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Trajectories of Sleep Disturbance and Daytime Sleepiness in Women Before and After Surgery for Breast Cancer

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Abstract

Context—Sleep disturbance is a problem for oncology patients.

Objectives—To evaluate how sleep disturbance and daytime sleepiness (DS) changed from before to six months following surgery and whether certain characteristics predicted initial levels and/or the trajectories of these parameters.

Methods—Patients (*n*=396) were enrolled prior to surgery and completed monthly assessments for six months following surgery. The General Sleep Disturbance Scale (GSDS) was used to assess sleep disturbance and DS. Using hierarchical linear modeling, demographic, clinical, symptom, and psychosocial adjustment characteristics were evaluated as predictors of initial levels and trajectories of sleep disturbance and DS.

Results—All seven GSDS scores were above the cutoff for clinically meaningful levels of sleep disturbance. Lower performance status; higher comorbidity, attentional fatigue, and physical fatigue; as well as more severe hot flashes predicted higher preoperative levels of sleep disturbance. Higher levels of education predicted higher sleep disturbance scores over time. Higher levels of depressive symptoms predicted higher preoperative levels of sleep disturbance, which declined over time. Lower performance status, higher body mass index, higher fear of future diagnostic tests, not having had sentinel lymph node biopsy, having had an axillary lymph node dissection, and higher depression, physical fatigue, and attentional fatigue predicted higher DS prior to surgery. Higher levels of education, not working for pay, and not having undergone neo-adjuvant chemotherapy predicted higher DS scores over time.

Conclusion—Sleep disturbance is a persistent problem for patients with breast cancer. The effects of interventions that can address modifiable risk factors need to be evaluated.

Keywords

Sleep disturbance; daytime sleepiness; breast cancer; hierarchical linear modeling; depression; fatigue

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Disclosure
Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Introduction

Sleep disturbance is a common and significant symptom in women undergoing treatment for breast cancer.[1,2] Prior to surgery for breast cancer, the occurrence of sleep disturbance ranges from 33%[3] to 88%.[4] In addition, during adjuvant chemotherapy (CTX) and radiation therapy (RT), reports of sleep disturbance range from 65%[5] to 66%,[6] respectively.

Several studies have evaluated for changes in sleep disturbance in women during and after CTX and RT.[6–13] Although the exact measurement times differed across these studies, sleep disturbance increased during and then decreased following the completion of CTX.[3,10,11,13] In a study that evaluated for changes in sleep disturbance during RT,[12] the severity of sleep disturbance and sleep onset latency decreased over time. No studies were found that evaluated for changes in sleep disturbance in women *prior* to breast cancer surgery and followed them during adjuvant treatment.

One of the consequences of sleep disturbance is the desire to sleep during the day. Daytime sleepiness (DS) describes the inability of an individual to remain awake during the daytime, which results in drowsiness or sleep.[14] The prevalence of and changes over time in DS in women with breast cancer are not well characterized. In one study,[15] DS was described as a mild problem for most women prior to adjuvant treatment for breast cancer. In another study,[16] DS increased during CTX administration.

Predictors of Sleep Disturbance and DS in Patients with Breast Cancer

In patients with breast cancer, higher levels of depressive symptoms[2,6] and fatigue[2,8,15,17] were associated with increased levels of sleep disturbance. However, less consistent associations were found between hot flashes and sleep disturbance.[6,18–22] In four of these studies that evaluated women prior to adjuvant treatment,[6,19–21] the presence of or increases in hot flashes were associated with increased sleep disturbance. In two studies,[18,22] no associations were found between hot flashes and sleep disturbance. These inconsistent findings may be related to differences in the timing of the assessments, as well as the relatively small sample sizes.

Only two studies have evaluated for predictors of DS.[15,23] In one study of women with metastatic breast cancer,[23] increased levels of depressive symptoms were associated with increases in DS over 12 months. In another study of women prior to adjuvant CTX,[15] increases in fatigue severity were associated with increases in DS.

Although several studies have identified sleep disturbance and DS as problems for women with breast cancer, no studies were found that evaluated predictors of sleep disturbance and DS prior to and following surgery for breast cancer. Additional research is warranted to determine which factors place women at higher risk for more severe problems with sleep disturbance and DS prior to surgery and during subsequent treatments for breast cancer. Therefore, the purposes of this study, in a sample of women who underwent surgery for breast cancer (n=396), were to examine how self-reports of sleep disturbance and DS changed from the time prior to surgery to six months following surgery and to evaluate whether specific demographic, clinical, symptom, and psychosocial adjustment characteristics predicted the initial levels of these sleep parameters and/or characteristics of the trajectories of these sleep parameters.

Methods

Patients and Settings

This longitudinal study was part of a larger study that evaluated neuropathic pain and lymphedema in a sample of women who underwent breast cancer surgery. Patients were recruited from breast care centers located in a comprehensive cancer center, two public hospitals, and four community practices. Women were eligible to participate if they: were >18 years of age; underwent breast cancer surgery on one breast; were able to read, write, and understand English; and provided written informed consent. Women were excluded if they were having bilateral breast cancer surgery and/or had distant metastasis at the time of diagnosis. A total of 516 patients were approached and 410 enrolled in the study (response rate of 79.4%). For this analysis, questionnaire booklets were completed by 396 patients. The major reasons for refusal were: too busy, overwhelmed with the cancer diagnosis, or insufficient time available to do the baseline assessment prior to surgery.

Instruments

At enrollment, demographic and clinical information were obtained. Medical records were reviewed for disease and treatment information. At each subsequent assessment, patients provided information on current treatments for breast cancer.

Functional status was evaluated using the Karnofsky Performance Status (KPS) score. Patients rated their functional status using the KPS scale that ranged from 30 (“I feel severely disabled and need to be hospitalized”) to 100 (“I feel normal; I have no complaints or symptoms.” The KPS scale has well-established validity and reliability.[24]

The Self-Administered Comorbidity Questionnaire (SCQ) consists of 13 common medical conditions that were simplified into language that could be understood without any prior medical knowledge. Patients indicated if they had the condition using a dichotomous “yes/no” format. If they indicated that they had a condition, they were asked if they received treatment for it (yes/no; proxy for disease severity) and if it limited their activities (yes/no; indication of functional limitations). Patients could add two additional conditions not listed on the instrument. For each condition, patients could receive a maximum of three points. Because 13 defined medical conditions are listed, the maximum score is 39 points. The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions.[25,26]

The 21-item General Sleep Disturbance Scale (GSDS) was used to evaluate overall sleep disturbance over the past week. Each item is rated on a scale that ranges from 0 (never) to 7 (everyday). The GSDS comprises seven subscales (i.e., quality of sleep, quantity of sleep, sleep onset latency, mid-sleep awakenings, early awakenings, medications for sleep, DS) that can range from 0 to 7 and a total score that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). A total GSDS score of ≥43 indicates a clinically meaningful level of sleep disturbance.[27] The GSDS has high internal consistency reliability among oncology samples.[28,29] Cronbach’s alpha for the GSDS total score was 0.86. The total GSDS score and the subscale score for DS were used in these analyses.

DS was evaluated using the seven items from the GSDS that make up the DS subscale.[30] This subscale ascertains the level of DS by asking questions about ability to stay awake and scheduled and unscheduled napping during the day. Additional questions evaluate irritability, alertness, and sleepiness during the daytime hours. Scores can range from 0 to 7 and represent the number of days a week a patient finds that DS is problematic. A score ≥3 indicates a clinically meaningful level of disturbance.

The Center for Epidemiological Studies-Depression Scale (CES-D) consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60, with scores of ≥16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well-established concurrent and construct validity.[31,32] Cronbach's alpha for the CES-D was 0.90.

The Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) contain 20 items each that are rated from 1 to 4. Scores are summed and can range from 20 to 80. Higher scores indicate greater anxiety. Cutoff scores of ≥31.8 and ≥32.2 indicate high levels of trait and state anxiety, respectively. The STAI-T and STAI-S inventories have well-established criterion and construct validity and internal consistency reliability coefficients.[33,34] Cronbach's alphas for the STAI-T and STAI-S were 0.88 and 0.95, respectively.

The Lee Fatigue Scale (LFS) comprises 18 items designed to assess *physical* fatigue and energy.[35] Each item is rated on a 0 (not at all) to 10 (extremely) numeric rating scale (NRS). Higher scores indicate greater fatigue severity and higher levels of energy. Cutoff scores of ≥4.4 and ≤4.8 indicate higher levels of fatigue and lower levels of energy, respectively. The LFS has well-established validity and reliability with oncology patients.[28,36] Cronbach's alphas for the fatigue and energy subscales were 0.96 and 0.93, respectively.

The Attentional Function Index (AFI) consists of 16-items designed to measure *attentional* fatigue in patients with cancer. Each item is rated on a 0 to 10 NRS. A mean AFI score was calculated, with higher scores indicating greater capacity to direct attention and, therefore, lower levels of attentional fatigue.[37] Based on a previously conducted analysis of the frequency distributions of the AFI scores,[38] attentional fatigue can be grouped into categories of functional status (i.e., patients who score <5.0 functioning poorly and experiencing high levels of attentional fatigue, patients who score 5.0 to 7.5 functioning moderately well and experiencing moderate levels of attentional fatigue, patients who score >7.5 functioning well and experiencing low levels of attentional fatigue). The AFI has established reliability and validity.[37] Cronbach's alpha for the AFI was 0.95.

The occurrence of breast pain prior to surgery was determined by asking "Are you experiencing pain in your affected breast?" If women responded yes, they rated the severity of their average and worst pain using a 0 (no pain) to 10 (worst pain imaginable) NRS.[39] Women were asked how many days a week and how many hours a day they experienced significant pain (i.e., How many days out of a typical week do you currently have pain in your affected breast that interferes with your mood and/or activities? On those days when you have pain in your affected breast, how many hours of the day does it currently last?).

The occurrence of hot flashes prior to surgery was determined by asking "Did you have hot flashes in the last week?" If women responded yes, they rated the severity and distress associated with the hot flashes on a 0 (none and not at all distressing, respectively) to 10 (intolerable and very distressing, respectively) NRS.

The Quality of Life-Patient Version (QOL-PV) is a valid and reliable 41-item instrument that measures four dimensions of QOL in cancer patients (i.e., physical well-being, psychological well-being, spiritual well-being, social well-being) as well as a total QOL score.[40,41] Cronbach's alpha for the QOL-PV total score was 0.86.

Individual items from the QOL-PV were used to assess a number of psychosocial adjustment characteristics (i.e., coping, distress, fear, control). One item asked patients to rate their difficulty coping as a result of cancer and its treatment. Another item asked patients to rate the distress associated with their initial cancer diagnosis. Fear was assessed with two questions, one regarding fear of future diagnostic tests and another regarding fear

of developing a second cancer. Finally, one question asked the patient to rate her level of control over things in her life. Each item was rated using a 0 to 10 NRS, with higher scores indicating a better QOL.

Study Procedures

The Committee on Human Research at the University of California, San Francisco and the Institutional Review Boards at each of the study sites approved the study. During the patient's preoperative visit, a staff member explained the study to the patient. For those women who were willing to participate, the staff member introduced the patient to the research nurse who met with the women, determined eligibility, and obtained written informed consent prior to surgery. After providing consent, patients completed the baseline study questionnaires (Assessment 0). Following the completion of these questionnaires, the research nurse obtained the patient's height and weight. Patients were contacted two weeks after surgery to schedule the first postoperative visit. The research nurse met with the patients in their home, the Clinical Research Center, or the clinic at one, two, three, four, five and six months after surgery. During each study visit, the women completed the study instruments.

Statistical Analysis

Descriptive statistics and frequency distributions were generated on the sample characteristics, baseline symptom severity scores, and QOL-PV scores using SPSS v. 18 (SPSS Inc., Chicago, IL).[42] For each of the seven assessments, mean total GSDS and DS subscale scores were calculated for use in the subsequent statistical analyses.

Hierarchical linear modeling (HLM), based on full maximum likelihood estimation, was done using the software developed by Raudenbush and Bryk.[43] The repeated measures of overall sleep disturbance and DS were conceptualized as being nested within individuals. Compared with other methods of analyzing change, HLM has two major advantages. First, HLM can accommodate unbalanced designs, which allows for the analysis of data when the number and the spacing of the assessments vary across respondents. Second, HLM has the ability to model individual change, which helps to identify more complex patterns of change that are often overlooked by other methods.[43,44]

With HLM, the repeated measures of the outcome variables (i.e., overall sleep disturbance and DS) are nested within individuals and the analysis of change in these scores has two levels: within persons (level 1) and between persons (level 2). At level 1, the outcome is conceptualized as varying within individuals and is a function of person-specific change parameters plus error. At level 2, these person-specific change parameters are multivariate outcomes that vary across individuals. These level 2 outcomes can be modeled as a function of demographic, clinical, and symptom characteristics that vary between individuals, plus an error associated with the individual. Combining level 1 and level 2 results in a mixed model with both fixed and random effects.

Separate HLM analyses were done to evaluate changes over time in ratings of overall sleep disturbance and DS. Each HLM analysis proceeded in two stages. First, intra-individual variability in the sleep parameter over time was examined. In this study, time, in months, refers to the length of time from the preoperative visit to six months after the completion of surgery (i.e., six months with a total of seven assessments). Three level 1 models, which represented that the patients' sleep parameter levels a) did not change over time (i.e., no time effect), b) changed at a constant rate (i.e., linear time effect), and c) changed at a rate that accelerates or decelerates over time (i.e., quadratic effect), were compared. At this

point, the level 2 model was constrained to be unconditional (i.e., no predictors), and the likelihood ratio tests were used to determine the best model.

The second stage of the HLM analysis, examined interindividual differences in the trajectories of overall sleep disturbance and DS by modeling the individual change parameters (i.e., intercept, linear, and quadratic slopes) as a function of proposed predictors at level 2. Table 1 presents a list of the proposed predictors that was developed based on a review of the literature of sleep disturbance in women with breast cancer.[2,6,8,15,17–23] To improve estimation efficiency and construct a model that was parsimonious, an exploratory level 2 analysis was done in which each potential predictor was assessed to see it if would result in a better fitting model if it alone was added as a level 2 predictor. Predictors with a t value of less than 2.0, which indicates a lack of a significant effect, were dropped from subsequent model testing. All of the potentially significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained a significant contribution in conjunction with other variables were retained in the final model. A P-value of <0.05 indicates statistical significance.

Results

Patient Characteristics and Symptom Severity Scores

Table 2 summarizes the demographic and clinical characteristics of the 396 women in this study. The mean age of the women was 55 years. These women were well-educated (15.7 years), had a mean SCQ score of 4.3 (+2.8), and 35% were non-white. Of this sample, approximately 48% were employed, 24% lived alone, and 41% were married. Approximately 38% had Stage I disease and 35% had Stage II disease. The majority of the women were post-menopausal (62%) and 32% were experiencing hot flashes. Only 20% of these women had undergone neoadjuvant CTX. The majority of the sample had breast conserving surgery (80%) and a sentinel lymph node biopsy (SLNB, 82%). Almost 22% underwent breast reconstruction at the time of surgery. The mean baseline symptom severity scores for the 396 women are listed in Table 2.

Individual and Mean Change in Overall Sleep Disturbance and DS

The first HLM analyses examined how overall sleep disturbance and DS changed from the time of the preoperative visit to six months after surgery. Two models were estimated in which the function of time was linear and quadratic. For both sleep parameters, the goodness-of-fit tests of the deviance between the linear and quadratic models indicated that a quadratic model fit the data significantly better than a linear model (both, P<0.001).

Sleep Disturbance—The estimates for the quadratic change model for sleep disturbance are presented in Table 3. Because the model had no covariates (i.e., unconditional), the intercept represents the estimated amount of sleep disturbance (i.e., 48.313 on a 0 to 147 point scale) at the preoperative assessment. The estimated linear rate of change in sleep disturbance, for each additional month, was 0.449 (P=0.346) and the estimated quadratic rate of change per month was −0.159 (P<0.05). The weighted combination of the linear and quadratic terms defines each curve. As shown in Fig. 1A, sleep disturbance increased slightly during the first month and then slowly declined over the remainder of the study. It should be noted that the mean sleep disturbance and DS scores for the various groups depicted in all of the figures are estimated or predicted means based on the HLM analyses.

Daytime Sleepiness—As shown in Table 3, in the unconditional model, the intercept represents the estimated amount of DS (i.e., 2.079 on a 0 to 7 scale) at the preoperative assessment. The estimated linear rate of change in DS, for each additional month, was 0.080

($P<0.05$), and the estimated quadratic rate of change per month was −0.020 ($P<0.01$). As shown in Fig. 1B, DS increased from the time prior to surgery to two months after surgery and then slowly declined throughout the remainder of the study.

Although the results indicate a sample-wide increase followed by a decrease in both sleep disturbance and DS, they do not imply that all patients exhibited the same trajectories. The variance in individual change parameters estimated by the models (i.e., variance components; Table 3) suggested that substantial interindividual differences existed in the trajectories of sleep disturbance and DS. These results suggest that further examination of interindividual differences in the individual change parameters were warranted.

Interindividual Differences in the Trajectories of Sleep Disturbance and DS

The second stage of the HLM analyses tested if the pattern of change over time in sleep disturbance and DS varied based on specific demographic, clinical, symptom, or psychosocial adjustment characteristics that were found to influence sleep disturbance and/or DS in patients with breast cancer.[2,6,8,15,17–23] Exploratory analyses were done with the potential predictors listed in Table 1.

Sleep Disturbance—As shown in the final model in Table 3, the variables that predicted interindividual differences in the intercept for sleep disturbance were: functional status, comorbidity, depressive symptoms, physical fatigue, severity of hot flashes, and attentional fatigue. The variables that predicted interindividual differences in the slope parameters for sleep disturbance were education, receipt of adjuvant CTX, and depressive symptoms.

The effects of each of the predictors on patients' trajectories of nocturnal sleep disturbance are illustrated in Figs. 2 and 3. In terms of the intercept predictors, a lower functional status (2B), a higher comorbidity score (2C), as well as a higher score for hot flashes (3A), attentional fatigue (3B), and physical fatigue (3C) were associated with higher levels of nocturnal sleep disturbance *prior* to surgery. In terms of slope predictors, higher levels of education (2A) and receipt of adjuvant CTX (2D) were associated with gradual increases in sleep disturbance that peaked at the third month and then decreased from three to six months following surgery. Higher depressive symptom scores (3D) were associated with higher levels of sleep disturbance prior to surgery that decreased slightly in the six months following surgery.

Daytime Sleepiness—As shown in the final model in Table 3, the variables that predicted interindividual differences in the intercept for DS were: functional status, body mass index (BMI), depressive symptoms, physical fatigue, and attentional fatigue, as well as underwent a SLNB, and underwent an axillary lymph node dissection (ALND). The variables that predicted interindividual differences in the slope parameters for DS were: education, employment status, fear of future diagnostic testing, receipt of neo-adjuvant CTX, and receipt of adjuvant CTX.

The effects of each of the predictors on patients' trajectories of DS are illustrated in Figs. 4, 5, and 6. In terms of intercept predictors, a lower functional status (5A), a higher BMI (5B), not having a SLNB (5C), having an ALND (5D), as well as higher levels of depressive symptoms (6A), physical fatigue (6B), and attentional fatigue (6C) were associated with higher levels of DS prior to surgery. In terms of slope predictors, higher levels of education (4A), not working for pay (4B), not having undergone neo-adjuvant CTX (5E), receipt of adjuvant CTX (5F), and less fear of future diagnostic tests (6D) predicted higher DS scores over time.

Discussion

This study is the first to evaluate the severity of sleep disturbance and DS in women prior to surgery for breast cancer, as well as the predictors of initial levels and predictors of changes in sleep disturbance and DS over time. Whereas several predictors were the same for both sleep parameters (i.e., education, functional status, depressive symptoms, physical fatigue, attentional fatigue, receipt of adjuvant CTX), a number were unique to sleep disturbance (i.e., comorbidity, hot flash severity rating) and DS (employment status, BMI, SLNB, ALND, receipt of neo-adjuvant CTX, fear of future diagnostic tests).

Trajectory and Predictors of Sleep Disturbance

Consistent with previous studies that used the GSDS to evaluate sleep disturbance in women prior to RT for breast cancer,[28,45] the preoperative GSDS score of 48.1 is above the cutoff for clinically meaningful levels of sleep disturbance (≥43). In addition, these findings are consistent with high levels of sleep disturbance reported by women prior to[2,15,17,46] and during CTX[46] for breast cancer. Of note, while women reported a slight increase followed by a decrease in GSDS scores over the six months of this study, at the six-month assessment, GSDS scores remained above the clinically meaningful cutoff.

As noted in a previous report,[47] women with more education showed a slight increase in sleep disturbance over the first three months of the study followed by a gradual decline over the last three months. One potential explanation for this positive association is that women with more education may experience higher levels of distress related to increased knowledge about their disease and its treatment. In terms of clinical characteristics and confirmed in previous reports of heterogeneous samples of oncology patients,[29,48,49] poorer functional status was associated with higher levels of sleep disturbance prior to surgery. Findings related to the influence of comorbidities on sleep disturbance are inconclusive. Although a study of breast cancer patients one year after diagnosis did not find an association between comorbidity and sleep disturbance,[50] positive associations were found in this study as well as in studies of patients with other chronic medical conditions.[51–54]

Higher preoperative levels of depressive symptoms were associated with preoperative levels of sleep disturbance that slowly decreased over the six months of the study. In contrast, women with lower depressive symptom scores had sleep disturbance scores that worsened and then improved after three months. This increase in depressive symptoms may be related to the initiation of CTX or RT. However, for both groups, GSDS scores remained above the clinically meaningful cutoff score (Fig. 3D). Although no studies have evaluated the effects of depressive symptoms on changes in the severity of sleep disturbance over time, in cross-sectional studies of women during CTX and/or RT, higher levels of depressive symptoms were associated with increased severity of sleep disturbance.[2,6,12,13]

As seen in studies of women before and during primary treatment for breast cancer,[2,6,8,11,13,15,17,46,47,55] higher levels of physical fatigue were associated with higher levels of sleep disturbance. Although a causal relationship between fatigue and sleep disturbance was not demonstrated in these studies, one study found that a behavioral intervention improved sleep quality, but not fatigue,[47] which reinforces the distinct differences between these two symptoms. Of note, as shown in Fig. 3C, in both the lower and higher fatigue groups, the predicted GSDS scores were above the cutoff for clinically meaningful levels of sleep disturbance prior to surgery.

Similar to findings from a study of breast cancer patients prior to initiation or RT,[56] higher levels of preoperative attentional fatigue were associated with higher preoperative sleep disturbance scores. Several questions on the AFI assess disorganized thought processes and

inability to complete tasks. It is possible that these disorganized thoughts and/or distress related to incomplete tasks during the day (i.e., higher attentional fatigue) lead to an inability to fall asleep or maintain sleep (i.e., increased sleep disturbance). This hypothesis is supported by a study of breast cancer survivors that found that dysfunctional sleep-related thoughts (e.g., anxiety about sleep) predicted decreased sleep efficiency and sleep quality.[57]

Finally, as found in other studies,[6,58,59] higher hot flash severity ratings were associated with higher preoperative levels of sleep disturbance. Whereas the incidence and frequency of hot flashes are the most common measurement parameters, it may be important to evaluate the severity of hot flashes. It is plausible that more severe hot flashes result in awakenings during the night that adversely effects sleep quality. However, additional research is warranted to confirm this hypothesis using both subjective and objective measures of hot flashes.

Trajectory and Predictors of DS

As found in a study of breast cancer patients prior to RT,[45] the preoperative DS score of 2.1 is below the cutoff for clinically meaningful DS (≥3). The DS subscale score can be interpreted as the number of days per week that DS is experienced. Therefore, on average these women experienced DS for two days per week prior to surgery. A slight increase in DS occurred through month two, followed by a slight decline through month six (Fig. 1B). However, throughout the study, the scores remained below the cutoff score for clinically meaningful DS. These findings are similar to reports of women prior to[2,15] and during CTX[16,46] for breast cancer, as well as for women during (i.e., 2.7) and after pregnancy (i.e., 2.2).[60] In contrast, the DS scores of the women with breast cancer were lower than those reported by women who worked night shifts (i.e., 3.4) and rotating shifts (i.e., 3.0).[30] Because no study was found that included changes over time in DS in breast cancer patients, these findings warrant confirmation in future studies.

Higher levels of education and not being employed predicted a small increase in DS from before to three months after surgery, followed by a gradual decline. Similar to our findings for sleep disturbance, women with higher levels of education may have more distress related to increased information that results in sleep disturbance, as well as DS. Our finding related to employment status is consistent with a study that found that breast cancer survivors who were not working reported disruptions in daily life.[61] These disruptions in daily life may result in sleep disturbance and subsequent reports of DS.

Although lower functional status scores were associated with higher levels of sleep disturbance in heterogeneous samples of cancer patients,[29,49,62] no studies were found that evaluated the association between functional status and DS in breast cancer patients. One potential explanation for why higher BMI was associated with higher preoperative levels of DS is that patients with a higher BMI may have obstructive sleep apnea.[63,64] Patients in this study were not screened for sleep disorders. However, this finding warrants additional investigation.

Women who did not undergo a SLNB at the time of surgery had slightly higher levels of DS prior to surgery than women who underwent a SLNB. In addition, these women were more likely to be diagnosed with Stage 0 disease, did not undergo reconstruction at the time of surgery, and had not received neo-adjuvant CTX (all $P<0.03$). In contrast, women who underwent an ALND at the time of surgery had slightly higher levels of DS prior to surgery than women who did not undergo an ALND. One possible explanation for this relationship is that women who were to undergo an ALND had more distress associated with their disease and subsequent treatment trajectory.

Fear of future diagnostic tests and receipt of neo-adjuvant and adjuvant CTX predicted the trajectories of DS. Women who reported a lower fear of diagnostic testing had a slight increase in DS from the time prior to surgery through month three, followed by a gradual decline through month six. The reason for this association is not readily apparent and requires additional research to refute or confirm. Women who had not received neo-adjuvant CTX and women who had received adjuvant CTX had a small increase in DS from baseline through month three, followed by a gradual decline through month six. The receipt of adjuvant CTX is associated with increased fatigue that may result in DS.[11,15]

The positive associations between depressive symptoms and DS, prior to surgery, is consistent with one study of women with metastatic breast cancer.[23] A positive association between physical fatigue and DS was observed in women prior to[15] and during CTX[8] for breast cancer. It is likely that fatigue throughout the day leads to DS. Although no studies examined the relationship between attentional fatigue and DS, one possible explanation for the positive association is that sleep disturbance during the night influences both attentional fatigue and DS.

Some study limitations warrant discussion. No objective measure of sleep disturbance was used to corroborate self-reported sleep disturbance and DS. In addition, sleep problems of the patients' bed partner, the environment in which patients slept, and employment-related stress and work schedules were not assessed as potential predictors and warrant evaluation in future studies.

Despite these limitations, the findings from this study suggest that sleep disturbance is a persistent problem for breast cancer patients prior to and following surgery. In addition, a number of modifiable risk factors associated with prolonged sleep disturbance were identified. Clinicians can use the demographic, clinical, symptom, and psychosocial adjustment characteristics associated with increased sleep disturbance and DS to identify high risk patients who warrant more in-depth assessments and interventions. Additional research needs to evaluate the effects of interventions that can address modifiable risk factors.

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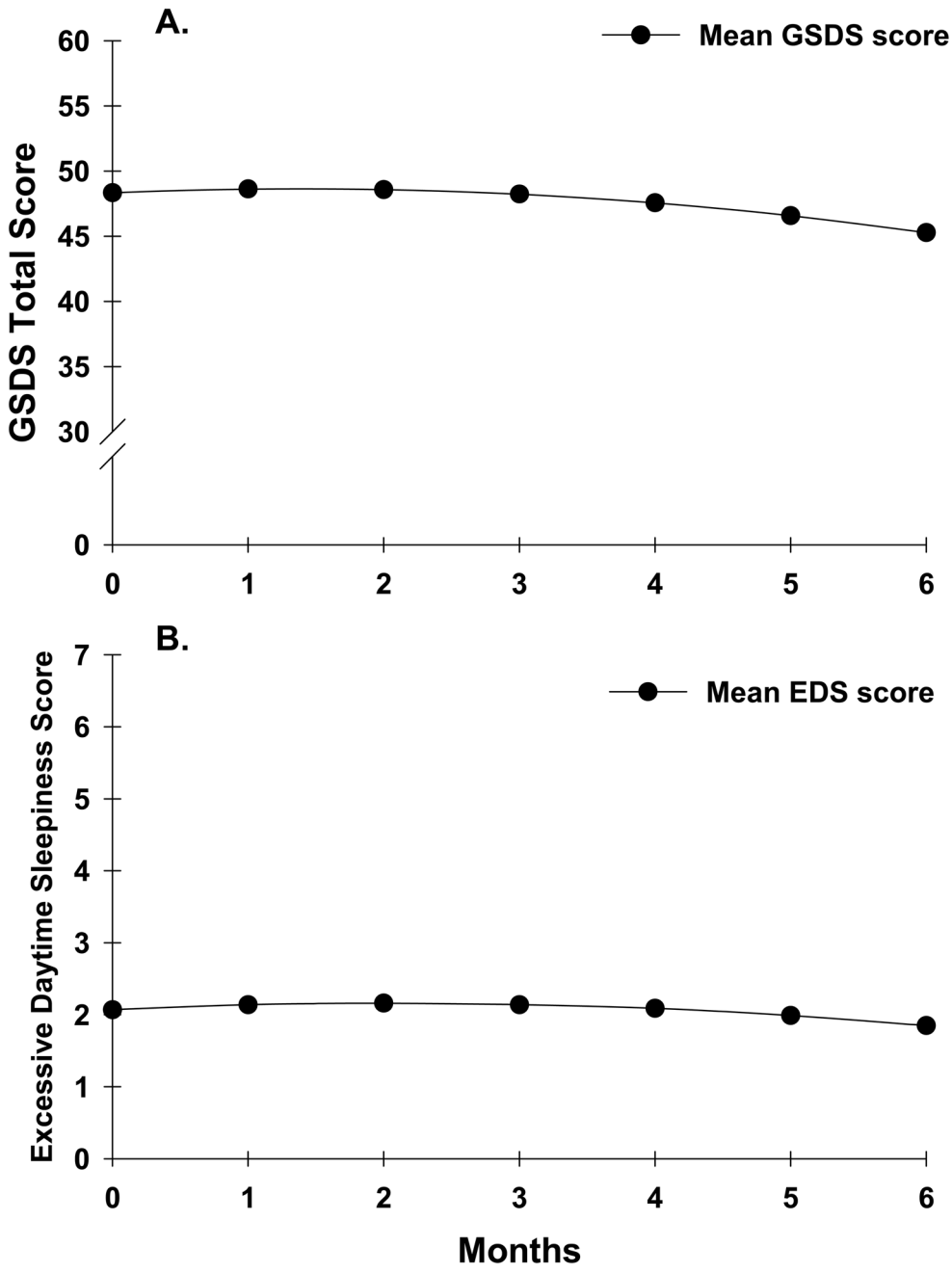

Fig. 1.
Trajectory of sleep disturbance (A) and daytime sleepiness (DS) (B) over the six months of the study.

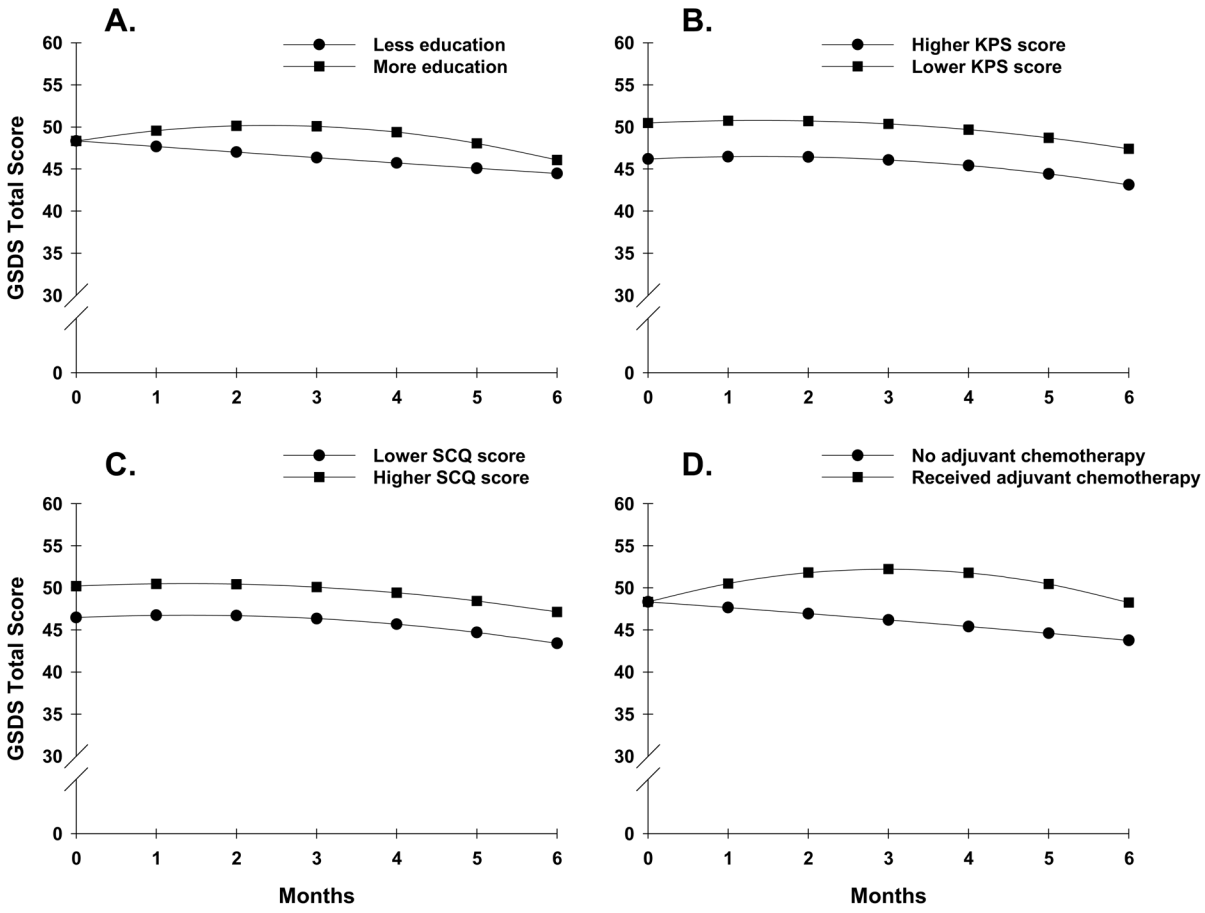

Fig. 2.

Influence of education (A: less/more education calculated based on 1 standard deviation (SD) above and below the mean years of education) on the slope parameters for sleep disturbance and influence of performance status (B: lower/higher functional status calculated based on 1 SD above and below the mean Karnofsky Performance Status score); comorbidities (C: lower/higher comorbidity calculated based on 1 SD above and below the mean Self-administered Comorbidity Questionnaire score), and receipt of adjuvant chemotherapy (CTX) (D: did or did not receive adjuvant CTX) on interindividual differences in the intercept for sleep disturbance.

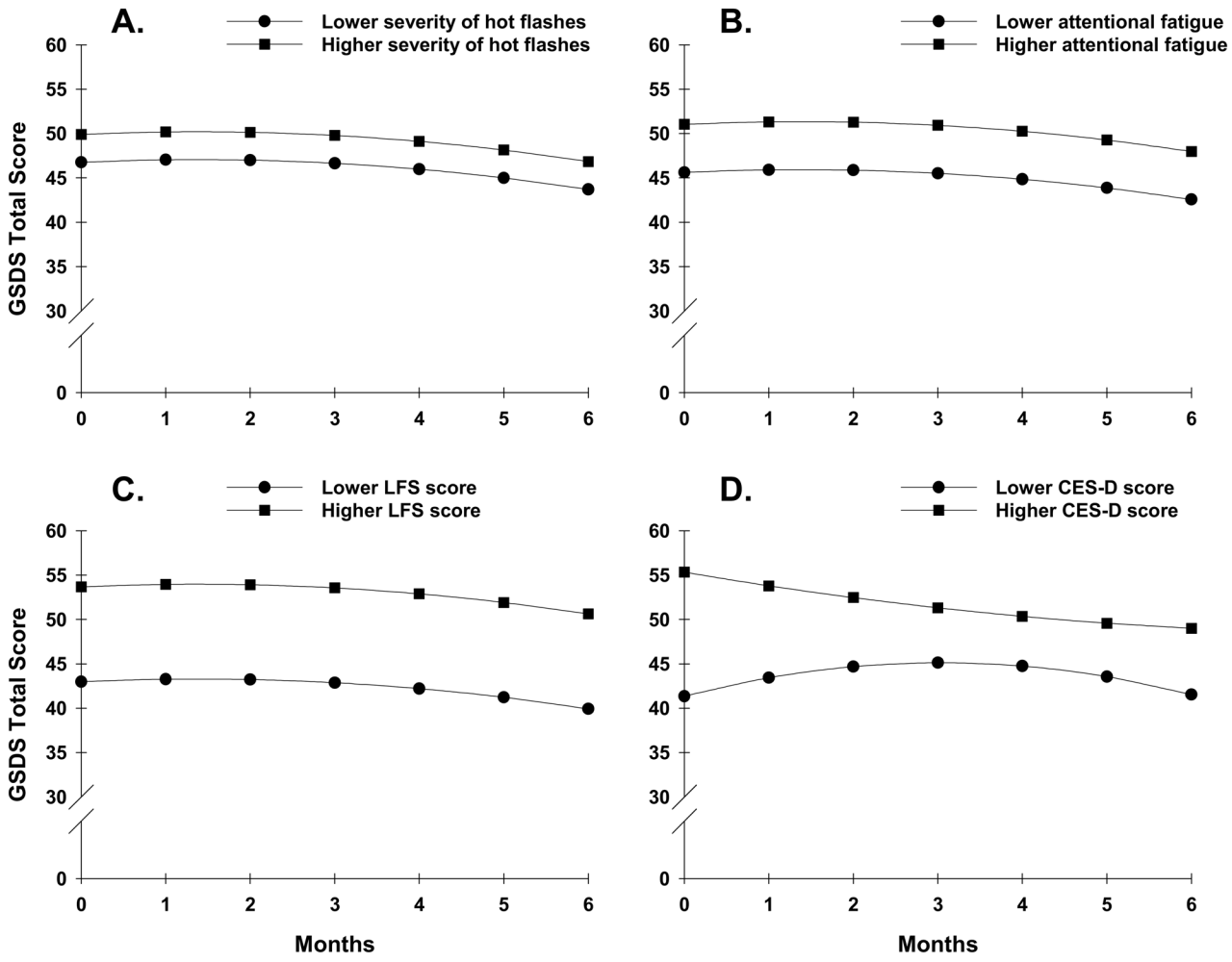

Fig. 3.

Influence of severity of hot flashes (A: lower/higher severity of hot flashes calculated based on 1 SD above and below the mean hot flash severity score), attentional fatigue (B: lower/higher attentional fatigue calculated based on 1 SD above and below the mean Attentional Function Index score), and physical fatigue (C: lower/higher physical fatigue calculated based on 1 SD above and below the mean Lee Fatigue Scale score) on interindividual differences in the intercept for sleep disturbance; and influences of depressive symptoms (D: i.e., lower/higher depressive symptoms calculated based on 1 SD above and below the mean Center for Epidemiological Studies-Depression score) on interindividual differences in the intercept and slope parameters for sleep disturbance.

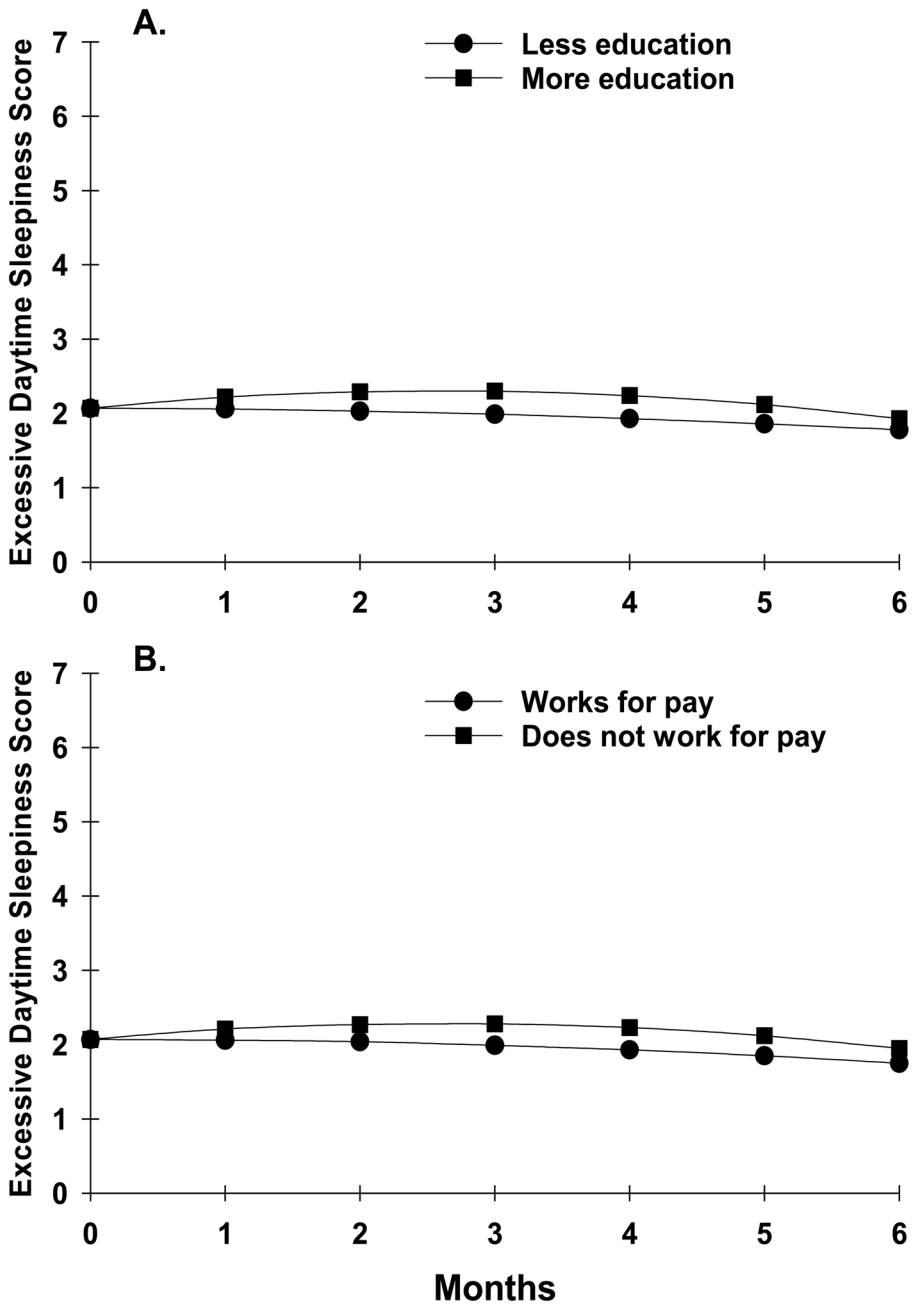

Fig. 4.

Influence of education (A: less/more education based on 1 SD above and below the mean years of education) and employment status (B: employed or not employed) on the slope parameters for daytime sleepiness.

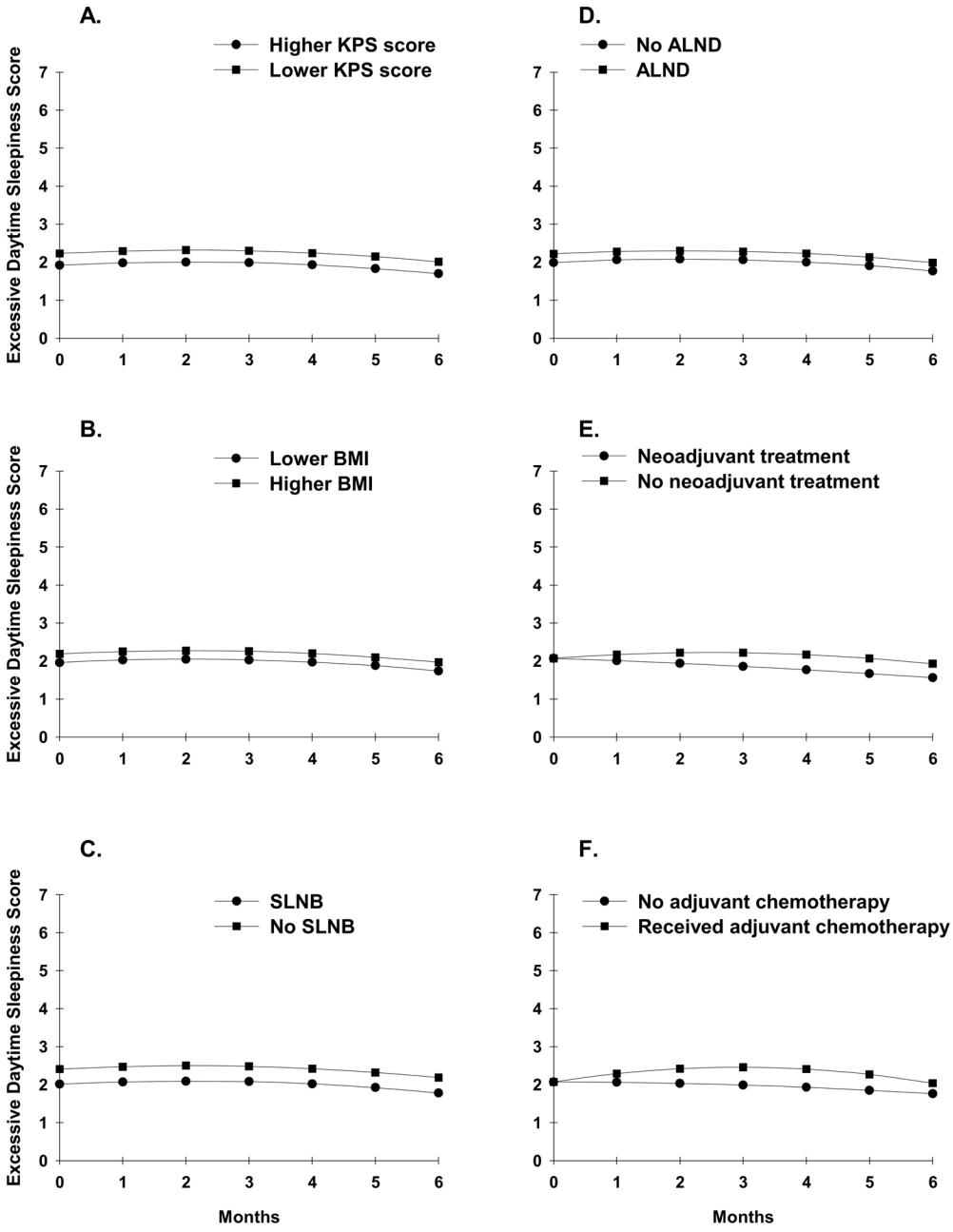

Fig. 5.

Influence of performance status (A: lower/higher functional status calculated based on 1 SD above and below the mean Karnofsky Performance Status score), body mass index (BMI) (B: lower/higher BMI calculated based on 1 SD above and below the mean BMI), underwent a sentinel lymph node biopsy (SLNB) (C: did or did not have SLNB) and underwent an axillary lymph node dissection (ALND) (D: did or did not have an ALND) on interindividual differences in the intercept for daytime sleepiness (DS) and neoadjuvant chemotherapy (CTX) (E: did or did not have neo-adjuvant CTX) and adjuvant CTX (F: did or did not have adjuvant CTX) on the slope parameters for DS.

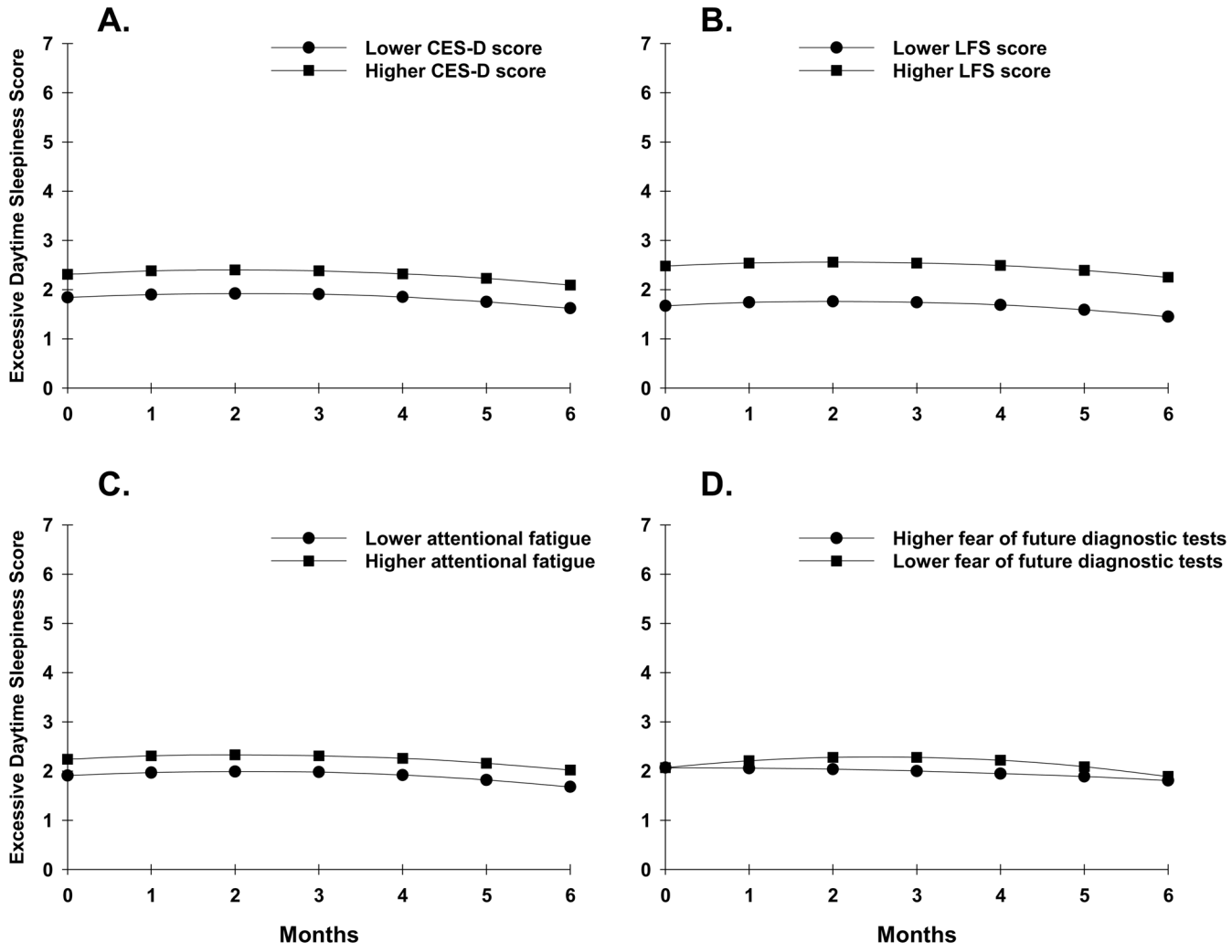

Fig. 6.

Influence of depressive symptoms (A: lower/higher depressive symptoms calculated based on 1 SD above and below the mean Center for Epidemiological Studies-Depression score), physical fatigue (B: lower/higher physical fatigue calculated based on 1 SD above and below the mean Lee Fatigue Scale score), and attentional fatigue (C: lower/higher attentional fatigue calculated based on 1 SD above and below the mean Attentional Function Index score) on interindividual differences in the intercept for daytime sleepiness and fear of future diagnostic tests (D: lower/higher fear calculated based on 1 SD above and below the mean fear of future diagnostic test score) on the slope parameters for DS.

Table 1

Potential Predictors of Intercepts (I), Linear Coefficients (LC), and Quadratic Coefficients (QC) for the Overall Sleep Disturbance and Daytime Sleepiness

Characteristics	Overall Sleep Disturbance			Daytime Sleepiness		
	I	LC	QC	I	LC	QC
Demographic						
Age						
Lives alone						
Marital status						
Education		■	■		■	■
Ethnicity						
Employment status					■	■
Clinical						
Body mass index				■		
SCQ score	■					
Karnofsky Performance Status score	■			■		
Stage of disease						
Neoadjuvant chemotherapy	■				■	
Type of surgery					■	
Sentinel lymph node biopsy				■		
Axillary lymph node dissection				■		
Breast reconstruction at time of surgery					■	
Menopausal status						
Adjuvant radiation therapy in first 6 months						
Adjuvant chemotherapy in first 6 months		■	■		■	■
Symptoms						
CES-D score	■	■	■	■		
Trait Anxiety score	■					
State Anxiety score		■	■	■		
Attentional Fatigue score	■			■		

Characteristics	Overall Sleep Disturbance			Daytime Sleepiness		
	I	LC	QC	I	LC	QC
LFS Fatigue score	■	■		■	■	
LFS Energy score						
Presence of hot flashes	■					
Severity of hot flashes						
Distress from hot flashes						
Presence of breast pain prior to surgery						
Worst pain score						
Average pain score						
Number of days per week in pain						
Number of hours per day in pain						
Psychosocial Adjustment						
Difficulty coping as a result of disease/treatment	■	■	■		■	■
Distress of initial diagnosis	■					
Fear of future diagnostic tests		■	■		■	■
Fear of metastasis	■					
Control of things in your life	■	■				■

CES-D = Center for Epidemiological Studies-Depression Scale; LFS = Lee Fatigue Scale; SCQ = Self-Administered Comorbidity Questionnaire.

■ = From exploratory analysis, had a *t* value of greater than 2.00.

Table 2

Demographic, Clinical, and Symptom Characteristics of the Patients (*n*=396)

Characteristic	Mean (SD)
Age (years)	54.9 (11.6)
Education (years)	15.7 (2.7)
Karnofsky Performance Status score	93.2 (10.3)
Self-Administered Comorbidity Questionnaire score	4.3 (2.8)
Body mass index (kg/m^2)	26.8 (6.2)
Postmenopausal, % (*n*)	62.3 (248)
Experiencing hot flashes, % (*n*)	31.9 (127)
Lives alone, % (*n*)	23.9 (95)
Married, % (*n*)	41.5 (165)
Non-white, % (*n*)	35.4 (141)
Employed, % (*n*)	47.5 (189)
Stage of disease, % (*n*)	
0	18.3 (73)
I	37.9 (151)
IIA, IIB	35.4 (141)
IIIA, IIIB, IIIC, IV	8.3 (33)
Neoadjuvant chemotherapy prior to surgery, % (*n*)	19.8 (79)
Type of surgery, % (*n*)	
Breast conservation	79.9 (318)
Mastectomy	20.1 (80)
Underwent breast reconstruction at the time of surgery, % (*n*)	21.6 (86)
Underwent sentinel lymph node biopsy, % (*n*)	82.4 (328)
Underwent axillary lymph node dissection, % (*n*)	37.4 (149)
Received adjuvant radiation therapy in first six months, % (*n*)	56.6 (224)
Received adjuvant chemotherapy in first six months, % (*n*)	33.6 (133)
Pain in the affected breast prior to surgery, % (*n*)	28.2 (110)
Mean symptom severity scores prior to surgery	
Center for Epidemiological Studies-Depression Scale score	13.7 (9.8)
Trait Anxiety score	35.3 (9.0)
State Anxiety score	41.8 (13.5)
Attentional Function Index score	6.6 (1.9)
Lee Fatigue Scale - Fatigue score	3.1 (2.4)
Lee Fatigue Scale - Energy score	4.9 (2.5)

Table 3

Hierarchical Linear Models of Sleep Disturbance and Daytime Sleepiness

	Coefficient (SE)	
Variable	**Unconditional Model**	**Final Model**
Sleep Disturbance		
Fixed effects		
Intercept	48.313 (1.072)[b]	48.335 (0.777)[b]
Time[a] (linear rate of change)	0.449 (0.475)[ns]	−0.667 (0.541)[ns]
Time^2 (quadratic rate of change)	−0.159 (0.073)[d]	−0.016 (0.086)[ns]
Time invariant covariates		
Intercept		
KPS score		−0.208 (0.074)[c]
SCQ score		0.660 (0.253)[d]
CES-D score		0.724 (0.096)[b]
Physical fatigue (LFS score)		2.283 (0.364)[b]
Hot flash severity rating		0.641 (0.296)[d]
AFI score		−1.416 (0.491)[c]
Linear		
Education (years) x time		0.420 (0.158)[c]
Adjuvant chemotherapy x time		3.277 (0.874)[b]
CES-D x time		−0.213 (0.047)[b]
Quadratic		
Education (years) x time^2		−0.061 (0.026)[d]
Adjuvant chemotherapy x time^2		−0.421 (0.144)[c]
CES-D x time^2		0.026 (0.007)[b]
Variance components		
In intercept	363.104[b]	148.392[b]
In linear rate	30.489[b]	23.409[b]
In quadratic fit	0.596[b]	0.473[b]
Goodness-of-fit deviance (parameters estimated)	20621.422 (10)	20337.292 (22)
Model comparison (χ^2_{12})		284.13 (12)[b]
Daytime Sleepiness		
Fixed effects		
Intercept	2.079 (0.064)[b]	2.328 (0.098)[b]
Time[a] (linear rate of change)	0.080 (0.031)[d]	0.107 (0.047)[d]
Time^2 (quadratic rate of change)	−0.020 (0.005)[b]	−0.022 (0.008)[c]
Time invariant covariates		
Intercept		

	Coefficient (SE)	
Variable	**Unconditional Model**	**Final Model**
KPS score		−0.015 (0.004)[b]
SLNB		−0.404 (0.099)[b]
ALND		0.222 (0.082)[c]
Body mass index (kg/m^2)		0.018 (0.006)[c]
CES-D score		0.025 (0.005)[b]
Physical fatigue (LFS score)		0.171 (0.020)[b]
AFI score		−0.088 (0.026)[c]
Linear		
Education (years) x time		0.035 (0.010)[c]
Employment status x time		−0.162 (0.054)[c]
Fear of future diagnostic tests x time		0.027 (0.008)[c]
Neo-adjuvant chemotherapy x time		−0.178 (0.069)[d]
Adjuvant chemotherapy x time		0.266 (0.056)[b]
Quadratic		
Education (years) x time^2		−0.005 (0.002)[c]
Employment status x time^2		0.021 (0.009)[d]
Fear of future diagnostic tests x time^2		−0.004 (0.001)[c]
Neo-adjuvant chemotherapy x time^2		0.019 (0.011)[ns]
Adjuvant chemotherapy x time^2		−0.036 (0.009)[b]
Variance components		
In intercept	1.160[b]	0.375[b]
In linear rate	0.097[b]	0.064[c]
In quadratic fit	0.002[c]	0.001[d]
Goodness-of-fit deviance (parameters estimated)	7000.780 (10)	6671.157 (27)
Model comparison (χ^2_{17})		329.623 (17)[b]

AFI = Attentional Function Index; ALND = axillary lymph node biopsy; CES-D = Center for Epidemiological Studies-Depression Scale; KPS = Karnofsky Performance Status; LFS = Lee Fatigue Scale; ns = not significant; SCQ = Self-Administered Comorbidity Questionnaire; SLNB = sentinel lymph node biopsy.

[a] Time was coded 0 at the time just prior to surgery.

[b] $P<0.001$.

[c] $P<0.01$.

[d] $P<0.05$.