

# Stress Exposures Contribute to Worse Joint Morning and Evening Fatigue Profiles in Patients With Cancer During Chemotherapy

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**OBJECTIVES:** To evaluate differences among stress, resilience, and coping strategies related to morning and evening fatigue profiles (both low, low morning and moderate evening, both moderate, and both high).

**SAMPLE & SETTING:** Data were collected from 1,334 adult patients with cancer receiving chemotherapy.

**METHODS & VARIABLES:** Morning and evening fatigue severity were rated over two cycles of chemotherapy using the Lee Fatigue Scale. Latent profile analysis was used to identify patient subgroups with distinct joint morning and evening profiles. Data were collected on global, cancer-specific, and cumulative life stress; resilience; and coping strategies. Differences among the latent classes were evaluated using parametric and nonparametric tests.

**RESULTS:** Compared to the other three classes, the both high class reported the highest stress scores, highest occurrence of and effects from a variety of stressful life events, lowest resilience scores, and higher use of disengagement coping strategies. The both high class met the criteria for subsyndromal post-traumatic stress disorder.

**IMPLICATIONS FOR NURSING:** When patients report high levels of fatigue, detailed assessments of stress are warranted to provide tailored interventions.

**KEYWORDS** cancer; chemotherapy; coping; fatigue; resilience; stress

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Fatigue is a common symptom that limits the daily activities and quality of life of patients with cancer (National Comprehensive Cancer Network, 2023). Although most studies evaluate average fatigue severity (i.e., fatigue score without consideration of diurnal variations), a growing body of evidence suggests that diurnal variations in fatigue severity warrant additional investigation because different types of interventions may be warranted (Dhruva et al., 2013; Dimsdale et al., 2007; Pietrowsky & Lahl, 2008). In the authors' previous studies of morning and evening fatigue as single symptoms, common and distinct risk factors (Wright, Cooper, et al., 2017; Wright et al., 2015, 2019) and underlying mechanisms (Kober et al., 2023; Wright, Hammer, et al., 2017) were identified.

More recently, to gain additional insights into patients who were at increased risk for high levels of both morning and evening fatigue, the authors used latent profile analysis to identify the following four classes of patients with distinct joint morning and evening fatigue profiles: both low (24%), low morning and moderate evening (26%), both moderate (39%), and both high (12%) (Wright et al., 2023). Risk factors associated with the worst severity profiles included younger age, decreased likelihood of being married or partnered, increased likelihood of living alone, and having a higher comorbidity burden and a lower functional status. In addition, patients with the worst severity profiles reported higher levels of anxiety, depression, sleep disturbance, and pain, as well as lower quality-of-life scores. The current article extends these findings by evaluating for differences in stress, resilience, and coping among the four distinct joint morning and evening fatigue profiles.

## Background

### Fatigue and Stress

In healthy individuals, fatigue is an adaptive response to acute stress that conserves energy and maintains homeostasis (Kop & Kupper, 2016). Intense, persistent, and/or cumulative life stress activates the autonomic nervous system and can overwhelm the regulatory feedback loop of the hypothalamic-pituitary-adrenal axis. This process results in a loss of homeostasis and an increase in allostatic load that leads to higher levels of physical fatigue (Shields & Slavich, 2017; Starr et al., 2019; Thorsteinsson et al., 2019). The chronicity and intensity of the stress, types of stressors, coping abilities, and environmental factors moderate an individual's responses to stress (Galatzer-Levy et al., 2018).

Previous studies of patients with cancer found that higher levels of average fatigue were associated with higher levels of global stress (Higgins et al., 2008; Ho et al., 2015; Reinertsen et al., 2017; Sakamoto et al., 2017; Yeh, 2021), cancer-specific stress (Bower et al., 2021; Cohen et al., 2019; Fagundes et al., 2012; Higgins et al., 2008; Von Ah et al., 2008; Yee et al., 2017), and cumulative life stress (Bean et al., 2021; Bower et al., 2014, 2019, 2021; Fagundes et al., 2012). However, most of these studies included only women with breast cancer (Bean et al., 2021; Bower et al., 2014, 2019, 2021; Cohen et al., 2019; Fagundes et al., 2012; Higgins et al., 2008; Ho et al., 2015; Reinertsen et al., 2017; Von Ah et al., 2008; Yee et al., 2017).

Although longitudinal studies evaluated for changes in average fatigue severity during chemotherapy, the wide range in the timing of the assessments, such as every third chemotherapy cycle (Yeh, 2021), every three months (Von Ah et al., 2008), every six months (Bower et al., 2021), and after completion of treatment (Bower et al., 2014; Cohen et al., 2019; Fagundes et al., 2012; Reinertsen et al., 2017), makes it difficult to determine how stress affects fatigue severity during chemotherapy. For example, in a study that evaluated fatigue severity for six days following a cycle of chemotherapy (Higgins et al., 2008), higher levels of pretreatment distress were associated with increased severity of average fatigue. However, only a single measure of global stress was used in this analysis. None of the studies evaluated for differences in three distinct types of stress (i.e., global, cancer-specific, and cumulative life stress) among patients with cancer who had distinct joint morning and evening fatigue profiles. An evaluation of distinct types of stress is important to be able to

provide individualized supportive care interventions; interventions may differ for patients with post-traumatic stress disorder (PTSD) and those with adverse childhood experiences (ACEs).

### Fatigue and Resilience

Resilience is an individualized, dynamic process of positive adaptation to stressors that can decrease allostatic load (Charney, 2004). In studies that evaluated for associations among resilience, fatigue, and stress in patients during cancer treatment, lower resilience scores were associated with higher levels of fatigue, global stress (Min et al., 2013), and cancer-specific stress (Alarcón et al., 2020). In one systematic review (Tamura et al., 2021), lower levels of resilience were associated with higher levels of depression, anxiety, and fatigue in patients with cancer. However, only 2 of the 39 studies included in this review evaluated for associations between fatigue and resilience (Ristevska-Dimitrovska et al., 2015; Zou et al., 2018). In two additional studies, higher levels of average fatigue were associated with lower levels of resilience (Lin et al., 2020; Öcalan & Üzar-Özçetin, 2022). These findings suggest that decreased resilience is a risk factor for more severe fatigue. Additional research is warranted because the three studies that evaluated patients during chemotherapy were cross-sectional (Öcalan & Üzar-Özçetin, 2021; Ristevska-Dimitrovska et al., 2015; Zou et al., 2018). In addition, the fourth longitudinal study evaluated only patients with colorectal cancer following surgery (Lin et al., 2020).

### Fatigue and Coping

Healthy individuals employ coping strategies to respond to stress and maintain homeostasis (Folkman et al., 1986; Lazarus & Folkman, 1984). Coping strategies can be broadly classified as engagement strategies (e.g., positive reframing, seeking instrumental and emotional support) or disengagement strategies (e.g., avoidance, denial) (Carver et al., 1989; Folkman et al., 1986; Langford et al., 2017; Lazarus & Folkman, 1984). Although engagement coping strategies are associated with decreased fatigue severity, across multiple cancer diagnoses (Dsouza et al., 2018; Narayanan et al., 2020; Reuter et al., 2006; van de Wiel et al., 2021; Yeun & Jeon, 2020), the use of disengagement coping strategies is associated with higher levels of average fatigue (Baussard et al., 2022; Bussell & Naus, 2010; Dahal & Meheta, 2018; Dong et al., 2021; Ichikura et al., 2018; Levkovich, 2021). However, because these studies evaluated only average fatigue, no information

is available on associations with diurnal variations in fatigue severity.

An examination of differences in stress, resilience, and the use of coping strategies among patients with worse joint morning and evening fatigue profiles may identify modifiable risk factors that can be targeted to decrease both types of physical fatigue (i.e., morning and evening). Therefore, this study aimed to evaluate for differences in global, cancer-specific, and cumulative life stress, as well as

resilience and coping, in subgroups of patients (i.e., latent classes) with distinct joint morning and evening fatigue profiles.

## Methods

### Patients and Settings

Details about the parent longitudinal study, which was guided by the theory of symptom management (Weiss et al., 2023) are published elsewhere (Miaskowski et al., 2014). In brief, eligible patients were aged 18 years

**TABLE 1. Differences in Stress and Resilience Measures Among the Joint am and pm Fatigue Latent Classes at Enrollment (N = 1,334)**

Measure	Low am and Low pm (0) (N = 313)		Low am and Moderate pm (1) (N = 348)		Moderate am and Moderate pm (2) (N = 518)		High am and High pm (3) (N = 155)		Statistics
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	
CDRS total score	31.4	6.8	31.4	5.5	29.2	6.1	27.3	7	F = 22.37, PWC = 0 and 1 > 2 and 3; 2 > 3
IES-R total score	14.1	10.4	14.9	9.8	21.3	13.1	29.3	16.6	F = 68.78, PWC = 0 and 1 < 2 and 3; 2 < 3
IES-R avoidance	0.8	0.6	0.8	0.6	1	0.7	1.2	0.8	F = 15.61, PWC = 0 and 1 < 2 and 3; 2 < 3
IES-R intrusion	0.6	0.6	0.7	0.5	1.1	0.7	1.4	0.9	F = 68.94, PWC = 0 and 1 < 2 and 3; 2 < 3
IES-R hyperarousal	0.4	0.5	0.4	0.4	0.8	0.7	1.3	0.9	F = 96.68, PWC = 0 and 1 < 2 and 3; 2 < 3
LSC-R total score	5.1	3.3	5.7	3.6	6.3	4	8.5	4.7	F = 22.13, PWC = 0, 1, and 2 < 3; 0 < 2
LSC-R affected sum score	8.6	7.4	10.2	9.9	13.1	11.1	18.9	14.4	F = 29.9, PWC = 0 and 1 < 2 and 3; 2 < 3
LSC-R PTSD sum score	2.2	2.5	2.8	2.8	3.4	3	4.8	3.9	F = 22.36, PWC = 0 < 2 and 3; 1 and 2 < 3
PSS total score	14.3	7	16.2	6.9	20.5	7.6	25.7	8.2	F = 105.4, PWC = 0 < 1 < 2 < 3

am—morning; CDRS—Connor–Davidson Resilience Scale; IES-R—Impact of Event Scale—Revised; LSC-R—Life Stressor Checklist—Revised; pm—evening; PSS—Perceived Stress Scale; PTSD—post-traumatic stress disorder; PWC—pairwise contrast

**Note.** For each measure, the p value is significant at  $p < 0.001$ .

**Note.** The CDRS total score has a possible range of 0–40, with higher scores indicating higher self-perceived resilience; the normative range of the CDRS total score for the U.S. population is 31.8 (SD = 5.4). The IES-R total score has a possible range of 0–88; an IES-R total score of greater than 24 indicates clinically meaningful PTSD symptomatology, and a score of greater than 33 indicates probable PTSD. Three IES-R subscales evaluate avoidance, intrusion, and hyperarousal, with higher scores indicating a higher level of symptoms. The LSC-R total score has a possible range of 0–30; the LSC-R total score is obtained by summing the total number of stressful life events endorsed, with higher scores indicating a greater number of stressful events. The LSC-R affected sum score has a possible range of 0–150, with higher scores indicating that stressors have had a greater effect on life in the past year. The LSC-R PTSD sum score has a possible range of 0–21, reflecting the number of positively endorsed items that reflect the Diagnostic and Statistical Manual of Mental Disorders (4th ed.) PTSD Criteria A for having experienced a traumatic event. The PSS total score has a possible range of 0–56, with higher scores indicating greater stress.

or older; had a diagnosis of breast, gastrointestinal, gynecologic, 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 National Cancer Institute–designated comprehensive cancer centers, one Veterans Affairs hospital, and four community-based oncology programs. A total of 2,234 patients were approached during their first or second cycle of chemotherapy and 1,343 consented to participate (60% accrual rate). The primary reason indicated for declining to participate in the study was being overwhelmed with their cancer treatment.

### 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 during their first or second cycle of chemotherapy to discuss the study procedures and their interest in study participation. Written informed consent was obtained from all patients. Patients completed the morning and evening fatigue measures in their homes using paper questionnaires. Measures were completed a total of six times over two cycles of chemotherapy: prior to chemotherapy (assessments 1 and 4), one week following the administration of chemotherapy (assessments 2 and 5), and two weeks following the administration of chemotherapy (assessments 3 and 6). The remaining questionnaires were completed at enrollment (i.e., prior to the second or third cycle of chemotherapy). Medical records were reviewed for disease and treatment information. The 1,334 patients who completed both the morning and evening fatigue measures were included in this analysis.

## Measures

### Demographic and Clinical Characteristics

Patients completed a demographic questionnaire, the Karnofsky Performance Status Scale (Karnofsky, 1977), and the Self-Administered Comorbidity Questionnaire (Sangha et al., 2003). Medical records were reviewed for disease and treatment information.

### Fatigue

The 18-item Lee Fatigue Scale (LFS) was designed to assess physical fatigue and energy (Lee et al., 1991).

Each item is rated on a 0–10 numeric rating scale. Total fatigue and energy scores are calculated as the mean of the 13 fatigue items and the mean of the 5 energy items, respectively. Higher scores on the fatigue items indicate greater fatigue severity, and higher scores on the energy items indicate 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 (morning fatigue) and before going to bed (evening fatigue). The LFS has established cutoff scores for clinically meaningful levels of fatigue (3.2 or greater for morning fatigue, 5.6 or greater for evening fatigue) and energy (6.2 or less for morning energy, 3.5 or less for evening energy) (Fletcher et al., 2008). Cronbach's alphas were 0.96 for morning fatigue and 0.93 for evening fatigue, and they were 0.95 for morning energy and 0.93 for evening energy.

### Global Stress

The 14-item Perceived Stress Scale (PSS) was used to measure global perceived stress according to the degree to which life circumstances during the previous week were appraised as stressful (Cohen et al., 1983). Each item is rated on a scale ranging from 0 (never) to 4 (very often). Total scores are summed and can range from 0 to 56. The Cronbach's alpha for the PSS was 0.85.

### Cancer-Specific Stress

The 22-item Impact of Event Scale–Revised (IES-R) was used to measure cancer-related distress (Horowitz et al., 1979). Patients rate 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 avoidance, intrusion, and hyperarousal perceived by the patient. For the IES-R total score, sum scores of 24 or greater indicate clinically meaningful post-traumatic symptomatology, and scores of 33 or greater indicate probable PTSD (Creamer et al., 2003). The Cronbach's alpha for the IES-R total score was 0.92.

### Cumulative Life Stress

The 30-item Life Stressor Checklist–Revised (LSC-R) is an index of lifetime trauma exposure (e.g., mugging, the death of a loved one, a sexual assault) (Wolfe & Kimmerling, 1997). The total LSC-R score is obtained by summing the total number of events endorsed. If patients endorse an event, they are asked to indicate how much that stressor affected their life in the past year. These responses are

**TABLE 2. Differences Among the Joint am and pm Fatigue Latent Classes in the Percentage of Patients Exposed to Various Stressful Life Events on the Life Stressor Checklist-Revised (N = 1,334)**

Stressful Life Event	Low am and Low pm (0) (N = 313)		Low am and Moderate pm (1) (N = 348)		Moderate am and Moderate pm (2) (N = 518)		High am and High pm (3) (N = 155)		Statistics	p
	n	%	n	%	n	%	n	%		
<b>Interpersonal violence, abuse, and neglect stressors</b>										
Emotional abuse	29	12	51	18	98	25	46	43	$\chi^2 = 46.7$ , PWC = 0 < 2 < 3; 1 < 3	< 0.001
Family violence in childhood	43	18	64	23	93	24	43	39	$\chi^2 = 20.13$ , PWC = 0, 1, and 2 < 3	< 0.001
Forced sex at age younger than 16 years	9	4	4	2	23	6	9	8	$\chi^2 = 11.64$ , PWC = 1 < 2 and 3	0.009
Forced sex at age 16 years or older	8	3	13	5	30	8	15	14	$\chi^2 = 15.75$ , PWC = 0 and 1 < 3	0.001
Forced to touch at age younger than 16 years	24	10	21	8	52	13	22	20	$\chi^2 = 13.57$ , PWC = 1 < 3	0.004
Forced to touch at age 16 years or older	6	3	12	4	33	8	11	10	$\chi^2 = 13.73$ , PWC = 0 < 2 and 3	0.003
Physical abuse at age younger than 16 years	24	10	34	12	60	15	29	27	$\chi^2 = 18.96$ , PWC = 0, 1, and 2 < 3	< 0.001
Physical abuse at age 16 years or older	21	9	33	12	55	14	29	27	$\chi^2 = 22.94$ , PWC = 0, 1 and 2 < 3	< 0.001
Physical neglect	5	2	12	4	20	5	13	12	$\chi^2 = 16.22$ , PWC = 0 and 1 < 3	0.001
Sexual harassment	20	8	45	16	88	22	33	31	$\chi^2 = 34.09$ , PWC = 0 < 1 < 3; 0 < 2	< 0.001
<b>Other stressors</b>										
Been in a serious disaster	101	42	120	43	151	38	49	43	$\chi^2 = 2.12$	0.547
Seen serious accident	74	30	91	33	131	33	42	37	$\chi^2 = 1.75$	0.627
Had serious accident or injury	61	25	62	23	93	24	32	28	$\chi^2 = 1.54$	0.672
Jail (family member)	49	20	46	17	81	21	36	32	$\chi^2 = 11.9$ , PWC = 1 < 3	0.008
Jail (self)	10	4	17	6	31	8	12	11	$\chi^2 = 6.44$	0.092
Foster care or put up for adoption	7	3	3	1	12	3	3	3	$\chi^2 = 2.98$	0.395
Separated/divorced (parents)	41	17	47	17	102	26	35	31	$\chi^2 = 17.91$ , PWC = 0 and 1 < 2 and 3	0.001

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**TABLE 2. Differences Among the Joint am and pm Fatigue Latent Classes in the Percentage of Patients Exposed to Various Stressful Life Events on the Life Stressor Checklist-Revised (N = 1,334) (Continued)**

Stressful Life Event	Low am and Low pm (0) (N = 313)		Low am and Moderate pm (1) (N = 348)		Moderate am and Moderate pm (2) (N = 518)		High am and High pm (3) (N = 155)		Statistics	p
	n	%	n	%	n	%	n	%		
Other stressors (continued)										
Separated/divorced (self)	85	34	103	37	137	34	49	44	$\chi^2 = 4.04$	0.257
Serious money problems	41	17	32	12	87	22	46	41	$\chi^2 = 46.56$ , PWC = 0, 1, and 2 < 3; 1 < 2	< 0.001
Had serious physical or mental illness (not cancer)	37	15	43	15	81	20	36	32	$\chi^2 = 17.75$ , PWC = 0 and 1 < 3	< 0.001
Abortion or miscarriage	80	45	96	45	137	42	47	51	$\chi^2 = 2.25$	0.522
Separated from child	1	-	4	2	11	3	5	5	$\chi^2 = 8.27$ , PWC = 0 < 3	0.041
Care for child with handicap	8	3	11	4	12	3	8	7	$\chi^2 = 4.43$	0.219
Care for someone with severe physical or mental handicap	47	19	60	22	103	27	38	35	$\chi^2 = 11.41$ , PWC = 0 < 3	0.01
Death of someone close (sudden)	115	47	147	54	181	47	60	55	$\chi^2 = 5.4$	0.145
Death of someone close (not sudden)	188	78	220	81	303	78	88	80	$\chi^2 = 1.02$	0.797
Seen robbery/mugging	43	17	58	21	90	23	36	32	$\chi^2 = 10.24$ , PWC = 0 < 3	0.017
Been robbed/mugged	56	23	67	24	109	28	41	38	$\chi^2 = 10.07$ , PWC = 0 and 1 < 3	0.018

am—morning; pm—evening; PWC—pairwise contrast

summed to yield a mean “affected sum” score. In addition, a PTSD sum score is created based on the number of positively endorsed items (out of 21) that reflect the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) PTSD Criteria A for having experienced a traumatic event.

### Resilience

The 10-item Connor–Davidson Resilience Scale (CDRS) evaluates a patient’s ability to handle adversity (e.g., “I am able to adapt when changes occur”) (Campbell-Sills

& Stein, 2007). Total scores range from 0 to 40, with higher scores indicating higher self-perceived resilience. The normative mean score for adults in the United States is 31.8 (SD = 5.4) (Campbell-Sills et al., 2009). The Cronbach’s alpha of the CDRS was 0.9.

### Coping Strategies

The 28-item Brief Coping Orientation to Problems Experienced Inventory scale was designed to assess a broad range of coping responses among adults (Carver, 1997; Carver et al., 1989). Each item is rated

on a Likert-type scale ranging from 1 (“I haven’t been doing this at all”) to 4 (“I have been doing this a lot”). Higher scores indicate greater use of the various coping strategies. In total, the following 14 dimensions are evaluated using this instrument (with their respective Cronbach’s alphas): self-distraction ( $\alpha = 0.46$ ), active coping ( $\alpha = 0.75$ ), denial ( $\alpha = 0.72$ ), substance use ( $\alpha = 0.87$ ), use of emotional support ( $\alpha = 0.77$ ), use of instrumental support ( $\alpha = 0.77$ ), behavioral disengagement ( $\alpha = 0.57$ ), venting ( $\alpha = 0.65$ ), positive reframing ( $\alpha = 0.79$ ), planning ( $\alpha = 0.74$ ), humor ( $\alpha = 0.83$ ), acceptance ( $\alpha = 0.68$ ), religion ( $\alpha = 0.92$ ), and self-blame ( $\alpha = 0.73$ ). Each dimension is evaluated using two items.

### Data Analysis

As previously reported by Wright et al. (2023), latent profile analysis was used to identify subgroups of patients with distinct joint morning and evening fatigue profiles (using the morning and evening LFS scores obtained during the six assessments in a single latent profile analysis). Mplus, version 8.4 (Muthén & Muthén, 1998–2017), was used to conduct the analysis. This approach provides a profile description of these two symptoms with parallel profiles over time.

Additional data were analyzed using IBM SPSS Statistics, version 28.0. Differences among the groups with distinct joint morning and evening fatigue profiles in global, cancer-specific, and cumulative life stress, as well as in resilience and the use of coping strategies at enrollment, were evaluated using parametric (e.g., analysis of variance) and nonparametric (e.g., Kruskal–Wallis) tests. A Bonferroni-corrected  $p$  value of  $p < 0.008$  was considered statistically significant for the pairwise contrasts (0.05/6 possible pairwise contrasts).

## Results

### Sample Characteristics

As previously noted by Wright et al. (2023), in brief, compared to the both low class, patients in the both high class were younger, were less likely to be married or partnered, were more likely to live alone, had a higher comorbidity burden, and had a lower functional status. In addition, patients in the both high class reported significantly higher anxiety, depression, sleep disturbance, and pain scores, and lower quality-of-life scores.

### Stress and Resilience

As shown in Table 1, across the four classes, significant increases in PSS scores were found to be consistent

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### KNOWLEDGE TRANSLATION

- More than 50% of patients receiving cancer chemotherapy experience moderate to high levels of both morning and evening fatigue.
  - Patients with higher levels of both morning and evening fatigue report high levels of global, cancer-specific, and cumulative life stress.
  - Patients with higher levels of both morning and evening fatigue report lower levels of resilience and a more frequent use of disengagement-type coping strategies (e.g., self-blame).
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with increased morning and/or evening fatigue. PSS scores occurred in the following order, from lowest to highest: both low, low morning and moderate evening, both moderate, and both high. Compared to the both low class and the low morning and moderate evening class, the other two classes had higher IES-R subscale and total scores. Compared to the other three classes, the both high class had higher LSC-R total scores. Compared to the both low class, the both moderate and both high classes had higher LSC-R affected and PTSD sum scores. In terms of resilience, compared to the both low and the low morning and moderate evening classes, the other two classes had lower CDRS scores.

### Occurrence of Stressful Life Events

Significant differences were found among the joint morning and evening fatigue classes for all the interpersonal violence, abuse, and neglect stressors evaluated using the LSC-R (see Table 2). Compared to the other three classes, the both high class was more likely to report family violence in childhood, emotional abuse, and physical abuse at younger than age 16 years and at age 16 years or older. Compared to the both low and low morning and moderate evening classes, the both high class was more likely to report being exposed to physical neglect and forced to have sex at age 16 years or older. Compared to the low morning and moderate evening class, the both high class was more likely to report being forced to sexually touch at younger than age 16 years and at age 16 years or older and to have been forced to have sex at younger than age 16 years. Compared to the both low class, the both moderate class was more likely to report emotional abuse and being forced to sexually touch at age 16 years or older.

In terms of other stressful life events (SLEs), compared to the both low class, the both high class was more likely to report parental separation or

**TABLE 3. Differences Among the Joint am and pm Fatigue Latent Classes in the Effect on Life During the Past Year of Each of the Various Stressful Life Events on the Life Stressor Checklist-Revised (N = 1,334)**

Stressful Life Event	Low am and Low pm (0) (N = 313)		Low am and Moderate pm (1) (N = 348)		Moderate am and Moderate pm (2) (N = 518)		High am and High pm (3) (N = 155)		Statistics	p
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD		
<b>Interpersonal violence, abuse, and neglect stressors</b>										
Emotional abuse	2.4	1.6	2.3	1.2	2.7	1.3	2.9	1.3	KW = 7.83	0.05
Family violence in childhood	1.7	1.1	1.7	1.1	1.9	1.2	2.3	1.2	KW = 8.68, PWC = 1 < 3	0.034
Forced sex at age younger than 16 years	1.5	1.1	2.5	1.3	2	1.3	2.3	1.5	KW = 2.7	0.44
Forced sex at age 16 years or older	1.8	1.5	1.3	0.5	2	1.3	1.6	1.1	KW = 3.4	0.334
Forced to touch at age younger than 16 years	1.5	1.1	1.8	1.2	2.1	1.3	2.6	1.5	KW = 10.77, PWC = 0 < 3	0.013
Forced to touch at age 16 years or older	1	-	1.5	0.7	2.2	1.3	2.1	1.4	KW = 6.77	0.079
Physical abuse at age younger than 16 years	1.6	1	1.8	1.3	2	1.3	2.3	1.3	KW = 7.12	0.068
Physical abuse at age 16 years or older	1.7	1.2	1.7	1	2	1.3	1.9	0.2	KW = 1.34	0.72
Physical neglect	3.4	1.5	2.6	1.2	2.8	1.4	2.8	1.4	KW = 1.47	0.69
Sexual harassment	1.6	1.3	1.3	0.8	1.6	1	1.5	0.8	KW = 3.53	0.317
<b>Other stressors</b>										
Been in a serious disaster	1.2	0.6	1.3	0.8	1.4	0.8	1.7	1	KW = 12.79, PWC = 0 and 1 < 3	0.005
Seen serious accident	1.4	0.8	1.4	0.7	1.5	0.9	1.6	1	KW = 3.37	0.339
Had serious accident or injury	1.4	0.9	1.6	1	1.7	1.1	1.7	1	KW = 5.41	0.144
Jail (family member)	1.8	1.2	1.7	1.3	1.9	1.3	2.2	1.5	KW = 2.89	0.409
Jail (self)	1.4	0.9	2.1	1.3	1.8	1.3	1.3	0.9	KW = 4.36	0.225
Foster care or put up for adoption	2.2	1.8	2.7	2.1	2.1	1	3	2	KW = 0.96	0.812
Separated/divorced (parents)	1.7	1	1.3	0.9	2	1.2	1.6	1	KW = 14.6, PWC = 1 < 3	0.002
Separated/divorced (self)	1.8	1.3	1.8	1.3	2.4	1.4	2.2	1.4	KW = 16.82, PWC = 0 and 1 < 2	0.001

*Continued on the next page*



**TABLE 3. Differences Among the Joint am and pm Fatigue Latent Classes in the Effect on Life During the Past Year of Each of the Various Stressful Life Events on the Life Stressor Checklist-Revised (N = 1,334) (Continued)**

Stressful Life Event	Low am and Low pm (0) (N = 313)		Low am and Moderate pm (1) (N = 348)		Moderate am and Moderate pm (2) (N = 518)		High am and High pm (3) (N = 155)		Statistics	p
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD		
Other stressors (continued)										
Serious money problems	2.2	1.5	2.2	1.6	2.8	1.7	3.3	1.7	KW = 12, PWC = 0 and 1 < 3	0.007
Had serious physical or mental illness (not cancer)	2.1	1.4	2.4	1.3	2.5	1.4	2.9	1.3	KW = 6.95	0.074
Abortion or miscarriage	1.3	0.6	1.3	0.9	1.8	1.2	1.7	1	KW = 12.21, PWC = 1 < 2 and 3	0.007
Separated from child	1	- <sup>a</sup>	3	0.8	2.7	1.9	3.4	1.5	KW = 2.47	0.481
Care for child with handicap	3.4	1.1	3.6	1.6	3.1	1.5	2.9	1.2	KW = 1.85	0.604
Care for someone with severe physical or mental handicap	2.1	1.4	2.4	1.4	2.8	1.5	2.7	1.5	KW = 10.14, PWC = 0 < 2	0.017
Death of someone close (sudden)	1.9	1.2	2	1.3	2.3	1.4	2.5	1.4	KW = 14.62, PWC = 0 < 2 and 3	0.002
Death of someone close (not sudden)	1.9	1.2	2	1.2	2.3	1.4	2.7	1.4	KW = 30.29, PWC = 0, 1, and 2 < 3; 0 < 2	<0.001
Seen robbery/mugging	1.4	0.8	1.4	1	1.6	1	1.7	1.3	KW = 5.04	0.169
Been robbed/mugged	1.5	0.9	1.6	1.2	1.7	1.1	1.7	1.2	KW = 0.97	0.808
<sup>a</sup> Sample size = 1; no SD reported am—morning; KW—Kruskal-Wallis test; pm—evening; PWC—pairwise contrast <b>Note.</b> Data on stressful life events are reported for patients who reported the occurrence of the stressful life event on the Life Stressor Checklist-Revised. Possible scores range from 1 (not at all) to 5 (extremely).										

divorce; serious physical or mental illness other than cancer; separation from their child; caring for someone with a severe physical or mental handicap; and having seen a robbery or a mugging and having been robbed or mugged. Compared to the low morning and moderate evening class, the both high class was more likely to report a family member being incarcerated, having a serious physical or mental illness other than cancer, and having been robbed or mugged. Compared to the other three classes, the both high class reported serious money problems. Compared to the low morning and moderate evening

class, the both moderate class was more likely to report parental separation or divorce and serious money problems.

#### Effect of SLEs

Significant differences were found among the joint morning and evening fatigue classes in the effect of various SLEs (see Table 3). Compared to the both low class, the both high class was more likely to have been affected by being forced to sexually touch at age younger than 16 years, being in a serious disaster, and having serious money problems. Compared to the low

morning and moderate evening class, the both high class was more likely to have been affected by exposure to family violence during childhood, a serious disaster, parental separation or divorce, and serious money problems. Compared to the low morning and moderate evening class, the both moderate and both high classes were more likely to have been affected by an abortion or miscarriage. Compared to the both low class, the both moderate class was more likely to have been affected by caring for someone with a physical or mental handicap. Compared to the both low class, the both moderate and both high classes were more likely to have been affected by someone close to them dying suddenly. Compared to the other three classes, the both high class was more likely to have been affected by someone close to them dying during the past year.

### Coping Strategies

Regarding engagement coping strategies, compared to the low morning and moderate evening class, the both high class was less likely to use active coping and the both moderate class was less likely to use acceptance (see Table 4). Compared to the both low class, the other three classes were more likely to use planning. Compared to the both low class, the low morning and moderate evening class was more likely to use emotional support and the both moderate class was more likely to use instrumental support.

In terms of disengagement coping strategies, compared to the both low class, the other three classes were more likely to use self-distraction and venting. Compared to the low morning and moderate evening class, the both high class was more likely to use venting and denial and the both moderate class was more likely to use behavioral disengagement. Compared to the other three classes, the both high class was more likely to use behavioral disengagement and self-blame. Compared to the both low and the low morning and moderate evening classes, the both moderate class was more likely to use self-blame.

### Discussion

Building on the authors' previous analysis of morning and evening fatigue as individual symptoms (Wright, Cooper, et al., 2017; Wright et al., 2019, 2020) and the authors' findings on various demographic, clinical, and symptom characteristics associated with joint morning and evening fatigue profiles (Wright et al., 2023), this study provides new insights into the association between joint fatigue profiles and global stress, cancer-specific stress, and the occurrence and

effect of SLEs and ACEs, as well as resilience and coping. Patients in the both high class reported the highest stress scores, the highest occurrence rates for and effects from a number of ACEs, the lowest resilience scores, and higher use of disengagement coping strategies. The remainder of the discussion places these findings in the context of the extant literature, describes relevant mechanisms to support the findings, and provides recommendations for research and clinical practice.

### Stress

The robust associations between all the stress measures and the worst joint morning and evening fatigue profiles can be partially explained by the fact that cancer and its treatment are significant stressors (Merluzzi et al., 2022) associated with dysregulation of the hypothalamic-pituitary-adrenal axis (Bower, 2019; Ravi et al., 2021). In terms of global stress, the both moderate and both high classes had PSS scores that are comparable to those of pregnant women in neighborhoods with high rates of violent crime (Shannon et al., 2020) and to those of men and women within one month after myocardial infarction (Xu et al., 2015). Higher levels of global stress were associated with greater fatigue severity in adults with inflammatory bowel disease (Luber et al., 2022), unexplained chronic fatigue (Campbell et al., 2017), and rheumatic conditions (Hung et al., 2020). Chronic stress activates the immune system with resultant increases in allostatic load and inflammation (Ravi et al., 2021). These processes may be common mechanisms that underlie these conditions, as well as the fatigue reported by patients and other chronic conditions. Future studies need to evaluate for additive or synergistic interactions between stress and inflammation and their contributions to the occurrence and severity of morning and/or evening fatigue.

In terms of cancer-specific stress, given the significant impact of a cancer diagnosis and its treatments (Merluzzi et al., 2022), the higher subscale and total IES-R scores for the both high class are not unexpected. The IES-R total score was higher than the clinically meaningful cutoff score for PTSD symptomatology of 24 or greater established in studies of earthquake survivors and survivors of the Tokyo subway sarin gas attack (Asukai et al., 2002; Creamer et al., 2003), and it met the criteria for subsyndromal PTSD (Weiss, 2007). The higher scores for the IES-R avoidance, intrusion, and hyperarousal subscales reported by the both high class suggest a PTSD diagnosis (Frances et al., 1995).

Exposure to ACEs during brain development (i.e., experiencing SLEs at age younger than 16 years) may alter neuroimmune interactions that increase the risk for PTSD (Andersen, 2022). The both high class endorsed the highest occurrence rates for several ACEs, including family violence in childhood (n = 43, 39%); emotional abuse (n = 46, 43%); physical neglect

(n = 13, 12%); and physical abuse (n = 29, 27%), forced touching (n = 22, 20%), and forced sex (n = 9, 8%) at age younger than 16 years. These findings are consistent with prior research that identified associations between average fatigue and multiple ACEs in healthy college students (Kalmakis et al., 2022), adults with multiple sclerosis (Pust et al., 2021), patients with

**TABLE 4. Differences in Brief COPE Subscale Scores Among the Joint am and pm Fatigue Latent Classes at Enrollment (N = 1,334)**

Subscale	Low am and Low pm (0) (N = 313)		Low am and Moderate pm (1) (N = 348)		Moderate am and Moderate pm (2) (N = 518)		High am and High pm (3) (N = 155)		Statistics	p
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD		
<b>Engagement coping strategies</b>										
Acceptance	4.8	1.4	4.9	1.2	4.6	1.3	4.7	1.4	F = 2.94, PWC = 1 > 2	0.032
Active coping	4	1.8	4.2	1.5	3.9	1.6	3.7	1.7	F = 2.86, PWC = 1 > 3	0.036
Humor	2.1	2	2.4	2	2.4	1.8	2.6	2.1	F = 2.14	0.094
Planning	3	1.9	3.4	1.8	3.4	1.7	3.5	1.8	F = 4.03, PWC = 0 < 1, 2, and 3	0.007
Positive reframing	3.3	2.1	3.4	1.9	3.6	1.9	3.4	2	F = 1.31	0.27
Religion	3.1	2.4	2.8	2.3	3.1	2.2	3.1	2.3	F = 1.88	0.131
Using emotional support	4.1	1.8	4.5	1.6	4.3	1.6	4.3	1.7	F = 3.44, PWC = 0 < 1	0.016
Using instrumental support	3	1.9	3.3	1.7	3.5	1.7	3.4	1.7	F = 4.61, PWC = 0 < 2	0.003
<b>Disengagement coping strategies</b>										
Behavioral disengagement	0.2	0.8	0.1	0.5	0.3	0.7	0.5	1.1	F = 10.46, PWC = 0, 1, and 2 < 3; 1 < 2	< 0.001
Denial	0.5	1	0.4	0.9	0.5	1.1	0.7	1.4	F = 4.34, PWC = 1 < 3	0.005
Self-blame	0.4	0.9	0.6	1	1.1	1.3	1.6	1.7	F = 44.31, PWC = 0 and 1 < 2 and 3; 2 < 3	< 0.001
Self-distraction	3.2	1.9	3.6	1.7	3.5	1.5	3.7	1.5	F = 4.35, PWC = 0 < 1, 2, and 3	0.005
Substance use	0.2	0.7	0.2	0.7	0.3	0.8	0.3	0.8	F = 2.13	0.095
Venting	1.5	1.5	1.9	1.7	2.1	1.6	2.7	1.7	F = 22.46, PWC = 0 < 1, 2, and 3; 1 and 2 < 3	< 0.001

am—morning; COPE—Coping Orientation to Problems Experienced Inventory; pm—evening; PWC—pairwise contrast  
**Note.** Each item on the COPE is rated on a 4-point Likert-type scale that ranges 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. Possible scores range from 2 to 8, with higher scores indicating greater use of each of the coping strategies.

chronic fatigue syndrome (De Venter et al., 2017), and women with breast cancer (Bower et al., 2014, 2021). The synergy between the occurrence of ACEs (Briggs et al., 2021; Parnes & Schwartz, 2022) and worse joint morning and evening fatigue profiles warrants additional investigation in patients with cancer. One potential explanation for this association is that ACEs increase allostatic load (Bower et al., 2014; Lacey et al., 2020; Steel et al., 2020). In addition, increasing evidence suggests that various neuroimmune interactions contribute to a higher symptom burden in patients with cancer (Bower, 2019; Scheff & Saloman, 2021).

Taken together, these findings suggest that interventions aimed at decreasing stress, such as exercise (Oppegaard et al., 2021), mindfulness meditation (Xie et al., 2020), and yoga (Danhauer et al., 2019; Selvan et al., 2022), may decrease morning and evening fatigue severity. Clinicians who care for patients with cancer need to evaluate their levels of stress and ACE exposures and provide referrals to psychological services. Given the paucity of research on SLEs and ACEs in patients with cancer, studies are warranted to confirm or refute these findings and evaluate the effects of stress reduction or resilience-enhancing interventions to decrease morning and/or evening fatigue severity.

### Resilience

Resilience is one factor that influences an individual's susceptibility to the adverse effects of SLEs (Macía et al., 2020; Weber & O'Brien, 2017). For the both moderate and both high classes, their CDRS scores were below the normative score for the general population of the United States (Campbell-Sills et al., 2009). These findings are consistent with two studies of patients with gastric cancer that found that resilience was negatively correlated with fatigue severity and explained 15% (Zou et al., 2018) to 16% (Tian & Hong, 2014) of the variance in average fatigue. Higher levels of resilience are associated with more adaptive coping to physical and emotional challenges (Macía et al., 2020). Interventions to increase resilience, such as making meaning of the cancer experience (Seiler & Jenewein, 2019), social support (Abbott et al., 2021; Borgi et al., 2020; Seiler & Jenewein, 2019), and attention and interpretation therapy (Lin et al., 2020), may decrease stress, alter neuroimmune responses (Borgi et al., 2020), and decrease fatigue. To the authors' knowledge, this study is the first to evaluate the impact of resilience on the co-occurrence of morning and evening fatigue.

### Coping Strategies

Compared to the both low class, the other three classes were more likely to use planning as a coping strategy. Given that the use of planning was found to help patients with cancer adjust to their current situation (Nilsen et al., 2021), these findings may reflect patients' efforts to mitigate the effects of morning and/or evening fatigue.

Compared to the other three classes, the both high class used more disengagement coping strategies. Of note, in studies of patients with end-stage kidney disease (Picariello et al., 2018), patients during cancer chemotherapy (Dahal & Meheta, 2018), and healthy working adults (Otsuka et al., 2009), disengagement coping strategies were used to decrease fatigue. Although engagement coping strategies are considered adaptive and encourage post-traumatic growth (Nik Jaafar et al., 2021; Shand et al., 2015), disengagement coping strategies were found to mediate the impact of ACEs on cancer-specific stress (Langford et al., 2017).

It is important to note that patients employ multiple coping strategies (Leonidou et al., 2019). Several qualitative studies highlight the need for clinicians to be aware of patients' beliefs about their coping efficacy (Dong et al., 2021; Yeun & Jeon, 2020). Higher levels of coping efficacy are associated with higher levels of emotional and physical well-being (Merluzzi et al., 2022). Therefore, additional research is warranted on the efficacy of interventions that support patients' coping efficacy and the development of more robust engagement strategies, such as personalizing support (Schellekens et al., 2021) and solution-focused interventions (Wang et al., 2021), to reduce fatigue and various types of stress.

### Strengths and Limitations

The strengths of this study include a large sample size, patients with heterogeneous types of cancer, and the evaluation of three different types of stress, as well as resilience and coping. However, stress, resilience, and coping strategies were evaluated only upon enrollment. Therefore, associations between changes in the co-occurrence of morning and evening fatigue and changes in the various stress measures warrant evaluation during and following the completion of chemotherapy. In addition, an evaluation of stress biomarkers will increase knowledge of the mechanisms that underlie the relationships between the co-occurrence of morning and evening fatigue and stress. Equally important, future studies need to evaluate the impact of various

social determinants of health (e.g., social support, neighborhood environments) that may contribute to both fatigue and stress.

### Conclusion and Implications for Practice

This study is the first to evaluate for associations between higher levels of joint morning and evening fatigue profiles in the same patients as well as levels of different types of stress, resilience, and use of coping strategies. In addition to the clinical implications noted previously, a coordinated approach is needed to decrease stress and provide supportive services to patients undergoing chemotherapy. Clinical assessment of patients' level of resilience, preferred coping strategies, and perceived coping efficacy has the potential to inform personalized supportive interventions such as referrals for psychosocial support, stress management, resilience training, and exercise. The diurnal nature of fatigue suggests that the timing of personalized interventions to decrease fatigue needs to be considered. Additional studies are needed to evaluate the prescription of personalized strategies based on a patient's morning and evening fatigue profile to decrease both fatigue and stress.

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## QUESTION GUIDE FOR A JOURNAL CLUB

Journal clubs can help to increase and translate findings to clinical practice, education, administration, and research. Use the following questions to start discussion at your next journal club meeting. Then, take time to recap the discussion and make plans to proceed with suggested strategies.

1. What characteristics related to stress may put individuals who are receiving chemotherapy at higher risk for fatigue?
2. How do the twice-daily measures of fatigue contribute to the knowledge gained about factors related to fatigue in individuals during chemotherapy?
3. What strategies could oncology nurses suggest to individuals during their chemotherapy to decrease stress?

Visit <https://bit.ly/1vUqbVj> for details on creating and participating in a journal club. Contact [pubONF@ons.org](mailto:pubONF@ons.org) for assistance or feedback. Photocopying of the article for discussion purposes is permitted.

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