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Abid, Hamza

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Common and Distinct Characteristics Are Associated With
Trajectories of Morning and Evening Energy in Oncology Patients
Receiving Chemotherapy

by

Hamza Abid

THESIS

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Dedication and Acknowledgments

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To my father, Mohammad Abid who fought lung cancer with great honor and dignity, my mother Adlah Abid and my entire family, I proffer my utmost gratitude, respect and love.

Abstract

Context. Energy conservation strategies are recommended in a number of clinical practice guidelines to manage fatigue associated with cancer and its treatments. However, little is known about changes in energy levels in oncology patients undergoing cancer treatment.

Objectives. An evaluation was done to identify variations in the trajectories of morning and evening energy levels and to determine which demographic, clinical, and symptom characteristics predicted initial levels as well as the trajectories of morning and evening energy.

Methods. Outpatients with breast, gastrointestinal, gynecological, and lung cancer, who were undergoing chemotherapy (CTX), completed demographic and symptom questionnaires a total of six times over two cycles of CTX. Morning and evening energy levels were evaluated using the energy subscale of the Lee Fatigue Scale. Hierarchical linear modeling was used to answer the study objectives.

Results. A large amount of inter-individual variability was found in both the morning and evening energy trajectories. A piecewise model fit the data best. Patients who lived alone, had child care responsibilities, had a lower functional status, did not exercise on regular basis, had lower hemoglobin levels, as well as lower attentional function, higher trait anxiety and higher sleep disturbance reported lower morning energy levels at enrollment. Variations in the trajectories of morning energy were associated with a higher body mass index, as well as higher levels of morning energy and higher sleep disturbance scores. In terms of evening energy, patients who were female, White, had lower functional status, and had lower attentional functional and higher sleep disturbance scores reported lower evening energy levels at enrollment. Evening energy levels at enrollment were associated with changes in evening energy over time.

Conclusion. Patients undergoing CTX experience decrements in both morning and evening energy. Different modifiable and non-modifiable characteristics were associated with decrements in morning and evening energy levels. These modifiable characteristics can be used to design intervention studies to increase energy levels in these patients.

Keywords: morning energy; evening energy; cancer; oncology; chemotherapy; hierarchical linear modeling; symptom trajectories; diurnal variations

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Introduction

Energy conservation strategies are recommended in a number of clinical practice guidelines to manage fatigue associated with cancer and its treatments.(1, 2) In fact, these strategies are listed second to self-monitoring of fatigue levels in the latest guideline published by the National Comprehensive Cancer Network (NCCN).(3) However, in most of the symptom management literature, the terms energy and fatigue are used interchangeably.(4, 5) For example, in the Memorial Symptom Assessment Scale, fatigue is evaluated using the phrase "lack of energy".(6)

However, a growing body of evidence suggests that energy and fatigue are distinct, but related symptoms.(7-9) For instance, the Lee Fatigue Scale (LFS), used in this study to assess morning and evening energy levels, has two subscales that distinguish energy from fatigue (i.e., a fatigue subscale with 13 items and an energy subscale with 5 items).(10) Moreover, in a recent Rasch analysis of the LFS, energy and fatigue were found to be distinct symptoms.(11)

Little is known about changes in energy levels in oncology patients undergoing cancer treatment. Only one study was identified that evaluated for changes in energy levels in patients who underwent radiation therapy (RT) and their family caregivers.(12) In this sample (n=252), the energy subscale scores from the LFS were used to identify groups of participants (i.e., latent classes) with distinct morning and evening energy trajectories. Using growth mixture modeling (GMM), for both morning and evening energy, two latent classes were identified. Participants were more likely to be in the lower morning energy class if they were younger, female, not partnered, Black, had more comorbidities and had a lower functional status. Participants were more likely to be in the lower evening energy class if they were younger, male, had a higher number of comorbidities, had a lower body weight, and had a lower functional status.

No studies were identified that evaluated for changes in energy levels in oncology patients receiving CTX. Therefore, the purposes of this study, in a sample of outpatients with breast, gastrointestinal (GI), gynecological (GYN), and lung cancer who were receiving two cycles of CTX, were to evaluate for variations in the trajectories of morning and evening energy levels and to determine which demographic, clinical, and symptom characteristics were associated with initial levels as well as with the trajectories of morning and evening energy.

Methods

Sample and Settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving CTX.(13-16) Eligible patients were ≥18 years of age; had a diagnosis of breast, GI, GYN, or lung cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.

Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income.

Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well established validity and reliability.(17) 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).(17, 18)

Self-Administered Comorbidity Questionnaire (SCQ) consists of 13 common medical conditions simplified into language that can be understood without prior medical knowledge.(19) Patients indicated if they had the condition; if they received treatment for it (proxy for disease severity); and if it limited their activities (indication of functional limitations). For each condition, the patient can receive a maximum of 3 points. The total SCQ score ranges from 0 to 39. The SCQ has well established validity and reliability.(20, 21)

Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire that assesses alcohol consumption, alcohol dependence, and the consequences of alcohol abuse in the last 12 months. The AUDIT gives a total score that ranges between 0 and 40. Scores of ≥8 are defined as hazardous use and scores of ≥16 are defined as use of alcohol that is likely to be harmful to health.(22, 23) The AUDIT has well established validity and reliability.(24-26) In this study, its Cronbach's alpha was 0.63.

Lee Fatigue Scale (LFS) consists of 18 items designed to assess physical fatigue and energy.(10) Each item was rated on a 0 to 10 numeric rating scale (NRS). Total fatigue and energy scores are 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) (27) and energy (i.e., ≤6.2 for morning energy, ≤3.5 for evening energy).(27) It was chosen for this study because it is relatively short, easy to administer, and has well established validity and

reliability.(4, 10, 28-31) In the current study, the 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.

Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) each have 20 items that are rated from 1 to 4. The summed scores for each scale can range from 20 to 80. The STAI-T measures a person's predisposition to anxiety as part of one's personality. The STAI-S measures a person's temporary anxiety response to a specific situation or how anxious or tense a person is "right now" in a specific situation. Cutoff scores of $\geq$31.8 and $\geq$32.2 indicate high levels of trait and state anxiety, respectively. The STAI-S and STAI-T inventories have well established validity and reliability.(32-34) In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

Center for Epidemiological Studies-Depression scale (CES-D) consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. A total score can range from 0 to 60, with scores of $\geq$16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well established validity and reliability.(35-37) In the current study, the Cronbach's alpha for the CES-D total score was 0.89.

General Sleep Disturbance Scale (GSDS) consists of 21-items designed to assess the quality of sleep in the past week. Each item was rated on a 0 (never) to 7 (everyday) NRS. The GSDS total score is the sum of the seven subscale scores that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). Each mean subscale score can range from 0 to 7. Higher total and subscale scores indicate higher levels of sleep disturbance. Subscales scores of $\geq$3 and a GSDS total score of $\geq$43 indicate a significant level of sleep disturbance.(27) The GSDS has well established validity and reliability.(29, 38, 39) In the current study, the Cronbach's alpha for the GSDS total score was 0.83.

Attentional Function Index (AFI) consists of 16 items designed to measure attentional function.(40) A higher total mean score on a 0 to 10 NRS indicates greater capacity to direct attention.(40) Total scores are grouped into categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function).(41) The AFI has well established reliability and validity.(40) In this study, the Cronbach's alpha for the AFI total score was 0.93.

Occurrence of pain was evaluated using the Brief Pain Inventory.(42) Patients who responded yes to the question about having pain were asked to indicate if their pain was or was not related to their cancer treatment. Patients were categorized into one of four groups (i.e., no pain, only noncancer pain, only cancer pain, both cancer and non-cancer pain).

Study Procedures

The study was approved by the Institutional Review Board at each of the study sites. Eligible patients were approached in the infusion unit by a member of the research team to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their CTX cycles (i.e., 14-day, 21-day, or 28-day), patients completed study questionnaires in their homes, a total of six times over two cycles of CTX (prior to CTX administration (i.e., recovery from previous CTX cycle; Assessment 1 and 4), approximately 1 week after CTX administration (i.e., acute symptoms; Assessments 2 and 4), and approximately 2 weeks after CTX administration (i.e., potential nadir; Assessments 3 and 6).

Data Analyses

Descriptive statistics and frequency distributions were generated on the sample characteristics and symptom severity scores at enrollment using the Statistical Package for the Social Sciences (SPSS) version 22.(43)

Hierarchal linear modeling (HLM) based on full maximum likelihood estimation was performed in two stages using software developed by Raudenbush and Bryk.(44) The HLM methods are described in detail elsewhere.(30, 45-48) Separate HLM analyses were done for morning and evening energy. In brief, during stage 1, intra-individual variability in morning and evening energy over time was examined. A piecewise model strategy was employed to evaluate the pattern of change in morning and evening energy over time because the six assessments encompassed two cycles of CTX. The six assessments were coded into two pieces.

Assessments 1, 2, and 3 comprised the first piece (PW1) that was used to model changes over time during the first CTX cycle. Assessments 4, 5, and 6 comprised the second piece (PW2) that was used to model changes over time during the second CTX cycle. A piecewise model can be more sensitive to the timing and sequencing of changes in a dependent variable than conventional HLM models that would have assessed linear, quadratic, or cubic changes over the six assessments and would not have paid attention to the two different CTX cycles.(49)

The second stage of the HLM analysis examined inter-individual differences in the piecewise trajectories of morning and evening energy by modeling the individual change parameters (i.e., intercept and slope parameters) as a function of proposed predictors at level 2. Supplementary Tables 1 and 2 list the potential predictors for morning and evening energy, respectively that were evaluated in this study.

To improve estimation efficiency and construct a parsimonious model, exploratory level 2 analyses were completed in which each potential predictor was assessed to determine whether it would result in a better fitting model if it alone were added as a level 2 predictor. Predictors with a t value of <2.0 were excluded from subsequent model testing. All potential significant predictors from the exploratory analyses were entered into the model to predict each individual

change parameter. Only predictors that maintained a statistically significant contribution in conjunction with other predictors were retained in the final model. A *p*-value of <.05 indicated statistical significance.

Results

Separate HLM analyses were done for morning and evening energy. The sample sizes for morning (n=1333) and evening (n=1332) were slightly different. Therefore, the analyses are presented separately.

Morning Energy

Sample Characteristics

The demographic, clinical, and symptom characteristics of the sample (n=1333) are presented Table 1. The sample was predominately female (78%) and white (69%), well educated (16 years), partnered (65%), currently not employed (65%), did not have child care responsibilities (78%), and had a mean age of 57 years. On average, the patients were 2 years from their cancer diagnosis (median = 0.42 year), primarily being treated with 21-day CTX cycles (51%), had one metastatic site, and had received previous cancer treatment (76%). At enrollment, the mean scores on the GSDS, STAI-T, and the STAI-S were above the clinically meaningful cutoff scores for sleep disturbance, trait anxiety, and state anxiety, respectively. In addition, patients reported clinically meaningful decrements in morning energy levels at enrollment, while evening energy levels were at the cut-off score for a clinically meaningful decrement.

Changes in Morning Energy Levels Over Time

The first HLM analysis examined how morning energy scores changed within the two cycles of CTX. The linear and quadratic trends for both cycles of CTX were significant (all, $p<00.1$; see Table 2).

The estimates for the initial piecewise model are presented in Table 2. Since the model was unconditional (i.e., no covariates), the intercept represents the average morning energy scores at enrollment (i.e., 4.393 on a scale of 0 to 10). The estimated linear piecewise rates of change in morning energy were -0.457 and -0.492 (both $p<.0001$) for piecewise linear 1 and piecewise linear 2, respectively. The estimated quadratic piecewise rates of change in morning energy were 0.386 and 0.166 (both $p<.0001$) for piecewise quadratic 1 and piecewise quadratic 2, respectively. The combination of each coefficient determines the curves for the two piecewise components' changes in morning energy scores over time.

Figure 1A displays the mean morning energy scores over two cycles of CTX. Morning energy levels declined at assessment 2 and increased with a peak at assessment 3, decreased slightly at assessment 4, remained unchanged at assessment 5, and increased slightly at assessment 6. These results indicate a sample-wide change in morning energy levels over time. However, they do not indicate that all of the patients' morning energy scores changed at the same rate over time. The variance components (Table 2) suggest that considerable inter-individual variability existed in the trajectories of morning energy (see Figure 1B).

Inter-Individual Differences in Initial Levels of Morning Energy

As shown in the final model (Table 2), the demographic characteristics that predicted inter-individual differences in the initial levels (i.e., intercept) of morning energy were living alone and having child care responsibilities. The clinical characteristics that predicted inter-

individual differences in the initial levels of morning energy were functional status, exercise on a regular basis, and hemoglobin (Hgb) level. The severity of trait anxiety and attentional function at enrollment were the symptom characteristics that predicted inter-individual differences in the intercept for morning energy.

To illustrate the effects of the various demographic, clinical, and symptom characteristics on initial levels of morning energy, Figures 2A-E display the adjusted change curves for morning energy that were estimated based on whether the patient lived alone (i.e., yes or no), had child care responsibilities (i.e., yes or no), differences in functional status (i.e., lower/higher calculated as one SD above and below the mean KPS score), exercises on a regular basis (i.e., yes or no), and differences in Hgb level (i.e., lower/higher calculated as one SD above and below the mean Hgb level). Figures 3A-B display the adjusted change curves for morning energy that were estimated based on the differences in trait anxiety (i.e., lower/higher calculated as one SD above and below the mean STAI-T score), and attentional function (i.e., lower/higher calculated as one SD above and below the mean AFI score).

Inter-individual Differences in the Trajectories of Morning Energy

As shown in the final model (Table 2), one clinical characteristic (i.e., BMI) and one symptom characteristic (i.e., initial level of morning energy) predicted inter-individual differences in the trajectories of morning energy. Figures 3C-D display the adjusted change curves for morning energy that were evaluated based on differences in BMI (i.e., lower/higher calculated as one SD above and below the mean BMI) and differences in morning energy (i.e., lower/higher calculated as one SD above and below the mean LFS morning energy score).

Inter-Individual Differences in Initial Levels and Trajectories of Morning Energy

As shown in the final model (Table 2), sleep disturbance was the only characteristic that predicted inter-individual differences in both initial levels as well as in the trajectories of morning energy. Figure 3F displays the adjusted change curves for morning energy that were evaluated based on differences in sleep disturbance (i.e., lower/higher calculated as one SD above and below the mean GSDS score).

Evening Energy

Sample Characteristics

The demographic, clinical, and symptom characteristics of the sample (n=1332) are presented Table 3. The sample was predominately female (78%), white (69%), partnered (65%), well educated (16 years), currently not employed (65%), did not have child care responsibilities (78%), with a mean age of 57 years. On average, the patients were 2 years from their cancer diagnosis (median = 0.42 year), primarily being treated with 21-day CTX cycles (51%), had one metastatic site, and had received previous cancer treatment (76%). At enrollment, the mean scores on the GSDS, STAI-T, and the STAI-S were above the clinically meaningful cutoff scores for sleep disturbance, trait anxiety, and state anxiety, respectively. In addition, patients reported clinically meaningful decrements in morning energy levels at enrollment, while evening energy levels were at the cut-off score for a clinically meaningful decrement.

Changes in Evening Energy Levels Over Time

The first HLM analysis examined how evening energy scores changed within the two cycles of CTX. The linear and quadratic trends for both cycles of CTX were significant (all, p<.05; Table 4).

The estimates for the initial piecewise model are presented in Table 4. Since the model was unconditional (i.e., no covariates), the intercept represents the average evening energy score at enrollment (i.e., 3.552 on a scale of 0 to 10). The estimated linear piecewise rates of change in evening energy were -0.275 (p<.05) and -0.323 (p<.0001) for piecewise linear 1 and piecewise linear 2, respectively. The estimated quadratic piecewise rates of change in evening energy were 0.195 and 0.096 (both *p*<.0001) for piecewise quadratic 1 and piecewise quadratic 2, respectively. The combination of each coefficient determines the curves for the two piecewise components' changes in evening energy scores over time.

Figure 1C displays the mean evening energy scores over the two cycles of CTX. Evening energy levels declined at assessment 2 and increased slightly at assessment 3, decreased through assessment 5, and then increased slightly at assessment 6.

The results indicate a sample-wide change in evening energy levels over time. However, they do not indicate that all of the patients' evening energy level scores changed at the same rate over time. The variance components (Table 4) suggest that a considerable amount of inter-individual variability existed in the trajectories of evening energy scores (See Figure 1D).

Inter-Individual Differences in Initial Levels of Evening Energy

As shown in the final model (Table 4), the demographic characteristics that predicted inter-individual differences in the initial levels (i.e., intercept) of evening energy were gender and ethnicity. Functional status was the only clinical characteristic that predicted inter-individual differences in the initial levels of evening energy. Sleep disturbance and attentional function at enrollment were the symptom characteristics that predicted inter-individual differences in the intercept for evening energy.

To illustrate the effects of the various demographic, clinical, and symptom characteristics, Figures 4A-C display the adjusted change curves for evening energy that were estimated based on gender (i.e., male or female), ethnicity (i.e., white or nonwhite) and performance status (i.e., lower/higher calculated as one SD above and below the mean KPS score). Figures 4D-E display the adjusted change curves for evening energy that were estimated based on the differences in sleep disturbance (i.e., lower/higher calculated as one SD above and below the mean GSDS score) and attentional function (i.e., lower/higher calculated as one SD above and below the mean AFI score).

Inter-Individual Differences in Trajectories of Evening Energy

As shown in the final model (Table 4), one symptom characteristic (i.e., initial level of evening energy) predicted inter-individual differences in the trajectories of evening energy. Figure 4F displays the adjusted change curves for evening energy that were evaluated based on differences in evening energy (i.e., lower/higher calculated as one SD above and below the mean LFS evening energy score).

Discussion

This study is the first to evaluate for inter-individual differences in morning and evening energy levels in oncology patients undergoing two cycles of CTX. In addition, common and distinct demographic, clinical, and symptom characteristics associated with more severe decrements in morning and evening energy were determined. As shown in Table 5, only three characteristics (i.e., functional status, sleep disturbance, and attentional function) were associated with decrements in both morning and evening energy. Findings regarding morning energy will be presented first. Contrasts will be made between the characteristics associated with decrements in initial levels as well as in the trajectories of morning and evening energy (see Table 5).

Morning Energy

It should be noted that across the entire sample, mean scores for morning energy at the first assessment (i.e., 4.40) were below the clinically meaningful cutoff score of ≤6.2. While Figure 1A illustrates that the changes in morning energy levels were relatively stable over the two cycles of CTX, a large amount of inter-individual variability in morning energy levels was found in the sample. Taken together, these findings suggest that prior to their next dose of CTX patients were experiencing clinically meaningful decrements in morning energy that persisted over the next 6 to 8 weeks.

Direct comparison of our findings regarding the characteristics associated with initial levels, as well as the trajectories of morning energy over the two cycles of CTX is not possible, because no studies were identified that used the same energy measure; the same assessment time points; and HLM as the analysis method. However, some information is available on the characteristics associated with decrements in morning energy levels. In a study that evaluated patients who underwent radiation therapy (RT) and their family caregivers,(12) GMM identified two classes of participants (i.e., low and moderate morning energy). Similar to the current study, participants in the low energy class reported morning energy scores of 4.7 (±1.6) prior to the initiation of RT. Consistent with the findings in the RT study,(12) in the current study, poorer functional status, higher trait anxiety, and poorer attentional function were associated with lower morning energy scores at enrollment. In addition, higher levels of sleep disturbance, as well as more severe decrements in morning energy were associated with worse trajectories of morning energy. While the timing of the assessments, the types of cancer treatments, and the statistical approaches used to identify the specific characteristics associated with more severe decrements in morning energy differed between the previous(12) and the current study, a relatively large

number of characteristics were similar in both studies. While these findings warrant confirmation, oncology clinicians can use these characteristics to identify patients who are at increased risk for decrements in morning energy.

It should be noted that in in the current study, an additional five characteristics were associated with decrements in morning energy. As shown in Table 5, living alone, having child care responsibilities, not exercising on regular basis, having a lower Hgb level, and having a higher BMI were associated with lower levels of morning energy. While no studies were found that examined the relationship between living alone and morning energy levels, our findings make clinical sense in that individuals who live alone may lack immediate support to care for themselves or their living situation.

In terms of child care responsibilities, in our previous RT study,(12) no associations were found between this characteristic and decrements in either morning or evening energy. However, in the current study, it is interesting to note, that having child care responsibilities was associated with decrements in both morning and evening energy. Given its impact on both morning and evening energy levels, clinicians may need to counsel patients to evaluate the need for assistance with child care during CTX.

The association between increased exercise and decreased levels of fatigue in oncology patients is well established.(50, 51) In fact, the current fatigue guidelines published by the National Comprehensive Cancer Network recommended exercise as the only evidenced-based intervention to decrease fatigue in oncology patients.(3) To our knowledge, this study is the first to demonstrate an association between lack of regular exercise and more severe decrements in morning energy levels. While this finding warrants replication, patients should receive ongoing

education and encouragement to participate in a regular exercise program during and following CTX.

Anemia is implicated as a potential mechanism for the development of fatigue in oncology patients.(52) In the current study, lower Hgb levels were associated with more severe decrements in morning energy levels. The mean Hgb level of our sample was 11.54 gm/dL. At one standard deviation below this mean level (i.e., 10.11 gm/dL), these patients would be classified as anemic. While this association makes sense clinically, it warrants confirmation in future studies.

The mean BMI of our sample (i.e., 26.17 kg/m^2) is considered overweight.(53) While no studies were found on the association between BMI and energy, studies of patients with breast cancer,(54, 55) and patients receiving CTX,(14, 56) reported that a higher BMI was associated with higher levels of fatigue. The exact reasons why a higher BMI is associated with higher levels of fatigue, as well as decrements in morning energy are not readily apparent. One potential explanation is that patients with higher BMI are more likely to be diagnosed with obstructive sleep apnea (OSA).(57) Increased levels of sleep disturbance associated with OSA may contribute to the decrements in morning energy levels found in the current study.

Evening Energy

Mean scores for evening energy at the first assessment (i.e., 3.54) were at the clinically meaningful cutoff score of ≤3.5. Like morning energy, a large amount of inter-individual variability was found in this symptom (see Figure 1D). Again, at the initiation of their next dose of CTX and throughout the remaining 6 to 8 weeks, these patients experienced clinically meaningful decrements in evening energy.

While no studies were found that evaluated for changes in evening energy over two cycles of CTX, findings from the previously cited RT study(12) are worth noting. In this RT study, two classes of participants (i.e., moderate and high evening energy) were identified using GMM. Prior to the initiation of RT, participants in the moderate energy class had evening energy scores of 4.1($\pm$1.6) which were slightly above the clinically meaningful cutoff score. Consistent with the findings in the RT study,(12) in the current study, poorer functional status and poorer attentional function were associated with lower evening energy scores at enrollment. In addition, higher levels of sleep disturbance, as well as more severe decrements in evening energy were associated with worse trajectories of evening energy. Although differences exist between the previous(12) and the current study (i.e., assessment time points, statistical analysis, and cancer treatment), a considerable number of the characteristics associated with decrements in evening energy were similar in both studies. From a clinical perspective, all three of these characteristics can be modified through targeted interventions. For example, functional status can be improved with regular exercise;(58, 59) improvements in attentional function can occur through the use of cognitive training tasks;(60) and sleep hygiene interventions can be used to reduce sleep disturbance.(61)

Two additional characteristics (i.e., gender, ethnicity) were associated with decrements in evening energy. Our finding that female gender was associated with more severe decrements in evening energy contrasts with the findings from the previously cited RT study, (12) which found that male patients were more likely to be classified in the lower evening energy class. Given that the findings on gender differences in a variety of symptoms are not consistent,(62, 63) this inconsistency warrants additional investigation.

In terms of ethnic differences in symptom severity, findings for a variety of symptoms (e.g., pain(64, 65), sleep disturbance(66, 67)) are also inconsistent. In our previous RT study,(12) while no association was found between ethnicity and evening fatigue, compared to White patients, Black patients were more likely to be classified in the lower morning energy class. However, in the current study, White patients were more likely to report decrements in evening energy at enrollment. Reasons for these inconsistent findings, in terms of both gender and ethnicity, may be related to differences in sample characteristics; differences in statistical methods used to evaluate the associations between gender or ethnicity and energy levels; and differences in the characterization of energy levels (i.e., mean energy levels versus diurnal variations in energy).

Limitations and Strengths

Several limitations and strengths need to be acknowledged. Because patients were recruited at various points in their CTX treatment, changes in energy levels from the initiation of CTX cannot be evaluated. In addition, the relationships between decrements in morning and evening energy levels and specific CTX regimens were not evaluated in this study. Patients rated their experience of morning and evening energy over a one week period of time. Daily assessments may provide more accurate information and insights into the variability of morning and evening energy during two cycles of CTX.(68) However, this large, representative sample of oncology outpatients undergoing CTX; the assessment and evaluation of changes in morning and evening energy over two cycles of CTX; and the use of HLM to identify characteristics associated with decrements in morning and evening energy are major strengths of this study. In addition, this study is the first to evaluate for variations in the trajectories of morning and evening energy levels and to determine which demographic, clinical, and symptom

characteristics were associated with initial levels as well as with the trajectories of these symptoms.

Clinical Implications

Our findings have important clinical implications. Assessment of diurnal variations in energy levels, as well as associated risk factors, need to be incorporated into clinical practice. These assessments may allow oncology clinicians to focus interventions on one or both of these symptoms. Several modifiable risk factors for decrements in morning and evening energy levels were identified. For morning energy, the modifiable risk factors were living alone, having child care responsibilities, lower functional status, lack of regular exercise, lower Hgb level, and higher BMI. For evening energy, the only modifiable risk factor was lower functional status. Interventions that improve functional status have the potential to increase both morning and evening energy levels.

Future Research

Longitudinal studies are needed to evaluate for decrements in morning and evening energy levels in oncology patients prior to the initiation of CTX, as well as during treatment and into survivorship. Studies are needed that evaluate for changes of morning and evening energy among patients undergoing different types of cancer treatment (e.g., surgery, RT). Additional research is needed that evaluates the impact of different types of CTX on morning and evening energy. Studies of how genetic variations contribute to decrements in morning and evening energy levels in oncology patients may increase our understanding of the mechanisms that underlie diurnal variations in energy levels.

Table 1: Demographic, Clinical, and Symptom Characteristics of the Patients in the Morning Energy Analysis (n=1333)

Demographic Characteristics	
Age (years; mean (SD))	57.18 (12.39)
Gender (% female (n))	77.9 (1039)
Ethnicity (% (n))	
White	69.5 (926)
Black	9.9 (132)
Asian/Pacific Islander	9.6 (128)
Hispanic/Mixed/Other	11.0 (147)
Education (years; mean (SD))	16.18 (2.98)
Married or partnered (% yes (n))	64.9 (865)
Lives alone (% yes (n))	21.2 (283)
Currently employed (% yes (n))	34.7 (463)
Child care responsibilities (% yes (n))	21.7 (289)
Income (% yes (n))	
Less than $30,000	18.4 (219)
$30,000 to <$70,000	21.1 (252)
$70,000 to < $100,000	16.9 (202)
More than $100,000	43.6 (520)
Clinical Characteristics	
Number of comorbidities (mean (SD))	2.40 (1.43)
Self-administered Comorbidity Questionnaire score (mean (SD))	5.47 (3.20)
Body mass index (kg/m^2; mean (SD))	26.17 (5.63)
Hemoglobin (gm/dL; mean (SD))	11.54 (1.43)
Karnofsky Performance Status score (mean (SD))	80.00 (12.39)
Have you ever considered yourself a smoker (% yes (n)	34.8 (464)
Exercise on a regular basis (% yes (n))	71.5 (953)
Specific comorbidities reported (% yes (n))	
High blood pressure	30.2 (402)
Back pain	25.7 (343)
Depression	19.3 (257)
Osteoarthritis	12.0 (160)
Anemia or blood disease	12.2 (163)
Lung disease	11.3 (151)
Diabetes	9.0 (120)
Liver disease	6.5 (86)
Heart disease	5.6 (75)
Rheumatoid arthritis	3.1 (41)
Ulcer or stomach disease	4.9 (65)
Kidney disease	1.4 (19)
Cancer diagnosis (% yes (n))	
Breast	40.4 (539)
Gastrointestinal	30.3 (404)
Gynecological	17.5 (233)
Lung	11.8 (157)
Time since cancer diagnosis (years; mean (SD))	1.97 (3.87)
Time since cancer diagnosis (years; median)	0.42
Any prior cancer treatments (% yes (n))	75.8 (1010)
Number prior cancer treatments (mean (SD))	1.59 (1.50)

Chemotherapy cycle length (% (n))
        14 days
        21 days
        28 days
	41.8 (557)
	50.9 (679)
	7.3 (97)

Presence of metastatic disease (% yes (n))	67.1 (894)
Number of metastatic sites including lymph node involvement (mean (SD))	1.24 (1.23)
Number of metastatic sites excluding lymph node involvement (mean (SD))	0.78 (1.05)
Symptom Characteristics at Enrollment	
Lee Fatigue Scale: evening fatigue score (mean (SD))	5.33 (2.15)
Lee Fatigue Scale: morning fatigue score (mean (SD))	3.13 (2.25)
Lee Fatigue Scale: evening energy score (mean (SD))	3.54 (2.04)
Lee Fatigue Scale: morning energy score (mean (SD))	4.40 (2.25)
Center for Epidemiological Studies-Depression Scale score (mean (SD))	12.97 (9.77)
General Sleep Disturbance Scale score (mean (SD))	52.57 (20.17)
Trait Anxiety score (mean (SD))	35.15 (10.39)
State Anxiety score (mean (SD))	33.98 (12.33)
Attentional Function Index score (mean (SD))	6.38 (1.82)
Pain present (% yes (n))	72.8 (971)

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilograms per meters squared; SD = standard deviation; RT = radiation therapy.

Table 2: Hierarchical Linear Model for Morning Energy

Morning Energy	Coefficient (SE)	
	Unconditional Model	Final Model
Fixed effects		
Intercept	4.393 (.062)[+]	4.393 (.058)[+]
Piecewise 1 – linear rate of change	-0.457 (.113)[+]	-0.466 (.110)[+]
Piecewise 1 – quadratic rate of change	0.386 (.054)[+]	0.389 (.053)[+]
Piecewise 2 – linear rate of change	-0.492 (.074)[+]	-0.506 (.072)[+]
Piecewise 2 – quadratic rate of change	0.166 (.024)[+]	0.170 (.023)[+]
Time invariant covariates		
Intercept		
Lives alone		-0.250 (.113)[*]
Child care responsibilities		0.355 (.112)[*]
Karnofsky Performance Status		0.019 (.004)[+]
Exercise on a regular basis		0.461 (.100)[+]
Hemoglobin level		0.104 (.032)[*]
Trait anxiety		-0.022 (.005)[+]
Sleep disturbance		-0.010 (.003)[+]
Attentional function		0.291 (.033)[+]
Piecewise 1 – linear rate of change		
Morning energy		-0.134 (.044)[*]
Piecewise 1 – quadratic rate of change		
Morning energy		0.026 (.021)
Piecewise 2 – linear rate of change		
Body mass index		-0.031 (.010)[*]
Sleep disturbance		-0.014 (.003)[+]
Piecewise 2 – quadratic rate of change		
Body mass index		0.010 (.004)[*]
Sleep disturbance		0.003 (.001)[*]
Variance components		
In intercept	1.618[+]	1.460[+]
Goodness-of-fit deviance (parameters estimated)	28656.390 (7)[**]	28033.617 (21)
Model comparison χ^2 (df)		622.773 (14)[+]

*p<.05, **p<.001, +p<.0001

Abbreviations: df = degrees of freedom; SE = standard error

Table 3: Demographic, Clinical, and Symptom Characteristics of the Patients in the Evening Energy Analysis (n=1332)

Demographic Characteristics	
Age (years; mean (SD))	57.16 (12.39)
Gender (% female (n))	77.9 (1038)
Ethnicity (% (n))	
White	69.4 (925)
Black	9.9 (132)
Asian/Pacific Islander	9.6 (128)
Hispanic/Mixed/Other	11.0 (147)
Education (years; mean (SD))	16.18 (2.99)
Married or partnered (% yes (n))	65.0 (866)
Lives alone (% yes (n))	21.2 (283)
Currently employed (% yes (n))	34.8 (463)
Child care responsibilities (% yes (n))	21.7 (289)
Income (% yes (n))	
Less than $30,000	18.4 (219)
$30,000 to <$70,000	21.1 (252)
$70,000 to < $100,000	16.9 (202)
More than $100,000	43.5 (519)
Clinical Characteristics	
Number of comorbidities (mean (SD))	2.40 (1.43)
Self-administered Comorbidity Questionnaire score (mean (SD))	5.47 (3.20)
Body mass index (kg/m^2; mean (SD))	26.17 (5.63)
Hemoglobin (gm/dL; mean (SD))	11.54 (1.43)
Karnofsky Performance Status score (mean (SD))	80.00 (12.39)
Have you ever considered yourself a smoker (% yes (n)	34.8 (463)
Exercise on a regular basis (% yes (n))	71.5 (952)
Specific comorbidities reported (% yes (n))	
High blood pressure	30.1 (401)
Back pain	25.8 (343)
Depression	19.3 (257)
Osteoarthritis	12.0 (160)
Anemia or blood disease	12.3 (164)
Lung disease	11.3 (151)
Diabetes	8.9 (119)
Liver disease	6.5 (86)
Heart disease	5.6 (75)
Rheumatoid arthritis	3.1 (41)
Ulcer or stomach disease	4.9 (65)
Kidney disease	1.4 (19)
Cancer diagnosis (% yes (n))	
Breast	40.4 (538)
Gastrointestinal	30.4 (405)
Gynecological	17.4 (232)
Lung	11.8 (157)
Time since cancer diagnosis (years; mean (SD))	1.97 (3.87)
Time since cancer diagnosis (years; median)	(0.42)
Any prior cancer treatments (% yes (n))	75.7 (1008)
Number prior cancer treatments (mean (SD))	1.59 (1.50)

Chemotherapy cycle length (% (n)) 14 days 21 days 28 days	41.7 (556) 51.0 (679) 7.3 (97)
Presence of metastatic disease (% yes (n))	67.0 (893)
Number of metastatic sites including lymph node involvement (mean (SD))	1.24 (1.23)
Number of metastatic sites excluding lymph node involvement (mean (SD))	0.78 (1.05)
Symptom Characteristics at Enrollment	
Lee Fatigue Scale: evening fatigue score (mean (SD))	5.33 (2.15)
Lee Fatigue Scale: morning fatigue score (mean (SD))	3.13 (2.25)
Lee Fatigue Scale: evening energy score (mean (SD))	3.54 (2.04)
Lee Fatigue Scale: morning energy score (mean (SD))	4.40 (2.25)
Center for Epidemiological Studies-Depression Scale score (mean (SD))	12.97 (9.77)
General Sleep Disturbance Scale score (mean (SD))	52.59 (20.19)
Trait Anxiety score (mean (SD))	35.15 (10.39)
State Anxiety score (mean (SD))	33.98 (12.33)
Attentional Function Index score (mean (SD))	6.38 (1.82)
Pain present (% yes (n))	72.8 (970)

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilograms per meters squared; SD = standard deviation; RT = radiation therapy.

Table 4: Hierarchical Linear Model for Evening Energy

Evening Energy	Coefficient (SE)	
	Unconditional Model	Final Model
Fixed effects		
Intercept	3.552 (.058)[+]	3.551 (.058)[+]
Piecewise 1 – linear rate of change	-0.275 (.109)[*]	-0.277 (.107)[*]
Piecewise 1 – quadratic rate of change	0.195 (.052)[+]	0.196 (.051)[+]
s Piecewise 2 – linear rate of change	-0.323 (.071)[+]	-0.327 (.070)[+]
Piecewise 2 – quadratic rate of change	0.096 (.023)[+]	0.097 (.022)[+]
Time invariant covariates		
Intercept		
Female		-0.337 (.108)[*]
Nonwhite		0.372 (.097)[+]
Karnofsky Performance Status		0.019 (.004)[+]
Sleep disturbance		-0.009 (.003)[*]
Attentional function		0.178 (.030)[+]
Piecewise 1 – linear rate of change		
Evening energy		-0.128 (.047)[*]
Piecewise 1 – quadratic rate of change		
Evening energy		0.037 (.023)
Variance components		
In intercept	1.462[+]	1.467[+]
Goodness-of-fit deviance (parameters estimated)	27573.766 (7)[**]	27365.202 (14)
Model comparison χ^2 (df)		208.564 (7)[+]

*p<.05, **p<.001, +p<.0001

Abbreviations: df = degrees of freedom; SE = standard error

Table 5: Comparison of Intercept and Slope Predictors of Morning and Evening Energy

Characteristics	Morning Energy	Evening Energy
Intercept predictors		
Nonwhite		♦
Lives alone	♦	
Female		♦
Child care responsibilities	♦	
Functional status	♦	♦
Exercise on a regular basis	♦	
Hemoglobin level	♦	
Trait anxiety	♦	
Sleep disturbance	♦	♦
Attentional function	♦	♦
Slope predictors		
Morning energy	♦	
Evening energy		♦
Body mass index	♦	
Sleep disturbance	♦	

Supplementary Table 1: Potential Predictors of Intercept, and Piecewise 1 and Piecewise 2 Linear and Quadratic Components for Morning Energy

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
Demographic Characteristics					
Age					
Sex				♦	♦
Ethnicity (White versus Non-White)					
Education	♦				
Marital status	♦				
Live alones	♦				
Employment status	♦			♦	♦
Child care responsibilities	♦				
Clinical Characteristics	♦				
Body mass index (kg/m^2)	♦			♦	♦
Past or current history of smoking					
Hemoglobin (gm/dL)	♦				
Karnofsky Performance Status Scale Score	♦			♦	♦
Self-administered Comorbidity Questionnaire score	♦			♦	
Exercise on a regular basis	♦				
Time since cancer diagnosis					
Any prior cancer treatments					
Number prior cancer treatments					
Presence of metastatic disease					
Number of metastatic sites including lymph node involvement					
Number of metastatic sites excluding lymph node involvement					
Symptom Characteristics					
Lee Fatigue Scale: Evening fatigue score at enrollment	♦	♦		♦	♦
Lee Fatigue Scale: Morning fatigue score at enrollment	♦			♦	♦
Lee Fatigue Scale: Evening energy score at enrollment	♦				
Lee Fatigue Scale: Morning energy score at enrollment		♦	♦	♦	♦
Center for Epidemiological Studies-Depression Scale score at enrollment	♦			♦	♦
General Sleep Disturbance Scale score at enrollment	♦			♦	♦
Trait Anxiety score at enrollment	♦			♦	♦

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
State Anxiety score at enrollment	♦			♦	♦
Attentional Function Index score at Enrollment	♦			♦	♦
Pain present at enrollment	♦				

♦ = From exploratory analysis had a *t*-value of ≥2.0.

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilogram per meters squared.

Supplementary Table 2: Potential Predictors of Intercept, and Piecewise 1 and Piecewise 2 Linear and Quadratic Components for Evening Energy

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
Demographic Characteristics					
Age					
Sex	♦				
Ethnicity (White versus Non-White)	♦				♦
Education	♦				
Marital status					♦
Live alones					
Employment status					
Child care responsibilities					
Clinical Characteristics	♦				
Body mass index (kg/m^2)					
Past or current history of smoking					
Hemoglobin (gm/dL)					
Karnofsky Performance Status Scale Score	♦	♦			♦
Self-administered Comorbidity Questionnaire score	♦				♦
Exercise on a regular basis	♦				
Time since cancer diagnosis	♦				♦
Any prior cancer treatments					
Number prior cancer treatments					
Presence of metastatic disease					
Number of metastatic sites including lymph node involvement					
Number of metastatic sites excluding lymph node involvement					
Symptom Characteristics					
Lee Fatigue Scale: Evening fatigue score at enrollment					
Lee Fatigue Scale: Morning fatigue score at enrollment	♦				♦
Lee Fatigue Scale: Evening energy score at enrollment	♦				
Lee Fatigue Scale: Morning energy score at enrollment		♦	♦		
Center for Epidemiological Studies-Depression Scale score at enrollment	♦				♦
General Sleep Disturbance Scale score at enrollment	♦				
Trait Anxiety score at enrollment	♦				♦

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
State Anxiety score at enrollment	♦				
Attentional Function Index score at Enrollment	♦				
Pain present at enrollment	♦				♦
	♦				

♦ = From exploratory analysis had a *t*-value of ≥2.0.

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilogram per meters squared.
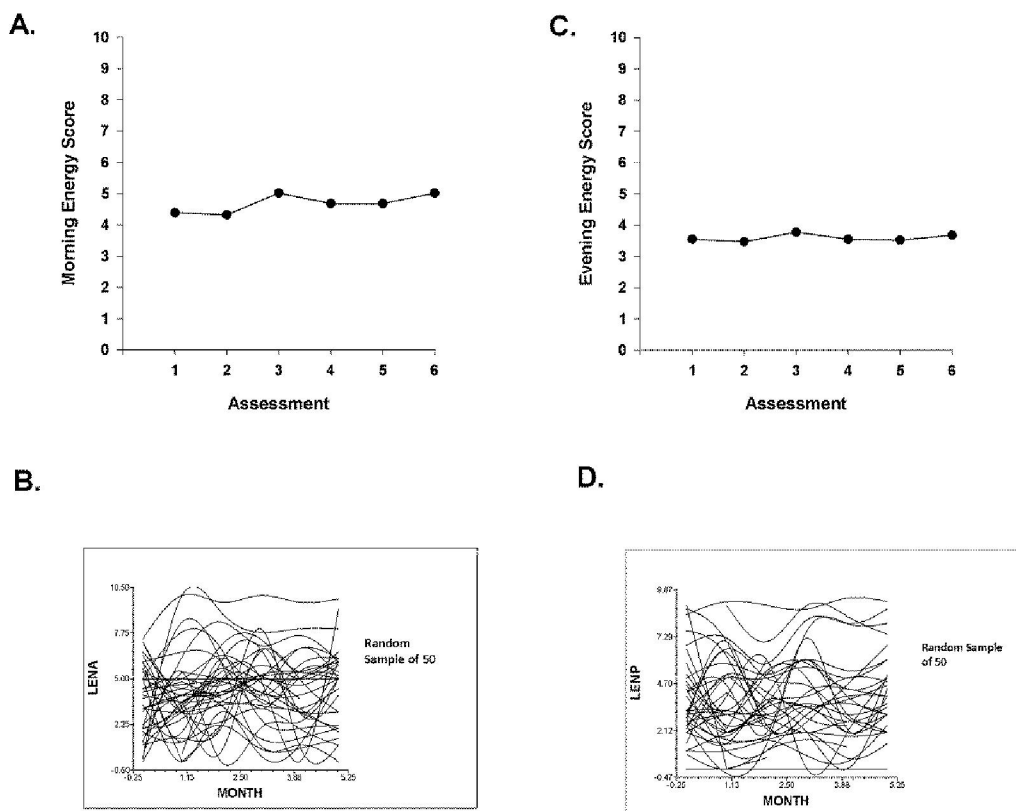
Figure Legends

Figure 1A – Piecewise model of mean morning energy scores for six assessment points over two cycles of chemotherapy (CTX).

Figure 1B - Spaghetti plots of individual morning energy trajectories for a random sample of 50 patients over two cycles of CTX. Abbreviation: LENA = Lee Fatigue Scale - Morning Energy subscale score.

Figure 1C – Piecewise model of mean evening energy scores for six assessment points over two cycles of chemotherapy (CTX).

Figure 1D - Spaghetti plots of individual evening energy trajectories for a random sample of 50 patients over two cycles of CTX. Abbreviation: LENP = Lee Fatigue Scale - Evening Energy subscale score.
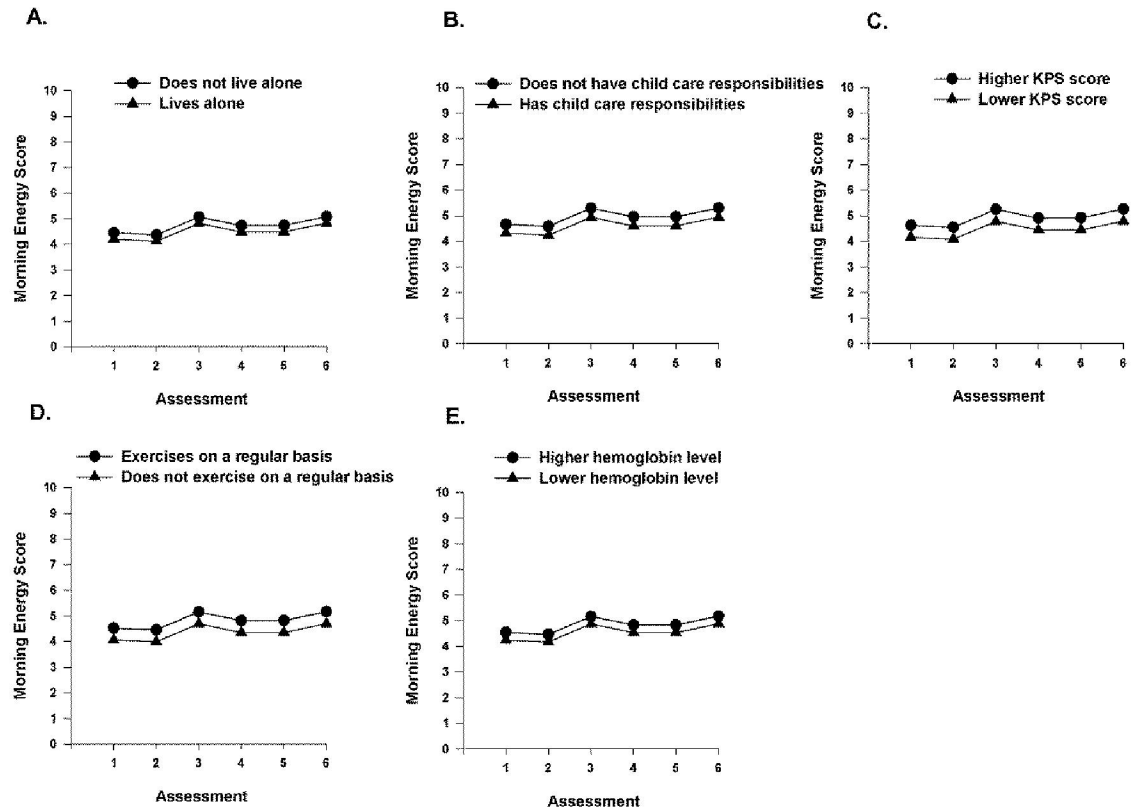
Figure 2 A-E- Influence of enrollment scores for living alone (A), child care responsibilities (B), Karnofsky Performance Status (KPS) score (C), exercise (D), and hemoglobin level (E), on inter-individual differences in the intercept for morning energy.
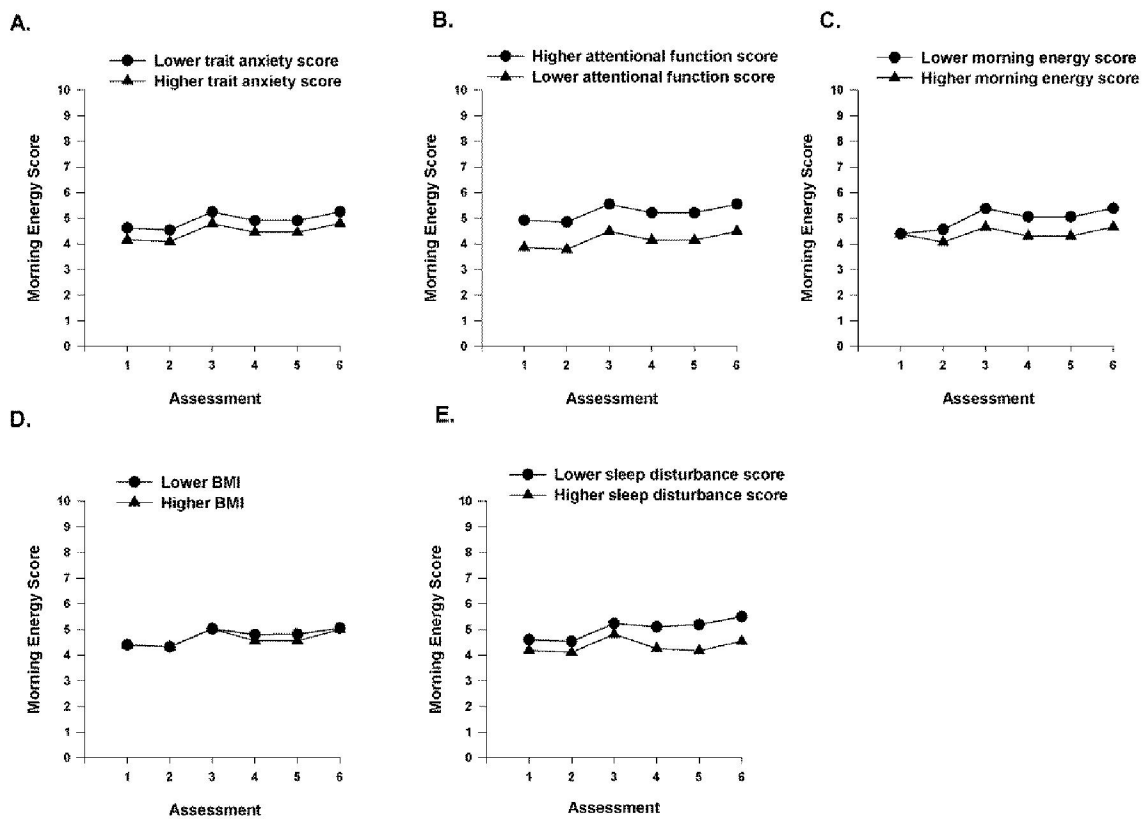
Figure 3A-E Influence of enrollment scores for trait anxiety (A) and attentional function (B), on inter-individual differences in the intercept for morning energy, and influence of morning energy (C) and body mass index (BMI, D) on the slope parameters for morning energy and influence of enrollment scores for sleep disturbance (E) on inter-individual differences in the intercept and slope parameters for morning energy.
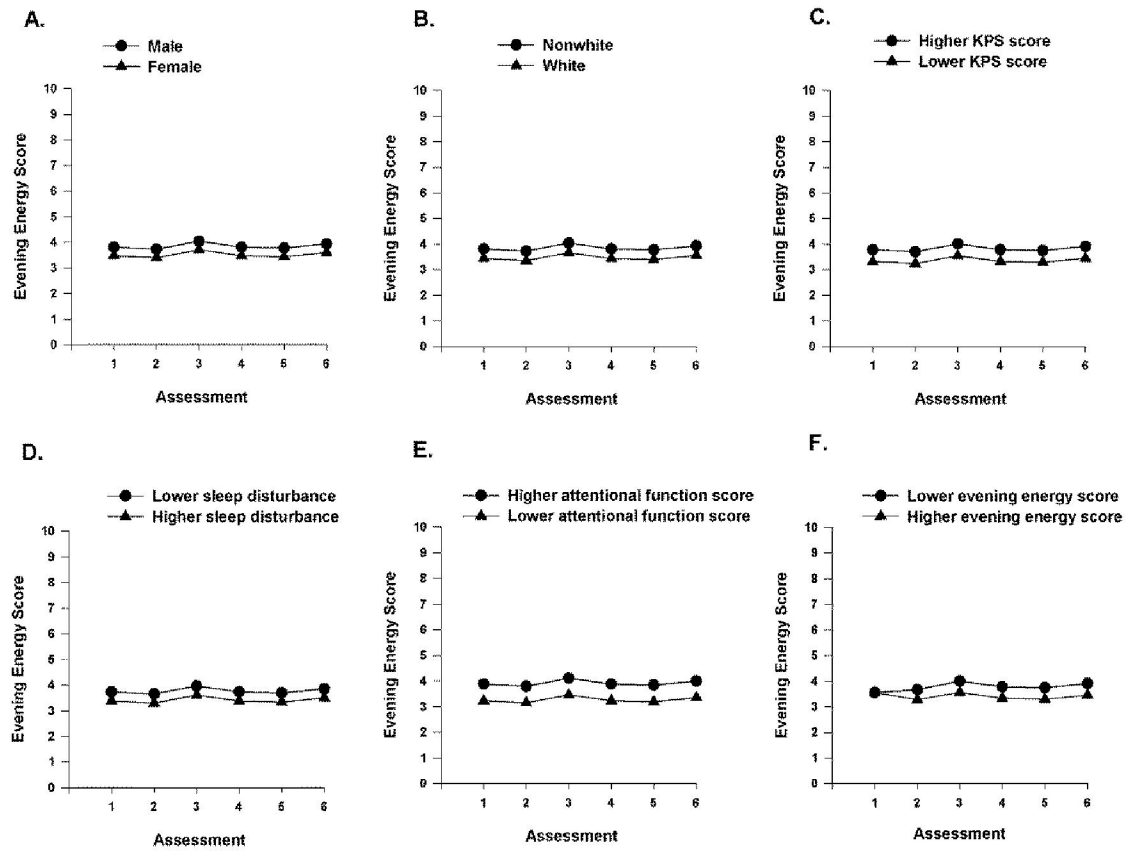
Figure 4 A-F Influence of gender (A), ethnicity (B), and enrollment scores Karnofsky

Performance Status (KPS, C), sleep disturbance (D) and attentional function (E) on inter-

individual differences in the intercept for evening energy, and influence of evening energy score

at enrollment (F) on the slope parameters for evening energy.

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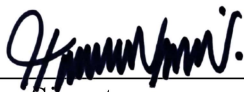
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