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Effects of a light therapy intervention on diurnal salivary cortisol in fatigued cancer survivors: A secondary analysis of a randomized controlled trial

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ABSTRACT

Objective: Altered diurnal cortisol rhythms are a potential mechanism through which symptoms of fatigue are maintained in post-treatment cancer survivors. Exposure to early morning bright light may target this underlying dysregulation, resulting in improved diurnal cortisol patterns, subsequently improving symptoms of fatigue. This research investigates the effects of a 4-week light therapy intervention on the diurnal cortisol slopes and output in fatigued cancer survivors.

Methods: Post-treatment adult cancer survivors who met diagnostic criteria for cancer-related fatigue were randomly assigned to receive either a bright white light (BWL) or dim red light (DRL) device, used daily for 30 min over four consecutive weeks. Assessments of fatigue and salivary cortisol were collected at baseline and post-intervention. Cortisol was sampled four times per day (waking, noon, 5 pm, bedtime) for three days at each timepoint. Diurnal cortisol slopes and total cortisol output were calculated at baseline and post-intervention. Linear mixed models were used to analyze the data.

Results: Seventy-seven participants were included in this analysis (BWL $n = 40$; DRL $n = 37$). Participants in both groups displayed increased steepness in cortisol slope (B = -0.02, $p = .01$, Cohen's d = 0.57) and increased total cortisol output (B = 9.58, $p = .03$, Cohen's d = 0.49) from baseline to post-intervention, indicating only a moderate effect of time. Neither diurnal cortisol slopes nor total cortisol output mediated the relationship between the light therapy intervention and fatigue levels.

Conclusion: Though the results of this trial are promising for light therapy as an effective intervention to reduce fatigue in cancer survivors, this does not appear to be achieved through alterations in neuroendocrine function.

ClinicalTrials.gov registration #: NCT01780623

1. Introduction

Cancer-related fatigue (CRF) is one of the most common and distressing treatment-related side-effects reported by cancer survivors in the months and years following the conclusion of cancer treatment [1]. This type of fatigue is generally described as impacting physical, emotional, and/or cognitive wellbeing, is not limited to the active phase of cancer or cancer treatment, and is not relieved by rest or sleep like typical fatigue [1]. Though common across many cancer types and treatments, the underlying physiological mechanisms that drive the development and severity of CRF are not clearly understood, and no gold standard of treatment exists. Although there is increasing evidence that physical activity and some psychoeducational interventions are promising and recommended in existing guidelines [1,2], research seeking to develop and test innovative, mechanism-driven interventions for the treatment and management of this condition is warranted.

Though the mechanisms underlying CRF are likely multi-dimensional, some research has linked increases in CRF symptomatology and

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severity to alterations in the typical diurnal cortisol rhythm [3–6]. It has been suggested that the regulation of the hypothalamic-pituitary-adrenal axis (HPA-axis), the system that controls the release of cortisol, may be disrupted by cancer and its treatments [7]. Cortisol, a multifunctional glucocorticoid hormone and key marker of HPA-axis function, is typically secreted in a diurnal pattern, with peak concentrations present in the morning, followed by a slow decrease over the day, and a nadir at bedtime [7,8]. Dysregulation in this system evidenced by 'flatter' diurnal slopes and/or higher cortisol output released over the day has been associated with disruptions in sleep-wake patterns, lower daytime activity levels, worse quality of life, and increased levels of fatigue [3,9]. Supporting this notion, one study reported that breast cancer survivors with significant fatigue displayed diurnal cortisol slopes that were flatter and showed a slower decline in output in the evening hours than those observed in healthy controls [3]. Similarly, in another sample of breast cancer survivors, higher levels of evening cortisol and greater overall cortisol output was associated with reports of physical fatigue, independent of depressive symptoms [5]. There is also some evidence that the association between dysregulated cortisol rhythms and CRF may be long term. Specifically, one study reported that in a sample of women with ovarian cancer who were five or more years post-diagnosis, those who displayed flatter cortisol slopes were more likely to experience fatigue than those with steeper cortisol slopes [10]. Finally, it is well documented that flattened diurnal cortisol slopes are not only associated with CRF, but also with shorter survival time [11–15]. Taken together, the evidence suggests that cortisol dysregulation may be a contributing factor to the ontogeny and severity of CRF.

Though cortisol dysregulation may be one potential mechanism by which CRF is maintained, research has revealed mixed results to support the ability of interventions to impact the diurnal cortisol rhythm (either the slope or total output) and reduced symptoms of fatigue subsequent to intervention are not always associated with changes in cortisol. For example, one study found that an 8-week Iyengar yoga intervention for breast cancer survivors was associated with lower morning and early evening cortisol output and improved fatigue [16], while another study examining a 12-week Iyengar yoga intervention for fatigued breast cancer survivors showed no impact on diurnal cortisol [17]. Another study examining the effects of an integrated yoga program on fatigue symptoms and diurnal salivary cortisol in 91 metastatic breast cancer survivors found a reduction in fatigue severity and diurnal variation in cortisol, relative to a supportive therapy group [18]. Research investigating other interventions that specifically target alterations in the normal diurnal cortisol rhythm (through regulation of HPA-axis functioning) may provide some insights into the role of diurnal cortisol as a mechanism of CRF and could potentially result in more effective treatments.

Light therapy is one treatment modality that has been used to successfully target circadian rhythm dysregulation in insomnia disorder [19] and some mood disorders [20]. Through consistent early morning exposure to bright light, the internal circadian system or body clock is cued to activate physiological systems that follow diurnal patterns [21], including cortisol. This consistent and systematic signaling to the circadian system can result in a realignment and harmonization of underlying rhythms, including those of the HPA-axis, the sleep-wake cycle, and other hormones such as melatonin [21]. This realignment in physiological systems is then hypothesized to subsequently reduce behavioral and psychological symptoms, which may include fatigue.

In the primary analysis of this study, we showed that systematic early morning exposure to bright white light was associated with improved symptoms of CRF in cancer survivors with persistent fatigue [22], a finding that was also reported in a different sample [23]. In this secondary analysis, we propose that the changes observed in CRF after a light therapy intervention may be explained by alterations in diurnal cortisol patterns and output. Previously, no published studies have closely examined the impact of light therapy on diurnal cortisol rhythms in cancer survivors with fatigue. The objectives of this study were to: 1) determine whether there is a difference in patterns of diurnal cortisol slope and output between and within light therapy conditions after a 4-week intervention period, and 2) examine whether changes in cortisol slope and output after 4-weeks mediate the association between the light therapy intervention and fatigue.

2. Method

This study was a secondary analysis of a 4-week blinded randomized controlled trial of light therapy for CRF in cancer survivors. The complete protocol for this trial and primary results are outlined in detail elsewhere (clinicaltrials.gov NCT01780623) [22,24]. All participants provided informed written consent before engaging in research related activities. Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board of the University of Calgary.

2.1. Participants

Participants were self-referred and recruited from Calgary, Alberta, Canada and surrounding areas using pamphlets distributed via cancer registry mailings, and at local clinics and fatigue education seminars between October 2013 to March 2014 and from October 2014 to March 2015. To control for seasonal changes in hours of daylight, participants were recruited during the fall and winter months only when daylight exposure was at its lowest. Adults with non-metastatic disease and treatment completion at least three months prior to enrollment were eligible. Participants were administered a screening questionnaire over the phone and were required to meet the diagnostic criteria for CRF outlined in the International Classification of Diseases – 10th Revision (ICD-10) and assessed using the Diagnostic Interview Guide for Cancer-Related Fatigue [25]. Individuals receiving ongoing hormonal or maintenance treatments and/or using psychotropic medications were eligible provided their dose had remained stable for the previous 6 weeks. Individuals were ineligible if they screened positive for the presence of another sleep or psychiatric condition (e.g., sleep apnea, restless legs syndrome, bipolar disorder), if they had been diagnosed with an ongoing medical condition that could influence fatigue levels (e.g., anemia, autoimmune disorder, heart failure), the presence of an eye disease, recent eye surgery, the use of photosensitizing medications, or if their employment required shift work. For this analysis, participants who were taking medications that may affect cortisol levels (i.e., corticosteroids or immune modulating medications) were also excluded. Given that participants largely self-selected into the study, it is possible that the sample may be prone to selection effects that could not be accounted for by randomization or blinding, such as being more open to novel treatments.

2.2. Blinding and random assignment

Participants were told they would be randomly assigned to receive one of two types of light devices during the informed consent procedure, but no further information was provided about the wavelength of light. Prior to recruitment, study identification numbers were assigned to either BWL or DRL using a blocked randomized design (blocks of 4,6,8) created by a computer program on a 1:1 allocation ratio. A research assistant not involved in the study used the predetermined randomization sequence to label each light device with a study identification number prior to study initiation. The light devices were then stored in non-descriptive packaging to ensure that both investigators and participants were blind to condition. Study identification numbers were assigned to eligible participants in the order of enrollment. The allocation sequence was not revealed until data entry was complete and the study outcomes had been calculated.

2.3. Intervention

The light therapy device used in this study was the Litebook Elite treatment device (The Litebook Company Ltd., Medicine Hat, AB). The Litebook is a small (12.5 cm × 12.5 cm × 12.5 cm), lightweight (284 g) device that is designed to be placed on a table approximately 30 to 60 cm from the user's face and offset at a 45-degree angle from the midline of the visual field. The Litebook in the BWL treatment condition contained 25 white light-emitting diode (LED) lights that emitted white light at 1250 lx and with a distribution of energy concentrated in the shorter wavelengths of visible light (peak between 464 and 466 nm). An identical-appearing Litebook device used in the DRL condition contained 25 red LEDs that emitted red light at < 400 lx with a distribution of energy concentrated in the longer wavelengths of visible light (peak between 632 and 633 nm). The devices were programmed to turn off after 30 min of continuous use. Each Litebook was modified to include an integrated logger device (HOBO State Data Logger, Onset Computer Corporation, Bourne, MA) that recorded the date and duration that the light device was on. Participants were also required to record their daily use of the device on a tracking sheet provided to them upon receiving the device.

2.4. Procedure

At baseline, participants provided demographic and medical history information, and completed a questionnaire package. Then, during a 1-week baseline period, participants were provided with a salivary collection kit to collect four saliva samples a day (i.e., waking, noon, 5 pm, bedtime) for three consecutive days, and returned the samples to the research team at the end of the week. Following the baseline period, participants were randomized to receive one of two types of light devices to take home, either bright white light (BWL) or dim red light (DRL), and were asked to use the device daily for 30 min, within 30 min of waking, for a period of 4 weeks (28 days). During the final week of light use (week 4), participants were provided with another salivary collection kit to collect four saliva samples per day for a period of three days and returned it to the researcher on the final day of the study. Participants then returned the light device and completed the questionnaire package again.

2.5. Measures

2.5.1. Fatigue

The Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) [26] is a 30-item comprehensive measure designed to assess the physical and psychological aspects of fatigue and was the primary outcome measure of cancer-related fatigue in this study (see Footnote 1). The scale is summed to obtain a total score that is within the range of −24 to 96, with higher scores indicating greater levels of fatigue. Internal consistency ranges from 0.83 to 0.93 with test-retest reliabilities ranging from 0.55 to 0.64 [27]. The MFSI-SF has been demonstrated appropriate for use in a wide range of cancer populations [27].

2.5.2. Salivary cortisol measurement and processing

Participants collected saliva samples using salivette collection vials (SARSTEDT AG & Co., Germany) at four time points (waking, noon, 5 pm, bedtime) over a period of three consecutive days at baseline and again during the final week of light use, as close to the end of the week as possible. Participants were asked to collect the samples on weekdays only and to avoid eating, drinking, or brushing their teeth at least 30 min prior to collection. Color coded, time stamped tubes and tracking sheets were provided to increase compliance. Though the tubes were labelled with times for collection, participants were also asked to track the exact time that each sample was completed on a provided tracking sheet. Samples were stored in a fridge or freezer in the participant's home once complete.

Once collected at the research site, all of the salivettes were stored in a freezer at -—80C until they were shipped for processing at an outside laboratory (TUD Biopsychology Laboratory, Dresden, Germany). The cortisol values were determined using a commercial chemiluminescence immunoassay (CLIA, IBL International, Hamburg, Germany) conducted according to manufacturer protocols. The intra-assay coefficients of variation for this process are less than 10%. Cortisol concentrations were calculated in nmol/L.

2.6. Sample size

Prior to trial initiation, we estimated medium effect size of 0.25 on the primary outcome of fatigue (MFSI-SF). The required sample size was estimated to be 28 participants per group (56 total) to provide adequate power (80%) to detect a medium effect on the primary outcome [28]. To obtain adequate power (80%) to examine the secondary outcomes of the trial, an estimated 49 participants in each group (98 total) was estimated. An anticipated attrition rate of 20% increased the total number of participants required to 62 per group (124 total). A more detailed sample size calculation can be found in the published protocol [24].

2.7. Data reduction strategy

Cortisol values greater than 4 standard deviations above the sample mean for that timepoint were removed [10]. Upon removal of all outliers, mean cortisol values at each timepoint (i.e., waking, noon, 5 pm, bedtime) were calculated at pre- and post-intervention within participants across days. To adjust for the non-normal distributions of the raw cortisol values, all values were transformed using a natural log transformation and the transformed values were used for all analyses.

To investigate changes in diurnal cortisol rhythms, we extracted two common cortisol indices from the data: the diurnal cortisol slope and total cortisol output. The diurnal slope is meant to capture circadian fluctuations in cortisol from day-to-day, while total cortisol output reflects cumulative exposure to cortisol across the day [29]. For the diurnal slope, we estimated the absolute change or rate of change in cortisol from immediately upon waking to late evening or bedtime [e.g., [30–31]]. The diurnal cortisol slope was calculated by regressing the log-transformed cortisol values on time since wake-up (in hours). The unstandardized beta weight was used as a measure of diurnal cortisol slope [14]. Smaller (higher magnitude negative) unstandardized values represent a steeper decline in cortisol levels over the course of the day, while larger unstandardized values reflect flatter diurnal rhythms.

Total cortisol output over three days at pre- and post-intervention were calculated as the area under the curve with respect to the ground (AUCg) based on the trapezoidal formula [32]. The AUCg was calculated within participants for each day, then averaged across days to arrive at one value for each participant at pre- and post-intervention.

Normality of the residuals and homogeneity of variance were examined. Using QQ plots and the Anderson-Darling normality test, no violations of the normality of errors for either cortisol slopes nor AUCg were observed. The plots of residuals vs. fitted values showed no severe violations of homogeneity of variance of errors.

2.8. Statistical analyses

2.8.1. Missing data

The variables used in the analysis were examined for missing data using the MissMech package in R [33]. The pattern of missing data as well as a non-significant Little's MCAR (missing completely at random)

Footnote 1 The Functional Assessment of Cancer Therapy – Fatigue or FACIT-F subscale was also administered in this study but was used as a supplementary secondary outcome measure to assess quality of life.

tests indicated that there was not enough evidence to reject the MCAR assumptions. Missing data were imputed using a multiple imputation with predictive mean matching method in the MICE package [34].

2.8.2. Objective 1 - Light therapy and cortisol

Multilevel modeling was used to determine whether diurnal cortisol slope and total cortisol output (AUCg) differed between groups (BWL vs. DRL) and over time (i.e., baseline to post-intervention) and whether a group by time interaction was observed. The model was estimated with a random intercept and fixed slopes for time and each covariate. The covariates age, BMI, anti-depressant use, and time since last treatment were included in each model as they have been previously identified as factors that can affect circulating levels of cortisol [3,35,36]. The covariance structure was set to autoregressive (AR1) and all data analyses were conducted in R Studio (R Studio Team, 2015) [37] using the *nlme* package [38].

2.8.3. Objective 2 – Fatigue and cortisol

The mediation effect of cortisol slope and output between the light therapy intervention and fatigue was examined using the multilevel structural equation modeling framework (MSEM) proposed by Preacher and colleagues [39,40]. Following Preacher, Zhang, and Zyphur [39] we tested two separate MSEM models with the light therapy intervention as the predictor variable and fatigue (as measured by the MFSI total score) as the dependent variable. In one model, cortisol slope was used as the mediator whereas total cortisol output (AUCg) was used as the mediator in the second model. Given that light therapy is a variable measured at the cluster level, a 2–1-1 model was examined, and only between-cluster mediation effects were estimated. Both models were tested using a robust maximum likelihood estimator (MLR) in Mplus 6.12 [41].

3. Results

3.1. Participants

Overall, data from 77 randomized participants (BWL $n = 40$; DRL $n = 37$) were eligible for inclusion in the intention-to-treat analysis. Of

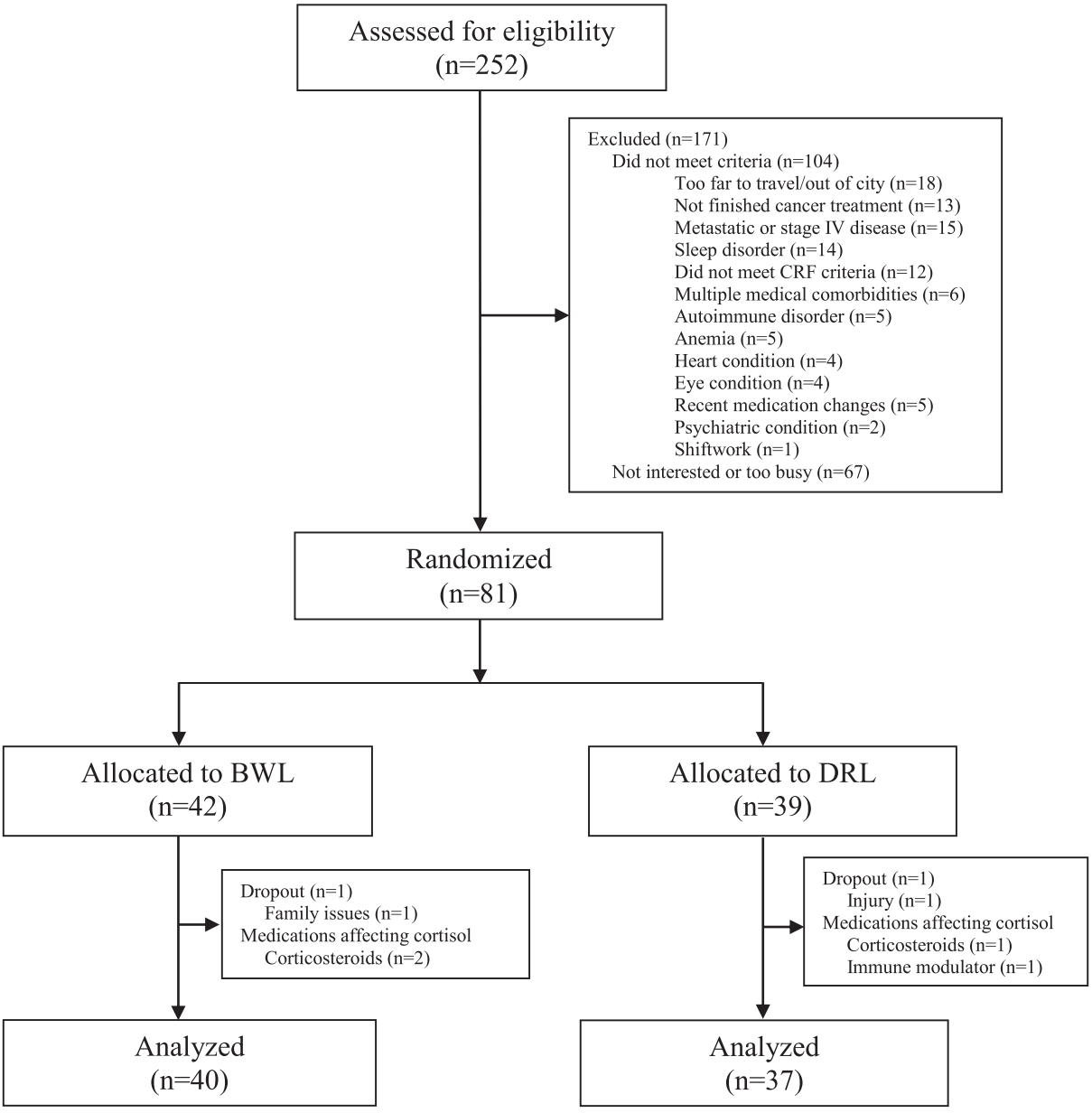

Fig. 1. Participant flow through the study.

Table 1
Demographics and clinical characteristics of sample.

	Intervention Group						
	BWL (n = 40)		DRL (n = 37)			Total (*N* = 77)	
Demographic or Clinical Characteristic	n	%	n	%	p	n	%
Sex					0.26		
Women	36	90.0	30	81.1		66	85.7
Men	4	10.0	7	18.9		11	14.3
Race/ethnicity					0.63		
White	37	92.5	35	94.6		72	93.5
Asian	2	5.0	2	5.4		4	5.2
Aboriginal	1	2.5	0	0		1	1.3
Marital status					0.09		
Partnered	32	80.0	23	62.2		55	71.4
Single	6	15.0	6	16.2		12	15.6
Divorced	0	0	5	13.5		5	6.5
Widowed	2	5.0	3	8.1		5	6.5
Employment					0.33		
Full-time	17	42.5	14	37.8		31	40.3
Part-time	8	20.0	4	10.8		12	15.6
Retired	9	22.5	15	40.5		24	31.2
Disability	5	12.5	2	5.4		7	9.1
Homemaker	1	2.5	2	5.4		3	3.9
Cancer type					0.67		
Breast	26	65.9	21	56.8		47	61.0
Gynecological	6	15.0	4	10.8		10	13.0
Colorectal	5	12.5	5	13.5		10	13.0
Lung	1	2.5	3	8.1		4	5.2
Prostate	1	2.5	1	2.7		2	2.6
Other	1	2.5	3	8.1		4	5.2
Previous tx							
Surgery	38	95.0	34	91.9	0.58	72	93.5
Chemotherapy	26	65.9	33	89.2	0.01	59	76.6
Radiation	29	72.5	25	67.6	0.64	54	70.1
Hormonal	12	30.0	13	35.1	0.63	25	32.5
Current tx							
Hormonal	12	30.0	16	43.2	0.23	28	36.4
Antidepressants	10	25.0	11	29.7	0.65	21	27.3
Hypnotic/Sedative	9	22.5	7	18.9	0.70	16	20.8
	Mean	SD	Mean	SD	p	Mean	SD
Age, years	56.8	10.7	59.5	9.1	0.25	58.1	10.0
Range	30–81		41–76			30–81	
BMI, kg/m^2	27.0	4.1	28.1	6.4	0.38	27.5	5.3
Range	20–40		18–45			18–45	
Months since diagnosis	24.0	17.9	32.4	29.6	0.13	28.0	24.5
Range	6–102		12–162			6–162	
Months since final tx	16.7	16.6	24.0	29.3	0.18	20.0	23.7
Range	4–94		3–160			3–160	

Note. BWL = bright white light; DRL = dim red light; tx = treatment.

the 81 recruited for the full trial, three were excluded from the analysis for current corticosteroid use (medications impacting salivary cortisol levels), and one was excluded for current use of Herceptin (an immune modulating medication; Fig. 1). Participant demographic and clinical characteristics for those included in these analyses are outlined in Table 1. A total of 2013 (93.7%) cortisol samples were available for analysis. After screening for outliers, 30 (1.5%) samples were removed.

3.2. Objective 1

A baseline model with a random intercept only was tested first. Results showed an overall intercept (diurnal cortisol slope) value of −0.16 (SE = 0.004, 95% CI [−0.17 to −0.15], $p < .001$). The negative unstandardized slope indicates that the log-transformed cortisol values decreased by 0.16 units every hour. The intraclass correlation of 0.5538 suggests that 55.38% of the variance in the diurnal cortisol slopes can be explained by differences between participants. A multilevel model on log-transformed cortisol slopes revealed that, after controlling for age (B = 0.001, $p = .06$), BMI (B = 0.001, $p = .65$), antidepressant medication (B = −0.01, $p = .25$), and time since last cancer treatment (B = 0.001, $p = .97$), only a significant effect of time was observed (B = −0.02, SE = 0.006, 95% CI [−0.03 to −0.003], $p = .01$, Cohen's d = 0.57). There was no significant effect of group (B = 0.01, SE = 0.01, 95% CI [−0.009–0.03], $p = .29$, Cohen's d = 0.25), nor a significant time by group interaction (B = 0.007, SE = 0.009, 95% CI [−0.01–0.02], $p = .49$, Cohen's d = 0.16). Therefore, the cortisol slopes increased in steepness from baseline to post-intervention across both groups, but this did not differ between groups after the 4-week intervention. The average raw cortisol values at each sampling time are presented for each group pre- and post-intervention in Table 2, and for illustrative purposes are presented in Fig. 2. The cortisol slope and AUCg values are presented in Table 3.

A similar multilevel model was tested on the total cortisol output (AUCg). The baseline model showed an overall cortisol output of 80.19 (SE = 4.51, 95% CI [71.20–89.17], $p < .001$). The intraclass correlation was 0.7699, indicating that 76.99% of the variance in the total cortisol output comes from differences between individuals. After controlling for age (B = −0.32, $p = .45$), BMI (B = −0.95, $p = .24$),

Table 2
Average raw cortisol values in nmol/L for bright white light and dim red light conditions at each sampling time pre- and post-intervention.

	Intervention Group		
	BWL (n = 40)	DRL (n = 37)	Overall (n = 77)
Sample Time	Mean (SD)	Mean (SD)	Mean (SD)
Waking			
Pre-Intervention	12.08 (7.49)	15.42 (9.32)	13.69 (8.53)
Post-Intervention	13.53 (7.93)	16.68 (9.21)	15.04 (8.66)
Noon			
Pre-Intervention	4.76 (2.67)	4.97 (2.90)	4.86 (2.77)
Post-Intervention	5.73 (3.61)	6.38 (4.44)	6.04 (4.01)
5 pm			
Pre-Intervention	2.65 (1.59)	2.76 (1.53)	2.70 (1.55)
Post-Intervention	2.65 (2.21)	2.94 (1.84)	2.79 (2.03)
Bedtime			
Pre-Intervention	1.74 (1.82)	1.63 (1.17)	1.68 (1.53)
Post-Intervention	1.50 (0.94)	1.58 (1.20)	1.54 (1.07)

Note. BWL: bright white light; DRL: dim red light.

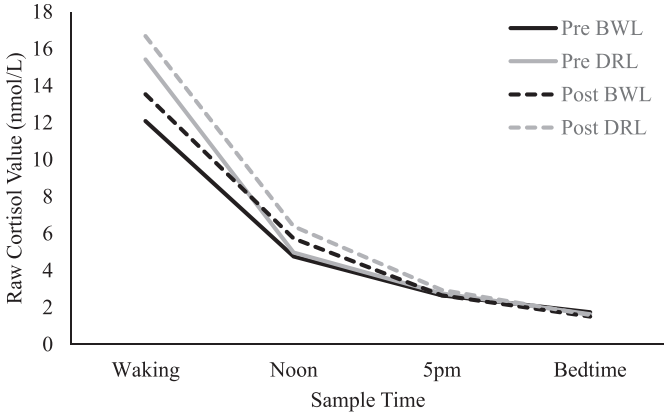

Fig. 2. Average raw cortisol values for bright white light and dim red light conditions at each sampling time pre- and post-intervention. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

antidepressant medication (B = 5.04, p = .59), and time since last cancer treatment (B = 0.55, p = .003), we found a significant effect of time (B = 9.58, SE = 4.47, 95% CI [0.67–18.48], p = .03, Cohen's d = 0.49). There was no group effect (B = −13.21, SE = 9.22, 95% CI [−31.60–5.17], p = .16, Cohen's d = 0.34), and no time by group interaction (B = 0.29, SE = 6.20, 95% CI [−12.06–12.64], p = .96, Cohen's d = 0.01). These results indicate that total cortisol output increased by 9.58 units between baseline and post-intervention, with both groups showing increased AUCg from baseline to post-intervention (Table 3).

3.3. Objective 2

Both mediation models can be seen in Figs. 3 and 4. The mediation model using cortisol slope as a mediator showed no significant mediation effect. Although light therapy was statistically significantly related to fatigue (B = 34.62, SE = 11.44, 95% CI [12.19–57.04], p = .002), the overall indirect effect from light therapy to fatigue through cortisol slope was not statistically significant (B = 11.37, SE = 15.06, 95% CI [−18.13–40.89], p = .45; see Fig. 3). Similarly,

Table 3
Cortisol values resulting from linear mixed models analyses.

	Intervention Group		
	BWL (n = 40)	DRL (n = 37)	Overall (N = 77)
AUCg at Pre-Intervention	68.02	76.69	72.64
AUCg at Post-Intervention	75.76	93.48	84.18
Slope at Pre-Intervention	−0.15	−0.16	−0.15
Slope at Post-Intervention	−0.16	−0.17	−0.17

Note: Analyses included log-transformed cortisol values and adjusted for age, BMI, antidepressant use, and time since last cancer treatment. BWL: bright white light; DRL: dim red light.

there was a significant effect of light therapy on total cortisol output (AUCg) at the between clusters level (B = 50.91, SE = 6.77, 95% CI [37.64–64.18], p < .001). However, the indirect effect from light therapy to fatigue through total cortisol output (AUCg) was not statistically significant (B = 1.26, SE = 9.13, 95% CI [−16.64–119.15], p = .89; see Fig. 4). These results suggest that diurnal cortisol rhythms do not mediate the relationship between light therapy and fatigue in this sample.

4. Discussion

This secondary analysis investigated the impact of a light therapy intervention on diurnal cortisol rhythms among cancer survivors with clinical levels of fatigue. After 4-weeks of light therapy intervention, participants receiving both bright white light and dim red light therapy displayed an increase in the steepness of cortisol slopes and an increase in total cortisol output from baseline to post-intervention. However, neither diurnal cortisol output nor cortisol slope mediated the relationship between light therapy and symptoms of fatigue. Though the results of this trial are promising for light therapy to serve as an intervention for CRF, the role of cortisol as the primary mechanism of CRF remains less clear.

It was anticipated that exposure to early morning BWL would be associated with an increase in the steepness of the diurnal slope and decrease in total cortisol output (AUCg), but an increase in both the steepness of the slope and total output were observed among participants in both light therapy conditions. These increases seem to be driven by an increase in morning cortisol output, whereby the morning cortisol peak was increased in both groups, leading to both steeper slopes and greater overall cortisol output. The observed increase in total cortisol output in this case, when paired with the increased slope, may be indicative of a more regulated cortisol rhythm. Previous research has suggested that higher morning cortisol coupled with lower evening levels have been associated with better health outcomes in cancer survivors [3] and is indicative of healthier HPA axis function. However, further research that includes measures of the cortisol awakening response (CAR), or the typical increase in cortisol secretion that occurs within 10–40 min of waking, would provide more information about the role of morning cortisol concentrations in this association.

There are a few potential explanations for why both groups showed improvements on these outcomes. First, it is possible that the lights used in both conditions emitted light at a wavelength and brightness that had the ability to impact the circadian system, resulting in regulated cortisol release (i.e., improvements in cortisol slope) and overall daily concentrations over time [42]. Second, it is possible that the behavioral changes associated with using the light each morning upon waking (i.e., developing a routine of waking up to use the device for 30 min each morning over a one month period) were able to impact this system and produce change on the outcomes in both groups. Finally, it

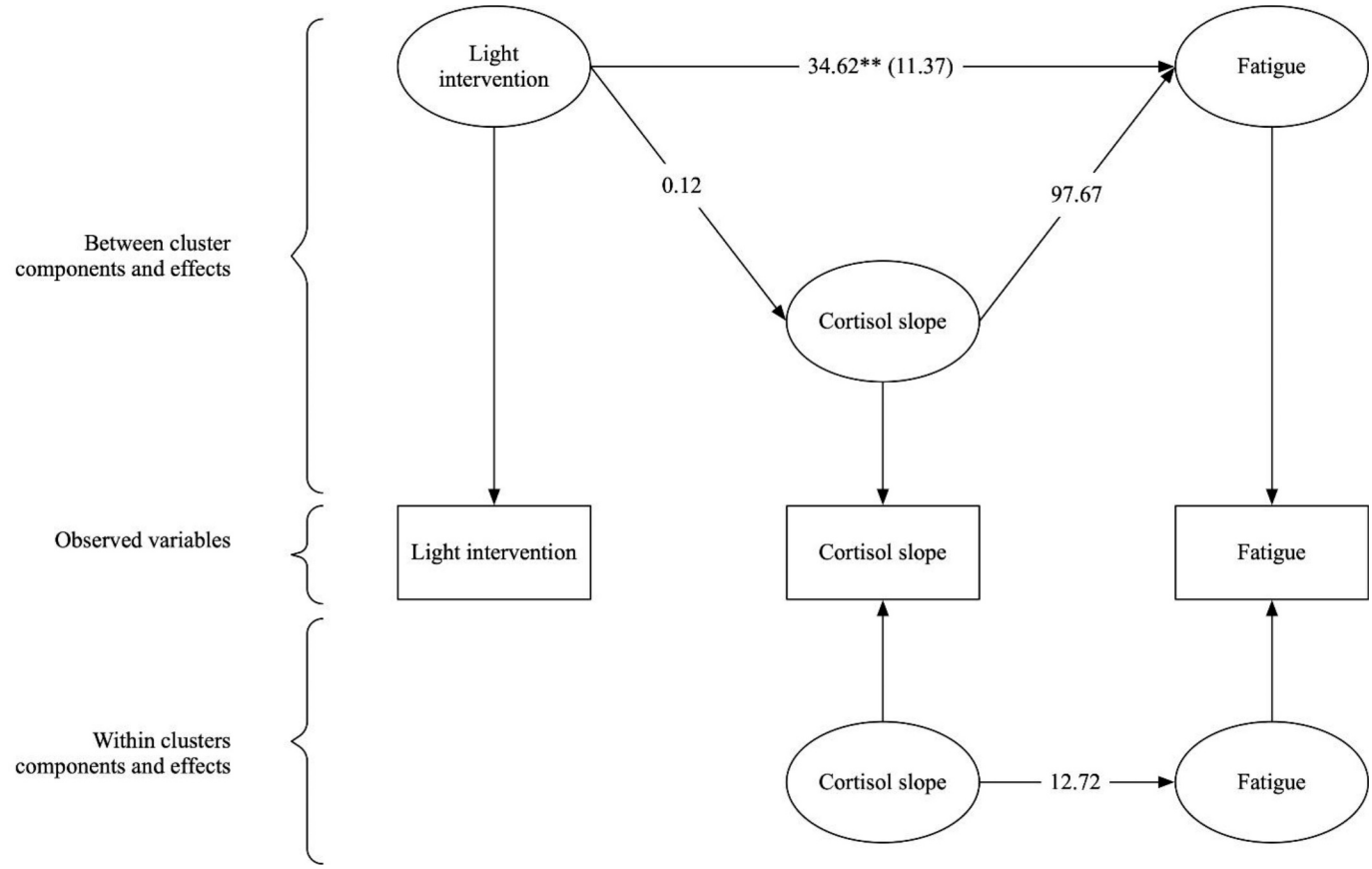

Fig. 3. Mediation model showing the effect of light therapy intervention on fatigue through cortisol slope. The indirect effect is shown in parentheses.
** $p < .01$.

is also possible that the light therapy devices could have produced a placebo effect, wherein diurnal cortisol outcomes were improved through some conditioned response to light use. Unfortunately, teasing apart the primary contributor to these results is difficult to do in this trial, especially given the very high adherence rates [22]. Though we were surprised by these findings, they are in line with the results of our initial report on the primary outcome of fatigue wherein both groups showed improvement in fatigue symptoms over time [22].

Several limitations of this study and analysis deserve mention. First, it is possible that other variables known to impact diurnal cortisol rhythms were not considered in this analysis. For example, disease characteristics (e.g., tumor stage or disease severity), some health conditions (e.g., thyroid disorders), and use of specific medications (e.g., use of NSAIDs), have been shown to impact circulating cortisol [5,43,44]. Second, we also did not measure life stress or social support. Some recent research has reported associations between higher cumulative life stress and/or life stress severity and flatter diurnal rhythms, as well as potential buffering effects of higher social attachment on cortisol rhythms [10]. Finally, it is possible that changes in diurnal cortisol rhythms associated with specific light use may require a longer intervention period to be detected at the between-group level. Given that the duration of this intervention was only 28 days and that cortisol was collected up to six days before the end of the intervention period, it is possible that a longer duration of light use is required to observe proposed changes to the underlying endogenous rhythms. For example, the yoga intervention described above that found significant differences in cortisol levels between groups had an intervention period of 8 weeks [16]. Research investigating the long-term outcomes of light therapy on CRF and its underlying mechanisms are required to achieve a thorough understanding of its impact.

5. Conclusion

Participants in both groups displayed measurable change in both the steepness of cortisol slope and total cortisol output, but light therapy did not influence fatigue through its impact on diurnal cortisol. Overall, the results of this trial are promising for light therapy as an effective intervention to reduce fatigue in cancer survivors, but this does not appear to be achieved through alterations in neuroendocrine function.

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Declaration of Competing Interest

None.

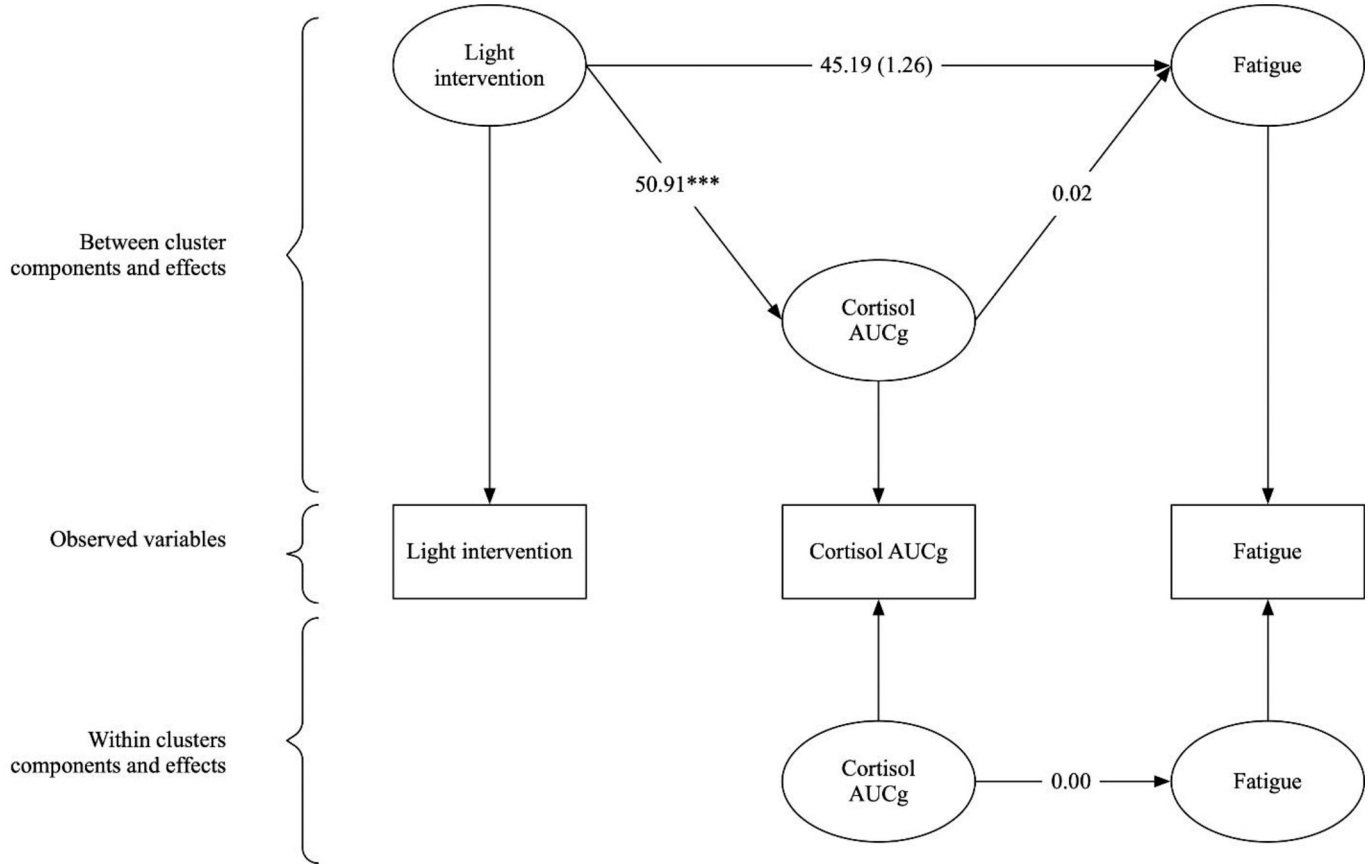

Fig. 4. Mediation model showing the effect of light therapy intervention on fatigue through total cortisol output (AUCg). The indirect effect is shown in parentheses. *** $p < .001$.

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