Title

Higher Stress in Oncology Patients is Associated With Cognitive and Evening Physical Fatigue Severity

Journal

Journal of Pain and Symptom Management, 65(3)

ISSN

0885-3924

Authors

Morse, Lisa
Paul, Steven M
Cooper, Bruce A
et al.

Publication Date

2023-03-01

DOI

10.1016/j.jpainsymman.2022.11.017

Peer reviewed

HHS Public Access

Author manuscript

J Pain Symptom Manage. Author manuscript; available in PMC 2024 June 20.

Published in final edited form as:

J Pain Symptom Manage. 2023 March ; 65(3): 203–215. doi:10.1016/j.jpainsymman.2022.11.017.

Higher Stress in Oncology Patients is Associated With Cognitive and Evening Physical Fatigue Severity

Lisa Morse, RN, MS,
School of Nursing, University of California, San Francisco, California

Steven M. Paul, PhD,
School of Nursing, University of California, San Francisco, California

Bruce A. Cooper, PhD,
School of Nursing, University of California, San Francisco, California

Kate Oppegaard, RN, MS,
School of Nursing, University of California, San Francisco, California

Joosun Shin, RN, MS,
School of Nursing, University of California, San Francisco, California

Alejandra Calvo-Schimmel, RN, PhD,
School of Nursing, University of California, San Francisco, California

Carolyn Harris, RN, PhD,
School of Nursing, University of Pittsburgh, Pittsburgh, Pennsylvania

Marilyn Hammer, RN, PhD,
Dana Farber Cancer Institute, Boston, Massachusetts

Yvette Conley, PhD,
School of Nursing, University of Pittsburgh, Pittsburgh, Pennsylvania

Fay Wright, RN, PhD,
Rory Meyers College of Nursing, New York University, New York, New York

Jon D. Levine, MD, PhD,
School of Medicine, University of California, San Francisco, California, USA

Kord M. Kober, PhD,
School of Nursing, University of California, San Francisco, California

Christine Miaskowski, RN, PhD
School of Nursing, University of California, San Francisco, California

School of Medicine, University of California, San Francisco, California, USA

Address correspondence to: Christine Miaskowski, RN, PhD, Department of Physiological Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143, USA. chris.miaskowski@ucsf.edu.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jpainsymman.2022.11.017.

Abstract

Context.—Cognitive and physical fatigue are common symptoms experienced by oncology patients. Exposure to stressful life events (SLE), cancer-related stressors, coping styles, and levels of resilience may influence the severity of both dimensions of fatigue.

Objectives.—Evaluate for differences in global, cancer-specific, and cumulative life stress, as well as resilience and coping in oncology patients (n=1332) with distinct cognitive fatigue AND evening physical fatigue profiles.

Methods.—Latent profile analysis, which combined the two symptom scores, identified three subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles (i.e., Low, Moderate, High). Patients completed measures of global, cancer-specific, and cumulative life stress as well measures of resilience and coping. Differences among the latent classes in the various measures were evaluated using parametric and nonparametric tests.

Results.—Compared to Low class, the other two classes reported higher global and cancer-specific stress. In addition, they reported higher occurrence rates for sexual harassment and being forced to touch prior to 16 years of age. Compared to the other two classes, High class reported lower resilience scores and higher use of denial, substance use, and behavioral disengagement.

Conclusion.—To decrease both cognitive and evening physical fatigue, clinicians need to assess for relevant stressors and initiate interventions to increase resilience and the use of engagement coping strategies. Additional research is warranted on the relative contribution of various social determinants of health to both cognitive and physical fatigue in oncology patients receiving chemotherapy.

Keywords

Cancer; chemotherapy; cognitive impairment; coping; fatigue; resilience; stress

Introduction

As noted in the National Comprehensive Cancer Network Guidelines,[1] fatigue is a multidimensional symptom that includes cognitive and physical dimensions and is influenced by a variety of risk factors. However, while no consistency exists in the definitions of or instruments used to assess physical and cognitive fatigue, based on the findings from a systematic review,[2] de Raaf and colleagues concluded that cognitive fatigue and physical fatigue are separate phenomenon that warrant evaluation.

It should be noted that similar to other chronic conditions (e.g., cardiac disease,[3] multiple sclerosis,[4–6] chronic fatigue syndrome[7–11]), stress associated with cancer and its treatments, including premorbid exposure to stressful life events (SLEs) and adverse childhood experiences (ACEs), may predispose patients to higher levels of fatigue.[12] This hypothesis is supported by a growing body of evidence that suggests that fatigue and stress are linked through bidirectional neuroinflammatory pathways that are mediated by the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis.[13] The experiences of acute and chronic stress, that exceed an individual's ability to adapt, results in increases in allostatic overload and associated increases in fatigue severity.[14–23] Equally

important, the occurrence of traumatic ACEs is associated with increases in allostatic load in adulthood and exaggerated physiologic responses to environmental challenges (e.g., cancer diagnosis, receipt of chemotherapy).[24–34]

Previous work by our group[35–38] and others[36–39] demonstrated that physical fatigue exhibits diurnal variability, This finding is supported by the fact that common and distinct phenotypic[40–43] and molecular[44–49] risk factors were identified for morning and evening physical fatigue. In addition, to support the question addressed in this paper, when morning physical fatigue and evening physical fatigue were evaluated as single symptoms using latent profile analysis (LPA),[50] patients with very high levels of morning physical fatigue or very high levels of evening physical fatigue reported higher levels of global stress and a higher number and greater impact from a variety of SLEs. In other studies that examined the links between fatigue and stress in patients undergoing chemotherapy,[51–57] higher levels of perceived stress were associated with greater average fatigue severity. However, the majority of these studies were cross-sectional; assessed average fatigue; evaluated only women with breast cancer; examined only one type of stress; and did not evaluate the impact of specific SLEs and ACEs on fatigue severity.

The cognitive and behavioral processes that individuals employ to respond and adapt to global stress, cancer-specific stress, ACEs, and other SLEs may influence inter-individual variability in both cognitive and physical fatigue severity. Lazarus and Folkman[58] describe coping as a person's cognitive and behavioral efforts to manage or adapt and respond to their environment. Coping styles are often categorized as engagement (e.g., positive reframing, seeking support) and disengagement (e.g., avoidance, denial) behaviors.[59] Engagement strategies use more direct approaches to deal with or reduce stress and are typically associated with more adaptive responses. Disengagement strategies tend to be viewed as more avoidant and maladaptive.[60] In studies that examined the mediating effect of coping in relationship to fatigue severity, while disengagement strategies were associated with higher fatigue scores,[61,62] engagement strategies were associated with lower levels of fatigue.[63,64]

Resilience is a psychological construct that provides resistance to distress.[65,66] Resilience is considered a dynamic mechanism that changes over time and can be influenced by life circumstances and one's environment.[67] Several studies found links among patients' level of resilience, fatigue, distress, and coping.[65,68,69] However, the majority of these studies evaluated only patients with breast cancer and none examined these associations in oncology patients undergoing chemotherapy.

As noted above, given that fatigue encompasses both cognitive and physical dimensions and that these dimensions are separate phenomenon, it is reasonable to model these two symptoms together; identify subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles; and evaluate for risk factors associated with the worst profiles. Therefore, in our previous study,[70] cognitive fatigue AND evening physical fatigue were modeled in a single joint LPA. Using clinically meaningful cutoff scores for the Attentional Function Index (i.e., cognitive fatigue)[71] and the Lee Fatigue Scale (i.e., evening physical fatigue),[72] three classes of patients with distinct cognitive AND evening physical fatigue profiles were identified (i.e., Low, Moderate, and High; Supplementary Fig. 1).

Given the paucity of research on the relationships between co-occurring cognitive and physical fatigue and stress, as well as their associations with coping and resilience, in this study of patients undergoing chemotherapy, we extend the findings from our previous report[70] and evaluated for differences in global, cancer-specific, and cumulative life stress, as well as resilience and coping among the three subgroups of patients with distinct cognitive and evening physical fatigue profiles. In addition, given the emerging evidence on the impact of SLEs and ACEs on fatigue in other chronic conditions,[73] differences in the occurrence rates and effects of SLEs among these fatigue classes were evaluated. Equally important, because it is challenging to interpret the results of three symptoms in a longitudinal LPA, evening physical fatigue was chosen for this analysis given its higher severity. Subsequent analyses will be done with co-occurring cognitive fatigue and morning physical fatigue.

Methods

Patients and Settings

This longitudinal study is described in detail elsewhere.[74] 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.—Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale,[75] Alcohol Use Disorders Identification Test (AUDIT),[76] and Self-Administered Comorbidity Questionnaire (SCQ). The SCQ evaluates the occurrence, treatments for, and impact of 13 common medical conditions.[77] The MAX-2 score was used to evaluate the toxicity of various chemotherapy regimens.[78]

Cognitive Fatigue and Evening Physical Fatigue Measures.—Cognitive fatigue was assessed using the Attentional Function Index (AFI) that evaluates an individual's perceived effectiveness in performing daily activities that are supported by attention and working memory.[71]

Physical fatigue was assessed using Lee Fatigue Scale (LFS).[72] Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the five energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Using separate questionnaires, patients rated 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).

Stress, Resilience, and Coping Measures.—The 14-item Perceived Stress Scale (PSS) was used as a measure of global perceived stress according to the degree that life circumstances are appraised as stressful over the course of the previous week.[79] Total PSS scores can range from 0 to 56. Its Cronbach's alpha was 0.89.

The 22-item Impact of Event Scale-Revised (IES-R) was used to measure cancer-related distress.[80,81] Patients rated each item based on how distressing each potential difficulty was for them during the past week "with respect to their cancer and its treatment." Three subscales evaluate levels of intrusion, avoidance, and hyperarousal perceived by the patient. The total score can range from 0 to 88. Sum scores of ≥24 indicate clinically meaningful post-traumatic symptomatology and scores of ≥33 indicate probable post-traumatic stress disorder (PTSD).[82] Cronbach's alpha for the IES-R total score was 0.92.

The 30-item Life Stressor Checklist-Revised (LSC-R) is an index of lifetime trauma exposure.[83] The total LSC–R score is obtained by summing the total number of events endorsed (range of 0 to 30). If the patient endorsed an event, the patient was asked to indicate how much that stressor affected their life in the past year, from one (not at all) to five (extremely). These responses were summed to yield a total "affected" sum score. PTSD sum score was created based on the number of positively endorsed items (out of 21) that reflect the DSM-IV PTSD Criteria A for having experienced a traumatic event.

The 10-item Connor-Davidson Resilience Scale (CDRS) evaluates a patient's personal ability to handle adversity (e.g., "I am able to adapt when changes occur").[84,85] Total scores range from 0 to 40, with higher scores indicative of higher self-perceived resilience. The normative adult mean score in the U.S. is 31.8 (standard deviation [SD], 5.4),[85,86] with an estimated minimal clinically important difference of 2.7.[87] Its Cronbach's alpha was 0.90.

The 28-item Brief COPE was used to assess patients' use of 14 coping strategies.[88] Use of each coping strategy was evaluated using two items and scores can range from two to eight, with higher scores indicating greater use of each strategy. Engagement coping strategies and their associated Cronbach's alphas include active coping (0.75), planning (0.74), positive reframing (0.79), acceptance (0.68), humor (0.83), religion (0.92), emotional support (0.77), and instrumental support (0.77). Disengagement coping strategies and their associated Cronbach's alphas include self-distraction (0.46), denial (0.72), venting (0.65), substance use (0.87), behavioral disengagement (0.57), and self-blame (0.73).

Study Procedures

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. Written informed consent was obtained from all patients. Patients completed questionnaires in their homes, a total of six times over two cycles of chemotherapy (i.e., in the week prior to chemotherapy administration (assessments one and four), one week after chemotherapy administration (assessments two and five) and two weeks after chemotherapy administration (assessments three and six). Medical records were reviewed for disease and treatment information.

Data Analysis

LPA was used to identify subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles, using Mplus version 8.4.[89] 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. Details of this procedure are described in our previous publication.[70] Additional data were analyzed using *SPSS* version 28 (IBM Corporation, Armonk, NY). Differences among the cognitive fatigue AND evening physical fatigue classes in stress, resilience, and coping were evaluated using parametric and nonparametric tests. Bonferroni corrected *P*-value of <0.017 was considered statistically significant for the pair-wise contrasts.

Results

Latent Class Solution

As noted in our previous publication,[70] three-class solution was selected as the best model fit. Cognitive fatigue AND evening physical fatigue classes were labeled as Low cognitive fatigue and Low evening physical fatigue (i.e., Low, 20.5%), Moderate cognitive fatigue and Moderate evening physical fatigue (i.e., Moderate, 39.6%), and High cognitive fatigue and high evening physical fatigue (i.e., High, 39.9%) based on clinically meaningful cut-off scores for the AFI and the LFS (Supplemental Fig. 1).

Demographic and Clinical Characteristics

As noted previously,[70] significant differences were found among the latent classes for many of the demographic and clinical characteristics (see Supplemental Table 1). In brief, compared to Low class, 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, High class was 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 Low class, High class was 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 other two classes, 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).

Stress and Resilience Characteristics

For the PSS, IES-R total, the IES-R intrusion and hyperarousal subscales, the LSC-R affected sum and PTSD sum, the scores followed the same pattern (i.e.,

Low<Moderate<High). Compared to Low and Moderate classes, High class reported higher IES-R avoidance subscale and LSC-R total scores and lower CDRS scores (Table 1).

Occurrence of Life Stressors

Compared to Low and Moderate classes, High class reported higher occurrence rates for family violence in childhood, emotional abuse, physical neglect, physical abuse before and after age of 16, being forced to touch ≥16 years of age, jail of a family member, serious money problems, and serious physical or mental illness other than cancer (Table 2). In terms of sexual harassment, the rates of occurrence followed the expected pattern (i.e., Low<Moderate<High). Compared to Moderate class, High class experienced higher rates of forced to touch before the age of 16. Compared to Low class, High class experienced higher rates of jail and forced sex at the age of 16 or older.

Effects of Various Stressors

Compared to Moderate class, High class reported higher effect scores for family violence in childhood and parental separation or divorce. Compared to Low class, High class reported higher scores related to physical abuse and forced to touch before the age of 16, having a serious physical or mental illness other than cancer, caring for someone with severe physical or mental handicap, and sudden death of someone close. Compared to Low and Moderate classes, High class reported higher effect scores related to separation or divorce (self) or death of someone close (not sudden) (Table 3).

Coping Strategies

For engagement coping strategies, compared to Low and Moderate classes, High class reported lower scores for active coping and acceptance. Compared to Low class, Moderate class reported higher scores for planning and humor. Compared to Low class, other two classes reported higher scores for the use of instrumental support.

For the disengagement coping strategies, compared to Low class, other two classes reported higher use of self-distraction. Compared to Low and Moderate classes, High class reported higher use of denial, substance use, and behavioral disengagement. For venting and self blame the scores followed the same pattern (i.e., Low<Moderate<High; Table 4).

Discussion

This study extends our previous work that identified three latent classes of patients with distinct cognitive fatigue AND evening physical fatigue severity profiles[70] to include associations with global, cancer-specific, and cumulative life stress, as well as coping and resilience. While our previous study found associations between higher levels of morning and evening physical fatigue severity (when they were evaluated as single symptoms) and stress in a sample of patients with heterogeneous types of cancer,[50] the current study is the first to evaluate both the occurrence and effects of SLEs associated with the severity of cognitive fatigue AND evening fatigue severity when both symptoms were modeled together.

Stress Measures

In terms of overall scores across the three stress measures (Table 1), the severity of global and cancer-specific stress, as well as the affected sum and PTSD sum scores, increased as the profiles of cognitive fatigue and evening physical fatigue worsened. One plausible explanation for this finding is that the cumulative effects of the various types of stress exceeded the patients' ability to adapt to demands with a resultant increase in allostatic overload. The clinical criteria for allostatic overload include the presence of generalized anxiety and low energy; significant impairments in social and/or occupational functioning; and the presence of a current identifiable source of distress.[14] This hypothesis is supported by the findings from our previous study that identified that the severity of state and trait anxiety, as well as decrements in evening energy, role functioning, and social functioning were significantly different among our three latent classes.[70]

Compared to Low class, High class reported higher occurrence rates for a number of ACEs including: family violence in childhood (31.2%), physical abuse (21%), and forced touching (17%) and forced sex (6.2%) at or before the age of 16 (Table 2). These findings highlight the importance of screening oncology patients for childhood maltreatment and previous stressful life events to develop individualized treatment plans that address past traumatic experiences. The Pediatric ACEs and Related Life Events Screener (PEARLS) can be used with adults and includes questions about bullying, discrimination, and food insecurity.[90] Additional research is needed to better understand the underlying mechanisms that link these ACEs with a higher symptom burden in adults undergoing chemotherapy.

While the IES-R total score for the High class (i.e., 24.2) meets the clinical criterion for subsyndromal PTSD,[82] 23.4% of the patients in this class had scores of ≥33. In addition, this class had the highest score for the PTSD subscale of the LSC-R and reported an average of four (range of 0 to 18) of the 21 stressors included in this subscale. These finding are consistent with previous reports that found positive associations with cognitive impairment[91,92] or fatigue[93,94] and PTSD in oncology patients.

Fatigue is a common symptom in individuals with inflammatory and autoimmune conditions as well as in individuals with psychiatric disorders provoked by stress.[4,6,10,95,96] These illnesses are characterized by an underlying inflammatory state that leads to changes in brain signaling that provoke fatigue. Changes in behavior (e.g., weakness, malaise, listlessness, hypersomnia, depressed activity) precipitated by proinflammatory cytokines is often referred to as "sickness behavior".[97] Given that both cancer and its treatments contribute to increased levels of systemic neuroinflammation, it is not unexpected that the burden of multiple types of stress is associated with higher levels of both cognitive and physical fatigue.

Coping

In our study, the High class reported the highest use of the majority of the disengagement coping strategies (Table 5). Given that, in a previous study, individuals who experienced four or more categories of significant childhood maltreatment have higher rates of alcohol and substance use disorders,[98] this relationship warrants evaluation in oncology patients. Future studies need to evaluate the socio-cultural contexts that influence coping styles including

associations with SLEs, ACE's, and other social determinants of health. For example, individuals with less education and lower income were more likely to use "maladaptive" coping strategies.[99] In addition, hypervigilant behaviors and the use of avoidance coping may be critical ways that individuals survive and adapt to harsh environments.[100]

It is interesting to note that while self-distraction is categorized as a disengagement or "maladaptive coping strategy,[60] compared to the other two classes, Low class reported significantly higher use of this behavior. Evidence suggests that in the face of extreme stress, individuals may gravitate towards "maladaptive" coping strategies because they provide immediate relief and are easily accessible despite socioeconomic factors or the availability of resources.[100] Our findings on the use of self-distraction are consistent with the results of a randomized controlled trial that found that patients with advanced cancer undergoing chemotherapy who participated in various self-distraction exercises experienced a greater reduction in stress than the control group.[101] Given the potential benefits of self-distraction to decrease symptom severity and distress in oncology patients undergoing chemotherapy, additional research is warranted to investigate the role of self-distraction as an adaptive rather than a maladaptive behavior.

Equally important, in a study of patients with advanced lung cancer,[102] self-blame was associated with increased levels of insomnia and worse emotional well-being. In contrast, positive reframing was associated with lower levels of fatigue. Given these findings, clinicians need to discourage the use of maladaptive coping strategies, particularly self-blame and promote the use of adaptive coping strategies such as positive reframing.

Resilience—Compared to normative data for adults in the U.S.,[85] the High class' CDRS scores represent clinically meaningful decrements in resilience. Evidence suggests that spirituality may help cancer patients make meaning from their cancer experience with a resultant enhancement of resilience.[103,104] In our previous report,[70] compared to Low class, High class reported lower spiritual well-being scores. In addition, patients' perception of social support is highly correlated with resilience.[105–108] Given that higher resilience is linked to better active coping with disease-related demands[67] and better recovery from traumatic events,[84,109] future research is warranted to better understand how clinicians can support improved perceptions of social support and spiritual well-being.

Limitations—Several limitations warrant consideration. While six assessments were done over two cycles of chemotherapy, patients were not assessed prior to the initiation of chemotherapy. Second, because the majority of the sample was well-educated, female, and homogenous in terms of race/ethnicity, findings may not generalize to men and minority patients. Because the major reason for refusal to participate was "being overwhelmed with treatment", these findings may under-estimate patients' level of stress.

Conclusions and Implications for Practice and Research—The clinical relevance of the use of engagement type coping strategies and enhancements in resilience to decrease fatigue and stress in oncology patients undergoing chemotherapy is apparent. The identification of patients who have experienced significant SLEs, including ACEs, that predate their cancer diagnosis through the use of screening tools would allow clinicians

to tailor stress reduction interventions. In addition, clinicians need to consider that coping strategies are interconnected to a larger socio-cultural context that allows for adaptation to a wide range of environmental conditions and circumstances.

Understanding the biological mechanism(s) through which social determinants of health influence disparities in coping strategies and resilience in oncology patients is an important focus for future studies. Large studies that include equitable representation of minority groups across socioeconomic strata are needed. The use of instruments that capture the influences of economic stability, access to education and health care, as well as neighborhood and environmental safety are important upstream contributors to disengagement type coping and increased symptom burden. Finally, future studies should investigate a variety of approaches to increase/improve patients' level of social support and use of engagement type coping strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures and Acknowledgments

Funding This study was funded by a grant from the National Cancer Institute (CA134900). Dr. Calvo-Schimmel is supported by a grant from the National Institute of Nursing Research (T32NR016920). Dr. Miaskowski is an American Cancer Society Clinical Research Professor. The study sponsors had no role in the study design, collection, analysis, interpretation of data, writing the report, or the decision to submit the information for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Berger AM, Mooney K, Banerjee A, et al. NCCN guidelines version 1.2020 - cancer- related fatigue. 2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf.
2. de Raaf PJ, de Klerk C, van der Rijt CC. Elucidating the behavior of physical fatigue and mental fatigue in cancer patients: a review of the literature. Psychooncology 2013;22:1919–1929. [PubMed: 23147803]
3. Doedee F, van den Houdt S, Widdershoven J, Kupper N. Chronic stress exposure in men and women, and implications for the course of fatigue after percutaneous coronary intervention; the THORESCI study. Gen Hosp Psychiatry 2021;72:45–52. [PubMed: 34280618]
4. Katarina V, Gordana T, Svetlana MD, Milica B. Oxidative stress and neuroinflammation should be both considered in the occurrence of fatigue and depression in multiple sclerosis. Acta Neurol Belg 2020;120:853–861. [PubMed: 30182258]
5. Morris G, Berk M, Galecki P, Walder K, Maes M. The neuro-immune pathophysiology of central and peripheral fatigue in systemic immune-inflammatory and neuro-immune diseases. Mol Neurobiol 2016;53:1195–1219. [PubMed: 25598355]
6. Morris G, Berk M, Walder K, Maes M. Central pathways causing fatigue in neuro- inflammatory and autoimmune illnesses. BMC Med 2015;13:28. [PubMed: 25856766]
7. Rusin A, Seymour C, Cocchetto A, Mothersill C. Commonalities in the features of cancer and chronic fatigue syndrome (CFS): Evidence for stress-induced phenotype instability? Int J Mol Sci 2022;23.
8. Bjorklund G, Dadar M, Pivina L, et al. Environmental, neuro-immune, and neuro- oxidative stress interactions in chronic fatigue syndrome. Mol Neurobiol 2020;57:4598–4607. [PubMed: 32761353]

9. Morris G, Puri BK, Walker AJ, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: From pathophysiological insights to novel therapeutic opportunities. Pharmacol Res 2019;148:104450. [PubMed: 31509764]
10. Morris G, Maes M, Berk M, Puri BK. Myalgic encephalomyelitis or chronic fatigue syndrome: how could the illness develop? Metab Brain Dis 2019;34:385–415. [PubMed: 30758706]
11. Morris G, Anderson G, Maes M. Hypothalamic-pituitary-adrenal hypofunction in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) as a consequence of activated immune-inflammatory and oxidative and nitrosative pathways. Mol Neurobiol 2017;54:6806–6819. [PubMed: 27766535]
12. Heim C, Wagner D, Maloney E, et al. Early adverse experience and risk for chronic fatigue syndrome: results from a population-based study. Arch Gen Psychiatry 2006;63:1258–1266. [PubMed: 17088506]
13. Antoni MH, Dhabhar FS. The impact of psychosocial stress and stress management on immune responses in patients with cancer. Cancer 2019;125:1417–1431. [PubMed: 30768779]
14. Guidi J, Lucente M, Sonino N, Fava GA. Allostatic load and its impact on health: a systematic review. Psychother Psychosom 2021;90:11–27. [PubMed: 32799204]
15. Shields GS, Slavich GM. Lifetime stress exposure and health: a review of contemporary assessment methods and biological mechanisms. Soc Personal Psychol Compass 2017;11.
16. Obeng-Gyasi S, Graham N, Kumar S, et al. Examining allostatic load, neighborhood socioeconomic status, symptom burden and mortality in multiple myeloma patients. Blood Cancer J 2022;12:53. [PubMed: 35365604]
17. Corrigan SL, Roberts S, Warmington S, Drain J, Main LC. Monitoring stress and allostatic load in first responders and tactical operators using heart rate variability: a systematic review. BMC Public Health 2021;21:1701. [PubMed: 34537038]
18. Blasche G, Baubock VM, Haluza D. Work-related self-assessed fatigue and recovery among nurses. Int Arch Occup Environ Health 2017;90:197–205. [PubMed: 27838889]
19. Maloney EM, Boneva R, Nater UM, Reeves WC. Chronic fatigue syndrome and high allostatic load: results from a population-based case-control study in Georgia. Psychosom Med 2009;71:549–556. [PubMed: 19414615]
20. Maloney EM, Gurbaxani BM, Jones JF, et al. Chronic fatigue syndrome and high allostatic load. Pharmacogenomics 2006;7:467–473. [PubMed: 16610956]
21. Goertzel BN, Pennachin C, de Souza Coelho L, et al. Allostatic load is associated with symptoms in chronic fatigue syndrome patients. Pharmacogenomics 2006;7:485–494. [PubMed: 16610958]
22. Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci Biobehav Rev 2005;29:3–38. [PubMed: 15652252]
23. Schnorpfeil P, Noll A, Schulze R, et al. Allostatic load and work conditions. Soc Sci Med 2003;57:647–656. [PubMed: 12821013]
24. Finlay S, Roth C, Zimsen T, et al. Adverse childhood experiences and allostatic load: a systematic review. Neurosci Biobehav Rev 2022;136:104605. [PubMed: 35278597]
25. Misiak B, Stanczykiewicz B, Pawlak A, et al. Adverse childhood experiences and low socioeconomic status with respect to allostatic load in adulthood: a systematic review. Psychoneuroendocrinology 2022;136:105602. [PubMed: 34861465]
26. Misiak B, Kowalski K, Piotrowski P, Grazlewski T, Samochowiec J. Neurodevelopmental aspects of adverse childhood experiences in psychosis: relevance of the allostatic load concept. Psychoneuroendocrinology 2022;143:105850. [PubMed: 35772280]
27. Sulaiman S, Premji SS, Tavangar F, et al. Total adverse childhood experiences and preterm birth: a systematic review. Matern Child Health J 2021;25:1581–1594. [PubMed: 34036452]
28. McLoughlin S, Kenny RA, McCrory C. Psychosocial adversity and allostatic load burden in midlife and older ages. Health Psychol 2021;40:468–471. [PubMed: 34435798]
29. Wallace M, Felker-Kantor E, Madkour A, et al. Adverse childhood experiences, smoking and alcohol use, and allostatic load among people living with HIV. AIDS Behav 2020;24:1653–1662. [PubMed: 31559525]

30. Currie CL, Copeland JL, Metz GA. Childhood racial discrimination and adult allostatic load: the role of Indigenous cultural continuity in allostatic resiliency. Soc Sci Med 2019;241:112564. [PubMed: 31605950]
31. McEwen BS. Neurobiological and systemic effects of chronic stress. Chronic Stress (Thousand Oaks); 2017. p. 1.
32. Tomasdottir MO, Sigurdsson JA, Petursson H, et al. Self reported childhood difficulties, adult multimorbidity and allostatic load. A cross-sectional analysis of the Norwegian HUNT Study. PLoS One 2015;10:e0130591. [PubMed: 26086816]
33. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav 2012;106:29–39. [PubMed: 21888923]
34. Schreier HMC, Kuras YI, McInnis CM, et al. Childhood physical neglect is associated with exaggerated systemic and intracellular inflammatory responses to repeated psychosocial stress in adulthood. Front Psychiatry 2020;11:504. [PubMed: 32581878]
35. Dhruva A, Aouizerat BE, Cooper B, et al. Differences in morning and evening fatigue in oncology patients and their family caregivers. Eur J Oncol Nurs 2013;17:841–848. [PubMed: 24012189]
36. Tell D, Mathews HL, Janusek LW. Day-to-day dynamics of associations between sleep, napping, fatigue, and the cortisol diurnal rhythm in women diagnosed as having breast cancer. Psychosom Med 2014;76:519–528. [PubMed: 25186656]
37. Claros-Salinas D, Bratzke D, Greitemann G, et al. Fatigue-related diurnal variations of cognitive performance in multiple sclerosis and stroke patients. J Neurol Sci 2010;295:75–81. [PubMed: 20510427]
38. Dimsdale JE, Ancoli-Israel S, Elsmore TF, Gruen W. Taking fatigue seriously: I. Variations in fatigue sampled repeatedly in healthy controls. J Med Eng Technol 2003;27:218–222. [PubMed: 12936048]
39. Lerdal A, Gay CL, Aouizerat BE, Portillo CJ, Lee KA. Patterns of morning and evening fatigue among adults with HIV/AIDS. J Clin Nurs 2011;20:2204–2216. [PubMed: 21752119]
40. Wright F, Cooper BA, Conley YP, et al. Distinct evening fatigue profiles in oncology outpatients receiving chemotherapy. Fatigue 2017;5:131–144. [PubMed: 29725554]
41. Wright F, D'Eramo Melkus G, Hammer M, et al. Trajectories of evening fatigue in oncology outpatients receiving chemotherapy. J Pain Symptom Manage 2015;50:163–175. [PubMed: 25828560]
42. Wright F, D'Eramo Melkus G, Hammer M, et al. Predictors and trajectories of morning fatigue are distinct from evening fatigue. J Pain Symptom Manage 2015;50:176–189. [PubMed: 25828559]
43. Wright F, Dunn LB, Paul SM, et al. Morning fatigue severity profiles in oncology outpatients receiving chemotherapy. Cancer Nurs 2019;42:355–364. [PubMed: 30024437]
44. Aouizerat BE, Dhruva A, Paul SM, et al. Phenotypic and molecular evidence suggests that decrements in morning and evening energy are distinct but related symptoms. J Pain Symptom Manage 2015;50:599–614. [PubMed: 26031709]
45. Dhruva A, Aouizerat BE, Cooper B, et al. Cytokine gene associations with self-report ratings of morning and evening fatigue in oncology patients and their family caregivers. Biol Res Nurs 2015;17:175–184. [PubMed: 24872120]
46. Flowers E, Flentje A, Levine J, et al. A pilot study using a multistaged integrated analysis of gene expression and methylation to evaluate mechanisms for evening fatigue in women who received chemotherapy for breast cancer. Biol Res Nurs 2019;21:142–156. [PubMed: 30701989]
47. Flowers E, Miaskowski C, Conley Y, et al. Differential expression of genes and differentially perturbed pathways associated with very high evening fatigue in oncology patients receiving chemotherapy. Support Care Cancer 2018;26:739–750. [PubMed: 28944404]
48. Kober KM, Dunn L, Mastick J, et al. Gene expression profiling of evening fatigue in women undergoing chemotherapy for breast cancer. Biol Res Nurs 2016;18:370–385. [PubMed: 26957308]
49. Wright F, Hammer M, Paul SM, et al. Inflammatory pathway genes associated with inter-individual variability in the trajectories of morning and evening fatigue in patients receiving chemotherapy. Cytokine 2017;91:187210.

50. Wright F, Kober KM, Cooper BA, et al. Higher levels of stress and different coping strategies are associated with greater morning and evening fatigue severity in oncology patients receiving chemotherapy. Support Care Cancer 2020;28:4697–4706. [PubMed: 31956947]
51. Bower JE. The role of neuro-immune interactions in cancer-related fatigue: biobehavioral risk factors and mechanisms. Cancer 2019;125:353–364. [PubMed: 30602059]
52. Araujo JKL, Giglio AD, Munhoz BA, et al. Chemotherapy-induced fatigue correlates with higher fatigue scores before treatment. Am J Hosp Palliat Care 2017;34:404–411. [PubMed: 26847709]
53. Reinertsen KV, Engebraaten O, Loge JH, et al. Fatigue during and after breast cancer therapy-A prospective Study. J Pain Symptom Manage 2017;53:551–560. [PubMed: 28042070]
54. Sakamoto N, Takiguchi S, Komatsu H, et al. Supportive care needs and psychological distress and/or quality of life in ambulatory advanced colorectal cancer patients receiving chemotherapy: a cross-sectional study. Jpn J Clin Oncol 2017;47:1157–1161. [PubMed: 29077931]
55. Abrahams HJG, Gielissen MFM, de Lugt M, et al. The Distress Thermometer for screening for severe fatigue in newly diagnosed breast and colorectal cancer patients. Psychooncology 2017;26:693–697. [PubMed: 27362532]
56. Von Ah DM, Kang DH, Carpenter JS. Predictors of cancer-related fatigue in women with breast cancer before, during, and after adjuvant therapy. Cancer Nurs 2008;31:134–144. [PubMed: 18490890]
57. Ho RT, Kwan TT, Cheung IK, et al. Association of fatigue with perceived stress in Chinese women with early stage breast cancer awaiting adjuvant radiotherapy. Stress Health 2015;31:214–221. [PubMed: 26252247]
58. Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company; 1984.
59. Langford DJ, Cooper B, Paul S, et al. Evaluation of coping as a mediator of the relationship between stressful life events and cancer-related distress. Health Psychol 2017;36:1147–1160. [PubMed: 28825498]
60. Connor-Smith J, Compas BE. Coping as a mediator of relations between reactivity to interpersonal stress, health status, and internalizing problems. Cognit Ther Res 2004;28:347–368.
61. Ahlberg K, Ekman T, Wallgren A, Gaston-Johansson F. Fatigue, psychological distress, coping and quality of life in patients with uterine cancer. J Adv Nurs 2004;45:205–213. [PubMed: 14706006]
62. Dahal A, Meheta RK. Fatigue experience and coping strategies among cancer patients receiving chemotherapy. J Nepal Health Res Counc 2018;16:285–290. [PubMed: 30455487]
63. Dsouza A, Kamboj R, Mandavkar S, et al. An evaluation of early-onset fatigue and the related coping strategies in patients with gastrointestinal cancer: aprospective pilot study. Indian J Cancer 2018;55:162–165. [PubMed: 30604729]
64. Reuter K, Classen CC, Roscoe JA, et al. Association of coping style, pain, age and depression with fatigue in women with primary breast cancer. Psychooncology 2006;15:772–779. [PubMed: 16362999]
65. Strauss B, Brix C, Fischer S, et al. The influence of resilience on fatigue in cancer patients undergoing radiation therapy (RT). J Cancer Res Clin Oncol 2007;133:511–518. [PubMed: 17576595]
66. Eriksson M, Lindstrom B. Antonovsky's sense of coherence scale and the relation with health: a systematic review. J Epidemiol Community Health 2006;60:376–381. [PubMed: 16614325]
67. Seiler A, Jenewein J. Resilience in Cancer Patients. Front Psychiatry 2019;10:208. [PubMed: 31024362]
68. Hiensch AE, Bolam KA, Mijwel S, May AM, Wengstrom Y. Sense of coherence and its relationship to participation, cancer-related fatigue, symptom burden, and quality of life in women with breast cancer participating in the OptiTrain exercise trial. Support Care Cancer 2020;28:5371–5379. [PubMed: 32140973]
69. Kenne Sarenmalm E, Browall M, Persson LO, Fall-Dickson J, Gaston-Johansson F. Relationship of sense of coherence to stressful events, coping strategies, health status, and quality of life in women with breast cancer. Psychooncology 2013;22:20–27. [PubMed: 21910162]

70. Morse L, Kober KM, Viele C, et al. Subgroups of patients undergoing chemotherapy with distinct cognitive fatigue and evening physical fatigue profiles. Support Care Cancer 2021;29:7985–7998. [PubMed: 34218321]
71. Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index–a self-report cognitive measure. Psychooncology 2011;20:194–202. [PubMed: 20213858]
72. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res 1991;36:291–298. [PubMed: 2062970]
73. Gordon JB. The importance of child abuse and neglect in adult medicine. Pharmacol Biochem Behav 2021;211:173268. [PubMed: 34499948]
74. Miaskowski C, Cooper BA, Aouizerat B, et al. The symptom phenotype of oncology outpatients remains relatively stable from prior to through 1 week following chemotherapy. Eur J Cancer Care (Engl) 2017;26.
75. Karnofsky D Performance scale. New York: Plenum Press; 1977.
76. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT: The alcohol use disorders identification test: guidelines for use in primary care. Geneva, Switzerland: World Health Organization; 2001.
77. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The self-administered comorbidity questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum 2003;49:156–163. [PubMed: 12687505]
78. Extermann M, Bonetti M, Sledge GW, et al. MAX2–a convenient index to estimate the average per patient risk for chemotherapy toxicity; validation in ECOG trials. Eur J Cancer 2004;40:1193–1198. [PubMed: 15110883]
79. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24:385–396. [PubMed: 6668417]
80. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med 1979;41:209–218. [PubMed: 472086]
81. Weiss DS, Marmar CR. The impact of event scale - revised. New York: Guilford Press; 1997.
82. Creamer M, Bell R, Failla S. Psychometric properties of the impact of event scale - revised. Behav Res Ther 2003;41:1489–1496. [PubMed: 14705607]
83. Wolfe J, Kimmerling R. Gender issues in the assessment of posttraumatic stress disorder. New York: Guilford; 1997.
84. Connor KM, Davidson JR. Development of a new resilience scale: the connor-davidson resilience scale (CD-RISC). Depress Anxiety 2003;18:76–82. [PubMed: 12964174]
85. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the Connor- davidson Resilience Scale (CD-RISC): validation of a 10-item measure of resilience. J Trauma Stress 2007;20:1019–1028. [PubMed: 18157881]
86. Campbell-Sills L, Forde DR, Stein MB. Demographic and childhood environmental predictors of resilience in a community sample. J Psychiatr Res 2009;43:1007–1012. [PubMed: 19264325]
87. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582–592. [PubMed: 12719681]
88. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. Int J Behav Med 1997;4:92–100. [PubMed: 16250744]
89. Muthen LK, Muthen BO. Mplus user's guide. 8th ed. Los Angeles, CA: Muthen & Muthen; 2020.
90. Thakur N, Hessler D, Koita K, et al. Pediatrics adverse childhood experiences and related life events screener (PEARLS) and health in a safety-net practice. Child Abuse Negl 2020;108:104685. [PubMed: 32898839]
91. Regier NG, Naik AD, Mulligan EA, et al. Cancer-related cognitive impairment and associated factors in a sample of older male oral-digestive cancer survivors. Psychooncology 2019;28:1551–1558. [PubMed: 31134710]
92. Hermelink K, Buhner M, Sckopke P, et al. Chemotherapy and post-traumatic stress in the causation of cognitive dysfunction in breast cancer patients. J Natl Cancer Inst 2017;109.

93. Li J, Yu L, Long Z, Li Y, Cao F. Perceived cognitive impairment in Chinese patients with breast cancer and its relationship with post-traumatic stress disorder symptoms and fatigue. Psychooncology 2015;24:676–682. [PubMed: 25345397]

94. Ni J, Feng J, Denehy L, et al. Symptoms of post-traumatic stress disorder and associated risk factors in patients with lung cancer: A longitudinal observational study. Integr Cancer Ther 2018;17:1195–1203. [PubMed: 30354698]

95. Kop WJ, Kupper HM. Fatigue and stress. In: Fink G, ed. Stress, concepts, cognition, emotion, and behavior, San Diego: Academic Press,; 2016:345–350.

96. Santos JC, Pyter LM. Neuroimmunology of behavioral comorbidities associated with cancer and cancer treatments. Front Immunol 2018;9:1195. [PubMed: 29930550]

97. Kelley KW, Bluthe RM, Dantzer R, et al. Cytokine-induced sickness behavior. Brain Behav Immun 2003;17 (Suppl 1):S112–S118. [PubMed: 12615196]

98. Felitti VJ, Anda RF, Nordenberg D, et al. Reprint of: relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the adverse childhood experiences (ACE) study. Am J Prev Med 2019;56:774–786. [PubMed: 31104722]

99. Brouwer AM, Menard L. Social determinants of health and health outcomes: the mediating role of coping strategies. WMJ 2020;119:56–61. [PubMed: 32348074]

100. Wadsworth ME. Development of maladaptive coping: a functional adaptation to chronic, uncontrollable stress. Child Dev Perspect 2015;9:96–100. [PubMed: 26019717]

101. Kwekkeboom K, Zhang Y, Campbell T, et al. Randomized controlled trial of a brief cognitive-behavioral strategies intervention for the pain, fatigue, and sleep disturbance symptom cluster in advanced cancer. Psychooncology 2018;27:2761–2769. [PubMed: 30189462]

102. van de Wiel M, Derijcke S, Galdermans D, et al. Coping strategy influences quality of life in patients with advanced lung cancer by mediating mood. Clin Lung Cancer 2021;22:e146–e152. [PubMed: 33060059]

103. Shin YJ, Oh EG. Factors influencing resilience among Korean adolescents and young adult survivors of childhood cancer. Eur J Oncol Nurs 2021;53:101977. [PubMed: 34144358]

104. Hunter-Hernandez M, Costas-Muniz R, Gany F. Missed opportunity: spirituality as a bridge to resilience in Latinos with cancer. J Relig Health 2015;54:2367–2375. [PubMed: 25711211]

105. Ruiz-Rodriguez I, Hombrados-Mendieta I, Melguizo-Garin A, Martos-Mendez MJ. The importance of social support, optimism and resilience on the quality of life of cancer patients. Front Psychol 2022;13:833176. [PubMed: 35356348]

106. Costa ALS, Heitkemper MM, Alencar GP, et al. Social support is a predictor of lower stress and higher quality of life and resilience in Brazilian patients with colorectal cancer. Cancer Nurs 2017;40:352–360. [PubMed: 27171810]

107. Somasundaram RO, Devamani KA. A comparative study on resilience, perceived social support and hopelessness among cancer patients treated with curative and palliative care. Indian J Palliat Care 2016;22:135–140. [PubMed: 27162423]

108. Zhang H, Zhao Q, Cao P, Ren G. Resilience and quality of life: exploring the mediator role of social support in patients with breast cancer. Med Sci Monit 2017;23:5969–5979. [PubMed: 29248937]

109. Cordova MJ, Riba MB, Spiegel D. Post-traumatic stress disorder and cancer. Lancet Psychiatry 2017;4:330–338. [PubMed: 28109647]

Key Message

This study evaluated for associations between cognitive fatigue and evening physical fatigue and stress, coping, and resilience in oncology patients undergoing chemotherapy. Higher levels of stress, lower levels of resilience, and increased use of disengagement coping strategies were associated with greater cognitive fatigue and evening physical fatigue.

Table 1

Differences in Stress and Resilience Measures Among the Cognitive Fatigue and Evening Physical Fatigue Latent Classes at Enrollment.

Measures[a]	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)	
PSS total score (range 0 to 56)	13.8 (6.9)	16.1 (6.5)	23.5 (7.7)	F=215.38, p<0.001 0 < 1 < 2
IES-R total score (≥24.0 –Clinically meaningful PTSD symptomatology) (≥33.0 –Probable PTSD)	13.8 (10.4)	16.1 (10.9)	24.2 (14.6)	F=81.07, p<0.001 0 <1 < 2
IES-R intrusion	0.6 (0.6)	0.8 (0.6)	1.2 (0.8)	F=69.68, p<0.001 0 < 1 < 2
IES-R avoidance	0.8 (0.7)	0.9 (0.6)	1.1 (0.7)	F=17.62, p<0.001 0 and 1 < 2
IES-R hyperarousal	0.3 (0.40)	0.5 (0.5)	1.0 (0.8)	F=139.58, p<0.001 0 < 1 < 2
LSC-R total score (range 0–30)	5.0 (3.3)	5.6 (3.4)	7.2 (4.5)	F=28.17, p<0.001 0 and 1 < 2
LSC-R affected sum score (range 0–150)	8.3 (7.2)	10.4 (9.7)	15.4 (12.7)	F=39.20, p<0.001 0 < 1 < 2
LSC-R PTSD sum score (range 0–21)	2.2 (2.5)	2.8 (2.6)	3.9 (3.5)	F=27.87, p<0.001 0 < 1 < 2
CDRS total score (range 0–40) (31.8 (±5.4) – normative mean score for the U.S.population)	32.0 (6.3)	31.7 (5.4)	27.4 (6.5)	F=81.83, p<0.001 0 and 1 > 2

Abbreviations: CDRS, Connor Davidson Resilience Scal;, IES-R, impact of event scale – revised; LSC-R, life stressor checklist-revised; PSS, perceived stress scale; PTSD, post-traumatic stress disorder; SD, standard deviation

[a]Clinically meaningful cutoff scores or range of scores

Table 2

Differences Among the Cognitive Fatigue and Evening Physical Fatigue Subgroups in the Percentage of Patients Exposed to Specific Stressors.

Stressful Life Event	Low cognitive Fatigue and Low Evening Physical Fatigue (0) 20.5% (n=273) % (n)	Moderate Cognitive Fatigue and Moderate Evening Physical Fatigue (1) 39.6% (n=528) % (n)	High Cognitive Fatigue and High Evening Physical Fatigue (2) 39.9% (n=531) % (n)	Statistics
Interpersonal Violence, Abuse, and Neglect Stressors				
Family violence in childhood	17.6 (38)	20.1 (85)	31.2 (120)	χ^2=19.36, *P*<0.001 0 and 1 < 2
Emotional abuse	10.9 (24)	17.9 (76)	32.0 (124)	χ^2=43.30, *P*<0.001 0 and 1 < 2
Physical neglect	1.8 (4)	2.8 (12)	8.7 (34)	χ^2=20.73, *P*<0.001 0 and 1 < 2
Sexual harassment	6.9 (15)	17.8 (75)	24.9 (96)	χ^2=30.19, *P*<0.001 0 < 1 < 2
Physical abuse - <16 years	12.0 (26)	9.4 (40)	21.0 (81)	χ^2=23.20, *P*<0.001 0 and 1 < 2
Physical abuse - ≥16 years	9.7 (21)	11.6 (49)	17.7 (68)	χ^2=9.85, *P*=0.007 0 and 1 < 2
Forced to touch - <16 years	10.4 (22)	7.4 (31)	17.0 (66)	χ^2=18.54, *P*<0.001 1 < 2
Forced to touch - ≥16 years	3.3 (7)	4.7 (20)	9.0 (35)	χ^2=10.14, *P*=0.006 0 and 1 < 2
Forced sex - <16 years	3.7 (8)	3.1 (13)	6.2 (24)	χ^2=4.88, *P*=0.087
Forced sex - ≥16 years	3.3 (7)	5.5 (23)	9.3 (36)	χ^2=9.40, *P*=0.009 0 < 2
Other Stressors				
Been in a serious disaster	40.7 (87)	40.9 (174)	40.9 (160)	χ^2=0.01, *P*=0.997
Seen serious accident	31.2 (67)	33.4 (142)	32.8 (129)	χ^2=0.33, *P*=0.847
Had serious accident or injury	24.2 (52)	21.4 (90)	27.4 (106)	χ^2=3.97, *P*=0.137
Jail (family member)	17.6 (38)	16.1 (68)	27.1 (106)	χ^2=16.63, *P*<0.001 0 and 1 < 2
Jail (self)	3.2 (7)	5.9 (25)	9.7 (38)	χ^2=10.07, *P*=0.007 0 < 2
Foster care or put up for adoption	2.3 (5)	1.9 (8)	3.1 (12)	χ^2=1.24, *P*=0.539

Stressful Life Event	Low cognitive Fatigue and Low Evening Physical Fatigue (0) 20.5% (n=273) % (n)	Moderate Cognitive Fatigue and Moderate Evening Physical Fatigue (1) 39.6% (n=528) % (n)	High Cognitive Fatigue and High Evening Physical Fatigue (2) 39.9% (n=531) % (n)	Statistics
Separated/divorced (parents)	17.4 (38)	20.2 (86)	25.8 (101)	χ^2=6.68, *P*=0.035 no significant pairwise contrasts
Separated/divorced (self)	32.4 (71)	34.0 (145)	40.5 (158)	χ^2=5.43, *P*=0.066
Serious money problems	15.1 (33)	13.9 (59)	29.2 (114)	χ^2=33.72, P<0.001 0 and 1 < 2
Had serious physical or mental illness (not cancer)	14.5 (32)	15.5 (66)	25.2 (99)	χ^2=16.05, *P*<0.001 0 and 1 < 2
Abortion or miscarriage	44.9 (70)	44.8 (148)	43.3 (142)	χ^2=0.19, *P*=0.908
Separated from child	1.0 (2)	1.7 (7)	3.2 (12)	χ^2=3.90, *P*=0.142
Care for child with handicap	3.9 (8)	3.6 (15)	4.2 (16)	χ^2=0.21, *P*=0.901
Care for someone with severe physical or mental handicap	22.5 (48)	22.7 (96)	27.3 (104)	χ^2=2.76, *P*=0.252
Death ofsomeone close (sudden)	45.2 (98)	48.5 (204)	52.8 (201)	χ^2=3.43, *P*=0.180
Death of someone close (not sudden)	77.5 (165)	80.8 (336)	78.0 (298)	χ^2=1.31, *P*=0.518
Seen robbery/mugging	18.3 (40)	19.9 (84)	26.4 (103)	χ^2=7.24, *P*=0.027 no significant pairwise contrasts
Been robbed/mugged	22.5 (49)	24.6 (104)	31.3 (120)	χ^2=7.02, *P*=0.030 no significant pairwise contrasts

Table 3

Differences Among the Cognitive Fatigue and Evening Physical Fatigue Latent Classes in the Effect of Stressors on Life in the Past Year.

Stressful Life Event[a]	Low Cognitive Fatigue and Low Evening Physical Fatigue (0) 20.5% (n=273) Mean (SD)	Moderate Cognitive Fatigue and Moderate Evening Physical Fatigue (1) 39.6% (n=528) Mean (SD)	High Cognitive Fatigue and High Evening Physical Fatigue (2) 39.9% (n=531) Mean (SD)	Statistics
Interpersonal violence, abuse, and neglect stressors				
Family violence in childhood	1.7 (1.0)	1.7 (1.1)	2.1 (1.2)	KW=8.73, *P*=0.013 1 < 2
Emotional abuse	2.3 (1.5)	2.4 (1.3)	2.8 (1.3)	KW=5.23, *P*=0.070
Physical neglect	3.3 (1.7)	2.9 (1.5)	2.7 (1.3)	KW=0.61, *P*=0.737
Sexual harassment	1.4 (1.1)	1.4 (0.9)	1.6 (1.0)	KW=1.96, *P*=0.376
Physical abuse - <16 years	1.4 (0.8)	1.9 (1.3)	2.1 (1.3)	KW=6.52, *P*=0.038 0 < 2
Physical abuse - ≥16 years	1.7 (1.2)	1.9 (1.2)	1.9 (1.2)	KW=0.86, *P*=0.651
Forced to touch - <16 years	1.4 (1.0)	2.0 (1.4)	2.3 (1.4)	KW=9.34, *P*=0.009 0 < 2
Forced to touch - ≥16 years	1.0 (0.0)	2.1 (1.4)	2.0 (1.2)	KW=6.10, *P*=0.047 no significant pairwise contrasts
Forced sex - <16 years	1.1 (0.4)	2.5 (1.5)	2.0 (1.3)	KW=4.60, *P*=0.100
Forced sex - ≥16 years	1.6 (1.5)	2.0 (1.3)	1.6 (1.0)	KW=2.58, *P*=0.276
Other Stressors				
Been in a serious disaster	1.2 (0.6)	1.4 (0.9)	1.4 (0.8)	KW=5.26, *P*=0.072
Seen serious accident	1.4 (0.8)	1.4 (0.8)	1.6 (0.9)	KW=2.92, *P*=0.232
Had serious accident or injury	1.4 (1.0)	1.5 (1.0)	1.7 (1.1)	KW=5.25, *P*=0.073
Jail (family member)	1.7 (1.1)	1.7 (1.2)	2.1 (1.5)	KW=3.35, *P*=0.188
Jail (self)	2.0 (1.3)	1.7 (1.1)	1.7 (1.3)	KW=2.53, *P*=0.767
Foster care or put up for adoption	2.8 (2.1)	2.0 (1.4)	2.3 (1.4)	KW=0.37, *P*=0.833
Separated/divorced (parents)	1.6 (1.0)	1.5 (0.9)	2.0 (1.3)	KW=8.43, *P*=0.015 1 < 2
Separated/divorced (self)	1.6 (1.1)	2.0 (1.3)	2.4 (1.5)	KW=16.55, *P*<0.001 0 and 1 < 2
Serious money problems	2.3 (1.5)	2.4 (1.7)	3.0 (1.7)	KW=6.82, *P*=0.033 no significant pairwise contrasts

Stressful Life Event[a]	Low Cognitive Fatigue and Low Evening Physical Fatigue (0) 20.5% (n=273) Mean (SD)	Moderate Cognitive Fatigue and Moderate Evening Physical Fatigue (1) 39.6% (n=528) Mean (SD)	High Cognitive Fatigue and High Evening Physical Fatigue (2) 39.9% (n=531) Mean (SD)	Statistics
Had serious physical or mental illness (not cancer)	1.9 (1.2)	2.4 (1.4)	2.7 (1.3)	KW=10.12, *P*=0.006 0 < 2
Abortion or miscarriage	1.4 (0.8)	1.5 (1.0)	1.7 (1.1)	KW=4.75, *P*=0.093
Separated from child	2.5 (2.1)	2.6 (1.6)	3.1 (1.6)	KW=0.68, *P*=0.712
Care for child with handicap	3.4 (1.1)	3.3 (1.6)	3.2 (1.4)	KW=0.06, *P*=0.971
Care for someone with severe physical or mental handicap	2.2 (1.4)	2.5 (1.4)	2.8 (1.5)	KW=6.13, *P*=0.047 0 < 2
Death of someone close (sudden)	1.8 (1.1)	2.1 (1.3)	2.4 (1.4)	KW=13.20, *P*=0.001 0 < 2
Death of someone close (not sudden)	1.9 (1.2)	2.1 (1.2)	2.5 (1.4)	KW=27.20, *P*<0.001 0 and 1 < 2
Seen robbery/mugging	1.4 (0.8)	1.5 (1.1)	1.6 (1.1)	KW=4.57, *P*=0.102
Been robbed/mugged	1.5 (1.0)	1.6 (1.1)	1.7 (1.1)	KW=2.90, *P*=0.235

Abbreviations: SD, standard deviation

[a] Range = 1 “not at all” to 5 “extremely”

[b] *These* data are reported for those patients who reported the occurrence of the stressor (see Table 4)

Table 4

Differences Among the Cognitive Fatigue and Evening Physical Fatigue Latent Classes in the Brief COPE Subscale Scores.

Subscale*	**Low Cognitive Fatigue and Low Evening Physical Fatigue (0) 20.5% (n=273)** **Mean (SD)**	**Moderate Cognitive Fatigue and Moderate Evening Physical Fatigue (1) 39.6% (n=528)** **Mean (SD)**	**High Cognitive Fatigue and High Evening Physical Fatigue (2) 39.9% (n=531)** **Mean (SD)**	**Statistics**
Engagement coping strategies				
Active coping	6.2 (1.8)	6.2 (1.6)	5.7 (1.6)	F=13.72, *P*<0.001 0 and 1 > 2
Planning	5.1 (2.0)	5.4 (1.8)	5.3 (1.7)	F=3.29, *P*=0.37 0 < 1
Positive reframing	5.4 (2.1)	5.5 (2.0)	5.3 (1.9)	F=0.63, *P*=0.531
Acceptance	6.9 (1.4)	6.9 (1.2)	6.5 (1.4)	F=11.48, *P*<0.001 0 and 1 > 2
Humor	4.1 (2.1)	4.5 (1.9)	4.3 (2.0)	F=4.41, *P*=0.012 0 < 1
Religion	5.2 (2.4)	4.9 (2.3)	5.1 (2.2)	F=1.62, *P*=0.199
Using emotional support	6.2 (1.8)	6.5 (1.7)	6.2 (1.6)	F=3.42, *P*=0.033 no significant pairwise contrasts
Using instrumental support	5.1 (1.9)	5.4 (1.8)	5.4 (1.7)	F=3.63, *P*=0.027 0 < 1 and 2
Disengagement coping strategies				
Self-distraction	5.1 (1.9)	5.6 (1.7)	5.5 (1.5)	F=7.53, *P*<0.001 0 < 1 and 2
Denial	2.4 (1.0)	2.3 (0.9)	2.7 (1.3)	F=12.11, *P*<0.001 0 and 1 < 2
Venting	3.4 (1.5)	3.9 (1.7)	4.3 (1.6)	F=25.99, *P*<0.001 0 < 1 < 2
Substance use	2.2 (0.7)	2.2 (0.6)	2.3 (0.9)	F=5.00, *P*=0.007 0 and 1 < 2
Behavioral disengagement	2.2 (0.7)	2.1 (0.5)	2.4 (0.9)	F=22.16, *P*<0.001 0 and 1 < 2
Self-blame	2.4 (0.9)	2.7 (1.1)	3.3 (1.4)	F=50.56, *P*<0.001 0 < 1 < 2

Abbreviation: SD = standard deviation

[a]Each item was rate on a 4-point Likert scale that ranged from 1 (“I haven’t been doing this at all”) to 4 (“I have been doing this a lot”). Each coping strategy is evaluated using 2 items. Scores can range from 2 to 8 with higher scores indicating greater use of each of the coping strategies.

Table 5

Characteristics Associated With Membership in the Moderate and High Cognitive Fatigue and Evening Physical Fatigue Latent Classes.

Characteristic[a]	Moderate Cognitive Fatigue and Moderate Evening Physical Fatigue	High Cognitive Fatigue and High Evening Physical Fatigue
Stress characteristics		
Higher perceived stress scale score	☐	☐
Higher impact of event scale-revised total score	☐	☐
Higher impact of event scale-revised intrusion score	☐	☐
Higher impact of event scale-revised avoidance score		☐
Higher impact of event scale-revised hyperarousal score	☐	☐
Higher life stressor checklist-revised total score		☐
Higher life stressor checklist-revised affected sum score	☐	☐
Higher life stressor checklist-revised PTDS sum score	☐	☐
Lower Connor Davidson Resilience Scale total score		☐
Higher occurrence of life stressors		
Family violence in childhood		☐
Emotional abuse		☐
Physical neglect		☐
Sexual harassment	☐	☐
Physical abuse - <16 years		☐
Physical abuse - ≥16 years		☐
Forced to touch - ≥16 years	☐	☐
Forced sex - ≥16 years		☐
Jail (family member)		☐
Jail (self)		☐
Serious money problems		☐
Had serious physical or mental illness (not cancer)		☐
Higher effect of life stressors		
Physical abuse- <16 years		☐
Forced to touch - <16 years		☐
Separated/divorced (self)		☐

Characteristic[a]	Moderate Cognitive Fatigue and Moderate Evening Physical Fatigue	High Cognitive Fatigue and High Evening Physical Fatigue
Had serious physical or mental illness (not cancer)		☐
Caring for someone with severe physical or mental handicap		☐
Death of someone close (sudden)		☐
Death of someone close (not sudden)		☐
Use of coping strategies		
Lower use of active coping		☐
Lower use of acceptance		☐
Higher use of planning	☐	
Higher use of humor	☐	
Higher use of instrumental support	☐	☐
Higher use of self-distraction	☐	☐
Higher use of denial		☐
Higher use of venting	☐	☐
Higher use of substance use		☐
Higher use of behavioral disengagement		☐
Higher use of self-blame	☐	☐

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