Mindfulness-Based Cognitive Therapy and Persistent Pain in Women Treated for Primary Breast Cancer: Exploring Possible Statistical Mediators - Results from a Randomized Controlled Trial

Johannsen M, MSc, O’Connor M, PhD, O’Toole MS, PhD, Jensen AB, PhD, Zachariae R, DMSc

1] Unit for Psychooncology and Health Psychology, Dept. of Oncology, Aarhus University Hospital and Dept of Psychology, Aarhus University, Bartholins Alle 9; Bld. 1340; DK-8000 Aarhus C, Denmark

2] Dept. of Oncology, Aarhus University Hospital, Nørrebrogade 55; DK-8000 Aarhus C, Denmark

*Corresponding author: Maja Johannsen, Unit for Psychooncology and Health Psychology, Dept. of Oncology, Aarhus University Hospital and Dept. of Psychology, Aarhus University, Bartholins Alle 9; Bld. 1340; DK-8000 Aarhus C, Denmark, Phone: +45 871 65956

Funding This study has been generously supported by The Danish Cancer Society (R49-A2564-11-S15), Aase & Ejnar Danielsen’s Fund (10-000938), Einar Willumsen’s Memorial Fund (6000073), Wedell-Borg Wedellborg’s Fund (24-15-2), and Radiumstationens Research Fund (AR3466_01).

Conflicts of interests: None to declare
ABSTRACT

Objectives: To investigate possible statistical mediators in a randomized controlled trial of Mindfulness-Based Cognitive Therapy (MBCT) on pain intensity in women treated for primary breast cancer.

Methods: The sample consisted of 129 women treated for breast cancer, presenting with persistent pain, who were randomly assigned to MBCT or a wait-list control. We previously reported a statistically significant and robust effect of MBCT on pain intensity (11-point Numeric Rating Scale), which was included as the primary outcome. Proposed mediators were mindfulness (the Five Facet Mindfulness Questionnaire, FFMQ), self-compassion (the Short-Form Self-Compassion Scale, SCS-SF), and pain catastrophizing (the Pain Catastrophizing Scale, PCS). Measurement points included baseline (T1), post-intervention (T2), 3 month (T3) and 6 month (T4) follow-up. All indirect effects of the mediators were tested in separate Multi-Level Models (MLMs), using the product-of-coefficients-approach with bias-corrected confidence intervals (95% BSCI). The statistically significant mediators were then included in a multiple mediator model.

Results: Statistically significant indirect effects were found for mindfulness non-reactivity (B=-0.17, BSCI [-0.32 to -0.04]) and pain catastrophizing (B=-0.76, BSCI [-1.25 to -0.47]). No statistically significant indirect effect was found for self-compassion (B=-0.09, BSCI [-0.30 to 0.04]). In a multiple mediator model, including mindfulness non-reactivity and pain catastrophizing, only pain catastrophizing remained statistically significant (B=-0.72, BSCI [-1.19 to -0.33]), explaining 78% of the effect.
Discussion: The results of the present study may have clinical implications. An increased focus on the proposed mediators may optimize the clinical use of MBCT for persistent pain in women treated for breast cancer.

Suggested keywords: pain; breast cancer; mindfulness; pain catastrophizing; mediation
INTRODUCTION

Persistent pain affects a substantial number of breast cancer patients. Psychosocial intervention may be one method to reduce pain in breast cancer patients and Mindfulness-Based Intervention (MBI), e.g., Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT), has been shown efficacious in reducing pain in diverse pain populations. Studies have also investigated the efficacy of MBI specifically for pain in breast cancer patients, and preliminary, recent studies show promising results. Most recently, we reported the effect of MBCT on persistent pain in women treated for breast cancer, which yielded a statistically significant and robust effect of MBCT on pain intensity. Furthermore, we have explored possible clinical and psychological moderators of the effect, i.e., for whom the intervention might be most efficacious, finding that higher levels of adult attachment avoidance, which is associated with deactivating strategies (e.g., suppression of distress-evoking thoughts and emotions), predicted a larger treatment gain. In addition, to optimize treatment effects, it would be clinically valuable to explore ‘how’ this intervention may work, i.e., the intervention’s active ingredients.

Theoretically, MBI may work through several mechanisms. First, MBI is assumed to increase mindful awareness, thereby teaching patients to adopt a stance of detached observation of physical and emotional discomfort. In relation to pain, mindful awareness is assumed to uncouple the sensory pain component from the affective and cognitive pain components by fostering a different way of relating to bodily sensations and emotional discomfort characterized by a higher degree of openness and acceptance. Self-compassion, a second potential mediator, may help patients respond to painful thoughts and feelings with self-kindness and by observing and acknowledging them without avoidance and over-identification. Finally, negative cognitive-affective responses to pain, i.e., pain catastrophizing, have been found predictive of the pain experience, and pain
catastrophizing has been theoretically suggested as a key mechanism in pain interventions\textsuperscript{18}. However, recent trials report mixed results, with one study failing to find support for this\textsuperscript{19}, while another study found that MBSR was associated with reductions in pain catastrophizing\textsuperscript{20}.

Several studies have explored mindfulness as a general mediator in MBI, with a systematic review and meta-analysis showing evidence for mindfulness as a mediator in 14 out of 16 studies\textsuperscript{21}. To our knowledge, only four studies have explored self-compassion as a possible mediator in MBI for various conditions (e.g., depression\textsuperscript{22}, stress\textsuperscript{23}, trait anxiety\textsuperscript{24} and, maladaptive behavior\textsuperscript{25}). While two of the studies found support for self-compassion as a mediator\textsuperscript{22,23}, none of the studies included pain as the primary outcome in their mediation analyses. Furthermore, the broad range of study populations investigated challenge the comparability and generalizability of the results.

On this background, the aim of the present study was to investigate possible mediators of the previously detected effect of MBCT compared to a wait-list control group on pain intensity in women treated for breast cancer with persistent pain\textsuperscript{9}. Specifically, we hypothesized that 1) increased levels of mindfulness, 2) increased levels of self-compassion and 3) reduced levels of pain catastrophizing during MBCT would statistically mediate the effect of MBCT on pain intensity\textsuperscript{9}. Although MBI is traditionally assumed to primarily target the negative impact of pain rather than the pain sensation per se, we selected pain intensity as the primary outcome based on our previously reported data showing a clinically relevant effect of MBCT on pain intensity\textsuperscript{9}.
MATERIALS AND METHODS

Study design and participants

The present study analyzed data from a randomized controlled trial evaluating the efficacy of Mindfulness-Based Cognitive Therapy (MBCT) on persistent pain. The trial has previously been described in detail elsewhere. In brief, the sample consisted of 129 women treated for primary breast cancer at the Department of Oncology, Aarhus University Hospital. Inclusion criteria were: a diagnosis of primary breast cancer, a time interval of ≥3 months after surgery, completed chemotherapy and/or radiotherapy, a score ≥3 on perceived pain intensity or pain burden on a 10-point numerical rating scale (NRS), and ability to understand Danish. Male patients and patients with metastatic breast cancer, other previous cancers, serious psychiatric diagnoses (e.g., psychosis), and severe medical conditions related to the musculoskeletal system (e.g., arthritis) were excluded. The study was approved by the Regional Science Ethical Committees (registration no.: 1-10-72-460-12) and pre-registered at clinicaltrials.gov (NCT01674881).

Procedures

Patients were recruited from October 2012 to December 2013. At follow-up visits at the Department of Oncology, the treating oncologists screened the patients concerning their current pain status and informed eligible patients about the study. Eligible women were informed both orally and in writing about the study. If interested, they were given a study package consisting of additional information about the study, a consent form, and a prepaid envelope. If the patient agreed to participate, she returned a signed consent form and was sent a baseline questionnaire.

The statistical software Power And Sample Size (PASS) v.12 (NCSS, Kaysville, Utah) was used for the randomization procedure. After having returned the completed baseline questionnaires,
participants were randomly allocated to the MBCT program or a wait-list control group. No blind-
ing of study condition was feasible due to the design of the present study (i.e., wait-list control
group).

Data collection

Data were collected at four time points: prior to randomization (baseline, (T1)) post-intervention
after the 8-week MBCT program (T2), and 3 months (T3) and 6 months (T4) after the intervention.

Study groups: MBCT and the waitlist control

The 8-week Mindfulness-Based Cognitive Therapy (MBCT) intervention generally adhered to the
program outlined in the original manual26, following the curriculum which consists of formal
mindfulness practices, group discussions, cognitive exercises, and discussions of home practice.
While MBCT was originally developed for recurrent depression26, the conceptualization of mala-
daptive cognitions as a key vulnerability has been applied to other conditions than depression, e.g.,
headache and health anxiety27,28. MBIs do not aim to change thought content, emotions, and bod-
ily sensations per se, but focus on how one relates to such experiences. As such, no specific pain
adaptations were made to the intervention, but as the women were included in our study based on
their pain levels, and as MBI focuses on how one relates to ‘the difficult’, ‘the difficult’ for the
participants in our study was their pain. Accordingly, pain-related issues were predominant in the
inquiries and group discussions.

All treatment groups were facilitated by an experienced mindfulness instructor with training from
Oxford University, receiving supervision from Centre for Mindfulness Research and Practice,
Bangor University, UK, during the study.
The wait-list control group was not contacted during the study period except from when asked to complete questionnaires at time points equal to T1, T2, T3, and T4.

**Measures**

*Sociodemographic and clinical data*

All patients provided relevant sociodemographic information, with the exception of ethnicity which was not included. Clinical data and information on comorbidity (Charlson Comorbidity Index (CCI)\textsuperscript{29}) were retrieved from the Danish Breast Cancer Cooperative Group (DBCG) registry, which contains information on diagnosis and treatment of the cancer disease reported by all breast cancer treating departments\textsuperscript{30}.

*Primary outcome*

All primary and secondary outcome measures have been fully described elsewhere\textsuperscript{9}. In the present study, the primary outcome was pain intensity, measured by an 11-point Numeric Rating Scale (NRS). Pain intensity measured by an 11-point NRS has proved a sensitive and reliable pain measure in cancer patients\textsuperscript{31}.

*Mediators*

Possible mediators included mindfulness measured by the 39-item Five Facet Mindfulness Questionnaire (FFMQ) measuring five mindfulness facets: acting with awareness, describing, nonjudging of inner experience, non-reactivity to inner experience, and observing\textsuperscript{32}. Participants rated their perceived levels of mindfulness in everyday life on a 5-point Likert scale (1 = never or rarely true, 5 = very often or always true). Higher scores indicate higher levels of the mindfulness facets. No total score is calculated. The FFMQ is an up-to-date, widely used measure of mindfulness due to
its multifaceted operationalization which has previously shown good internal consistency in cancer populations. In the present sample, Cronbach’s alphas for all subscales were acceptable, ranging from 0.71 to 0.90.

Another possible mediator was self-compassion, which was measured by the short-form 12-item version of the Self-Compassion Scale (SCS-SF). Participants reported their perceived levels of self-compassion on a 5-point Likert scale (1 = almost never, 5 = almost always). Higher scores indicate higher levels of self-compassion. The total score of SCS-SF has shown good psychometric properties, whereas use of the SCS-SF subscales is not recommended. In the present sample, Cronbach’s alpha for the SCS-SF total score was 0.84.

The 13-item Pain Catastrophizing Scale (PCS) yields subscale scores for rumination, magnification, and helplessness and was included as a measure of pain catastrophizing. Only the PCS total score was calculated in the current study. Participants indicate the extent to which certain thoughts and feelings are associated with their experienced pain on a 5-point Likert scale (0 = not at all, 4 = all the time). Higher scores indicate higher levels of pain catastrophizing. The PCS has shown good validity and has previously been used in cancer populations. This was also the case in the present sample with the PCS total score showing high internal consistency (Cronbach’s alpha: 0.92).

**Adherence**

Adherence was measured by 1) number of sessions attended, 2) total number of minutes spent on home practice during the 8-week program (T1-T2), and 3) total number of minutes spent on mindfulness practice during the previous week from T2-T4.
Statistical analysis

Stata® version 14 (College Station, Texas, USA) was used for all analyses. The main effect of MBCT on pain has previously been established using Mixed Linear Models (MLMs). The aim of the present study was to explore possible mediators of the previously reported statistically significant and robust effect of MBCT on pain intensity in women treated for primary breast cancer.

We performed all mediation analyses in MLMs based on the Intent-to-Treat (ITT) sample, estimated with the maximum likelihood method. MLMs tolerate missing values and thus does not unnecessarily compromise statistical power. We used a three-step approach to establish indirect effects, namely: 1) we investigated the indirect effects of the proposed mediators (the five mindfulness facets, self-compassion total score, and pain catastrophizing total score) in separate mediation models, 2) we investigated the robustness of statistically significant mediators by performing sensitivity analyses: a) last-observation-carried-forward (LOCF) due to an unbalanced dropout at T2 (cf. Figure 1) and b) per protocol analyses including only women who attended ≥4 sessions (cf.22), and 3) we investigated statistically significant and robust mediators in a multiple mediation model.

The mediation analyses were conducted as 2-level models, where level 1 refers to the four time points (i.e., T1-T4) that were nested within the individual at level 2, and thus followed the principles of lower-level mediation. Determination of indirect effects was based on the product-of-coefficients approach. This correlation-based approach calculates the product term between two paths; path \( a \) (between the independent variable and the mediator) and path \( b \) (between the mediator and the dependent variable controlling for the independent variable). The independent variable
here refers to group (treatment vs. waitlist), the explored mediators were mindfulness (5 subscales), self-compassion, and pain catastrophizing, and the dependent variable was pain intensity. Following the principles of Bauer et al. (2006)\(^{38}\), all paths necessary (i.e., \(a, b, c,\) and \(c'\)) for determining indirect and direct effects are estimated in one model. A new outcome variable is formed \((Z)\) by stacking the dependent \((Y)\) variable and the process variable \((P)\) for each time unit \(i\) within each individual \(j\). In order to distinguish the two variables stacked in \(Z\), two selection variables are created that specify when \(Z\) refers to the process variable or the dependent variable. In the multiple mediator MLM, the statistically significant mediators and the corresponding selection variable were included.

In all mediation models (i.e., the separate and multiple mediation models), indirect effects were treated as fixed since models with random effects specified did not converge. This may under-estimate the variance of the indirect effect, since the covariance of path \(a\) and path \(b\) \((\sigma_{ab})\) is not taken into account as otherwise recommended when exploring lower-level mediation in multilevel models \(^{38,39}\). When having obtained the necessary paths, results were bootstrapped with 5000 iterations in order to obtain both bootstrapped standard errors (BSSE) and bootstrapped confidence intervals (BSCI). Bootstrapping is a nonparametric resampling procedure that does not impose the assumption of normality of the sampling distribution. By repeating this process, an empirical approximation of the sampling distribution of \(ab\) is built and used to construct confidence intervals for the indirect effect\(^{42}\).

Effect sizes were expressed as the proportion of the total effect accounted for by the proposed mediator, i.e., mediated effect / total effect based on absolute values\(^{39,43}\).
Scale or subscale totals with > 50% missing values were coded as missing and no total score calculated. Missing values on scales with an internal consistency > 0.7 were substituted with the mean of the remaining completed items. This is considered an appropriate method for handling missing items on a scale. 

RESULTS

Descriptives

Study flow is summarized in Figure 1. The dropout rates were unbalanced between study groups, with higher dropout rates in the intervention group (31.3% (T2), 37.3% (T3), and 41.8% (T4)) compared with the waitlist control (1.6% (T2) and 8.1% (T3, T4)). Descriptive data are summarized in Table 1.

Previously conducted dropout analyses, focusing on dropout at T2 due to the unbalance between study groups (cf. Figure 1), did not reveal statistically significant differences on any primary outcome measures between dropouts compared with participants returning the questionnaires. However, dropouts were less motivated ($p=0.009$), reported more comorbidity ($p=0.01$), and had a higher use of non-prescription pain medication ($p=0.03$) than participants returning the questionnaires.

Data on pain intensity and the proposed mediators at all assessment points are reported in Table 2. A correlation matrix of pain intensity and the proposed mediators is shown in Table 3.
Primary outcome

Main effects: Pain intensity

In summary, the main effect analyses revealed a statistically significant time×group effect for pain intensity ($p=0.002, d=0.61$). As we had included several pain outcomes, we corrected for multiple comparisons using the Benjamini-Hochberg procedure (False Discovery Rate (FDR): 0.05) and conducted sensitivity analyses, finding that the effect on pain intensity remained statistically significant. Due to the unbalanced dropout between groups at T2 (see Figure 1), we conducted a logistic regression with pain intensity at baseline as the independent variable and dropout at T2 as the dependent variable. Pain intensity did not predict dropout (OR=0.96, $p=0.69$). When we conducted sensitivity analyses based on the assumption that dropouts experienced zero effect of the intervention, pain intensity remained statistically significant ($p=0.034, d=0.39$).

Mediators

Mindfulness

A statistically significant indirect effect was found for the mindfulness facet non-reactivity ($B=-0.17, BSCI [-0.32 - -0.04]$), with changes in mindfulness non-reactivity showing an indirect effect of MBCT on pain intensity. The larger the increase in non-reactivity, the larger the effect on pain intensity. The indirect effect accounted for 24% of the total effect. None of the results for the remaining mindfulness facets reached statistical significance (Table 4).
Self-compassion

No statistically significant indirect effect was found for the SCS-SF total score (B=-0.09, BSCI [-0.30 - 0.04]) on the effect of MBCT on pain intensity (Table 4).

Pain catastrophizing

A statistically significant indirect effect was found for pain catastrophizing (B=-0.76, BSCI [-1.25 - -0.47]), with changes in pain catastrophizing showing an indirect effect of MBCT on pain intensity (Table 4). Greater reductions in pain catastrophizing were associated with larger effect. As suggested by Baron & Kenny, when $c'$ is reduced close to zero, this is conceptualized as complete mediation$^{45}$, corresponding to our effect size parameter of 98% of the effect explained.

Adherence

The mean number of sessions attended was five (SD=2.19) with 47 women (70%) attending ≥ 4 sessions. We explored the associations between adherence and the statistically significant mediators with MLMs, with adherence variables entered as predictors of change in mediators over time. Total minutes of home practice during the previous week at T2-T4 did not predict changes in mindfulness non-reactivity ($p=0.13$, $d=0.29$) or changes in pain catastrophizing ($p=0.58$, $d=0.11$) over time. In contrast, more sessions attended predicted both increases in mindfulness non-reactivity ($p=0.006$, $d=0.64$) and reductions in pain catastrophizing ($p=0.03$, $d=0.56$) over time. Finally, more homework practice during the 8-week program predicted increases in mindfulness non-reactivity ($p=0.02$, $d=0.70$), but did not predict reductions in pain catastrophizing ($p=0.57$, $d=0.22$) over time.
Sensitivity analyses

Due to the unbalanced dropout at T2 (Figure 1), we conducted sensitivity analyses for mindfulness non-reactivity and pain catastrophizing, testing the assumption that that dropouts had experienced no effect of the intervention (i.e., last-observation-carried-forward). The indirect effects of mindfulness non-reactivity ($B=-0.16$, BSCI $[-0.38 - -0.03]$, ES=31%) and the pain catastrophizing ($B=-0.65$, BSCI $[-1.10 - -0.27]$, ES=90%) remained statistically significant. We also conducted per protocol analyses, including only women who had attended $\geq 4$ sessions in the analyses. This did not substantially change the results for either mindfulness non-reactivity ($B=-0.20$, BSCI $[-0.45 - -0.06]$, ES=27%) or pain catastrophizing ($B=-0.81$, BSCI $[-1.31 - -0.38]$, ES=96%).

Multiple Mediation model

Finally, the statistically significant mediators, i.e., mindfulness non-reactivity and pain catastrophizing, were included in a multiple mediation model (Figure 2). In this model, statistically significant indirect effects were only found for pain catastrophizing ($B=-0.72$, BSCI $[-1.19 - -0.33]$), explaining 78% of the proportion of the effect. In contrast, non-reactivity did not reach statistical significance ($B=-0.07$, BSCI $[-0.20- <0.01]$), explaining only 8% of the effect.

[Insert Figure 2 near here]

DISCUSSION

Pain catastrophizing and, although less robust, mindfulness non-reactivity showed statistically significant indirect effects of MBCT on pain intensity. Our results thereby point towards statistical mediators that include both mindfulness-related and cognitive components of potential importance.
in reducing persistent pain. It should, however, here be noted that our statistical approach did not take temporality of the mediators and outcome into account.

Our finding, based on the individual mediation analyses, that mindfulness non-reactivity had indirect effects of MBCT on pain is in line with the results of a recent meta-analysis of studies with various clinical samples (e.g., depression, anxiety, stress), which generally supports mindfulness as a mediator in MBIs. Our results expand on existing studies by establishing an indirect effect of mindfulness in a sample with persistent pain. Non-reactivity, the only mindfulness component found to statistically mediate the effect of MBCT in the present study, may be conceptually interpreted in relation to the mechanism of acceptance, i.e., accepting the pain experience as opposed to reactivity such as avoidance or ruminative thought patterns. In the multiple mediator model, however, non-reactivity was no longer statistically significant. One possible explanation could be that including both non-reactivity and pain catastrophizing in the same model may have caused issues of multicollinearity as these constructs have previously been found to be associated. However, no indications of multicollinearity were found in our study (Table 3). Taken together, the importance of mindfulness non-reactivity as a mediator of MBCT for pain remains unclear, as the detected effect was negligible and found only for one out of five facets. A large three-armed trial, also including pain patients, did not find that MBSR increased long-term levels of mindfulness, further supporting the unclear role of mindfulness as a mediator in MBIs for pain populations.

In contrast, pain catastrophizing was found to be a statistical mediator of the effect of MBCT on pain intensity, explaining 78% of the effect in the multiple mediation model. While this suggests that pain catastrophizing may be an important statistical mediator, it remains unclear whether this effect is specific to MBCT. Indeed, the large, three-arm trial of MBSR and CBT cited above also
explored changes in pain catastrophizing and found that CBT and MBSR showed similar effects on pain catastrophizing. Likewise, it has been proposed that changes in pain catastrophizing might be a mechanism shared across a variety of psychosocial pain interventions. In future studies, it would be clinically relevant to empirically address the specificity of the statistical mediators found in the present study by comparing MBCT with other efficacious psychosocial interventions for pain. In addition, the relationship between mindfulness and pain catastrophizing is yet to be clarified. Potential overlap between the two constructs, e.g., the possibility that both mindfulness and pain catastrophizing may be accounted for by a more general negative affectivity, should be taken into consideration in future dismantling studies.

With respect to the final hypothesized mediator of MBCT, self-compassion, no support was found for an indirect effect on pain intensity in our sample. In the case of statistically non-significant results, ceiling effects could be one possible explanation. However, this does not appear to be the case in the present study as the observed self-compassion baseline levels were lower than those found in the original validation study of SCS-SF with healthy student samples. Previous studies exploring the mediating role of self-compassion show mixed results. Existing studies, including ours, have used a variety of primary outcomes, and it is possible that self-compassion plays different mediating roles depending on the clinical issue targeted. Our study is the first to investigate self-compassion as a statistical mediator in a clinical pain sample, and our results suggest that self-compassion is not a mediator of relevance to pain in our study population. Another possible explanation for our null-finding could be that we used a short version of the SCS which, regardless of its good internal consistency (0.84), could be insufficiently sensitive to detect an effect.

Taken together, our results suggest that pain catastrophizing could be an important statistical mediator in MBCT for pain. While less robust, this could potentially also apply to mindfulness non-
reactivity. One interpretation of our findings could be that practicing to notice that thoughts, feelings, and bodily sensations fluctuate over time may reduce the tendency to ruminate over the pain and/or the perceived need to avoid the discomfort. Thus, facilitating a more decentered approach and teaching the participants to contain – as opposed to avoid or overidentify with – the physical discomfort during meditation practices might have reduced maladaptive pain cognitions, i.e., pain catastrophizing, as well as maladaptive pain responses, i.e., increased mindfulness non-reactivity.

Overall, the present study offers preliminary results on what works in MBCT for persistent pain and may have clinical relevance in terms of optimizing MBCT as a pain intervention by increasing focus on the identified mediators. However, some limitations should also be noted. First, we did not include an active control group, and it thus remains unresolved whether the mediators found in our study are MBCT-specific or general, non-specific mediators in psychosocial interventions for pain. On a related note, we did not include documentation of treatment fidelity, e.g., by video recordings, or of the minor adaptations made to the manual. Second, we were unable to meet the suggested requirement of temporal precedence in mediation\textsuperscript{11}. As such, our results cannot establish causality between mediator and treatment outcome. However, experiments investigating the causal link between mindfulness and pain suggest that mindfulness mediation is associated with reduction of experimentally-induced pain when compared to a sham mindfulness and a control condition\textsuperscript{47}. Future studies should investigate the change mechanisms during the intervention, e.g., by including session-by-session measures, thereby allowing for a more fine-grained temporal analysis. Third, we did not conduct an a priori mediation power analysis, and thus our study might be underpowered. We therefore recommend that the results are interpreted in terms of their effect sizes. Fourth, there was a relatively large, unbalanced dropout at T2. However, this issue was taken into account by a) including the only statistically significant and robust outcome (i.e., pain intensity),
b) testing whether pain intensity predicted dropout, which was not the case, and c) conducting sensitivity analyses. Finally, all participants included in the study were women treated for primary breast cancer with pain issues, and while this increases the internal reliability of the study, it may limit the generalizability of our results to other pain populations. In order to identify the most efficacious pain interventions for different pain patient groups, future studies should investigate the efficacy of MBCT and explore possible mediators in other clinical pain samples.

CONCLUSION

Pain catastrophizing mediated the effect of MBCT on persistent pain in women treated for breast cancer, explaining 78% of the effect of MBCT on pain. The results also tentatively suggest that mindfulness non-reactivity may be a mediator to be targeted in MBCT, although this finding is less robust. The identification of mediators affecting pain outcomes is clinically important for refining treatments to more efficiently target relevant mediators. Further studies are needed to establish if a causal relationship exist between the statistical mediators identified and to determine whether adapting MBCT to pain populations by increasing the focus on the identified mediators could optimize the effect.
ACKNOWLEDGMENTS

We thank all women who participated in the study, the Danish Breast Cancer Cooperative Group (DBCG), Rigshospitalet, Denmark, for delivering the clinical data, Inger Højris, MD, PhD, for invaluable advice and competent supervision during the design and recruitment phase of this study, and Jacob Piet, MSc., PhD, for valuable discussions during the design phase of the study.
REFERENCES


Table 1
Socio-demographic and clinical characteristics of the study sample at baseline\textsuperscript{a}

<table>
<thead>
<tr>
<th>Demographics\textsuperscript{b}</th>
<th>(p)</th>
<th>Intervention group (n=67)</th>
<th>Control group (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean (SD) [N]</td>
<td>0.96</td>
<td>56.8 (9.99) [67]</td>
<td>56.7 (8.10) [62]</td>
</tr>
<tr>
<td>Marital status, N (%)</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td></td>
<td>47 (70.1)</td>
<td>40 (64.5)</td>
</tr>
<tr>
<td>Not cohabiting/single</td>
<td></td>
<td>20 (29.9)</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>Educational level, N (%)\textsuperscript{d}</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower (&lt;2 years of further education)</td>
<td></td>
<td>21 (31.3)</td>
<td>28 (45.2)</td>
</tr>
<tr>
<td>Medium (2-4 years of further education)</td>
<td></td>
<td>36 (53.7)</td>
<td>29 (46.8)</td>
</tr>
<tr>
<td>Long (&gt;5 years of further education)</td>
<td></td>
<td>9 (13.4)</td>
<td>4 (6.5)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>1 (1.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Occupational status, N (%)</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full- or part-time employed</td>
<td></td>
<td>29 (43.3)</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>Unemployed or on sickness benefit</td>
<td></td>
<td>10 (14.9)</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>Retired</td>
<td></td>
<td>24 (35.8)</td>
<td>28 (45.2)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>4 (6.0)</td>
<td>4 (6.5)</td>
</tr>
</tbody>
</table>
### Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) [N]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time since surgery (months)</strong></td>
<td>0.54  0.54</td>
</tr>
<tr>
<td><strong>Type of surgery, N (%)</strong></td>
<td>0.26</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>27 (40.3)</td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>38 (56.7)</td>
</tr>
<tr>
<td>Not reported</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td><strong>Axillary Lymph Node Dissection (ALND), N (%)</strong></td>
<td>0.32</td>
</tr>
<tr>
<td>Yes</td>
<td>39 (58.2)</td>
</tr>
<tr>
<td>No</td>
<td>26 (38.8)</td>
</tr>
<tr>
<td>Not reported</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td><strong>Chemotherapy, N (%)</strong></td>
<td>0.47</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (56.7)</td>
</tr>
<tr>
<td>No</td>
<td>29 (43.3)</td>
</tr>
<tr>
<td><strong>Radiotherapy, N (%)</strong></td>
<td>0.20</td>
</tr>
<tr>
<td>Yes</td>
<td>54 (80.6)</td>
</tr>
<tr>
<td>No</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Not reported</td>
<td>6 (9.0)</td>
</tr>
<tr>
<td><strong>Endocrine treatment, N (%)</strong></td>
<td>0.26</td>
</tr>
<tr>
<td>Yes</td>
<td>46 (68.7)</td>
</tr>
<tr>
<td>No</td>
<td>21 (31.3)</td>
</tr>
</tbody>
</table>
The total sample consists of 129 women.

When reporting categorical variables, number of patients and percent are shown. When reporting continuous variables, Mean (M), Standard Deviation (SD), and number of patients [N] are shown.

Statistically significant group differences (\( p < 0.05 \)) are shown in boldface.

"Further education" refers to years of education further than high school.

The Charlson Comorbidity Index (CCI)\textsuperscript{25}

<table>
<thead>
<tr>
<th>Comorbidity(^a), N (%)</th>
<th>0.71</th>
</tr>
</thead>
<tbody>
<tr>
<td>No comorbidity</td>
<td>39 (58.2)</td>
</tr>
<tr>
<td>Comorbidity (( \geq 1 ))</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Not reported</td>
<td>23 (34.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain related to BC, N (%)</th>
<th>0.27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>62 (92.5)</td>
</tr>
<tr>
<td>No</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

\(^a\)The total sample consists of 129 women

\(^b\)When reporting categorical variables, number of patients and percent are shown. When reporting continuous variables, Mean (M), Standard Deviation (SD), and number of patients [N] are shown.

\(^c\)Statistically significant group differences (\( p < 0.05 \)) are shown in boldface.

\(^d\)"Further education" refers to years of education further than high school.

\(^e\)The Charlson Comorbidity Index (CCI)\textsuperscript{25}
Table 2
Pain intensity and proposed mediators at T1-T4

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MBCT</td>
<td>Control</td>
<td>MBCT</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Pain intensity</strong></td>
<td><strong>11-point NRS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Baseline</em></td>
<td>5.5 (2.1) [60]</td>
<td>5.3 (2.6) [56]</td>
<td>4.0 (1.9) [43]</td>
<td>5.3 (2.5) [57]</td>
</tr>
<tr>
<td><strong>MEDIATORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FFMQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acting with</td>
<td>27.7 (6.39) [67]</td>
<td>25.2 (6.28) [62]</td>
<td>28.0 (5.36) [45]</td>
<td>25.5 (6.30) [61]</td>
</tr>
<tr>
<td>Nonjudging</td>
<td>27.5 (6.51) [67]</td>
<td>25.9 (6.69) [62]</td>
<td>29.4 (5.99) [45]</td>
<td>26.5 (6.74) [61]</td>
</tr>
<tr>
<td>Nonreactivity</td>
<td>18.9 (4.48) [67]</td>
<td>19.8 (2.94) [62]</td>
<td>21.3 (4.27) [45]</td>
<td>18.95 (3.42) [61]</td>
</tr>
<tr>
<td>Observing</td>
<td>26.7 (6.31) [67]</td>
<td>29.0 (5.28) [62]</td>
<td>29.5 (5.61) [45]</td>
<td>28.6 (5.38) [61]</td>
</tr>
<tr>
<td><strong>SCS-SF</strong></td>
<td>38.9 (7.16) [66]</td>
<td>37.2 (8.05) [61]</td>
<td>41.6 (7.01) [41]</td>
<td>37.7 (8.66) [59]</td>
</tr>
<tr>
<td><strong>PCS</strong></td>
<td>18.5 (8.87) [66]</td>
<td>21.7 (11.4) [62]</td>
<td>10.7 (8.19) [46]</td>
<td>18.32 (10.7) [60]</td>
</tr>
</tbody>
</table>

* Means, standard deviations (SD), and number of patients included in the analysis [N]
Running head: MEDIATORS OF MBCT FOR PERSISTENT PAIN

b The Five Facet Mindfulness Questionnaire (FFMQ)²⁸; higher scores indicating higher levels of mindfulness (facets)

c The Short Form Self-Compassion Scale (SF-SCS)³¹; higher scores indicating higher levels of self-compassion

d The Pain Catastrophizing Scale (PCS)³³; higher scores indicating higher levels of pain catastrophizing
### Table 3

Correlations between the primary outcome of pain intensity and proposed mediators at baseline

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Pain intensity</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Acting with awareness (FFMQ(^b))</td>
<td>0.14</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Describing (FFMQ)</td>
<td>-0.05</td>
<td><strong>0.25</strong></td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) Nonjudging (FFMQ)</td>
<td>-0.07</td>
<td><strong>0.56</strong></td>
<td><strong>0.26</strong></td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) Non-reactivity (FFMQ)</td>
<td>-0.12</td>
<td><strong>-0.18</strong></td>
<td><strong>0.27</strong></td>
<td>-0.04</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6) Observing (FFMQ)</td>
<td>0.02</td>
<td>-0.10</td>
<td><strong>0.36</strong></td>
<td>-0.08</td>
<td><strong>0.46</strong></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7) Self-compassion (SCS(^c))</td>
<td>-0.03</td>
<td><strong>0.56</strong></td>
<td><strong>0.38</strong></td>
<td><strong>0.68</strong></td>
<td><strong>0.31</strong></td>
<td>0.15</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>(8) Pain catastrophizing (PCS(^d))</td>
<td><strong>0.44</strong></td>
<td><strong>-0.20</strong></td>
<td><strong>-0.18</strong></td>
<td><strong>-0.33</strong></td>
<td><strong>-0.12</strong></td>
<td>0.07</td>
<td><strong>-0.34</strong></td>
<td>1.00</td>
</tr>
</tbody>
</table>

\(^a\) Statistically significant correlation (\(p<0.05\)) are shown in boldface

\(^b\) The Five Facet Mindfulness Questionnaire (FFMQ)\(^28\)

\(^c\) The Short Form Self-Compassion Scale (SF-SCS)\(^31\)

\(^d\) The Pain Catastrophizing Scale (PCS)\(^33\)
Table 4

Mediation analyses: Indirect effects of the proposed mediators on the effect of MBCT on pain intensity

<table>
<thead>
<tr>
<th>Proposed mediators*</th>
<th>a path (B)</th>
<th>b path (B)</th>
<th>c path (B)</th>
<th>c’ path (B)</th>
<th>The indirect effect (ab) (B)</th>
<th>BSSE_{ab}^b</th>
<th>95% BSCI_{ab}^b</th>
<th>% Total effect explained by mediator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acting with awareness (FFMQ)</td>
<td>2.69*</td>
<td>-0.01</td>
<td>-0.79*</td>
<td>-0.68</td>
<td>-0.03</td>
<td>0.08</td>
<td>-0.23 - 0.10</td>
<td>4%</td>
</tr>
<tr>
<td>Describing (FFMQ)</td>
<td>1.66*</td>
<td>-0.001</td>
<td>-0.79*</td>
<td>-0.70</td>
<td>-0.02</td>
<td>0.06</td>
<td>-0.18 - 0.06</td>
<td>2%</td>
</tr>
<tr>
<td>Nonjudging (FFMQ)</td>
<td>2.55*</td>
<td>-0.02</td>
<td>-0.79*</td>
<td>-0.64</td>
<td>-0.07</td>
<td>0.08</td>
<td>-0.28 - 0.02</td>
<td>9%</td>
</tr>
<tr>
<td>Non-reactivity (FFMQ)</td>
<td>1.44*</td>
<td>-0.12*</td>
<td>-0.79*</td>
<td>-0.55</td>
<td>-0.17</td>
<td>0.09</td>
<td>-0.39 - 0.04</td>
<td>24%</td>
</tr>
<tr>
<td>Observing (FFMQ)</td>
<td>0.31</td>
<td>-0.02</td>
<td>-0.79*</td>
<td>-0.71</td>
<td>-0.01</td>
<td>0.03</td>
<td>-0.11 - 0.04</td>
<td>1%</td>
</tr>
<tr>
<td>Self-compassion (SCS)</td>
<td>2.86*</td>
<td>-0.04</td>
<td>-0.79*</td>
<td>-0.60</td>
<td>-0.09</td>
<td>0.08</td>
<td>-0.31 - 0.04</td>
<td>13%</td>
</tr>
<tr>
<td>Pain catastrophizing (PCS)</td>
<td>-5.90*</td>
<td>0.13*</td>
<td>-0.79*</td>
<td>0.01</td>
<td>-0.76</td>
<td>0.22</td>
<td>-1.25 - 0.37</td>
<td>98%</td>
</tr>
</tbody>
</table>

*The a path refers to the association between the Independent Variable (IV) and the Mediator (M). The b path refers to the association between M and the dependent variable (DV). The c path refers to association between the IV and the DV. The c’ path refers to the association between the IV and the DV when holding M constant in the analyses. Statistically significant (p<0.05) paths are marked with *. Statistically significant mediators are highlighted in bold. B refers to the unstandardized Beta coefficient. Estimation of the indirect effect (95% CI) by use of the bootstrap method of Preacher and Hayes (2004)^38

^bBSSE: Bootstrapped standard error, reported for ab; BSCI: Bias Corrected confidence interval, reported for ab

^cThe Five Facet Mindfulness Questionnaire (FFMQ)^28
Running head: MEDIATORS OF MBCT FOR PERSISTENT PAIN

d The Short Form Self-Compassion Scale (SF-SCS)\textsuperscript{31}

e The Pain Catastrophizing Scale (PCS)\textsuperscript{33}
Figure 1
CONSORT study flow diagram

Patients screened for eligibility (n=1546) (79.7%)

Pain ≤2 (n=1162)
No valid pain assessment (n=61)
Ineligible (n=9)

Eligible patients (n=314) 20.3%

Not interested (refused to contact) (n=114)

Eligible and interested patients (n=200) 12.9%

Declined due to:
Transportation challenges (n=2)
Schedule conflict (n=34)
Lack of energy (n=2)
Use of other pain treatment (n=2)
Reason unknown (n=27)

Informed consent received (n=132) 8.5%

Withdraw consent (reason unknown) (n=3)

Returned baseline questionnaires (n=129) 8.3%

Randomized (n=129)

Dropped out before the intervention due to:
Schedule conflict (n=4)
Family concerns (n=1)
Reason unknown (n=1)

Allocated to MBCT (n=57)

Dropped out during the intervention due to:
Schedule conflict (n=3)
Hearing- and language difficulties (n=2)
Too emotionally challenging (n=1)
Lack of motivation (n=2)

Allocated to wait list control (n=52)

Did not want to be on the wait list (n=1)

Lost to follow-up (reason unknown) (n=7)

Post-intervention (6 weeks) Returned questionnaires (n=46) 69.7%

Withdraw (n=3)
Lost to follow-up (reason unknown) (n=1)

Lost to follow-up (reason unknown) (n=1)

Post-intervention (6 weeks) Returned questionnaires (n=51) 98.4%

3 months follow-up Returned questionnaires (n=42) 62.7%

Death in family (n=1)
Lost to follow-up (reason unknown) (n=3)

Included in analyses (Intent-To-Treat Sample) (n=57)

6 months follow-up Returned questionnaires (n=39) 58.2%

Included in analyses (Intent-To-Treat Sample) (n=52)
Figure 2
The multiple mediation model

Non-reactivity (1) → Pain catastrophizing (2) → Pain intensity

Group_{MBCT versus control}

\[ a_1 = 0.41^* \]
\[ a_2 = -5.86^* \]

\[ b_1 = -0.05 \]
\[ b_2 = 0.13^* \]

\[ c = -0.79^*; c' = 0.06 \]
\[ ab_1 = -0.07 (8\%) \]
\[ ab_2 = -0.72 (78\%) \]

Notes: \( a-b_1, ab_1 \) refer to FFMQ non-reactivity; \( a-b_2, ab_2 \) refer to the PCS; values refer to the unstandardized Beta coefficient (B); statistically significant (\( p<0.05 \)) pathways are marked with *; statistically significant mediators (\( p<0.05 \)) are highlighted in bold.