A Longitudinal Study of Depression, Fatigue, and Sleep Disturbances as a Symptom Cluster in Women with Breast Cancer

Sheau-Yan Ho, BA, **Kelly J. Rohan, PhD**, **Justin Parent, BA**, **Felice A. Tager, PhD**, and **Paula S. McKinley, PhD**

University of Vermont (S.Y.H., K.J.R., J.P.), Burlington, Vermont; and Columbia University Medical Center (F.A.T., P.S.M.), New York, New York, USA

Abstract

Context—Depression, fatigue, and sleep disturbances have been identified as a symptom cluster among breast cancer patients. However, few longitudinal studies have examined the temporal relations between these symptoms surrounding diagnosis and treatment.

Objectives—The current study investigated the co-occurrence of and interrelations between non-somatic depressive symptoms, fatigue, and sleep disturbances in breast cancer patients at three time points: prior to, after, and six to eight months following adjuvant chemotherapy treatment.

Methods—Separate samples of premenopausal ($N = 67$) and postmenopausal ($N = 67$) breast cancer patients completed self-report measures of depression, fatigue, and sleep disturbances at all three time points. Path analysis was used to explore within- and cross-symptom paths across time.

Results—Depression, fatigue, and sleep disturbances were correlated within each time point. Continuity paths, whereby prior levels of symptom severity tended to predict subsequent severity of the same symptom at the subsequent time point, were significant in both samples, except for depression in the premenopausal sample. Instead, significant cross-symptom paths emerged whereby baseline fatigue predicted post-chemotherapy depression, and post-chemotherapy fatigue predicted depression at follow-up in the premenopausal patients. No significant cross-symptom paths emerged for the postmenopausal sample.

Conclusion—Findings supported the notion that depression, fatigue, and sleep disturbances manifest as a symptom cluster. Fatigue may precede non-somatic symptoms of depression among premenopausal breast cancer patients and represents a potential intervention target.

Address correspondence to: Sheau-Yan Ho, BA, University of Vermont, John Dewey Hall, 2 Colchester Avenue, Burlington, VT 05405, USA, Sheau-Yan.Ho@uvm.edu.

Disclosures

The authors report no conflicts of interest.

Keywords

cancer; oncology; fatigue; depression; sleep disturbance; symptom cluster

Introduction

Receiving a breast cancer diagnosis and undergoing cancer treatment is commonly associated with depression, fatigue, and sleep disturbances (1–3). These distressing symptoms not only affect patients at diagnosis and during cancer treatment, but also persist years beyond the end of treatment (4, 5). Given the growing number of breast cancer survivors (6) and the impact of receiving a cancer diagnosis and undergoing treatment on mood and quality of life, it is important to understand cancer-related mental health symptoms in order to inform treatment and prevention efforts.

Considerable research has examined individual symptoms of depression, fatigue, and sleep disturbances in cancer populations (7–9); however, a growing body of literature indicates that certain symptoms tend to co-occur as symptom clusters in cancer patients. A symptom cluster consists of three or more concurrent symptoms that are correlated to each other (10). Extant literature supports the notion that depression, fatigue, and insomnia are a symptom cluster across cancer types, as indicated by moderate, positive correlations between all pairings of these symptoms when measured concurrently (11, 12).

Recent longitudinal studies have reported mixed findings in the investigation of temporal relationships between cancer-related symptoms. Brown and colleagues (13) failed to find a directional relationship between depression and fatigue in a heterogeneous sample of cancer patients. However, in a recent study that examined anxiety, depression, insomnia, fatigue, and pain over an 18-month period in mixed cancer patients, fatigue predicted depression, insomnia, and pain at subsequent time points, indicating that fatigue was the most contributive predictor over time (14). In another heterogeneous sample of cancer patients, fatigue at baseline prospectively predicted depressive mood after treatment, rather than the opposite relation (15). Current research implicates biological and behavioral mechanisms in the development of depression, fatigue, and sleep disturbances. Some evidence indicates that elevated inflammatory processes contribute to fatigue, but not sleep disturbances or depression (16). However, further research is needed to support the notion that fatigue may be a primary or "core" symptom in depression. Moreover, it remains to be demonstrated whether this pattern generalizes to a homogeneous breast cancer sample. Further investigation also is needed around the extent to which these symptoms occur alone versus in combination to better delineate directionality and to aid the development of effective interventions.

The current project makes a unique contribution to the literature as the first longitudinal study that utilizes path analysis to examine symptom interrelations in a purported symptom cluster in breast cancer patients. The current project had three major aims: 1) to test a purported symptom cluster in the cancer literature, 2) to explore the individual course of depression, fatigue, and sleep disturbances, and 3) to explore the predictive nature of each symptom on the other two symptoms. We examined the co-occurrence, course, and

interrelations between depression, fatigue, and sleep disturbances at three important time points surrounding adjuvant chemotherapy (CT) treatment for early stage breast cancer (i.e., before, after, and six to eight months post-treatment). Because this was a secondary analysis of data from two separate studies that examined the effects of CT on cognitive functioning, we explored these symptom relations in two different samples of breast cancer patients: older, postmenopausal women (Study 1) and younger, premenopausal women (Study 2).

We proposed to test an exploratory model of all possible associations between depressive symptoms, fatigue, and sleep disturbances. In accordance with Aim 1, we expected to find correlations similar in value to those previously reported in support of the assertion that depression, fatigue, and sleep disturbances co-occur as a symptom cluster. In order to address Aim 2, we hypothesized that the severity of each symptom would predict severity of the same symptom at later time points. We anticipated that this pattern would be maintained even after adjusting for concurrent and previous levels of the other two symptoms. Last, in accordance with Aim 3, we hypothesized that baseline severity of each symptom would predict subsequent levels of the other two symptoms. Given that past studies have indicated that fatigue is an important predictor of other symptoms in cancer patients (14, 15), we expected that fatigue would be a stronger predictor of the other two symptoms at later time points, compared with depression and sleep disturbances.

Methods

Participants

Participants were recruited for one of two studies from the patient pool of collaborating breast surgeons and oncologists affiliated with Columbia University Medical Center in New York City. Study 1 was conducted between 2001 and 2007, whereas Study 2 was conducted between 2005 and 2011. Patients across both studies were females, newly diagnosed with Stage I-IIIa breast cancer. Possible adjuvant treatments included CT, radiation, and endocrine therapy. Exclusion criteria included prior breast cancer diagnosis; prior exposure to CT or radiation; neoadjuvant CT; and neurological, psychological, or medical comorbidities that might affect cognitive functioning.

Eligibility criteria across the two studies differed primarily in patient age, menopausal status, and use of CT treatment. Study 1 included postmenopausal women aged 45–70 with postmenopausal status defined as no menstrual cycles for at least 12 months or surgical menopause. From a total of 129 patients who were approached, 81 patients completed a screen for eligibility, of which 67 eligible patients were enrolled in Study 1. Approximately half of the patients in Study 1 received adjuvant CT ($n = 36$), whereas the others were treated with surgery but no CT ($n = 31$). Chemotherapy treatment was decided between the patients and their oncologists prior to study enrollment. Study 2 included younger, premenopausal women aged 21–50, who reported regular menstrual cycles in the past year. From a total of 272 patients who were approached for Study 2, 156 patients completed a screen for eligibility, of which 67 eligible patients participated in Study 2. All patients in Study 2 received CT treatment ($N = 67$).

Study Designs

Both studies included three time points when self-report psychological and quality of life questionnaires were administered: baseline or T1 (i.e., at least two weeks after breast surgery but prior to beginning CT), T2 (i.e., within one month after completing a three- to six-month CT regimen, or approximately six months after T1 for patients who did not receive CT in Study 1), and T3 (i.e., six to eight months after T2). Because CT treatment has been associated with more severe depressive and fatigue symptoms and circadian rhythm changes (17, 18), and cancer-related impairment tends to extend beyond the course of treatment (5, 8), these time points were especially relevant in assessing symptom changes.

Measures

Participants completed the following self-report measures at each of the three time points to assess depression, fatigue, and sleep disturbances. Study 1 and Study 2 used the same measures of fatigue and sleep disturbances, but different measures of depression.

Beck Depression Inventory®-Second Edition (BDI-II)—Postmenopausal women in Study 1 completed the BDI-II (19), a self-report measure that assesses current depressive symptom severity. The BDI-II has been used widely in medical populations and demonstrates good reliability and validity (19). Confirmatory factor analysis of the BDI-II supports a two-factor structure that maps onto underlying cognitive-affective and somatic depressive symptoms (20). In Study 1 analyses, we used the cognitive-affective subscale to capture non-somatic depressive symptoms, in an effort to exclude items that overlapped with the other two symptoms of interest. In this sample, the alpha coefficient of 0.90 indicated excellent internal consistency across all three time points.

Hospital Anxiety and Depression Scale (HADS)—Premenopausal women in Study 2 completed the HADS depression subscale (HADS-D) to assess symptoms of depression. The HADS (21) is a brief, self-administered rating scale that assesses for depression and anxiety in patients with physical illness. Somatic symptoms such as dizziness, headaches, insomnia, and fatigue were excluded from the HADS in order to prevent false positives resulting from underlying medical conditions. The HADS-D score was calculated by summing all seven items that comprise the depression subscale. The HADS has shown good validity and test-retest reliability in a variety of medical populations, including breast cancer patients (22). The alpha coefficient of 0.84 demonstrated good reliability across time in Study 2.

Multidimensional Fatigue Symptom Inventory- Short Form (MFSI-SF)—The MFSI-SF (23) contains 30 items that comprise five subscales to assess somatic, affective, cognitive, behavioral, and global fatigue. The total fatigue score is calculated by subtracting the vigor scale from the sum of the other four scales (general, physical, emotional, and mental fatigue). The MFSI-SF is a reliable and valid tool for assessing the full spectrum of symptoms that characterize cancer-related fatigue (CRF) (24). The alpha coefficient values across time, 0.85 and 0.88 in Study 1 and Study 2, respectively, indicated a high degree of internal consistency.

Pittsburgh Sleep Quality Index (PSQI)—The PSQI (25) is a 19-item questionnaire that was used to assess subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The total PSQI score was calculated by summing the domain scores. The PSQI has demonstrated internal consistency reliability and construct validity in breast cancer patients (26). In the current project, the reliability coefficients across time were 0.65 and 0.78 in Study 1 and Study 2, respectively.

Statistical Analysis

Preliminary Analyses—Study 1 and Study 2 were analyzed separately for the purposes of this project because of the use of different measures of depression and different study designs. Participant and outcome measure descriptive statistics were examined in SPSS v. 21 (SPSS, Inc./IBM, Chicago, IL). Bivariate associations between measures of depressive symptoms, fatigue, and sleep disturbances were examined at each time point across all groups.

Primary Analyses—Path analysis was employed to model associations from a saturated model (i.e., $df = 0$; Fig. 1). All models were tested with Mplus v. 6.11 (Muthén & Muthén, Los Angeles, CA) (27) and used maximum likelihood estimation with robust standard errors to account for skewed data. Standard fit statistics were examined to evaluate nested model fit: Chi-square (χ^2: $P > 0.05$ excellent), Comparative Fit Index (CFI; > 0.90 acceptable, > 0.95 excellent), Root Mean Square Error of Approximation (RMSEA; < 0.08 acceptable, < 0.05 excellent) and the Standardized Root Mean Square Residual (SRMR; < 0.08 acceptable, < 0.05 excellent) (28, 29). Missing data were treated as missing at random, and full information maximum likelihood estimation techniques were used for inclusion of all available data at each time point. The Model Indirect command was utilized to calculate standardized indirect effect parameters and biased-corrected bootstrap confidence intervals.

Control Variables—The effects of covariates were explored with multiple-indicator/ multiple-cause (MIMIC) models (30), in which all major constructs at each time point in the final model were regressed on the covariates. If paths in the model remained significant with the inclusion of a given variable, it was concluded that the covariate did not influence the relations among variables in the model. Covariates included sociodemographics (i.e., age, ethnicity, race, years of education), medically relevant variables (i.e., cancer stage, duration of CT, adjuvant radiation and endocrine therapy), and psychological history (i.e., past diagnosis of a depressive or anxiety disorder) variables.

Results

Study 1: Postmenopausal Sample

Participants—A total of 70 postmenopausal women with breast cancer were eligible and enrolled in Study 1. The study utilized data from 67 women who provided data for at least one time point. Missing data were consistent across measures of depression, fatigue, and sleep disturbances: 1.5% at T1, 10.4% at T2, and 23.9% at T3. Table 1 presents descriptive statistics for sociodemographic and medical variables. Additional descriptives are reported

by Tager et al. (31). The CT and no CT treatment groups were generally well-balanced on sociodemographics, medical variables, and psychological history. However, they significantly differed in stage of cancer diagnosis ($\chi^2(2) = 24.44$, $P < 0.001$); treatment with CT was associated with higher cancer stage.

Preliminary Analyses—Table 2 presents the depression, fatigue, and sleep disturbance statistics at each time point. Symptom correlations were examined across CT status and time. We found no significant differences between symptom correlations for patients treated with versus without CT. Across treatments, the overall correlations were 0.77 for depression and fatigue, 0.34 for fatigue and sleep disturbances, and 0.44 for depression and sleep disturbances (all Ps < 0.01). Depression and fatigue were more strongly correlated at all three time points compared with the correlations between other symptom pairs. In general, symptom correlations increased after CT treatment (i.e., at T2 and T3) compared with baseline.

Primary Analyses—The saturated model (Fig. 1) was tested to explore associations between the three symptoms of interest across the three time points, using the entire sample ($N = 67$) of postmenopausal women. We failed to observe any significant within-or cross-symptom parameters between T1 and T3; therefore, these paths were dropped in order to create a more parsimonious model. The final model demonstrated excellent fit (χ^2 (9, $N = 67$) = 7.69, $P > 0.05$, CFI = 1.00, RMSEA = 0.00, 90% CI 0.00, 0.12, SRMR = 0.02).

Table 3 presents the statistically significant standardized path coefficients in the final model (Fig. 2 represents the corresponding model). All within-time symptom correlations were significant, with the exception of fatigue and sleep disturbances at T3. As expected, continuity paths for all three symptoms emerged as significant. Contrary to hypotheses, we did not observe significant cross-symptom paths. The indirect effect from each major construct at T1 to the same construct at T3 through T2 was significant for depression ($\beta = 0.39$, $P = 0.01$), fatigue ($\beta = 0.20$, $P = 0.01$), and sleep disturbances ($\beta = 0.50$, $P < 0.001$). All pathways were unaffected by the inclusion of covariates in MIMIC models.

Study 2: Premenopausal Sample

Participants—Table 1 presents descriptive information for sociodemographic and medical variables in Study 2. A total of 67 patients completed at least one assessment. Missing data were consistent across measures of depression, fatigue, and sleep disturbances: 3.0% at T1, 4.5% at T2, and 10.4% at T3.

Preliminary Analyses—Table 2 presents outcome measure descriptive statistics. Overall correlations were 0.79 for depression and fatigue, 0.59 for fatigue and sleep disturbances, and 0.45 for depression and sleep disturbances (all Ps < 0.01). Depression and fatigue emerged as the most strongly correlated pair of symptoms at all three time points and became more strongly correlated over time. Contrastingly, the strength of association between fatigue and sleep disturbances decreased over time.

Primary Analyses—The saturated model (Fig. 1) was tested in the premenopausal cancer sample ($N = 67$). We did not observe significant within- or cross-symptom parameters

between T1 and T3 as proposed in the conceptual model; therefore, these paths were dropped. The final model demonstrated excellent fit of the data (χ^2 (9, $N = 67$) = 11.32, $P > 0.05$, CFI = 0.99, RMSEA = 0.06, 90% CI 0.00, 0.16, SRMR = 0.04).

Table 3 presents all statistically significant standardized path coefficients in the final model (Fig. 3). Symptom correlations at each time point were significant, with the exception of depression and sleep disturbances at T3. As expected, continuity paths for fatigue and sleep disturbances were highly significant. Indirect effects from fatigue ($\beta = 0.40$, $P < 0.01$) and sleep disturbances ($\beta = 0.33$, $P < 0.001$) at T1 to the same construct at T3 through T2 were significant. The continuity path between depressive symptoms at T1 and T2 approached significance, whereas depressive symptoms at T2 did not predict T3. However, two significant cross-symptom paths emerged: fatigue at T1 → depression at T2, and fatigue at T2 → depression at T3. According to MIMIC models, the path from depressive symptoms at T2 → depressive symptoms at T3 decreased in significance (Ps ranged from 0.08 to 0.13) after the inclusion of education level and past depression or anxiety; however, the standardized estimate remained close to original value. All other pathways were unaffected by the inclusion of covariates.

Discussion

The primary aim of this study was to examine the predictive utility of three symptoms belonging to a putative symptom cluster over a one-year period in postmenopausal and premenopausal breast cancer patients. We specifically aimed to demonstrate that depression, fatigue, and sleep disturbances co-occur as a symptom cluster over the course of breast cancer treatment, and explored the extent to which the severity of each symptom predicted severity of the same symptom and the other two symptoms at subsequent time points.

Consistent with the literature (32, 33) and stated hypotheses, findings revealed moderate to large, positive bivariate associations between the symptoms of interest across both samples. These findings support the notion that depression, fatigue, and sleep disturbances co-occur as a symptom cluster, prior to and following adjuvant chemotherapy treatment in postmenopausal and premenopausal women with breast cancer. Depression and fatigue emerged as the most strongly correlated symptom pair in both samples and were more strongly correlated across time.

Next, we tested a model of all temporal associations between depression, fatigue, and sleep disturbances. Results generally supported within-symptom continuity paths such that symptom severity at T1 and T2 predicted severity of the same symptom at the subsequent time point. Interestingly, the final model in the premenopausal sample pointed to fatigue being a predictor of depressive symptoms at subsequent time points, above and beyond prior levels of depressive symptoms and sleep disturbances. These findings are consistent with fatigue being a significant predictor of subsequent fatigue and depression in heterogeneous cancer patients (14, 15). We demonstrated that this pattern might generalize uniquely to premenopausal women with breast cancer. It is worth considering why fatigue did not significantly predict subsequent depressive symptoms in the postmenopausal sample. This may be explained by younger age being a strong risk factor for psychological distress and a

better predictor of depressive symptoms in breast cancer patients (34). Depression epidemiology research has found that women between ages 40 to 59 may be at higher risk of depression compared to women older than 60 (35), thus suggesting different pathways to depression across age groups. Fatigue may represent one potential pathway that gives rise to depression in younger women with breast cancer. Further research with larger samples and uniform measures of depression is needed to replicate this finding. Other variables associated with age also may account for differing pathways. Hormonal changes may be particularly important, in light of the effect of CT on the acceleration of menopause (36) and the effect of endocrine therapies on hormone levels.

There are several plausible reasons why fatigue may lead to subsequent mood problems in cancer patients. Decreased energy may lead to reduced activity levels, which may result in less positive reinforcement derived from pleasurable activities and the development of depression (14). Alternatively, the development of fatigue and depression in cancer patients may result from shared biological or pathophysiological factors (37, 38). Additional research is needed to elucidate the interrelations between fatigue, depression, and sleep disturbances surrounding diagnosis and treatment of breast cancer.

Understanding mechanisms for symptom relations over time could inform the development of effective psychological interventions for breast cancer patients. A variety of non-pharmacological interventions have been recommended for treating CRF, including exercise, psychosocial, nutritional, and sleep interventions (38–40). Further research should examine whether multimodal treatment reduces CRF and, in turn, reduces depressive symptoms.

There were a number of limitations to the current project. First, temporal relations explored were correlational and do not imply causality. Second, it is important to point out that sample sizes were small; however, several statistically significant paths emerged and four of six within-symptom paths were replicated across both study samples. Another drawback to the current project was the inability to directly compare results between samples because of the use of different measures of depression, although we used well-validated measures.

The current study also had a number of strengths. First, the longitudinal study design allowed us to examine temporal relations at three important time points in relation to adjuvant CT treatment. Second, the study aims and proposed model were explored in two separate samples. Study replication provided us with higher confidence in our findings that spanned both samples. Third, we utilized MIMIC models to examine covariates and observed that pathways were not significantly affected by demographic, medical, or psychological variables. Lastly, we used the cognitive-affective subscale of the BDI-II and the HADS-D to focus on non-somatic depressive symptoms. The use of these measures prevented inflation of cross-symptom parameters in the symptom cluster of interest.

The current study demonstrated that depression, fatigue, and sleep disturbances tend to co-occur during the first year after diagnosis, thus providing further evidence for this symptom cluster in two distinct samples of breast cancer patients. Path analyses indicated that prior severity predicted subsequent severity of the same symptom, whereas significant cross-

symptom paths were limited to fatigue at T1 and T2 predicting depression at T2 and T3, respectively, in premenopausal breast cancer patients. The clinical implications of this study may be important for assessment, prevention, and intervention of psychological symptoms related to breast cancer diagnosis and treatment. In addition to reducing severity of a given symptom by treating the same symptom earlier in time, this work provides preliminary evidence that targeting fatigue may have a meaningful effect on other related symptoms over time and potentially offset the development of depressive symptoms in younger women with breast cancer.

Acknowledgments

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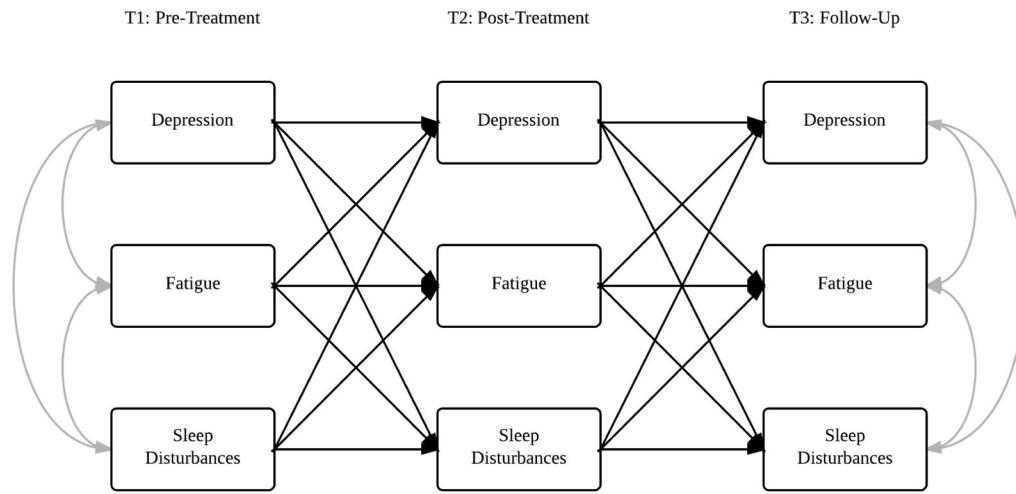
Fig. 1.
Saturated model of within- and cross-symptom temporal relations in breast cancer patients.
Note: Between symptom correlations at T2, and T1–T3 within- and cross-symptom paths are not depicted in order to keep the figure legible.
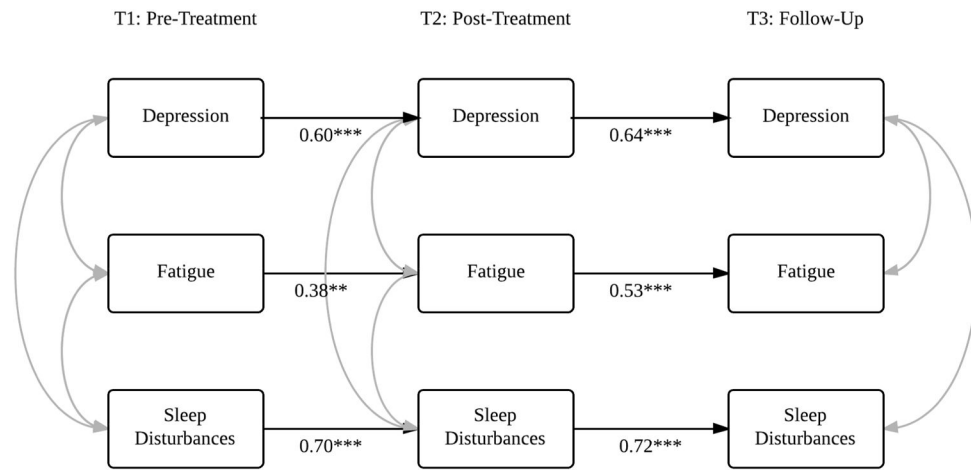
Fig. 2.
Model 1: Depression, fatigue, and sleep disturbances in the postmenopausal sample. *Note*: Only statistically significant pathways are displayed in the model. **P 0.01, ***P 0.001. Refer to Table 3 for model statistics.
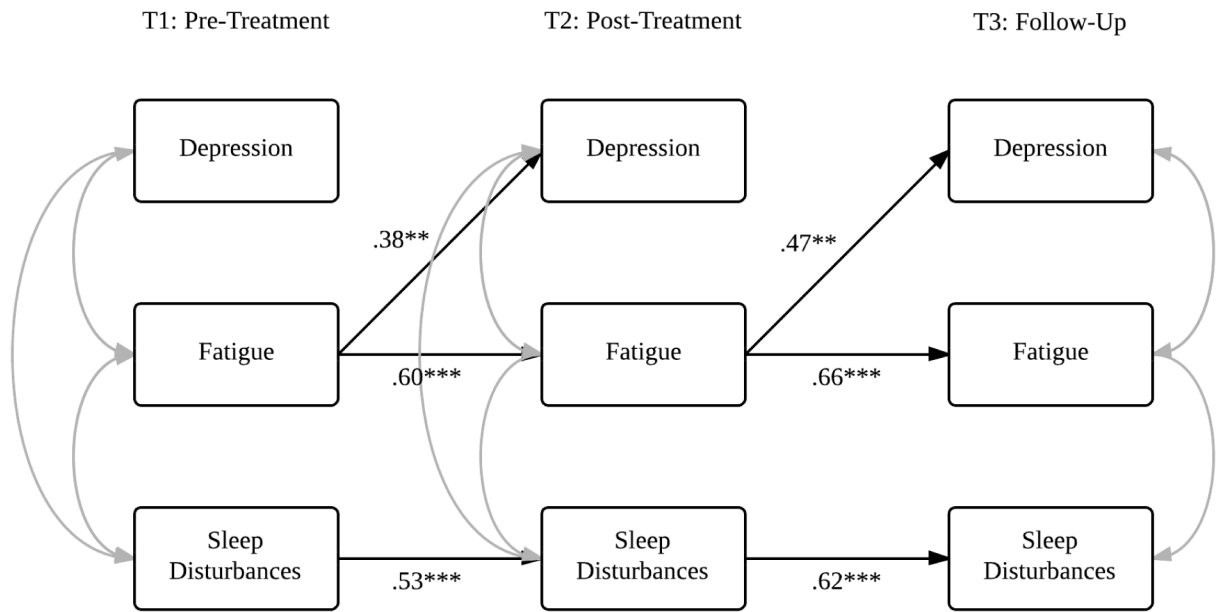
Fig. 3.
Model 2: Depression, fatigue, and sleep disturbances in the premenopausal sample. *Note*:
Only statistically significant pathways are displayed in the model. **P ≤ 0.01, ***P ≤ 0.001.
Refer to Table 3 for model statistics.

Table 1

Sociodemographic and Medical Variables at Baseline (T1) in the Postmenopausal (Study 1) and Premenopausal (Study 2) Samples

	Study 1: Postmenopausal Sample			Study 2: Premenopausal Sample
	Total (N = 67)	CT Group (n = 36)	No CT Group (n = 31)	Total (N = 67)
Age, yrs, M (SD)	60.0 (5.9)	59.4 (5.6)	60.6 (6.3)	41.4 (5.2)
Highest Education in Years, M (SD)	16.3 (3.2)	16.6 (3.2)	16.1 (3.2)	15.6 (2.4)
Ethnicity				
Asian or Pacific Islander	6/67 = 9%	4/36 = 11%	2/31 = 7%	3/67 = 5%
African American	9/67 = 13%	6/36 = 17%	3/31 = 10%	21/67 = 31%
Hispanic	7/67 = 10%	5/36 = 14%	2/31 = 7%	11/67 = 16%
White	45/67 = 67%	21/36 = 58%	24/31 = 77%	31/67 = 46%
Other	0/67 = 0%	0/36 = 0%	0/31 = 0%	1/67 = 2%
Main Surgery Type				
Biopsy Only	0/67 = 0%	0/36 = 0%	0/31 = 0%	0/67 = 0%
Lumpectomy	45/67 = 67%	22/36 = 61%	23/31 = 74%	28/67 = 42%
Mastectomy	22/67 = 33%	14/36 = 39%	8/31 = 26%	39/67 = 58%
Cancer Stage				
Invasive DCIS	11/67 = 16%	0/36 = 0%	11/31 = 36%	3/67 = 5%
Stage I	29/67 = 43%	13/36 = 36%	16/31 = 52%	23/67 = 34%
Stage II, IIIa	27/67 = 40%	23/36 = 64%	4/31 = 13%	40/67 = 60%
CT Regimen				
AC	9/67 = 13%	9/36 = 25%		10/67 = 14.9%
T	0/67 = 0%	0/36 = 0%		8/67 = 11.9%
ACT	16/67 = 24%	16/36 = 44%		46/67 = 68.7%
CMF	11/67 = 16%	11/36 = 31%		3/67 = 4.5%
Other Adjuvant Treatment				
Radiation	41/67 = 61%	22/36 = 61%	19/31 = 61%	29/67 = 43.3%
Endocrine therapy	49/67 = 73%	26/36 = 72%	23/31 = 74%	46/67 = 68.7%

| | Study 1: Postmenopausal Sample | | | Study 2: Premenopausal Sample |
	Total (*N* = 67)	CT Group (*n* = 36)	No CT Group (*n* = 31)	Total (*N* = 67)
Psychological History[a]				
Past Depressive Disorder	17/67 = 25%	8/36 = 22%	9/31 = 29%	10/67 = 15%
Past Anxiety Disorder	12/67 = 18%	4/36 = 11%	8/31 = 26%	4/67 = 6%

Data are presented as Mean (*SD*) or proportions, as indicated.

CT = chemotherapy; No-CT = no chemotherapy; AC = doxorubicin, cyclophosphamide; ACT = doxorubicin, cyclophosphamide, docetaxel; CMF = cyclophosphamide, methotrexate, 5-flourouracil.

[a]Psychological history was ascertained by diagnostic categories on the Structured Clinical Interview for DSM-IV Axis I Disorders.

Table 2

Descriptive Statistics for Outcome Variables at Each Time Point in the Postmenopausal and Premenopausal Samples

	T1: Pre-Tx Mean (*SD*)	T2: Post-Tx Mean (*SD*)	T3: Follow-Up Mean (*SD*)
Study 1: Postmenopausal Women			
BDI-II (Depression)			
CT	4.11 (4.07)	4.07 (4.23)	3.24 (3.82)
No-CT	5.13 (6.26)	4.45 (6.03)	5.81 (7.14)
Total	4.57 (5.34)	4.27 (5.19)	4.55 (5.85)
MFSI-SF (Fatigue)			
CT	8.50 (18.98)	9.52 (16.94)	4.04 (14.77)
No-CT	7.10 (14.81)	5.55 (17.59)	7.50 (21.13)
Total	7.86 (17.10)	7.47 (17.25)	5.80 (18.20)
PSQI (Sleep Quality)			
CT	6.94 (3.32)	6.55 (3.00)	6.36 (4.05)
No-CT	8.00 (3.96)	6.94 (3.91)	8.08 (4.58)
Total	7.42 (3.63)	6.75 (3.47)	7.24 (4.37)
Study 2: Premenopausal Women			
HADS-D (Depression)	3.25 (3.04)	3.95 (3.13)	3.55 (3.60)
MFSI-SF (Fatigue)	9.11 (18.30)	17.88 (20.33)	11.82 (23.54)
PSQI (Sleep Quality)	7.35 (4.19)	8.94 (4.35)	7.28 (4.10)

CT = chemotherapy group; No-CT = no chemotherapy group; BDI-II = Beck Depression Inventory-Second Edition (Cognitive-Affective subscale); PSQI = Pittsburgh Sleep Quality Index; MFSI-SF = Multidimensional Fatigue Symptom Inventory-Short Form; HADS-D = Hospital Anxiety and Depression Scale-Depression subscale.

Table 3

Statistically Significant Paths in Models 1 & 2

Model 1: Postmenopausal Sample

Time	Estimated Path	β	S.E.	95% CI	P
Within-Time Point Correlations					
T1	Depression – Fatigue	.63	.07	.49 to .77	<0.001
	Depression – Sleep	.26	.10	.07 to .46	0.008
	Fatigue – Sleep	.24	.12	.01 to .47	0.038
T2	Depression – Fatigue	.77	.06	.64 to .89	<0.001
	Depression – Sleep	.33	.14	.29 to .65	0.019
	Fatigue – Sleep	.47	.09	.29 to .65	<0.001
T3	Depression – Fatigue	.55	.07	.42 to .68	<0.001
	Depression – Sleep	.33	.12	.10 to .57	0.006
Within-Symptom Paths					
T1 → T2	Depression	.60	.16	.28 to .93	<0.001
	Fatigue	.38	.12	.13 to .62	0.002
	Sleep	.70	.08	.55 to .85	<0.001
T2 → T3	Depression	.64	.15	.34 to .94	<0.001
	Fatigue	.53	.14	.26 to .81	<0.001
	Sleep	.72	.09	.55 to .89	<0.001

Model 2: Premenopausal Sample

Time	Estimated Path	β	S.E.	95% CI	P
Within-Time Point Correlations					
T1	Depression – Fatigue	.69	.06	.56 to .81	<0.001
	Depression – Sleep	.43	.09	.26 to .60	<0.001
	Fatigue – Sleep	.66	.08	.51 to .81	<0.001
T2	Depression – Fatigue	.75	.05	.65 to .85	<0.001
	Depression – Sleep	.51	.09	.34 to .69	<0.001
	Fatigue – Sleep	.47	.09	.29 to .66	<0.001
T3	Depression – Fatigue	.70	.07	.57 to .82	<0.001
	Fatigue – Sleep	.35	.14	.07 to .62	0.013
Within-Symptom Paths					
T1 → T2	Fatigue	.60	.15	.30 to .89	<0.001
	Sleep	.53	.12	.29 to .78	<0.001
T2 → T3	Fatigue	.66	.16	.35 to .98	<0.001
	Sleep	.62	.13	.37 to .87	<0.001
Cross-Symptom Paths					
T1 → T2	Fatigue - Depression	.38	.15	.08 to .67	0.013
T2 → T3	Fatigue - Depression	.47	.16	.15 to .79	0.004

S.E. = standard error; CI = confidence interval.

COMP: pls add placeholder zeros where appropriate.