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ORIGINAL ARTICLE

The impact of mindfulness on cancer-related cognitive impairment in breast cancer survivors with cognitive complaints

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Abstract

Background: Interventions that target cancer-related cognitive impairment (CRCI) to improve the quality of life of cancer survivors are needed. In this study, the potential of a mindfulness-based intervention to reduce CRCI in breast cancer survivors, compared with physical training and a wait list control group, was investigated.

Methods: Breast cancer survivors with cognitive complaints (N = 117) were randomly allocated to a mindfulness (n = 43), physical training (n = 36), or wait list control condition (n = 38). Participants completed neuropsychological tests and questionnaires before the intervention, immediately after, and 3 months after intervention. The primary outcome measure was the change in cognitive complaints over time. Secondary outcomes were objective cognitive impairment and psychological well-being. All outcomes were compared between groups over time using linear mixed models, including participants with missing values.

Results: Of the 117 included participants, 96 completed the three assessments. Participants in the three groups reported decreased cognitive complaints after intervention, without group differences. There were no between-group differences in objective cognitive impairment after intervention compared with baseline. Compared with the wait list control group, participants reported increased

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mindfulness skills and reduced emotional distress after mindfulness and reduced emotional distress and fatigue after physical training.

Conclusion: Contrary to the hypothesis, all groups reported an improvement in cognitive complaints over time. It is suggested that priming and acknowledgment of CRCI might alter the experience of cognitive impairment. Additionally, both mindfulness-based intervention and physical training can improve psychological well-being of breast cancer survivors with cognitive complaints.

KEYWORDS
breast cancer, cognition, CRCI, longitudinal, MBI, mindfulness, physical training

INTRODUCTION

After cancer treatment, approximately one in five breast cancer survivors experience problems with their memory, attention, executive function, and processing speed.[1] This is referred to as cancer-related cognitive impairment (CRCI) and affects patients' quality of life.[2] Survivors report problems with remembering, focusing, and multitasking, which might lead to problems when returning to work. Unfortunately, there is currently no standard treatment available.[3]

Because CRCI is a multifactorial problem, it requires an intervention that can simultaneously target underlying mechanisms. Several mechanisms have been proposed, including direct and indirect neurotoxic effects of chemotherapy. After chemotherapy, structural and functional changes in the brain have been observed, which might alter cognitive performance.[4] Additionally, increased levels of stress, depression, anxiety, and fatigue have been associated with CRCI.[3] In recent years, research has focused on behavioral and pharmacological interventions to target CRCI.[5] The results of these studies have been mixed, possibly because of small sample sizes, lack of objective cognitive testing, and not including CRCI as a primary outcome measure. More robust and large-scale studies to investigate interventions are needed.[3,6]

Mindfulness-based interventions (MBI) teach participants to pay attention to present-moment experiences in a compassionate and nonjudgmental manner.[7] MBI can help breast cancer survivors deal with fatigue, stress, anxiety, and depressive feelings[8] and indirectly improve cognitive functioning.[9,10]

In our pilot study, we investigated breast cancer survivors with cognitive complaints. Participants were randomized into an MBI or wait list control condition and completed magnetic resonance imaging (MRI) scans, neuropsychological tests, questionnaires, and blood measurements before the start of the intervention, after intervention, and 3 months later. We found a reduction in self-reported cognitive complaints, stress, and fatigue after MBI compared with a wait list control group, but no effect on neuropsychological outcomes measuring attention, memory, executive function, and processing speed. Additionally, we found increased functional connectivity between attention- and emotion-related brain networks.[11] Because functional connectivity refers to the coactivation of brain regions, it suggests a functional link between these areas.[12] To our knowledge, only two other studies examined the effects of MBI on CRCI using both subjective and objective assessments and showed mixed results.[13,14] Larger randomized controlled trials (RCTs) are needed that include CRCI as a primary outcome measure,[13,14] an extensive neuropsychological test battery,[13] and active control group.[11,14]

In this study, we used physical training to control for nonspecific intervention effects such as group support.[15] The physical training program was an extended and adapted version of the standard of care rehabilitation program at University Hospitals Leuven. Physical training might positively impact self-reported CRCI, fatigue, depression, anxiety, and stress, but results on objective cognitive tests have been mixed.[16,17] If results show that MBI has an added value on top of the positive effects of physical therapy, MBI could be added to the existing rehabilitation program.

In this RCT, we evaluated the potential of MBI to reduce CRCI. Our primary outcome was the change in cognitive complaints. Secondary outcomes included objective cognitive impairment and psychological well-being. We compared mindfulness with physical training and a wait list control group using questionnaires and neuropsychological tests. We hypothesized that both MBI and physical training improved CRCI compared with the wait list control group, but that MBI would be more effective than physical training. Based on previous reviews, we expected to find the largest improvements in executive functions such as working memory after MBI.[18,19] Additionally, MBI might directly train attention skills as participants learn to focus attention and monitor present-moment experiences.[5,20,21]

MATERIALS AND METHODS

Participants

Recruitment took place at the Multidisciplinary Breast Cancer Center, University Hospitals Leuven, and via flyers on social media. Patients were identified through the outpatient database and study eligibility was determined using medical records. Potential candidates received a letter with the general outline of the study and were contacted by telephone to evaluate their interest. Interested

candidates were sent the informed consent form and the Cognitive Failure Questionnaire (CFQ). Participants were eligible if they were aged 18 to 65 years, diagnosed with breast cancer with or without solitary metastases (except solitary brain metastases), received chemotherapy and ended this treatment 6 to 60 months before enrollment, and were native Dutch speakers. Participants were excluded if they had MRI contraindications, previously received meditation training, or were diagnosed with intellectual disability or neurologic or psychiatric disorder. Only participants with significant cognitive complaints (CFQ total score >42.9 [mean + 1 SD, Ponds et al.] or at least two of the four extra CFQ questions > mean + 1 SD, Ponds et al.), were eligible for this study[22] Supporting Information S1). The study was approved by the ethics committee of UZ/KU Leuven (S59396) and conducted in accordance with the Declaration of Helsinki.

Design and study procedure

The study was registered at ClinicalTrials.gov (NCT03736460); the protocol has been published elsewhere.[23] Power calculation was done based on a simulation on the CFQ data from our pilot study.[11] To be able to detect changes with a medium effect size (0.7) in our primary outcome measure (CFQ), 32 participants in each group were needed to reach the desired power level (>80%). Participants were randomized across a mindfulness, active control (physical training), or wait list control condition. Randomization was done using the online random number generator MinimPy (http://minimpy.sourceforge.net/) by an independent researcher. Groups were stratified by time since chemotherapy, age, and antihormone therapy. Researchers collecting the data were blinded to participants' group allocation.

Assessments included neuropsychological tests and questionnaires, MRI of the brain, and blood samples. The MRI and blood results are beyond the scope of this manuscript. Participants in the three groups were assessed at three time points: (1) before the intervention (t1), (2) immediately after the intervention (t2), and (3) 3 months after intervention (t3). Participants in both control groups could follow MBI after finishing all assessments. Participants could withdraw without follow-up.

Interventions

Mindfulness-based intervention

The intervention was based on Mindfulness-Based Stress Reduction[24] and Mindfulness-Based Cognitive Therapy for patients with cancer.[25] The program consisted of four 3-hour group sessions spread over 8 weeks, with in-between online support. The number of in-person group sessions was reduced to anticipate dropout by accommodating participants' other responsibilities, including jobs, housekeeping, and caretaking.[26] Participants had to practice daily at home with audio recordings. Each session consisted of guided experiential mindfulness exercises (e.g., focus on the breath, body scan, breathing space, mindful yoga, insight, walking meditation), sharing experiences, reflection, psychoeducation, and review of home practices. The program was led by two clinical psychologists/certified mindfulness trainers who followed standardized procedures.[24,25] Attendance to the group sessions and the amount of home practice was documented.

Physical training

This intervention was based on the recommended levels of physical activity for adults[27] and the existing cancer rehabilitation program at University Hospitals Leuven. The program consisted of four 2-hour group sessions spread over 8 weeks. Each session consisted of psychoeducation related to physical training, endurance and resistance training, stretching, balance and relaxation exercises, sharing experiences, and reviewing homework exercises. Participants were expected to do homework exercises that built endurance for 150 minutes a week and resistance two to three times per week.[27] The physical training was led by a physiotherapist experienced in oncology rehabilitation. Attendance to group sessions and the amount of home practice was documented.

Measures

Subjective cognitive impairment

Our primary outcome measure was self-reported cognitive complaints as measured with the CFQ.[28] The CFQ consists of 25 items assessing self-reported cognitive failures in daily activities, such as forgetting what the person was planning to do. Subscales on distraction, distraction in social situations, names and wordfinding, orientation, and a total summary score are available. Four extra questions assess whether symptoms increased over the past 5 years. The total score was used, with higher scores reflecting more cognitive complaints. We calculated Cronbach's alpha (and accompanying 95% CIs) as a measure of internal consistency in R, version 4.0.3 (ltm).[29] Cronbach's alpha ranges between 0 and 1, with higher values indicating higher reliability. The scale showed good internal consistency ($\alpha = 0.863$; 95% CI, 0.846–0.875) in our sample.

Objective cognitive impairment

Objective cognitive impairment was measured using a neuropsychological test battery that took approximately 1 h to complete. Tests were administered in the same order for every individual. The following domains were assessed: (1) attention (Bourdon-Wiersma Dot Cancellation Test, Trail Making Test[30,31]); (2) memory (Auditory Verbal Learning Test part A and B, Wechsler Adult Intelligence Scale [WAIS] III forward digit span[32,33]); (3) executive function (Stroop

Color Word Test, Controlled Oral Word Association Test, Trail Making Test form B, WAIS III backward digit span, and WAIS III letter-number sequencing[33–36]); and (4) psychomotor processing speed (WAIS III digit symbol-coding, Nine-hole Grooved Pegboard Test, and Trail Making Test form[31,33,37]). Verbal IQ was measured with the Dutch Adult Reading Test.[38] The neuropsychological test battery showed high reliability and good validity in our population.[39]

Psychological outcomes

Depression, anxiety, and stress were measured with the Depression Anxiety Stress Scale.[40] We refer to the total score as a measure of emotional distress, with higher scores indicating more depression, anxiety, and stress. The Depression Anxiety Stress Scale showed excellent internal consistency (α = 0.906; 95% CI, 0.878–0.924) in our sample. Quality of life was measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ).[41] In this study, we used the global health status/quality of life scale. The EORTC-QLQ global health status subscale showed an acceptable internal consistency (α = 0.758; 95% CI, 0.629–0.838) in our sample. Additionally, fatigue was evaluated with the Checklist Individual Strength.[42] The total score was used, with higher scores reflecting more fatigue. The Checklist Individual Strength showed excellent internal consistency (α = 0.911; 95% CI, 0.893–0.923) in our sample. Finally, mindfulness skills were measured with the Comprehensive Inventory of Mindfulness Experiences.[43] The total score was used, with higher scores reflecting more mindfulness skills. The Comprehensive Inventory of Mindfulness Experiences showed good internal consistency (α = 0.898; 95% CI, 0.876–0.910) in our sample.

Statistical analysis

To compare descriptive characteristics of the groups at baseline, we calculated the mean, SDs, and CIs for continuous variables and frequencies and proportions for categorical variables. To test for intervention effects, we used two-level linear mixed models with a random intercept (participant) and with group, time point, and their interaction as fixed effects in R version, 4.0.3 (lme4).[44] Age, verbal IQ, and time since chemotherapy were added as covariates to the models based on backward selection. All values were scaled so that the standardized coefficients provide information about the effect size.[45] We corrected for multiple comparisons with the Benjamini-Hochberg procedure[46] by adjusting the p values for all comparisons for each questionnaire and for all neuropsychological tests within each cognitive domain (e.g., Trail Making Test B: t2-t1 MBI-wait list, and t2-t1 MBI-physical training, and t2-t1 wait list-physical training). Corrected outcomes were considered significant at $p < .05$. To identify influential values, the Cook's distance was computed for each test and questionnaire. If the Cook's distance was larger than 0.5, the data were omitted and a sensitivity analysis was performed.[47]

RESULTS

Enrollment and attrition

Letters were sent out to 657 potentially eligible participants, and all of them were contacted by telephone to evaluate their interest. Of these candidates, 78 did not respond to the telephone call or letter, and 435 declined to participate. Of the 144 candidates that were interested in participating, 23 had to be excluded because they scored below the cutoff for cognitive complaints on the CFQ (Figure 1). The informed consent was signed by 121 breast cancer survivors with cognitive complaints. Before the baseline measure, four participants dropped out because of a lack of time; therefore, 117 participants were randomly allocated to a mindfulness (n = 43), physical training (n = 36), or wait list control condition (n = 38). In total, 96 participants completed the assessments at the three time points. Data of all participants were analyzed, regardless of dropout. Based on the calculation of the Cook's distance, no data had to be excluded (see Figure 1).

Participant characteristics

Table 1 shows the demographic information of the participants at baseline. All women were aged 28 to 63 years (mean = 48.4, SD = 8.7). The average time since chemotherapy completion was 25 months (SD = 14.4). Detailed information on the distribution of chemotherapy regimens can be found in Table S1. Furthermore, 11% to 23% of the participants indicated they were receiving additional psychotherapy while participating in the study. As shown in Table S2, 72% of the MBI participants and 43% of the physical training group followed all training sessions. Participants who missed a session were contacted by the trainer for an update of the session and were requested to continue their daily home practice. The five participants that followed only two or fewer mindfulness sessions all dropped out of the study because it was too time consuming to combine the study with their personal life. Only 19% of the MBI participants practiced daily during the intervention, and only 6% practiced daily during the 3-month follow-up. However, 50% (t2) and 46% (t3) practiced several times a week. Of the physical training participants, 55% (t2) and 35% (t3) practiced several times a week. For more information regarding home practice, see Table S3.

Subjective cognitive impairment

We did not include covariates in the questionnaire models based on backward selection. For the descriptive statistics of the cognitive outcomes, see Table S4. There were no baseline differences between groups for cognitive complaints. Contrary to our hypothesis, wait list participants did not significantly differ from MBI (t2: β = −0.04; 95% CI, −0.32 to 0.25; p = .79; t3: β = −0.09; 95% CI, −0.38 to 0.20; p = .55) or physical training participants (t2: β = −0.24; 95% CI, −0.53

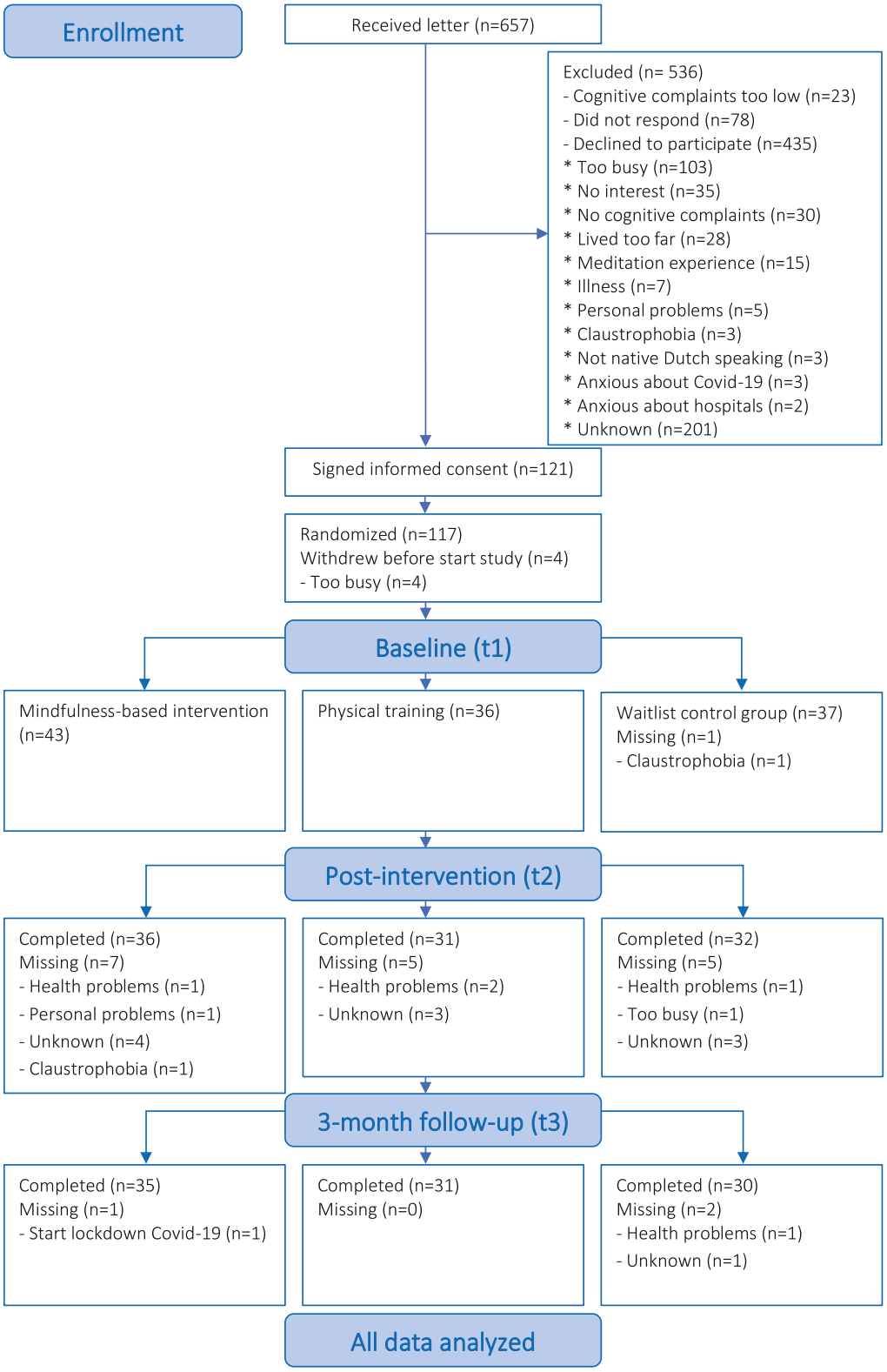

FIGURE 1 CONSORT flow diagram.

to 0.06]; $p = .15$; t3: β = −0.20; 95% CI , −0.50 to 0.10; $p = .19$) on cognitive complaints after the intervention compared with baseline. Additionally, no differences were found between MBI and physical training participants (t2: β = −0.20; 95% CI, −0.48 to 0.09; $p = .41$; t3: β = −0.11; 95% CI , −0.40 to 0.17; $p = .75$). Within each group, improvements in cognitive complaints were reported over time with small to medium effect sizes (0.17–0.57). This improvement was significant immediately after the intervention for the physical

TABLE 1 Demographic and medical characteristics of participants at baseline

	Mindfulness (n = 43)		Physical training (n = 36)		Wait list (n = 38)	
	Mean (SD) or N (%)	95% CI	Mean (SD) or N (%)	95% CI	Mean (SD) or N (%)	95% CI
Age	47.2 (8.14)	44.7–49.7	48.0 (7.73)	45.4–50.6	50.1 (10.1)	46.8–53.4
Verbal IQ	110 (7.24)	108–112	111 (5.25)	109–113	107 (5.15)	105–109
Time since chemotherapy	24.9 (14.8)	20.4–29.5	24.5 (13.6)	19.9–29.1	26.3 (15.1)	21.3–31.2
Employed	32 (74%)		27 (75%)		27 (71%)	
Education						
Secondary school	12 (28%)		11 (31%)		8 (21%)	
Higher education	31 (72%)		25 (69%)		30 (79%)	
Antihormone therapy	30 (70%)		27 (75%)		26 (68%)	
Radiotherapy	27 (63%)		24 (67%)		34 (89%)	
Psychotherapy	10 (23%)		4 (11%)		5 (13%)	

TABLE 2 Results from multilevel mixed models estimating the intervention effects on cognitive complaints over time

Cognitive Failure Questionnaire	Estimate	SE	p_{FDR}	95% CI
Group-by-time interaction effects with wait list as reference group				
Intercept	0.17	0.16	.53	−0.14 to 0.48
t2 x Mindfulness	−0.04	0.15	.79	−0.32 to 0.25
t3 x Mindfulness	−0.09	0.15	.55	−0.38 to 0.20
t2 x Physical training	−0.24	0.15	.15	−0.53 to 0.06
t3 x Physical training	−0.20	0.15	.19	−0.50 to 0.10
Group-by-time interaction effects with mindfulness as reference group				
Intercept	0.36	0.15	.05	0.07 to 0.65
t2 x Physical training	−0.20	0.15	.41	−0.48 to 0.09
t3 x Physical training	−0.11	0.15	.75	−0.40 to 0.17
Within group effects				
Intercept	0.36	0.15	.05	0.07 to 0.65
t2:Mindfulness	−0.21	0.10	.05	−0.41 to −0.02
t3:Mindfulness	−0.46	0.10	<.001***	−0.65 to −0.26
t2:Physical training	−0.41	0.11	<.001***	−0.62 to −0.20
t3:Physical training	−0.57	0.11	<.001***	−0.78 to −0.36
t2:Wait list	−0.17	0.11	.25	−0.38 to 0.03
t3:Wait list	−0.37	0.11	<.001***	−0.58 to −0.16

Abbreviations: FDR, false discovery rate; SE, standard error; t2, postintervention; t3, 3-month follow-up.
***$p < .001$.

training group and at the 3-month follow-up for all three groups (Table 2 and Figure 2). Despite the reduction in cognitive complaints, mean scores of all groups remained above the clinical cutoff, meaning participants still reported elevated cognitive complaints compared with a healthy population.[22] Because the improvement in cognitive complaints in the wait list group was unexpected, we performed post hoc analyses to better understand these findings (see Supporting Information S1 and Tables S5 and S6).

Objective cognitive impairment

The neuropsychological models were adjusted for age, verbal IQ, and time since chemotherapy based on backward selection of the covariates. For the descriptive statistics of the cognitive outcomes, see Table S4. We found no baseline differences in cognitive impairment between the groups. Participants in the wait list condition did not significantly differ from MBI or physical training participants on any

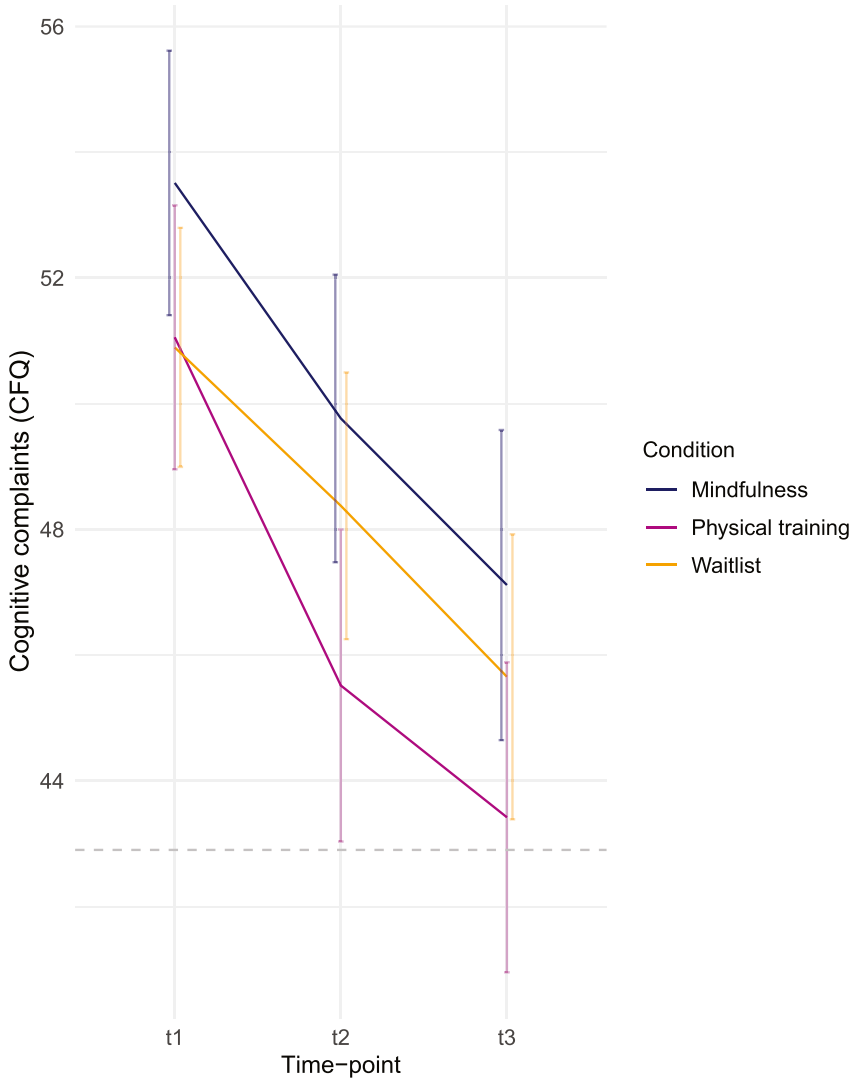

FIGURE 2 Mean scores and 95% CIs for the Cognitive Failure Questionnaire (CFQ) at each time point per group. Dotted line represents the cutoff for significant cognitive complaints based on the study of Ponds et al. (2006) (total CFQ score > 42.9 [mean + 1 SD]). $p_{FDR} < .001$ = significant difference compared with baseline within each group; t1 = baseline; t2 = postintervention; t3 = 3-month follow-up

of the objective cognitive outcomes over time. Additionally, no differences were found between MBI and physical training participants. Improvements over time were found within each group on tests measuring attention, executive function, and information processing speed (see Supporting Information S1 and Table S7).

Psychological outcomes

The descriptive statistics of the psychological outcomes are summarized in Table S8. Groups did not differ on psychological outcomes at baseline. Compared with baseline, MBI participants reported an increase in mindfulness skills compared with wait list participants immediately after the intervention (β = 0.44; 95% CI, 0.13–0.75; p = .03) and at 3-month follow-up (β = 0.41; 95% CI, 0.09–0.72; p = .03). Furthermore, MBI participants reported less feelings of emotional distress than wait list participants 3 months after intervention compared with baseline (β = −0.57; 95% CI, −0.98 to −0.16; p = .03). When comparing the physical training to the wait list control group, the reduction in emotional distress was significant immediately after the intervention compared with baseline (β = −0.60; 95% CI, −1.02 to −0.18; p = .02) and at 3-month follow-up (β = −0.62; 95% CI, −1.04 to −0.19; p = .01). Additionally, fatigue reduced immediately after the intervention (β = −0.53; 95% CI, −0.89 to −0.17; p = .02) and at 3-month follow-up (β = −0.53; 95% CI, −0.90 to −0.16; p = .01). No differences between groups were found on the quality-of-life measure. Additionally, no differences were found between the mindfulness and physical training group over time on any of the questionnaires (Figure 3 and Table 3). Within-group effects are provided in Table S9 and Figure 3.

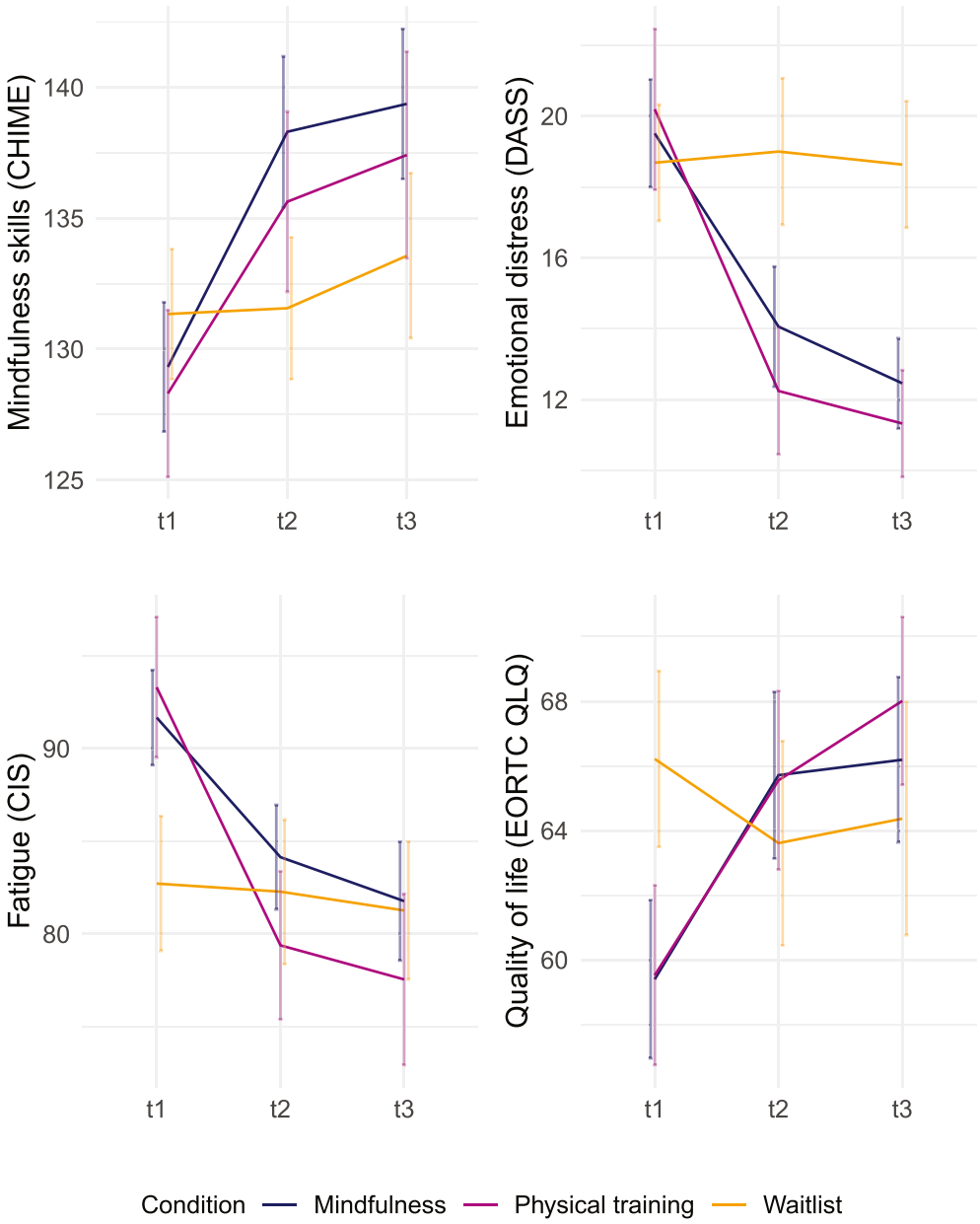

FIGURE 3 Mean scores and 95% CIs for the psychological outcomes at each time point per group. $p_{FDR} < .05$ = significant difference compared with baseline within each group; t1 = baseline; t2 = postintervention; t3 = 3-month follow-up

DISCUSSION

In this longitudinal RCT, we investigated the impact of MBI on (1) subjective cognitive complaints and (2) objective cognitive performance and psychological well-being in breast cancer survivors with cognitive complaints. Contrary to our hypothesis, we found no differences between the MBI and wait list or physical training group. More specifically, cognitive complaints decreased in all three groups with small to medium effect sizes.

Although MBI participants reported decreased cognitive complaints at the 3-month follow-up, this reduction was not significant immediately after intervention. These findings are in contrast with other studies showing that MBI can improve cognitive complaints immediately after intervention.[5,48] However, a recent study showed an improvement in subjective memory complaints after MBI compared with a wait list control group over time, but no difference between both groups in overall cognitive complaints. Similar to our study, both groups reported an improvement in overall cognitive impairment over time, regardless of group allocation.[14]

One potential explanation for the decline in cognitive complaints in the wait list control group might be acknowledging CRCI. By recruiting participants with cognitive complaints for our intervention study, we acknowledged that CRCI is a common side effect of chemotherapy. This might have led to a reduction in cognitive complaints in the wait list control group because it is known that acknowledging CRCI as a side effect of chemotherapy might help

TABLE 3 Results from multilevel mixed models estimating the intervention effects on psychological outcomes over time

Questionnaire	Estimate	SE	p_{FDR}	95% CI
Depression Anxiety Stress Scale				
Group-by-time interaction effects with wait list as reference group				
Intercept	0.21	0.16	.53	−0.09 to 0.52
t2 x Mindfulness	−0.48	0.21	.05	−0.89 to −0.08
t3 x Mindfulness	−0.57	0.21	.03*	−0.98 to −0.16
t2 x Physical training	−0.60	0.22	.02*	−1.02 to −0.18
t3 x Physical training	−0.62	0.22	.01*	−1.04 to −0.19
Group-by-time interaction effects with mindfulness as reference group				
Intercept	0.29	0.15	.07	0.00 to 0.58
t2 x Physical training	−0.11	0.21	.74	−0.52 to 0.29
t3 x Physical training	−0.05	0.21	.97	−0.45 to 0.36
Checklist Individual Strength				
Group-by-time interaction effects with wait list as reference group				
Intercept	−0.07	0.16	.66	−0.38 to 0.24
t2 x Mindfulness	−0.31	0.18	.10	−0.67 to 0.04
t3 x Mindfulness	−0.33	0.18	.09	−0.69 to 0.03
t2 x Physical training	−0.53	0.19	.02*	−0.89 to −0.17
t3 x Physical training	−0.53	0.19	.01*	0.90 to −0.16
Group-by-time interaction effects with mindfulness as reference group				
Intercept	0.35	0.15	.05	0.06 to 0.64
t2 x Physical training	−0.21	0.18	.41	−0.57 to 0.14
t3 x Physical training	−0.20	0.18	.75	−0.55 to 0.16
Comprehensive Inventory of Mindfulness Experiences				
Group-by-time interaction effects with wait list as reference group				
Intercept	−0.13	0.16	.53	−0.44 to 0.18
t2 x Mindfulness	0.44	0.16	.03*	0.13 to 0.75
t3 x Mindfulness	0.41	0.16	.03*	0.09 to 0.72
t2 x Physical training	0.24	0.17	.15	−0.08 to 0.56
t3 x Physical training	0.25	0.17	.17	−0.07 to 0.58
Group-by-time interaction effects with mindfulness as reference group				
Intercept	−0.24	0.15	.11	−0.54 to 0.05
t2 x Physical training	−0.20	0.16	.41	−0.51 to 0.12
t3 x Physical training	−0.15	0.16	.75	−0.47 to 0.16
EORTC Quality of life questionnaire subscale Quality of Life				
Group-by-time interaction effects with wait list as reference group				
Intercept	0.13	0.16	.53	−0.19 to 0.45
t2 x Mindfulness	0.51	0.23	.05	0.05 to 0.96
t3 x Mindfulness	0.49	0.24	.06	0.03 to 0.95
t2 x Physical training	0.45	0.24	.12	−0.03 to 0.92
t3 x Physical training	0.50	0.25	.07	0.03 to 0.98
Group-by-time interaction effects with mindfulness as reference group				
Intercept	−0.29	0.15	.07	−0.59 to 0.01
t2 x Physical training	−0.06	0.24	.80	−0.52 to 0.40
t3 x Physical training	0.01	0.23	.97	−0.45 to 0.46

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; FDR, false discovery rate; SE, standard error; t2, postintervention; t3, 3-month follow-up.

*$p < 0.05$.

survivors cope with cognitive impairment.[49] Another explanation might be priming effects. Goal priming refers to the activation of a goal by external cues, which can affect information processing and behavior to pursue the primed goal.[50] In this study, the goal was to reduce CRCI, which might have (unconsciously) motivated participants to guide cognition and behavior to accomplish that goal. The goal might also have been triggered by the published results of our pilot study, which showed an improvement in cognitive complaints in the mindfulness compared to the wait list control group over time.[11]

Similar to our pilot study,[11] we did not find differences in objective cognitive impairment between the MBI and control groups over time. Within each group, we found improvements on tests measuring attention, executive function, and information processing speed. Although only the MBI group improved on specific subtests measuring working and short-term memory, more complex tests might be needed to elucidate these findings. A more detailed discussion can be found in Supporting Information S1. The improvements in objective cognitive impairment could be related to practice effects because no improvements were found when parallel tests were used.[51] Moreover, because neuropsychological tests were originally developed to detect severe cognitive impairment, and CRCI is more subtle, the tests might not be sensitive and specific enough to detect CRCI.[52]

In line with meta-analyses,[8,17] our study confirmed that both MBI and physical training can help breast cancer survivors deal with fatigue, stress, anxiety, and depressive feelings, and enhance their quality of life. No improvements were found within the wait list control group over time. Because psychological factors might influence cognitive complaints,[3] we expected to find a larger decrease in cognitive complaints in the intervention groups from the improvement in psychological outcomes.[9,10] Surprisingly, we did not find evidence for this hypothesis. Nevertheless, our findings show that both MBI and physical training might be suitable treatments to improve psychological well-being of breast cancer survivors with cognitive complaints. By providing a treatment choice, survivors can opt for the therapy that aligns with their values and preferences, possibly leading to enhanced effectiveness of the intervention.[53]

Additionally, almost one-half of the eligible participants declined to participate because they were too busy, mostly with resuming work and the combination with household duties. Furthermore, the participants that dropped out of the study during MBI reported that it was too time consuming to combine the study with their personal obligations. This shows the importance of reducing the standard number of group sessions in this population. Based on previous research[54] and our pilot study,[11] four sessions can be considered an adequate minimal dose to improve cognitive performance.[55]

Strengths and limitations

Strengths of the study include using an active control condition to control for nonspecific intervention effects.[15] Furthermore, we excluded participants with a history of psychiatric disorders to eliminate potential confounding factors such as concomitant treatment, which might alter cognition. However, it has been shown that MBI is more effective in psychiatric populations, possibly because of lower preintervention distress in nonpsychiatric populations.[56] Additionally, it would have been interesting to perform single-case analysis given the lack of between-group differences. Unfortunately, this requires more data points per individual. Future studies could use experience sampling methods to investigate individual profiles and provide a patient-tailored therapy approach. Additionally, although MBI participants were asked to practice daily between group sessions, only 19% followed these instructions. However, an additional 50% practiced several times a week. Because we could not find a relationship between the amount of home practice and cognitive complaints, this could not explain the lack of between-group differences. Moreover, shorter MBI doses have been suggested to be as effective as larger doses.[57,58] However, it has recently been suggested that at least 3 months of mindfulness practice might be needed to induce structural brain changes.[59] Therefore, it would be interesting to investigate MBIs with longer follow-ups and link potential brain changes to changes in cognition. This way, brain imaging might be helpful to better understand CRCI. Another potential explanation for the lack of between-group differences might be that our power calculation was based on the comparison of MBI and wait list controls from our pilot study.[11] Hence, this study might be underpowered to detect differences between MBI and physical training. Additionally, the power calculation was based to detect differences in our primary measure (CFQ), so this study might not be powered to detect effects in secondary measures such as objective cognitive outcomes. Furthermore, participants in the wait list control group were asked to continue their activities as usual. It is possible that this included sports, which might have confounded our results. Although this would likely result in baseline differences between the groups, future research could benefit from adding questions about the frequency of practicing sports in all groups. Finally, some of the participants received additional psychotherapy while participating in our study. This was not an exclusion criterion because breast cancer survivors might need psychological support to help them cope with disease-related experiences. Our results did not change when removing the participants who received psychotherapy from the total sample.

CONCLUSIONS

All groups reported an improvement in cognitive complaints over time, without between-group differences. We believe that our findings highlight the importance of acknowledging CRCI and the role of priming to reduce cognitive complaints. Additionally, both MBI and physical training might be used to improve psychological well-being of breast cancer survivors with cognitive complaints. This way, we can move away from a one-size-fits-all approach and create more diversity in the treatment program.

AUTHOR CONTRIBUTIONS

Michelle Melis: Data curation, project administration, investigation, methodology, formal analysis, writing (original draft), and writing (review and editing). **Gwen Schroyen:** Methodology, visualization, and writing (review and editing). **Nicolas Leenaerts:** Methodology, visualization, and writing (review and editing). **Ann Smeets:** Conceptualization and writing (review and editing). **Stefan Sunaert:** Conceptualization, supervision, and writing (review and editing). **Katleen Van der Gucht:** Conceptualization, funding acquisition, methodology, supervision, and writing (review and editing). **Sabine Deprez:** Project administration, conceptualization, funding acquisition, project administration, supervision, and writing (review and editing). All authors approved the final manuscript.

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CONFLICTS OF INTEREST

Katleen Van der Gucht is cofounder and director of the managing committee of the Leuven Mindfulness Centre Fund. The Leuven Mindfulness Centre receives payments for workshops and presentations related to mindfulness. The other authors made no disclosures.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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