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Lisa Morse

by

Lisa Morse

THESIS

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Lisa Morse

Subgroups of Patients Undergoing Chemotherapy with Distinct Cognitive Fatigue and Evening Physical Fatigue Profiles

Author: Lisa Morse

Abstract

Purpose – Purpose was to model cognitive fatigue and evening physical fatigue together to determine subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles. Once these profiles were identified, differences among the subgroups in demographic and clinical characteristics, co-occurring symptoms, and quality of life outcomes were evaluated.

Methods – Oncology patients (n=1332) completed self-report measures of cognitive fatigue and evening physical fatigue, six times over two cycles of chemotherapy. Latent profile analysis, that combined the two symptom scores, was done to identify subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles.

Results – Three distinct profiles (i.e., Low (20.5%), Moderate (39.6%), High (39.6%) were identified. Compared to the Low class, patients in the High class were younger, female, more likely to live alone and had a higher comorbidity burden and a lower functional status. In addition, these patients had a higher symptom burden and a poorer quality of life.

Conclusion – Based on clinically meaningful cutoff scores, 80% of the patients in this study had moderate to high levels of both cognitive fatigue and evening physical fatigue. In addition, these patients experienced high levels of other common symptoms (e.g., anxiety, depression, sleep disturbance, pain). These co-occurring symptoms and other modifiable characteristics associated with membership in the Moderate and High classes may be potential targets for individualized symptom management interventions.

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Introduction

Fatigue occurs in approximately 80% of oncology patients undergoing treatment [7]. This highly prevalent and distressing symptom can decrease patients' adherence with treatments [31], and impairs their quality of life (QOL) [24]. In addition, cancer-related fatigue may be associated with decreased survival [23, 53]. Cancer-related fatigue is more severe, persistent, and debilitating than fatigue experienced by the general population [10]. Cancer-related fatigue is defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [7]. This definition emphasizes the multidimensional nature of fatigue.

As noted in one review [18], while researchers have designed instruments to measure the multiple dimensions of fatigue, consensus does not exist on the number of dimensions that warrant evaluation. For example, the Fatigue Questionnaire evaluates two dimensions (i.e., physical, mental). In contrast, both the Multidimensional Fatigue Inventory (i.e., general fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity) [61] and the Multidimensional Fatigue Symptom Inventory (i.e., global, somatic, affective, cognitive, behavioral) [63] evaluate five dimensions. The authors of the review commented that at a consensus conference of the European Association of Palliative Care [54], an expert panel endorsed the existence of at least physical and cognitive or mental fatigue in oncology patients.

Given the large amount of inter-individual variability in the prevalence [20] and severity [70-74] of fatigue in oncology patients, one needs to consider how to characterize the multiple dimensions of fatigue. As noted by deRaaf and colleagues [18], three possible conceptualizations of fatigue exist (i.e., unidimensional, multidimensional, and multiple symptom). In their multiple symptom concept, they described that "physical fatigue and mental fatigue are separate symptoms and have a different pathogenesis and require different

treatments" (p.1920). Based on the results of their systematic review that focused on an evaluation of the "behavior of physical fatigue and mental fatigue in cancer patients" [18], they concluded that physical fatigue and mental fatigue may be separate phenomenon.

Two of the studies cited in the above referenced review [18] evaluated for changes over time in physical [15] and cognitive [16] fatigue in 157 women with breast cancer receiving adjuvant chemotherapy. Fatigue was assessed at the first, third, and fifth cycle, as well as at 4 and 12 weeks after the last cycle of chemotherapy using the Multidimensional Fatigue Inventory [61]. While physical fatigue increased over the course of chemotherapy and declined following the completion of treatment, cognitive fatigue remained relatively stable over the course of treatment. While this study evaluated for changes over time in the same sample of patients, each dimension of the fatigue experience was analyzed separately.

In a more recent cross-sectional study of long-term survivors of colorectal cancer (n=1183) [64], latent class analysis was used to identify subgroups of survivors with distinct fatigue profiles using the five dimensions of the Multidimensional Fatigue Inventory. Three distinct profiles were identified (i.e., no fatigue and distress (56%), low fatigue and moderate distress (22%), high fatigue and moderate distress (22%)). Compared to the no fatigue and distress class, survivors in the high fatigue and moderate distress class were more likely to be female and overweight, had co-occurring diabetes, and had received radiation therapy. In addition, survivors in the two higher classes were more likely to have comorbid heart disease and higher levels of anxiety and sleep disturbance. Of note, across the three classes cognitive fatigue scores were low. While this study provides insights into fatigue subtypes, using different dimensions of the fatigue experience, it was cross-sectional and focused on only cancer survivors.

Recent work from our group has focused on an evaluation of inter-individual differences in and risk factors for physical fatigue, using the Lee Fatigue Scale [41], in a sample of patients with heterogeneous types of cancer undergoing chemotherapy [70-74]. Using latent profile

analysis (LPA), four subgroups of patients with distinct morning (i.e., Very Low, Low, High, and Very High) [73] and four subgroups with distinct evening (i.e., Low, Moderate, High, and Very High) [70] fatigue profiles were identified. Given that the severity and trajectories of fatigue differed between the morning and evening fatigue latent classes and different demographic and clinical characteristics were associated with membership in the higher morning and evening fatigue classes, we concluded that diurnal variations in physical fatigue occurred over two cycles of chemotherapy and that morning and evening fatigue were distinct but related symptoms. In terms of cognitive fatigue [4], in the same sample of patients receiving chemotherapy (n=1329), we used LPA to evaluate for distinct cognitive fatigue profiles using the Attentional Function Index (AFI) [13]. Three subgroups of patients with distinct cognitive fatigue profiles were identified (i.e., Low, Moderate, and High). Patients with moderate and high levels of cognitive fatigue were younger, more likely to be female, and were less likely to be employed.

Given the paucity of research on the relationships among multiple dimensions of the fatigue experience and on the identification of subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles, in this study, we modeled cognitive fatigue and evening physical fatigue together to determine subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles. Once these profiles were identified, we evaluated for differences among the subgroups in demographic and clinical characteristics, co-occurring symptoms, and QOL outcomes.

Patients and Methods

Patients and Settings

This longitudinal study, that evaluated the symptom experience of oncology outpatients receiving chemotherapy is described in detail elsewhere [44, 45]. In brief, eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two

additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. A total of 2234 patients were approached and 1343 consented to participate (60.1% response rate). The major reason for refusal was being overwhelmed with their cancer treatment.

Instruments

Demographic and clinical characteristics

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. In addition, they completed the Karnofsky Performance Status (KPS) scale [34, 35], the Alcohol Use Disorders Identification Test (AUDIT) [5, 6], and the Self-Administered Comorbidity Questionnaire (SCQ). The SCQ evaluates the occurrence, treatments for, and impact of 13 common medical conditions.[57] Total SCQ scores range from 0 to 39. The SCQ has well-established validity and reliability [9, 11].

Measures of Cognitive Fatigue and Evening Physical Fatigue

The 16-item Attentional Function Index (AFI) assesses an individual's perceived effectiveness in performing daily activities that are supported by attention and working memory [13]. It is the measure of cognitive fatigue in this study. A higher total mean score on a 0 to 10 numeric rating scale (NRS) indicates greater capacity to direct attention [13]. Total scores can be grouped into categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function) [12]. In this study, the Cronbach's alpha for the total AFI scores was 0.93.

The 18-item Lee Fatigue Scale (LFS) was designed to assess physical fatigue and energy [41]. Each item was rated on a 0 to 10 NRS. Total fatigue and energy scores 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) [22] and energy (i.e., ≤6.2 for morning energy, ≤3.5 for evening energy) [22]. 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. The evening fatigue scores from the LFS were used in the evaluation of evening physical fatigue in this study.

Measures of Common Symptoms

To assess the severity of common symptoms associated with cancer and its treatment, patients completed: Center for Epidemiological Studies-Depression scale (CES-D) [55], Spielberger State-Trait Anxiety Inventories (STAI-S, STAI-T) [62], General Sleep Disturbance Scale (GSDS) [40], and Brief Pain Inventory [14].

Quality of Life Measures

Quality of life was evaluated using generic (i.e., Medical Outcomes Study-Short Form-12 (SF-12)) [66] and disease-specific (i.e., Quality of Life Scale-Patient Version (QOL-PV)) [49, 50] measures. The SF-12 consists of 12 questions about physical and mental health as well as overall health status. The individual items on the SF-12 are evaluated and the instrument is scored into two components (i.e., physical component summary (PCS) and mental component summary (MCS) scores). These scores can range from 0 to 100. Higher PCS and MCS scores indicate a better QOL. The SF-12 has well established validity and reliability.[66]

The 41-item Quality of Life-Scale-Patient Version (QOL-PV) measures four dimensions of QOL (i.e., physical, psychological, social and spiritual well-being) in cancer patients, as well as a total QOL score. Each item was rated on a 0 to 10 NRS with higher scores indicating a better QOL. In the current study, the Cronbach's alpha for the QOL-PV total score was 0.92.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites. Eligible patients were approached by a research staff member in the infusion unit to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their chemotherapy cycles, patients completed questionnaires in their homes, a total of six times over two cycles of chemotherapy (i.e., prior to chemotherapy administration (i.e., recovery from previous chemotherapy cycle), approximately 1 week after chemotherapy administration (i.e., acute symptoms), approximately 2 weeks after chemotherapy administration (i.e., potential nadir)). Medical records were reviewed for disease and treatment information.

Data Analysis

Latent profile analysis (LPA) was used to identify subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles. This LPA was done with the combined set of variables over time (i.e., using the AFI AND evening LFS scores obtained during the six assessments in a single LPA). This approach provides a profile description of these **two symptoms** with parallel profiles over time. The LPA was done using Mplus version 8.4 [47].

In order to incorporate expected correlations among the repeated measures of the same variable and cross-correlations of the series of the two variables (i.e., evening LFS and AFI scores), we included covariance parameters among measures at the same occasion and those that were one or two occasions apart. Covariances of each variable with the other at the same assessments were included in the model and autoregressive covariances were estimated with a lag of two with the same measures and with a lag of one for each variable's series with the other variable. We limited the covariance structure to a lag of two to accommodate the expected reduction in the correlations that would be introduced by two chemotherapy cycles within each set of three measurement occasions and to reduce model complexity [33].

Data were analyzed using SPSS version 27 (IBM Corporation, Armonk, NY). Descriptive statistics and frequency distributions were calculated for demographic and clinical characteristics. Differences among the cognitive fatigue AND evening physical fatigue classes in demographic, clinical, and symptom characteristics and QOL outcomes were evaluated using parametric and nonparametric tests. A Bonferroni corrected p-value of <0.017 (i.e., 0.05/3) was considered statistically significant for the pairwise contrasts.

RESULTS

As shown in Table 1, a three-class solution was selected because the Bayesian Information Criterion (BIC) for that solution was lower than the BIC for the 2-class solution. In addition, the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) was significant for the three-class solution, indicating that three classes fit the data better than two classes. While the BIC was lower for the 4-class solution, the VLMR was not significant for the 4-class solution, indicating that too many classes were extracted.

The cognitive fatigue AND evening physical fatigue classes were labeled as Low cognitive fatigue and Low evening physical fatigue (i.e., Low), Moderate cognitive fatigue and Moderate evening physical fatigue (i.e., Moderate), and High cognitive fatigue and high evening physical fatigue (i.e., High) based on clinically meaningful cut-off scores for cognitive fatigue (i.e. AFI score of <5.0 low function, 5.0–7.5 moderate function, >7.5 high function) and for evening physical fatigue (i.e., LFS score of ≥5.6). As shown in Figure 1-3, the trajectories for the two symptoms that were modeled together (i.e., cognitive fatigue and evening physical fatigue) were relatively similar across the three latent classes. For the Low (20.5%), Moderate (39.6%), and High (39.9%) classes, cognitive fatigue and evening physical fatigue scores increased slightly at the second and fifth assessments (i.e., assessments following the administration of chemotherapy).

Differences in Demographic and Clinical Characteristics

As shown in Table 2, significant differences were found among the latent classes for many of the demographic and clinical characteristics. Compared to the Low class, patients in the other two classes were significantly younger, more likely to be female, more likely to be White, less likely to be Black, less likely to exercise on a regular basis, more likely to be diagnosed with breast cancer, less likely to be diagnosed with gastrointestinal cancer, more likely to self-report a diagnosis of depression, and more likely to have received previous cancer treatments.

Compared to the other two classes, patients in the High class were less likely to be married/partnered, less likely to be employed, more likely to self-report a diagnosis of back pain, and had a higher number of comorbidities. Compared to the Low class, patients in the High class were more likely to live alone, more likely to have child care responsibilities, more likely to report a past or current history of smoking, had received a higher number of previous cancer treatments, and had a higher MAX 2 score.

Compared to the other two classes, patients in the Moderate class had more years of education and a higher annual household income. Among the three classes, KPS scores followed the expected pattern (Low > Moderate > High).

Differences in symptom severity

As shown in Table 3, for trait anxiety, state anxiety, depressive symptoms, morning fatigue, evening fatigue, and sleep disturbance, the scores followed the expected pattern (i.e., Low < Moderate < High). In terms of evening energy and cognitive fatigue, the scores followed the expected pattern (i.e., Low > Moderate > High). Compared to the Low and Moderate classes, patients in the High class had lower evening energy scores. In terms of types of pain, the proportion of patients who reported no pain was in the expected direction (i.e., Low > Moderate > High). Compared to the other two classes, a higher percentage of patients in the

High class reported the occurrence of both cancer and non-cancer pain and higher worst pain intensity scores. Pain interference scores followed a similar patter to other symptoms (i.e., Low < Moderate < High).

Differences in QOL

As shown in Table 4, in terms of the SF-12, for the physical functioning, role functioning, bodily pain, vitality, social functioning, mental health, as well as for the PCS and MCS, the scores followed the expected pattern (i.e., Low > Moderate > High). For general health and role emotional subscales, compared to the other two classes, patients in the High class reported lower scores.

In terms of the QOL-PV, for the physical well-being, psychological well-being, social well-being subscales and total QOL scale, the scores followed the expected pattern (i.e., Low > Moderate > High). For the spiritual well-being subscale, compared to the Low class, patients in the High class reported lower scores.

DISCUSSION

This study is the first to use LPA to identify subgroups of oncology patients with distinct cognitive fatigue AND evening physical fatigue profiles over two cycles of chemotherapy. While our previous LPAs, for this sample, found three distinct profiles for cognitive fatigue [4] and four distinct profiles for evening physical fatigue [70], in the current analysis when these two dimensions of fatigue were modeled together, three distinct profiles were identified. Of note, based on the clinically meaningful cutoff scores for these two symptoms, 80% of patients in our sample were categorized in either the Moderate or High classes. This percentage is consistent with previous reports of the overall prevalence of cancer-related fatigue [7, 8, 27].

A comparison of the trajectories of the cognitive fatigue and evening physical fatigue scores among the latent classes suggest that when the two symptoms are modeled together both scores fluctuate in a similar pattern over the two cycles of chemotherapy regardless of

class assignment. Consistent with previous reports of the **individual** symptoms from our group [4, 70] and others [15-17], both types of fatigue increase following the administration of chemotherapy and then decline prior to the next infusion.

In their systematic review [18], de Raaf and colleagues suggested that if cognitive fatigue and physical fatigue were different symptoms within the multiple symptom concept of fatigue (versus that fatigue was a multidimensional concept that is experienced in different ways), these two symptoms would differ in the following ways: their intensity would differ in cross sectional studies of various groups of patients; their intensity would vary across courses of treatment; the variables associated with each symptom would differ; and their response to interventions would differ. Unfortunately, like the findings from the systematic review, no definitive conclusions can be made regarding this question. While we found three groups of patients with distinct cognitive fatigue and evening physical fatigue profiles, the severity of the pairs of symptoms and their changes over time remained relatively similar across the three groups. However, as shown in Table 5, some of the characteristics associated with the Moderate and High groups were different. Two criteria that de Raaf and colleagues failed to include in their review were whether the mechanisms that underlie the single symptoms are similar or different and whether objective measures of cognitive fatigue and physical fatigue evaluated in the same patients are correlated with each other. Information on the common and distinct aspects of cognitive and physical fatigue, including common and distinct underlying mechanisms, are essential in order to answer the multiple symptom versus multidimensional symptom question.

One of the purposes of this study was to identify demographic, clinical, and symptom characteristics that were associated with a higher level of symptom burden. As shown in Table 5, compared to the Low class, some of characteristics associated with membership in the Moderate and High classes were common while others were distinct. In terms of demographic characteristics, compared to the Low class, patients in the other two classes shared the

following characteristics: younger age, more likely to be female, more likely to be White, and less likely to be Black. While findings regarding age differences in cognitive and physical are inconsistent [3, 28], for both symptoms, potential explanations for the association with younger age include that older patients may be given lower doses of chemotherapy [67]; age-related changes occur that modify inflammatory responses [8]; and/or a “response shift” can occur in the symptom perceptions of older patients [25]. Another potential explanation for this finding is the emerging evidence that suggests that younger age is associated with higher rates of social isolation [48]. For example, in a study of 340 community dwelling adults between the ages of 27 to 101 [39], those who reported experiencing social isolation had worse mental and physical functioning. In addition, recent evidence from cognitive aging research suggests that compensatory neural changes may occur in older adults that offset cognitive fatigue [19].

Findings regarding gender differences in cognitive fatigue and physical fatigue are inconclusive [3]. In one study that evaluated different dimensions of fatigue but only reported an overall fatigue score [60], across the three years of the study, the prevalence rates for fatigue were higher in women. Some of these inconsistencies may be related to the gender distribution of patients in the previous studies. Future studies need to evaluate for gender differences in these two symptoms, in patients who have cancers with an equal gender distribution (e.g., lung gastrointestinal) and treatment regimens. In terms of ethnicity, given the paucity of research on the association between this demographic characteristic and either symptom, direct comparisons with our findings cannot be made.

A larger number of unique characteristics were associated with membership in the High class (Table 5). Consistent with previous studies of physical fatigue [70, 72], patients who were not married or partnered, were living alone, and had child care responsibilities were in the High class. Within the context of undergoing chemotherapy, it is readily apparent why patients with the additional burden of child care would be classified in the High class. A plausible explanation for the associations between the other two characteristics and membership in the High class is

the recent findings that perceptions of lack of social support and loneliness are associated with higher levels of cancer-related fatigue [52, 59]. While it is difficult to disentangle the causal relationships between lack of social support and cancer-related fatigue, future studies should incorporate measures of loneliness, social isolation, and social support to evaluate these associations. While we cannot change a patient's marital status and/or living arrangements, interventions can be designed and implemented to modify loneliness, social isolation, and social support.

In terms of common and distinct clinical characteristics, compared to the Low class, patients in the other two classes had a higher comorbidity burden and a lower functional status, and were more likely to have breast cancer, were less likely to have gastrointestinal cancer, were more likely to have received prior cancer treatments, and were more likely to self-report diagnosis of depression. Previous studies of oncology patients receiving chemotherapy have found that both symptoms are associated with a higher comorbidity burden [70] and poorer functional status [70]. As noted in one review [75], the prevalence of cancer-related fatigue increases as the number of comorbid conditions increases. A potential explanation for this finding is that the fatigue associated with various chronic conditions may share similar underlying mechanisms [43]. In addition, the occurrence of multiple chronic conditions may potentiate symptom severity in a synergistic manner [30]. These hypotheses are supported by our findings that patients in the Moderate class were more likely to self-report a diagnosis of heart disease and patients in the Severe class were more likely to self-report a diagnosis of back pain.

In terms of differences in the occurrence of cognitive and physical fatigue among patient with different types of cancer, comparisons are difficult because of differences in the measures used to assess the two symptoms and the timing of the measures. In one study that controlled for age and sex in their analysis [60], the highest prevalence rates for fatigue were found in patients with gall bladder cancer, as well as in patients with head and neck, pancreatic,

gynecologic, and hematologic malignancies. Findings from a recent study, that used the EORTC-QLQ-FA-12, a multi-dimensional fatigue inventory, to assess physical, cognitive, and emotional fatigue in 2224 patients with fifteen different types of cancer approximately two years after their diagnosis [58], suggest that all three types of fatigue were lowest in patients with breast cancer.

In terms of the unique clinical characteristics associated with membership in the High class, these patients reported a higher number of comorbidities, a higher number of previous cancer treatments, were receiving a more toxic chemotherapy regimen (i.e., higher MAX2 score) and were more likely to self-report a diagnosis of back pain. As noted above, all of these characteristics may potentiate cognitive fatigue and physical fatigue in a synergistic manner [30].

This suggestion of synergistic interactions among co-occurring symptoms is supported by the differences in symptom severity scores among the three classes. As shown in Table 3, for all of the symptoms except morning energy and pain severity, the symptom severity scores increased in a stepwise fashion (i.e., Low < Moderate < High; NB for evening energy and cognitive fatigue the pattern was Low > Moderate > High). Equally important, all of the symptom severity scores for the High class were above the clinically meaningful cutpoints. While some evidence suggests that pain, fatigue, sleep disturbance, cognitive dysfunction, and depression occur as a psychoneurological symptom cluster and have shared biological mechanisms [36], additional research is warranted to determine the common and unique mechanisms that contribute to a higher symptom burden.

Less is known about the relationship between anxiety and fatigue severity. Our findings are consistent with previous reports that found that higher rates of trait anxiety were associated with higher levels of fatigue in patients with breast cancer undergoing chemotherapy [68] and in cancer survivors [32, 52, 65]. One explanation for this association is that higher levels of anxiety

cause dysregulation of the hypothalamic–pituitary–adrenal axis, which may increase cytokine production and associated increases in both cognitive and physical fatigue [8].

As shown in Table 4, for all of the QOL outcomes, except general health and spiritual well-being, the scores decreased in a stepwise fashion (i.e., Low > Moderate > High). As noted in a number of reviews [1, 56], the association between higher levels of cancer-related fatigue and decrements in QOL are well established. It stands to reason that patients who are not able to engage fully in their daily activities due to both cognitive and physical fatigue would experience decrements in QOL. These decreases were found in both the general and disease-specific measures of QOL. In fact, the PCS and MCS scores for the patients in the High class were below the normative scores for the US population.

Several study limitations and strengths warrant consideration. While a total of six assessments were done over two cycles of chemotherapy, the patients in this study were not assessed prior to the initiation of chemotherapy. Second, our assessment of cognitive function was limited to a self-report measure that primarily evaluates attention and executive function. Third, the findings related to ethnicity need to be interpreted with caution given the relatively small sample sizes for the different ethnic groups. However, this large representative sample of oncology patients undergoing chemotherapy; the evaluation of both cognitive fatigue and evening physical fatigue across two cycles of chemotherapy; and the use of LPA to identify risk factors associated with cognitive fatigue AND evening physical fatigue are major strengths of this study.

Of note, this study is the first to identify subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles. The phenotypic characteristics associated with membership in the High class can be used to identify high risk patients. The identification of nonmodifiable (e.g., age, gender) and modifiable (e.g., childcare responsibilities, depressive symptoms, sleep disturbance, lack of regular exercise) risk factors allows clinicians to tailor interventions for specific patients. For example, a growing body of evidence suggests that

exercise can decrease cognitive and physical fatigue [38, 46]. For example, in a meta-analysis that compared the effectiveness of pharmacological, psychological, and exercise treatments on cancer-related fatigue [46], exercise and psychological interventions significantly reduced cancer-related fatigue during and after cancer treatment. In addition, behavioral interventions to improve sleep may reduce both cognitive and physical fatigue. Equally important, programs that offer support to patients with childcare responsibilities and improve the perception of social connection may benefit patients with both types of fatigue.

Given that pre-treatment fatigue was found to predict post-treatment fatigue [42, 51], future studies should include measures of pre-treatment fatigue. To determine whether cognitive fatigue and evening physical fatigue are multiple symptoms or a multidimensional concept, future research should investigate whether the mechanisms that underlie the single symptoms are similar or different. In addition, studies are need that use objective measures of cognitive and physical fatigue to determine if latent class membership differs depending on the assessment method used (i.e., subjective or objective measures) and the domains of cognitive (e.g., executive function, working memory) and physical (e.g., gait speed, balance) function that are evaluated. Finally, given the compelling evidence that childhood adversity [26, 37, 69], coping styles [21, 29], and perceptions of social support [2] influence the severity of fatigue, future studies should include measures of psychosocial and behavioral risk factors for both cognitive and physical fatigue.

FIGURES AND TABLES

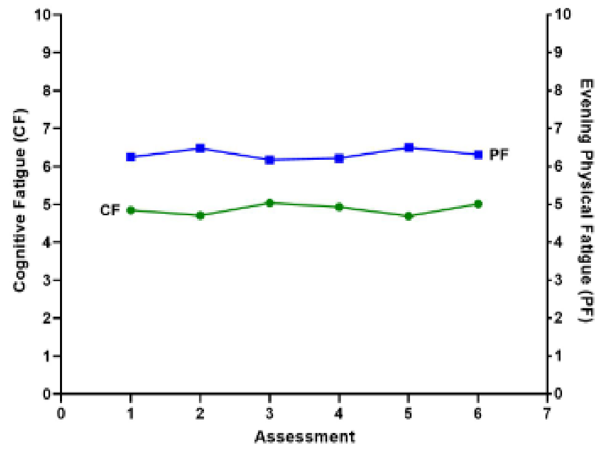

Figure 1*- High Cognitive Fatigue and High Evening Physical Fatigue (39.9%)*

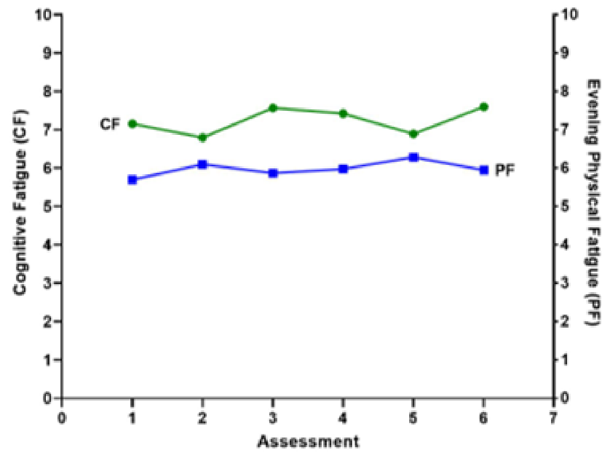

Figure 2*- Moderate Cognitive Fatigue and Moderate Evening Fatigue (39.6%)*

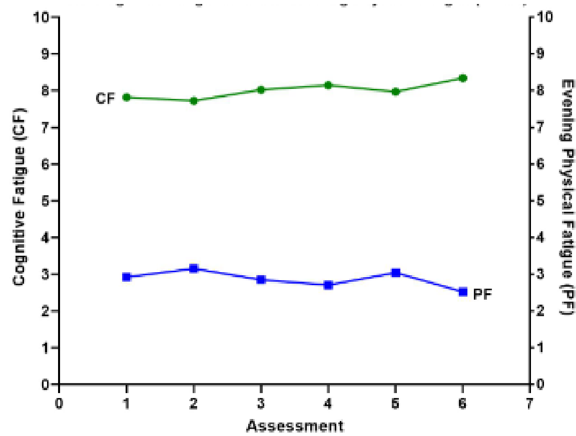

Figure 3*- Low Cognitive Fatigue and Low Evening Physical Fatigue (20.5%)*

Figure legend

Changes in cognitive fatigue (CF, left y-axis; lower scores indicate higher levels of cognitive fatigue) and evening physical fatigue (PF, right y-axis; higher scores indicate higher levels of physical fatigue) scores over two cycles of chemotherapy for subgroups of oncology patients with High Cognitive Fatigue and High Evening Physical Fatigue (panel A), Moderate Cognitive Fatigue and Moderate Evening Physical Fatigue (panel B) and Low Cognitive Fatigue and Low Evening Physical Fatigue (panel C).

***Table 1**- Evening Physical Fatigue and Cognitive Fatigue Over Six Assessments - Latent Profile Solutions and Fit Indices for One Through Four Class Solutions*

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-24456.76	49029.52	49330.80	n/a	n/a
2 Class	-23838.86	47819.73	48188.53	.78	1235.80+
3 Class[a]	-23559.85	47287.71	47724.04	.77	558.02+
4 Class	-23389.03	46972.06	47457.92	.76	341.65[ns]

Baseline LL is not applicable for the one class solution

+$p < .00005$

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

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

***Table 2**- Differences in Demographic and Clinical Characteristics Among the Cognitive Fatigue and Evening Physical Fatigue Subgroups at Enrollment*

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n=273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n=528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n=531)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	60.3 (11.7)	56.5 (11.8)	56.1 (12.9)	F=11.47, p<0.001 0 > 1 and 2
Education (years)	15.9 (3.1)	16.6 (3.1)	16.0 (2.9)	F=6.31, p=0.002 1 > 0 and 2
Body mass index (kg/m^2)	26.1 (5.4)	26.2 (5.5)	26.2 (5.9)	F=0.03, p=0.969
Karnofsky Performance Status score	86.2 (11.1)	82.0 (11.4)	74.8 (12.2)	F=95.23, p<0.001 0 > 1 > 2
Number of comorbidities out of 13	2.2 (1.4)	2.2 (1.3)	2.7 (1.5)	F=16.11, p<0.001 0 and 1 < 2
SCQ score out of 13 conditions	4.6 (2.8)	5.1 (2.9)	6.3 (3.5)	F=32.03, p<0.001 0 < 1 and 2
AUDIT score	2.9 (2.5)	2.9 (2.2)	3.1 (2.8)	F=0.89, p=0.412
Hemoglobin	11.6 (1.5)	11.6 (1.5)	11.5 (1.4)	F=1.86, p=0.156
Hematocrit	34.9 (4.1)	34.7 (4.2)	34.2 (4.0)	F=3.23, p=0.040 no significant pairwise contrasts
Time since cancer diagnosis (years)	1.7 (3.2)	2.1 (4.1)	2.0 (4.0)	KW, p=0.347
Median time since diagnosis (years)	0.43	0.40	0.45	
Number of prior cancer treatments	1.4 (1.4)	1.6 (1.5)	1.7 (1.6)	F=3.54, p=0.029 0 < 2
Number of metastatic sites including lymph node involvement	1.3 (1.2)	1.2 (1.2)	1.3 (1.3)	F=0.48, p=0.620
Number of metastatic sites excluding lymph node involvement	0.8 (1.1)	0.8 (1.0)	0.8 (1.	F=0.30, p=0.738
MAX2 score	0.16 (0.08)	0.18 (0.08)	0.18 (0.08)	F=3.81, p=0.022 0 < 2

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n=273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n=528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n=531)	Statistics
	% (n)	% (n)	% (n)	
Female	68.9 (188)	77.1 (407)	83.4 (442)	χ^2 =22.46, p<0.001 0 < 1 and 2, 1 < 2
Ethnicity				χ^2 =24.39, p<0.001
White	58.9 (159)	74.2 (386)	70.3 (369)	0 < 1 and 2
Asian or Pacific Islander	16.3 (44)	11.5 (60)	11.6 (61)	NS
Black	11.9 (32)	5.8 (30)	6.3 (33)	0 > 1 and 2
Hispanic, Mixed, or Other	13.0 (35)	8.5 (44)	11.8 (62)	NS
Married or partnered (% yes)	69.3 (187)	69.0 (359)	57.6 (301)	χ^2 =18.38, p<0.001 0 and 1 > 2
Lives alone (% yes)	16.3 (44)	19.8 (103)	25.9 (136)	χ^2 =11.19, p=0.004 0 < 2
Child care responsibilities (% yes)	15.9 (43)	23.1 (118)	24.5 (128)	χ^2 =8.02, p=0.018 0 < 2
Care of adult responsibilities (% yes)	7.5 (19)	6.5 (31)	9.6 (46)	χ^2 =3.22, p=0.200
Currently employed (% yes)	38.7 (104)	42.5 (222)	26.0 (137)	χ^2 =33.30, p<0.001 0 and 1 > 2
Annual household income				KW , p<0.001 0 and 2 < 1
<$30,000+	17.4 (40)	11.1 (53)	26.0 (126)	
$30,000 to <$70,000	25.2 (58)	16.8 (80)	23.5 (114)	
$70,000 to <$100,000	17.8 (41)	19.3 (92)	14.2 (69)	
>$100,000	39.6 (91)	52.8 (252)	36.3 (176)	
Specific comorbidities (% yes)				
Heart disease	7.3 (20)	3.0 (16)	7.3 (39)	χ^2 =11.13, p=0.004 0 and 2 > 1
High blood pressure	34.8 (95)	29.5 (156)	28.2 (150)	χ^2 =3.81, p=0.149
Lung disease	10.6 (29)	9.7 (51)	13.4 (71)	χ^2 =3.80, p=0.149

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n=273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n=528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n=531)	Statistics
	% (n)	% (n)	% (n)	
Diabetes	7.7 (21)	9.1 (48)	9.4 (50)	χ^2 =0.69, p=0.710
Ulcer or stomach disease	4.4 (12)	3.8 (20)	6.2 (33)	χ^2 =3.53, p=0.171
Kidney disease	1.8 (5)	1.1 (6)	1.5 (8)	χ^2 =0.66, p=0.719
Liver disease	7.0 (19)	7.6 (40)	5.1 (27)	χ^2 =2.86, p=0.239
Anemia or blood disease	9.5 (26)	11.6 (61)	14.5 (77)	χ^2 =4.60, p=0.100
Depression	6.6 (18)	12.9 (68)	32.2 (171)	χ^2 =99.06, p<0.001 0 < 1 and 2, 1 < 2
Osteoarthritis	9.9 (27)	11.9 (63)	13.2 (70)	χ^2 =1.86, p=0.3960
Back pain	20.9 (57)	19.9 (105)	34.1 (181)	χ^2 =32.18, p<0.001 0 and 1 < 2
Rheumatoid arthritis	2.6 (7)	2.7 (14)	3.8 (20)	χ^2 =1.41, p=0.495
Exercise on a regular basis (% yes)	75.0 (201)	73.4 (383)	66.0 (338)	χ^2 =9.63, p<0.008 0 and 1 > 2
Smoking, current or history of (% yes)	29.7 (80)	34.2 (179)	39.2 (203)	χ^2 =7.34, p=0.025 0 < 2
Cancer diagnosis				χ^2 =29.21, p<0.001
Breast	31.1 (85)	43.4 (229)	42.2 (224)	0 < 1 and 2
Gastrointestinal	43.2 (118)	28.2 (149)	26.0 (138)	0 > 1 and 2
Gynecological	14.7 (40)	16.9 (89)	19.4 (103)	NS
Lung	11.0 (30)	11.6 (61)	12.4 (66)	NS
Type of prior cancer treatment				χ^2 =19.06, p=0.004
No prior treatment	32.8 (86)	23.2 (119)	22.8 (119)	0 > 1 and 2
Only surgery, CTX, or RT	34.7 (91)	45.5 (234)	42.0 (219)	0 < 1
Surgery & CTX, or Surgery & RT, or CTX & RT	22.1 (58)	19.5 (100)	19.2 (100)	NS
Surgery & CTX & RT	10.3 (27)	11.9 (61)	15.9 (83)	NS

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n=273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n=528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n=531)	Statistics
	% (n)	% (n)	% (n)	
Cycle length				χ^2 =5.84, p=0.212
14 day cycle	47.6 (130)	41.7 (219)	39.1 (204)	
21 day cycle	45.8 (125)	50.5 (265)	53.8 (281)	
28 day cycle	6.6 (18)	7.8 (41)	7.1 (37)	
Emetogenicity of the CTX regimen				KW, p=0.758
Minimal/low	19.0 (52)	18.7 (98)	20.7 (108)	
Moderate	64.5 (176)	61.9 (325)	58.3 (305)	
High	16.5 (45)	19.4 (102)	21.0 (110)	
Antiemetic regimen				χ^2 =3.25, p=0.777
None	7.1 (19)	7.0 (36)	7.3 (37)	
Steroid alone or serotonin antagonist alone	21.4 (57)	20.4 (105)	20.2 (103)	
Serotonin antagonist and steroid	50.8 (135)	47.6 (245)	46.2 (235)	
NK-1 receptor antagonist and two other antiemetics	20.7 (55)	25.0 (129)	26.3 (134)	

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, CF = cognitive function, CTX = chemotherapy, kg = kilograms, KW = Kruskal Wallis; m^2 = meter squared, NK = neurokinin, PF = physical function, RT = radiation therapy, SCQ = Self-Administered Comorbidity Questionnaire, SD = standard deviation

+Reference group

Table 3- *Differences in Symptom Severity Scores Among the Cognitive Fatigue and Evening Physical Fatigue Subgroups at Enrollment*

Symptoms*	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n=273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n=528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n=531)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Trait anxiety (≥31.8)	29.1 (7.7)	31.9 (8.0)	41.7 (10.5)	F=223.89, p<0.001 0 < 1 < 2
State anxiety (≥32.2)	27.7 (9.2)	30.7 (10.1)	40.3 (13.0)	F=145.82, p<0.001 0 < 1 < 2
Depressive symptoms (≥16)	7.1 (6.0)	9.8 (7.1)	19.0 (10.2)	F=242.16, p<0.001 0 < 1 < 2
Morning fatigue (≥3.2)	1.4 (1.5)	2.7 (1.9)	4.5 (2.1)	F=256.40, p<0.001 0 < 1 < 2
Evening fatigue (≥5.6)	2.8 (1.7)	5.7 (1.7)	6.2 (1.8)	F=363.56, p<0.001 0 < 1 < 2
Morning energy (≤6.2)	4.9 (2.7)	4.7 (2.2)	3.8 (1.9)	F=33.19, p<0.001 0 and 1 > 2
Evening energy (≤3.5)	4.2 (2.2)	3.6 (2.0)	3.2 (2.0)	F=21.98, p<0.001 0 > 1 > 2
Cognitive function (<5 = low, 5 to 7.5 = moderate, >7.5 = high)	7.9 (1.4)	7.2 (1.2)	4.8 (1.2)	F=708.99, p<0.001 0 > 1 > 2
Sleep disturbance (≥43)	38.2 (16.6)	49.5 (18.2)	63.0 (18.1)	F=178.79, p<0.001 0 < 1 < 2

Symptoms*	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n=273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n=528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n=531)	Statistics
	% (n)	% (n)	% (n)	
Pain type				χ^2 =86.45, p<0.001
No pain	39.8 (107)	29.8 (155)	18.5 (96)	0 > 1 > 2
Only non-cancer pain	20.1 (54)	16.7 (87)	12.7 (66)	0 < 2
Only cancer pain	22.3 (60)	28.8 (150)	25.9 (134)	NS
Both cancer and non-cancer pain	17.8 (48)	24.6 (128)	42.9 (222)	0 and 1 < 2
For patients with pain	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score	5.4 (2.6)	5.8 (2.5)	6.5 (2.4)	F=12.82, p<0.001 0 and 1 < 2
Pain interference score	1.7 (1.8)	2.6 (2.2)	4.0 (2.6)	F=63.79, p<0.001 0 < 1 < 2

*Numbers in parentheses indicate clinically meaningful cutpoints for symptom severity.Abbreviations: PM = evening, SD = standard deviation

***Table 4**- Differences in Quality of Life Outcomes Among the Cognitive Fatigue and Evening Physical Fatigue Subgroups at Enrollment*

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n=273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n=528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n=531)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Medical Outcomes Study – Short Form-12				
Physical functioning	66.2 (33.7)	57.8 (33.7)	39.8 (31.3)	F=66.50, p<0.001 0 > 1 > 2
Role physical	69.7 (27.2)	59.4 (27.3)	36.0 (24.0)	F=177.82, p<0.001 0 > 1 > 2
Bodily pain	87.4 (20.8)	81.6 (24.0)	63.4 (31.4)	F=92.84, p<0.001 0 > 1 > 2
General health	70.8 (23.6)	66.6 (26.9)	54.1 (29.2)	F=42.64, p<0.001 0 and 1 > 2
Vitality	64.5 (22.0)	49.5 (24.5)	31.2 (23.9)	F=185.28, p<0.001 0 > 1 > 2
Social functioning	83.0 (23.7)	73.6 (27.4)	51.8 (30.4)	F=132.60, p<0.001 0 > 1 > 2
Role emotional	86.2 (21.2)	85.0 (21.9)	60.4 (28.3)	F=160.14, p<0.001 0 and 1 > 2
Mental health	82.2 (17.2)	77.3 (16.3)	60.9 (21.7)	F=149.15, p<0.001 0 > 1 > 2
Physical component summary score	45.9 (9.9)	42.8 (10.0)	37.3 (10.1)	F=70.24, p<0.001 0 > 1 > 2
Mental component summary score	54.6 (8.0)	52.2 (8.0)	42.8 (10.8)	F=184.44, p<0.001 0 > 1 > 2
Multidimensional Quality of Life Scale – Cancer				
Physical well-being	7.9 (1.5)	6.9 (1.6)	5.7 (1.7)	F=195.89, p<0.001 0 > 1 > 2
Psychological well-being	6.8 (1.7)	5.8 (1.6)	4.5 (1.6)	F=196.06, p<0.001 0 > 1 > 2

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n=273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n=528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n=531)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Multidimensional Quality of Life Scale – Cancer				
Social well-being	7.1 (1.8)	6.0 (1.8)	4.7 (1.8)	F=162.30, p<0.001 0 > 1> 2
Spiritual well-being	5.8 (2.2)	5.4 (2.1)	5.3 (2.0)	F=4.74, p=0.009 0 > 2
Total quality of life score	6.9 (1.2)	6.0 (1.2)	4.9 (1.3)	F=249.38, p<0.001 0 > 1 > 2

Abbreviations: CF = cognitive function, PF = physical function, SD = standard deviation

Table 5*- Characteristics Associated with Membership in the Moderate and High Cognitive Fatigue and Evening Physical Fatigue Groups*

Characteristic[a]	Moderate cognitive fatigue and moderate evening physical fatigue	High cognitive fatigue and high evening physical fatigue
Demographic Characteristics		
Younger age	■	■
Higher education	■	
More likely to be female	■	■
More likely to be White	■	■
Less likely to be Black	■	■
Less likely to be married/partnered		■
More likely to live alone		■
More likely to have child care responsibilities		■
Less likely to be employed		■
More likely to have a higher annual income	■	
Less likely to exercise on a regular basis		■
More likely to have a past or current history of smoking		■
Clinical Characteristics		
Lower functional status	■	■
Higher number of comorbidities		■
Higher comorbidity burden	■	■
Higher number of cancer treatments		■
Higher MAX2 score		■
Less likely to self-report heart disease	■	
More likely to self-report depression	■	■
More likely to self-report back pain		■
More likely to have breast cancer	■	■
Less likely to have gastrointestinal cancer	■	■
More likely to have had prior cancer treatments	■	■

Symptom Characteristics	Moderate cognitive fatigue and moderate evening physical fatigue	High cognitive fatigue and high evening physical fatigue
Higher trait anxiety	■	■
Higher state anxiety	■	■
Higher depressive symptoms	■	■
Higher morning physical fatigue	■	■
Higher evening physical fatigue	■	■
Lower morning energy		■
Lower evening energy	■	■
Higher cognitive fatigue	■	■
Higher sleep disturbance	■	■
Lower occurrence rate of no pain	■	■
Higher occurrence rate of both cancer and noncancer pain		■
Higher worst pain intensity		■
Higher pain interference	■	■

[a]Comparisons done with the low cognitive fatigue and low evening physical fatigue group

REFERENCES

1. Abrahams HJG, Gielissen MFM, Verhagen C, Knoop H (2018) The relationship of fatigue in breast cancer survivors with quality of life and factors to address in psychological interventions: A systematic review Clin Psychol Rev 63: 1-11
2. Adams RN, Mosher CE, Winger JG, Abonour R, Kroenke K (2018) Cancer-related loneliness mediates the relationships between social constraints and symptoms among cancer patients J Behav Med 41: 243-252
3. Al Maqbali M, Al Sinani M, Al Naamani Z, Al Badi K, Tanash MI (2021) Prevalence of fatigue in patients with cancer: A systematic review and meta-analysis J Pain Symptom Manage 61: 167-189 e114
4. Atallah M, Cooper B, Munoz RF, Paul SM, Anguera J, Levine JD, Hammer M, Wright F, Chen LM, Melisko M, Conley YP, Miaskowski C, Dunn LB (2020) Psychological symptoms and stress are associated with decrements in attentional function in cancer patients undergoing chemotherapy Cancer Nurs 43: 402-410
5. Babor TF, de la Fuente JR, Saunders J, Grant M (1992) AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. In: The Alchohol Use Disorders Identification Test: Guidelines for Use in Primary Care. World Health Organization, Geneva, Switzerland
6. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG (2001) AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. World Health Organization, Geneva, Switzerland
7. Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, Cleeland C, Dotan E, Eisenberger MA, Escalante CP, Jacobsen PB, Jankowski C, LeBlanc T, Ligibel JA, Loggers ET, Mandrell B, Murphy BA, Palesh O, Pirl WF, Plaxe SC, Riba MB, Rugo HS, Salvador C, Wagner LI, Wagner-Johnston ND, Zachariah FJ, Bergman

MA, Smith C, National comprehensive cancer n (2015) Cancer-Related Fatigue, Version 2.2015 J Natl Compr Canc Netw 13: 1012-1039

8. Bower JE (2019) The role of neuro-immune interactions in cancer-related fatigue: Biobehavioral risk factors and mechanisms Cancer 125: 353-364

9. Brunner F, Bachmann LM, Weber U, Kessels AG, Perez RS, Marinus J, Kissling R (2008) Complex regional pain syndrome 1--the Swiss cohort study BMC Musculoskelet Disord 9: 92

10. Cella D, Lai JS, Chang CH, Peterman A, Slavin M (2002) Fatigue in cancer patients compared with fatigue in the general United States population Cancer 94: 528-538

11. Cieza A, Geyh S, Chatterji S, Kostanjsek N, Ustun BT, Stucki G (2006) Identification of candidate categories of the International Classification of Functioning Disability and Health (ICF) for a Generic ICF Core Set based on regression modelling BMC Med Res Methodol 6: 36

12. Cimprich B, So H, Ronis DL, Trask C (2005) Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer Psychooncology 14: 70-78

13. Cimprich B, Visovatti M, Ronis DL (2011) The Attentional Function Index--a self-report cognitive measure Psychooncology 20: 194-202

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

15. de Jong N, Candel MJ, Schouten HC, Abu-Saad HH, Courtens AM (2004) Prevalence and course of fatigue in breast cancer patients receiving adjuvant chemotherapy Ann Oncol 15: 896-905

16. de Jong N, Candel MJ, Schouten HC, Abu-Saad HH, Courtens AM (2005) Course of mental fatigue and motivation in breast cancer patients receiving adjuvant chemotherapy Ann Oncol 16: 372-382

17. de Jong N, Kester AD, Schouten HC, Abu-Saad HH, Courtens AM (2006) Course of fatigue between two cycles of adjuvant chemotherapy in breast cancer patients Cancer Nurs 29: 467-477
18. de Raaf PJ, de Klerk C, van der Rijt CC (2013) Elucidating the behavior of physical fatigue and mental fatigue in cancer patients: a review of the literature Psychooncology 22: 1919-1929
19. Dew IT, Buchler N, Dobbins IG, Cabeza R (2012) Where is ELSA? The early to late shift in aging Cereb Cortex 22: 2542-2553
20. Dimsdale JE, Ancoli-Israel S, Ayalon L, Elsmore TF, Gruen W (2007) Taking fatigue seriously, II: variability in fatigue levels in cancer patients Psychosomatics 48: 247-252
21. Dupont A, Bower JE, Stanton AL, Ganz PA (2014) Cancer-related intrusive thoughts predict behavioral symptoms following breast cancer treatment Health Psychol 33: 155-163
22. Fletcher BS, Paul SM, Dodd MJ, Schumacher K, West C, Cooper B, Lee K, Aouizerat B, Swift P, Wara W, Miaskowski CA (2008) Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer J Clin Oncol 26: 599-605
23. Groenvold M, Petersen MA, Idler E, Bjorner JB, Fayers PM, Mouridsen HT (2007) Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients Breast Cancer Res Treat 105: 209-219
24. Gupta D, Lis CG, Grutsch JF (2007) The relationship between cancer-related fatigue and patient satisfaction with quality of life in cancer J Pain Symptom Manage 34: 40-47

25. Hamidou Z, Dabakuyo TS, Bonnetain F (2011) Impact of response shift on longitudinal quality-of-life assessment in cancer clinical trials Expert Rev Pharmacoecon Outcomes Res 11: 549-559
26. Han TJ, Felger JC, Lee A, Mister D, Miller AH, Torres MA (2016) Association of childhood trauma with fatigue, depression, stress, and inflammation in breast cancer patients undergoing radiotherapy Psychooncology 25: 187-193
27. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D (2008) Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S Support Care Cancer 16: 791-801
28. Huehnchen P, van Kampen A, Boehmerle W, Endres M (2020) Cognitive impairment after cytotoxic chemotherapy Neurooncol Pract 7: 11-21
29. Hughes A, Suleman S, Rimes KA, Marsden J, Chalder T (2020) Cancer-related fatigue and functional impairment - Towards an understanding of cognitive and behavioural factors J Psychosom Res 134: 110127
30. Institute. of. Medicine. (2012) Living Well with Chronic Illness: A Call for Public Health Sction. In: Living Well with Chronic Illness: A Call for Public Health Sction. The National Academies Press, Washington, DC
31. Jacobs JM, Ream ME, Pensak N, Nisotel LE, Fishbein JN, MacDonald JJ, Buzaglo J, Lennes IT, Safren SA, Pirl WF, Temel JS, Greer JA (2019) Patient experiences with oral chemotherapy: adherence, symptoms, and quality of life J Natl Compr Canc Netw 17: 221-228
32. Jung JY, Lee JM, Kim MS, Shim YM, Zo JI, Yun YH (2018) Comparison of fatigue, depression, and anxiety as factors affecting posttreatment health-related quality of life in lung cancer survivors Psychooncology 27: 465-470
33. Jung T, Wickrama KAS (2008) An introduction to latent class growth analysis and growth mixture modeling Soc Personal Psychol Compass 2: 302-317

34. Karnofsky D (1977) Performance scale. Plenum Press, New York

35. Karnofsky D, Abelmann WH, Craver LV, Burchenal JH (1948) The use of nitrogen mustards in the palliative treatment of carcinoma Cancer 1: 634-656

36. Kim HJ, Barsevick AM, Fang CY, Miaskowski C (2012) Common biological pathways underlying the psychoneurological symptom cluster in cancer patients Cancer Nurs 35: E1-E20

37. Kuhlman KR, Chiang JJ, Horn S, Bower JE (2017) Developmental psychoneuroendocrine and psychoneuroimmune pathways from childhood adversity to disease Neurosci Biobehav Rev 80: 166-184

38. Lange M, Joly F, Vardy J, Ahles T, Dubois M, Tron L, Winocur G, De Ruiter MB, Castel H (2019) Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors Ann Oncol 30: 1925-1940

39. Lee EE, Depp C, Palmer BW, Glorioso D, Daly R, Liu J, Tu XM, Kim HC, Tarr P, Yamada Y, Jeste DV (2019) High prevalence and adverse health effects of loneliness in community-dwelling adults across the lifespan: role of wisdom as a protective factor Int Psychogeriatr 31: 1447-1462

40. Lee KA (1992) Self-reported sleep disturbances in employed women Sleep 15: 493-498

41. Lee KA, Hicks G, Nino-Murcia G (1991) Validity and reliability of a scale to assess fatigue Psychiatry Res 36: 291-298

42. Liu L, Fiorentino L, Natarajan L, Parker BA, Mills PJ, Sadler GR, Dimsdale JE, Rissling M, He F, Ancoli-Israel S (2009) Pre-treatment symptom cluster in breast cancer patients is associated with worse sleep, fatigue and depression during chemotherapy Psychooncology 18: 187-194

43. Matura LA, Malone S, Jaime-Lara R, Riegel B (2018) A systematic review of biological mechanisms of fatigue in chronic illness Biol Res Nurs 20: 410-421

44. Miaskowski C, Cooper BA, Aouizerat B, Melisko M, Chen LM, Dunn L, Hu X, Kober KM, Mastick J, Levine JD, Hammer M, Wright F, Harris J, Armes J, Furlong E, Fox P, Ream E, Maguire R, Kearney N (2017) The symptom phenotype of oncology outpatients remains relatively stable from prior to through 1 week following chemotherapy Eur J Cancer Care (Engl) 26
45. Miaskowski C, Cooper BA, Melisko M, Chen LM, Mastick J, West C, Paul SM, Dunn LB, Schmidt BL, Hammer M, Cartwright F, Wright F, Langford DJ, Lee K, Aouizerat BE (2014) Disease and treatment characteristics do not predict symptom occurrence profiles in oncology outpatients receiving chemotherapy Cancer 120: 2371-2378
46. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, Leach CR, Mohr D, Palesh OG, Peppone LJ, Piper BF, Scarpato J, Smith T, Sprod LK, Miller SM (2017) Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: A meta-analysis JAMA Oncol 3: 961-968
47. Muthen LK, Muthen BO (1998-2020) Mplus User's Guide (8th ed.). Muthen & Muthen, Los Angeles, CA
48. Nguyen TT, Lee EE, Daly RE, Wu TC, Tang Y, Tu X, Van Patten R, Jeste DV, Palmer BW (2020) Predictors of loneliness by age decade: Study of psychological and environmental factors in 2,843 community-dwelling Americans aged 20-69 years J Clin Psychiatry 81
49. Padilla GV, Ferrell B, Grant MM, Rhiner M (1990) Defining the content domain of quality of life for cancer patients with pain Cancer Nurs 13: 108-115
50. Padilla GV, Presant C, Grant MM, Metter G, Lipsett J, Heide F (1983) Quality of life index for patients with cancer Res Nurs Health 6: 117-126
51. Pertl MM, Hevey D, Collier S, Lambe K, O'Dwyer AM (2014) Predictors of fatigue in cancer patients before and after chemotherapy J Health Psychol 19: 699-710

52. Puigpinos-Riera R, Serral G, Sala M, Bargallo X, Quintana MJ, Espinosa M, Manzanera R, Domenech M, Macia F, Grau J, Vidal E (2020) Cancer-related fatigue and its determinants in a cohort of women with breast cancer: the DAMA Cohort Support Care Cancer 28: 5213-5221

53. Quinten C, Maringwa J, Gotay CC, Martinelli F, Coens C, Reeve BB, Flechtner H, Greimel E, King M, Osoba D, Cleeland C, Ringash J, Schmucker-Von Koch J, Taphoorn MJ, Weis J, Bottomley A (2011) Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival J Natl Cancer Inst 103: 1851-1858

54. Radbruch L, Strasser F, Elsner F, Goncalves JF, Loge J, Kaasa S, Nauck F, Stone P, Research Steering Committee of the European Association for Palliative C (2008) Fatigue in palliative care patients -- an EAPC approach Palliat Med 22: 13-32

55. Radloff LS (1977) The CES-D Scale: A self-report depression scale for research in the general population Applied Psychological Measurement 1: 385-401

56. Rau KM, Shun SC, Chiou TJ, Lu CH, Ko WH, Lee MY, Huang WT, Yeh KH, Chang CS, Hsieh RK (2020) A nationwide survey of fatigue in cancer patients in Taiwan: an unmet need Jpn J Clin Oncol 50: 693-700

57. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN (2003) The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research Arthritis Rheum 49: 156-163

58. Schmidt ME, Hermann S, Arndt V, Steindorf K (2020) Prevalence and severity of long-term physical, emotional, and cognitive fatigue across 15 different cancer entities Cancer Med 9: 8053-8061

59. Schmidt ME, Wiskemann J, Schneeweiss A, Potthoff K, Ulrich CM, Steindorf K (2018) Determinants of physical, affective, and cognitive fatigue during breast cancer therapy and 12 months follow-up Int J Cancer 142: 1148-1157

60. Singer S, Kuhnt S, Zwerenz R, Eckert K, Hofmeister D, Dietz A, Giesinger J, Hauss J, Papsdorf K, Briest S, Brown A (2011) Age- and sex-standardised prevalence rates of fatigue in a large hospital-based sample of cancer patients Br J Cancer 105: 445-451
61. Smets EM, Garssen B, Bonke B, De Haes JC (1995) The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue J Psychosom Res 39: 315-325
62. Spielberger CG, Gorsuch RL, Suchene R, Vagg PR, Jacobs GA (1983) Manual for the State-Anxiety (Form Y): Self Evaluation Questionnaire. Consulting Psychologists Press, Palo Alto, CA
63. Stein KD, Martin SC, Hann DM, Jacobsen PB (1998) A multidimensional measure of fatigue for use with cancer patients Cancer Pract 6: 143-152
64. Thong MSY, Mols F, van de Poll-Franse LV, Sprangers MAG, van der Rijt CCD, Barsevick AM, Knoop H, Husson O (2018) Identifying the subtypes of cancer-related fatigue: results from the population-based PROFILES registry J Cancer Surviv 12: 38-46
65. Tsaras K, Papathanasiou IV, Mitsi D, Veneti A, Kelesi M, Zyga S, Fradelos EC (2018) Assessment of depression and anxiety in breast cancer patients: Prevalence and associated factors Asian Pac J Cancer Prev 19: 1661-1669
66. Ware J, Jr., Kosinski M, Keller SD (1996) A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity Med Care 34: 220-233
67. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, Falandry C, Artz A, Brain E, Colloca G, Flamaing J, Karnakis T, Kenis C, Audisio RA, Mohile S, Repetto L, Van Leeuwen B, Milisen K, Hurria A (2014) International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer J Clin Oncol 32: 2595-2603

68. Williams AM, Khan CP, Heckler CE, Barton DL, Ontko M, Geer J, Kleckner AS, Dakhil S, Mitchell J, Mustian KM, Peppone LJ, Kipnis V, Kamen CS, O'Mara AM, Janelsins MC (2021) Fatigue, anxiety, and quality of life in breast cancer patients compared to non-cancer controls: a nationwide longitudinal analysis Breast Cancer Res Treat
69. Witek Janusek L, Tell D, Albuquerque K, Mathews HL (2013) Childhood adversity increases vulnerability for behavioral symptoms and immune dysregulation in women with breast cancer Brain Behav Immun 30 Suppl: S149-162
70. Wright F, Cooper BA, Conley YP, Hammer MJ, Chen LM, Paul SM, Levine JD, Miaskowski C, Kober KM (2017) Distinct evening fatigue profiles in oncology outpatients receiving chemotherapy Fatigue : Biomed Health Behav 5: 131-144
71. Wright F, D'Eramo Melkus G, Hammer M, Schmidt BL, Knobf MT, Paul SM, Cartwright F, Mastick J, Cooper BA, Chen LM, Melisko M, Levine JD, Kober K, Aouizerat BE, Miaskowski C (2015) Predictors and trajectories of morning fatigue are distinct from evening fatigue J Pain Symptom Manage 50: 176-189
72. Wright F, D'Eramo Melkus G, Hammer M, Schmidt BL, Knobf MT, Paul SM, Cartwright F, Mastick J, Cooper BA, Chen LM, Melisko M, Levine JD, Kober K, Aouizerat BE, Miaskowski C (2015) Trajectories of evening fatigue in oncology outpatients receiving chemotherapy J Pain Symptom Manage 50: 163-175
73. Wright F, Dunn LB, Paul SM, Conley YP, Levine JD, Hammer MJ, Cooper BA, Miaskowski C, Kober KM (2019) Morning fatigue severity profiles in oncology outpatients receiving chemotherapy Cancer Nurs 42: 355-364
74. Wright F, Hammer M, Paul SM, Aouizerat BE, Kober KM, Conley YP, Cooper BA, Dunn LB, Levine JD, G DEM, Miaskowski C (2017) Inflammatory pathway genes associated with inter-individual variability in the trajectories of morning and evening fatigue in patients receiving chemotherapy Cytokine 91: 187-210

75. Wright F, Hammer MJ, D'Eramo Melkus G (2014) Associations between multiple chronic conditions and cancer-related fatigue: an integrative review Oncol Nurs Forum 41: 399-410

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