Depression and Inflammation in Women With Breast Cancer: Risk and Resilience Factors

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Objective: Diagnosis with breast cancer is a profound stressor associated with increases in depression and inflammation. However, considerable variability in these outcomes is currently unexplained. We examined risk and resilience factors that may influence depressive symptoms and inflammatory markers in recently diagnosed breast cancer patients, including lifetime stressor exposure and psychological and behavioral resources. We focused on modifiable resources—sleep, physical activity, and coping resources—that can be leveraged to enhance women's recovery.

Methods: Women with stage 0-IIIA breast cancer ($N = 180$) were assessed before radiation, chemotherapy, or endocrine therapy. The Stress and Adversity Inventory (STRAIN) was administered to measure total count and severity of lifetime stressors. Blood samples assessed plasma protein markers of inflammation (TNF-α, IL-6, and CRP) that were combined into a composite score. Self-report questionnaires evaluated depressive symptoms, sleep, physical activity, social support, self-esteem, optimism, and mastery.

Results: Total lifetime stressor count ($\beta = 0.30$, $p < .0001$) and severity ($\beta = 0.12$, $p < .0001$) were positively associated with depressive symptoms. Total lifetime stressor count ($\beta = 0.01$, $p = .04$), but not severity ($\beta = 0.001$, $p = .17$), was associated with higher inflammation. Sleep quality, social support, optimism, and mastery buffered the negative effects of lifetime stressor severity on depressive symptoms; social support and optimism also buffered stressor count on depressive symptoms ($p < .04$). None of the moderators influenced the stress-inflammation association (all ps $> .20$).

Conclusions: Lifetime stressor exposure is associated with inflammation and depression in breast cancer patients. Interventions enhancing sleep quality, social support, optimism, and mastery may help prevent depression in this vulnerable group.

Key Words: lifetime stressor exposure, breast cancer survivors, depression, inflammation, resilience

Abbreviations: **BMI** = body mass index, **CES-D** = Center for Epidemiological Studies Depression Scale, **CBT-I** = Cognitive Behavioral Therapy for Insomnia, **CRP** = C-reactive protein, **IL-6** = interleukin-6, **LOT-R** = Life Orientation Test-Revised, **PA** = physical activity, **PSQI** = Pittsburgh Sleep Quality Index, **RISE** = Research on Inflammation, Stress, and Energy, **STRAIN** = Stress and Adversity Inventory, **TNF-α** = tumor necrosis factor-α

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INTRODUCTION

Adversity is a certainty in life, and exposure to stressful life events is ubiquitous in the human experience. Acute stressful experiences are associated with a variety of physiological and psychological effects, including the development of depressive symptoms[1,2] and the activation of inflammatory processes.[3–6] These effects may be particularly pronounced among individuals with a greater lifetime history of stressor exposure. Indeed, although most studies focus on the negative health effects of recent stressors, growing evidence suggests a positive association between lifetime stressor exposure and poorer physical and mental health outcomes.[7–9] Understanding the impact of cumulative lifetime stressor exposure as a risk factor for adverse outcomes in response to a subsequent stressor, and identifying modifiable resilience factors that may buffer against these adverse outcomes, is vitally important.

One of the most profound stressful experiences is being diagnosed with a life-threatening illness such as breast cancer. Breast cancer is the most prevalent form of cancer for women worldwide,[10] and women in the United States have a 1 in 8 chance of developing breast cancer in their lifetime.[11] Diagnosis with breast cancer is a risk factor for the development of several adverse physical and psychological outcomes,[12] including depression and inflammation. Both inflammation and depression have negative implications for longer-term health and well-be-

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ing in women with breast cancer, as they are associated with treatment nonadherence[13] and resistance,[14] recurrence,[15] and overall survival.[16] Importantly, these outcomes have considerable unexplained variability.[17–20] For example, in a study investigating several predictors (marital status, prior history of depression, and problem-focused coping use) of depressive symptom severity trajectories in 147 women diagnosed with breast cancer, Donovan et al[21] found that while marital status [coded as either married (1) or not married (0)] and problem-focused coping use were significant predictors of depressive symptoms, their full model only explained 18% of the variance in depressive symptoms. Here, we consider the role of lifetime stressor exposure as a risk factor and psychological and behavioral resources as resilience factors in the context of breast cancer diagnosis.

Risk Factors: Lifetime Stressor Exposure

Recent research has begun to examine the association between lifetime stressor exposure and psychological, biological, and health-related outcomes.[4,8,22–24] There is a large body of evidence demonstrating that major stressful events are a robust predictor of depression in the general population,[25,26] with a significant life event preceding nearly 80% of major depressive episodes.[27] In addition, recent findings demonstrate associations between cumulative lifetime stressor exposure and depressive symptoms.[28–31] Despite an appreciation for the critical role that distinct types of stressors play in the development of depressive symptoms,[32] relatively few studies have examined whether lifetime stressor exposure increases the risk for poor outcomes among individuals facing an acute stressor, including a diagnosis of breast cancer.

Similarly, an extensive evidence base demonstrates that stressor exposure can have adverse physiological effects, including activating proinflammatory biology. Acute psychological stressors are known to elicit increases in circulating inflammatory markers,[33] and chronic stress is associated with low-level inflammation.[34] Indeed, one pathway through which stress may lead to adverse health outcomes (eg, cardiovascular disease, diabetes) is through increased systemic inflammation.[35–37] However, although theoretical models[38] propose that accumulated stressor exposure is a risk factor for heightened inflammatory activity, relatively few studies have assessed this association using a comprehensive measure of lifetime stressor exposure.[4,6,39–42] Further, no studies to our knowledge have examined how lifetime stressor exposure is associated with inflammation in the context of a breast cancer diagnosis.

Resilience Factors

Although stressful events can have adverse psychological and physiological consequences, many individuals are resilient and do not experience lasting adverse effects from their stressor exposure.[43–45] Resilience is the ability to return to homeostasis in the aftermath of a stressor.[43,46,47] Recent evidence suggests that roughly 66% of individuals undergoing potentially traumatic events are robust and demonstrate the ability to withstand difficulty without lingering adverse effects,[48] leaving nearly a third of individuals with lasting aftereffects. This variability in resilience outcomes highlights a clear need to identify factors that buffer against the harmful effects of lifetime stressor exposure, especially factors that can be enhanced through targeted interventions. Here, we focus on 3 key behavioral and psychosocial factors: sleep, physical activity, and coping resources (ie, social support, self-esteem, optimism, and a sense of mastery).[49] Coping resources are conceptualized as the precursors of specific coping actions and serve as beneficial attributes in and of themselves.[49–51] These resources include social support, self-esteem, optimism, and a sense of mastery.[49] Sleep, physical activity, and coping resources have all been shown to be protective against the development of depressive symptoms[52–61] and influential in regulating biological processes relevant to inflammation.[62–74] Given that we are interested in identifying intervention targets, all of these factors are modifiable and previously shown to be influenced by psychosocial interventions[75–80] and thus offer the potential for improvement. However, to our knowledge, no study has investigated the extent to which these protective factors moderate the effects of stressors occurring over the entire life course on depression and systemic inflammation.

Present Study

To address this issue, we examined how lifetime stressor exposure was related to depressive symptoms and circulating protein markers of inflammation in women recently diagnosed with breast cancer enrolled in the Research on Inflammation, Stress, and Energy (RISE) study.[81,82] Although many theoretical models of stress and health propose that greater exposure to adversity across the lifespan is associated with worse outcomes, the measurement of lifetime stressor exposure is often problematic and limited to select periods of time (eg, early life; past week or month.[83,84]) To address this issue, Slavich et al[85] developed an interview-based assessment of lifetime stressor exposure called the Stress and Adversity Inventory (STRAIN), which is a well-validated interview that assesses an individual's exposure to, and perceived severity of, 55 different acute and chronic stressors across the lifespan that are known to impact health. As such, the STRAIN yields both a count of stressful life experiences and an index of the severity of those experiences, as rated by the participant.

Considering that both total count and subjective severity of lifetime stressors have been associated with adverse mental and physical health outcomes,[7] we hypothesized that both count and severity of lifetime stressor exposure would be associated with higher depressive symptoms and inflammation. Given prior research demonstrating associations between stress exposure, interleukin (IL)-6, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP),[6,86–91] and that these markers have been associated with poor outcomes in the context of breast cancer,[92–94] we focused on these specific markers and created a composite measure of inflammation, con-

sistent with prior research.[6,86–91] Of note, we considered depression and inflammation as independent outcomes, given prior research in the RISE sample showing no association between inflammation and depression.[95–97]

We also investigated the extent to which several modifiable behavioral factors (ie, sleep and engagement in physical activity) and psychosocial factors (ie, social support, optimism, self-esteem, and mastery) moderated these effects. These factors have been shown to buffer the effects of acute stressors on biobehavioral outcomes.[54,59,61,66,70,72–74,95,98] We have previously shown that a resilience index (including sleep, physical activity, social support, optimism, mastery, self-esteem, positive affect, and trait mindfulness) buffered the association between intrusive thoughts about cancer and depressive symptoms and CRP in RISE study participants.[95] However, these resources have yet to be tested in the context of stressors occurring across the life course. Based on the research summarized above, we hypothesized that sleep, physical activity, and coping resources (social support, optimism, self-esteem, and mastery) would buffer the detrimental effects of lifetime stressor exposure on depressive symptoms and inflammation levels.

METHODS

Participants

Women recently diagnosed with stage 0-IIIA breast cancer were recruited from oncology clinics in the Los Angeles metro area to participate in the RISE study. The study is a prospective, longitudinal investigation designed to identify risk factors for the development and persistence of adverse, post-cancer treatment outcomes in breast cancer patients.[81,82] Eligibility criteria included (1) recently diagnosed with early-stage (0-IIIA) breast cancer, (2) not yet started adjuvant or neoadjuvant treatment (including chemotherapy, radiation, or endocrine therapy), and (3) ability to complete questionnaires in English. Recruitment occurred between January 2013 and July 2015. Two hundred seventy women provided written consent and were enrolled in the study. Of the 270 participants in the study, 72 women refused to provide a blood sample. Of the 198 women who provided a blood sample, 10 women did not have STRAIN data, 4 women did not have data on cancer stage, 2 blood samples did not yield usable data, and 2 samples were removed because of a later diagnosis of an autoimmune condition. Therefore, 180 women had complete data for inflammatory markers, depressive symptoms, lifetime stressor exposure, and included covariates at the baseline assessment. Therefore, the final analytic sample included these 180 participants. The original study sample size was determined based on the primary aims of the larger study.[81,82] All procedures were approved by the University of California, Los Angeles Institutional Review Board.

Procedures

At the initial (baseline) study visit, participants completed a battery of self-report questionnaires through Qualtrics and provided a blood sample. The STRAIN interview was also completed at or around the time of the initial visit, depending on participant preference. Participants returned to complete follow-up assessments after the completion of treatment (for those participants who received radiation and/or chemotherapy) and at 6, 12, and 18 months after treatment. Of note, most women (90%) had completed surgery (lumpectomy or mastectomy) before the baseline assessment. Given that depressive symptoms are typically highest immediately after diagnosis,[99] and to avoid the potential confounding of adjuvant treatment-induced increases in inflammation,[100–102] we focus here on the baseline assessment.

Measures

Demographic and Clinical Characteristics

Demographic information was assessed through self-report questionnaires. Body mass index (BMI) was measured by trained technicians and was calculated as weight in kilograms divided by the square of height in meters. Clinical characteristics were collected through medical chart review.

Lifetime Stressor Exposure

The Stress and Adversity Inventory (STRAIN)[85] assessed the occurrence and severity of acute and chronic stressors occurring over the entire life course before cancer diagnosis. The STRAIN is a NIMH/RDoC-recommended system that evaluates an individual's exposure to, and perceived severity of, 55 different acute and chronic stressors spanning 12 major life domains (eg, housing, finances, relationships, education, health) and 5 different core social-psychological characteristics (ie, interpersonal loss, physical danger, humiliation, entrapment, and role change/disruption).[85] For each stressor an individual endorses, they are asked a series of follow-up questions using extensive branching logic to quantify the severity, frequency, timing, and duration of exposure (see https://www.strainsetup.com). To index each participant's cumulative lifetime stressor exposure, we calculated the total lifetime count of stressors and the severity of those stressors endorsed. The possible range of scores for the total lifetime count of stressors is 0 to 166, and the possible range of scores for the total lifetime severity of stressors is 0 to 265. The STRAIN has excellent test-retest reliability (r_{icc} = 0.936 and 0.953 for total lifetime stressor count and severity, respectively), as well as very good concurrent and discriminant validity and predictive utility in relation to numerous psychological, biological, and clinical outcomes,[8,103,104] including in the context of cancer.[22,105,106] The STRAIN was administered by a trained interviewer under the supervision of Dr. Slavich.

Depressive Symptoms

Depressive symptoms were based on scores on the Center for Epidemiologic Studies-Depression Scale (CES-D), a commonly used depression measure.[107] The CES-D is a reliable, validated, and widely used measure that includes central components of depressive symptomatology,

including depressed mood, worthlessness, hopelessness, loss of appetite, and psychomotor retardation.[107] Respondents responded to 20 statements that assessed how often the individual felt or behaved during the past week (eg, "I felt that I could not shake off the blues even with help from my family and friends") on a 4-point Likert Scale from 0 [rarely or none of the time (< 1 d)] to 3 [most or all of the time (5 to 7 d)]. The possible range of scores is 0 to 60, with higher scores indicating greater depressive symptomology.

Protein Markers of Inflammation

Inflammation was assessed with circulating levels of 3 proinflammatory markers: IL-6, CRP, and TNF-α. These inflammatory biomarkers were chosen because they have previously been associated with acute and chronic stressors.[6,86–91] Blood samples for protein inflammatory markers were collected through venipuncture. Blood draws were nonfasted, typically occurred before noon, and scheduled to coincide with clinic visits, when possible. The blood samples were collected into EDTA tubes and transported on dry ice to the Inflammatory Biology laboratory at the Cousins Center for Psychoneuroimmunology, where they were processed and stored at −80 °C until being assayed.

Circulating levels of IL-6 and TNF-α were quantified using a V-PLEX Custom Human Cytokine Proinflammatory Panel on the Meso Scale Discovery (MSD) electrochemiluminescence platform and Discovery Workbench software[108]; the assay lower limit was 0.2 pg/mL for IL-6 and 0.1 pg/mL for TNF-α. Circulating levels of CRP were quantified using Human Quantikine ELISA[108]; the assay's lower limit was 0.2 mg/L. Samples were processed in duplicate with inter-assay coefficients of variation $< 10\%$ and intra-assay coefficients of variation $< 5\%$. Values below the lower limit of detection (LLD) were replaced with values halfway between 0 and the LLD. For example, values below the LLD of 0.2 mg/L for CRP were replaced with values of 0.1 mg/L. Approximately 13% of values were replaced (24 total values across the 3 markers). Thirteen values for IL-6 (7.2% of values replaced), 11 values for CRP (6.1% of values replaced), and zero values for TNF-α (0% of values replaced) were replaced.

Potential Moderators

"Sleep quality" was assessed using the 19-item Pittsburgh Sleep Quality Index (PSQI.[109]) The PSQI is a reliable and valid self-report measure with good test-retest reliability ($r = 0.84$[110]) that evaluates the quality and disturbance of sleep over the past month. The possible range of scores on the PSQI is 0 to 21, with higher scores indicating worse sleep quality, with scores ≥ 5 indicative of clinically significant sleep disturbance.

Engagement in "physical activity" was quantified using the Godin-Shepard Leisure-Time Physical Activity Questionnaire.[111] The Godin-Shepard questionnaire assesses how often an individual engages in several types of exercise for at least 15 minutes during a typical week, including mild, moderate, and strenuous activity. The 3 weighted values correspond to the metabolic equivalent of task (MET) value categories of the activities listed. The possible range of scores on the Godin-Shepard is 0 to 98, with higher values indicating more strenuous physical activity engagement. The authors of the scale have proposed 3 categories based on the Surgeon General's physical activity recommendations: active (≥ 24 total weekly units), moderately active (14-23 total weekly units), and insufficiently active (< 14 weekly units).[111]

Coping resources were assessed using reliable and valid measures that have been widely used in previous research. "Social support" was assessed using the 4-item attachment subscale of the Social Provisions Scale.[112] The attachment subscale assesses perceived closeness in an individual's current relationships. The possible range of scores on the attachment subscale is 4 to 16, with higher scores indicating a stronger sense of social support and closeness. "Self-esteem" was assessed using the 10-item Rosenberg Self-Esteem Scale.[113] The Rosenberg Self-Esteem Scale is a general measure of self-esteem that assesses how an individual typically relates to each of the 10 statements on the questionnaire (eg, "I feel that I have a number of good qualities"). Scores range from 10 to 40, with higher scores indicating greater self-esteem. "Optimism" was assessed using the 10-item Life Orientation Test-Revised.[114] The Life Orientation Test is an overall assessment of an individual's view about the future (ie, optimistic vs pessimistic). Test scores range from 0 to 24, with higher scores indicating greater optimism. "Mastery" was evaluated using the 7-item Pearlin Mastery Scale.[115] The Pearlin Mastery Scale is a general measure of the extent to which one regards one's life chances as being under one's control. The scale has a score range of 7 to 28, with higher scores indicating greater levels of mastery. All measures have good test-retest reliability ($r > 0.70$). Given that we are interested in identifying possible intervention targets, we elected to assess each coping resource individually rather than creating a resilience composite. This approach allows the identification of specific factors, rather than a broad construct, that buffer against the effects of lifetime stressor exposure.

Statistical Analysis

Descriptive analyses were conducted to establish means and SDs of primary study variables. Pearson correlations were computed to examine associations between each independent variable (ie, lifetime stressor count, lifetime stressor severity, sleep quality, engagement in physical activity, social support, self-esteem, optimism, and mastery) and each dependent variable (ie, depressive symptoms and the inflammatory composite).

Raw IL-6, TNF-α, and CRP scores were non-normally distributed and were log-transformed to produce a normal distribution. After log-transformation, inflammatory scores were z-scored. Based on similar analyses in previous studies,[6] the log-transformed and z-scored IL-6, CRP, and TNF-α were summed to create a composite measure of inflammation. Based on prior recommendations,[116] we confirmed that all 3 markers were correlated with one another ($p < .042$) to ensure composite reliability.

Separate linear regression models were fit to examine how each stress dimension (stressor count or stressor severity) predicted either depressive symptoms or the inflammatory composite and whether any behavioral moderators influenced that association. Each model included the stressor exposure index (lifetime count or lifetime severity), the moderator of interest, and the interaction term between the stressor index variable and the moderator (moderator × lifetime stressor count or moderator × lifetime stressor severity) as well as covariates, to evaluate the degree to which each moderator buffered the association between lifetime stressor exposure and the dependent variable (depressive symptoms or the inflammatory composite). Covariates in each model included the following participant characteristics: age, BMI, cancer stage [dichotomized as stage 0 to I (0) and stage II to IIIA (1)], surgery type [none (0), lumpectomy (1), mastectomy (2)], and time since initial cancer diagnosis (days). Before entering the equations, variables were centered at the grand mean.[117] In all analyses, a significant interaction was evidence of moderation.

When a significant moderator × stressor variable interaction was observed, the interaction was probed further using the pick-a-point procedure outlined by Hayes and Montoya.[118] For our analyses, the moderator was tested at "low" (1 *SD* below the mean), "moderate" (at the mean), and "high" (1 *SD* above the mean) levels to determine if there were significant differences in the association between the stressor variable and the dependent variable across levels of the moderator. A significance level of $\alpha = 0.05$ was used across all analyses, and all analyses were performed with R version 4.1.3 in RStudio.[119]

RESULTS

Sample Characteristics

Table 1 reports descriptive data for the sample, including baseline values of all proposed moderators and covariates. The women were approximately 55 years old on average, predominantly white (75%), and well-educated (72.1% with a college or postgraduate degree). Most women were diagnosed with stage 0 or I breast cancer (60.5%) and were treated with a lumpectomy (58.3%). Of the women who received surgery before study enrollment ($n = 162$), the average time since surgery was 33.12 days ($SD = 24.22$). On average, women showed slightly elevated depressive symptoms ($M = 13.4$, $SD = 10.5$) at baseline, with 33% reporting depressive symptoms above the clinical threshold (CES-D ≥ 16). On average, participants reported 30.5 ($SD = 14.6$; sample range = 1 to 89; theoretical range = 0 to 166) lifetime stressors and an average severity of those stressors of 78.9 ($SD = 39.8$; sample range = 1 to 216; theoretical range = 0 to 265).

Table S1 (Supplemental Digital Content, http://links.lww.com/PSYMED/B94) reports the Pearson correlations between each dependent variable, each independent variable (ie, lifetime stressor count, lifetime stressor severity, sleep quality, physical activity, social support, self-esteem, optimism, and mastery), and each covariate (ie, BMI, age, surgery type, cancer stage, and time since initial diagnosis). Depressive symptoms were strongly correlated with all variables (all $ps < .018$) except the inflammatory composite, physical activity, BMI, and cancer stage. The correlations were in the expected direction, such that the higher the depressive symptom frequency, the greaterhigher the lifetime stressor count and severity, the lower the sleep quality, and the lower the coping resources. The inflammatory composite was correlated with lifetime stressor count, physical activity, BMI, and age (all $ps < .043$). All correlations were in the expected direction, such that the higher the inflammatory composite, the higher the lifetime stressor count, the lower

TABLE 1. Participant Characteristics

Demographic and Clinical Characteristics	$N = 180$
Age (y), mean (*SD*)	55.4 (11.1)
Race, *N* (%)	
Asian	20 (11.1)
Black	8 (4.4)
Other	17 (9.4)
White	135 (75)
Ethnicity (Hispanic), *N* (%)	17 (9.4)
Education, *N* (%)	
No college degree	53 (29.4)
College degree	73 (40.5)
Postgraduate degree	54 (31.6)
Employment status (employed; full-time or part-time), *N* (%)	116 (64.4)
Annual income, *N* (%)	
Under $60,000	44 (24.4)
$60,000-$100,000	38 (21.1)
$100,000 or more	98 (54.5)
BMI (kg/m^2), mean (SD)	25.4 (5.6)
Cancer stage, *N* (%)	
0 or I	109 (60.5)
II, IIIA, or neoadjuvant	71 (39.5)
Surgery, *N* (%)	
No surgery (neoadjuvant)	18 (10)
Lumpectomy	105 (58.3)
Unilateral or bilateral mastectomy (with or without reconstruction)	57 (31.6)
Predictor and outcome variables	
Lifetime stressor exposure, mean (*SD*)	
Total count	30.5 (14.6)
Total severity	78.9 (39.8)
CES-D, mean (*SD*)	13.4 (10.5)
IL-6 (pg/mL), mean (*SD*)	0.8 (0.8)
Median (IQR)	0.4-1.0
CRP (mg/dL), mean (*SD*)	3.5 (5.2)
Median (IQR)	0.6-3.8
TNF-α (pg/mL), mean (*SD*)	2.1 (0.8)
Median (IQR)	1.6-2.4
Moderator variables	
Sleep quality, PSQI, mean (*SD*)	7.6 (4.0)
Physical activity, Godin-Shepard, mean (*SD*)	27.1 (22.3)
Social support, SPS, mean (*SD*)	15.1 (1.6)
Self-esteem, Rosenberg Self-Esteem Scale, mean (*SD*)	34.1 (4.8)
Optimism, LOT-R, mean (*SD*)	19.0 (5.1)
Mastery, Pearlin Mastery Scale, mean (*SD*)	22.2 (4.2)

BMI = body mass index; CES-D = Center for Epidemiologic Studies–Depression; CRP = C-reactive protein; IL-6 = interleukin-6; LOT-R = Life Orientation Test-Revised; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; SPS = Social Provisions Scale; TNF-α = tumor necrosis factor-α–alpha.

the engagement in physical activity, the higher the BMI, and the older the participant's age.

Depressive Symptoms

Linear regression analyses examined the association between lifetime stressor exposure and depressive symptoms and potential moderators of these effects, controlling for applicable covariates (ie, age, BMI, cancer stage, surgery type, and time since initial cancer diagnosis). Table 2 provides the point estimate, CI, and *P*-value for the primary predictors (ie, lifetime stressor exposure variable and moderator variable) and the interaction term from the adjusted models. Supplemental Table S2 (Supplemental Digital Content, http://links.lww.com/PSYMED/B94) provides the point estimate, CI, and *P*-value for all variables in the adjusted models.

Stressor Exposure and Depressive Symptoms

Consistent with hypotheses, both lifetime stressor count (beta = 0.29, $p < .001$) and severity (beta = 0.12, $p < .001$) were positively associated with depressive symptoms in models controlling for all covariates.

Moderation by Behavioral Resources

Sleep quality was associated with depressive symptoms (beta = 1.28, $p < .001$). The sleep quality × lifetime stressor count interaction approached but did not reach significance (beta = 0.01, $p = .14$). The sleep quality × lifetime stressor severity interaction was significant (beta = 0.01, $p = .008$). As hypothesized and shown in Figure 1E, women with greater lifetime stressor severity had lower levels of depressive symptoms if they had better sleep quality (PSQI score ≤ 5). Engagement in physical activity was not associated with depressive symptoms (beta = −0.03, $p = .35$). Neither the physical activity × lifetime stressor count interaction (beta = −0.002, $p = .91$) nor the physical activity × lifetime stressor severity interaction were significant (beta = −0.001, $p = .26$).

Moderation by Coping Resources

Social support was negatively associated with depressive symptoms (beta = −1.91, $p < .001$). The social support × lifetime stressor count interaction was significant (beta = −0.06, $p = .013$). As hypothesized and as shown in Figure 1A, women with greater lifetime stressor exposure had lower levels of depressive symptoms if they had higher levels of social support. Similarly, the social support × lifetime stressor severity interaction was significant (beta = −0.02, $p = .007$). As hypothesized and as shown in Figure 1B, greater social support buffered against the negative effects of lifetime stressor severity on depressive symptoms.

Self-esteem was negatively associated with depressive symptoms (beta = −0.68, $p < .001$). Neither the self-esteem × lifetime stressor count interaction (beta = −0.01, $p = .18$) nor the self-esteem × lifetime stressor severity interaction were significant (beta = −0.003, $p = .28$).

Optimism was negatively associated with depressive symptoms (beta = −0.84, $p < .001$). The optimism × lifetime stressor count interaction was significant (beta = −0.02, $p = .004$). As hypothesized and as shown in Figure 1C, women with the highest lifetime stressor counts had lower depressive symptoms if they had higher levels of optimism (LOT-R score > 23). Further, the optimism × lifetime stressor severity interaction was significant (beta = −0.01, $p = .011$). Figure 1D shows how optimism buffered against the adverse effects of lifetime stressor severity on depressive symptoms.

Mastery was negatively associated with depressive symptoms (beta = −0.55, $p < .001$). The mastery × lifetime stressor count interaction was not significant (beta = −0.01, $p = .23$). The mastery × lifetime stressor severity interaction was significant (beta = −0.01, $p = .035$). As hypothesized and as shown in Figure 1F, women with the greatest lifetime stressor severity had lower levels of depressive symptoms if they had higher levels of mastery.

Inflammatory Composite

Linear regression analyses examined the association between lifetime stressor exposure and the inflammatory composite and potential moderators of these effects, controlling for applicable covariates (ie, age, BMI, cancer stage, surgery type, and time since initial cancer diagnosis). Table 2 provides the point estimate, CI, and *p*-value for the primary predictors (stressor exposure variable and moderator variable) and the interaction term from the adjusted models. Table S3 (Supplemental Digital Content, http://links.lww.com/PSYMED/B94) summarizes the point estimate, CI, and *P*-value for all variables in the adjusted models.

Stressor Exposure and Inflammation

Lifetime stressor count (beta = 0.01, $p = .043$), but not severity (beta = 0.002, $p = .17$), was positively associated with the inflammatory composite, controlling for all covariates. We ran exploratory analyses to determine which of the 3 inflammatory markers drove the association, and results showed that lifetime stressor count was a significant predictor of TNF-α (beta = 0.005, $p = .024$), approached significance for CRP (beta = 0.01, $p = .069$), and was a nonsignificant predictor of IL-6 (beta = 0.003, $p = .40$). In addition, we ran further exploratory analyses that included education level as a covariate to account for socioeconomic status. There was only one minor change to the results from the models that examined the association between the inflammatory composite and lifetime stressor count and severity. Namely, the significant association between lifetime stressor count and the inflammatory composite changed from a *p* value of .043 to .058, but the coefficient for lifetime stressor count remained the same (beta = 0.01; Table S5, Supplemental Digital Content, http://links.lww.com/PSYMED/B94).

Behavioral Resources

Sleep quality was not associated with the inflammatory composite (beta = 0.001, $p = .88$). Neither the sleep quality × lifetime stressor count interaction (beta = −0.0001, $p = .89$) nor the sleep quality × lifetime

TABLE 2. Individual Regression Models of the Association Between Lifetime Stressor Exposure, Depression, and Inflammation, and Moderation by Behavioral and Psychosocial Resources

Depression				**Inflammation**			
Main Effects Models							
Predictor	**Estimate**	**CI**	***p***	**Predictor**	**Estimate**	**CI**	***p***
Total lifetime stressor count	0.29	0.21–0.38	**< .001**	Total lifetime stressor count	0.01	0.001–0.01	**.043**
Total lifetime stressor severity	0.12	0.09–0.15	**< .001**	Total lifetime stressor severity	0.002	−0.001–0.001	.17
Moderator models: PSQI							
Total lifetime stressor count	0.17	0.09–0.25	**< .001**	Total lifetime stressor count	0.003	−0.01–0.01	.280
PSQI	1.28	1.00–1.56	**< .001**	PSQI	0.002	−0.02–0.03	.84
Stressor count X PSQI	0.01	−0.01–0.03	.14	Stressor count X PSQI	0.0001	0.00–0.01	.89
Delta R^2 (*p*-value)		0.005 ($p = .14$)		Delta R^2 (*p*-value)		0.0002 ($p = .84$)	
Total lifetime stressor severity	0.07	0.04–0.10	**< .001**	Total lifetime stressor severity	0.001	−0.01–0.01	.28
PSQI	1.18	0.90–1.46	**< .001**	PSQI	0.002	−0.02–0.03	.82
Stressor severity X PSQI	0.01	0.00–0.01	**.008**	Stressor severity X PSQI	−0.0001	−0.001–0.002	.71
Delta R^2 (*p*-value)		**0.02 ($p = .009$)**		Delta R^2 (*p*-value)		0.001 ($p = .71$)	
Moderator models: physical activity							
Total lifetime stressor count	0.30	0.21–0.38	**< .001**	Total lifetime stressor count	0.003	−0.001–0.01	.25
Physical activity	−0.03	−0.08–0.03	.35	Physical activity	−0.002	−0.01–0.001	.19
Stressor count X physical activity	−0.002	0.00–0.03	.91	Stressor count x physical activity	−0.0001	−0.002–0.001	.84
Delta R^2 (*p*-value)		0.00004 ($p = .91$)		Delta R^2 (*p*-value)		0.0002 ($p = .84$)	
Total lifetime stressor severity	0.12	0.09–0.15	**< .001**	Total lifetime stressor severity	0.001	−0.001–0.002	.26
Physical activity	−0.02	−0.08–0.03	.43	Physical activity	−0.002	−0.01–0.001	.19
Stressor severity x physical activity	−0.001	0.00–0.03	.26	Stressor severity x physical activity	−0.00003	−0.001–0.003	.69
Delta R^2 (*p*-value)		**0.03 ($p = .004$)**		Delta R^2 (*p*-value)		0.001 ($p = .69$)	
Moderator models: social support							
Total lifetime stressor count	0.28	0.20–0.36	**< .001**	Total lifetime stressor count	0.003	−0.002–0.01	.28
Social support	−1.91	−2.61– −1.21	**< .001**	Social support	0.01	−0.04–0.06	.80
Stressor count x social support	−0.06	−0.10– −0.01	**.013**	Stressor count x social support	0.003	−0.002–0.01	.086
Delta R^2 (*p*-value)		**0.02 ($p = .013$)**		Delta R^2 (*p*-value)		0.01 ($p = .086$)	
Total lifetime stressor severity	0.12	0.09–0.14	**< .001**	Total lifetime stressor severity	0.001	−0.002–0.001	.31
Social support	−1.87	−2.55– −1.19	**< .001**	Social support	0.01	−0.05–0.06	.84
Stressor severity x social support	−0.02	−0.04– −0.01	**.007**	Stressor severity x social support	0.001	−0.002–0.005	.15
Delta R^2 (*p*-value)		**0.02 ($p = .007$)**		Delta R^2 (*p*-value)		0.01 ($p = .15$)	
Moderator models: self-esteem							
Total lifetime stressor count	0.22	0.13–0.30	**< .001**	Total lifetime stressor count	0.004	−0.002–0.01	.24
Self-esteem	−0.68	−0.91– −0.44	**< .001**	Self-esteem	−0.01	−0.02–0.01	.67
Stressor count x self-esteem	−0.01	−0.03–0.01	.18	Stressor count x self-esteem	0.0004	−0.005–0.001	.55
Delta R^2 (*p*-value)		0.01 ($p = .18$)		Delta R^2 (*p*-value)		0.001 ($p = .55$)	
Total lifetime stressor severity	0.09	0.06–0.12	**< .001**	Total lifetime stressor severity	0.001	−0.002–0.001	.29
Self-esteem	−0.61	−0.85– −0.38	**< .001**	Self-esteem	−0.004	−0.02–0.01	.69
Stressor severity x self-esteem	−0.003	−0.01–0.00	.28	Stressor severity x self-esteem	0.0001	−0.004–0.002	.69
Delta R^2 (*p*-value)		0.003 ($p = .28$)		Delta R^2 (*p*-value)		0.003 ($p = .36$)	
Moderator models: optimism							
Total lifetime stressor count	0.25	0.17–0.32	**< .001**	Total lifetime stressor count	0.004	−0.002–0.01	.22
Optimism	−0.84	−1.06– −0.61	**< .001**	Optimism	−0.003	−0.02–0.01	.69
Stressor count x optimism	−0.02	−0.04– −0.01	**.004**	Stressor count x optimism	0.0005	−0.005–0.001	.36
Delta R^2 (*p*-value)		**0.02 ($p = .004$)**		Delta R^2 (*p*-value)		0.003 ($p = .36$)	
Total lifetime stressor severity	0.1	0.07–0.13	**< .001**	Total lifetime stressor severity	0.001	−0.006–0.001	.22
Optimism	−0.77	−0.99– −0.55	**< .001**	Optimism	−0.004	−0.02–0.01	.67
Stressor severity x optimism	−0.01	−0.01– −0.01	**.011**	Stressor severity x optimism	0.0002	−0.004–0.003	.37
Delta R^2 (*p*-value)		**0.02 ($p = .011$)**		Delta R^2 (*p*-value)		0.003 ($p = .37$)	
Moderator models: mastery							
Total lifetime stressor count	0.25	0.16–0.34	**< .001**	Total lifetime stressor count	0.004	−0.007–0.01	.24
Mastery	−0.55	−0.82– −0.28	**< .001**	Mastery	−0.01	−0.03–0.01	.45
Stressor count x mastery	−0.01	−0.03–0.01	.23	Stressor count x mastery	0.001	−0.002–0.003	.33
Delta R^2 (*p*-value)		0.01 ($p = .23$)		Delta R^2 (*p*-value)		0.004 ($p = .33$)	
Total lifetime stressor severity	0.1	0.07–0.13	**< .001**	Total lifetime stressor severity	0.001	−0.007–0.006	.22
Mastery	−0.49	−0.75– −0.23	**< .001**	Mastery	−0.01	−0.03–0.01	.46
Stressor severity x mastery	−0.01	−0.01–0.01	**.035**	Stressor severity x mastery	0.0003	−0.005–0.001	.19
Delta R^2 (*p*-value)		**0.01 ($p = .035$)**		Delta R^2 (*p*-value)		0.01 ($p = .19$)	

PA = physical activity; PSQI = Pittsburgh Sleep Quality Index.

The models have been adjusted for age, BMI, cancer stage, surgery type, and time since initial cancer diagnosis (days). Bold values indicate *P*-value < 0.05. Delta R^2 is the change in R^2 from the model that did not include the interaction term to the model that included the interaction term.

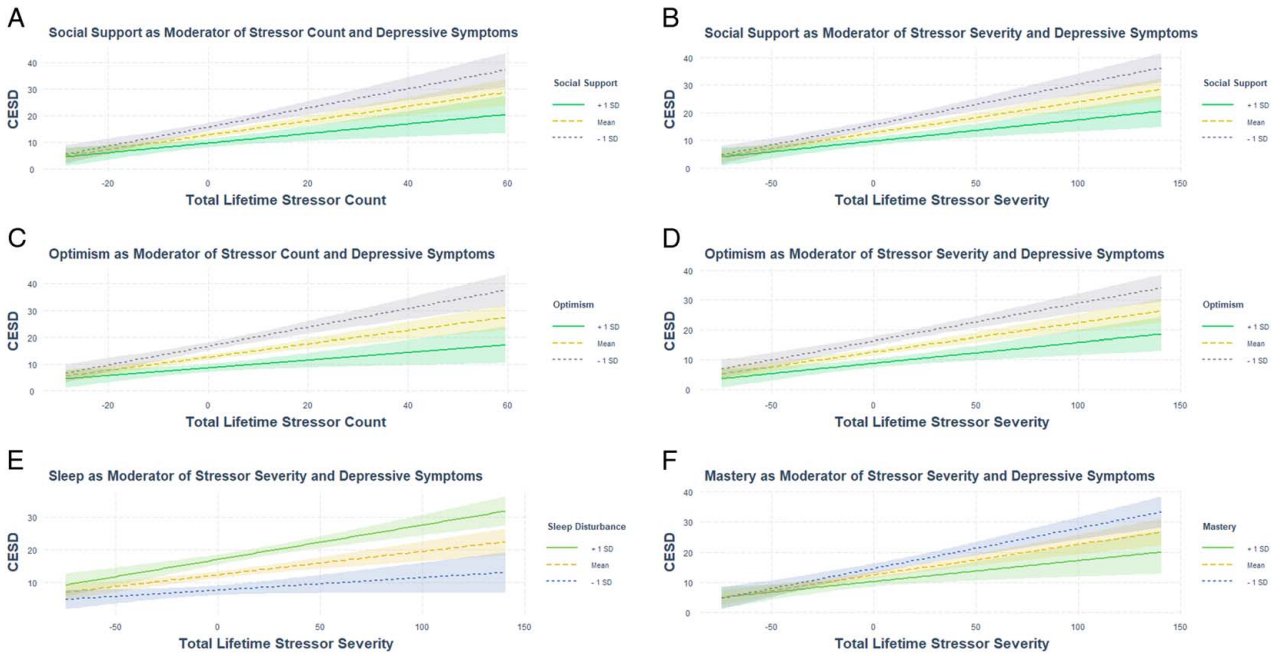

FIGURE 1. A–F, Moderators of the association between lifetime stressor exposure and depressive symptoms (CESD). Color image is available only in online version.

stressor severity interaction (beta = −0.0001, p = .71) were significant. Similarly, engagement in physical activity was not associated with the inflammatory composite (beta = −0.002, p = .19). Neither the physical activity × lifetime stressor count interaction (beta = −0.0001, p = .84) nor the physical activity × lifetime stressor severity interaction (beta = −0.00003, p = .69) were significant.

Coping Resources

None of the psychosocial factors, including social support (beta = 0.01, p = .80), self-esteem (beta = −0.01, p = .67), optimism (beta = −0.003, p = .69), and mastery (beta = −0.01, p = .45), were associated with the inflammatory composite, and none of the variables moderated the association between lifetime stressor exposure and inflammation (all ps > .086).

DISCUSSION

Although stress appears to have harmful disease and quality-of-life-related implications for breast cancer patients,[95,120–123] we are not aware of any studies that have systematically investigated the impact of lifetime stressor exposure on depression and inflammation outcomes in this population, either alone or in combination with factors that could potentially moderate these associations. We addressed these issues in a sample of 180 women recently diagnosed with breast cancer and found that, as hypothesized, greater lifetime stressor count and severity were positively associated with depressive symptoms. Several behavioral and psychosocial variables—namely, better sleep quality, more social support, greater optimism, and a stronger sense of mastery—buffered against the negative effects of lifetime stressor exposure on depressive symptoms. In addition, lifetime stressor count, but not perceived severity, was associated with protein markers of inflammation, as measured by an inflammatory composite including IL-6, TNF-α, and CRP. Exploratory analyses investigating associations between the lifetime stressor variables and individual inflammatory markers showed that, of the 3 inflammatory markers, TNF-α was most strongly associated with lifetime stressor severity. None of the modifiable behavioral or psychosocial variables moderated the association between lifetime stressor exposure and the inflammatory composite.

The association between stressor exposure and the development of depression is well-established.[27] However, many studies to date have viewed stressor exposure through a restricted lens that fails to capture stressors occurring over the entire lifespan and/or how lifetime stressor exposure operates as a risk factor for the subsequent development of depressive symptoms in response to an additional stressor, such as a diagnosis of cancer. We attempted to answer these calls[38,124] for a life-course perspective on stressor exposure that assesses stressors occurring across the entire lifespan and that illuminates the implications of repeated stressor exposure on mental and biological health outcomes. The encompassing assessment of stressors occurring across the lifespan that the STRAIN provides enabled us to examine the importance of accumulated stressor burden, including both count and severity, and how it impacts psychological responses to subsequent threats. Our findings suggest that greater lifetime exposure to stressors may increase the risk for the development of depressive symptoms in response to a new challenge—namely, a breast cancer diagnosis. From a

clinical perspective, these results underscore the utility of assessing lifetime stressor exposure to identify women most at risk of developing behavioral symptoms in response to their diagnosis to ensure they have adequate resources in place to support them if depressive symptoms emerge.

We also identified several modifiable variables that may buffer against the negative impact of stress exposure on depressive symptoms. Specifically, our results suggest that psychosocial resources—including social support, optimism, and mastery—beneficially modify the association between lifetime stressor exposure and depressive symptoms. These results have treatment implications and highlight the possible utility of using interventions targeting these variables (eg, mindfulness-based interventions[125–127]) to improve outcomes in cancer populations.

Further, we found that sleep quality buffers the association between lifetime stressor severity and depressive symptoms. These findings suggest that sleep interventions might be effective options for preventing depression in this high-risk group. Women diagnosed with breast cancer experience a high degree of sleep disruption, with insomnia prevalence ranging from 20% to 70%.[128] Indeed, 63% of women in the current sample reported clinically relevant sleep problems (PSQI score > 5). Various sleep interventions are feasible and effective at improving sleep in cancer populations, including mindfulness-based interventions,[129,130] Tai Chi,[131] and Cognitive Behavioral Therapy for Insomnia (CBT-I).[132] Our findings indicate that these interventions may also buffer against the detrimental effects of lifetime stressors.

While the link between stressor exposure and inflammation has a solid theoretical[5,133] and biological foundation,[34,134] surprisingly few studies have demonstrated direct associations between cumulative lifetime stressor exposure and blood protein markers of inflammation.[34,42,135] Our results indicate that the total number (but not severity) of acute and chronic stressors that one has experienced over the life course is associated with elevated plasma markers of inflammation. One possible reason for why this effect was evident for stressor count and not severity may be that repeated stressor exposure exclusive of perceived intensity can lead to exaggerated inflammatory responses, as shown in priro studies.[136] In addition, it is possible that combining across stressor severity mutes the effect of individual stressors. Our findings expand upon prior studies demonstrating that a variety of acute and chronic stressors are associated with elevated levels of inflammation,[4,6,33,86,87,89,90,95,136–138] but extend this work in an important new direction by having assessed the cumulative burden of acute and chronic stressors occurring across the entire life course.

Of note, none of the behavioral modifiers evaluated buffered against the adverse effects of lifetime stressor exposure on circulating inflammatory markers. These results suggest different targets of intervention are needed, possibly ones explicitly aimed at reducing inflammation, to address the adverse physiological effects of lifetime stressor exposure on the immune system. Moreover, and consistent with previous investigations in this sample, inflammation was not significantly associated with depressive symptoms in this study.

Strengths and Limitations

This study has several strengths, including our assessment of a variety of both acute and chronic stressors occurring over the entire life course; our examination of both behavioral and psychosocial resources that may buffer the effects of stress exposure; and our focus on key biobehavioral outcomes that are known to predict poor outcomes in cancer survivorship and in the general population, depression and inflammation. Several limitations should also be noted. First, our analyses are cross-sectional, so causality and directionality cannot be inferred. Second, retrospective reports of lifetime stressor exposure, especially adult reports of adverse childhood experiences, have been shown to have some bias and reporting inaccuracies.[139,140] Although some errors are inevitable in retrospective self-reports, we used a validated, comprehensive, interview-based measure of cumulative lifetime stressor exposure[85] that inquires about 55 different stressors to mitigate the potential unreliability of self-reports. In addition, the measurement tools used to assess some moderators may not paint the most complete picture. Specifically, the literature is mixed on the accuracy of evaluating physical activity with subjective, self-report questionnaires,[141,142] and the possible inaccurate assessment of one's engagement in physical activities using the Godin-Shepard questionnaire may have contributed to the lack of effects. Future studies should also assess engagement in physical activity with an objective measure (eg, using a pedometer) to capture that variable more completely.

Given our belief that lifetime stressor count and lifetime stressor severity capture 2 distinct characteristics of lifetime stressor exposure and our desire to identify modifiable resilience factors, we conducted a large number of analyses without a correction for multiple tests. Our objective was to identify risk and resilience factors of depression and heightened inflammation in this sample, intending to highlight factors that should be more thoroughly examined in future investigations. Therefore, our results and conclusions should be considered preliminary evidence. That said, the results provide support for the inclusion of the risk and resilience factors tested in this trial in future investigations. Further, our power to detect moderated effects may have been limited (between 70% and 75%). Of the 270 women enrolled in the study, only 180 had complete data on all variables included in the analyses, limiting our ability to leverage the power of the entire sample. Given that the patient population in this trial was recruited from 2 major medical centers in West Los Angeles and were generally of higher socioeconomic status (SES), it will be important for future investigations to interrogate associations between stress, depression, and inflammation in more SES-diverse samples. Indeed, it is possible that different populations may have different life experiences (both prediagnosis and postdiagnosis) that influence these processes generally and in the aftermath of a breast cancer diagnosis specifically.

CONCLUSION

In conclusion, the present study indicates that the accumulated burden of lifetime stressor exposure can lay the foundation for adverse psychological and physiological responses to a new stressor (ie, a breast cancer diagnosis) in women recently diagnosed with breast cancer. Results extend our prior research on the same sample,[95] build upon previous examinations of the adverse biological effects of lifetime stressors, and show that objective experiences of stressors across the lifespan are associated with elevated levels of inflammation in the context of cancer. These results thus suggest a pathway through which stress may lead to adverse cancer-related outcomes (eg, progression, recurrence). Further, we also found that several modifiable behavioral variables—namely, social support, optimism, mastery, and sleep quality—protect against the development of depressive symptoms, suggesting the possible utility of interventions that enhance these protective qualities. Looking forward, additional research is needed to further investigate these effects.

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Data Availability Statement: De-identified data from this study are not available in a public archive. However, they may be made available (as allowable according to institutional IRB standards) by emailing the corresponding author. The analytic code used to conduct the analyses presented in this study is not available in a public archive. However, it may be available by emailing the corresponding author. Materials used to conduct the study are not publicly available. The analysis plan was not formally preregistered.

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