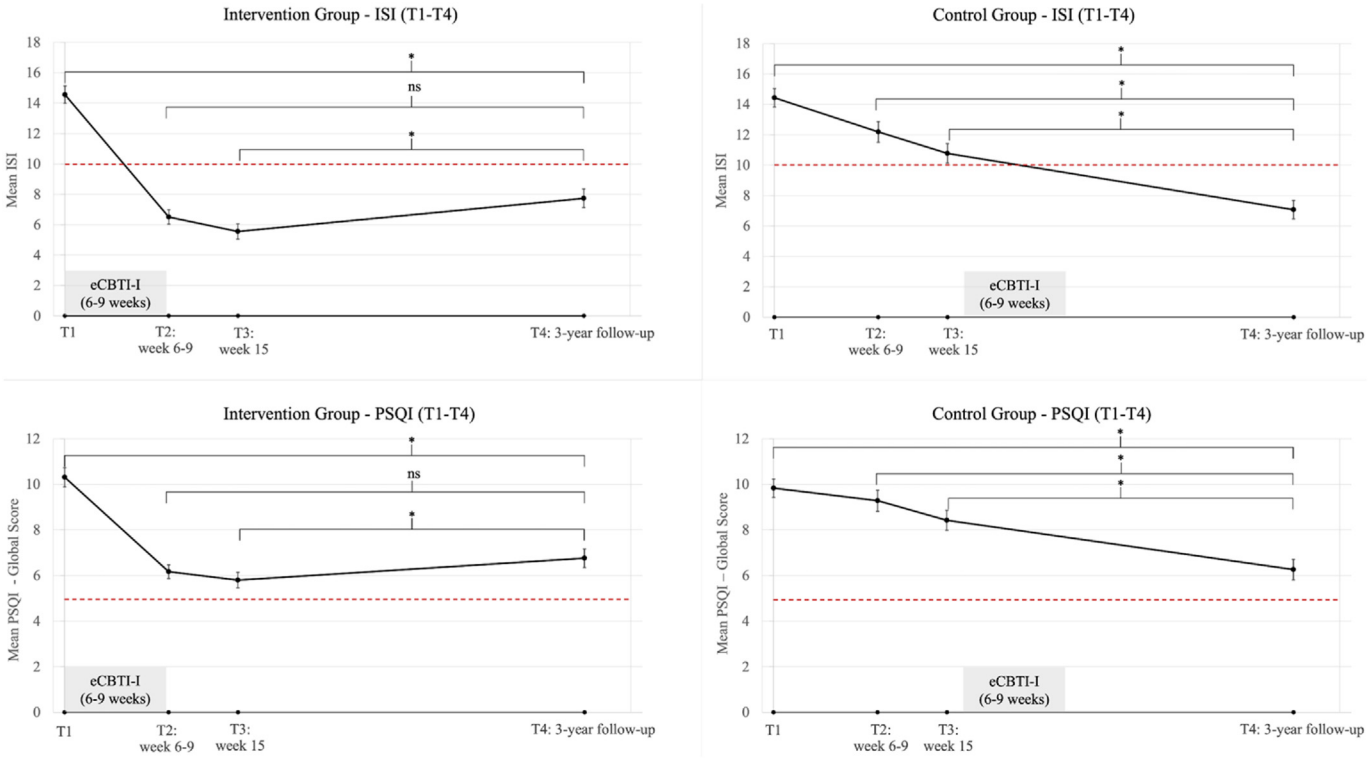

Fig. 2. Changes in ISI and PSQI from T1-T4 for each randomized group
ISI: Insomnia Severity Index; PSQI: Pittsburg Sleep Quality Index; ns: non-significant; *: statistically significant, *p* (Sidak-adjusted) < .05; eCBT-I: Internet-delivered Cognitive Behavioral Therapy for Insomnia; Highlighted areas indicate 6–9 weeks of treatment period. Dotted lines represent established cut-offs for clinical levels of sleep disturbance for each outcome.

Table 2
Overall and within-group changes in sleep outcomes (ISI, PSQI), cancer-related fatigue (FACIT-F), and depression (BDI-II) from baseline (T1) to long-term follow-up (T4).

	Total (n = 131) Mean (SD)		Effect size (Cohen's *d*) 95% CI	Intervention group (n = 77) Mean (SD)		Effect size (Cohen's *d*) 95% CI	Control group (n = 54) Mean (SD)		Effect size (Cohen's *d*) 95% CI
	T1	T4		T1	T4		T1	T4	
PSQI,	10.0 (3.4)	6.6 (3.4)	1.0 [0.78, 1.21]	10.3 (3.7)	6.8 (3.5)	.89 [.61, 1.27]	9.8 (3.0)	6.3 (3.2)	1.17 [0.83, 1.5]
ISI	14.5 (4.8)	7.5 (5.0)	1.36 [1.12, 1.59]	14.6 (5.0)	7.7 (5.4)	1.19 [0.90, 1.48]	14.4 (4.5)	7.1 (4.4)	1.69 [1.27, 2.10]
FACIT − F	35.7 (9.2)	39.9 (5.5)	.48 [0.30, 0.66]	35.7 (9.3)	40.3 (5.4)	.50 [0.26, 0.74]	35.7 (9.2)	39.2 (5.6)	.44 [0.16, 0.72]
BDI-II	12.3 (7.3)	6.7 (6.3)	.80 [0.60, 0.99]	11.6 (7.3)	6.4 (6.2)	.73 [0.48, 0.98]	13.4 (7.4)	7.1 (6.5)	.88 [0.57, 1.20]

PSQI: Pittsburg Sleep Quality Index (global score); ISI: Insomnia Severity index; FACIT - F: The Functional Assessment of Chronic Illness Therapy − Fatigue; BDI-II: Beck Depression Inventory − II.

3.4. Changes in fatigue and depression from baseline to long-term follow-up

MLMs revealed statistically significant changes across time in each of the randomization groups on the FACIT-fatigue scale (FACIT-$F_{Intervention}$, F(3, 76.21) = 22.27, p < .01; FACIT-$F_{Controls}$, F(3, 53.65) = 5.48, p < .01). In the intervention group, adjusted pairwise comparisons revealed that at T4, mean FACIT-F was significantly higher (less fatigue) compared with T1 (p < .001). Compared with T3, T4 scores were significantly lower (more fatigue) (p's < 0.01), while no statistically significant differences were observed between T2 and T4. In the initial control group, pairwise comparisons indicated that mean score on FACIT-F at T4 was significantly higher (less fatigue) than at T1 (p < .01), but different from T2 or T3 (See supplementary materials).

Repeated-measures ANOVAs revealed statistically significant main effects of time from baseline to long-term follow-up on both FACIT - Fatigue, F(1,129) = 27.43, p < .001, and the BDI-II, F(1,129) = 82.95, p < .001, with changes corresponding to medium to large effect sizes (See Table 2). No main effects of group or group × time interactions were observed (p's > .23). Clinically significant fatigue was observed in 34.4% (n = 45) of participants at baseline and 12.2% (n = 16) at long-term follow-up. Poorer scores on both the PSQI (r = −0.38, p < .001) and the ISI (r = −0.47, p < .001) were associated with more severe fatigue at T4. Similarly, higher levels of depressive symptoms were associated with poorer scores on the PSQI (r = 0.41, p < .001), and the ISI (r = 0.53, p < .001). In both unadjusted (see supplementary materials) and adjusted regression models, improvement on FACIT-F were predicted by changes in ISI (β = 0.54, p < .001) and PSQI scores (β = 0.45, p < .001). Similarly, improvement on BDI-II was predicted by changes in ISI (β = 0.40, p < .001) and PSQI (β = 0.39, p < .001).

4. Discussion

We have previously shown that internet-delivered CBT-I (e-CBT-

I) is an effective treatment in breast cancer survivors with clinically significant sleep disturbances with effects maintained at six weeks post-intervention [17]. However, given the complexity of post-treatment symptomatology, as well continuous use of antihormone therapy, it is important to investigate long-term intervention effects beyond the first year. To the best of our knowledge, the results of the present study comprise the longest follow-up duration after the completion of e-CBT-I. In the present study, we add to our previous findings by reporting long-term changes in sleep quality and insomnia severity at approximately three years after initial intervention completion. Compared with baseline levels, we observed significantly lower sleep disturbances in our sample of breast cancer survivors with the magnitude of effects corresponded to large effect sizes. More fine-grained analyses of within-group changes from T1-T4 revealed that while the initial intervention group reported a slight increase in sleep disturbances from T3 to T4 the levels remained comparable to their post-intervention (T2) levels. Within the initial control group, a steady improvement in sleep outcomes was observed at each time point with the largest improvement seen from T3 to T4 after gaining access to e-CBT-I. In a previous study of breast cancer patients by Ref. [26]; it was shown that the effects of both face-to-face administered and video-based CBT-I were generally well-sustained at 12 months after intervention completion and comparable to the post-intervention levels. Similarly, in a recent meta-analysis by Ref. [14]; it was shown that CBT-I (both face-to-face-delivered and online) in women treated for breast cancer resulted in sustained long-term improvements at 12 months corresponding to small to medium effect sizes. While our results are not directly comparable with these studies, due to a longer follow-up period and a lack of a proper control group at the long-term follow-up, we do believe that our results may be taken as an indication of maintenance of improvements of e-CBT-I beyond 12 months. While we did observe a slight worsening in sleep outcomes from T3 to T4 in the initial intervention group, these levels were still significantly lower than the pre-treatment levels and, on average, remained below established cut-offs for the PSQI and the ISI. Nevertheless, it is noteworthy that a substantial percentage of women still experienced clinical levels of sleep disturbances as indicated by scores exceeding established cut-offs on the ISI (29.8%) and PSQI (56.1%). Also, relapse from T3 to T4 was observable in a subgroup of patients.

Other perpetuating factors beyond those targeted in CBT-I may contribute to long-term sleep disturbances in breast cancer populations. For example, previous research has shown that unfavorable circumstances such as hot flashes due to the use of antihormone therapy is associated with sleep disturbances [27]. Although women receiving antihormones in the present study did evidence long-term improvements in their sleep, these improvements were generally smaller compared with those who had not received antihormone therapy with the difference in improvements across time corresponding to a small to medium effect size.

Targeting other perpetuating factors may be an important venue for future interventions. Given the complex post-treatment symptomatology, several factors may play a key role in enabling sleep disturbances [28]. Multi-treatment approaches with possible synergistic effects are warranted. For example, chronic pain has been shown to be a significant contributor to sleep disturbances in both non-cancer [29] and cancer populations [30]. Integrating interventions targeting pain alongside CBT-I in cancer patients could prove to be a fruitful avenue.

In addition to sleep improvements, our results also revealed indications of long-term improvements in cancer-related fatigue and depressive symptoms with medium to large effect sizes for the combined group. Cancer-related fatigue (CRF) remains the most frequently reported and debilitating late-effect with no standard treatment available [31]. While CRF is not simply tiredness caused by sleep disturbances, the two symptoms often co-occur, suggesting a partly shared etiology [32]. Thus, treatment of one symptom may result in improvements on the other, a point that has previously been raised [33]. Our results revealed that improvements in sleep outcomes from baseline to long-term follow-up were significant predictors of reduced fatigue levels. This is in accordance with results from the main RCT of the present study, where we reported improvements on CRF from baseline to 6 weeks post-intervention with a medium effect size [17]. These results replicate findings from other studies reporting similar effects of CBT-I on CRF in sleep-disturbed breast cancer populations (e.g., Ref. [34].

Finally, although the general level of depressive symptoms fell within the minimal range in the present sample (See Table 2), we nevertheless observed a significant reduction in depressive symptoms corresponding to a large effect size, which, in turn, was associated with the improvements observed on the sleep outcomes. Although beneficial effects of CBT-I on depressive symptoms have previously been reported in cancer populations (e.g., Ref. [35], our results indicate that such effects may be maintained.

While our results thus add to our knowledge about long-term changes in sleep following CBT-I, some limitations of the present study should also be noted. First, we did not have access to a non-intervention control group at the long-term follow-up assessment. Due to ethical reasons, we used a waitlist-design with control participants being offered access to the e-CBT-I intervention after the short-term follow-up at six weeks post-intervention. Without a proper control group, the observed improvements could theoretically be due to spontaneous recovery over time rather than the e-CBT-I intervention. Nevertheless, reports of long-term sleep disturbances in cancer patients suggests that when untreated, sleep disturbances are likely to become chronic [2,36].

Second, to maximize participation, we did not ask participants to complete sleep diaries at the long-term follow-up, which would have increased the participation burden significantly. Thus, we were unable to examine long-term changes in important sleep diary outcomes such as sleep onset latency, sleep efficiency, and total sleep time, which were reported in our previous publication [17].

Third, within the initial intervention group, those who decided to participate in the long-term follow-up had on average completed a higher number of e-CBT-I cores and program logins compared with those who did not participate. This could potentially indicate a selection bias at T4 in this group, however, given that there were no statistically significant differences between participants and non-participants on the magnitude of improvements on sleep outcomes from T1 to T3, we believe that these differences pose a minimal risk to the generalizability of our findings.

In sum, our results represent an important contribution to the literature providing information about the long-term maintenance of gains in sleep following e-CBT-I. Given the limited availability of effective treatment for insomnia, there is an urgent need to further develop and widely disseminate digitalized CBT-I to improve the quality of life of the many cancer patients who continue to be burdened by sleep disturbances.

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CRediT authorship contribution statement

Ali Amidi: Conception, data collection, data Formal analysis, manuscript draft. **Cecilie R. Buskbjerg:** Data collection, data Formal

analysis, manuscript revision. **Malene F. Damholdt:** Conception, data collection, manuscript revision. **Jesper Dahlgaard:** Data collection, manuscript draft, manuscript revision. **Frances P. Thorndike:** Conception, data collection, manuscript revision. **Lee Ritterband:** Conception, data collection, manuscript revision. **Robert Zachariae:** Conception, data Formal analysis, manuscript revision.

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