Comprehensive Psychoneuroendocrinology 20 (2024) 100269

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology

# Distress and inflammation are independently associated with cancer-related symptom severity

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ARTICLE INFO

*Keywords:*
Longitudinal
Clinical
Translational
Oncology
Psychosocial stress
Biological markers

ABSTRACT

*Objective:* To evaluate longitudinal associations of distress and inflammation with somatic and depressive symptom severity in breast cancer patients, from before to six months after neoadjuvant chemotherapy. We also explored feasibility and effects of an early mindfulness-based intervention for preventing or reducing somatic and depressive symptoms.

*Methods:* Longitudinal pilot study with a randomized waitlist-controlled intervention design. Women with breast cancer were randomized to receive access to a smartphone application offering meditation exercises, either immediately after baseline testing (intervention group) or after study completion (control group) in a 1:1 ratio. Assessments (self-report questionnaires and a blood draw when feasible) were completed before, halfway through, immediately after, and 6 months after completing neoadjuvant chemotherapy.

*Results:* Fifty evaluable women were enrolled. Somatic symptom severity increased during chemotherapy, whereas depressive symptom severity was at its peak before treatment and declined gradually thereafter. Distress was positively associated with depressive symptom severity. Only Distress Thermometer-results were positively associated with somatic symptom severity. Inflammation was positively associated with both types of symptoms, and distress did not moderate the associations between inflammation and symptom severity. Intervention adherence was low and no intervention effect on symptom experience was observed.

*Conclusion:* Inflammation and distress are independently associated with somatic and depressive symptoms experienced during breast cancer treatment.

## 1. Introduction

Breast cancer is the most commonly diagnosed malignancy among women, comprising approximately 30 % of all newly diagnosed cancers among women in the United States each year [1]. Whereas the incidence of breast cancer has increased over the past four decades, mortality rates have steadily declined since peaking in 1989 [2]. However, first-line treatments for breast cancer that have reduced mortality rates, such as radiation therapy and chemotherapy, can also lead to severe somatic (such as pain, nausea, and fatigue) and mood symptoms (such as symptoms of depression and anxiety) that can negatively affect a patient's quality of life [3]. As many as one-half of patients with breast cancer will experience moderate to severe somatic symptoms (grade 2–4) during therapy [4,5]—a foremost reason for treatment-dose reductions, which in turn lead to suboptimal cancer care [6,7]. In addition, up to one-third of breast cancer patients suffer from depression [8,9], which has been linked to poorer survival rates [10].

The mechanisms that underlie the somatic and depressive symptoms experienced during treatment are likely multifactorial. Moreover, the fact that somatic and mood symptoms frequently co-occur has led to the hypothesis that common underlying mechanisms and predictors, including inflammation and psychosocial distress, contribute to the development of these symptoms [11].

A diagnosis of cancer is a strong psychosocial stressor that can lead to

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https://doi.org/10.1016/j.cpnec.2024.100269
Received 27 March 2024; Received in revised form 29 September 2024; Accepted 30 September 2024
Available online 11 October 2024

stress (the physiological or psychological response to a stressor) and ultimately to psychosocial distress (the type of stress that results from being overwhelmed by the stressor) [12,13]. In psycho-oncology, psychosocial distress is usually defined as "a multifactorial unpleasant experience of a psychological (i.e., cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with one's ability to cope effectively with cancer, its physical symptoms, and its treatment" [13]. In patients with breast cancer, distress is highly prevalent: On average, approximately 30 % of patients experience clinical levels of distress during their cancer trajectory, with the highest levels typically found around the time of diagnosis and in the early treatment phase [14,15]. Although the association of distress with somatic and mood symptoms is well-established [14,16,17], how distress contributes to these symptoms remains unclear. One possibility is that it exacerbates the effects of treatment-induced inflammation.

The role of inflammation in the experience of cancer-related symptoms has not been definitively characterized. On the one hand, in patients with breast cancer, positive associations between proinflammatory biomarkers and both somatic and depressive symptoms have been reported [18–20]. On the other hand, the reported low-to-moderate effect sizes in those studies suggest that inflammation alone insufficiently explains symptom severity [18–21]. Accumulating studies have found that psychological distress may be moderating the relationship between inflammation and symptoms such as depression [22,23]. It has been found that psychological stressors can lead to chronic inflammation via the neuroendocrine system when stress remains unabated. Focusing on the association between inflammation and depressive symptoms, Manigault et al. showed that the effect of inflammation may depend on the level of psychological distress: In breast cancer survivors (i.e., those who have completed primary treatment), more-severe depressive symptoms were observed when inflammation was higher than the person's average, but only in survivors who reported greater distress at baseline [18]. This finding is in line with experimental studies showing that distress can aggravate inflammation-induced symptoms [24–26].

If distress moderates the association between tumor- or treatment-induced inflammation and symptom-experience during breast cancer treatment, then reducing distress may dampen symptom severity. Stress-reduction interventions for breast cancer patients have predominantly been tested after the completion of primary treatment and therefore produced only small, transient effects on distress and quality-of-life measures overall [27]. Conversely, implementing a stress-reduction intervention before or early in the treatment trajectory may be more effective, as it targets the window of greater inflammation and greater distress.

The objective of the study described herein was to evaluate the longitudinal associations of distress and inflammation with somatic and depressive symptoms in breast cancer patients, from before treatment to 6 months after neoadjuvant chemotherapy, and to examine the moderating role of psychological distress on the associations between inflammation and symptom severity. We further explored the efficacy and effects of a mindfulness-based intervention in preventing or reducing somatic and depressive symptoms during and after treatment for primary breast cancer. Although originally powered to detect associations and intervention effects of small effect size (i.e., 100 evaluable patients), study recruitment was prematurely halted due to pandemic-related restrictions in patient access, resulting in a reduced sample size akin to that of a pilot study.

## 2. Methods

### 2.1. Study design

The study design and sample are described in a previous publication [28]. The study was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board (protocol #2016-0600) and registered in clinicaltrials.gov (NCT03429907). All participants provided written informed consent.

#### 2.1.1. Recruitment and baseline assessment

Women aged 18 years or older who spoke English, were newly diagnosed with stage I-IIIc breast cancer and were planned to undergo neoadjuvant chemotherapy were identified through chart review and recruited from the Breast Medical Oncology clinic at MD Anderson between February 2, 2018, and March 10, 2020. Once consented, an appointment for baseline ($T_0$) testing was set up, often coinciding with the first day of chemotherapy infusion. The $T_0$ assessment included a set of patient-reported outcomes questionnaires (described below) and blood-sample collection.

For logistical reasons, patients were randomized in a 1:1 ratio to the intervention or control arm before the $T_0$ assessment. The allocation was not shared with the patient until after the $T_0$ assessments were completed.

#### 2.1.2. Intervention

The commercially available mobile application Headspace (www.headspace.com; Headspace Inc.), which provides guided meditation exercises, was used as a stress-reduction intervention. At the time of the study, the app started with 10 introductory sessions of 10 min in length. Only after completing the introductory sessions could users proceed to sessions customized to specific goals (e.g., more advanced instructions; reducing stress; dealing with cancer). Participants in the intervention arm were set up with a Headspace account, and the app was installed on their smartphone. After a brief introduction to the app, patients were asked to complete at least one session per day for at least 14 consecutive days, thus covering the 10 introductory sessions and four sessions of the participant's choice. The rationale for this short "mandatory" app use was to expose the participant to the meditation exercises with the expectation that they would continue using it as needed afterward. Automated reminders were sent to the participants' phones to prompt daily use of the app during the first 14 days.

Intervention adherence was defined as having completed 14 sessions within the first 14 days immediately following $T_0$. When the 14 days ended relative to T1 differed between participants, as $T_1$ was defined as the midpoint of chemotherapy treatment, which differed between participants. After the initial 14 days, participants were free to use the Headspace app for the remainder of one year, with no further instruction on its use.

Patients in the control arm received one year of free access to Headspace after completing all follow-up assessments.

#### 2.1.3. Follow-up

Follow-up assessments were conducted halfway through chemotherapy ($T_1$), immediately after completion of chemotherapy ($T_2$), and approximately 6 months later, after completion of any adjuvant radiation ($T_3$). All assessments included the patient-reported outcomes questionnaires and, when feasible, a blood-sample collection.

Initially, only the $T_1$ questionnaires could be completed remotely; after the start of the COVID-19 pandemic, remote completion was allowed at any timepoint.

### 2.2. Cancer-related symptom assessment

#### 2.2.1. Somatic symptoms

The MD Anderson Symptom Inventory (MDASI) was used to assess overall somatic symptom severity [29]. The MDASI is a patient-reported outcomes questionnaire that measures the severity of 13 cancer-related symptoms, including 11 somatic and two mood symptoms, rated on a 0–10 scale ranging from "not present" to "as bad as you can imagine." The MDASI is designed specifically for symptom assessment in cancer patients and has shown excellent psychometric properties in patients with breast cancer [30].

For the purpose of this study, scores on the 11 somatic items (pain, fatigue, nausea, disturbed sleep, shortness of breath, problems remembering things, lack of appetite, drowsiness, dry mouth, vomiting, numbness or tingling) were summed into one symptom severity score (referred to as "somatic symptom severity") as the main outcome.

#### 2.2.2. Depressive symptoms

Depressive symptoms were assessed using the Center for Epidemiology Studies Depression Scale 10-item version (CESD-10) [31]. The CESD-10 is a widely used patient-reported outcomes questionnaire designed to measure depressive symptomatology. The CESD-10 items are rated for their presence in the past week on a four-point Likert scale. The psychometric properties of the scale in nonpsychiatric populations are good, with reported Cronbach alphas of approximately 0.70 and a composite reliability score of 0.72 [32].

### 2.3. Distress assessment

The Distress Thermometer is a single-item patient-reported outcomes questionnaire that measures the distress experience in the past week, including today, on a 0–10 thermometer-like scale ranging from "no distress" to "extreme distress" [13,33]. The Distress Thermometer is recommended for distress screening in patients with cancer, with a score of $\geq$4 indicating clinically significant distress [13].

Because the validity of the Distress Thermometer scale as a continuous outcome has not been definitively established, we additionally assessed the patient's perception of stress by using the Perceived Stress Scale, a 10-item patient-reported outcomes questionnaire wherein respondents indicate on a 0–4 Likert scale how often they experienced feelings of stress and distress in the past month [34]. A higher sum score across all items (range 0–40) indicates higher perceived stress. The Perceived Stress Scale has been used extensively in cancer patient populations and has excellent psychometric properties: Cronbach alpha values range from 0.86 to 0.92, and sensitivity to change over time is adequate [35].

Although the Distress Thermometer and Perceived Stress Scale measure different aspects of distress (distress experience versus perceived stress), they are referred to as "distress measures" throughout the remainder of this article.

### 2.4. Inflammation assessment

Inflammatory cytokines and cytokine receptors previously associated with somatic and depressive symptoms [36,37] were selected: Interleukin (IL)-5, IL-6, and tumor necrosis factor (TNF)α, IL-6 receptor (IL-6R), and TNF receptor I and II (TNFRI and II). Plasma concentrations of circulating proinflammatory cytokines and cytokine receptors were determined by using Luminex bead arrays and Milliplex® Analyst Software (version 5.1.0.0) (Merck, Germany) to compute the concentrations. Blood samples were collected in sodium citrate tubes from which plasma was collected and stored at −80 °C for batchwise analysis. Analyses were performed in 2019 and 2021 to ensure samples were stored no longer than 2 years; internal controls were used to ensure consistency across batches.

Interleukin-5, IL-6, TNFα were simultaneously assessed in 1:2 diluted plasma samples; IL-6R and TNFRI and II were simultaneously assessed in 1:5 diluted plasma samples. Detection ranges were as follows: IL-5: 0.12–4301 pg/mL, IL-6: 0.068–1832 pg/mL, TNFa: 0.22–2933 pg/mL, sIL-6R: 5.49–60543 pg/mL, TNFRI: 6.45–51518 pg/mL, and TNFRII: 7.75–69065 pg/mL.

### 2.5. Statistical analysis plan

Continuous variables were inspected for normality of distribution. Descriptive analyses were performed using IBM SPSS Statistics (version 26.0.0.0) [38]. Multilevel models were computed in R (version 4.3.2) by using the lme function of the nlme package (version 3.1–164) [39].

As previously described [28], only patients with patient-reported outcomes data from $T_0$ and $T_2$ were included in the intervention analyses. Any patient who had both biomarker data and valid patient-reported outcomes data on at least one timepoint was included in the inflammatory markers analyses. Possible patterns in missing data due to dropout in the intervention arm were investigated by comparing dropouts to those who completed the $T_2$ study assessments on their use of the Headspace intervention and their self-reported distress and symptom severity at $T_0$ and $T_2$.

Due to the explorative nature of the study, effect estimates with 95 % CIs that did not include 0 were considered significant; no adjustment was made for multiple testing.

#### 2.5.1. Symptom severity; effects of distress

Multilevel models on patient-reported data included all available observations and were specified with an unstructured covariance matrix for the repeated measures and a random intercept and slope. Initial growth models included the following covariates: age (continuous; grand-mean centered), body mass index (BMI) (continuous; grand-mean centered), race/ethnicity (dichotomous: non-Hispanic White versus any minority), and relationship status (dichotomous: alone versus in a relationship). To establish growth models for somatic and depressive symptom severity, both linear and quadratic effects of time (continuous) were assessed using information criteria to determine the best fit model.

Associations with distress were analyzed by adding the two distress measures to the growth models (separate models for the two distress measures).

#### 2.5.2. Inflammation

Standardized values of the proinflammatory cytokines (z-values based on sample log-mean and standard deviation across timepoints) were summed into a composite score. The composite score showed adequate reliability in our sample, with Cronbach alphas ranging from 0.61 at $T_0$ to 0.75 at $T_3$. For assessing inflammation's effects on somatic and depressive symptom severity, growth models with symptom severity as a dependent variable were computed, including observations with available inflammation data. Models were specified with a random intercept, because including a random slope often led to non-convergence. To account for the smaller number of observations with inflammation data, adjusted models included only race/ethnicity and BMI as covariates. Significant associations between the inflammatory composite index and symptom experience were followed up with inflammation effect disaggregated into within- and between-subjects effects, as well as analyses of effects for the individual inflammatory analyte.

#### 2.5.3. Distress-as-moderator analyses

The moderating effects of distress on the associations between inflammation and symptom experience were investigated by adding an inflammatory composite-by-distress interaction to the base model.

#### 2.5.4. Intervention usage and effects

The Headspace company logs the frequency and duration of use of the app, and these data were pulled for analysis for the time between $T_0$ and $T_3$. App usage was summarized as the number of completed sessions within 14 days from $T_0$ (adherence criterion), between $T_0$ and $T_1$, and after $T_1$. The effect of the intervention on symptom severity was determined in intention-to-treat analyses (intervention vs. control) and intervention-completion (intervention adherent vs. control + non-adherent) contrasts by adding group and group-by-time interaction to the initial growth models for somatic and depressive symptom severity. Self-reported use of stress management strategies was added as an additional covariate in these models.

## 3. Results

### 3.1. Patient sample characteristics

Of 62 consented and randomized patients, 50 (81 %; n = 22 in the intervention group and n = 28 in the control group) completed questionnaire assessments at both $T_0$ and $T_2$ and were included in the analysis. Thus, 193 sampling occasions from 50 patients were available for analyses of symptom severity trajectories, associations with distress, and intervention effects; 152 sample occasions from 48 patients were available for analyses including proinflammatory biomarkers (Fig. 1).

The patient sample is fully described elsewhere [28]; the current sample includes one additional patient who was excluded in previous analyses due to missing data on the biomarker of interest. No significant differences in demographic or clinical variables were observed between the intervention and control groups (Table 1).

### 3.2. Symptom severity trajectories

Intraclass correlations for somatic symptom and depressive symptom severity were 0.37 and 0.52, respectively, suggesting sufficient variability at the between-subjects and within-subjects levels (Table 2), thereby justifying longitudinal analyses for both symptom outcomes. Correlations (Pearson's *r*; Table 3) between somatic and depressive symptom severity ranged from 0.47 for $T_1$ to 0.58 for $T_2$. Correlations between distress and symptom severity were stronger for the Distress Thermometer (0.26–0.67) than for the Perceived Stress Scale (0.13–0.47). The proinflammatory composite score showed positive correlations with both somatic and depressive symptom severity but associations with distress were overall weak and nonsignificant.

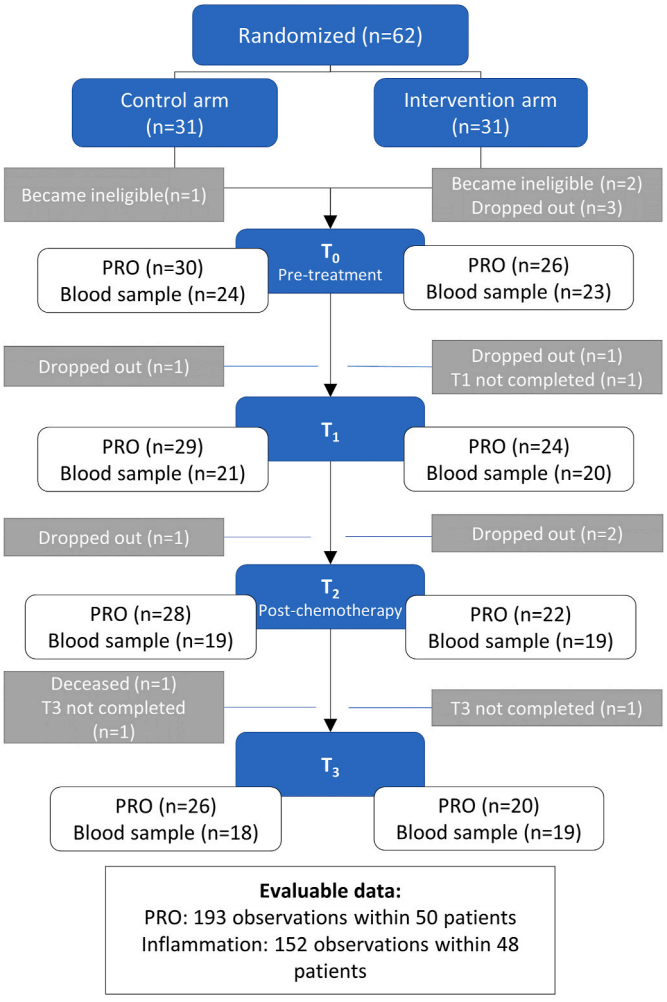


**Fig. 1.** Study flow chart.
*Note*: PRO = patient-reported outcomes, which include assessment of somatic and depressive symptom severity and distress.

**Table 1**
Patient characteristics per study arm; n (%) unless otherwise noted.

| Variable | Control (n = 28) | Intervention (n = 22) | *p*-value for group comparison |
|---|---|---|---|
| Age, years (mean ± SD) | 46.46 ± 10.88 | 49.95 ± 11.16 | 0.27 |
| Race | | | |
| White | 21 (75) | 15(68) | 0.20 |
| Black | 3 (11) | 7 (32) | |
| Asian | 2 (7) | 0 (0) | |
| Other | 2 (7) | 0 (0) | |
| Ethnicity | | | 0.24 |
| Hispanic or Latino | 6 (21) | 2 (9) | |
| Employment status at $T_0$ | | | 0.94 |
| Employed, full-time | 16 (57) | 10 (45) | |
| Retired | 3 (11) | 3 (14) | |
| Homemaker | 3 (11) | 3 (14) | |
| Unemployed | 3 (11) | 2 (9) | |
| Employed, part-time | 2 (7) | 2 (9) | |
| Medical leave of absence | 1 (3) | 2 (9) | |
| Relationship status at $T_0$ | | | 0.23 |
| In a relationship | 21 (75) | 13 (59) | |
| Single | 7 (25) | 9 (41) | |
| Psychotropic medication at $T_0$ | | | |
| Antidepressants | 5 (18) | 6 (27) | 0.43 |
| Anxiolytics[2] | 5 (18) | 5 (23) | 0.67 |
| Body mass index at $T_0$ (mean ± SD) | 27.96 ± 6.86 | 29.89 ± 5.19 | 0.28 |
| Breast cancer stage at $T_0$ | | | |
| I | 8 (29) | 6 (27) | 0.98 |
| II | 15 (53) | 11 (50) | |
| IIIB | 3 (11) | 3 (14) | |
| IIIC | 2 (7) | 2 (9) | |
| Neoadjuvant chemotherapy regimen | | | 0.98 |
| Doxorubicin, cyclophosphamide, and paclitaxel | 21 (75) | 17 (77) | |
| Pertuzumab, docetaxel, carboplatin, trastuzumab | 3 (11) | 2 (9) | |
| Other | 4 (14) | 3 (14) | |
| Treatments received during study[a] | | | |
| Surgery | 27 (96) | 22 (100) | 0.37 |
| Radiation | 24 (86) | 19 (86) | 0.95 |
| Adjuvant chemotherapy | 7 (26) | 2 (10) | 0.15 |
| Treatment status at $T_3$ | | | 0.33 |
| No active primary treatment[b] | 17 (63) | 18 (82) | |
| Adjuvant chemotherapy | 6 (22) | 2 (9) | |
| Monoclonal antibody therapy | 4 (15) | 2 (9) | |
| Used stress management[c] | | | |
| $T_0$ | 8 (29) | 10 (45) | 0.22 |
| $T_1$ | 6 (21) | 8 (36) | 0.24 |
| $T_2$ | 6 (21) | 9 (41) | 0.14 |
| $T_3$ | 9 (32) | 11 (50) | 0.20 |

[a] Information is missing from one patient who moved treatment to a different facility after completing neoadjuvant chemotherapy.
[b] Includes 17 (n = 9 in control and n = 8 in intervention) on endocrine maintenance treatment.
[c] Self-reported use of any stress management strategies (investigational app use in the intervention group not included).

#### 3.2.1. Trajectories in somatic and depressive symptom severity

Somatic symptom severity showed quadratic growth, with an increase between $T_0$ and $T_1$ followed by stable, elevated scores thereafter (Table 4, Model 0). Overall, the most-severe individual symptoms were fatigue, drowsiness, and disturbed sleep (Supplemental Fig. S1). No

**Table 2**
Raw scores on the main outcome measures.

| | ICC | $T_0$ | | $T_1$ | | $T_2$ | | $T_3$ | |
|---|---|---|---|---|---|---|---|---|---|
| | | M | SD | M | SD | M | SD | M | SD |
| Somatic symptom score (N = 50) | 0.37 | 1.467 | 1.128 | 2.496 | 1.706 | 2.120 | 1.410 | 2.079 | 1.594 |
| Depressive symptom score (N = 50) | 0.52 | 8.400 | 5.206 | 6.729 | 4.971 | 6.580 | 5.515 | 6.467 | 5.106 |
| Distress score – DT (N = 50) | 0.52 | 5.20 | 2.406 | 2.860 | 2.466 | 2.480 | 2.541 | 2.690 | 2.867 |
| Distress score – PSS (N = 50) | 0.32 | 21.840 | 3.383 | 19.729 | 3.260 | 19.840 | 3.158 | 20.467 | 3.823 |
| Inflammatory composite (N = 48) | 0.45 | −1.304 | 3.317 | 0.322 | 3.175 | 0.064 | 2.864 | 0.969 | 3.262 |

*Note:* DT = Distress Thermometer; ICC = intraclass correlation; M = mean; PSS = Perceived Stress Scale; $T_0$ = baseline assessment; $T_1$ = assessment halfway through chemotherapy; $T_2$ = assessment immediately after completion of chemotherapy; $T_3$ = final assessment after completion of any adjuvant radiation. Means and SDs per time point and ICCs indicate distribution of within-person and between-person variance.

**Table 3**
Pearson *r* correlations between variables of interest at each time point.

| | Depressive symptoms | | | | Perceived stress - DT | | | | Perceived stress - PSS | | | | Inflammatory composite | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $T_0$ | $T_1$ | $T_2$ | $T_3$ | $T_0$ | $T_1$ | $T_2$ | $T_3$ | $T_0$ | $T_1$ | $T_2$ | $T_3$ | $T_0$ | $T_1$ | $T_2$ | $T_3$ |
| Somatic symptom score | .55*** | .47** | .58*** | .48** | .42** | .26 | .36* | .29 | .25 | .13 | .28 | .18 | .36* | .36* | .31 | .03 |
| Depressive symptom score | | | | | .57*** | .61*** | .66*** | .67*** | .38** | .41** | .31* | .47** | .17 | .44** | .31 | .20 |
| Distress score – DT | | | | | | | | | .21 | .11 | .29* | .48** | .22 | .36* | .27 | .17 |
| Distress score – PSS | | | | | | | | | | | | | -.24 | .04 | -.21 | .09 |

*Note:* DT = Distress Thermometer; PSS = Perceived Stress Scale; $T_0$ = baseline assessment; $T_1$ = assessment halfway through chemotherapy; $T_2$ = assessment immediately after completion of chemotherapy; $T_3$ = final assessment after completion of any adjuvant radiation.
*p < 0.05; **p < 0.01; ***p < 0.001.

significant associations with the tested covariates, including patient-reported use of stress management strategies, were observed.

Depressive symptom severity showed a linear decrease from baseline (Table 4, Model 0). Race/ethnicity was a significant predictor of depressive symptoms: non-white or Hispanic individuals reported lower depression scores on average.

### 3.3. Longitudinal associations of symptom severity with distress

The Perceived Stress Scale data included one severely low outlier at $T_0$ and $T_2$ (the same patient scored 0 at these timepoints); these scores were winsorized to the next lowest value.

Somatic symptom severity was associated with distress measured using the Distress Thermometer but not the Perceived Stress Scale (Table 4, Models 1a and 1b). In contrast, depressive symptom severity was associated with both distress measures (Table 4, Models 1a and 1b).

### 3.4. Longitudinal associations of symptom severity with inflammation

The proinflammatory composite score showed a linear increase over time in an unadjusted growth model ($\beta = 0.789$, SE = 0.131, $p < 0.001$). Race/ethnicity was a marginally significant predictor of inflammation ($\beta = -1.430$, SE = 0.795, $p = 0.08$), indicating potentially higher proinflammation in non-Hispanic Whites. Effects of other covariates were not significant ($p > 0.10$).

The growth model for somatic symptom severity within the smaller dataset (152 observations) confirmed quadratic growth with estimates similar to those presented in Table 4, model 0. The proinflammatory composite score was significantly associated with somatic symptom severity (Table 4, Model 2a), and this effect remained in a model adjusted for age, BMI, and race/ethnicity (adjusted $\beta = 0.116$, SE = 0.031, 95 % CI = 0.055–0.177, $p = 0.004$). Disaggregating the effect showed that within-subject variations in inflammation over time, but not between-subject differences, predicted somatic symptom experience (Model 2b): When inflammation increased relative to an individual's average, somatic symptom severity also increased. Exploratory analyses of individual proinflammatory cytokines (including effects for time and group) showed significant associations with somatic symptoms for TNF-α ($\beta = 1.339$, SE = 0.620, $p = 0.03$), TNFRI ($\beta = 1.993$, SE = 0.553, $p < 0.001$), TNFRII ($\beta = 1.519$, SE = 0.635, $p = 0.02$), and IL-5 ($\beta = 0.777$, SE = 0.376, $p = 0.04$, respectively). Conversely, IL-6 was not associated with somatic symptom experience ($\beta = 0.414$, SE = 0.322, $p = 0.20$).

The depressive symptom growth model in the smaller dataset showed the same significant decrease over time in depressive symptom severity as that described in **model 0**. Inflammation was significantly associated with depressive symptoms (Table 4, Model 2a), although adjusting for age, BMI, and race/ethnicity yielded weakened the association to nonsignificance ($\beta = 0.232$, SE = 0.121, $p = 0.057$). Disaggregating the effect of inflammation showed a significant between-person effect (Model 2b): Individuals with overall higher inflammation also reported more-severe depressive symptoms. Analyses for individual proinflammatory cytokines showed marginally significant associations with depressive symptom severity for IL-6 ($\beta = 2.081$, SE = 1.098, $p = 0.06$), IL-5 ($\beta = 2.529$, SE = 1.359, $p = 0.07$), and TNF-α ($\beta = 3.600$, SE = 2.110, $p = 0.09$). No significant associations were observed for TNFRI ($\beta = 2.144$, SE = 2.052, $p = 0.30$), TNFRII ($\beta = -0.294$, SE = 2.099, $p = 0.89$).

#### 3.4.1. Moderating effects of distress

The interaction between the composite inflammatory score and distress showed no significant association with somatic symptom severity or depressive symptom severity (Table 4, Models 3a and b).

### 3.5. Intervention use and effects on symptom severity

Between $T_0$ and $T_1$, 50 % of participants in the intervention group used the app for at least 10 days; after $T_1$, app use was negligible. More than 90 % (n = 20/22) of intervention participants engaged with the app at least once (Supplemental Table S1). The study's original definition of adherence (completing 14 sessions within the first 14 days) was not met by any participant. Therefore, for the adherence analyses, we redefined adherence as having started at least 14 sessions between $T_0$ and $T_1$, which reclassified 32 % (n = 7/22) of intervention participants as adherent.

Intention-to-treat analyses showed no difference between the control and the intervention group in somatic or depressive symptom severity (Table 4, Model 4a). Comparing those who were adherent to those who were nonadherent or control showed no difference in somatic symptom

**Table 4**
Growth models in symptom severity, hypothesized associations with distress (N = 50) and inflammation (N = 48) and intervention effects (N = 50).

| Dependent variable | Model | Predictors | β | SE | 95 % CI | T | *p* |
|---|---|---|---|---|---|---|---|
| Somatic symptoms (MDASI somatic symptom sum-score) | Model 0 | Intercept | 1.564 | 0.265 | 1.051 to 1.564 | 5.906 | <0.001 |
| | | Age | −0.010 | 0.015 | −0.039 to 0.019 | −0.682 | 0.50 |
| | | Race/ethnicity | −0.155 | 0.333 | −0.811 to 0.502 | −0.465 | 0.64 |
| | | BMI | −0.002 | 0.026 | −0.051 to 0.048 | −0.061 | 0.95 |
| | | Relationship | 0.015 | 0.346 | −0.538 to 0.827 | 0.418 | 0.68 |
| | | Time (linear growth) | 0.817 | 0.210 | **0.411 to 1.223** | 3.898 | **<0.001** |
| | | Time[a]time (quadratic growth) | −0.236 | 0.073 | **−0.377 to −0.096** | −3.255 | **0.001** |
| | Model 1a | DT | 0.130 | 0.039 | **0.055 to 0.205** | 3.358 | **0.001** |
| | Model 1b | PSS | 0.038 | 0.031 | −0.025 to 0.099 | 1.186 | 0.24 |
| | Model 2a | **Inflammation** | 0.117 | 0.031 | **0.056 to 0.178** | 3.760 | **<0.001** |
| | Model 2b | Inflammation_between | 0.071 | 0.059 | −0.045 to 0.187 | 1.213 | 0.23 |
| | | **Inflammation_within** | 0.137 | 0.036 | **0.067 to 0.207** | 3.782 | **<0.001** |
| | Model 3a | Inflammation[a]distress (DT) | −0.001 | 0.010 | −0.024 to 0.014 | −0.103 | 0.92 |
| | Model 3b | Inflammation[a]distress (PSS) | 0.011 | 0.008 | −0.005 to 0.027 | 1.304 | 0.20 |
| | Model 4 | Stress management | 0.122 | 0.258 | −0.356 to 0.601 | 0.494 | 0.62 |
| | Model 4a | Intervention: group[a] | 0.104 | 0.162 | −0.207 to 0.415 | 0.644 | 0.52 |
| | Model 4b | Intervention: adherence[b] | 0.058 | 0.194 | −0.315 to 0.430 | 0.297 | 0.78 |
| Depressive symptoms (CESD sum-score) | Model 0 | Intercept | 9.027 | 0855 | 7.364 to 10.690 | 10.562 | <0.001 |
| | | Age | −0.033 | 0.053 | −0.138 to 0.073 | −0.616 | 0.54 |
| | | Race/ethnicity | −2.617 | 1.222 | **−5.038 to −0.197** | −2.142 | **0.04** |
| | | BMI | 0.208 | 1.254 | −0.182 to 0.177 | 0.165 | 0.87 |
| | | Relationship | −0.003 | 0.092 | −2.277 to 2.693 | −0.027 | 0.98 |
| | | Time (linear growth) | −0.656 | 0.245 | **−1.134 to −0.179** | −2.675 | **0.008** |
| | Model 1a | DT | 1.007 | 0.102 | **0.809 to 1.206** | 9.841 | **<0.001** |
| | Model 1b | PSS | 0.520 | 0.090 | **0.346 to 0.696** | 5.778 | **<0.001** |
| | Model 2a | **Inflammation** | 0.254 | 0.120 | **0.019 to 0.489** | 2.112 | **0.04** |
| | Model 2b | **Inflammation_between** | 0.498 | 0.225 | **0.051 to 0.944** | 2.208 | **0.03** |
| | | Inflammation_within | 0.146 | 0.144 | −0.134 to 0.427 | 1.018 | 0.31 |
| | Model 3a | Inflammation[a]distress (DT) | 0.008 | 0.035 | −0.059 to 0.076 | 0.242 | 0.81 |
| | Model 3b | Inflammation[a]distress (PSS) | 0.028 | 0.028 | −0.026 to 0.082 | 1.011 | 0.31 |
| | Model 4 | Stress management | −0.773 | 0.814 | −2.354 to 0.807 | −0.949 | 0.34 |
| | Model 4a | Intervention: group[a] | −0.173 | 0.501 | −1.141 to 0.795 | −0.345 | 0.73 |
| | Model 4b | Intervention: adherence[b] | 1.145 | 0.583 | **0.021 to 2.270** | 1.966 | 0.051 |

*Note:* Model 0: Growth models for somatic and depressive symptoms, including random effects for intercept and time. Models 1 and 4 were built on Model 0. Models 4a and b additionally included stress management as a covariate and show estimates for intervention-by-time interaction to account for the intervention implementation after baseline testing. Models 2 and 3 included time (and time*time for somatic symptoms), group, and a random effect for intercept. Bold indicates significant per 95 % CI.

BMI = body mass index; CESD = Center for Epidemiology Studies Depression Scale 10-item version; DT = Distress Thermometer; PSS = Perceived Stress Scale; SE = standard error of the mean.

[a] Control group is reference.

[b] Control group + nonadherent is reference.

severity (Table 4, Model 4b). However, a marginally significant difference was observed for depressive symptom severity. When comparing adherent versus non-adherent participants in the intervention group, the difference was stronger (β = 1.73, standard error [SE] = 0.779, 95 % CI = 0.261–3.201, $p = 0.03$). Inspection of raw depression scores for the control versus intervention-nonadherent versus intervention-adherent groups showed that intervention-nonadherent participants had higher depression scores at $T_0$ (mean [SE of the mean] = 7.88 [0.96], 10.55 [1.70], and 7.64 [1.51], respectively; Supplemental Fig. S2). Thus, higher depression may have interfered with intervention adherence in addition to, or through, the use of other stress management strategies.

## 4. Discussion

Results of this study following newly diagnosed breast cancer patients from pretreatment to approximately 6 months after neoadjuvant chemotherapy, showed that distress and inflammation were positively associated with somatic and depressive symptom severity. We found no support for the hypothesis that distress aggravates the association between inflammation and symptom severity. Adherence to a brief, unmonitored mindfulness-based intervention implemented immediately after baseline testing was poor and no effect on either somatic or depressive symptom severity during treatment was observed.

In line with previously published findings [4,40], somatic symptom severity increased during neoadjuvant chemotherapy and remained elevated six months later. In contrast, depressive symptom severity in our sample was highest before treatment began and showed a linear decline thereafter, which is contrary to findings from other studies in which depression symptoms worsened during treatment [40]. It is noteworthy that changes over time explained 63 % and 48 % of variance in somatic and depressive symptom severity, respectively, leaving a rather high between-person variance.

Whereas both somatic and depressive symptoms were associated with elevated inflammation, the effect was more robust for somatic symptoms and was driven by within-person changes. In other words, when inflammation increased relative to an individual's average level, somatic symptom severity also increased. The association of elevated inflammation with more-severe somatic symptoms has been reported,

both for individual symptoms, such as fatigue [41], and for symptom clusters [19]. The association between inflammation and depressive symptoms was driven by between-person differences only: Those with overall higher inflammation levels also reported more-severe depressive symptoms. That said, adjustment for demographic variables reduced the association to nonsignificance, and post-hoc analyses gauging the contributions of individual proinflammatory biomarkers did not yield significant associations with depressive symptoms. However, we note that the study's purpose was not to investigate which cytokine is associated with a given symptom, but rather to determine if inflammation overall (from the calculated inflammation composite score) associates with symptom experience at different phases of the breast cancer care trajectory. The attenuating effect of demographic variables was most likely related to the observed associations of race/ethnicity with both depressive symptoms and inflammation: Non-Hispanic White participants reported more severe depressive symptoms overall and had higher proinflammatory composite scores, compared with non-White and Hispanic participants. Published research examining the specific relationship between inflammation and depressive symptoms during cancer treatment among various racial groups is limited; however, several studies have investigated particular components of this interaction. Specifically, Hu et al. [42] reported more-severe pretreatment symptoms in Black versus white patients with breast cancer, with Black patients reporting higher levels of general physical symptoms, distress, and despair. In a separate study focused on the general population in an urban community, Beydoun et al. [43] showed that markers of inflammation were linked to depressive symptom trajectories over time and were differentially expressed across sex and racial groups. Furthermore, the Survey of Midlife in the US revealed that Black individuals had higher inflammatory marker concentrations than white individuals [44].

While we did not observe an interaction between distress and inflammation, the small sample size prohibits any firm conclusions on this absence of an effect. Future studies further exploring interactions between distress and inflammation will be critical. As Hu et al. [42] reported, pretreatment symptoms in breast cancer patients differ between racial groups; in our sample, it is possible that the amplifying effects of distress were nuanced enough to remain undetectable. It is also possible that we observed no amplifying effects of distress on the inflammation-related symptom experience because the effect of cancer treatment was so strong that any further, more subtle increase would not have achieved statistical significance. Lastly, fluctuations in distress may be associated with inflammation in breast cancer patients, as shown in a recent study [45]—a notion we did not account for in our analyses due to limitations in sample size.

### 4.1. Lessons learned: methodological considerations regarding the implementation of a psychosocial intervention in pre-/early-treatment cancer patients

While we did not observe an effect of the intervention on somatic and depressive symptom severity, the low intervention adherence precludes any conclusions on intervention effectivity. The rationale for implementing an intervention before or at the start of treatment for breast cancer was based on our and other's observations of high distress at this particular time [15]. At the same time, we were aware that this is also a busy time for patients who are navigating numerous clinical visits in a short time and are preparing both emotionally and functionally for the start of chemotherapy and its associated side effects and thus, we chose an intervention that could be completed at a time and place of the patient's choosing. In addition, the intervention was meant to be cost-effective and easily accessible for patients to increase its usability in an oncological clinic. Thus, we did not implement coaching on the use of the app. However, the low intervention adherence suggest that *unmonitored* interventions implemented at this phase of the cancer-care trajectory are ineffective. Our results suggest that the low adherence to the intervention instructions could at least partly be explained by the presence of depressive symptoms at the time of the intervention. Regarding the former, patients with more severe depressive symptoms may benefit from motivational interviewing to help them overcome barriers to the use of stress-management strategies. While we excluded patients who used mediation-based exercises (including yoga) and asked them about any stress management strategies at every time point, we did not keep a detailed report of said strategies. It may be worthwhile to screen patients for specific stress-management strategies already in place. At the very least, recording the strategies patients use would inform on any potential gaps and needs.

### 4.2. Limitations and future directions

The smaller than planned sample size of this study, limits its power to detect more-subtle effects. In addition, adherence to the intervention was poor, despite expressed excitement on the part of most participants about participating in the intervention component. Importantly, we did not stratify for race and ethnicity in our randomization of the control versus the intervention group—yet race and ethnicity, although not the focus of our analyses, were significantly associated with our outcomes of interest: Overall, non-Hispanic Whites reported more severe depressive symptoms and stress, and possibly had higher inflammation levels. These results contrast with results from other studies, which have generally shown that individuals from minority populations have more severe depression and stress as well as higher inflammation levels, compared with non-Hispanic White populations. Our results should be interpreted with caution, as Black participants were overrepresented in the intervention group and Hispanics in the control group (albeit not significantly so). In addition, most of the sample identified as non-Hispanic white. In future studies, it will be imperative to overrecruit from minority populations to further investigate these racial and ethnic disparities.

### 4.3. Conclusion

The results of this pilot study suggest that inflammation and psychological stress are independently associated with somatic and depressive symptoms during treatment for breast cancer. We were unable to discern whether the mindfulness-based intervention affected the symptom experience, because adherence to the intervention was low; results from follow-up analyses suggested that depression could have interfered with intervention adherence.

To our knowledge, this study is one of very few that follow breast cancer patients throughout their curative treatment, starting before the initiation of any treatment, including surgery. Most often, studies of pretreatment experiences include patients who have already undergone surgery. Furthermore, following patients longitudinally allowed us to disentangle the associations between inflammation and symptom severity to determine whether these were driven by variations within a patient or merely by between-patient differences. The study also identified some caveats for stress-intervention implementation—for example, that depressive symptoms and preexisting stress-management strategies may have an impact on adherence to new interventions—that should be further explored in better-powered studies.

## CRediT authorship contribution statement

**Tamara E. Lacourt:** Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **D. Tripathy:** Writing – review & editing, Funding acquisition, Conceptualization. **Maria C. Swartz:** Writing – review & editing, Investigation. **Emily C. LaVoy:** Writing – review & editing, Investigation. **Cobi J. Heijnen:** Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

## Funding

This work was supported by the National Institutes of Health/NCI under award number P30CA016672 and by an award from the Hackett Family Foundation.

## Declaration of Competing interest

No conflict.

## Acknowledgements

Jeanie F. Woodruff, BS, ELS, contributed to the editing of the manuscript. Emily Tullos contributed to patient recruitment and data collection.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2024.100269.

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