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Phenotypic and Molecular Evidence Suggest That Decrements in Morning and Evening Energy Are Distinct But Related Symptoms

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Abstract

Context—Little is known about energy levels in oncology patients and their family caregivers (FCs).

Objectives—This study sought to identify latent classes of participants, based on self-reported energy levels and to evaluate for differences in phenotypic and genotypic characteristics between these classes.

Methods—Energy subscale scores from the Lee Fatigue Scale were used to determine latent class membership. Morning and evening energy scores were obtained just prior to, during, and for four months following the completion of radiation therapy. Genetic associations were evaluated for fifteen pro- and anti-inflammatory cytokine genes.

Results—Two latent classes with distinct morning energy trajectories were identified. Participants who were younger, female, not married/partnered, Black, and had more comorbidities, and a lower functional status were more likely to be in the Low Morning Energy class. Two polymorphisms (*IL2* rs1479923, *NFKB1* rs4648110) were associated with morning energy latent class membership. Two latent classes with distinct evening energy trajectories were identified. Participants who were younger and male and who had more comorbidities, decreased body weight, and a lower functional status were more likely to be in the Moderate Evening Energy class. Five different polymorphisms (*IL1R2* rs4141134, *IL6* rs4719714, *IL17A* rs8193036, *NFKB2* rs1056890, *TNFA* rs1800683) were associated with evening energy latent class membership.

Conclusion—This study provides preliminary evidence that decrements in morning and evening energy are associated with different phenotypic risk factors as well as cytokine gene variations.

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Disclosures

The authors declare no conflicts of interest.

NOTE: SUPPLEMENTAL TABLE 1 IS ONLINE ONLY

Keywords

energy; fatigue; radiation therapy; growth mixture modeling; cytokines; single nucleotide polymorphisms; cancer; family caregivers

Introduction

Energy conservation is one of the earliest interventions that was recommended to reduce fatigue associated with cancer and its treatment.[1,2] In fact, this strategy is included in the latest Fatigue Guidelines published by the National Comprehensive Cancer Network.[3] Energy (also termed perceived energy, vigor, vitality) and fatigue are often thought to be interchangeable symptoms.[4,5] For example, on the Memorial Symptom Assessment Scale,[6] fatigue is assessed using the phrase “lack of energy.”

However, increasing evidence suggests that fatigue and energy are distinct but related constructs.[7-9] For example, instruments like the Profile of Mood States (POMS)[10] have separate subscales for fatigue-inertia and energy-vigor. The energy subscale of the POMS evaluates the intensity of energy using a variety of descriptors (e.g., energetic, full of pep, vigorous, active, lively). Like the POMS, the Lee Fatigue Scale (LFS) has two subscales (i.e., a fatigue subscale with 13 items and an energy subscale with five items). The LFS asks participants to rate their level of energy using a 0 to 10 numeric rating scale (NRS) on five descriptors (i.e., energetic, active, vigorous, efficient, lively). The original psychometric evaluation of the LFS identified these two distinct subscales.[11] In addition, a recent Rasch analysis of the LFS found that fatigue and energy represented different symptoms.[12] Given these findings, additional research is warranted that provides a more detailed characterization (e.g., diurnal variations, changes in severity) of the symptom of energy.

Our research team has used growth mixture modeling (GMM) to identify subgroups (i.e., latent classes) of oncology patients and their family caregivers (FCs) who differed in their experiences with depression,[13] sleep disturbance,[14] fatigue,[15] and attentional fatigue.[16] In all of these GMM analyses, the phenotypic and molecular data from patients and their FCs were combined for a number of reasons. First, both patients and their FCs experience the stress associated with a cancer diagnosis. For the FC, numerous physical, psychological, social, and economic stressors impact their mental and physical health.[17-23] In addition, both groups of individuals have other chronic medical conditions and demands on their time that could result in decreased energy. Finally, both patients and FCs experience significant and comparable levels of sleep disturbance,[24,25] which contribute to decreases in both morning and evening energy levels.

Inflammation may influence energy levels through a variety of mechanisms including: activation of immunomodulators,[26] alterations in mitochondrial function,[27] and/or changes in the activity of the hypothalamic-pituitary-adrenal axis.[28] Inflammation is mediated in part by changes in pro- and anti-inflammatory proteins, their receptors, and a number of transcriptional regulators that affect both the peripheral and the central nervous systems. Therefore, it is reasonable to hypothesize that variations in cytokine genes may contribute to interindividual variability in morning and evening energy levels.

Given the paucity of research on variations in energy levels in oncology patients and their FCs, the purposes of this study were to identify subgroups of individuals (i.e., latent classes derived using GMM) based on their subjective reports of morning and evening energy levels from prior to the initiation to four months after the completion of the patients' radiation therapy (RT) and to evaluate for differences in demographic, clinical, and symptom characteristics between these latent classes. In addition, based on the results of the GMM analyses for morning and evening energy, variations in a number of genes that encode for cytokines, their receptors, and related transcription factors were evaluated between the latent classes. Separate analyses were done for morning and evening energy.

Methods

Participants and Settings

This descriptive study is part of a larger, longitudinal study that evaluated multiple symptoms in both patients who underwent primary or adjuvant RT and their FCs. The methods for this study are described in detail elsewhere.[13] In brief, patients and their FCs were recruited from two RT departments located in a Comprehensive Cancer Center and a community-based oncology program at the time of the patient's simulation visit.

Patients were eligible to participate if they: were 18 years of age or older; were scheduled to receive primary or adjuvant RT for breast, prostate, lung, or brain cancer; were able to read, write, and understand English; gave written informed consent; and had a Karnofsky Performance Status (KPS) score of ≥60. Patients were excluded if they had: metastatic disease; more than one cancer diagnosis; or a diagnosed sleep disorder. FCs were eligible to participate if they were 18 years of age or older; were able to read, write, and understand English; gave written informed consent; had a KPS score of ≥60; were living with the patient; and did not have a diagnosed sleep disorder.

Instruments

The demographic questionnaire obtained information on age, gender, marital status, education, ethnicity, employment status, and the presence of a number of comorbid conditions.

Lee Fatigue Scale—The LFS comprises 18 items designed to assess *physical* fatigue and energy.[11] Each item was rated on a 0 to 10 NRS. The energy subscale score was calculated as the mean of the five energy items, with higher scores indicating higher levels of energy. Participants were asked to rate each item based on how they felt "right now," within 30 minutes of awakening (i.e., morning energy) and prior to going to bed (i.e., evening energy). Cutoff scores of ≤6.0 and ≤3.5 indicate low levels of morning and evening energy, respectively.[29] The LFS was chosen for this study because it is relatively short, easy to administer, and has well-established validity and reliability.[30,31] In this study, Cronbach's alphas for evening and morning energy were 0.95 and 0.96 for patients and 0.95 and 0.96 for FCs, respectively.

Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S)—These inventories consist of 20 items each that are rated from 1 to 4. The scores for each scale are summed and can range from 20 to 80. Cutoff scores of ≥31.8 and ≥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] In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.95 for patients and 0.89 and 0.93 for FCs, respectively.

Center for Epidemiological Studies-Depression scale (CES-D)—The CES-D comprises 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60, with scores of ≥16 indicating the need for individuals to seek a clinical evaluation for major depression. The CES-D has well-established validity and reliability.[33,34] In the current study, the Cronbach's alpha for the CES-D was 0.88 for patients and 0.84 for FCs.

Pittsburgh Sleep Quality Index (PSQI)—The PSQI consists of 19 items designed to assess the quality of sleep in the *past month*. The global PSQI score is the sum of the seven component scores. Each component score ranges from 0 to 3 and the global PSQI score ranges from 0 to 21. Higher global and component scores indicate a higher level of sleep disturbance. A global PSQI score of >5 indicates a significant level of sleep disturbance. The PSQI has well-established validity and reliability.[35] In this study, the Cronbach's alphas for the global PSQI score were 0.72 for patients and 0.68 for FCs.

General Sleep Disturbance Scale (GSDS)—The GSDS consists of 21 items designed to assess the quality of sleep in the *past week*. Each item is rated on a 0 (never) to 7 (every day) NRS. The GSDS total score is the sum of the seven subscale scores, which 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 ≥3 and a GSDS total score of ≥43 indicate a significant level of sleep disturbance.[29] The GSDS has well-established validity and reliability.[36] In the current study, the Cronbach's alphas for the GSDS total score were 0.84 for patients and 0.79 for FCs.

Attentional Function Index (AFI)—The AFI consists of 16 items designed to measure attentional function.[37] Higher mean scores on a 0 to 10 NRS indicate greater capacity to direct attention. 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).[37] The AFI has well-established reliability and validity. In this study, Cronbach's alpha was .95 for both patients and FCs.

Brief Pain Inventory (BPI)—Occurrence of pain was evaluated using the BPI.[38] Participants who responded yes to the question about having pain were asked to indicate the cause of their pain and to rate its intensity (i.e., now, least, average, and worst) using a 0 (no pain) to 10 (worst pain imaginable) NRS.

Objective Measure of Sleep Disturbance—Objective data on sleep-wake activity rhythms were obtained by continuous noninvasive monitoring of activity over 48 hours using a wrist motion sensor (Mini Motionlogger Actigraph, Ambulatory Monitoring, Inc.,

Ardsley, NY).[39,40] Seven sleep/wake and one activity/rest parameters were selected that were identified by a National Cancer Institute-sponsored conference,[41] an expert panel that recommended a standard set or research assessments in insomnia,[42] and published studies.[43,44]

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and at the second site. Approximately one week prior to the start of RT, patients were invited to participate in the study. If the FC was present, a research nurse explained the study protocol to both the patient and FC, determined eligibility, and obtained written informed consent. FCs who were not present were contacted by phone to determine their interest in participation. These FCs completed the enrollment procedures at home.

At the time of the simulation visit (i.e., enrollment), participants (patients and FCs) completed the self-report questionnaires. After the initiation of RT, participants completed the symptom questionnaires at four weeks after the initiation of RT, at the end of RT, and at 4, 8, 12, and 16 weeks after the completion of RT (i.e., seven assessments over six months). In addition, patients' medical records were reviewed for disease and treatment information.

At each of the seven assessments, participants completed the LFS before going to bed each night (i.e., evening energy) and upon arising each morning (i.e., morning energy) for two consecutive days. Participants wore the wrist actigraph to monitor nocturnal sleep/rest and daytime wake/activity continuously for two consecutive weekdays and completed a two-day diary. Participants were asked to use the event marker on the wrist actigraph to indicate "lights out" and "lights on" time. Because the actual time is important in the calculation of the amount of sleep obtained in the amount of time designated for sleep, having an additional source of information about nap times, bed times, and wake times is important. This information was recorded in a two-day diary. Upon awakening, the participants used the diary to indicate the number of awakenings during the night.

Methods of Analysis for Phenotypic Data

Data were analyzed using SPSS v. 22 (IBM Corp. Armonk, NY) and Mplus v. 7.11 (Muthén & Muthén, Los Angeles, CA). Descriptive statistics and frequency distributions were generated on the sample characteristics and symptom severity scores. Independent sample *t*-tests and Chi-square analyses were done to evaluate for differences in demographic, clinical, and symptom characteristics between patients and FCs and between the GMM latent classes.

Actigraphy files in zero-crossing mode, with 30-second intervals, were analyzed using the Cole-Kripke Algorithm in the Action 4 software (Ambulatory Monitoring Inc.) by two of the researchers. First, the file was scanned for missing data. Time limits were set for the 48-hour period. The file was reviewed and intervals were individually set for each day and night period using in order of priority as decision guides: the event marker, diary data, channel data, and cascading movement data.

GMM with robust maximum likelihood estimation was used to identify latent classes (i.e., subgroups of participants) with distinct morning and evening energy trajectories over the six months of the study.[45] Separate GMM analyses were done for morning and evening energy levels. Because 65% of the participants were in patient-caregiver dyads, models were estimated with "dyad" as a clustering variable, to ensure that any dependency between the morning and evening energy scores for patients and FCs in the same dyad were "controlled for" in the GMM analysis.

The GMM methods are described in detail elsewhere.[46] In brief, a single growth curve that represented the "average" change trajectory was estimated for the total sample. Then the number of latent growth classes that best fit the data was identified using guidelines recommended by a number of experts.[47,48] Missing data for the morning or evening energy scores were accommodated in MPlus 7.11 through the use of Full Information Maximum Likelihood and the use of the Expectation-Maximization algorithm. This method assumes that any missing data are ignorable (i.e., missing at random).[49]

Adjustments were not made for missing data in comparisons of the classes identified with the GMM. Therefore, the cohort for each analysis was dependent on the largest set of available data across classes. Differences in demographic, clinical, and symptom characteristics between patients and FCs and between the latent classes were considered statistically significant at the $P < 0.05$ level.

Methods of Analysis for Genomic Data

Gene Selection—Genes that encode for pro-inflammatory cytokines and their receptors include interleukin 2 (*IL2*), *IL8*, *IL17A*, and tumor necrosis factor alpha (*TNFA*), as well as interferon gamma receptor 1 (*IFNGR1*) and IL1 receptor, type 1 (*IL1R1*). Genes that encode for anti-inflammatory cytokines and their receptors include *IL4*, *IL10*, and *IL13*, as well as *IL1R2*. Genes that encode for cytokines with both pro- and anti-inflammatory functions include *IFNG*, IL1 beta (*IL1B*), and *IL6*. Genes that encode for transcription factors, which moderate the levels of cytokine production, include nuclear factor kappa B 1 (*NFKB1*) and *NFKB2*.[50]

Blood Collection and Genotyping—Genomic DNA was extracted from archived buffy coats using the PUREGene DNA Isolation System (Invitrogen, Carlsbad, CA). Of the 287 participants recruited, DNA was recovered for 253 (i.e., 168 patients and 85 FCs). No differences were found in any demographic and clinical characteristics between participants who did and did not choose to participate in the study or in those participants for whom DNA could not be recovered from archived specimens.

DNA samples were quantitated with a Nanodrop Spectrophotometer (ND-1000) and normalized to a concentration of 50 ng/ L. Genotyping was performed blinded to clinical status. Samples were genotyped using the GoldenGate genotyping platform (Illumina, San Diego, CA) and processed using GenomeStudio (Illumina, San Diego, CA). Signal intensity profiles and resulting genotype calls for each single nucleotide polymorphism (SNP) were visually inspected by two blinded reviewers.

SNP Selection—A combination of tagging SNPs and literature driven SNPs were selected for analysis. Tagging SNPs were required to be common (defined as having a minor allele frequency ≥0.05) in public databases. In order to ensure robust genetic association analyses, quality control filtering of SNPs was performed. SNPs with call rates of <95% or Hardy-Weinberg *P*-values of <0.001 were excluded.

As shown in Supplemental Table 1 (available at jpsmjournal.com), a total of 92 SNPs among the 15 candidate genes passed all quality control filters and were included in the genetic association analyses. Potential functional roles for these SNPs were examined using PUPASuite 2.0.[51]

Statistical Analyses—Allele and genotype frequencies were determined by gene counting. Hardy-Weinberg equilibrium was assessed by the Chi-square or Fisher Exact tests. Measures of linkage disequilibrium (i.e., D' and r^2) were computed from the participants' genotypes with Haploview 4.2. Linkage disequilibrium (LD)-based haplotype block definition was based on D' confidence interval.[52] Haplotypes were constructed using the program PHASE version 2.1.[53] In order to improve the stability of haplotype inference, the haplotype construction procedure was repeated five times using different seed numbers with each cycle. Only haplotypes inferred with a probability of >0.85, across the five runs, were retained for analysis.

Ancestry informative markers (AIMs) were used to minimize confounding due to population stratification.[54,55] Homogeneity in ancestry among participants was verified by principal component analysis,[56] using Helix Tree (Golden Helix, Bozeman, MT). One hundred and six AIMs were included in the analysis.

For association tests, three genetic models were assessed for each SNP: additive, dominant, and recessive. Barring trivial improvements (i.e., delta <10%), the genetic model that best fit the data, by maximizing the significance of the *P*-value, was selected for each SNP. The first three principal components were selected to adjust for potential confounding due to population substructure (i.e., race/ethnicity) by including the three covariates in all regression models.

A backwards stepwise approach was used to create a parsimonious model. Except for self-reported race/ethnicity and AIMs, only predictors with a *P*-value of <0.05 were retained in the final model. Genetic model fit and both unadjusted and covariate-adjusted odds ratios (OR) were estimated using STATA v. 13 (StataCorp LP, College Station, TX).

As was done in our previous studies,[14-16] based on recommendations in the literature,[57,58] the implementation of rigorous quality controls for genomic data, the non-independence of SNPs/haplotypes in LD, and the exploratory nature of the analyses, adjustments were not made for multiple testing. In addition, significant SNPs identified in the bivariate analyses were evaluated using regression analyses that controlled for differences in phenotypic characteristics, potential confounding due to population stratification, and variation in other SNPs/haplotypes within the same gene. Only those SNPs that remained significant were included in the final presentation of the results. Therefore, the significant independent

associations reported are unlikely to be due solely to chance. Unadjusted associations are reported for all SNPs that passed quality control criteria in Supplemental Table 1 to allow for subsequent comparisons and meta-analyses.

Results

Overall Sample

Participant Characteristics—Complete phenotypic and genotypic data were available for 252 participants. The majority of the participants were Caucasian, well educated, and married/partnered. Patients made up 66.3% of the total sample. The mean age of the total sample was 61.5 years. The average participant had more than four comorbid conditions and a mean KPS score of 92. Gender was evenly represented within the total sample, with 46.4% male and 53.6% female participants. The majority of the FCs (93%) were the patients' spouses. Approximately 33% of the patients had breast cancer, 54% had prostate cancer, 8% had brain cancer, and 6% had lung cancer.

At enrollment, no significant differences were found between patients and FCs in their ratings of morning energy (5.9 ± 1.9 vs. 5.8 ± 2.1), evening energy (4.5 ± 1.8 vs. 4.3 ± 1.9), morning fatigue (2.3 ± 1.9 vs. 2.3 ± 1.9), evening fatigue (4.2 ± 2.0 vs. 4.5 ± 2.0), attentional fatigue (7.2 ± 1.8 vs. 7.3 ± 1.8), trait anxiety (33.8 ± 10.0 vs. 34.7 ± 9.7), state anxiety (31.0 ± 10.9 vs. 31.0 ± 10.7), worst pain (2.0 ± 3.2 vs. 1.5 ± 3.1), sleep disturbance (39.0 ± 19.6 vs. 38.7 ± 16.7), and depressive symptoms (9.2 ± 8.7 vs. 8.3 ± 7.2).

Morning Energy

Results of GMM Analysis for Morning Energy—Two distinct latent classes of morning energy trajectories were identified using GMM (Fig. 1A). The fit indices for the various models are shown in Table 1. A two-class model was selected because its Bayesian Information Criterion (BIC) was smaller than the one-class and three-class models. In addition, each class in the two-class model had a reasonable size and interpretability.[47]

The parameter estimates for the two latent classes are listed in Table 2. The latent classes were named based on the cutpoints for a clinically meaningful decrement in morning energy (i.e., ≤6.0). The largest percentage of participants was classified into the Low Morning Energy class (50.8%). These participants had a mean morning energy score of 4.7 at enrollment that increased slightly and then leveled off over the course of the study. Participants in the Moderate Morning Energy class (49.2%) had a mean morning energy score of 6.9 that was stable initially and then increased slightly over the course of the study. No differences were found in the percentage of patients and FCs in the Low and Moderate Morning Energy classes.

Differences in Demographic and Clinical Characteristics Between the Moderate Morning Energy and Low Morning Energy Classes—As summarized in Table 3, no differences were found between the two Morning Energy classes for the majority of demographic and clinical characteristics. However, participants in the Low Morning Energy class were more likely to be younger ($P<0.001$), female ($P=0.002$), not

married or partnered (P=0.039), Black as compared to White (P=0.005); have a higher number of comorbid conditions (P=0.014), and have a lower KPS score (P<0.001).

Differences in Symptom Characteristics Between the Moderate Morning Energy and Low Morning Energy Classes—As summarized in Table 4, significant differences were found between the two Morning Energy classes for the majority of the symptoms assessed prior to the initiation of RT. For those symptom scores with significant between-group differences, participants in the Low Morning Energy class reported higher symptom severity scores than participants in the Moderate Morning Energy class.

Candidate Gene Analyses of the Two Morning Energy GMM Classes—As summarized in Supplemental Table 1, the genotype frequency was significantly different between the two morning energy classes for eight SNPs and one haplotype: *IL1B* rs1143643, *IL1B* rs1143633, *IL1B* HapA4, *IL2* rs1479923, *IL6* rs4719714, *IL6* rs35610689, *NFKB1* rs4648110, *TNFA* rs1800683, and *TNFA* rs1041981.

Regression Analyses of Candidate Genes and Morning Energy GMM Latent Classes—In order to better estimate the magnitude (i.e., OR) and precision (95% confidence interval [CI]) of genotype on morning energy class membership (i.e., Moderate Morning Energy vs. Low Morning Energy), multivariable logistic regression analyses were performed that included the following variables in the models: genotype, age, number of comorbid conditions, functional status, and self-reported (i.e., White, Black, Asian/Pacific Islander, Hispanic/Mixed ethnic background/other) and genomic estimates of race/ethnicity.

The only genetic associations that remained significant in the multivariable analyses were for *IL2* rs1479923 (Table 5, Fig. 2A) and *NFKB1* rs4648110 (Table 5, Fig. 2B). In the regression analysis for *IL2* rs1479923, being homozygous for the rare T allele (i.e., CC + CT versus TT) was associated with a 75% decrease in the odds of belonging to the Low Morning Energy class. In the regression analysis for *NFKB1* rs4648110, being heterozygous or homozygous for the rare A allele (i.e., TT versus TA + AA) was associated with a 42% decrease in the odds of belonging to the Low Morning Energy class.

Evening Energy

Results of GMM Analysis for Evening Energy—Two distinct latent classes of evening energy trajectories were identified using GMM (Fig. 1B). The fit indices for the various models are shown in Table 1. A two-class model was selected because its BIC was smaller than the one-class and three-class models. In addition, each class in the two-class model had a reasonable size and interpretability.[47]

The parameter estimates for the two latent classes are listed in Table 2. The latent classes were named based on the cutpoints for a clinically meaningful decrement in evening energy (i.e., ≤3.5). The largest percentage of participants was classified into the Moderate Evening Energy class (79.4%). These participants had a mean evening energy score of 4.0 at enrollment that decreased slightly and then leveled off over the course of the study. Participants in the High Evening Energy class (20.6%) had a mean evening energy score of 5.8 that increased and then decreased slightly over the course of the study. No differences

were found in the percentage of patients and FCs in the High and Moderate Evening Energy classes.

Differences in Demographic and Clinical Characteristics Between the High Evening Energy and Moderate Evening Energy Classes—As summarized in Table 3, no differences were found between the two evening energy latent classes for the majority of demographic and clinical characteristics. However, participants in the Moderate Evening Energy class were more likely to be younger ($P<0.001$) and male ($P=0.001$); and have a greater number of comorbid conditions ($P=0.025$), decreased body weight ($P=0.035$), and a lower KPS score ($P<0.001$).

Differences in Symptom Characteristics Between the High Evening Energy and Moderate Evening Energy Classes—As summarized in Table 4, significant differences were found between the two evening energy classes for the majority of the symptoms assessed prior to the initiation of RT. For those symptom scores with significant between-group differences, participants in the Moderate Evening Energy class reported higher symptom severity scores than participants in the High Evening Energy class.

Candidate Gene Analyses of the Two Evening Energy GMM Classes—As summarized in Supplemental Table 1, the genotype frequency was significantly different between the two latent classes for seven SNPs: *IL1R2* rs4141134, *IL6* rs4719714, *IL17A* rs8193036, *NKFB2* rs1056890, *TNFA* rs1800683, *TNFA* rs1041981, and *TNFA* rs1800629.

Regression Analyses of Candidate Genes and Evening Energy GMM Latent Classes—In order to better estimate the magnitude (i.e., OR) and precision (95% CI) of genotype on evening energy class membership (i.e., High Evening Energy vs. Moderate Evening Energy), multivariable logistic regression analyses were performed that included the following variables in the models: genotype, age, gender, functional status, and self-reported (i.e., White, Black, Asian/Pacific Islander, Hispanic/Mixed ethnic background/other) and genomic estimates of race/ethnicity.

The genetic associations that remained significant in the multivariable logistic regression analyses were for *ILR2* rs4141134 (Table 5, Fig. 3A), *IL6* rs4719714 (Table 5, Fig. 3B), *IL17A* rs8193036 (Table 5, Fig. 3C), *NFKB2* rs1056890 (Table 5, Fig. 3D), and *TNFA* rs1800683 (Table 5, Fig. 3E). In the regression analysis for *ILR2* rs4141134, being heterozygous or homozygous for the rare C allele (i.e., TT versus TC + CC) was associated with a 64% decrease in the odds of belonging to the Moderate Evening Energy class. In the regression analysis for *IL6* rs4719714, being heterozygous or homozygous for the rare T allele (i.e., AA versus AT + TT) was associated with a 73% decrease in the odds of belonging to the Moderate Evening Energy class. In the regression analysis for *IL17A* rs8193036, being heterozygous or homozygous for the rare C allele (TT versus CT + CC) was associated with a 61% decrease in the odds of belonging to the Moderate Evening Energy class. In the regression analysis for *NFKB2* rs1056890, being homozygous for the rare T allele (i.e., CC + CT versus TT) was associated with a 9.7-fold increase in the odds of belonging to the Moderate Evening Energy class. In the regression analysis for *TNFA* rs1800683, being homozygous for the rare A allele (i.e., GG + GA versus AA) was

associated with a 64% decrease in the odds of belonging to the Moderate Evening Energy class.

Discussion

This study is the first to identify subgroups of oncology patients and FCs based on their distinct experiences of morning and evening energy and to evaluate for associations between these subgroups and polymorphisms in a number of cytokine genes. While two distinct latent classes were identified for both morning and evening energy, different demographic and clinical characteristics, as well as different cytokine gene variations, were associated with latent class membership. These findings support our hypothesis that morning and evening energy are distinct but related symptoms.

In terms of the overall phenotypic findings, over 50% of the participants reported morning energy levels that were well below the cutpoint for clinically meaningful decrements in energy (i.e., ≤6.0). Of note, these clinically meaningful decrements in morning energy levels persisted for four months after the completion of RT (Fig. 1A). In contrast, decrements in evening energy levels were reported by about 80% of the participants. While the cutoff score for a clinically meaningful decrement in evening energy is ≤3.5, the patients and FCs in the Moderate Evening Energy class had evening energy scores of approximately 4.0 for the entire six months of the study. Across the morning and evening energy classes, 18.7% (*n*=47) of the participants were classified into the Moderate Morning and High Evening Energy classes; 1.9% (*n*=5) were in the Low Morning and High Evening Energy classes; 30.6% (*n*=77) were in the Moderate Morning and Moderate Evening Energy classes; and 48.8% (*n*=123) were in the Low Morning and Moderate Evening Energy classes. These findings suggest that a significant number of patients and their FCs have persistent decrements in both morning and evening energy levels.

In terms of demographic and clinical characteristics, younger age, as well as a higher number of comorbid conditions, and a lower KPS score were associated with membership in both the Low Morning and Moderate Evening Energy classes. A consistent finding across all of our GMM studies of common symptoms in oncology patients and their FCs[13-15,59] is that younger participants are classified in the higher symptom class. As explained previously, these age differences may be associated with physiologic (e.g., changes in stress responses[60,61]) and/or psychological (e.g., response shift[62,63]) adaptations associated with aging. While the most common comorbid conditions in this sample were back problems (49%), arthritis (44%), allergies (43%), and hypertension (30%), additional research is needed to determine which comorbid conditions are associated with more severe decrements in energy.

Again, consistent with our previous analyses of common symptoms in this same sample,[13-15,64] participants with lower KPS scores were more likely to be classified in both the Low Morning and Moderate Evening Energy classes. The difference in KPS scores between the two morning and the two evening energy classes represent not only statistically significant but clinically meaningful decrements in functional status (i.e., Cohen's d = 0.64 and d = 0.55, respectively).[65] Of note, age and KPS scores were retained in the final

phenotypic regression models for both morning and evening energy (Table 5). Taken together, these consistent findings across multiple symptoms suggest that clinicians need to consider an individual's age and KPS score as part of their evaluation of symptom burden.

In this study, the findings regarding ethnic differences in energy levels are inconsistent. In the bivariate, but not in the multivariate analyses, Whites compared to Blacks were less likely to be classified in the Low Morning Energy class. In contrast, in the multivariate analysis for evening energy, which controlled for self-report and genomic estimates of race/ethnicity, being Black as compared to White was associated with a 95% reduction in the odds of belonging to the Moderate Evening Energy class. These inconsistent findings may be related to the relatively small number of ethnic minorities in this sample and warrant evaluation in future studies.

As shown in Table 2, only two demographic and one clinical characteristic distinguished between the morning and evening energy latent classes. First, women were more likely to be classified into the Lower Morning Energy class and men were more likely to be classified into the Moderate Evening Energy class. However, gender remained significant in the final regression model only for evening energy. While no studies were found on gender differences in energy levels, findings on gender differences in the occurrence and severity of other symptoms are inconsistent.[66] Second, participants who were married or partnered were less likely to be classified in the Low Morning Energy class. This finding may be attributed to increased levels of social support.[67] Finally, while an explanation is not readily apparent and warrants investigation in future studies, participants in the Moderate Evening Energy class had a lower body weight than participants in the High Evening Energy class.

It should be noted that no differences were found in the distribution of patients and FCs in either the morning or the evening energy latent classes. This finding suggests that the mechanisms that contribute to lower levels of morning and evening energy are not solely dependent on the characteristics of the cancer or its treatment.

This study is the first to report on differences in a number of symptom severity scores between the morning and the evening energy latent classes (Table 4). In terms of state and trait anxiety, both the Low Morning and Moderate Evening Energy classes had anxiety scores at enrollment that were above the clinically meaningful cutoff scores. Previous research has documented that 10% to 20% of patients experience clinically significant levels of anxiety at the initiation of RT.[68] In addition, equally high numbers of FCs experience psychological distress associated with providing care to cancer patients.[69] It is reasonable to hypothesize that higher levels of anxiety could contribute to sleep disturbance, as well as decrements in energy.

For both of the sleep disturbance measures, participants in the Low Morning and Moderate Evening Energy latent classes, reported total GSDS and PSQI global scores that were above the clinically meaningful cutoff scores. The use of sleep medications was the only subscale score on both of the sleep disturbance measures that differentiated between the morning and evening energy classes. While detailed information on the specific sleep medications and

their duration of use are not available, the chronic use of sleep medications is associated with disrupted sleep patterns and drowsiness upon awakening.[70]

In terms of the objective sleep parameters, except for total sleep time, no differences were found in any of the actigraphy parameters between either the morning or evening energy latent classes. However, patients in the Moderate Evening Energy class reported a significantly longer sleep time (i.e., 26.6 minutes) than the High Evening Energy class. Additional research is warranted to confirm these findings.

This study is the first to identify genotypic differences in morning and evening energy. Variations in two genes (*IL2*, *NFKB1*) were associated with morning energy. The SNP in *IL2* (rs1479923) is located immediately downstream of the *IL2* gene and has no known function. Presumably, it is in linkage disequilibrium with an unmeasured causal polymorphism(s). In the current study, being homozygous for the rare T allele was associated with a 64% decrease in the odds of being in the Low Morning Energy class. While IL2 plays a role in immune activation and homeostasis,[71] ongoing characterization of this cytokine continues to reveal novel functions. For example, the demonstration of altered *IL2* gene expression in peripheral leukocytes in response to psychological stress[72] suggests that changes in energy levels can mediate and be mediated by immune activation.

For *NFKB1*, the SNP rs4648110 is located in the intronic region of the gene and has no known function. However, NFKB is an important nuclear transcription factor that regulates a large number of cytokines and is critical for the regulation of inflammation. Increased transcription of NFKB can increase inflammation and angiogenesis, as well as cell survival and growth.[73] In two studies,[74,75] rs4648110 was associated with a decreased risk of colon cancer. In the current study, individuals who were heterozygous or homozygous for the rare A allele had a 42% decrease in the odds of being in the Low Morning Energy class. Consistent with findings from our study, these authors suggested that this SNP might be in linkage disequilibrium with a functional SNP that decreases the transcription of *NFKB1*, which results in decreases in inflammatory responses and the associated occurrence of colon cancer.[74,75] One could hypothesize that a decrease in inflammatory responses would result in higher energy levels.

Variations in five different genes (*IL1R2*, *IL6*, *IL17A*, *NFKB2*, *TNFA*) were associated with evening energy. *IL1R2* rs4141134 is located in the immediate promoter of the gene in a glucocorticoid receptor binding site. Carrying one or two doses of the rare C allele was associated with a 64% decrease in the odds of being in the Moderate Evening Energy class. In a previous analysis with the same sample (13), this SNP was part of an *IL1R2* haplotype that was associated with an increased odds of belonging to a group of participants with subsyndromal levels of depressive symptoms. It is unknown if being homozygous for the common T allele results in alterations in glucocorticoid receptor binding to the IL1R2 promoter, which results in altered expression of the IL-1-RII protein. Changes in glucocorticoid signaling under situations of perceived stress results in redistribution of energy levels so that an individual has the capacity to respond to the potential threat. Persistent stress (e.g., due to cancer or the need to care for a family member with cancer),

coupled with suboptimal cytokine function due to gene variations, may result in dysregulation of glucocorticoid function and subsequent energy impairments.[61]

Consistent with findings from our previous study in this same sample,[76] where we observed an association between carrying one or two doses of the rare T allele in *IL6* rs4719714 with overall lower levels of morning and evening fatigue and sleep disturbance, a similar association was observed with evening energy. Being heterozygous or homozygous for the rare T allele was associated with a 73% decrease in the odds of being in the Moderate Evening Energy class. Although it does not appear to be functional, rs4719714 is in near perfect linkage disequilibrium with rs10499563.[77] The rare allele at rs10499563 is associated with decreased production of *IL-6*. Decreased production of this pro-inflammatory cytokine could result in decreased fatigue and/or increased energy.

IL-17A, a pro-inflammatory cytokine that regulates localized inflammatory responses within tissues (78), was associated with evening but not morning energy. Being heterozygous or homozygous for the rare C allele in rs8193036 was associated with a 61% decrease in the odds of being in the Moderate Evening Energy class. While this SNP, which is located in the promoter region of *IL17A*, has no known function, it could influence the regulation of *IL17A* gene expression by altering transcription factor binding in this region.

NFKB2 and *NFKB1* each encode for one-half of the heterodimeric protein NFKB, which is a central transcriptional modulator of inflammation.[79] Being homozygous for the rare T allele in *NFKB2* rs1056890 was associated with a 9.7-fold increase in the odds of being in the Moderate Evening Energy class. This SNP is located immediately downstream of the gene. Previously, we identified an association between sleep disturbance and variations in *NFKB2* in both the current (rs7897947)[14] and an independent sample (rs1056890).[80] In both of these studies, being homozygous or heterozygous for the rare allele was associated with less sleep disturbance. These inconsistent findings warrant confirmation in future studies.

In terms of *TNFA*, being homozygous for the rare A allele in rs1800683 was associated with a 64% decrease in the odds of being in the Moderate Evening Energy class. *TNFA* rs1800629 is located in the promoter region of the gene. Although this SNP is associated with altered *TNFA* gene expression, the direction of the relationship differs among studies reported in the literature.[81,82]

Limitations

Some study limitations need to be acknowledged. While the sample sizes for the GMM analyses were adequate,[81] larger samples may identify additional latent classes as well as different phenotypic and molecular characteristics associated with latent class membership. Although vigorous quality control analyses and adjustment for potential confounding due to population substructure were performed, some of the relationships identified may be due to Type 1 error. The common and unique predictors associated with latent class membership for both morning and evening energy must be interpreted with caution until they are replicated in future studies. The genetic associations observed in the current study require validation in an independent cohort. Ideally, future studies need to evaluate for changes in serum cytokines and gene expression associated with these polymorphisms.

Conclusion

In summary, both the phenotypic and molecular findings suggest that morning and evening energy are distinct but related symptoms. Additional research is warranted to identify specific demographic and clinical characteristics that contribute to more severe decrements in morning and evening energy. In addition, future molecular analyses will assist with the identification of common and distinct mechanisms for morning and evening energy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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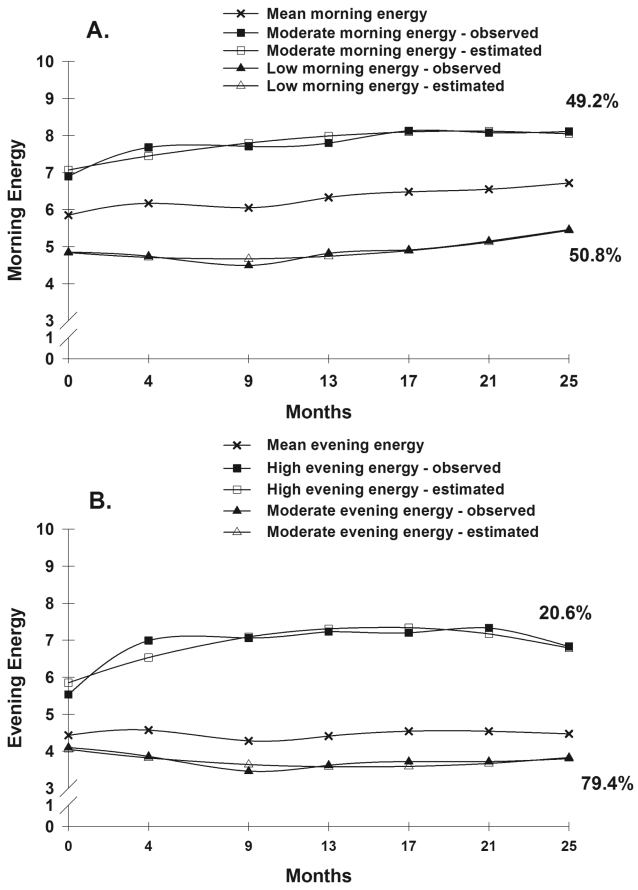

Fig. 1.

Observed and estimated morning (A) and evening (B) energy trajectories for participants in each of the latent classes, as well as the mean energy scores for the total sample

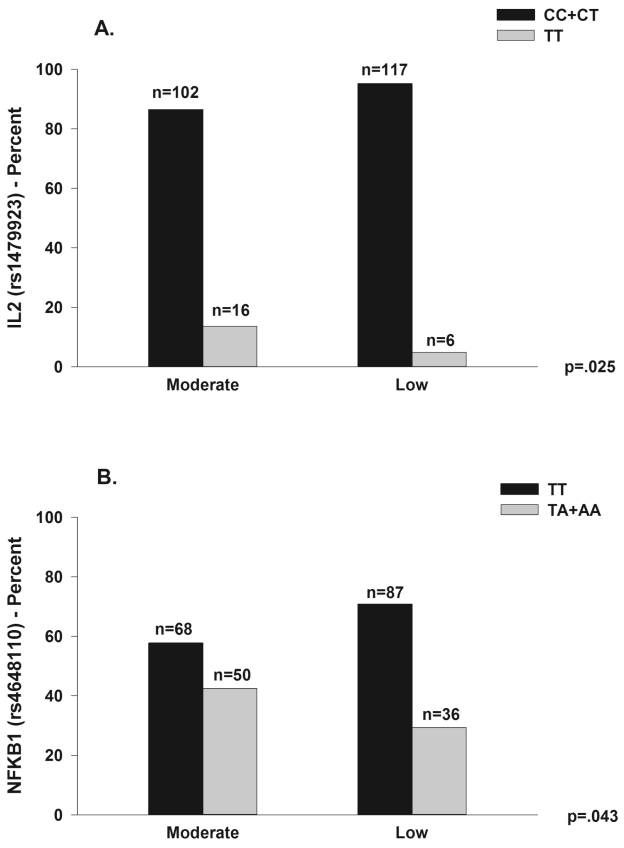

Fig. 2A.

Differences between the latent classes in the percentages of participants who were homozygous or heterozygous for the common allele (CC+CT) or homozygous for the rare allele (TT) for rs1479923 in interleukin 2 (*IL2*). Values are plotted as unadjusted proportions with corresponding *P*-value.

B. Differences between the latent classes in the percentages of patients who were homozygous for the common allele (TT) or heterozygous or homozygous for the rare allele (TA+AA) for rs4648110 in nuclear factor kappa beta 1 (*NFKB1*). Values are plotted as unadjusted proportions with corresponding *P*-value.

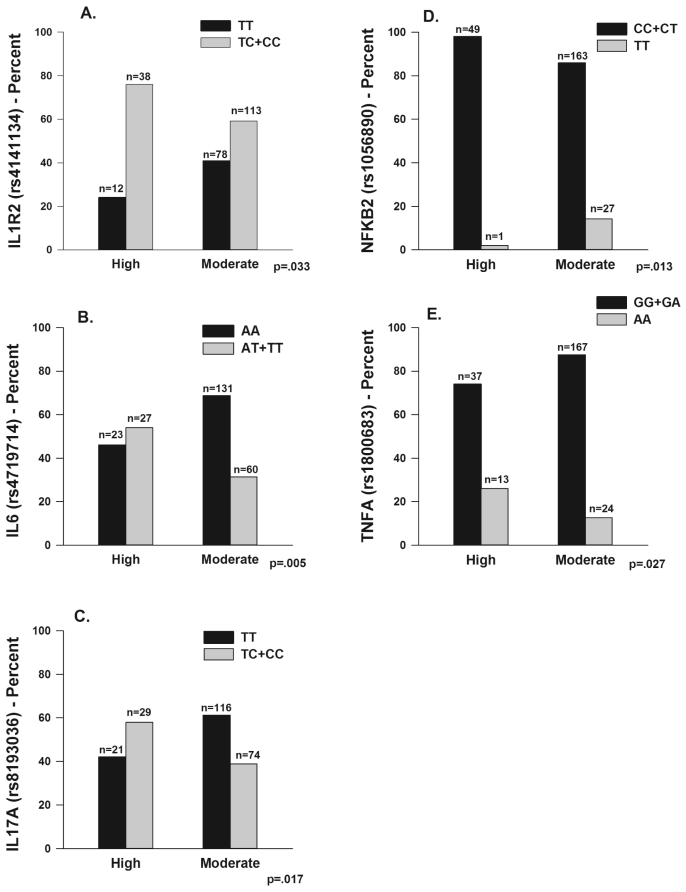

Fig. 3A.

Differences between the latent classes in the percentages of patients who were homozygous for the common allele (TT) or heterozygous or homozygous for the rare allele (TC+CC) for rs4141134 in interleukin 1 receptor 2 (*IL1R2*). Values are plotted as unadjusted proportions with corresponding *P*-value.

B. Differences between the latent classes in the percentages of patients who were homozygous for the common allele (AA) or heterozygous or homozygous for the rare allele (AT+TT) for rs4719714 in *IL6*. Values are plotted as unadjusted proportions with corresponding *P*-value.

C. Differences between the latent classes in the percentages of patients who were homozygous for the common allele (TT) or heterozygous or homozygous for the rare allele (TC+CC) for rs8193036 in *IL17A*. Values are plotted as unadjusted proportions with corresponding *P*-value.

D. Differences between the latent classes in the percentages of patients who were homozygous or heterozygous for the common allele (CC+CT) or homozygous for the rare allele (TT) for rs1056890 in *NFKB2*. Values are plotted as unadjusted proportions with corresponding *P*-value.

E. Differences between the latent classes in the percentages of patients who were homozygous or heterozygous for the common allele (GG+GA) or homozygous for the rare

allele (AA) for rs1800683 in tumor necrosis factor alpha (*TNFA)*. Values are plotted as unadjusted proportions with corresponding *P*-value.

Table 1

Fit Indices for Morning and Evening Energy GMM Solutions over Seven Assessments, with Dyad as a Clustering Variable

GMM		LL	AIC	BIC	Entropy	VLMR[c]
Morning Energy	1-Class[a]	−2901.424	5834.847	5891.318	n/a	n/a
	2-Class[b]	−2872.180	5788.361	5866.008	0.667	58.487**
	3-Class	−2865.486	5784.973	5880.267	0.728	13.388n.s.
Evening Energy	1-Class[d]	−2928.876	5889.752	5946.223	n/a	n/a
	2-Class[b]	−2900.571	5847.143	5928.320	0.708	56.609*
	3-Class	−2897.195	5850.390	5949.214	0.613	6.753n.s.

*p < .05,

**p < .01, n.s. = not significant

[a]Random coefficients latent growth curve model with linear and quadratic components; Chi^2 = 47.070, 26 df, p < 0.01, CFI = 0.979, RMSEA = 0.057

[b]2-class model was selected, based on its having the smallest BIC and a significant VLMR. Further, the VLMR is not significant for the 3-class model.

[c]This number is the Chi^2 statistic for the VLMR. When significant, the VLMR test provides evidence that the K-class model fits the data better than the K-1-class model.

[d]Random coefficients latent growth curve model with linear and quadratic components; Chi^2 = 86.548, 26 df, p < 0.00005, CFI = 0.945, RMSEA = 0.096

Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criterion; CFI = comparative fit index; df = degrees of freedom; GMM = Growth mixture model; LL = log likelihood; RMSEA = root mean square error of approximation; VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test;.

Table 2

GMM Parameter Estimates for Morning and Evening Energy Latent Class[a] Solutions with 7 Assessments, with Dyad as a Clustering Variable

Parameter Estimates[b]	**Moderate Morning Energy n = 124 (49.2%)**	**Low Morning Energy n = 128 (50.8%)**	**High Evening Energy n = 52 (20.6%)**	**Moderate Evening Energy n = 200 (79.4%)**
Means	Mean (S.E.)			
Intercept	6.945*** (0.276)	4.704*** (0.261)	5.759*** (0.845)	3.955*** (0.225)
Linear slope	0.345*** (0.102)	−0.253* (0.127)	0.706*** (0.197)	−0.333* (0.147)
Quadratic slope	−0.033* (0.015)	0.053** (0.019)	−0.093** (0.030)	0.044* (0.020)
Variances	Variance (S.E.)			
Intercept	0.967*** (0.201)	0.891*** (0.207)	2.056n.s. (1.449)	1.239*** (0.290)
Linear Slope	0[c]	0.033** (0.011)	0.001n.s. (0.014)	0.012n.s. (0.010)

* p < .05,

** p < .01,

*** p < .001, n.s. = not significant

[a] Trajectory group sizes are for classification of individuals based on their most likely latent class probabilities

[b] Growth mixture model estimates were obtained with robust maximum likelihood, with dyad as a clustering variable to account for dependency between patients and family caregivers within the same dyad. Quadratic slope variances were fixed at zero to improve estimation.

[c] Fixed at zero.

Abbreviations: GMM = Growth Mixture Model; S.E. = Standard Error

Table 3

Differences in Demographic and Clinical Characteristics at Enrollment Between the Two Latent Classes for Morning and Evening Energy

Characteristic	Moderate Morning Energy 124 (49.2%)	Low Morning Energy 128 (50.8%)	p-value	High Evening Energy 52 (20.6%)	Moderate Evening Energy 200 (79.4%)	p-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age (years)	65.2 (9.0)	57.9 (12.1)	<.001	66.2 (8.7)	60.3 (11.6)	<.001
Education (years)	16.2 (3.1)	15.7 (3.0)	NS	15.8 (3.2)	16.0 (3.0)	NS
Number of comorbid conditions	4.2 (2.6)	5.0 (2.8)	.014	3.9 (2.8)	4.8 (2.7)	.025
Weight (pounds)	178.6 (35.8)	172.1 (41.6)	NS	185.0 (36.4)	172.2 (38.8)	.035
KPS Score	95.6 (8.3)	88.2 (13.0)	<.001	96.9 (8.3)	90.6 (11.9)	.001
	n (%)	n (%)		n (%)	n (%)	
Gender (% female)	54 (43.5)	81 (63.3)	.002	37 (71.2)	80 (40.0)	.001
Ethnicity[A]						
% White	99 (79.8)	88 (69.3)	.026	38 (73.1)	149 (74.9)	NS
% Asian/Pacific Islander	12 (9.4)	4 (3.2)		2 (3.8)	14 (7.0)	
% Black	16 (12.6)	18 (14.5)		10 (19.2)	24 (12.1)	
% Hispanic/Mixed/Other	11 (8.7)	3 (2.4)		2 (3.8)	12 (6.0)	
Lives alone (% yes)	22 (28.2)	31 (34.8)	NS	41 (78.8)	133 (67.2)	NS
Married or partnered (% yes)	94 (75.8)	80 (63.5)	.039	53 (73.6)	121 (68.0)	NS
Children at home (% yes)	16 (15.4)	20 (18.7)	NS	4 (8.9)	32 (19.3)	NS
Older adult at home (% yes)	1 (1.0)	6 (5.5)	NS	1 (2.2)	6 (3.6)	NS
Work for pay (% yes)	50 (41.0)	65 (52.0)	NS	20 (38.5)	95 (48.7)	NS
Patient/FC (% Patient)	78 (62.5)	89 (69.5)	NS	35 (67.3)	132 (66.0)	NS

Abbreviations: FC = family caregiver; KPS = Karnofsky Performance Status; NS = not significant.

[A]Post-hoc contrasts revealed that the difference in ethnicity observed in the Low Morning Energy GMM class as compared to the Moderate Morning Energy GMM class was due to a decreased number of White participants in the Low Morning energy GMM class as compared to Black participants (p=0.005).

Table 4

Differences in Symptom Severity Scores at Enrollment Between the Two Latent Classes for Morning and Evening Energy

Characteristic	Moderate Morning Energy 122 (49.2%) Mean (SD)	Low Morning Energy 128 (50.8%) Mean (SD)	p-value	High Evening Energy 112 (20.6%) Mean (SD)	Moderate Evening Energy 128 (79.4%) Mean (SD)	p-value
Psychological Symptoms at Enrollment						
STAI-T	30.4 (8.3)	37.6 (10.0)	<.001	27.5 (6.4)	35.8 (9.9)	<.001
STAI-S	27.4 (8.1)	34.4 (11.9)	<.001	25.2 (6.0)	32.5 (11.3)	<.001
CES-D Total	5.6 (5.8)	12.0 (8.9)	<.001	4.0 (4.3)	10.1 (8.5)	<.001
Pittsburgh Sleep Quality Index (PSQI) Scores at Enrollment						
Subjective sleep quality	0.8 (0.7)	1.1 (0.7)	<.001	0.6 (0.5)	1.0 (0.7)	<.001
Sleep latency	0.7 (0.9)	1.2 (0.9)	<.001	0.5 (0.8)	1.1 (0.9)	<.001
Sleep duration	0.7 (0.8)	1.2 (1.0)	<.001	0.7 (0.7)	1.0 (0.9)	.020
Habitual sleep efficiency	0.5 (0.8)	0.9 (1.0)	.002	0.3 (0.7)	0.8 (1.0)	.003
Sleep disturbance	1.3 (0.5)	1.5 (0.6)	.001	1.2 (0.5)	1.4 (0.6)	.003
Use of sleeping medication	0.4 (0.9)	0.9 (1.2)	.002	0.5 (1.0)	0.7 (1.1)	.304
Daytime dysfunction	0.5 (0.6)	1.0 (0.6)	<.001	0.4 (0.6)	0.8 (0.6)	<.001
PSQI Global score	4.8 (2.9)	7.6 (3.7)	<.001	4.1 (2.3)	6.8 (3.7)	<.001
General Sleep Disturbance Scores at Enrollment						
Quality	1.9 (1.6)	2.9 (1.9)	<.001	1.5 (1.5)	2.7 (1.8)	<.001
Sleep onset latency	1.2 (1.8)	1.9 (2.1)	.003	0.8 (1.4)	1.7 (2.1)	.002
Quantity	4.1 (1.1)	4.7 (1.4)	.002	4.1 (0.9)	4.5 (1.4)	.031
Sleep medication	0.2 (0.4)	0.4 (0.7)	.003	0.2 (0.4)	0.3 (0.6)	.232
Mid-sleep awakenings	4.2 (2.6)	4.7 (2.5)	.114	4.1 (2.6)	4.5 (2.5)	.219
Early awakenings	1.8 (1.9)	2.8 (2.4)	.001	1.3 (1.7)	2.6 (2.3)	<.001
Excessive daytime sleepiness	1.4 (1.2)	2.2 (1.3)	<.001	1.1 (1.0)	2.0 (1.3)	<.001
Total GSDS score	32.0 (15.3)	45.6 (19.2)	<.001	27.9 (13.1)	41.7 (18.8)	<.001
Actigraphy Parameters at Enrollment						
Sleep period time (minutes)	479.5 (72.5)	489.2 (76.9)	.323	473.2 (76.9)	487.3 (74.2)	.238

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Characteristic	Moderate Morning Energy 122 (49.2%) Mean (SD)	Low Morning Energy 128 (50.8%) Mean (SD)	p-value	High Evening Energy 112 (20.6%) Mean (SD)	Moderate Evening Energy 128 (79.4%) Mean (SD)	p-value
Total sleep time (minutes)	391.4 (82.4)	407.7 (84.3)	.135	378.6 (95.7)	405.2 (79.5)	.047
Sleep efficiency	81.5 (14.0)	83.4 (11.7)	.265	79.3 (16.8)	83.3 (11.6)	.053
Wake after sleep onset (% of TST)	15.2 (12.8)	12.7 (11.2)	.124	16.6 (15.1)	13.2 (11.1)	.078
Wake number	17.7 (8.9)	15.8 (8.6)	.104	18.7 (9.7)	16.2 (8.5)	.073
Wake duration (minutes)	3.9 (2.8)	4.2 (6.1)	.587	3.9 (3.1)	4.1 (5.1)	.842
Sleep onset latency (minutes)	12.7 (11.8)	16.9 (22.9)	.081	15.3 (16.6)	14.7 (18.8)	.844
Fatigue and Energy Scores at Enrollment						
Evening fatigue	3.7 (2.1)	4.8 (1.9)	<.001	2.6 (1.9)	4.7 (1.8)	<.001
Morning fatigue	1.3 (1.4)	3.2 (2.0)	<.001	1.2 (1.7)	2.6 (1.9)	<.001
Evening energy	5.0 (2.0)	3.8 (1.5)	<.001	5.8 (2.0)	4.1 (1.6)	<.001
Morning energy	7.0 (1.7)	4.7 (1.6)	<.001	7.0 (2.1)	5.4 (1.9)	<.001
Attentional fatigue	7.9 (1.5)	6.5 (1.8)	<.001	8.4 (1.1)	6.9 (1.8)	<.001
	n (%)	n (%)		n (%)	n (%)	
Pain (% yes)	43 (36.1)	77 (57.9)	.001	29 (40.3)	91 (50.6)	.163

Abbreviations: STAI-S = Spielberger State-Trait Anxiety Inventory – State subscale; STAI-T = Spielberger State-Trait Anxiety Inventory – Trait subscale; CES-D = Center for Epidemiological Studies – Depression scale; GSDS = General Sleep Disturbance Scale; TST = Total sleep time

Table 5

Multiple Logistic Regression Analyses for Morning Energy and Evening Energy

Predictor	Odds Ratio	Standard Error	95% CI	Z	p-value
Morning Energy					
IL2 rs1479923	0.25	0.151	0.077, 0.816	−2.30	.022
Age	0.70	0.058	0.599, 0.826	−4.29	<.001
Number of comorbid conditions	1.15	0.070	1.020, 1.294	2.28	.023
KPS score	0.57	0.091	0.415, 0.776	−3.55	<.001
Overall model fit: $\chi^2 = 64.5$, p <.0001 $R^2 = 0.1990$					
NFKB1 rs4648110	0.58	0.159	0.337, 0.990	−2.00	.046
Age	0.70	0.057	0.600, 0.827	−4.29	<.001
Number of comorbid conditions	1.15	0.070	1.020, 1.296	2.29	.022
KPS score	0.57	0.090	0.414, 0.772	−3.58	<.001
Overall model fit: $\chi^2 = 62.7$, p <.0001 $R^2 = 0.1934$					
Evening Energy					
IL1R2 rs4141134	0.36	0.157	0.153, 0.845	−2.35	.019
Age	0.78	0.079	0.641, 0.951	−2.46	.014
Gender	0.40	0.152	0.189, 0.842	−2.41	.016
Ethnicity	0.03	0.042	0.001, 0.655	−2.22	.027
KPS score	0.50	0.121	0.310, 0.801	−2.88	.004
Overall model fit: $\chi^2 = 43.97$, p <.0001 $R^2 = 0.1811$					
IL6 rs4719714	0.27	0.102	0.126, 0.563	−3.46	.001
Age	0.77	0.078	0.631, 0.938	−2.59	.010
Gender	0.38	0.148	0.180, 0.817	−2.48	.013
Ethnicity	0.02	0.037	0.001, 0.736	−2.13	.033
KPS score	0.48	0.119	0.293, 0.780	−2.96	.003
Overall model fit: $\chi^2 = 50.42$, p <.0001 $R^2 = 0.2077$					
IL17A rs8193036	0.39	0.145	0.192, 0.811	−2.53	.011
Age	0.78	0.078	0.643, 0.951	−2.47	.014
Gender	0.38	0.147	0.181, 0.811	−2.51	.012
KPS score	0.50	0.123	0.312, 0.811	−2.82	.005
Overall model fit: $\chi^2 = 43.97$, p <.0001 $R^2 = 0.1815$					
NFKB2 rs1056890	9.70	10.267	1.218, 77.225	2.15	.032
Age	0.76	0.077	0.628, 0.932	−2.66	.008
Gender	0.41	0.155	0.196, 0.862	−2.35	.019
KPS score	0.52	0.126	0.327, 0.839	−2.69	.007
Overall model fit: $\chi^2 = 46.23$, p <.0001 $R^2 = 0.1904$					
TNFA rs1800683	0.36	0.161	0.148, 0.863	−2.29	.022
Age	0.77	0.077	0.631, 0.934	−2.65	.008

Predictor	Odds Ratio	Standard Error	95% CI	Z	p-value
Gender	0.39	0.148	0.186, 0.821	−2.48	.013
Ethnicity	0.03	0.048	0.001, 0.826	−2.07	.038
KPS score	0.51	0.123	0.322, 0.822	−2.78	.005
Overall model fit: $\chi^2 = 43.00$, $p < .0001$ $R^2 = 0.1771$					

Multiple logistic regression analysis of Moderate versus Low Morning Energy GMM classes (n=234) and of High versus Moderate Evening Energy classes. For each model, the first three principle components identified from the analysis of ancestry informative markers as well as self-report race/ethnicity were retained in all models to adjust for potential confounding due to race or ethnicity (data not shown). For Morning Energy GMM regression analyses, predictors evaluated in each model included genotype (IL2 rs1479923 genotype: CC+CT versus TT; NFKB1 rs4648110 genotype: TT versus TA+AA), age (5 years increments), number of comorbid conditions, and functional status (KPS score in 10 unit increments). For Evening Energy GMM regression analyses, predictors evaluated in each model included genotype (IL1R2 rs4141134: TT versus TC+CC; IL6 rs4719714: AA versus AT+TT; IL17A rs8193036: TT versus TC+CC; NFKB2 rs1056890: CC+CT versus TT; TNFA rs1800683: GG+GA versus AA), age (5 years increments), gender (female), ethnicity (Black as compared to White), and functional status (KPS score in 10 unit increments).

Abbreviations; CI =confidence interval; GMM = growth mixture model; IL1R2 = interleukin 1 receptor 2; IL6 = interleukin 6; IL17A = interleukin 17A; KPS, Karnofsky Performance Status; NFKB1 = Nuclear Factor Kappa Beta 1; NFKB2 = Nuclear Factor Kappa Beta 2; TNF = Tumor Necrosis Factor Alpha.