Title
Sleep Disturbance and Decrements in Morning Energy Contribute to a Higher Symptom Burden in Oncology Patients

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Publication Date
2023

Peer reviewed|Thesis/dissertation

Sleep Disturbance and Decrements in Morning Energy Contribute to a Higher Symptom Burden in Oncology Patients

by

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THESIS

Submitted in partial satisfaction of the requirements for degree of

MASTER OF SCIENCE

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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ABSTRACT

Objective/Background: An emerging area of research is the relationship between sleep disturbance and decrements in energy. Given the paucity of research on the co-occurrence of these two symptoms, study purposes were to identify subgroups of oncology patients with distinct joint sleep disturbance AND morning energy profiles and evaluate for differences among the subgroups in demographic, clinical, and sleep disturbance characteristics, as well as the severity of other common symptoms and QOL outcomes.

Patients/Methods: Patients (n=1336) completed measures of sleep disturbance and energy six times over two cycles of chemotherapy. All of the other measures were completed at enrollment. Latent profile analysis was used to identify the distinct joint sleep disturbance and morning energy profiles.

Results: Three distinct profiles were identified (i.e., Low Sleep Disturbance and High Morning Energy (Normal, 20.6%), Moderate Sleep Disturbance and Low Morning Energy (Moderately Severe, 52.1%), Very High Sleep Disturbance and Very Low Morning Energy (Very Severe, 27.3%). Compared to Normal class, other two classes were more likely to be female, less likely to be employed, and had higher comorbidity burden and poorer functional status. Symptom scores and QOL outcomes exhibited a dose response effect (i.e., as the profile worsened, symptom scores increased and QOL scores decreased).

Conclusions: Given the associations between sleep disturbance and decrements in morning energy and a higher symptom burden, poorer QOL outcomes, and increased mortality,

assessment of these two symptoms needs to be a high priority for clinicians and appropriate interventions initiated.

Key words: cancer; chemotherapy; depression; energy; fatigue; insomnia; pain; quality of life; sleep disturbance

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LIST OF ABBREVIATIONS

BIC	Bayesian Information Criterion
BMI	body mass index
GSDS	General Sleep Disturbance Scale
KPS	Karnofsky Performance Status
LFS	Lee Fatigue Scale
LPA	latent profile analysis
MCS	mental component summary
MQOLS-PV	Multidimensional QOL Scale-Patient Version
NRS	numeric rating scale
PCS	physical component summary
QOL	quality of life
SCQ	Self-Administered Comorbidity Questionnaire
SF-12	Medical Outcomes Study-Short Form-12
VLMR	Vuong-Lo-Mendell-Rubin likelihood ratio

1. INTRODUCTION

While sleep disturbance is one of the most common symptoms in oncology patients [1, 2], it displays a significant amount of inter-individual variability [3, 4]. A growing body of evidence suggests that this symptom warrants additional investigation because in these patients it is associated with decrements in functional status [5] and quality of life (QOL) [6], as well as disease progression [7] and increased mortality [2, 8, 9].

One approach to increase our understanding of the inter-individual variability in sleep disturbance is to utilize person centered analytic approaches like latent variable modeling [10]. For example, in our study that evaluated for subgroups of women with distinct sleep disturbance profiles from prior to through six months following breast cancer surgery [4], three distinct subgroups were identified (i.e., Low Sustained, Decreasing, High Sustained). In terms of risk factors, compared to the Low Sustained class, women in the High Sustained class were significantly younger and had a higher level of comorbidity and a poorer functional status. In another study by our team [3], subgroups of patients with Low, High, and Very High levels of sleep disturbance were identified across two cycles of chemotherapy. In terms of risk factors for membership in the High and Very High classes, these patients were younger, more likely to be female, more likely to have childcare responsibilities, less likely to be employed, less likely to have gastrointestinal cancer, had higher levels of comorbidity and a lower functional status. These types of studies provide insights into the identification of oncology patients with an increased likelihood to experience significant amounts of sleep disturbance.

Equally important, in both cross-sectional and longitudinal studies of oncology patients, positive associations were identified between sleep disturbance and fatigue [11-13], depression [12, 14-16], and anxiety [6, 17-20]. In a longitudinal study that evaluated for changes in the co-occurrence of sleep disturbance and fatigue in women undergoing chemotherapy for breast cancer using latent profile analysis (LPA) [21], three groups of patients were identified prior to the initiation of chemotherapy (i.e., Fatigued with Sleep Complaints, Average, Minimal

Symptoms). Compared to the Minimal Symptoms group, patients in the other two groups were younger. In addition, compared to the Minimal Symptoms group, patients in the Average group were more likely to have received a lumpectomy or single mastectomy followed by chemotherapy. These types of studies support the evaluation of co-occurring symptoms and associated risk factors in oncology patients receiving chemotherapy.

As noted above, while positive associations between sleep disturbance and fatigue are well documented [11-13], an emerging area that warrants investigation is the association between sleep disturbance and decrements in energy. While the terms fatigue and energy are often used interchangeably, a growing body of evidence suggests that fatigue and energy are distinct, but related symptoms [22, 23]. In fact, Loy and colleagues proposed that the symptoms of fatigue and energy evolved to serve different purposes (i.e., energy for approach-oriented behaviors such as hunting and gathering; fatigue for avoidance-orienting behaviors such as rest during injuries or illnesses) [22]. They adopted Lerdal's definition of energy (i.e., "an individual's potential to perform mental and physical activity") [24, 25] and noted that synonyms included "vigor", "vitality", "lively" and "full of pep" [26]. In terms of oncology patients, our findings support the hypothesis that fatigue and energy are distinct symptoms with different phenotypic and molecular risk factors [27, 28]. In addition, while not evaluated in oncology patients, recent evidence from a study of older adults suggests that decreases in energy levels over time are associated with an increased risk for disability and mortality [29].

Specific to this analysis, emerging evidence suggests that diurnal variations exist in self-reported levels of energy [30, 31]. In the first study [30], growth mixture modeling was used to identify distinct morning and evening energy profiles and associated risk factors in patients undergoing radiation therapy and their family caregivers. For morning energy, Low (50.8%) and Moderate (49.2%) profiles were identified. Characteristics associated with membership in the Low morning energy class included: younger age, being female, not being married or partnered, self-reported being Black, having a higher comorbidity burden and a poorer functional status. In

terms of evening energy, Moderate and High profiles were identified. Membership in the Moderate energy class was associated with younger age, being male, decreased body weight, a worse comorbidity profile, and a poorer functional status. Of note, variations in different cytokine genes were associated with decrements in morning and evening energy.

In another study of patients undergoing chemotherapy [31], common and distinct risk factors associated with the trajectories of morning and evening energy were evaluated using hierarchical linear modeling [32]. Risk factors associated with decrements in morning energy included: living alone, having childcare responsibilities, lack of regular exercise, having a higher body mass index (BMI), lower hemoglobin levels, as well as having a lower functional status and higher levels of sleep disturbance. In terms of decrements in evening energy, risk factors included: being female, being White, having a poorer functional status and higher level of sleep disturbance. These findings suggest that morning and evening energy are distinct symptoms that are associated with sleep disturbance and warrant evaluation in oncology patients receiving chemotherapy.

Given the paucity of research on the co-occurrence of sleep disturbance and decrements in morning energy, the purposes of this study were to identify subgroups of patients with distinct joint sleep disturbance AND morning energy profiles. In addition, differences among the subgroups in demographic, clinical, and sleep disturbance characteristics, as well as the severity of other common symptoms and QOL outcomes were evaluated. The determination of modifiable and non-modifiable risk factors associated with these profiles will assist with the identification of high-risk patients and allow for the initiation of more tailored symptom management interventions.

2. METHODS

2.1. Patients and Settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy. Briefly, patients were ≥18 years of age; had a diagnosis of

breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and provided written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.

2.2. Study Procedures

The study was approved by the Institutional Review Board at each of the study sites. Of the 2234 patients approached, 1343 consented to participate. The major reason for refusal was being too overwhelmed with their cancer treatments. These patients completed the sleep disturbance and morning energy measures, a total of six times over two chemotherapy cycles (i.e., prior to chemotherapy administration (Assessments 1 and 4), approximately 1 week after chemotherapy administration (Assessments 2 and 5), and approximately 2 weeks after chemotherapy administration (Assessments 3 and 6)). The remaining measures were completed at enrollment (i.e., prior to the second or third cycle of chemotherapy). A total of 1336 patients who had complete data on both the sleep disturbance and morning energy measures were included in this analysis.

2.3. Instruments

2.3.1. Demographic and clinical measures

Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale [33], Self-Administered Comorbidity Questionnaire (SCQ) [34], Alcohol Use Disorders Identification Test [35], and a smoking history questionnaire. The toxicity of each patient’s chemotherapy regimen was rated using the MAX2 score [36]. Medical records were reviewed for disease and treatment information.

2.3.2. Sleep disturbance and morning energy measures

The 21-item General Sleep Disturbance Scale (GSDS) was designed to assess various aspects of sleep disturbance (i.e., quality, quantity, onset latency, mid and early awakenings,

sleep medications, daytime sleepiness). Each item was rated on a 0 (never) to 7 (everyday) numeric rating scale (NRS). The GSDS total score ranges from 0 (no disturbance) to 147 (extreme sleep disturbance). Each mean subscale score ranges from 0 to 7 [37-39]. Subscale scores of $\geq$3 and a GSDS total score of $\geq$43 indicate a significant level of sleep disturbance that warrants clinical evaluation and management [40]. In this study, Cronbach's alpha for the GSDS total score was 0.83.

The 18-item Lee Fatigue Scale (LFS) was designed to assess physical fatigue and energy [41]. Each item was rated on a 0 to 10 NRS. Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy.

Using separate LFS questionnaires, patients were asked to rate each item based on how they felt within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). The LFS has established cut-off scores for clinically meaningful levels of fatigue (i.e., ≥3.2 for morning fatigue, ≥5.6 for evening fatigue) and energy (i.e., $\leq$6.2 for morning energy, $\leq$3.5 for evening energy) [40]. Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue and 0.95 for morning and 0.93 for evening energy. Patients' ratings of morning energy were used in this analysis to evaluate their association with sleep disturbance. The energy items on the LFS used the descriptors: energetic, active, vigorous, efficient, and lively.

2.3.3. Other symptom measures

An evaluation of other common symptoms was done using valid and reliable instruments. The symptoms and their respective measures were: depressive symptoms (Center for Epidemiological Studies-Depression scale [42]); state and trait anxiety (Spielberger State-Trait Anxiety Inventories [43]); cognitive function (Attentional Function Index [44]); and pain (Brief Pain Inventory [45]).

QOL measures

QOL was evaluated using generic (i.e., Medical Outcomes Study-Short Form-12 (SF-12) [46]) and disease-specific (i.e., Multidimensional QOL Scale-Patient Version (MQOLS-PV) [47]) measures. The individual items on the SF-12 were evaluated and the instrument was scored into two component scores (i.e., physical component summary (PCS) and mental component summary (MCS)). MQOLS-PV measures four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being), as well as a total QOL score. For both measures, higher scores indicate a better QOL.

2.4. Data Analysis

LPA was used to identify subgroups of patients with distinct joint sleep disturbance AND morning energy profiles. Using Mplus version 8.4 [48], this LPA was done with the combined set of variables over time (i.e., using the GSDS AND morning energy scores obtained during the six assessments in a single LPA). This approach provides a profile description of these two symptoms with parallel profiles over time.

In order to incorporate expected correlations among the repeated measures of the same variable and cross-correlations of the series of the two variables (i.e., GSDS and morning energy scores), we included covariance parameters among measures at the same occasion and those that were one or two occasions apart. Covariances of each variable with the other at the same assessments were included in the model and autoregressive covariances were estimated with a lag of two with the same measures and with a lag of one for each variable's series with the other variable. We limited the covariance structure to a lag of two to accommodate the expected reduction in the correlations that would be introduced by two chemotherapy cycles within each set of three measurement occasions and to reduce model complexity [49].

Estimation was carried out with full information maximum likelihood with standard errors and a Chi-square test that are robust to non-normality and non-independence of observations ("estimator=MLR"). Model fit was evaluated to identify the solution that best characterized the

observed latent class structure with the Bayesian Information Criterion (BIC), Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR), entropy, and latent class percentages that were large enough to be reliable [50]. Missing data were accommodated for with the use of the Expectation-Maximization algorithm [51].

Data were analyzed using SPSS version 28 (IBM Corporation, Armonk, NY). Differences among the sleep disturbance AND morning energy classes in demographic, clinical, and symptom characteristics, and QOL outcomes at enrollment were evaluated using parametric and nonparametric tests. Bonferroni corrected p-value of <0.017 was considered statistically significant for the pairwise contrasts (i.e., 0.05/3 possible pairwise contrasts).

3. RESULTS

3.1. Latent classes for sleep disturbance and energy

The three-class solution was selected because the BIC for the three-class solution was lower than the BIC for the two-class solution (**Table 1**). In addition, the VLMR was significant for the three-class solution indicating that the three-class solution fit the data better than the two-class solution. While the BIC was smaller for the four-class solution than for the three-class solution, the VLMR was not significant for the four-class solution indicating that too many classes were extracted.

The latent classes were named based on clinically meaningful cutoff scores for the sleep disturbance and morning energy measures (i.e., Low Sleep Disturbance and High Morning Energy (Normal, 20.6%), Moderate Sleep Disturbance and Low Morning Energy (Moderately Severe, 52.1%), and Very High Sleep Disturbance and Very Low Morning Energy (Very Severe, 27.3%). The trajectories for sleep disturbance and morning energy differed among the latent classes (**Figure 1**). For the Normal class, sleep disturbance scores decreased and morning energy scores increased over the six assessments. For the Moderately Severe class, sleep disturbance and morning energy scores worsened at assessments 2 and 5 (i.e., weeks following

the administration of chemotherapy). For the Very Severe class, the sleep disturbance and morning energy scores remained relatively constant across the six assessments.

3.2. Differences in demographic and clinical characteristics

As shown in **Table 2**, compared to Normal class, the other two classes were more likely to be female and more likely to be unemployed. In addition, they were less likely to have gastrointestinal cancer and more likely to self-report ulcer or stomach disease, more likely to have received only chemotherapy, and had a higher MAX 2 score. Compared to the Normal class, the Very Severe class was less likely to self-identify as Asian/Pacific Islander, less likely to exercise on a regular basis, more likely to self-report osteoarthritis, more likely to have had previous cancer treatment, and had a higher number of metastatic sites.

Compared to the other two classes, the Very Severe class was younger, less likely to be married/partnered, more likely to live alone, and had a lower annual household income. In addition, they had a higher body mass index (BMI) and were more likely to report anemia or blood disease. Among the three classes, differences in KPS scores (Normal > Moderately Severe > Very Severe) and number of comorbid conditions, SCQ scores, and the occurrence of self-reported depression and back pain (i.e., Normal < Moderately Severe < Very Severe) followed similar patterns.

3.3. Differences in GSDS subscale and total scores

As shown in **Table 3**, differences among the latent classes in all of the GSDS subscale (i.e., sleep quality, sleep quantity, sleep onset latency, mid-sleep awakenings, early awakenings, medications for sleep, excessive daytime sleepiness) and total scores followed the same pattern (i.e., Normal < Moderately Severe < Very Severe).

3.4. Differences in common symptoms

As shown in **Table 4**, differences among the latent classes in depression, trait and state anxiety, morning and evening fatigue, worst pain intensity, and pain interference scores, as well as the occurrence of both cancer and non-cancer pain, followed the same pattern (i.e., Normal

< Moderately Severe < Very Severe). At enrollment, differences among the latent classes in evening energy were as follows: Normal > Moderately Severe and Very Severe. For attentional function scores, differences among the latent classes were as follows: Normal > Moderately Severe > Very Severe.

3.5. Differences in QOL outcomes

As shown in **Table 5**, differences among the latent classes in the MQOLS-PV physical, psychological, and social well-being subscale scores, as well as the total QOL score followed the same pattern (i.e., Normal > Moderately Severe > Very Severe). For the spiritual well-being subscale, compared to the Normal class, the other two classes reported lower scores. For all the SF-12 subscale scores, as well as the PCS and MCS scores, differences among the classes followed the same pattern (i.e., Normal > Moderately Severe > Very Severe).

4. DISCUSSION

This study is the first to use LPA to identify subgroups of oncology patients with distinct joint sleep disturbance AND morning energy profiles. Of note, almost 80% of these patients reported Moderately Severe to Very Severe levels of both sleep disturbance and decrements in morning energy. Our occurrence rate for sleep disturbance is higher than the 60.7% reported in a recent meta-analysis [1]. In addition, our occurrence rate for decrements in morning energy is higher than the 50.8% found in our sample of patients undergoing radiation therapy and their family caregivers who were evaluated over 6 months [30].

4.1. Sleep Disturbance and Morning Energy Trajectories

As illustrated in **Figure 1**, the trajectories of the two symptoms differed among the latent classes. For the Normal class, over the six assessments, sleep disturbance scores decreased and morning energy scores increased. One potential explanation for this finding is that these patients received effective symptom management interventions during chemotherapy. An equally plausible hypothesis is that these patients used a variety of strategies to conserve energy and/or improve sleep quality during chemotherapy. In contrast, in the Moderately Severe

class, higher levels of sleep disturbance and decrements in morning energy occurred in the weeks following the administration of chemotherapy (i.e., Assessments 2 and 5). These cyclic changes may be related to unrelieved symptoms (e.g., nausea and vomiting) in the week following the administration of chemotherapy that disrupted sleep and resulted in ratings of decreased morning energy following a poor night's sleep. This hypothesis is supported by a previous latent class analysis of this sample that identified four distinct nausea profiles (i.e., None (40.8%), Increasing-decreasing (21.5%), Decreasing (8.9%), and High (28.8%)) and by the findings that High class had a higher MAX2 score (i.e., higher toxicity associated with the chemotherapy regimen). Additional research is warranted to determine the relationships between acute symptoms following chemotherapy administration and their impact on sleep and energy. The trajectories for both symptoms in the Very Severe class remained relatively constant over the two cycles of chemotherapy. While the exact reasons for this very high symptom burden in 27.3% of the sample warrants additional investigation, plausible explanations include: high levels of unrelieved stress, ineffective symptom management interventions; and lack of information on effective strategies to improve sleep and/or conserve energy.

4.2. Differences in Sleep Disturbance Scores

An evaluation of the seven GSDS subscale scores at enrollment provides some insights into the types of sleep disturbance (i.e., initiation or maintenance) the two highest classes were experiencing. While not unexpected, all of the GSDS subscale scores at enrollment (i.e., prior to the second or third cycle of chemotherapy) exhibited a dose response effect (i.e., as the sleep disturbance and morning energy profiles worsened, these subscale scores increased). While their GSDS total score was not above the clinically meaningful cutoff, patients in the Normal class reported scores for quantity of sleep (i.e., not enough) and mid-sleep awakenings that were above the cutoff score of $\geq$3 which suggests some difficulty with sleep maintenance. In terms of the Severe class, given that they reported scores for both mid-sleep awakenings and

early awakenings that were above the clinically meaningful cutoff suggest that they experienced more severe problems with sleep maintenance.

Of note, in the Very Severe class, except for the use of sleep medications, all of the subscale scores were ≥3 including sleep onset latency which suggests that these patients had problems with both sleep initiation and maintenance. It is interesting to note that across all three classes, the use of sleep medications was low. This result is not consistent with recent studies that found that 30% [52] to 40% [53] of cancer patients with sleep disturbances take sleep medications. These inconsistent findings may be related to the methods used to collect information on the use of sleep medications and/or differences in the demographics of the patient samples (i.e., current study both male and female patients versus only women with breast [52] or ovarian [53] cancer). Given the differences, among the classes, in the trajectories of the GSDS total scores, as well as the differences in the GSDS subscale scores at enrollment, additional LPAs are warranted on each of the subscale scores to increase our knowledge of risk factors for problems with sleep initiation and maintenance in patients receiving chemotherapy.

4.3. Demographic and Clinical Characteristics

As noted in the Introduction, one of the goals of this study was to identify modifiable and non-modifiable risk factors for a worse joint sleep disturbance AND morning energy profile. While risk factors for higher sleep disturbance in oncology patients are reported in the literature, the extant literature, albeit limited, on decrements in energy that will be used for comparative purposes focuses primarily on healthy individuals and older adults. In addition, except for our study in oncology patients and family caregivers [30], the studies in other populations did not examine diurnal variations in energy.

As shown in **Table 6**, most of the differences in demographic characteristics were associated with membership in the Very Severe class. As noted in one systematic review [54], findings regarding associations between age and sleep disturbance are inconsistent. However, in our previous study of women who were followed from prior to through six months after breast

cancer surgery [4] and in our study of patients and family caregivers [55] that utilized latent variable modeling, younger age was associated with being in the higher sleep disturbance class. In terms of decrements in morning energy, in our previous study [30], participants in the Low class were significantly younger.

Being female was associated with membership in the Severe and Very Severe classes. This finding is consistent for both self-reported sleep disturbance [15, 56] and decrements in energy [30, 57] in both patients with and without cancer. As noted in one review [56], gender differences in sleep disturbance may be related to women's predisposition to report symptoms and seek medical care as well as to differences in neurotransmitters and hormones that influence sleep and circadian rhythms. The reasons for gender differences in morning energy warrant additional investigation.

In terms of marital status and living alone, the socioecological context of sleep is receiving increased attention [58]. For example, as noted in one review [59], co-sleeping with a partner is associated with longer sleep duration if the individuals are in a highly functioning relationship. In addition, living alone was associated with poorer sleep quality [54] and decrements in morning energy [31] in oncology patients.

While no associations were found between being unemployed or lower annual household income in our previous studies of sleep disturbance [4] and morning energy [30], as noted in one review [60], personal and social factors including unemployment and low income are associated with an increased incidence of sleep problems. In addition, in a study that evaluated patients from prior to through twelve months after breast cancer surgery [61], higher sleep disturbance scores were associated with higher employment interference scores at enrollment and over the duration of the study. Given that patients undergoing cancer treatments experience a significant amount of financial toxicity [62], these associations warrant additional research. In addition, clinicians need to refer patients to social services and/or financial counseling.

Some of the most robust associations for sleep disturbance and/or decrements in energy were found for an increased BMI, a lack of regular exercise, a higher comorbidity burden, and a poorer functional status. In terms of sleep disturbance, given that the BMI of the Very Severe class was in the overweight to obese range [63], these patients may have undiagnosed obstructive sleep apnea that occurs in 3% to 7% of men and 2% to 5% of women in the general population [64].

As noted in one systematic review [65], a substantial amount of evidence supports the fact that both acute bouts of exercise, as well as regular exercise improve sleep and that these effects are preserved across adult age groups and genders. In terms of associations between energy and physical activity, while most of the research in cancer patients suggests that fatigue is reduced with regular exercise [66], findings from other studies that evaluated for changes in energy in other populations are worth noting. For example, sedentary behaviors (e.g., sitting at desks, watching television) have a stronger tendency to decrease energy than increase fatigue [67]. In addition, in a meta-analysis of 16 acute exercise studies [67], vigorous intensity exercise increased energy but did not decrease fatigue. As noted in one review [22], moderate or vigorous intensity exercise appears to increase energy while having less of an impact on reducing fatigue and that these changes in energy may be mediated by dopamine. These findings suggest that future studies of the effects of exercise in oncology patients should include evaluations of changes in morning and evening fatigue, as well as changes in morning and evening energy and sleep disturbance.

In general, sleep disturbance is associated with a number of chronic conditions (e.g., chronic obstructive pulmonary disease [68], cardiovascular disease [69], diabetes [70]) and cancer [54]). In terms of the specific medical conditions associated with membership in the Very Severe class, some associations with sleep disturbance were reported previously. For example, in a study of older adults [71], sleeping less than 6 hours per night was associated with the occurrence of stomach/duodenal ulcers. In addition, in studies of the general population,

positive associations were found between sleep disturbance and osteoarthritis [72, 73] and back pain [74]. Given these strong associations, additional research is warranted on the relationships between decrements in energy and multimorbidity in oncology patients.

4.4. Common Symptoms

Differences among the classes in depression, trait and state anxiety, morning and evening fatigue, attentional function, and worse pain scores, as well as the occurrence of both cancer and non-cancer pain exhibited a dose-response effect (**Table 4**). In addition, all of the symptom scores for the Very Severe class were above the clinically meaningful cut-off scores. These findings are consistent with previous studies that found positive associations between sleep disturbance and depression and anxiety [75-77], fatigue and pain [54], and decrements in cognitive function [78]. In terms of energy, in a study of graduate students [79], increased severity of depressive mood states was associated with lower trait physical energy. In another study of older adults [80], higher levels of depressive symptoms were associated with lower levels of energy.

4.5. QOL Outcomes

Similar to the common symptoms, except for the spiritual well-being subscale, all of the other subscale and total scores on the MQOLS-PV and SF-12 for the three classes exhibited a dose response effect. Of particular importance is the vitality subscale of the SF-12 which is sometimes uses as a proxy measure for energy. Not only are the differences among the classes in the vitality scores statistically significant, they represent clinically meaningful differences between the None and the Moderately Severe ($d = 0.85$), as well as between the Moderately Severe and the Very Severe ($d = 0.50$) classes [81]. In addition, both the PCS and MCS scores for the Moderately Severe and Very Severe classes are below the normative score of 50 for the general population of the United States. Taken together, these findings suggest that the co-occurrence of sleep disturbance and decrements in morning energy results in clinically meaningful decrements in QOL for almost 80% of our sample.

4.6. Limitations

Several limitations warrant consideration. Because patients were recruited during their first or second cycle of chemotherapy, pretreatment levels of sleep disturbance and morning energy were not evaluated. In addition, specific causes of sleep disturbance (insomnia, obstructive sleep apnea) and more detailed information on the use of sleep medications were not evaluated. Given that diet [82, 83] and caffeine consumption [84-86] can influence sleep quality and energy levels, these variables warrant evaluation in future studies. Because sleep disturbance was assessed using only a subjective measure, future studies need to examine the relationship between objective measures of sleep disturbance and decrements in morning energy.

4.7. Implications for Practice and Research

Given the associations between sleep disturbance and decrements in morning energy and a higher symptom burden, poorer QOL outcomes, and increased mortality, assessment of these two symptoms needs to be a high priority for clinicians. Based on the strong associations between enhancements in physical activity and improvements in both sleep and energy, patients need to be referred to physical therapy for the development of an exercise prescription and be monitored for adherence with their exercise regimen. Equally important, patients need to receive education on lifestyle interventions that can improve sleep quality. The key elements of this educational program should include: achieving 7 to 9 hours of sleep per night; maintaining a consistent sleep/wake schedule; having a regular bedtime routine; engaging in regular exercise; and performing relaxation exercises. Equally important, patients should be taught to avoid caffeine, alcohol, heavy meals, and light exposure late in the day [86].

In terms of recommendations for research, future studies need to include evaluations of both morning and evening fatigue and energy and determine the overlap between these symptoms, as well as with sleep disturbance. Equally important, given the emerging evidence that fatigue and energy may have common and distinct underlying mechanisms [22, 27, 30],

additional research is warranted to support or refute this hypothesis. Equally valuable would be studies that uses analytic techniques (e.g., parallel process growth modeling) to determine which symptom is driving the severity of the other symptom over time.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Funding

This study was funded by a grant from the National Cancer Institute (CA134900). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr. Miaskowski is an American Cancer Society Clinical Research Professor.

REFERENCES

[1] Al Maqbali M, Al Sinani M, Alsayed A, Gleason AM. Prevalence of sleep disturbance in patients with cancer: A systematic review and meta-analysis. Clin Nurs Res. 2022;31:1107-23.

[2] Büttner-Teleagă A, Kim YT, Osel T, Richter K. Sleep disorders in cancer - A systematic review. Int J Environ Res Public Health. 2021;18.

[3] Tejada M, Viele C, Kober KM, Cooper BA, Paul SM, Dunn LB, et al. Identification of subgroups of chemotherapy patients with distinct sleep disturbance profiles and associated co-occurring symptoms. Sleep. 2019;42.

[4] Van Onselen C, Cooper BA, Lee K, Dunn L, Aouizerat BE, West C, et al. Identification of distinct subgroups of breast cancer patients based on self-reported changes in sleep disturbance. Support Care Cancer. 2012;20:2611-9.

[5] Lin S, Chen Y, Yang L, Zhou J. Pain, fatigue, disturbed sleep and distress comprised a symptom cluster that related to quality of life and functional status of lung cancer surgery patients. J Clin Nurs. 2013;22:1281-90.

[6] Palagini L, Miniati M, Massa L, Folesani F, Marazziti D, Grassi L, et al. Insomnia and circadian sleep disorders in ovarian cancer: Evaluation and management of underestimated modifiable factors potentially contributing to morbidity. J Sleep Res. 2022;31:e13510.

[7] Huang J, Song P, Hang K, Chen Z, Zhu Z, Zhang Y, et al. Sleep deprivation disturbs immune surveillance and promotes the progression of hepatocellular carcinoma. Front Immunol. 2021;12:727959.

[8] Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. J Sleep Res. 2009;18:148-58.

[9] Stone CR, Haig TR, Fiest KM, McNeil J, Brenner DR, Friedenreich CM. The association between sleep duration and cancer-specific mortality: a systematic review and meta-analysis. Cancer Causes Control. 2019;30:501-25.

[10] Muthen BO. Beyond SEM: General latent variable modeling. Behaviormetrika. 2002;29:81-117.

[11] Gregoire C, Faymonville ME, Jerusalem G, Gosseries O, Vanhaudenhuyse A. Psycho-oncology interventions focusing on fatigue and sleep disturbances. Curr Opin Oncol. 2022;34:270-8.

[12] Hammer MJ, Cooper B, Paul SM, Kober KM, Cartwright F, Conley YP, et al. Identification of distinct symptom profiles in cancer patients using a pre-specified symptom cluster. J Pain Symptom Manage. 2022;64:17-27.

[13] Wu IHC, Balachandran DD, Faiz SA, Bashoura L, Escalante CP, Manzullo EF. Characteristics of cancer-related fatigue and concomitant sleep disturbance in cancer patients. J Pain Symptom Manage. 2022;63:e1-e8.

[14] Acker KA, Carter P. Sleep-wake disturbances in oncology. Nurs Clin North Am. 2021;56:175-87.

[15] Price SN, Hamann HA, Halaby L, Trejo JI, Corella F, Weihs KL. Poor subjective sleep quality among patients with cancer and comorbid depression: An opportunity to inform screening and intervention. Behav Sleep Med. 2022:1-16.

[16] Calvo-Schimmel A, Paul SM, Cooper BA, Harris C, Shin J, Oppegaard K, et al. Oncology outpatients with worse depression and sleep disturbance profiles are at increased risk for a higher symptom burden and poorer quality of life outcomes. Sleep Med. 2022;95:91-104.

[17] Matthews EE, Wang SY. Cancer-related sleep wake disturbances. Semin Oncol Nurs. 2022:151253.

[18] Cai T, Huang Y, Huang Q, Xia H, Yuan C. Symptom trajectories in patients with breast cancer: An integrative review. Int J Nurs Sci. 2022;9:120-8.

[19] Calvo-Schimmel A, Paul SM, Cooper BA, Shin J, Harris C, Oppegaard K, et al. Oncology outpatients with worse anxiety and sleep disturbance profiles are at increased risk for a higher symptom burden and poorer quality of life. Cancer Nurs. 2022.

[20] Oppegaard K, Harris CS, Shin J, Paul SM, Cooper BA, Levine JD, et al. Anxiety profiles are associated with stress, resilience and symptom severity in outpatients receiving chemotherapy. Support Care Cancer. 2021;29:7825-36.

[21] Fox RS, Ancoli-Israel S, Roesch SC, Merz EL, Mills SD, Wells KJ, et al. Sleep disturbance and cancer-related fatigue symptom cluster in breast cancer patients undergoing chemotherapy. Support Care Cancer. 2020;28:845-55.

[22] Loy BD, Cameron MH, O'Connor PJ. Perceived fatigue and energy are independent unipolar states: Supporting evidence. Med Hypotheses. 2018;113:46-51.

[23] Boolani A, O'Connor PJ, Reid J, Ma S, Monda S. Predictors of feelings of energy differ from predictors of fatigue. Fatigue. 2019;7:12-28.

[24] Lerdal A. A concept analysis of energy. Its meaning in the lives of three individuals with chronic illness. Scand J Caring Sci. 1998;12:3-10.

[25] Lerdal A. A theoretical extension of the concept of energy through an empirical study. Scand J Caring Sci. 2002;16:197-206.

[26] Shacham S. A shortened version of the Profile of Mood States. J Pers Assess. 1983;47:305-6.

[27] Kober KM, Smoot B, Paul SM, Cooper BA, Levine JD, Miaskowski C. Polymorphisms in cytokine genes are associated with higher levels of fatigue and lower levels of energy in women after breast cancer surgery. J Pain Symptom Manage. 2016;52:695-708 e4.

[28] Eshragh J, Dhruva A, Paul SM, Cooper BA, Mastick J, Hamolsky D, et al. Associations between neurotransmitter genes and fatigue and energy levels in women after breast cancer surgery. J Pain Symptom Manage. 2017;53:67-84 e7.

[29] Sprague BN, Zhu X, Ehrenkranz RC, Tian Q, Gmelin TA, Glynn NW, et al. Declining energy predicts incident mobility disability and mortality risk in healthy older adults. J Am Geriatr Soc. 2021;69:3134-41.

[30] Aouizerat BE, Dhruva A, Paul SM, Cooper BA, Kober KM, Miaskowski C. Phenotypic and molecular evidence suggests that decrements in morning and evening energy are distinct but related symptoms. J Pain Symptom Manage. 2015;50:599-614 e3.

[31] Abid H, Kober KM, Smoot B, Paul SM, Hammer M, Levine JD, et al. Common and distinct characteristics associated with trajectories of morning and evening energy in oncology patients receiving chemotherapy. J Pain Symptom Manage. 2017;53:887-900 e2.

[32] Raudenbush S, Bryk A. Hierarchical Linear Models: Applications and Data Analysis Methods. 2 ed. Thousand Oaks, CA: Sage Publications; 2002.

[33] Karnofsky D. Performance scale. New York: Plenum Press; 1977.

[34] Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services esearch. Arthritis Rheum. 2003;49:156-63.

[35] Bohn MJ, Babor TF, Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. J Stud Alcohol. 1995;56:423-32.

[36] Extermann M, Bonetti M, Sledge GW, O'Dwyer PJ, Bonomi P, Benson AB, 3rd. MAX2--a convenient index to estimate the average per patient risk for chemotherapy toxicity; validation in ECOG trials. Eur J Cancer. 2004;40:1193-8.

[37] Miaskowski C, Lee KA. Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: a pilot study. J Pain Symptom Manage. 1999;17:320-32.

[38] Lee KA. Self-reported sleep disturbances in employed women. Sleep. 1992;15:493-8.

[39] Lee KA, DeJoseph JF. Sleep disturbances, vitality, and fatigue among a select group of employed childbearing women. Birth. 1992;19:208-13.

[40] Fletcher BS, Paul SM, Dodd MJ, Schumacher K, West C, Cooper B, et al. Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer. J Clin Oncol. 2008;26:599-605.

[41] Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res. 1991;36:291-8.

[42] Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Appl Psychol Measure. 1977;1:385-401.

[43] Spielberger CG, Gorsuch RL, Suchene R, Vagg PR, Jacobs GA. Manual for the State-Anxiety (Form Y): Self Evaluation Questionnaire. Palo Alto, CA: Consulting Psychologists Press; 1983.

[44] Cimprich B, So H, Ronis DL, Trask C. Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer. Psychooncology. 2005;14:70-8.

[45] Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983;17:197-210.

[46] Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220-33.

[47] Padilla GV, Ferrell B, Grant MM, Rhiner M. Defining the content domain of quality of life for cancer patients with pain. Cancer Nurs. 1990;13:108-15.

[48] Muthen LK, Muthen BO. Mplus User's Guide (8th ed.). 8th ed. Los Angeles, CA: Muthen & Muthen; 1998-2020.

[49] Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. Soc Personal Psychol Compass. 2008;2:302-17.

[50] Muthén L, Muthén B. Mplus. Statistical analysis with latent variables User's guide. 2009;7.

[51] Muthen B, Shedden K. Finite mixture modeling with mixture outcomes using the EM algorithm. Biometrics. 1999;55:463-9.

[52] Carroll JE, Small BJ, Tometich DB, Zhai W, Zhou X, Luta G, et al. Sleep disturbance and neurocognitive outcomes in older patients with breast cancer: Interaction with genotype. Cancer. 2019;125:4516-24.

[53] Ross TL, DeFazio A, Friedlander M, Grant P, Nagle CM, Williams M, et al. Insomnia and its association with quality of life in women with ovarian cancer. Gynecol Oncol. 2020;158:760-8.

[54] Souza R, Dos Santos MR, das Chagas Valota IA, Sousa CS, Costa Calache ALS. Factors associated with sleep quality during chemotherapy: An integrative review. Nurs Open. 2020;7:1274-84.

[55] Miaskowski C, Cooper BA, Dhruva A, Dunn LB, Langford DJ, Cataldo JK, et al. Evidence of associations between cytokine genes and subjective reports of sleep disturbance in oncology patients and their family caregivers. PLoS One. 2012;7:e40560.

[56] Suh S, Cho N, Zhang J. Sex differences in insomnia: From epidemiology and etiology to intervention. Curr Psychiatry Rep. 2018;20:69.

[57] Kowalski KL, Boolani A, Christie AD. State and trait fatigue and energy predictors of postural control and gait. Motor Control. 2021;25:519-36.

[58] Grandner MA. Sleep, health, and society. Sleep Med Clin. 2022;17:117-39.

[59] Decker AN, Fischer AR, Gunn HE. Socio-ecological context of sleep: Gender differences and couples' relationships as exemplars. Curr Psychiatry Rep. 2022;24:831-40.

[60] Garbarino S, Lanteri P, Durando P, Magnavita N, Sannita WG. Co-morbidity, mortality, quality of life and the healthcare/welfare/social costs of disordered sleep: A rapid review. Int J Environ Res Public Health. 2016;13.

[61] Chan RJ, Cooper B, Koczwara B, Chan A, Tan CJ, Paul SM, et al. A longitudinal analysis of phenotypic and symptom characteristics associated with inter-individual variability in employment interference in patients with breast cancer. Support Care Cancer. 2020;28:4677-86.

[62] Hussaini SMQ, Gupta A, Dusetzina SB. Financial toxicity of cancer treatment. JAMA Oncol. 2022;8:788.

[63] Centers for Disease Control and Prevention. About adult BMI, healthy weight. 2016.

[64] Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5:136-43.

[65] Kline CE, Hillman CH, Bloodgood Sheppard B, Tennant B, Conroy DE, Macko RF, et al. Physical activity and sleep: An updated umbrella review of the 2018 Physical Activity Guidelines Advisory Committee report. Sleep medicine reviews. 2021;58:101489.

[66] Zhang YB, Zhong XM, Han N, Tang H, Wang SY, Lin WX. Effectiveness of exercise interventions in the management of cancer-related fatigue: a systematic review of systematic reviews. Support Care Cancer. 2023;31:153.

[67] Loy BD, O'Connor PJ, Dishman RK. The effect of a single bout of exercise on energy and fatigue states: A systematic review and meta-analysis. Fatigue. 2013;1:223-42.

[68] Sunwoo BY, Owens RL. Sleep deficiency, sleep apnea, and chronic lung disease. Clin Chest Med. 2022;43:337-52.

[69] Figueiro MG, Pedler D. Cardiovascular disease and lifestyle choices: Spotlight on circadian rhythms and sleep. Prog Cardiovasc Dis. 2023.

[70] Ansu Baidoo V, Knutson KL. Associations between circadian disruption and cardiometabolic disease risk: A review. Obesity (Silver Spring). 2023;31:615-24.

[71] Smagula SF, Koh WP, Wang R, Yuan JM. Chronic disease and lifestyle factors associated with change in sleep duration among older adults in the Singapore Chinese Health Study. J Sleep Res. 2016;25:57-61.

[72] Ni J, Zhou W, Cen H, Chen G, Huang J, Yin K, et al. Evidence for causal effects of sleep disturbances on risk for osteoarthritis: a univariable and multivariable Mendelian randomization study. Osteoarthr Cartil. 2022;30:443-50.

[73] Jacob L, Smith L, Konrad M, Kostev K. Association between sleep disorders and osteoarthritis: A case-control study of 351,932 adults in the UK. J Sleep Res. 2021;30:e13367.

[74] Kelly GA, Blake C, Power CK, O'Keeffe D, Fullen BM. The association between chronic low back pain and sleep: a systematic review. Clin J Pain. 2011;27:169-81.

[75] Whisenant M, Wong B, Mitchell SA, Beck SL, Mooney K. Symptom trajectories are associated with co-occurring symptoms during chemotherapy for breast cancer. J Pain Symptom Manage. 2019;57:183-9.

[76] King AL, Shuboni-Mulligan DD, Vera E, Crandon S, Acquaye AA, Boris L, et al. Exploring the prevalence and burden of sleep disturbance in primary brain tumor patients. Neurooncol Pract. 2022;9:526-35.

[77] Grayson S, Sereika S, Harpel C, Diego E, Steiman JG, McAuliffe PF, et al. Factors associated with sleep disturbances in women undergoing treatment for early-stage breast cancer. Support Care Cancer. 2022;30:157-66.

[78] Crouch A, Von Ah D. Incidence and factors associated with attentional fatigue in working long-term breast cancer survivors. Clin Nurse Spec. 2018;32:177-81.

[79] Boolani A, Yager C, Reid J, Lackman J, Smith ML. Correlates of depressive mood among graduate-level allied health students: An exploratory study examining trait energy and fatigue. J Am Coll Health. 2021:1-12.

[80] Ehrenkranz R, Rosso AL, Sprague BN, Tian Q, Gmelin T, Bohnen N, et al. Functional correlates of self-reported energy levels in the Health, Aging and Body Composition Study. Aging Clin Exp Res. 2021;33:2787-95.

[81] Osoba D. Interpreting the meaningfulness of changes in health-related quality of life scores: lessons from studies in adults. Int J Cancer Suppl. 1999;12:132-7.

[82] Pattnaik H, Mir M, Boike S, Kashyap R, Khan SA, Surani S. Nutritional elements in sleep. Cureus. 2022;14:e32803.

[83] Yeung SSY, Kwan M, Woo J. Healthy diet for healthy aging. Nutrients. 2021;13.

[84] Jagim AR, Harty PS, Tinsley GM, Kerksick CM, Gonzalez AM, Kreider RB, et al. International society of sports nutrition position stand: energy drinks and energy shots. J Int Soc Sports Nutr. 2023;20:2171314.

[85] Fuller DT, Smith ML, Boolani A. Trait energy and fatigue modify the effects of caffeine on mood, cognitive and fine-motor task performance: A post-hoc study. Nutrients. 2021;13.

[86] Baranwal N, Yu PK, Siegel NS. Sleep physiology, pathophysiology, and sleep hygiene. Prog Cardiovasc Dis. 2023.

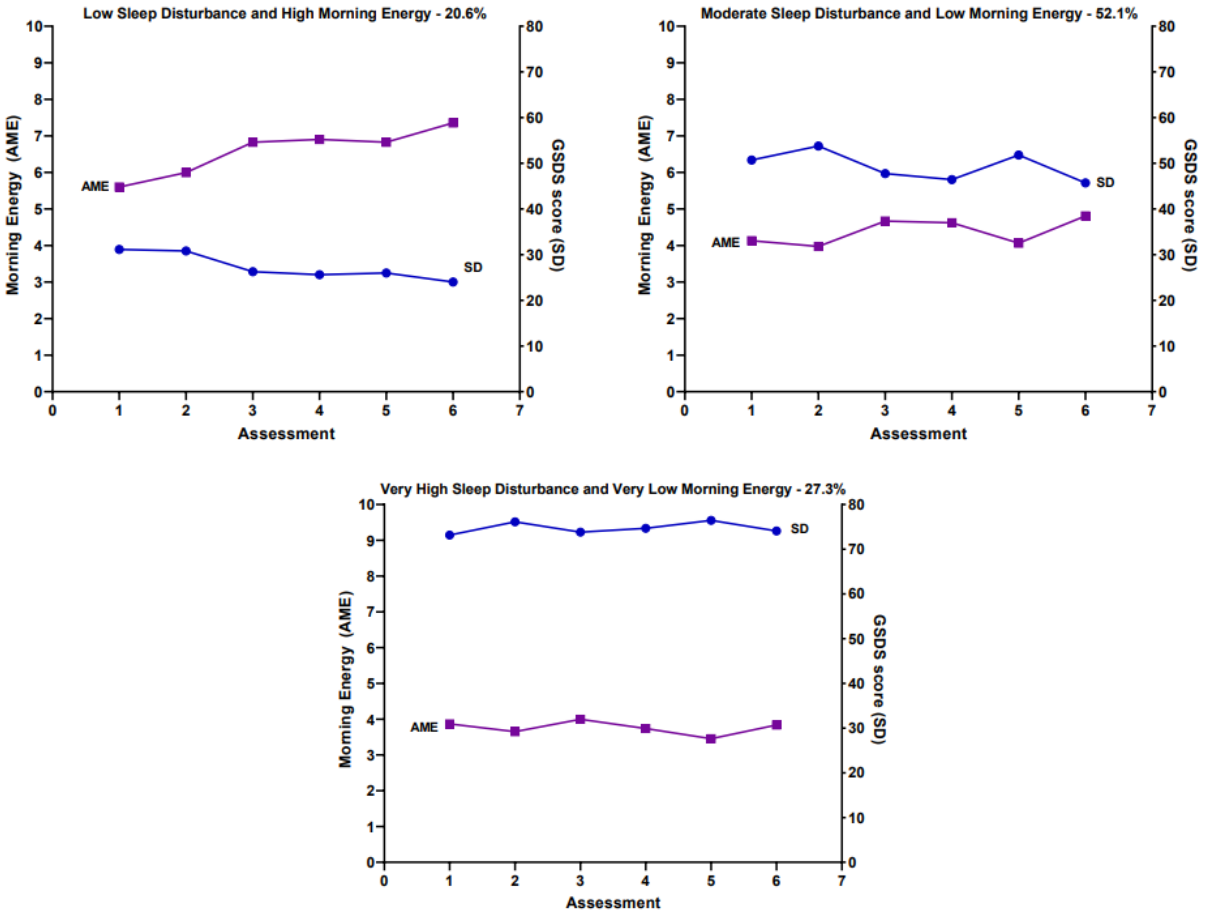

Figure 1: The Trajectories for Sleep Disturbance and Morning Energy Among the Latent Classes

Table 1 – Latent Profile Solutions and Fit Indices for One Through Four Classes for Sleep Disturbance AND Morning Energy Scores

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-42554.43	85224.85	85526.30	n/a	n/a
2 Class	-41984.38	84110.77	84479.78	0.75	1140.09 ‡
3 Class[a]	-41673.17	83514.33	83950.92	0.78	622.44 +
4 Class	-41530.90	83255.79	83759.94	0.77	ns

Baseline entropy and VLMR are not applicable for the one-class solution

+p <.001; ‡p <.00005

[a]The 3-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. Although the BIC was smaller for the 4-class than for the 3-class solution, the VLMR was not significant for the 4-class solution, indicating that too many classes were extracted.

Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; LL = log-likelihood; n/a = not applicable; ns = not significant, VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs. K-1 model

Table 2 – Differences in Demographic and Clinical Characteristics Among the Sleep Disturbance and Morning Energy Latent Classes at Enrollment

Characteristic	**Low Sleep Disturbance and High Morning Energy (0) 20.6% (n = 275)**	**Moderate Sleep Disturbance and Low Morning Energy (1) 52.1% (n = 696)**	**Very High Sleep Disturbance and Very Low Morning Energy (2) 27.3% (n = 365)**	**Statistics**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Age (years)	57.7 (11.4)	57.9 (12.9)	55.3 (11.8)	F = 5.94, p = 0.003 0 and 1 > 2
Education (years)	16.3 (3.1)	16.2 (2.9)	16.1 (3.1)	F = 0.18, p = 0.837
Body mass index (kg/m^2)	25.6 (4.9)	25.9 (5.6)	27.1 (6.2)	F = 6.47, p = 0.002 0 and 1 < 2
Alcohol Use Disorders Identification Test score	3.1 (2.6)	2.9 (2.4)	3.0 (2.6)	F = 0.64, p = 0.528
KPS score	87.3 (10.8)	80.2 (11.8)	74.3 (12.1)	F = 93.55, p <0.001 0 > 1 > 2
Number of comorbid conditions	2.0 (1.2)	2.4 (1.4)	2.8 (1.5)	F = 24.73, p <0.001 0 < 1 < 2
SCQ score	4.3 (2.4)	5.4 (3.1)	6.5 (3.6)	F = 40.41, p <0.001 0 < 1 < 2
Time since diagnosis (years)	2.0 (3.6)	2.1 (4.1)	1.9 (3.7)	KW = 1.04, p = 0.594
Time since diagnosis (years, median)	0.42	0.43	0.42	
Number of prior cancer treatments	1.6 (1.6)	1.6 (1.5)	1.6 (1.4)	F = 0.17, p = 0.842
Number of metastatic sites including lymph node involvement[a]	1.4 (1.3)	1.2 (1.2)	1.2 (1.2)	F = 4.26, p = 0.0.14 0 > 2
Number of metastatic sites excluding lymph node involvement	0.9 (1.1)	0.8 (1.0)	0.7 (1.0)	F = 3.84, p = 0.022 0 > 2
MAX2 score	0.16 (0.08)	0.18 (0.08)	0.18 (0.08)	F = 4.44, p = 0.012 0 < 1 and 2
	% (n)	**% (n)**	**% (n)**	
Gender (% female)	68.4 (188)	78.8 (548)	83.3 (304)	X^2 = 21.05, p < 0.001 0 < 1 and 2

Characteristic	Low Sleep Disturbance and High Morning Energy (0) 20.6% (n = 275)	Moderate Sleep Disturbance and Low Morning Energy (1) 52.1% (n = 696)	Very High Sleep Disturbance and Very Low Morning Energy (2) 27.3% (n = 365)	Statistics
Self-reported ethnicity White Asian or Pacific Islander Black Hispanic, Mixed, or Other	 63.2 (172) 17.3 (47) 9.9 (27) 9.6 (26)	 71.5 (490) 11.8 (81) 6.4 (44) 10.2 (70)	 70.7 (256) 10.2 (37) 6.6 (24) 12.4 (45)	X^2 = 13.77, p =0.032 0 < 1 0 > 2 NS NS
Married or partnered (% yes)	71.0 (193)	65.6 (450)	57.1 (205)	X^2 = 13.86, p < 0.001 0 and 1 > 2
Lives alone (% yes)	16.1 (44)	20.1 (138)	28.4 (102)	X^2 = 15.60, p < 0.001 0 and 1 < 2
Currently employed (% yes)	45.9 (124)	34.4 (238)	28.6 (103)	X^2 = 20.67, p < 0.001 0 > 1 and 2
Annual household income Less than $30,000 $30,000 to $70,000 $70,000 to $100,000 Greater than $100,000	 14.0 (32) 21.5 (49) 14.0 (32) 50.4 (115)	 14.4 (91) 22.9 (145) 18.9 (120) 43.8 (278)	 29.0 (97) 17.4 (58) 15.0 (50) 38.6 (129)	KW = 16.39, p < 0.001 0 and 1 > 2
Child care responsibilities (% yes)	21.1 (57)	19.8 (134)	27.6 (99)	X^2 = 8.53, p = 0.014 1 < 2
Elder care responsibilities (% yes)	6.4 (16)	9.0 (56)	7.1 (24)	X^2 = 2.15, p = 0.341
Past or current history of smoking (% yes)	29.0 (79)	37.7 (257)	35.6 (128)	X^2 = 6.37, p = 0.041 0 < 1
Exercise on a regular basis (% yes)	78.1 (214)	70.8 (479)	65.1 (231)	X^2 = 12.69, p = 0.002 0 > 2
Specific comorbid conditions (% yes)				
Heart disease	4.4 (12)	4.6 (32)	8.8 (32)	X^2 = 8.89, p = 0.012 1 < 2
High blood pressure	28.7 (79)	29.9 (208)	31.8 (116)	X^2 = 0.75, p = 0.688
Lung disease	9.1 (25)	12.2 (85)	11.2 (41)	X^2 = 1.92, p = 0.383
Diabetes	7.6 (21)	8.6 (60)	10.7 (39)	X^2 = 2.02, p = 0.365

Characteristic	Low Sleep Disturbance and High Morning Energy (0) 20.6% (n = 275)	Moderate Sleep Disturbance and Low Morning Energy (1) 52.1% (n = 696)	Very High Sleep Disturbance and Very Low Morning Energy (2) 27.3% (n = 365)	Statistics
Ulcer or stomach disease	1.5 (4)	5.9 (41)	5.5 (20)	$X^2 = 8.79$, p = 0.012 0 < 1 and 2
Kidney disease	0.7 (2)	1.1 (8)	2.5 (9)	$X^2 = 4.15$, p = 0.125
Liver disease	7.6 (21)	7.0 (49)	4.4 (16)	$X^2 = 3.63$, p = 0.163
Anemia or blood disease	9.1 (25)	11.2 (78)	16.7 (61)	$X^2 = 10.00$, p = 0.007 0 and 1 < 2
Depression	4.7 (13)	18.2 (127)	32.1 (117)	$X^2 = 76.30$, p < 0.001 0 < 1 < 2
Osteoarthritis	9.1 (25)	11.2 (78)	15.9 (58)	$X^2 = 7.82$, p = 0.020 0 < 2
Back pain	15.3 (42)	24.3 (169)	36.4 (133)	$X^2 = 38.39$, p < 0.001 0 < 1 < 2
Rheumatoid arthritis	3.3 (9)	2.7 (19)	3.8 (14)	$X^2 = 0.98$, p = 0.613
Cancer diagnosis Breast cancer Gastrointestinal cancer Gynecological cancer Lung cancer	 35.3 (97) 40.7 (112) 13.1 (36) 10.9 (30)	 41.1 (286) 27.9 (194) 18.4 (128) 12.6 (88)	 42.7 (156) 27.7 (101) 18.9 (69) 10.7 (39)	$X^2 = 19.13$, p =0.004 NS 0 > 1 and 2 NS NS
Prior cancer treatment No prior treatment Only surgery, CTX, or RT Surgery+CTX, or Surgery+RT, or CTX+RT Surgery+CTX+RT	 30.0 (80) 37.1 (99) 19.5 (52) 13.5 (36)	 25.2 (170) 42.4 (286) 20.3 (137) 12.1 (82)	 20.9 (75) 45.1 (162) 19.2 (69) 14.8 (53)	$X^2 = 8.87$, p = 0.181 0 > 2 NS NS NS
Metastatic sites No metastasis Only lymph node mets Only metastatic disease in other sites Metastatic disease in lymph nodes and other sites	 26.5 (72) 20.6 (56) 23.9 (65) 29.0 (79)	 32.7 (225) 23.1 (159) 20.8 (143) 23.5 (162)	 36.3 (130) 20.9 (75) 19.8 (71) 22.9 (82)	$X^2 = 9.71$, p = 0.138 0 < 2 NS NS NS

Characteristic	Low Sleep Disturbance and High Morning Energy (0) 20.6% (n = 275)	Moderate Sleep Disturbance and Low Morning Energy (1) 52.1% (n = 696)	Very High Sleep Disturbance and Very Low Morning Energy (2) 27.3% (n = 365)	Statistics
CTX regimen Only CTX Only targeted therapy Both CTX and targeted therapy	61.8 (168) 5.9 (16) 32.4 (88)	71.8 (488) 1.9 (13) 26.3 (179)	73.1 (261) 2.8 (10) 24.1 (86)	X^2 = 17.89, p = 0.001 0 < 1 and 2 0 > 1 NS
Cycle length 14-day cycle 21-day cycle 28-day cycle	46.5 (128) 45.8 (126) 7.6 (21)	39.9 (275) 52.6 (363) 7.5 (52)	42.9 (154) 50.7 (182) 6.4 (23)	KW = 3.10, p = 0.213
Emetogenicity of the CTX regimen Minimal/low Moderate High	20.7 (57) 61.1 (168) 18.2 (50)	18.3 (126) 61.7 (426) 20.0 (138)	20.8 (75) 59.7 (215) 19.4 (70)	KW = 1.17, p = 0.557
Antiemetic regimen None Steroid alone or serotonin receptor antagonist alone Serotonin receptor antagonist and steroid NK-1 receptor antagonist and two other antiemetics	9.7 (26) 17.6 (47) 52.8 (141) 19.9 (53)	6.1 (41) 21.3 (144) 47.0 (318) 25.6 (173)	7.1 (25) 21.1 (74) 45.0 (158) 26.8 (94)	X^2 = 10.42, p = 0.108

[a]Total number of metastatic sites evaluated was 9.

Abbreviations: CTX = chemotherapy, kg = kilograms, KPS- Karnofsky Performance Status, KW = Kruskal Wallis, m^2 = meters squared, pw = pairwise, n/a = not applicable, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SCQ- Self-Administered Comorbidity Questionnaire, SD = standard deviation

Table 3 – Differences in Subscale and Total Scores on the General Sleep Disturbance Scale Among the Sleep Disturbance and Morning Energy Classes at Enrollment

Sleep Disturbance Subscales[a]	**Low Sleep Disturbance and High Morning Energy (0) 20.6% (n = 275)**	**Moderate Sleep Disturbance and Low Morning Energy (1) 52.1% (n = 696)**	**Very High Sleep Disturbance and Very Low Morning Energy (2) 27.3% (n = 365)**	**Statistics**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Quality of sleep (≥3.0)	1.7 (1.4)	3.2 (1.5)	4.7 (1.4)	F = 384.42, p < 0.001 0 < 1 < 2
Quantity of sleep (≥3.0)	3.8 (1.3)	4.5 (1.5)	5.5 (1.6)	F = 103.39, p < 0.001 0 < 1 < 2
Sleep onset latency (≥3.0)	1.2 (1.5)	2.4 (2.0)	4.4 (2.2)	F = 230.96, p < 0.001 0 < 1 < 2
Mid-sleep awakenings (≥3.0)	3.7 (2.4)	4.8 (2.2)	6.1 (1.4)	F = 102.45, p < 0.001 0 < 1 < 2
Early awakenings (≥3.0)	1.9 (2.0)	3.4 (2.3)	5.2 (2.0)	F = 181.77, p < 0.001 0 < 1 < 2
Medications for sleep (≥3.0)	0.3 (0.5)	0.6 (0.7)	1.0 (1.0)	F = 88. 21, p < 0.001 0 < 1 < 2
Excessive daytime sleepiness (≥3.0)	1.3 (1.0)	2.6 (1.2)	3.8 (1.2)	F = 342.37, p < 0.001 0 < 1 < 2

Abbreviations: GSDS = General Sleep Disturbance Scale, SD = standard deviation

[a]Clinically meaningful cutoff scores

Table 4 – Differences in Co-Occurring Symptom Severity Scores Among the Sleep Disturbance and Morning Energy Latent Classes at Enrollment

Symptoms[a]	**Low Sleep Disturbance and High Morning Energy (0) 20.6% (n = 275)**	**Moderate Sleep Disturbance and Low Morning Energy (1) 52.1% (n = 696)**	**Very High Sleep Disturbance and Very Low Morning Energy (2) 27.3% (n = 365)**	**Statistics**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Depressive symptoms (≥16.0)	6.1 (5.2)	12.0 (8.0)	32.1 (117)	F = 194.12, p < 0.001 0 < 1 < 2
Trait anxiety (≥31.8)	28.2 (6.8)	34.5 (9.0)	41.6 (11.6)	F = 157.02, p < 0.001 0 < 1 < 2
State anxiety (≥32.2)	26.7 (8.0)	33.1 (11.1)	40.8 (13.8)	F = 119.68, p < 0.001 0 < 1 < 2
Morning fatigue (≥3.2)	1.3 (1.3)	3.0 (2.0)	4.7 (2.1)	F = 243.24, p < 0.001 0 < 1 < 2
Evening fatigue (≥5.6)	4.1 (2.1)	5.3 (2.1)	6.3 (1.8)	F = 91.52, p < 0.001 0 < 1 < 2
Evening energy (≤3.5)	4.2 (2.1)	3.5 (2.0)	3.2 (2.1)	F = 18.05, p < 0.001 0 > 1 and 2
Attentional function (<5.0 = Low, 5 to 7.5 = Moderate, >7.5 = High)	7.8 (1.5)	6.4 (1.6)	5.4 (1.8)	F = 161.66, p < 0.001 0 > 1 > 2
Type of pain % (n) No pain Only non-cancer pain Only cancer pain Both cancer and non-cancer pain	 42.2 (114) 20.4 (55) 21.5 (58) 15.9 (43)	 27.4 (186) 25.3 (104) 29.3 (199) 28.1 (191)	 16.3 (59) 13.6 (49) 24.7 (89) 45.4 (164)	X^2 = 94.26, p < 0.001 0 > 1 > 2 NS 0 < 1 0 < 1 < 2
Worst pain intensity score (0 to 10) 0 to 3 = mild 4 to 6 = moderate ≥7 = severe	5.0 (2.6)	5.8 (2.4)	6.9 (2.4)	F = 27.33, p < 0.001 0 < 1 <2
Pain interference score (0 to 10)	1.7 (1.9)	2.8 (2.3)	4.2 (2.6)	F = 56.69, p < 0.001 0 < 1 <2

Abbreviation: SD = standard deviation

[a]Clinically meaningful cutoff scores

Table 5 – Differences in Quality of Life Outcomes Among the Sleep Disturbance and Morning Energy Latent Classes at Enrollment

Domains	Low Sleep Disturbance and High Morning Energy (0) 20.6% (n = 275)	Moderate Sleep Disturbance and Low Morning Energy (1) 52.1% (n = 696)	Very High Sleep Disturbance and Very Low Morning Energy (2) 27.3% (n = 365)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Multidimensional Quality of Life Scale Cancer – Patient Version				
Physical well-being	8.2 (1.)	6.6 (1.5)	5.4 (1.7)	F = 282.17, p < 0.001 0 > 1 > 2
Psychological well-being	6.8 (1.5)	5.5 (1.7)	4.5 (1.7)	F = 151.22, p < 0.001 0 > 1 > 2
Social well-being	7.0 (1.7)	5.7 (1.9)	4.7 (2.0)	F = 112.61, p < 0.001 0 > 1 > 2
Spiritual well-being	5.8 (2.2)	5.4 (2.0)	5.3 (2.1)	F = 6.64, p = 0.001 0 > 1 and 2
Total quality of life score	7.0 (1.1)	5.7 (1.3)	4.8 (1.3)	F = 221.02, p < 0.001 0 > 1 > 2
Medical Outcomes Study – Short Form-12				
Physical functioning	72.0 (31.4)	51.4 (33.0)	39.6 (32.6)	F = 74.51, p < 0.001 0 > 1 > 2
Role physical	73.1 (25.0)	51.6 (27.8)	37.9 (26.3)	F = 132.04, p < 0.001 0 > 1 > 2
Bodily pain	90.5 (16.8)	76.7 (27.2)	62.1 (31.5)	F = 86.73, p < 0.001 0 > 1 > 2
General health	73.2 (22.8)	64.2 (26.6)	51.6 (30.6)	F = 50.77, p < 0.001 0 > 1 > 2
Vitality	67.2 (20.7)	44.3 (24.6)	30.7 (24.5)	F = 180.47, p < 0.001 0 > 1 > 2
Social functioning	85.1 (23.2)	67.5 (28.7)	52.1 (31.5)	F = 102.78, p < 0.001 0 > 1 > 2
Role emotional	89.6 (17.4)	77.1 (25.7)	62.2 (30.5)	F = 88.59, P < 0.001 0 > 1 > 2
Mental health	83.2 (14.9)	73.4 (19.0)	60.2 (22.3)	F = 114.81, p < 0.001 0 > 1 > 2
Physical component summary score	47.6 (8.6)	40.9 (10.2)	37.0 (10.3)	F = 83.03, p < 0.001 0 > 1 > 2
Mental component summary score	55.2 (7.3)	49.7 (9.5)	42.9 (11.1)	F = 122.50, p < 0.001 0 > 1 > 2

Abbreviation: SD = standard deviation

Table 6 – Characteristics Associated with Membership in the Other Two Sleep Disturbance and Morning Energy Latent Classes Compared to the Low Sleep Disturbance and High Morning Energy Class

Characteristic[a]	Moderate Sleep Disturbance + Low Morning Energy	Very High Sleep Disturbance + Very Low Morning Energy
Demographic Characteristics		
More likely to be younger		■
More likely to be female	■	■
More likely to be White	■	
Less likely to be Asian or Pacific Islander		■
Less likely to be married or partnered		■
More likely to live alone		■
Less likely to be currently employed	■	■
More likely to have a lower annual household income		■
Less likely to exercise on a regular basis		■
Clinical Characteristics		
Higher body mass index		■
Lower functional status (Karnofsky Performance Status score)	■	■
Higher number of comorbid conditions	■	■
Higher comorbidity burden (Self-administered Comorbidity Questionnaire)	■	■
Lower number of metastatic sites including lymph node involvement		■
Lower number of metastatic sites excluding lymph node involvement		■
Higher MAX2 score	■	■
More likely to have a current or past history of smoking	■	
More likely to self-report ulcer or stomach disease	■	■
More likely to self-report anemia or blood disease		■
More likely to self-report depression	■	■
More likely to self-report osteoarthritis		■
More likely to self-report back pain	■	■
Less likely to have gastrointestinal cancer	■	■
Less likely to have received no prior cancer treatment		■
More likely to have metastatic disease		■
More likely to have received only chemotherapy	■	■
Less likely to have received only targeted therapy	■	
Sleep Disturbance Characteristics		
Higher sleep quality scores (i.e., worse sleep quality)	■	■
Higher quantity of sleep scores (i.e., fewer hours of sleep)	■	■
Higher sleep onset latency scores	■	■
Higher mid-sleep awakening scores	■	■
Higher early awakening scores	■	■
Higher use of medications for sleep scores	■	■
Higher excessive daytime sleepiness scores	■	■
Higher total sleep disturbance scores	■	■
Symptom Characteristics		
Higher depression	■	■
Higher trait anxiety	■	■
Higher state anxiety	■	■
Higher morning fatigue	■	■
Higher evening fatigue	■	■

Characteristic[a]	Moderate Sleep Disturbance + Low Morning Energy	Very High Sleep Disturbance + Very Low Morning Energy
Symptom Characteristics		
Lower morning energy	■	■
Lower evening energy	■	■
Lower cognitive function	■	■
More likely to report pain	■	■
More likely to report cancer pain	■	
More likely to report both cancer and non-cancer pain	■	■
Higher worst pain intensity	■	■
Higher pain interference	■	■
Quality of Life Outcomes		
Multidimensional Quality of Life Scale Cancer – Patient Version		
Lower physical well-being	■	■
Lower psychological well-being	■	■
Lower social well-being	■	■
Lower spiritual well-being	■	■
Lower overall quality of life	■	■
Medical Outcomes Study – Short Form 12		
Lower physical functioning	■	■
Lower role functioning	■	■
Higher bodily pain	■	■
Lower general health	■	■
Lower vitality	■	■
Lower social functioning	■	■
Lower role emotional	■	■
Lower mental health	■	■
Lower physical component summary score	■	■
Lower mental component summary score	■	■

[a]Comparisons done with the Low Sleep Disturbance and High Morning Energy Class

■ – Indicates the presence of the risk factor compared to the Low Sleep Disturbance and High Morning Energy Class

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