Light therapy for cancer-related fatigue in (non-)Hodgkin lymphoma survivors

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CHAPTER 3

EFFICACY OF LIGHT THERAPY FOR CANCER-RELATED FATIGUE IN (NON-)HODGKIN LYMPHOMA SURVIVORS: RESULTS OF A RANDOMIZED CONTROLLED TRIAL.

Cancers, 2021; 13(19): 4948
doi.org/10.3390/cancers13194948

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ABSTRACT

Purpose

To evaluate the short- and long-term effects of light therapy on fatigue (primary outcome) and sleep quality, depression, anxiety, quality of life and circadian rhythms (secondary outcomes) in survivors of (non-)Hodgkin lymphoma presenting with chronic cancer-related fatigue.

Methods

We randomly assigned 166 survivors (mean survival 13 years) to a bright white light intervention (BWL) or dim white light comparison (DWL) group. Measurements were completed at baseline (T0), post-intervention (T1) and at three (T2) and nine (T3) months follow-up. A mixed-effect modeling approach was used to compare linear and non-linear effects of time between groups.

Results

There were no significant differences between BWL and DWL in the reduction of fatigue over time. Both BWL and DWL significantly ($p < .001$) improved fatigue levels during the intervention which only slightly diminished during follow-up ($ES_{T0\text{-}T1} = -0.71$; $ES_{T1\text{-}T3} = 0.15$). Similar results were found for depression, sleep quality, and some aspects of quality of life. Light therapy had no effect on circadian rhythms.

Conclusions

BWL was not superior in reducing fatigue compared to DWL in HL and DLBCL survivors. Remarkably, the total sample showed clinically relevant and persistent improvements on fatigue not commonly seen in longitudinal observational studies in these survivors.

INTRODUCTION

Cancer-related fatigue (CRF) is one of the most frequently reported symptoms with prevalence rates of 25 to 60 percent in survivors of Hodgkin lymphoma (HL) and Diffuse Large B-cell lymphoma (DLBCL)[1, 2]. CRF is related to a lower quality of life and often described as part of a symptom cluster including sleep disturbances, depression, anxiety, and pain[1, 3-7]. In cancer patients, these symptoms are associated with circadian disruptions, e.g., more sleep disruptions during the night and/or napping during the day[8-13]. Light therapy, in which individuals are exposed to bright light, is known for its positive effect on seasonal affective disorders[14-16] and circadian rhythm disorders[17, 18]. It is assumed to work via its restorative effect on circadian rhythms through stimulation of the suprachiasmatic nucleus (the biological clock)[19, 20] although other mechanisms of action, for example stimulation of mood regulation areas, have also been reported[21].

Three studies showed promising results of morning bright light therapy as a treatment for CRF in cancer patients undergoing chemotherapy[22] and in cancer survivors[23, 24]. These results also suggested that light therapy improved sleep quality, quality of life, and restored circadian sleep-wake cycles[24-29]. However, these studies had several methodological limitations, including small sample sizes[22, 23] and short follow-up assessments (3 weeks post intervention)[22-24].

Therefore, the present study investigated the effect of light therapy on CRF in a randomized controlled trial in a large sample of cancer survivors and a follow-up of 9 months. The primary aim was to investigate the short- and long-term efficacy of light therapy in decreasing CRF and improving sleep quality, depression, anxiety, quality of life, and circadian disruptions in HL and DLBCL survivors with CRF. We hypothesized that participants exposed to bright white light (BWL), the intervention group, would show an improvement in fatigue compared to participants exposed to dim white light (DWL), the comparison group. Secondly, we expected improvements in associated symptoms, including sleep quality, depression, anxiety, and quality of life, and entrainment of circadian rhythms.

PATIENTS AND METHODS

Research design and study sample

The study design of this double-blind randomized controlled trial has been described in detail elsewhere[30]. Briefly, survivors with a history of lymphoma were recruited from ten hospitals in the Netherlands. Inclusion criteria were: (1) age between 18 and 70 years; (2) primary diagnosis of HL or DLBCL at least 2 years prior to study entry; (3) moderate to severe fatigue since diagnosis and/or treatment. Exclusion criteria covered other factors that could have affected acute fatigue or circadian rhythms. The study was approved by the institutional review board of the Netherlands Cancer Institute (number NL61017.031.17) and all participating hospitals, and is registered at ClinicalTrials.gov (NCT03242902).

Procedure, randomization, and timing of assessments

Participant enrollment took place between September 2017 and October 2019. Figure 1 provides the CONSORT diagram. Briefly, survivors were recruited via referrals from clinicians or through participation in a survey study on bedtime, sleep quality, and CRF[31]. Survivors received an information brochure, screening questionnaire, and response card to indicate interest in participation, or reasons for nonparticipation. Interested survivors were screened by telephone to confirm eligibility. Eligible survivors received a patient information letter.

After providing written informed consent, participants were randomly assigned to the BWL or DWL group at a 1:1 ratio, stratified by diagnosis, time since diagnosis, and gender, by a research assistant not involved in the study. All other study personnel were blinded to the condition until a participant had completed the final assessment. Participants were informed that two intensities of light therapy were being compared without being informed regarding the hypotheses.

Participants were assessed at baseline (T0), after 25 days of light therapy (T1), and at three (T2), and nine months (T3) after treatment. T0 and T1 included a visit to the hospital to provide instructions and exchange study materials. T2 and T3 were completed at home. After completion of T3, participants received information on their assigned condition.

Intervention

In line with previous studies[22, 23], the first 37 participants used the Litebook Edge (Litebook, Ltc. Medicine Hat, Canada). Confirmatory spectral measurements of the Litebook established a light intensity of 351 lux at eye level for the BWL condition. As this is comparable to 'office lighting' and may not be sufficient for light therapy, we changed to Luminette glasses (Lucimed SA, Villers-le-Bouillet, Belgium). This light source exposed individuals to broad-spectrum, white light enriched at 468 nm and 570 nm of 1.500 lux at eye level for BWL, and 8 lux for DWL (see Appendix 1). All participants, including Litebook users, were included in the intention-to-treat analyses.

The light therapy protocol, based on previous studies[22, 23], instructed participants to use light therapy for 30 minutes, daily, within 30 minutes after awakening, for a duration of 25 days at home. Other activities like reading or having breakfast were permitted during therapy. A member of the research staff called on the fifth day to check for side effects.

Study measures

Sociodemographic information was collected with the screening and baseline questionnaire. Clinical information was abstracted from patient's medical records. Primary outcomes included general fatigue (Visual Analogue Scale [VAS]-fatigue[32] from 0 [no fatigue] to 10 [worst imaginable fatigue], Multidimensional Fatigue Inventory [MFI] general fatigue scale[33, 34]), and restrictions caused by fatigue (Works and Social Adjustment Scale [WSAS])[35].

Secondary outcomes included questionnaires to assess sleep quality (Pittsburg Sleep Quality Index [PSQI][36]), depression (Center for epidemiological studies - depression scale [CES-D][37]), anxiety (State Trait Anxiety Inventory - 6 items [STAI-6][38]), quality of life (RAND 36-item Health Survey [RAND 36][39, 40]), and assessments of sleep (wrist actigraphy[41, 42]), and salivary

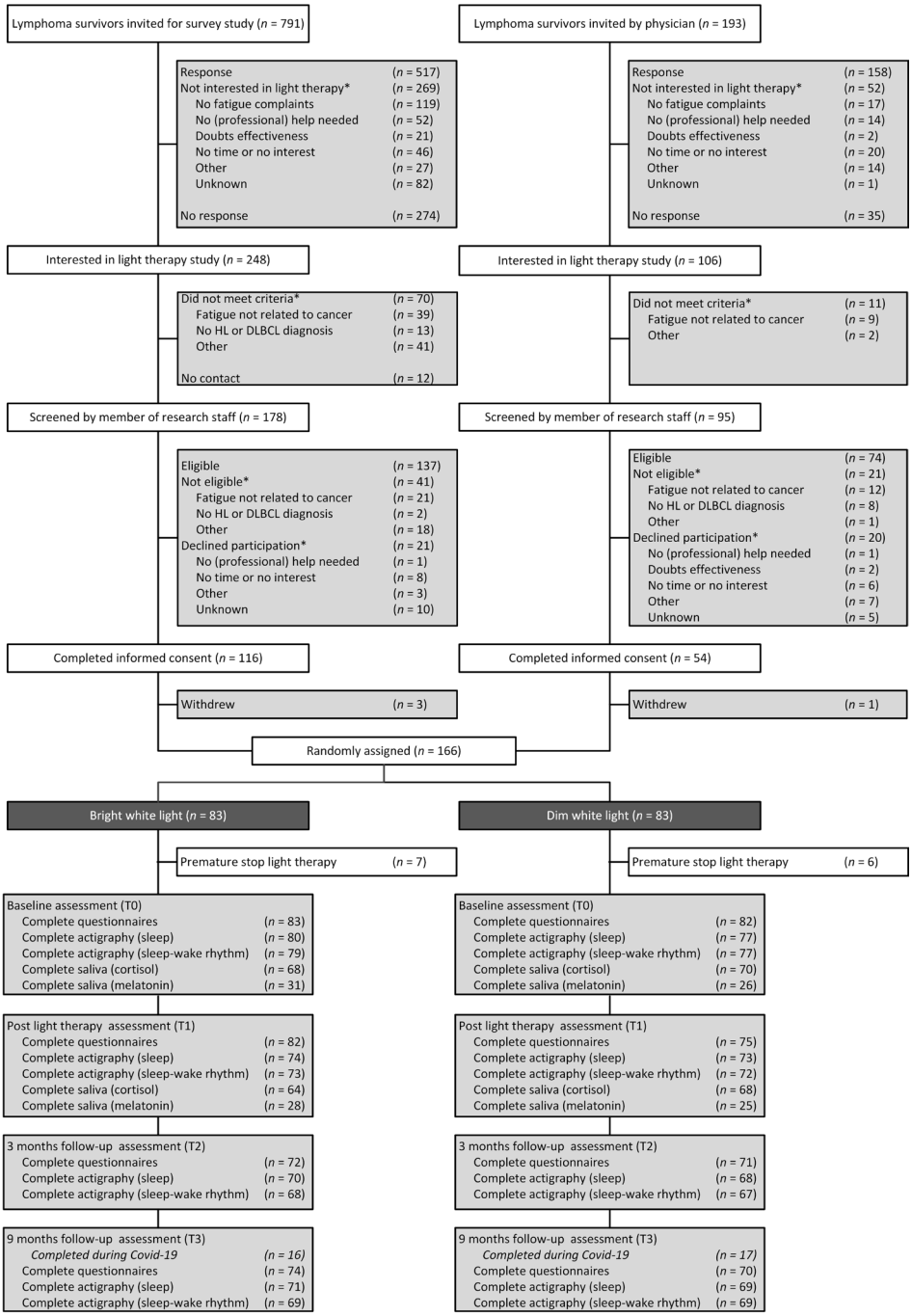

Figure 1: CONSORT diagram.
HL Hodgkin lymphoma; **DLBCL** Diffuse Large B-cell lymphoma
* Patients could provide more than one reason for nonparticipation or could be excluded for more than one reason. No. of missing assessments at T1, T2, and T3 were not necessarily cumulative.

concentrations of cortisol[43] and melatonin[44, 45] (see Appendix 2). A detailed description of the outcomes is provided in Table 1.

Statistical analyses

With ≥ 64 participants per group, the study had 80% power to detect an effect size (ES) of .50 with a two-tailed *p*-value of .05. Thirty-seven additional participants were recruited to ensure sufficient power for the sensitivity analyses in Luminette users. Comparisons of baseline characteristics between groups were performed using independent samples t-test, Mann Whitney, Chi-square, or Fisher's Exact tests. Scores on patient-reported outcome measures were calculated according to published algorithms. Missing values were replaced by the average score of the completed items in the same scale for each individual, provided that at least 50% of the items of a scale had been completed.

To evaluate differences between groups over time in primary and secondary outcomes, we used a mixed effect modelling approach with random intercept and slope with a maximum likelihood solution. We modeled linear and quadratic time effects to determine if an initial change in the outcome was maintained during follow-up. The choice for models with linear or non-linear effects, for models with different covariance structures (UN, AR1, CS), and models corrected for potential non-ignorable dropout were determined by using the Bayesian Information Criterion (BIC)[46] and the Akaike's Information Criterion (AIC)[47]. The overall mean change and difference in mean change scores over time between groups during the active treatment phase (T0-T1) and follow-up period (T1-T3) were accompanied by standardized effect sizes (ES) calculated based on the estimated marginal means and pooled SD: ($mean_{T1}$-$mean_{T0}$)/pooled $SD_{T0\text{-}T1}$ or ($mean_{T3}$-$mean_{T1}$)/pooled $SD_{T1\text{-}T3}$. ESs of 0.20 were considered small, 0.50 moderate, and 0.80 large[48]. An ES ≥ .50 was considered clinically relevant[49]. To limit type-I errors due to multiple testing, a p-value of .01 was considered statistically significant.

At the individual patient level, clinically relevant improvement was determined on a 1.1-point decrease on the VAS-fatigue[50, 51], a 2.0-point decrease on the general fatigue subscale of the MFI[52], or a 4.1-point decrease (0.5 standard deviation[49, 53]) on the WSAS. Chi-square tests were used to compare differences in improvement between the intervention and comparison group.

All analyses were conducted on an intention-to-treat (ITT) basis. Additionally, we performed one per-protocol analysis including participants who used light therapy on all 25 treatment days and two sensitivity analyses on data from participants who used (1) Luminette glasses; and (2) light therapy during autumn/winter (October to March). All statistical analyses were conducted in SPSS version 25.

RESULTS

In total, 984 survivors were invited to participate in the study, of whom 321 (33%) returned a response card indicating that they were not interested, and 309 (31%) did not respond (Fig. 1). Of the 354 interested survivors, 273 (77%) survivors met criteria for further screening and 211 (60%) were eligible for participation, of whom 170 (48%) signed informed consent. Four participants withdrew informed consent prior to randomization. The remaining 166 participants

Table 1. Study outcome measures and corresponding questionnaires

Variable	Assessment	Details
PRIMARY OUTCOMES		
Cancer-related fatigue	VAS-fatigue	• 1 item; 11-point Likert scale • Total score: 0-10; higher scores indicate more fatigue • Time frame: this moment
	MFI	• 20 items; 5-point Likert scales • Subscales: general fatigue, mental fatigue, physical fatigue, reduced motivation, reduced activity. Only general fatigue is used since psychometric validation of this scale indicated that this subscale is the most reliable[29] • Subscale score: 4-20; higher scores indicate more fatigue • Time frame: past few days
Restrictions caused by fatigue	WSAS	• 5 item; value range between 0.00 and 8.00 • Total score: 0-40; higher scores indicate higher levels of disability • Time frame: influence of fatigue on daily life
SECONDARY OUTCOMES		
Sleep quality	PSQI	• 19 items; 4-point Likert scale and open-ended questions • Subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction • Total score: 0-21; Subscale scores: 0-3; higher scores indicate more acute sleep disturbances • Time frame: past month
Depression	CES-D	• 20 items; 4-point Likert scale • Total score: 0-60; higher scores indicate greater depressive symptoms • Time frame: past week
Anxiety	STAI-6	• 6 items; 4-point Likert scale • Total score: 20-80; higher scores indicate increased anxiety • Time frame: this moment
Quality of life	RAND-36	• 36 items; dichotomous and 3- to 6-point Likert scale • Scales: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy, emotional well-being, social functioning, pain, general health • Scale scores: 0-100; higher scores indicates higher levels of functioning/well-being • Time frame: past 4 weeks
Sleep	Wrist actigraphy	• Device: MotionWatch8 (Camntech, Cambridgeshire, United Kingdom) • Technical settings: epoch length 60 seconds, tri-axial mode • Location: non-dominant wrist • Time period: 10 days (Friday 18:00 h till Monday 12:00 h) • Actigraphy log included: bedtime, attempted time to fall asleep, wake-up time, out-of-bed time, nap times, non-wear times • Derived sleep variables: sleep efficiency, mid sleep, and total bed time. • Derived sleep-wake rhythm variables: Interdaily stability (IS; an estimate of the 24-hour sleep-wake rhythm) and intradaily variability (IV; an estimate of the stability of the sleep-wake rhyhtm)[37].

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Table 1. (*continued*)

Variable	Assessment	Details
Sleep *(continued)*	Wrist actigraphy *(continued)*	• A measurements point was excluded from the sleep variables analyses when the actigraphy was worn for less than 4 nights and from the sleep-wake rhythm variables analyses when the actigraphy was worn for less than 72 consecutive hours. • Scores: IS: 0-2; higher scores indicate a more fragmented rhythm; IV: 0-1; 1 indicates perfect synchronization
Cortisol	Salivary cortisol	• Saliva collection via a passive drool technique in a propylene vial at the participants' home. • Sample collection on five different time points during 24 consecutive hours: 1) at personal waking time, 2) 30 minutes after awakening, 3) 45 minutes after awakening, 4) at 16.00 o'clock, and 5) at bedtime. • Saliva collection was on the Friday prior to light therapy (start day Monday) and the Friday after completion of light therapy (finish day was Thursday). • After sample collection, saliva samples were stored in the refrigerator and mailed to the lab via post where the samples were stored in a freezer at a -80°C until processing. • Cortisol values (nmol/l) were determined using liquid chromatography tandem mass spectrometry. Method imprecisions were ≤ 13.9% and lower limits of quantitation were 0.5 nmol/l. • Derived variables: cortisol awakening response, diurnal cortisol slope, area under the curve. • For further details on the analytical method and performance characteristic, see Appendix 2
Melatonin	Salivary melatonin	• Subsample (n=60) • Collection of five additional saliva samples starting 5 hours prior to bedtime followed by one sample every sequential hour. • Collection and handling of samples was similar to the procedure described for cortisol. Method imprecisions were ≤ 11.9% and lower limits of quantitation were 0.01 nmol/l. • Derived variables: Dim Light Melatonin Onset (DLMO) based on the hockey-stick method[40]. • For further details on the analytical method and performance characteristic, see Appendix 2

CES-D Center for Epidemiological Studies – Depression scale; **CWS** Cancer Worry Scale; **FCS** Fatigue catastrophizing Scale; **MFI** Multidimensional Fatigue Inventory; **PSQI** Pittsburgh Sleep Quality Index; **RAND-36** Medical Outcome Studies short form; **SES-28** Self-efficacy Scale 28; **STAI-6** State Trait Anxiety Inventory-6 items; **VAS** Visual Analogue Scale; **WSAS** Work and Social Adjustment Scale.

were randomized to the BWL (n = 83) or the DWL (n = 83) group and were included in the intention-to-treat analysis. Completion rates of self-reported questionnaires at baseline assessment T0 (99%) and follow-up assessment T1 (95%), T2 (86%), and T3 (87%) differed significantly between groups at T1 (BWL: 99% *v* DWL: 90%; p = .03). Correction for non-ignorable dropout did not improve model fit (Appendix 3). The completion of T3 during Covid-19 restrictions (n = 33; 23%) did not differ between groups and did not affect the study results (Appendix 4). Presented results are uncorrected for these factors. Availability rates of actigraphy-derived sleep and circadian variables at T0 (95% and 94%, respectively), T1 (89% and 87%, respectively), T2 (83% and 81%, respectively), and T3 (84% and 83%, respectively)

did not differ between groups. Availability rates of cortisol and melatonin concentrations at T0 (100% and 100%, respectively) and T1 (96% and 93%, respectively) were similar between groups (see Appendix 2).

Most participants were HL survivors (83%). Their mean age was 45.7 years and the average time since lymphoma was 12.9 years. Almost all participants had received chemotherapy (93%) and/or radiotherapy (72%). Baseline levels of fatigue were high (mean VAS-fatigue = 6.1; mean MFI general fatigue = 15.7; mean WSAS = 20.5). Except for marital status (p = .03), all baseline characteristics were balanced between the groups (see Table 2).

Table 3 shows the characteristics of light therapy use by the participants. According to the light therapy diaries (n = 155), 37% used light therapy all 25 days and 56% used light therapy for 14 to 25 days with a median time between sleep offset and light therapy start of 19 minutes (range: 5-109 minutes). In the complete sample (N = 166), 13 survivors stopped prematurely with the study. Reasons for attrition were self-reported side effects (n = 7), time constraints or personal circumstances (n = 6).

Primary outcomes

There were no significant differences between BWL and DWL in the improvement of fatigue over time (Figure 2 and Appendix Table A5.1). Both BWL and DWL (Appendix Table A5.2) led to a statistically significant, clinically relevant, improvement of fatigue during the intervention which slightly diminished during follow-up (VAS fatigue: $ES_{T0\text{-}T1}$= −0.71, $ES_{T1\text{-}T3}$= 0.15; MFI general fatigue: $ES_{T0\text{-}T1}$= −0.81, $ES_{T1\text{-}T3}$= 0.13). The improvement of restrictions caused by fatigue showed a moderate effect during the intervention which slightly further improved during follow-up (WSAS: $ES_{T0\text{-}T1}$= −0.32, $ES_{T1\text{-}T3}$= −0.07). At an individual level, results showed no differences in the number of participants with clinically relevant improvements on primary outcomes between both groups (Table 4).

Secondary outcomes

There were no significant differences between BWL and DWL on secondary outcomes (Figure 2, Appendix Table A5.1). Both BWL and DWL (Appendix Table A5.2) led to statistically significant improvements, indicating moderate effects during the intervention which slightly diminished across later follow-up, for sleep quality ($ES_{T0\text{-}T1}$= −0.44, $ES_{T1\text{-}T3}$= 0.10) and depression ($ES_{T0\text{-}T1}$= −0.41, $ES_{T1\text{-}T3}$= 0.16). Three aspects of health-related quality of life showed statistically significant improvements of moderate effects of moderate effects during the intervention which slightly further improved during follow-up: role limitations due to physical functioning ($ES_{T0\text{-}T1}$= 0.33, $ES_{T1\text{-}T3}$= 0.11), energy ($ES_{T0\text{-}T1}$= 0.48, $ES_{T1\text{-}T3}$= 0.05), and social functioning ($ES_{T0\text{-}T1}$= 0.35, $ES_{T1\text{-}T3}$= 0.09). No significant group differences or overall time effects were observed for anxiety, the remaining subscales of the RAND-36, and actigraphy-derived sleep. Moreover, no effects were observed for cortisol and melatonin (Figure 3, Appendix Table A5.1 and A5.2).

The per protocol analysis including individuals who adhered to 25 days of light therapy showed similar results except for a group difference in the effect of light therapy on sleep efficiency (Appendix Table A5.3). Sleep efficiency improved in the BWL group and deteriorated in the DWL group between T2 and T3 suggesting that this effect did not result from light therapy. The sensitivity analyses for individuals who used Luminette glasses or light therapy during autumn/winter yielded similar results (Appendix Table A5.4 and A5.5).

Table 2. Baseline sociodemographic, clinical and fatigue characteristics (N = 166) [a]

Characteristic	No. (%)[b] All survivors	BWL (n=83)	DWL (n=83)	*p*	N
Age, years					166
Mean	45.7	46.7	44.8	.30	
SD	12.2	11.9	12.5		
Female	99 (59.6)	50 (60.2)	49 (59.0)	.87	166
Education				.24	165
None/primary	2 (1.2)	0 (0.0)	2 (2.4)		
High school and vocational	85 (51.5)	43 (51.8)	42 (51.2)		
College or university	78 (47.3)	40 (48.2)	38 (46.3)		
Married or in relationship	130 (78.8)	71 (85.5)	59 (72.0)	.03	165
Part- or full-time job	85 (51.5)	42 (50.6)	43 (52.4)	.81	165
Chronotype				.44	165
Morning type	29 (35.4)	56 (33.9)	27 (32.5)		
Evening type	33 (40.2)	74 (44.8)	41 (49.4)		
No specific type	20 (24.4)	35 (21.2)	15 (18.1)		
Recruitment				.86	166
Asked by physician	50 (30.1)	24 (28.9)	26 (31.3)		
Survey study	98 (59.0)	49 (59.0)	49 (59.0)		
Applied for participation	18 (10.8)	10 (12.0)	8 (9.6)		
Diagnosis				.68	166
HL	138 (83.1)	70 (84.3)	68 (81.9)		
DLBCL	28 (16.9)	13 (15.7)	15 (18.1)		
Ann Arbor stage				.64	155
I	21 (12.7)	10 (12.0)	11 (13.3)		
II	87 (52.4)	40 (48.2)	47 (56.6)		
III	25 (15.1)	14 (16.9)	11 (13.3)		
IV	22 (13.3)	13 (15.7)	9 (10.8)		
Time since diagnosis, years[c]				.88	166
Mean	12.9	13.0	12.9		
SD	9.9	9.6	10.3		
2-5 years	41 (24.7)	20 (24.1)	21 (25.3)	.97	
5-10 years	50 (30.1)	24 (28.9)	26 (31.3)		
10-20 years	39 (23.5)	20 (24.1)	19 (22.9)		
> 20 years	36 (21.7)	19 (22.9)	17 (20.5)		

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Table 2. *(continued)*

Characteristic	No. (%)[b] All survivors	BWL (n=83)	DWL (n=83)	*p*	N
Treatments received					
Radiotherapy	116 (72.0)	56 (69.1)	60 (75.0)	.41	161
Chemotherapy	151 (93.2)	76 (92.7)	75 (93.8)	.79	162
Stem cell transplantation	19 (11.8)	8 (9.9)	11 (13.8)	.45	161
Total body irradiation[d]	2 (1.2)	0 (0.0)	2 (2.5)	.24	162
Surgery (splenectomy)[d]	6 (3.7)	3 (3.7)	3 (3.8)	1.0	162
Relapse	25 (15.4)	13 (15.9)	12 (15.0)	.88	162
Second malignancies	25 (15.7)	13 (15.7)	12 (15.4)	.91	159
Hyperthyroidism[d, e]	1 (0.6)	0 (0.0)	1 (1.3)	.49	156
Hypothyroidism[e]	36 (23.1)	21 (26.3)	15 (19.7)	.34	156
Heart complaints, NYHA class 1 or 2	33 (20.8)	19 (23.5)	14 (17.9)	.39	159
Fatigue (baseline)					
VAS				.09	164
Mean	6.1	5.9	6.3		
SD	1.6	1.8	1.4		
MFI general fatigue				.76	165
Mean	15.7	15.6	15.8		
SD	2.7	2.9	2.5		
Work and social restrictions caused by fatigue (WSAS)				.73	165
Mean	20.5	20.7	20.2		
SD	8.2	7.8	8.5		
Sleep medication use	25 (15.2)	11 (13.3)	14 (17.1)	.49	165

BWL bright white light; **DWL** dim white light; **SD** standard deviation; **HL** Hodgkin lymphoma; **DLBCL**: Diffuse large B-cell lymphoma; **VAS** visual analogue scale.
[a] Medical information was available by less than the total number of participants due to missing data in the medical information form completed by treating physician or researcher. [b] Unless otherwise specified. [c] Based on Mann-Whitney Test. [d] Based on Fisher's Exact Test.[e] Survivors were included when their medication use was stable for ≥ 6 months and fatigue complaints remained.

Adverse effects

Two participants were hospitalized for at least one night because of serious adverse events not related to the study (stress-related symptoms and pancreatitis). Self-reportedside effects, e.g. headache and/or nausea (22%) and tired eyes (19%), were balanced between groups (Table 2). These effects were temporary and disappeared within five days despite continuation of light therapy.

Table 3. Light therapy characteristics.

Characteristic	No. (%)[a] All survivors	BWL (n=83)	DWL (n=83)	*p*	N
Season LT start				.94	164
Autumn	42 (25.6)	23 (27.7)	19 (23.5)		
Winter	47 (28.7)	23 (27.7)	24 (29.6)		
Spring	47 (28.7)	23 (27.7)	24 (29.6)		
Summer	28 (17.1)	14 (16.9)	14 (17.3)		
LT device					
Litebook Edge	37 (22.6)	18 (21.7)	19 (23.5)		164
Luminette	127 (77.4)	65 (78.3)	62 (76.5)		
Days of LT use based on LT diary[b]				.52	155
Mean	22.7	22.5	22.9		
SD	4.4	4.6	4.0		
> 25 days[c]	3 (1.9)	0 (0.0)	3 (3.9)	.13	155
25 days	58 (37.4)	33 (41.8)	25 (32.9)		
14-24 days	87 (56.1)	41 (51.9)	46 (60.5)		
1-13 days (premature stop)	7 (4.5)	5 (6.3)	2 (2.6)		
Time difference sleep end and LT start (min)[d]				.13	155
Mean	25.0	27.4	22.6		
SD	19.5	22.6	15.3		
Time difference DLMO and LT start (h)			.17		
Mean	11.4	11.1	11.7		
SD	1.5	1.0	1.9		
n	45	23	22		
Self-reported side effects					
Head ache/nausea	35 (21.6)	21 (25.6)	14 (17.5)	.21	162
Agitated feeling[b]	5 (3.1)	1 (1.2)	4 (5.0)	.21	162
Tired eyes	30 (18.5)	11 (13.4)	19 (23.8)	.09	162
Change in vision[b]	8 (4.9)	5 (6.1)	3 (3.8)	.72	162
Other self-reported side effects[e]	15 (9.3)	6 (7.3)	9 (11.3)	.39	162
Premature stop of LT	13 (7.8)	7 (8.4)	6 (7.2)	.77	166
Reasons for premature stop[b]				.21	13
Self-reported side effects	7 (53.8)	5 (71.4)	2 (33.3)		
No time or personal circumstances	6 (46.2)	2 (28.6)	4 (66.7)		

BWL Bright white light; **DLMO** dim light melatonin onset; **DWL** Dim white light; **LT** light therapy
[a] Unless otherwise specified. [b] Categorical test results is based on Fisher's Exact Test. [c] Some individuals misinterpreted the protocol and used light therapy for 28, 30, or 33 days. [d] Based on Mann Whitney Test. [e] Other self-reported side effects: worse sleep quality (n = 7), feeling more fatigued (n = 2), feeling rushed (n = 1), shingles (n = 1), feeling confused (n = 1), sensitive gingiva (n = 1), and a dry mouth (n = 1).

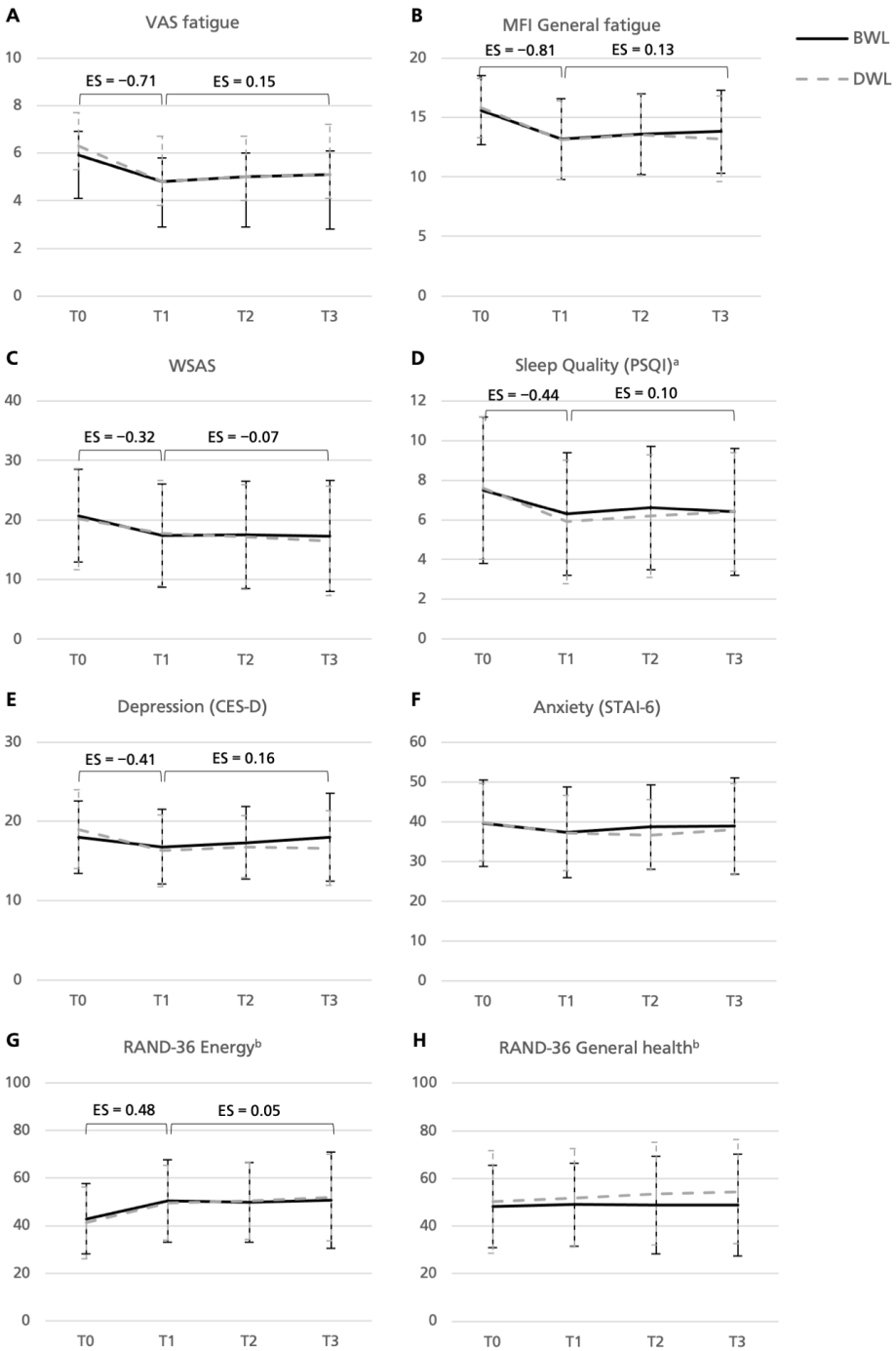

Figure 2 Changes in raw mean levels of primary and secondary self-reported outcomes from baseline to nine months follow-up in groups receiving bright white light therapy (BWL; n = 83) and dim white light therapy (DWL; n = 83).

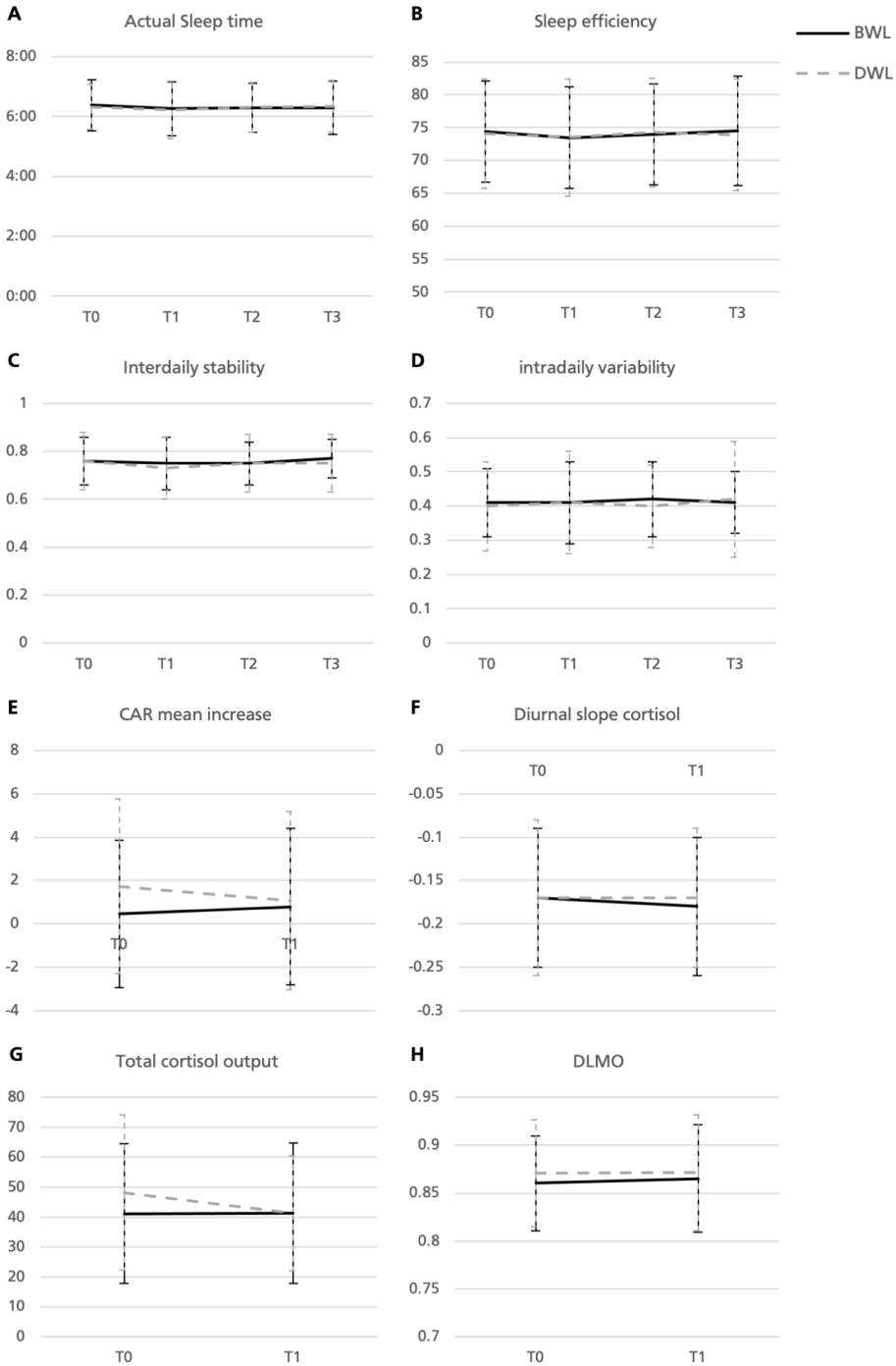

Figure 3. Changes in raw mean levels of actigraphy-derived sleep variables (A, B, C, D) and cortisol and melatonin variables (E, F, G, H) in groups receiving bright white light therapy (BWL; n = 83) and dim white light therapy (DWL; n = 83).

Notes figures 2 and 3
Bars indicate standard deviations.
BWL Bright white light; **CES-D** Center for Epidemiological Studies – Depression; **DWL** Dim white light; **MFI** Multidimensional Fatigue inventory; **PSQI** Pittsburgh Sleep Quality Index; **RAND-36** RAND 36-item Health Survey; **STAI-6** State Trait Anxiety Index – short form; **VAS** fatigue Visual Analogue Scale fatigue; **WSAS** Work and Social Adjustment Scale. **T0** indicates baseline, **T1** directly post intervention, **T2** 3 months after the end of light therapy and **T3** 9 months after finishing light therapy.
[a] The total score of the PSQI is shown. Based on the AIC and BIC criteria, the model with the best fit excluded a random slope and included an autoregressive covariance structure. The effect of light therapy on the seven subscales of the PSQI is described in Appendix 6. [b] The Energy and General Health subscales of the RAND-36 are shown. The remaining subscales are described in Appendix Table A5.1.

Table 4. Number (percentage) of participants with clinically meaningful improvement based on fatigue assessments.

	T0-T1[a]		T0-T2[a]		T0-T3[a]	
	No. (%)		No. (%)		No. (%)	
	BWL	DWL	BWL	DWL	BWL	DWL
VAS fatigue						
Improved	34 (42)	41 (55)	25 (35)	37 (52)	24 (33)	27 (39)
Not improved	47 (58)	34 (45)	46 (65)	34 (48)	49 (67)	43 (61)
n	81	75	71	71	73	70
p[b]	.11		.04		.48	
OR[c]	0.60		0.50		0.78	
MFI general fatigue						
Improved	49 (60)	47 (63)	35 (49)	37 (52)	36 (49)	40 (57)
Not improved	33 (40)	28 (37)	37 (51)	34 (48)	38 (51)	30 (43)
n	82	75	72	71	74	70
p[b]	.71		.68		.31	
OR[c]	0.89		0.87		0.71	
WSAS						
Improved	33 (40)	26 (35)	31 (43)	27 (39)	31 (42)	29 (41)
Not improved	49 (60)	49 (65)	41 (57)	43 (61)	43 (58)	41 (59)
n	82	75	72	70	74	70
p[b]	.47		.59		.96	
OR[c]	1.27		1.20		1.02	

MFI Multidimensional Fatigue inventory; **OR** Odds Ratio; **VAS** Visual Analogue Scale; **WSAS** Work and Social Adjustment Scale.
[a] **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy [b] *p* value of the Pearson chi-square test. [c] Odds ratios of 1.5 were considered small, 2.0 as moderate, and 3.0 as large.

DISCUSSION

In this double blind, randomized controlled trial, exposure to morning BWL showed no superiority to morning DWL on fatigue and related symptoms in long-term HL and DLBCL survivors presenting with chronic cancer-related fatigue. Remarkably, both groups showed clinically relevant improvements on fatigue and restrictions caused by fatigue, and improvements on sleep quality, depression, and three aspects of quality of life (role limitations due to physical functioning, energy, and social functioning). This improvement slightly diminished during follow-up but was still clinically relevant nine months post intervention. Neither BWL nor DWL had an effect on anxiety, other aspects of quality of life, actigraphy-derived sleep, and cortisol or melatonin concentrations.

In contrast to two earlier studies that investigated the effect of light therapy on cancer-related fatigue in adult cancer survivors[23, 24], the current larger phase-III trial did not observe superiority of BWL over DWL. There were several differences between these studies. First, the average time since diagnosis was much longer in our study (13 years) compared to previous studies (17 months[23] and 28 months[24]). Second, previous studies used dim red light (DRL; 50 lux[23] or 400 lux[24]) as a comparison condition, instead of DWL (20 lux). As the circadian system is most strongly affected by white light enriched around 470 nm[20], the DWL condition in our study might still have been somewhat effective. This effect is not expected for DRL. However, Johnson et al.[24] only showed superiority of BWL to DRL on the total score of fatigue, with effect sizes of 1.20 and 0.93, respectively, indicating that both groups improved. No superiority of BWL to DRL was reported for five dimensions of fatigue (including general fatigue), mood, depression, quality of life, and sleep quality on which both groups showed improvements, suggesting that the selection of DWL or DRL as comparison may not fully explain the discrepancies[54].

It is notable that study participation led to clinically relevant improvements (ES= −0.71 [VAS-fatigue]; ES= −0.81 [MFI general fatigue]) in long-term cancer survivors suffering from chronic fatigue. Although we cannot explain this by differences in light intensity, it is important to further investigate which aspects of the study protocol caused this effect. First, the positive effects might result from lifestyle changes. For example, some participants spontaneously self-reported that they exercised more (36%), which may have increased their light exposure if it was outside, or kept a more regular sleep-wake cycle following light therapy (17%). These activities have been associated with reduced CRF[55-57]. Second, the improvement might be explained by the personal attention during participation[58] or as a placebo response which has been reported previously for CRF[59]. Third, the decrease of fatigue might reflect a natural improvement over time, although we believe this is unlikely in our study because longitudinal observational studies in long-term cancer survivors showed persisting fatigue[60, 61]. Finally, we cannot exclude the possibility that regression towards the mean explained a small part of the positive effects observed in this trial.

Contrary to our expectations, we found no effect of light therapy on actigraphy-derived sleep or cortisol and melatonin, which follow a circadian rhythm. This is in line with a previous study showing that changes in cortisol levels did not mediate the positive effect of light therapy on CRF in cancer survivors[62]. Moreover, baseline values of actigraphy-derived sleep in the current sample suggest the presence of sleep problems but no circadian disruptions compared

to the general population[63-65]. Two recent studies also suggested an absence of an association between circadian disruptions and CRF in long-term cancer survivors[31, 66]. Therefore, it is unclear whether circadian disruptions are associated with CRF in cancer survivors although research in this group is limited and further exploration is necessary.

Our trial had several limitations. First, we did not include an objective assessment of total daily light exposure. Therefore, we could not confirm self-reported compliance, assess the duration of light therapy, or correct for exposure to natural light. Second, although the compliance rate of 91% in the current study was high compared to previous studies[24, 25] (91% vs. 67-95%, respectively), only a minority (37%) of the participants used light therapy on all 25 days. However, the majority (56%) used light therapy for 14-25 days, which is enough to show improvements according to the guidelines of light therapy for SAD [67]. Third, our study sample was limited to (non-)Hodgkin lymphoma survivors, which might reduce generalizability to other populations. However, similar findings are expected in other populations because no associations are reported between fatigue and disease-related factors [68-70]. Finally, the completion rate of the post intervention questionnaire differed between groups with fewer cases available for the comparison group. However, correction for missing data patterns yielded similar results.

Our study had several strengths, including its multicenter RCT design, larger sample size, high follow-up rates and the assessment of self-reported as well as behavioral and biological effects of light therapy.

In conclusion, our data showed no superiority of exposure to BWL compared to DWL. Light therapy, irrespective of light intensity, led to clinically relevant and relatively stable improvements of fatigue, and improved sleep quality, depression, and quality of life in long-term HL and DLBCL survivors with chronic CRF. Therefore, it is important to further investigate which component(s) of the light therapy study protocol explain clinical improvements observed after intervention as well as comparison light conditions.

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APPENDIX 1 SPECIFICS OF LIGHT THERAPY DEVICES

The Litebook Edge (Litebook, Ltc. Medicine Hat, Canada) is a small (15 x 12 x 1 cm) lightweight box that contains 60 premium white light emitting diode (LED) lights that mimic the visible spectrum of sunlight. Participants placed this device on a table at a distance of 45 cm in an angle of 45° from the face. The Luminette glasses contain 8 LEDs that are directed to the lens via a holographic field. Table A1.1 shows estimations of irradiance for both devices. Figure A1.1 and A1.2 show the light spectrum of both devices.

Table A1.1 Estimations of irradiance for the Litebook Edge and Luminette glasses.

	LB BWL lat	**LB BWL cl**	**LB DWL lat**	**LB DWL cl**	**LUM BWL**	**LUM DWL**
Peak spectral irradiance, nm	450	450	455	455	465	470
Visibility, lux	351.44	148.71	2.49	0.65	1012.75	8.37
S cone sensitivity, α-opic lux	530.57	228.54	3.36	0.9	1966.49	17.51
Melanopsin sensitivity, α-opic lux	373.99	160.55	2.59	0.69	1934.17	20.84
Rod sensitivity, α-opic lux	364.89	156.19	2.54	0.68	1639.64	16.84
M cone sensitivity, α-opic lux	357.48	152.01	2.52	0.67	1277.56	11.99
L cone sensitivity, α-opic lux	343.95	145.53	2.44	0.64	1056.78	9.2
Irradiance, μW/cm^2	126.05	53.6	0.9	0.26	438.74	4.1
Photon flux, 1/cm^2/s	3.38E+14	1.43E+14	2.45E+12	7.45E+11	1.14E+15	1.06E+13
Log photon flux, log10 (1/cm^2/s)	14.53	14.16	12.39	11.87	15.06	13.02

BWL Bright White light; **cl** contralateral eye (eye furthest from light source); **DWL** Dim White Light; **lat** lateral eye (eye closest to light source) **LB** Litebook Edge; **LUM** Luminette.
Note: estimations of irradiance are based on the average values of five measurements performed with a radio spectrometer.
Derived from: Lucas RJ, Peirson SN, Berson D, Brown T, Cooper H, Czeisler CA, Figueiro MG, Gamlin PD, Lockley SW, O'Hagan JB, Price LLA, Provencio I, Skene DJ, Brainard G. Irradiance Toolbox, 2013

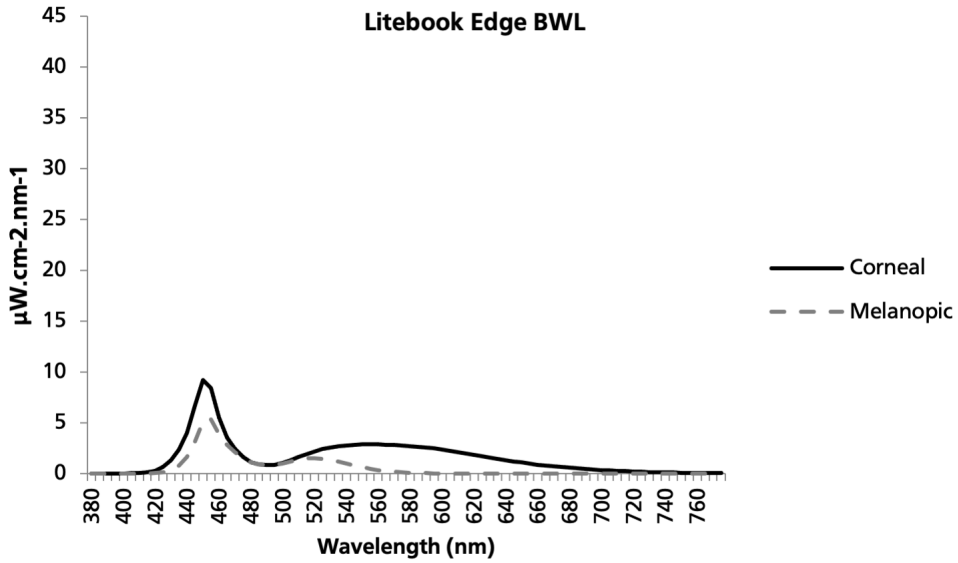

Figure A1.1. Light spectrum of the BWL Litebook Edge.

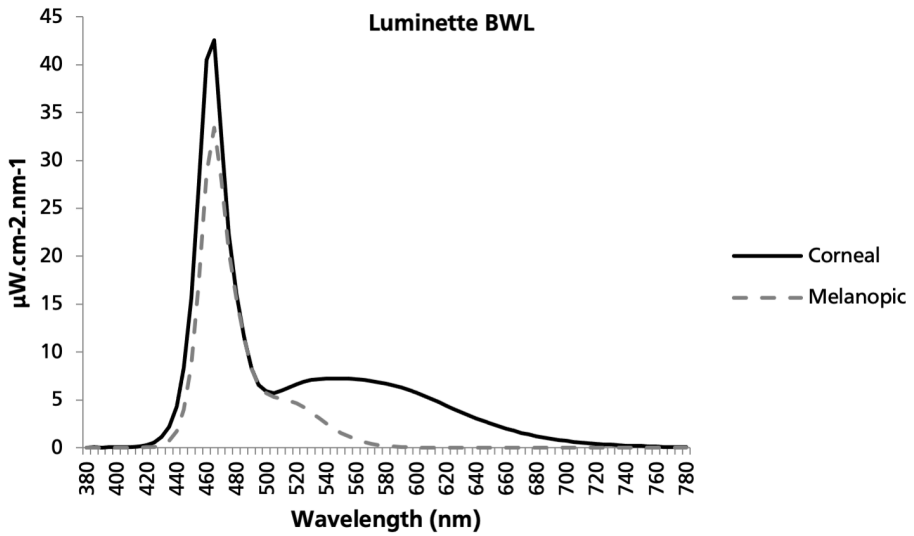

Figure A1.2. Light spectrum of the BWL Luminette glasses

APPENDIX 2: COLLECTION, HANDLING, AND PROCESSING OF SALIVA SAMPLES

METHODS

Procedure

All participants were asked to collect saliva on the Friday before the start of light therapy and the Friday after the end of light therapy to assess cortisol. Five saliva samples were collected at waking time, 30 minutes and 45 minutes after awakening, at 4 pm, and at bedtime. A subsample of 60 participants were asked to collect five additional samples at -5h, -4h, -3h, -2h, and -1h before bedtime to explore the effect of light therapy on melatonin secretion. Saliva was collected by a passive drool technique in a propylene vial. Participants were asked to avoid smoking, vigorous exercise, caffeinated and alcoholic drinks, chocolate, bananas, and food containing food colouring. Eating and drinking of other nourishments and brushing teeth was not allowed 15 and 30 min prior to sampling, respectively. Participants were instructed to note the time of sampling on a tracking sheet and store the samples in their home refrigerator. Samples were sent to the Netherlands Cancer Institute on the Monday after saliva collection. Samples were subsequently stored in a freezer at a -80°C until processing. Cortisol and melatonin values were determined using liquid chromatography - mass spectrometry (LC-MS). Cortisol and melatonin concentrations were calculated in nmol/l and pmol/l with a lower limit of quantitation of 0.5 nmol/l and 10.0 pmol/l, respectively.

Salivary cortisol and melatonin assay

Reagents were Melatonin d4; N-Acetyl-5-methoxytryptamine-α,α,β,β-d_4 from CDN Isotopes (Quebec, Canada), Cortisol C13; Cortisol-2,3,4- $^{13}C_3$, melatonin standard >98%, cortisone standard >98% and cortisol standard >98% from Sigma Aldrich (St. Louis, MO, USA).

Samples were prepared by adding a 250 µL salivary aliquot to a 2 mL Safe-lock Eppendorf tube and 10 µL of internal standard solution was added. Analytes were extracted by adding 1 mL of ethyl acetate, 15 minutes shaking of the samples, centrifuging the samples (5 minutes, RT, 8000g), snap freezing the hydrophilic phase and collecting and evaporating the organic phase. Next, the extracts were dissolved in 100 µL of injection fluid (20% methanol, 80% water) and spun down (5 minutes, RT, 12000g), before analysis. All samples were analyzed.

The cortisol and melatonin concentrations were analyzed in a single analytical measurement using liquid chromatography isotope-dilution tandem mass spectrometry. The Shimadzu Nexera X2 ultra high performance liquid chromatographer (Columbia, MD, USA) was employed to provide a flow of 0.6 mL/min through a C-18 Column (2,6 µm 50 mm x 2,10 mm) from Phenomenex (Torrance, California, USA). Column temperature was maintained at 30 °C. Chromatography was performed using a linear gradient between an aqueous phase containing 0.1% formic acid and 2 mM ammonium acetate and methanol. Here, a mobile phase of 30% methanol increased to 46.5% in 2.8 minutes, then mobile phase is changed to 100% methanol for 1.4 minutes before equilibrating tot the starting mobile phase containing 30% methanol.

Cortisol and melatonin quantitation was performed using multiple reaction monitoring mode on a QTRAP6500+ mass spectrometer (Sciex, Concord, ON, Canada). Ionization was achieved with an IonDrive™ Turbo V Source operated in positive mode. The mass transitions used for the analytes and their international standards (IS) are presented in Table A2.1.

Table A2.1. Applied MS/MS settings.

	Q1 massa (Da)	Q3 massa (Da)	Analyte
1	233,190	174,000	Melatonine Quan
2	233,190	159,000	Melatonine Qual
3	237,212	178,100	Melatonine d4 quan
4	237,212	163,200	Melatonine d4 qual
5	363,065	327,100	Cortisol quan
6	363,065	121,000	Cortisol qual
7	366,243	124,100	Cortisol C13 Quan
8	366,243	126,100	Cortisol C13 qual

Salivary cortisol and melatonin assay performance characteristics

The method was calibrated by weighted stock standards. A method comparison study with the published method from UMC Groningen (n = 20) confirmed proper method calibration (Table A2.2). Method imprecision was determined by running three control levels in quadruple in seven individual runs. The obtained imprecisions are presented in Tables A2.3.

Table A2.2. Method relation and correlation with other method[1].

	Cortisol	Melatonin
Slope	1.12	1.01
Intercept	0.398	0.0026
Pearsons' R^2	0.99	0.99

Table A2.3. Method imprecision for cortisol and melatonin.

	Average (nmol/L)	SD	CV (%)
Cortisol			
QC-high	39,3	5,46	13,9%
QC-intermediate	29,2	3,37	11,6%
QC-low	4,8	0,52	10,9%
Melatonin			
QC-high:	0,900	0,075	8,3%
QC-intermediate:	0,355	0,034	9,6%
QC-low:	0,049	0,006	11,6%

Lower limit of quantitation (LLOQ) was based on lowest concentration with a CV of ≤ 20% and a Singal/Noise ratio of ≥ 10. The LLOQs were 0.010 nmol/L for melatonin and 0.50 nmol/L for cortisol. Samples with identifiable peaks below the LLOQ were quantified but are associated with higher inaccuracy.

No interference was observed for DHEA, prednisone, androstenedione, 17-hydroxyprogesterone, progesterone, testosterone, 17β-estradiol, serotonin, L-tryoptophan, 5-OH-trytophan, aldosterone, 5-HIAA and N-actetyl-5-hydroxytryptamine. Prednisolone did interfere with cortisol, but this interference could be identified from the chromatogram and was not observed in the study samples.

Data reduction

The five cortisol samples were used to determine the cortisol awakening response (CAR), diurnal slope, and total cortisol output. The *CAR* is the rapid increase in cortisol concentrations during the first 30 to 45 minutes after awakening[2]. The CAR mean increase (MnInc) was calculated using the formula: (awakening + 30 min + awakening + 45 min)/2 – awakening[3]. The *diurnal slope* reflects circadian fluctuations in cortisol[4]. It was determined by regressing the natural log-transformed cortisol values of awakening, 4 pm, and bedtime on time since waking (in hours). The unstandardized coefficient was used as a measure for diurnal slope. A flatter decline in cortisol levels over the course of the day is represented by larger (smaller magnitude negative) unstandardized values, while a steeper decline in cortisol values is represented by smaller unstandardized values. The *total cortisol output* reflects the exposure during the day[4] and was calculated as the area under the curve with respect to the ground (AUC_g) based on the trapezoidal formula using all five cortisol samples[5].

For the subsample that collected five additional samples at -5h, -4h, -3h, -2h, and -1h before bedtime, these 5 samples and the bedtime sample were used to determine the *dim light melatonin onset* (DLMO), which represents the start of the secretion of melatonin in dim light situations. A hockey-stick method was used to determine the DLMO using the hockey-stick program module designed[6]. For this purpose, melatonin concentrations were converted from pmol/l to pg/ml by dividing detected concentrations by 4.3.

RESULTS

Participants

From the 166 participants, 155 participants agreed to collect saliva for the cortisol assessment. Seventeen participants were excluded from the cortisol analyses because of corticosteroid use leaving to a total sample of 138 participants. The availability of cortisol profiles at T0 (100%) and T1 (96%) were similar between groups. For an overview, see Consort diagram. A total number of 1334 samples were available for analysis. Thirty-six samples (2.7%) had undetectable cortisol levels and were imputed with the lower limit of quantitation divided by two (0.25 nmol/l). After screening for outliers (≥ 3.5 standard deviation), 23 (1.7%) samples were removed. Figure A2.1 shows the raw cortisol values at each sampling point per group at pre- and post intervention. As the CAR is easily underestimated when collection of the first samples

is delayed by more than 15 minutes after awakening[7], the time point of the first collection was compared to actigraphy-derived awakening time. Therefore, 26 and 22 profiles were excluded at baseline and post-intervention, respectively due to a delay of ≤ 15 min between waking and first sample collection.

From the 155 participants that agreed to collect saliva, 57 (34%) were willing to collect additional samples in the evening to determine the DLMO. A total number of 659 samples were available for analysis. Samples with undetectable melatonin levels (n = 178, 27.0%) were imputed with the lower limit of quantitation divided by two (5.0 pmol/l). The availability of melatonin profiles at T0 (100%) and T1 (93%) were similar between groups. It was possible to detect a DLMO for 48 profiles (84%) at T0 and 37 profiles (65%) at T1. Table A2.4 provides an overview of reasons for missing DLMO's and figure A2.2 shows the change in DLMO from pre- to post-intervention.

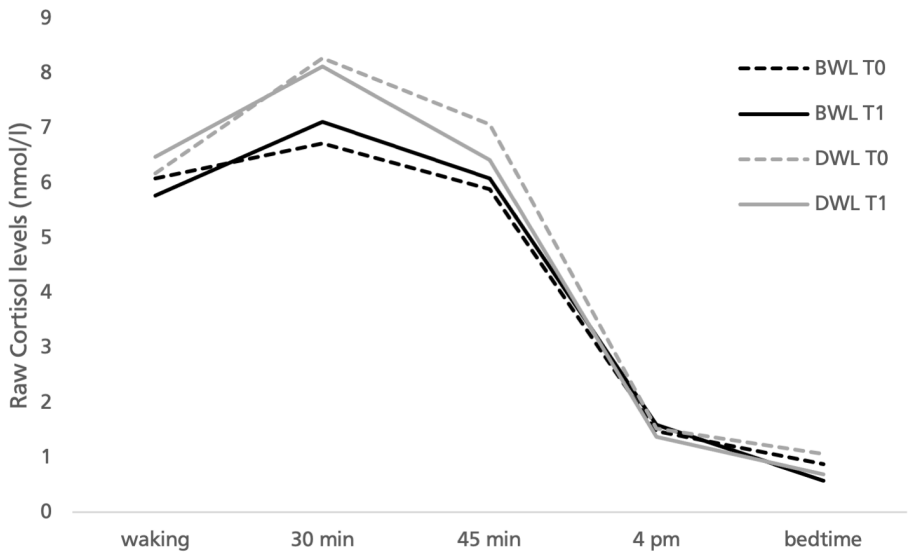

Figure A2.1. Average raw cortisol values for bright white light (BWL) and dim white light (DWL) conditions at each sampling time pre- and post-intervention.

Table A2.4. Overview of reasons for missing DLMO's.

	Baseline	Post intervention
Profiles available	57 (100%)	53 (93%)
Deviation from protocol	4 (7%)	5 (9%)
Determined DLMO	48 (84)	37 (65)
Missing	9	20
No dynamic part	5	3
No base part		3
Insufficient number of data points	1	8
Time of collection not available/samples missing	3	6

Note: Deviation from protocol include drinking coffee or tea, eating chocolate, taking external melatonin, no closure of curtains, or withdrawal of consent to collect additional saliva in the evening.

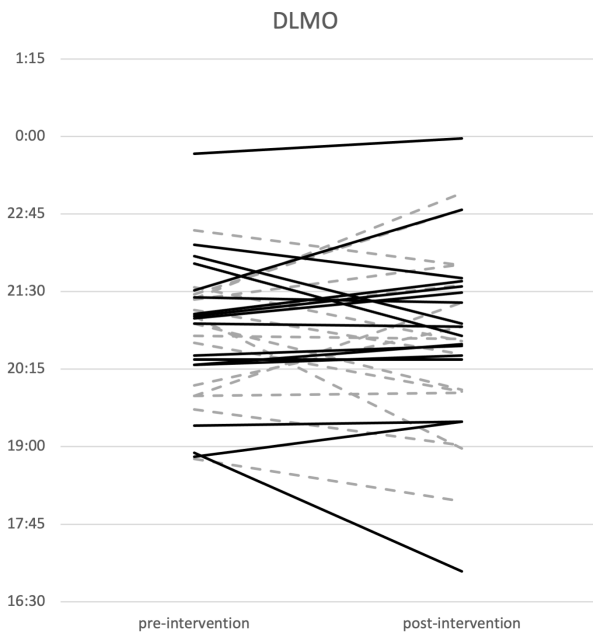

Figure A2.2. Overview of individual changes in DLMO in BWL (black) and DWL (grey) from pre- to post-intervention.

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APPENDIX 3: CORRECTION FOR MISSING DATA

INTRODUCTION

The rate of missing T1 questionnaires was significantly different between the intervention and control group (see the results section of the manuscript), with more missing data in the DWL group compared to the BWL group. This could lead to a potential bias in the results because the number of individuals that stopped prematurely with light therapy more often did not complete all assessments (Table A3.1). Consequently, fatigue levels might have been worse in the unobserved group compared to the observed group, which might affect the conclusions of the primary analyses.

Table A3.1. Missing data patterns (for groups that successfully completed light therapy or stopped light therapy

	n (%)	
Missing data pattern	**Successfully completed**	**Premature stop**
OOOO	136 (88.9)	3 (23.1)
OOOM / OOMO	8 (5.2)	4 (7.7)
OOMM	6 (3.9)	4 (23.1)
OMMM	3 (2.0)	5 (38.5)

O=observed; M=missing

METHOD

To evaluate the possible effects of missing data on the study results, we used a pattern-mixture model in our primary growth curve model analyses. Appendix Table A3.2 shows the possible patterns of missing data. The pattern of missingsness was included as an independent variable in the growth curve model, as well as the interaction with group and time, to adjust for non-ignorable drop-out. A significant interaction between the missing data pattern and time or group indicates that having missing data predicted change in the dependent variables. In the analysis, we combined the patterns OOOM and OOMO as groups were small, and excluded the MMMM pattern (O=observed, M=Missing). The SPSS syntax for the dependent variable VAS-fatigue is as follows:

```
MIXED VAS with time_lin time_sq BY group marstat_cat patternmiss
/CRITERIA=CIN(95) MXITER(100) MXSTEP(10) SCORING(1) SINGULAR(0.000000000001)
HCONVERGE(0, ABSOLUTE) LCONVERGE(0, ABSOLUTE) PCONVERGE(0.000001, ABSOLUTE)
/FIXED time_lin time_sq group marstat_cat patternmiss time_lin*group time_sq*group
time_lin*marstat_cat time_sq*marstat_cat group*marstat_cat time_lin*patternmiss time_
sq*patternmiss group*patternmiss
/METHOD ML
/PRINT SOLUTION TESTCOV
/RANDOM intercept time_lin | subject(ID) covtype(VC).
```

Where time_lin: 0 = T0; 1 = T1; 3.91 = T2; 9.44 = T3
time_sq: 0 = T0; 1 = T1; 15.29 = T2; 89.11 = T3
group: 0 = BWL; 1 = DWL
marstat_cat: 0 = single / widow; 1 = married or in a relationship
patternmiss: 1 = OOOM / OOMO; 2 = OOMM; 3= OMMM; 4 = OOOO.
Note: SPSS uses the category with the highest value as the reference group.

Table A3.2. Possible missing data patterns and their number of occurrence in the BWL and DWL group (Fisher's exact test $p = .06$).

					n (%)		
Missing data pattern	**T0**	**T1**	**T2**	**T3**	**BWL**	**DWL**	**Total**
OOOO	Obs	Obs	Obs	Obs	71 (85.5)	68 (81.9)	139 (83.7)
OOOM	Obs	Obs	Obs	Mis	1 (1.2)	3 (3.6)	4 (2.4)
OOMM	Obs	Obs	Mis	Mis	7 (8.4)	2 (2.4)	9 (5.4)
OMMM	Obs	Mis	Mis	Mis	1 (1.2)	7 (8.4)	8 (4.8)
MMMM	Mis	Mis	Mis	Mis	0 (0.0)	1 (1.2)	1 (0.6)
OOMO	Obs	Obs	Mis	Obs	3 (3.6)	2 (2.4)	5 (3.0)

Mis missing; **Obs** observed; **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy

RESULTS

The results of the growth curve model with adjustment for non-ignorable drop-out led to the same conclusions as the models without this adjustment: the significance levels were slightly different (ranging from −.21 to .11), and the effect sizes were slightly different (ranging from −.02 to .03; Appendix Table A3.3).

DISCUSSION

The results of the pattern mixture model showed similar results compared to the non-adjusted models. Therefore, they support the robustness of the conclusions drawn from the primary analyses that BWL showed no superiority over DWL in the treatment of cancer-related fatigue, sleep quality, depression and anxiety.

Table A3.3. Mean values and standard deviations per time-point, and between-group difference for the growth curve models of primary and secondary measures corrected for non-ignorable dropout and marital status.

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
PRIMARY OUTCOMES						
Fatigue						
VAS fatigue						
BWL	82	5.9 [1.8]	82	4.8 [1.9]	72	5.0 [2.1]
DWL[c]	82	6.3 [1.4]	75	4.8 [1.9]	71	5.0 [1.7]
MFI general fatigue						
BWL	83	15.6 [2.9]	82	13.2 [3.4]	72	13.6 [3.4]
DWL[c]	82	15.8 [2.5]	75	13.1 [3.3]	71	13.5 [3.4]
Restrictions caused by fatigue (WSAS)						
BWL	83	20.7 [7.8]	82	17.4 [8.7]	72	17.5 [9.0]
DWL[c]	82	20.2 [8.5]	75	17.8 [8.8]	70	17.2 [8.8]
SECONDARY OUTCOMES						
Sleep quality (PSQI)[d]						
BWL	83	7.5 [3.7]	82	6.3 [3.1]	72	6.6 [3.1]
DWL[c]	82	7.6 [3.6]	75	5.9 [3.1]	69	6.2 [3.1]
Depression (CES-D)						
BWL	83	18.0 [4.6]	82	16.8 [4.7]	72	17.3 [4.6]
DWL[c]	82	19.0 [5.0]	75	16.3 [4.5]	69	16.8 [3.9]
Anxiety (STAI-6)						
BWL	83	39.6 [10.9]	82	37.4 [11.4]	72	38.7 [10.7]
DWL[c]	82	39.9 [9.8]	75	37.2 [9.5]	69	36.7 [8.9]
Quality of life (RAND-36)						
Physical functioning						
BWL	83	73.8 [20.5]	82	75.1 [20.6]	72	74.4 [21.5]
DWL[c]	82	75.1 [19.5]	75	74.3 [21.7]	69	78.6 [19.5]
Role functioning/physical						
BWL	83	33.7 [36.7]	82	49.1 [42.0]	72	38.2 [37.0]
DWL[c]	82	39.0 [36.0]	75	49.7 [38.7]	69	55.1 [41.7]
Role functioning/emotional						
BWL	83	71.9 [38.4]	82	74.8 [38.7]	72	74.5 [36.0]
DWL[c]	82	72.4 [38.4]	75	76.9 [35.9]	69	73.9 [36.6]

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
	74	5.1 [2.3]	0.19	0.15	.21	-0.02	0.01	.31	0.18	0.08
	70	5.1 [2.1]								
	74	13.8 [3.5]	0.08	0.24	.72	0.00	0.02	.98	0.05	0.17
	70	13.2 [3.6]								
	74	17.3 [9.3]	-0.25	0.39	.52	0.03	0.04	.42	-0.15	0.15
	70	16.5 [9.2]								
	74	6.4 [3.2]	0.02	0.21	.94	-0.01	0.02	.74	0.13	-0.16
	70	6.4 [3.0]								
	74	18.0 [5.5]	0.21	0.33	.52	-0.01	0.03	.87	0.28	0.22
	70	16.6 [4.7]								
	74	39.0 [12.1]	0.62	0.70	.38	-0.06	0.07	.41	0.04	0.06
	69	38.1 [11.5]								
	74	75.2 [24.0]	-0.43	0.24	.07				0.12	-0.26
	69	78.9 [18.9]								
	74	50.7 [39.9]	-0.59	0.71	.41				0.14	-0.22
	69	59.1 [41.8]								
	74	70.7 [38.2]	0.11	0.65	.87				-0.04	-0.04
	69	74.4 [37.1]								

(Continued on next page)

Table A3.3. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
Role functioning/emotional						
BWL	83	71.9 [38.4]	82	74.8 [38.7]	72	74.5 [36.0]
DWL[c]	82	72.4 [38.4]	75	76.9 [35.9]	69	73.9 [36.6]
Energy						
BWL	83	42.9 [14.9]	82	50.4 [17.2]	72	49.9 [16.7]
DWL[c]	82	41.2 [15.2]	75	49.7 [15.6]	69	50.4 [16.1]
Emotional well-being						
BWL	83	73.0 [14.6]	82	75.0 [16.1]	72	72.7 [17.6]
DWL[c]	82	69.9 [16.8]	75	75.0 [15.9]	69	75.6 [16.1]
Social functioning						
BWL	83	59.6 [19.8]	82	68.0 [20.4]	72	66.8 [22.0]
DWL[c]	82	61.4 [20.2]	75	67.2 [19.1]	69	65.9 [19.4]
Pain						
BWL	83	73.0 [25.3]	82	76.3 [22.3]	72	74.7 [25.1]
DWL[c]	82	70.2 [24.7]	75	71.3 [23.3]	69	74.4 [21.8]
General health						
BWL	83	48.3 [17.3]	82	49.0 [17.4]	72	48.8 [20.6]
DWL[c]	82	50.2 [21.5]	75	51.9 [20.7]	69	53.6 [21.5]

Raw means and standard deviations are reported. Models were adjusted for non-ignorable drop-out and marital status

BWL Bright white light; **CES-D** Center for Epidemiological Studies – Depression; **CWS** Cancer Worry Scale; **DWL** Dim white light; **FCS** Fatigue Catastrophizing Scale; **IS** Interdaily Stability; **IV** Intradaily Variability; **MFI** Multidimensional Fatigue inventory; **PSQI** Pittsburgh Sleep Quality Index; **RAND-36** RAND 36-item Health Survey; **SES** Self-efficacy Scale; **STAI-6** State Trait Anxiety Index – short form; **VAS fatigue** Visual Analogue Scale fatigue; **WSAS** Work and Social Adjustment Scale.

[a] **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy.

[b] The effect size was calculated based on the t test statistic $(2*t)/(\sqrt{df})$; small .20; moderate .50; large .80.

[c] DWL is reference group. [d] Based on the AIC and BIC criteria, the model with the best fit excluded a random slope and included an autoregressive covariance structure.

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
	74	70.7 [38.2]	0.11	0.65	.87				-0.04	-0.04
	69	74.4 [37.1]								
	73	50.7 [20.3]	-0.79	1.02	.44	0.05	0.10	.65	-0.03	-0.15
	69	51.9 [18.2]								
	73	71.2 [18.9]	-1.75	0.94	.06	0.14	0.09	.15	-0.18	-0.18
	69	74.6 [16.8]								
	74	69.6 [24.8]	0.97	1.29	.45	-0.10	0.13	.44	0.14	-0.10
	69	70.3 [21.8]								
	74	72.8 [25.7]	-0.92	1.25	.46	0.03	0.12	.79	0.07	-0.25
	69	74.8 [22.2]								
	73	48.8 [21.3]	-0.32	0.25	.21				-0.01	-0.16
	69	54.5 [21.9]								

APPENDIX 4: COMPLETION DURING COVID-19 RESTRICTIONS.

INTRODUCTION

Thirty-three participants completed the 9 months follow-up assessment during the restrictions for the Covid-19 pandemic. This meant that these participants were encouraged to work from home and social activities were restricted. Consequently, sleep and work patterns could change and influence our results.

METHOD

To correct for this, we asked these participants to complete a survey on how the Covid-19 restrictions changed their sleep-wake cycle and whether it affected their fatigue level. We also performed the growth curve model with the exclusion of the final assessment of these participants.

RESULTS

Results of the survey (Table A4.1) showed that the majority of the participants did not change their bedtimes (70%), nor did they experience a change in sleep quality (82%), although they reported changes in daily routine (88%). Sixty-three percent of the participants reported no effect of the Covid-19 restrictions on fatigue levels, 19% felt more fatigued and 11% felt less fatigue. The restrictions led to changes in the time that individuals spend outside. One third spend more time outside, 26% spend less time outside and 37% reported no change in time spend outside. Results of the growth curve model excluding the final assessments completed during Covid-19 restrictions led to similar conclusions as the unadjusted growth curve models (Appendix Table A4.2).

DISCUSSION

Although the majority of the participants did not change their sleep behaviors because of the work and social activities restrictions due to Covid-19, the majority also mentioned that their daily activities and time spent outside changed. Yet, this did not affect self-reported sleep quality and fatigue levels. Moreover, the sensitivity analyses with the exclusion of the final assessment completed during Covid-19 restrictions showed similar results compared to the primary analyses.

Table A4.1. Overview of the self-reported influence of Covid-19 restrictions on sleep times, daily routine, and fatigue (n = 26).

	n (%)
1a. Did your bedtimes change because of the Covid-19 restrictions?	
No	19 (70,4)
Yes	7 (25.9)
1b. If your bedtimes changes, how did they change?	
I go to bed earlier	3 (11.1)
I go to bed later	6 (22.2)
I get up earlier	2 (7.4)
I get up later	2 (7.4)
2. Do you feel like your sleep quality changed since the Covid-19 restrictions?	
No	22 (81.5)
Yes, I sleep better	2 (7.4)
Yes, I sleep worse	2 (7.4)
3. Is your daily routine more busy or more relaxed since the Covid-19 restrictions?	
Remained the same	6 (22.2)
Became more busy	3 (11.1)
Became more relaxed	7 (25.9)
My daily routine changed, but it wasn't more busy or relaxed	10 (37.0)
4. Do you spend more or less time outside since the Covid-19 restrictions?	
Remained the same	10 (37.0)
More time outside	9 (33.3)
Less time outside	7 (25.9)
5. Do you think that the Covid-19 restrictions had an effect on your fatigue?	
No	17 (63.0)
Yes, I feel more fatigued	5 (18.5)
Yes, I feel less fatigued	3 (11.1)

Notes Table A4.2 *(next pages)*:
Raw means and standard deviations are reported. Models were adjusted for marital status.
BWL Bright white light; **CES-D** Center for Epidemiological Studies – Depression; **CWS** Cancer Worry Scale; **DWL** Dim white light; **FCS** Fatigue Catastrophizing Scale; **IS** Interdaily Stability; **IV** Intradaily Variability; **MFI** Multidimensional Fatigue inventory; **PSQI** Pittsburgh Sleep Quality Index; **RAND-36** RAND 36-item Health Survey; **SES** Self-efficacy Scale; **STAI-6** State Trait Anxiety Index – short form; **VAS fatigue** Visual Analogue Scale fatigue; **WSAS** Work and Social Adjustment Scale.
[a] **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy. [b] The effect size was calculated based on the t test statistic (2*t)/(√df); small .20; moderate .50; large .80. [c] DWL is reference group. [d] Based on the AIC and BIC criteria, the model with the best fit excluded a random slope and included an autoregressive covariance structure. [e] Due to convergence problems, an identity covariance matrix instead of variance components covariance structure was used.

Table A4.2. Mean values and standard deviations per time-point, and between-group difference for the growth curve models of primary and secondary measures excluding the final assessments completed during Covid-19 restrictions.

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
PRIMARY OUTCOMES						
Fatigue						
VAS fatigue						
BWL	82	5.9 [1.8]	82	4.8 [1.9]	72	5.0 [2.1]
DWL[c]	82	6.3 [1.4]	75	4.8 [1.9]	71	5.0 [1.7]
MFI general fatigue						
BWL	83	15.6 [2.9]	82	13.2 [3.4]	72	13.6 [3.4]
DWL[c]	82	15.8 [2.5]	75	13.1 [3.3]	71	13.5 [3.4]
Restrictions caused by fatigue (WSAS)						
BWL	83	20.7 [7.8]	82	17.4 [8.7]	72	17.5 [9.0]
DWL[c]	82	20.2 [8.5]	75	17.8 [8.8]	70	17.2 [8.8]
SECONDARY OUTCOMES						
Sleep quality (PSQI)[d]						
BWL	83	7.5 [3.7]	82	6.3 [3.1]	72	6.6 [3.1]
DWL[c]	82	7.6 [3.6]	75	5.9 [3.1]	69	6.2 [3.1]
Depression (CES-D)						
BWL	83	18.0 [4.6]	82	16.8 [4.7]	72	17.3 [4.6]
DWL[c]	82	19.0 [5.0]	75	16.3 [4.5]	69	16.8 [3.9]
Anxiety (STAI-6)						
BWL	83	39.6 [10.9]	82	37.4 [11.4]	72	38.7 [10.7]
DWL[c]	82	39.9 [9.8]	75	37.2 [9.5]	69	36.7 [8.9]
Quality of life (RAND-36)						
Physical functioning						
BWL	83	73.8 [20.5]	82	75.1 [20.6]	72	74.4 [21.5]
DWL[c]	82	75.1 [19.5]	75	74.3 [21.7]	69	78.6 [19.5]
Role functioning/physical						
BWL	83	33.7 [36.7]	82	49.1 [42.0]	72	38.2 [37.0]
DWL[c]	82	39.0 [36.0]	75	49.7 [38.7]	69	55.1 [41.7]
Role functioning/emotional						
BWL	83	71.9 [38.4]	82	74.8 [38.7]	72	74.5 [36.0]
DWL[c]	82	72.4 [38.4]	75	76.9 [35.9]	69	73.9 [36.6]

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
	58	5.1 [2.3]	0.20	0.15	.17	-0.02	0.02	.19	0.18	-0.04
	53	5.2 [2.2]								
	58	13.9 [3.5]	0.10	0.24	.68	0.00	0.02	.93	0.05	0.13
	53	13.6 [3.7]								
	58	17.8 [9.5]	-0.23	0.39	.55	0.03	0.04	.41	-0.15	0.17
	53	16.8 [9.6]								
	58	6.5 [3.3]	0.05	0.21	.81	-0.01	0.02	.74	0.13	-0.13
	53	6.5 [3.0]								
	58	18.0 [5.4]	0.28	0.33	.40	-0.01	0.03	.74	0.28	0.19
	53	16.9 [4.8]								
	58	39.1 [11.9]	0.64	0.70	.36	-0.05	0.07	.51	0.04	0.12
	53	38.0 [12.0]								
	58	72.4 [25.2]	-0.60	0.28	.03				0.12	-0.33
	53	78.3 [19.2]								
	58	46.6 [41.2]	-0.85	0.81	.30				0.14	-0.27
	53	56.6 [43.9]								
	58	72.4 [37.5]	-0.15	0.74	.84				-0.04	-0.11
	53	75.5 [36.5]								

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Table A4.2. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
Energy						
BWL	83	42.9 [14.9]	82	50.4 [17.2]	72	49.9 [16.7]
DWL[c]	82	41.2 [15.2]	75	49.7 [15.6]	69	50.4 [16.1]
Emotional well-being						
BWL	83	73.0 [14.6]	82	75.0 [16.1]	72	72.7 [17.6]
DWL[c]	82	69.9 [16.8]	75	75.0 [15.9]	69	75.6 [16.1]
Social functioning						
BWL	83	59.6 [19.8]	82	68.0 [20.4]	72	66.8 [22.0]
DWL[c]	82	61.4 [20.2]	75	67.2 [19.1]	69	65.9 [19.4]
Pain						
BWL	83	73.0 [25.3]	82	76.3 [22.3]	72	74.7 [25.1]
DWL[c]	82	70.2 [24.7]	75	71.3 [23.3]	69	74.4 [21.8]
General health						
BWL	83	48.3 [17.3]	82	49.0 [17.4]	72	48.8 [20.6]
DWL[c]	82	50.2 [21.5]	75	51.9 [20.7]	69	53.6 [21.5]
Sleep actigraphy						
Sleep efficiency, %						
BWL	80	74.38 [7.71]	74	73.43 [7.75]	70	73.99 [7.68]
DWL[c]	77	74.04 [8.3]	73	73.48 [8.91]	68	74.23 [8.32]
Mid-sleep time, hh:mm						
BWL	80	3:46 [0:46]	74	3:41 [0:47]	70	3:46 [0:46]
DWL[c]	77	3:45 [0:52]	73	3:42 [0:52]	68	3:44 [0:47]
Total sleep time, min						
BWL	80	6:23 [0:51]	74	6:16 [0:54]	70	6:18 [0:49]
DWL[c]	77	6:20 [0:46]	73	6:14 [0:58]	68	6:19 [0:50]
IS [e]						
BWL	79	0.76 [0.10]	73	0.75 [0.11]	68	0.75 [0.09]
DWL[c]	77	0.76 [0.12]	72	0.73 [0.13]	67	0.75 [0.12]
IV						
BWL	79	0.41 [0.10]	73	0.41 [0.12]	68	0.42 [0.11]
DWL[c]	77	0.40 [0.13]	72	0.41 [0.15]	67	0.40 [0.12]

T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
57	50.9 [20.3]	-0.92	1.03	.37	0.06	0.10	.54	-0.03	-0.11
53	49.7 [18.4]								
57	72.1 [19.1]	-1.99	0.93	.03	0.17	0.09	.07	-0.18	-0.09
53	72.2 [17.5]								
58	68.3 [24.9]	0.87	1.27	.50	-0.07	0.13	.60	0.14	-0.02
53	67.0 [22.6]								
58	69.6 [26.8]	-0.66	1.26	.60	-0.01	0.13	.96	0.07	-0.29
53	74.2 [22.9]								
58	46.1 [19.6]	-0.49	0.30	.11				-0.01	-0.22
53	54.3 [21.8]								
55	74.29 [8.95]	0.04	0.07	.62				-0.04	0.08
53	73.35 [8.85]								
55	3:43 [0:41]	-20.58	42.00	.63				-0.05	0.00
53	3:46 [0:57]								
55	6:16 [0:56]	90.68	119.86	.45	-13.04	12.21	.29	-0.06	-0.04
53	6:20 [0:51]								
54	0.77 [0.08]	0.00	0.01	1.00	0.00	0.00	.98	0.25	-0.07
53	0.75 [0.11]								
54	0.42 [0.10]	0.01	0.01	.37	0.00	0.00	.51	-0.16	0.16
53	0.41 [0.14]								

APPENDIX 5 ADDITIONAL TABLES FOR INTENTION-TO-TREAT, PER PROTOCOL AND SENSITIVITY ANALYSES.

Table A5.1. Mean values and standard deviations per time-point, and between-group differences of the primary and secondary measures for the growth curve models of the intention-to-treat analysis.

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
PRIMARY OUTCOMES						
Fatigue						
VAS fatigue						
BWL	82	5.9 [1.8]	82	4.8 [1.9]	72	5.0 [2.1]
DWL[c]	82	6.3 [1.4]	75	4.8 [1.9]	71	5.0 [1.7]
MFI general fatigue						
BWL	83	15.6 [2.9]	82	13.2 [3.4]	72	13.6 [3.4]
DWL[c]	82	15.8 [2.5]	75	13.1 [3.3]	71	13.5 [3.4]
Restrictions caused by fatigue (WSAS)						
BWL	83	20.7 [7.8]	82	17.4 [8.7]	72	17.5 [9.0]
DWL[c]	82	20.2 [8.5]	75	17.8 [8.8]	70	17.2 [8.8]
SECONDARY OUTCOMES						
Sleep quality (PSQI)[d]						
BWL	83	7.5 [3.7]	82	6.3 [3.1]	72	6.6 [3.1]
DWL[c]	82	7.6 [3.6]	75	5.9 [3.1]	69	6.2 [3.1]
Depression (CES-D)						
BWL	83	18.0 [4.6]	82	16.8 [4.7]	72	17.3 [4.6]
DWL[c]	82	19.0 [5.0]	75	16.3 [4.5]	69	16.8 [3.9]
Anxiety (STAI-6)						
BWL	83	39.6 [10.9]	82	37.4 [11.4]	72	38.7 [10.7]
DWL[c]	82	39.9 [9.8]	75	37.2 [9.5]	69	36.7 [8.9]
Quality of life (RAND-36)						
Physical functioning						
BWL	83	73.8 [20.5]	82	75.1 [20.6]	72	74.4 [21.5]
DWL[c]	82	75.1 [19.5]	75	74.3 [21.7]	69	78.6 [19.5]
Role limitations/physical						
BWL	83	33.7 [36.7]	82	49.1 [42.0]	72	38.2 [37.0]
DWL[c]	82	39.0 [36.0]	75	49.7 [38.7]	69	55.1 [41.7]

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
	74	5.1 [2.3]	0.18	0.15	.23	-0.01	0.01	.32	0.18	0.08
	70	5.1 [2.1]								
	74	13.8 [3.5]	0.08	0.24	.73	0.00	0.02	.98	0.05	0.17
	70	13.2 [3.6]								
	74	17.3 [9.3]	-0.23	0.39	.56	0.03	0.04	.45	-0.15	0.15
	70	16.5 [9.2]								
	74	6.4 [3.2]	0.07	0.21	.73	-0.01	0.02	.59	0.13	-0.16
	70	6.4 [3.0]								
	74	18.0 [5.5]	0.27	0.33	.41	-0.01	0.03	.75	0.28	0.22
	70	16.6 [4.7]								
	74	39.0 [12.1]	0.72	0.69	.30	-0.07	0.07	.34	0.04	0.06
	69	38.1 [11.5]								
	74	75.2 [24.0]	-0.42	0.23	.08				0.12	-0.26
	69	78.9 [18.9]								
	74	50.7 [39.9]	-0.59	0.71	.41				0.14	-0.22
	69	59.1 [41.8]								

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Table A5.1. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
Role limitations/emotional						
BWL	83	71.9 [38.4]	82	74.8 [38.7]	72	74.5 [36.0]
DWL[c]	82	72.4 [38.4]	75	76.9 [35.9]	69	73.9 [36.6]
Energy						
BWL	83	42.9 [14.9]	82	50.4 [17.2]	72	49.9 [16.7]
DWL[c]	82	41.2 [15.2]	75	49.7 [15.6]	69	50.4 [16.1]
Emotional well-being						
BWL	83	73.0 [14.6]	82	75.0 [16.1]	72	72.7 [17.6]
DWL[c]	82	69.9 [16.8]	75	75.0 [15.9]	69	75.6 [16.1]
Social functioning						
BWL	83	59.6 [19.8]	82	68.0 [20.4]	72	66.8 [22.0]
DWL[c]	82	61.4 [20.2]	75	67.2 [19.1]	69	65.9 [19.4]
Pain						
BWL	83	73.0 [25.3]	82	76.3 [22.3]	72	74.7 [25.1]
DWL[c]	82	70.2 [24.7]	75	71.3 [23.3]	69	74.4 [21.8]
General health						
BWL	83	48.3 [17.3]	82	49.0 [17.4]	72	48.8 [20.6]
DWL[c]	82	50.2 [21.5]	75	51.9 [20.7]	69	53.6 [21.5]
Actigraphy						
Sleep efficiency, %						
BWL	80	74.4 [7.7]	74	73.4 [7.8]	70	74.0 [7.7]
DWL[c]	77	74.0 [8.3]	73	73.5 [8.9]	68	74.2 [8.3]
Mid-sleep time, hh:mm						
BWL	80	3:46 [0:46]	74	3:41 [0:47]	70	3:46 [0:46]
DWL[c]	77	3:45 [0:52]	73	3:42 [0:52]	68	3:44 [0:47]
Total sleep time, hh:mm						
BWL	80	6:23 [0:51]	74	6:16 [0:54]	70	6:18 [0:49]
DWL[c]	77	6:20 [0:46]	73	6:14 [0:58]	68	6:19 [0:50]
IS						
BWL	79	0.76 [0.10]	73	0.75 [0.11]	68	0.75 [0.09]
DWL[c]	77	0.76 [0.12]	72	0.73 [0.13]	67	0.75 [0.12]

T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
74	70.7 [38.2]	0.02	0.64	.97				-0.04	-0.04
69	74.4 [37.1]								
73	50.7 [20.3]	-0.92	1.01	.37	0.05	0.10	.59	-0.03	-0.15
69	51.9 [18.2]								
73	71.2 [18.9]	-1.85	0.94	.05	0.14	0.09	.13	-0.18	-0.18
69	74.6 [16.8]								
74	69.6 [24.8]	1.05	1.28	.41	-0.11	0.13	.40	0.14	-0.10
69	70.3 [21.8]								
74	72.8 [25.7]	-0.74	1.25	.55	0.02	0.12	.90	0.07	-0.25
69	74.8 [22.2]								
73	48.8 [21.3]	-0.35	0.26	.17				-0.01	-0.16
69	54.5 [21.9]								
71	74.5 [8.3]	0.04	0.07	.55				-0.04	0.10
69	73.8=9 [8.5]								
71	3:50 [0:47]	8.82	36.75	.81				-0.05	0.08
69	3:44 [0:52]								
71	6:18 [0:54]	84.26	119.02	.48	-11.76	11.81	.32	-0.06	-0.05
69	6:21 [0:52]								
69	0.77 [0.08]	0.00	0.01	.95	0.00	0.00	.99	0.25	-0.09
69	0.75 [0.12]								

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Table A5.1. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
IV						
BWL	79	0.41 [0.10]	73	0.41 [0.12]	68	0.42 [0.11]
DWL[c]	77	0.40 [0.13]	72	0.41 [0.15]	67	0.40 [0.12]
Circadian rhythm						
Cortisol awakening response						
BWL	52	0.5 [3.4]	52	0.8 [3.6]		
DWL[c]	57	1.7 [4.0]	52	1.1 [4.1]		
Diurnal cortisol slope						
BWL	63	-0.17 [0.08]	58	-0.18 [0.08]		
DWL[c]	66	-0.17 [0.09]	61	-0.17 [0.08]		
Total cortisol output						
BWL	60	41.2 [23.4]	48	41.3 [23.4]		
DWL[c]	64	48.2 [26.0]	56	41.3 [19.2]		
DLMO, hh:mm						
BWL	24	20:39 [1:11]	18	20:46 [1:21]		
DWL[c]	20	20:54 [1:20]	18	20:55 [1:27]		

Raw means and standard deviations are reported. Models were adjusted for marital status
BWL Bright white light; **CES-D** Center for Epidemiological Studies – Depression; **CWS** Cancer Worry Scale; **DLMO** Dim light melatonin onset; **DWL** Dim white light; **FCS** Fatigue Catastrophizing Scale; **IS** Interdaily Stability; **IV** Intradaily Variability; **MFI** Multidimensional Fatigue inventory; **PSQI** Pittsburgh Sleep Quality Index; **RAND-36** RAND 36-item Health Survey; **SES** Self-efficacy Scale; **STAI-6** State Trait Anxiety Index – short form; **VAS fatigue** Visual Analogue Scale fatigue; **WSAS** Work and Social Adjustment Scale.
[a] **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy.
[b] The effect size was calculated based on the t test statistic $(2*t)/(\sqrt{df})$; small .20; moderate .50; large .80. [c] DWL is reference group. [d] Based on the AIC and BIC criteria, the model with the best fit excluded a random slope and included an autoregressive covariance structure.

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
	69	0.41 [0.09]	0.01	0.01	.28	0.00	0.00	.28	-0.16	0.03
	69	0.42 [0.17]								
			1.17	0.84	.17				0.27	
			0.00	0.02	.93				-0.06	
			7.52	5.16	.15				0.26	
			-0.10	0.34	.77				-0.17	

Table A5.2. Mean values and standard deviations per time-point and time effects for growth curve models of primary and secondary measures for the total sample.

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
PRIMARY OUTCOMES						
Fatigue						
VAS fatigue	164	6.1 [1.6]	157	4.8 [1.9]	143	5.0 [1.9]
MFI general fatigue	165	15.7 [2.7]	157	13.1 [3.3]	143	13.6 [3.4]
Restrictions caused by fatigue (WSAS)	165	20.5 [8.2]	157	17.6 [8.7]	142	17.3 [8.9]
SECONDARY OUTCOMES						
Sleep quality (PSQI)[c]	165	7.6 [3.7]	157	6.1 [3.1]	141	6.4 [3.1]
Depression (CES-D)	165	18.5 [4.8]	157	16.6 [4.6]	141	17.1 [4.3]
Anxiety (STAI-6)	165	39.8 [10.4]	157	37.4 [10.5]	141	37.7 [9.9]
Quality of Life (RAND-36)						
Physical functioning	165	74.4 [20.0]	157	74.7 [21.1]	141	76.4 [20.6]
Role functioning/physical	165	36.4 [36.4]	157	49.4 [40.3]	141	47.0 [40.0]
Role functioning/emotional	165	72.1 [38.3]	157	75.8 [37.3]	141	74.2 [36.2]
Energy	165	42.1 [15.1]	157	50.1 [16.4]	141	50.1 [16.4]
Emotional well-being	165	71.5 [15.8]	157	75.0 [15.9]	141	74.1 [16.9]
Social functioning	165	60.5 [19.9]	157	67.6 [19.8]	141	66.4 [20.7]
Pain	165	71.6 [25.0]	157	73.9 [22.8]	141	74.5 [23.5]
General health	165	49.2 [19.4]	157	50.4 [19.0]	141	51.1 [21.1]
Actigraphy						
Sleep efficiency, %	157	74.2 [8.0]	147	73.5 [8.3]	138	74.1 [8.0]
Mid-sleep time, hh:mm	157	3:45 [0:49]	147	3:41 [0:49]	138	3:45 [0:46]
Total sleep time, hh:mm	157	6:21 [0:49]	147	6:15 [0:55]	138	6:19 [0:49]
IS	156	0.76 [0.11]	145	0.74 [0.12]	135	0.75 [0.10]
IV	156	0.41 [0.12]	145	0.41 [0.14]	135	0.41 [0.12]
Circadian rhythm						
Cortisol awakening response	109	1.1 [3.8]	104	0.9 [3.9]		
Diurnal cortisol slope	129	-0.17 [0.08]	119	-0.18 [0.08]		
Total cortisol output	124	44.8 [24.9]	104	41.3 [21.1]		
DLMO, hh:mm	44	20:46 [1:15]	36	20:50 [1:23]		

Raw means and standard deviations are reported.
CES-D Center for Epidemiological Studies – Depression; **CWS** Cancer Worry Scale; **DLMO** Dim light melatonin onset; **FCS** Fatigue Catastrophizing Scale; **IS** Interdaily Stability; **IV** Intradaily Variability; **MFI** Multidimensional Fatigue inventory; **PSQI** Pittsburgh Sleep Quality Index; **RAND-36** RAND 36-item Health Survey; **SES** Self-efficacy Scale; **STAI-6** State Trait Anxiety Index – short form; **VAS fatigue** Visual Analogue Scale fatigue; **WSAS** Work and Social Adjustment Scale. [a] **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy. [b] The effect size was calculated based on the t test

	T3[a]		Linear time effect			Quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
	144	5.1 [2.2]	-0.40	0.07	<.001	0.03	0.01	<.001	-0.71	0.15
	144	13.5 [3.5]	-0.74	0.12	<.001	0.06	0.01	<.001	-0.81	0.13
	144	16.9 [9.2]	-1.07	0.19	<.001	0.08	0.02	<.001	-0.32	-0.07
	144	6.4 [3.1]	-0.40	0.10	<.001	0.03	0.01	.001	-0.44	0.10
	144	17.3 [5.1]	-0.47	0.16	.004	0.04	0.02	.007	-0.41	0.16
	143	38.6 [11.8]	-0.79	0.34	.02	0.08	0.03	.02	-0.23	0.13
	143	77.0 [21.7]	0.17	0.12	.14				0.01	0.07
	143	54.7 [40.9]	1.35	0.35	<.001				0.33	0.11
	143	72.5 [37.6]	-0.08	0.32	.80				0.10	-0.08
	142	51.3 [19.2]	2.86	0.50	<.001	-0.23	0.05	<.001	0.48	0.05
	142	72.9 [17.9]	1.11	0.46	.02	-0.11	0.05	.01	0.21	-0.13
	143	69.9 [23.3]	1.97	0.63	.002	-0.13	0.06	.03	0.35	0.09
	143	73.8 [24.0]	1.06	0.61	.08	-0.10	0.06	.10	0.11	-0.04
	142	51.6 [21.7]	0.17	0.13	.19				0.05	0.04
	140	74.2 [8.4]	0.02	0.04	.55				-0.10	0.09
	140	3:47 [0:50]	31.41	18.01	.08				-0.02	0.11
	140	6:19 [0:53]	-58.72	58.94	.32	6.50	5.85	.27	-0.11	0.08
	138	0.76 [0.10]	-0.01	0.00	.07	0.00	0.00	.04	-0.24	0.22
	138	0.41 [0.14]	0.00	0.00	.55	0.00	0.00	.78	0.02	0.06
			-0.27	0.42	.52				-0.07	
			-0.01	0.01	.49				-0.08	
			-3.04	2.55	.24				-0.13	
			-0.01	0.16	.94				-0.01	

statistic (2*t)/(√df); small .20; moderate .50; large .80. [c] Based on the AIC and BIC criteria, the model with the best fit excluded a random slope and included an autoregressive covariance structure.

Table A5.3: Mean values and standard deviations per time-point, and between-group differences of the primary and secondary measures for the growth curve models for individuals who adhered to 25 days of light therapy.

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
PRIMARY OUTCOMES						
Fatigue						
VAS fatigue						
BWL	32	6.3 [1.9]	33	5.0 [1.9]	31	5.2 [2.3]
DWL[c]	28	6.3 [1.8]	28	4.8 [2.0]	27	4.8 [1.8]
MFI general fatigue						
BWL	33	15.7 [3.1]	33	13.7 [3.4]	31	13.9 [4.1]
DWL[c]	28	16.0 [2.3]	28	12.6 [2.9]	27	13.4 [3.4]
Restrictions caused by fatigue (WSAS)						
BWL	33	23.6 [8.4]	33	19.0 [8.9]	31	20.2 [9.1]
DWL[c]	28	22.1 [8.5]	28	19.3 [9.2]	26	18.4 [10.0]
SECONDARY OUTCOMES						
Sleep quality (PSQI)[d]						
BWL	33	8.2 [4.0]	33	6.4 [2.9]	31	6.2 [3.1]
DWL[c]	28	7.0 [3.7]	28	5.6 [2.5]	26	5.3 [2.8]
Depression (CES-D)						
BWL	33	19.2 [4.3]	33	16.7 [4.3]	31	17.4 [4.1]
DWL[c]	28	17.0 [4.1]	28	15.5 [3.4]	26	16.1 [4.7]
Anxiety (STAI-6)						
BWL	33	41.2 [11.8]	33	36.1 [10.6]	31	38.3 [10.8]
DWL[c]	28	36.7 [8.0]	28	34.5 [7.6]	26	34.7 [8.6]
Quality of life (RAND-36)						
Physical functioning[e]						
BWL	33	67.7 [22.6]	33	70.0 [22.9]	31	66.6 [22.7]
DWL[c]	28	74.8 [20.5]	28	70.2 [22.2]	26	74.2 [19.5]
Role functioning/physical						
BWL	33	28.0 [34.7]	33	46.2 [40.6]	31	32.3 [37.7]
DWL[c]	28	42.0 [38.5]	28	47.3 [35.6]	26	51.9 [44.1]
Role functioning/emotional						
BWL	33	74.7 [37.3]	33	79.8 [36.3]	31	73.1 [35.9]
DWL[c]	28	86.9 [24.6]	28	90.5 [25.4]	26	87.2 [23.2]

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
	32	5.4 [2.3]	0.18	0.24	.44	-0.02	0.02	.45	0.11	-0.06
	28	5.3 [2.4]								
	32	14.3 [3.5]	0.34	0.36	.34	-0.03	0.04	.41	0.40	-0.15
	28	13.6 [3.6]								
	32	19.9 [8.4]	0.46	0.64	.48	-0.04	0.06	.51	-0.20	0.14
	28	18.7 [10.7]								
	32	6.5 [3.1]	0.06	0.35	.86	-0.02	0.03	.57	-0.13	-0.21
	28	6.4 [2.8]								
	32	18.1 [5.8]	-0.29	0.50	.56	0.03	0.05	.58	-0.24	0.14
	28	16.4 [5.6]								
	32	39.2 [11.2]	-0.14	1.15	.90	0.00	0.11	.99	-0.30	0.06
	27	36.5 [10.4]								
	32	68.8 [25.9]	-0.12	0.90	.89				0.31	-0.26
	27	74.6 [21.1]								
	32	41.4 [41.5]	-0.14	1.14	.91				0.33	-0.21
	27	50.9 [43.6]								
	32	76.0 [36.2]	0.60	0.99	.55				0.05	0.08
	27	84.0 [31.2]								

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Table A5.3. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
Energy						
BWL	33	41.1 [15.7]	33	50.0 [15.8]	31	47.9 [17.6]
DWL[c]	28	40.2 [15.2]	28	47.9 [13.8]	26	51.9 [15.7]
Emotional well-being						
BWL	33	73.0 [15.0]	33	78.1 [13.4]	31	73.5 [19.0]
DWL[c]	28	72.1 [14.5]	28	80.3 [12.7]	26	80.9 [13.8]
Social functioning						
BWL	33	59.1 [20.6]	33	67.4 [22.1]	31	67.7 [23.9]
DWL[c]	28	61.2 [21.3]	28	68.3 [20.5]	26	65.9 [21.1]
Pain						
BWL	33	69.7 [22.7]	33	69.5 [24.2]	31	69.7 [25.2]
DWL[c]	28	67.6 [27.4]	28	69.1 [23.4]	26	70.5 [23.3]
General health						
BWL	33	47.1 [16.7]	33	46.7 [17.3]	31	45.8 [21.2]
DWL[c]	28	50 [19.0]	28	54.3 [17.9]	26	55.2 [19.1]
Sleep (actigraphy)						
Sleep efficiency, %						
BWL	32	74.0 [8.7]	32	73.7 [8.6]	30	74.1 [8.9]
DWL[c]	28	75.6 [7.6]	28	75.6 [8.4]	26	75.2 [8.1]
Mid-sleep time, hh:mm						
BWL	32	3:36 [0:42]	32	3:36 [0:49]	30	3:41 [0:42]
DWL[c]	28	3:37 [0:41]	28	3:36 [0:42]	26	3:43 [0:49]
Total sleep time, min						
BWL	32	6:18 [0:56]	32	6:13 [0:57]	30	6:23 [0:51]
DWL[c]	28	6:18 [0:49]	28	6:20 [1:00]	26	6:19 [0:53]
IS						
BWL	32	0.76 [0.12]	32	0.73 [0.11]	30	0.75 [0.08]
DWL[c]	28	0.79 [0.09]	28	0.76 [0.12]	26	0.77 [0.11]
IV						
BWL	32	0.42 [0.11]	32	0.41 [0.14]	30	0.43 [0.13]
DWL[c]	28	0.39 [0.08]	28	0.40 [0.10]	26	0.40 [0.09]

T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
31	48.5 [22.5]	-2.57	1.53	.10	0.23	0.15	.13	0.07	-0.20
27	49.6 [19.5]								
31	71.9 [19.4]	-3.55	1.43	.01	0.35	0.14	.02	-0.19	0.00
27	74.4 [18.0]								
32	65.6 [27.9]	0.48	2.15	.82	-0.06	0.21	.78	0.05	-0.06
27	67.6 [27.6]								
32	68.9 [26.9]	-1.46	1.99	.47	0.11	0.20	.59	-0.07	-0.08
27	70.7 [26.2]								
31	44.4 [20.9]	-0.25	0.39	.52				-0.25	0.03
27	51.9 [21.2]								
30	75.8 [8.8]	0.35	0.11	.002				-0.02	0.40
27	74.0 [9.4]								
30	3:40 [0:41]	16.42	57.56	.78				0.01	0.07
27	3:38 [0:55]								
30	6:24 [0:55]	321.82	172.87	.07	-21.16	17.20	.22	-0.12	0.35
27	6:12 [0:58]								
30	0.78 [0.07]	0.00	0.01	.80	0.00	0.00	.91	0.02	0.33
27	0.77 [0.14]								
30	0.40 [0.08]	0.01	0.01	.58	0.00	0.00	.42	-0.12	-0.25
27	0.42 [0.21]								

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Table A5.3. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
Circadian rhythm						
Cortisol Awakening Response						
BWL	22	-0.4 [2.5]	25	0.6 [3.6]		
DWL[c]	19	2.4 [4.5]	20	0.9 [4.0]		
Diurnal cortisol slope						
BWL	26	-0.15 [0.06]	25	-0.19 [0.08]		
DWL[c]	21	-0.18 [0.08]	19	-0.20 [0.08]		
Total cortisol output						
BWL	26	36.2 [16.9]	21	37.8 [22.0]		
DWL[c]	20	50.1 [20.7]	17	46.1 [22.1]		
DLMO, hh:mm						
BWL	12	20:23 [1:17]	9	20:14 [1:11]		
DWL[c]	8	20:36 [1:26]	8	20:09 [1:31]		

Raw means and standard deviations are reported. Models were adjusted for marital status
BWL Bright white light; **CES-D** Center for Epidemiological Studies – Depression; **CWS** Cancer Worry Scale; **DLMO** Dim light melatonin onset; **DWL** Dim white light; **FCS** Fatigue Catastrophizing Scale; **IS** Interdaily Stability; **IV** Intradaily Variability; **MFI** Multidimensional Fatigue inventory; **PSQI** Pittsburgh Sleep Quality Index; **RAND-36** RAND 36-item Health Survey; **SES** Self-efficacy Scale; **STAI-6** State Trait Anxiety Index – short form; **VAS fatigue** Visual Analogue Scale fatigue; **WSAS** Work and Social Adjustment Scale.
[a] **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy
[b] The effect size was calculated based on the t test statistic (2*t)/(√df); small .20; moderate .50; large .80.
[c] DWL is reference group. [d] Based on the AIC and BIC criteria, the model with the best fit excluded a random slope and included an autoregressive covariance structure. [e] identity covariance matrix

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
			2.64	1.33	.05				0.67	
			-0.02	0.03	.52				-0.29	
			5.15	8.12	.53				0.29	
			-0.06	0.30	.86				0.12	

Table A5.4: Mean values and standard deviations per time-point, and between-group differences of the primary and secondary measures for the growth curve models for individuals who used the Luminette glasses.

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
PRIMARY OUTCOMES						
Fatigue						
VAS fatigue						
BWL	65	5.9 [1.8]	64	4.7 [2.0]	55	4.8 [2.1]
DWL[c]	62	6.3 [1.5]	58	4.9 [1.9]	55	5.3 [1.5]
MFI general fatigue						
BWL	65	15.5 [2.8]	64	13.2 [3.4]	55	13.5 [3.2]
DWL[c]	62	15.7 [2.5]	58	12.9 [3.5]	55	14.0 [3.3]
Restrictions caused by fatigue (WSAS)						
BWL	65	20.8 [7.3]	64	17.1 [8.3]	55	17.2 [8.6]
DWL[c]	62	20.2 [8.5]	58	17.8 [9.1]	54	17.5 [8.5]
SECONDARY OUTCOMES						
Sleep quality (PSQI)[d]						
BWL	65	7.7 [3.8]	64	6.2 [3.0]	55	6.6 [3.0]
DWL[c]	62	7.2 [3.6]	58	5.5 [2.8]	53	6.2 [3.2]
Depression (CES-D)[e]						
BWL	65	18.0 [4.7]	64	16.8 [4.7]	55	17.6 [4.8]
DWL[c]	62	19.0 [4.9]	58	16.3 [4.7]	53	16.8 [4.0]
Anxiety (STAI-6)						
BWL	65	39.5 [10.8]	64	38.5 [11.8]	55	39.5 [11.1]
DWL[c]	62	39.8 [9.4]	58	37.4 [10.2]	53	36.8 [8.5]
Quality of life (RAND-36)						
Physical functioning						
BWL	65	74.2 [20.3]	64	75.9 [19.9]	55	75.8 [21.4]
DWL[c]	62	76.5 [17.3]	58	75.6 [19.4]	53	78.2 [18.6]
Role functioning/physical						
BWL	65	33.8 [37.6]	64	50.4 [41.9]	55	38.2 [36.3]
DWL[c]	62	41.5 [35.6]	58	50.9 [37.7]	53	52.8 [41.2]
Role functioning/emotional[e]						
BWL	65	71.8 [38.3]	64	74.0 [39.2]	55	73.3 [36.5]
DWL[c]	62	71.5 [39.0]	58	77.0 [34.9]	53	73.6 [35.4]

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
	57	5.0 [2.3]	-0.05	0.17	.78	0.01	0.02	.68	0.08	0.05
	55	5.2 [1.9]								
	57	13.8 [3.4]	-0.17	0.27	.54	0.03	0.03	.36	0.13	0.08
	55	13.3 [3.4]								
	57	17.1 [9.1]	-0.45	0.47	.34	0.05	0.05	.25	-0.20	0.16
	55	16.3 [8.7]								
	57	6.5 [3.1]	-0.16	0.23	.49	0.01	0.02	.54	-0.01	-0.02
	55	5.9 [2.9]								
	57	17.9 [5.4]	0.55	0.47	.24	-0.04	0.05	.43	0.29	0.25
	55	16.4 [4.5]								
	57	38.9 [12.1]	0.96	0.77	.22	-0.09	0.08	.26	0.12	0.01
	54	37.6 [11.2]								
	57	76.7 [23.1]	-0.32	0.26	.23				0.17	-0.25
	54	80.3 [17.0]								
	57	50.4 [40.2]	-0.65	0.84	.44				0.20	-0.26
	54	60.2 [41.9]								
	57	67.3 [39.6]	-0.80	1.05	.45				-0.08	-0.15
	54	75.9 [35.1]								

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Table A5.4. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
Energy						
BWL	65	42.0 [15.0]	64	49.8 [17.5]	55	49.8 [16.9]
DWL[c]	62	41.4 [14.9]	58	50.0 [15.7]	53	49.4 [16.3]
Emotional well-being						
BWL	65	71.6 [15.1]	64	74.7 [16.3]	55	70.9 [18.4]
DWL[c]	62	70.5 [16.9]	58	74.6 [16.3]	53	75.1 [15.5]
Social functioning						
BWL	65	58.8 [19.0]	64	67.8 [20.0]	55	66.4 [19.8]
DWL[c]	62	62.5 [18.4]	58	67.5 [19.7]	53	63.0 [19.3]
Pain						
BWL	65	72.9 [25.8]	64	75.4 [21.5]	55	74.5 [24.9]
DWL[c]	62	70.4 [24.4]	58	71.7 [23.0]	53	73.8 [22.2]
General health						
BWL	65	48.1 [17.6]	64	49.2 [17.0]	55	49.3 [20.5]
DWL[c]	62	50.5 [19.2]	58	52.5 [20.2]	53	52.2 [21.3]
Sleep (actigraphy)						
Sleep efficiency, %						
BWL	63	74.90 [7.21]	57	73.68 [7.43]	53	74.39 [7.10]
DWL[c]	59	74.37 [6.71]	56	73.72 [7.68]	52	74.74 [7.26]
Mid-sleep time, hh:mm						
BWL	63	3:49 [0:48]	57	3:41 [0:48]	53	3:48 [0:50]
DWL[c]	59	3:37 [0:40]	56	3:38 [0:48]	52	3:42 [0:42]
Total sleep time, min						
BWL	63	6:23 [0:50]	57	6:14 [0:52]	53	6:20 [0:48]
DWL[c]	59	6:21 [0:42]	56	6:16 [0:51]	52	6:21 [0:47]
IS						
BWL	62	0.76 [0.10]	56	0.74 [0.11]	51	0.74 [0.09]
DWL[c]	59	0.77 [0.10]	56	0.73 [0.14]	52	0.74 [0.11]
IV						
BWL	62	0.41 [0.09]	56	0.40 [0.12]	51	0.42 [0.11]
DWL[c]	59	0.39 [0.11]	56	0.41 [0.12]	52	0.40 [0.11]

T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
57	50.4 [19.6]	0.02	1.17	.98	-0.04	0.12	.70	-0.02	-0.15
54	53.1 [18.1]								
57	70.2 [18.7]	-1.31	1.06	.22	0.08	0.11	.47	-0.04	-0.32
54	76.1 [15.4]								
57	69.5 [24.4]	3.16	1.38	.02	-0.33	0.14	.02	0.23	-0.19
54	72.9 [20.0]								
57	72.6 [24.5]	-0.65	1.46	.66	0.00	0.15	.98	0.03	-0.23
54	74.4 [21.6]								
57	49.3 [19.9]	-0.39	0.29	.18				-0.02	-0.16
54	54.5 [22.1]								
54	74.51 [7.68]	-0.03	0.08	.76				-0.10	0.07
55	74.43 [7.71]								
54	3:53 [0:51]	-2.57	43.53	.95				-0.14	0.09
55	3:43 [0:50]								
54	6:17 [0:54]	48.63	134.39	.72	-8.74	13.31	.51	-0.11	-0.05
55	6:21 [0:51]								
52	0.76 [0.09]	0.00	0.01	.94	0.00	0.00	.92	0.17	-0.07
55	0.75 [0.12]								
52	0.40 [0.09]	0.01	0.01	.48	0.00	0.00	.44	-0.18	-0.04
55	0.42 [0.17]								

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Table A5.4. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
Circadian rhythm						
Cortisol Awakening Response						
BWL	42	0.4 [3.6]	41	1.1 [3.5]		
DWL[c]	44	1.8 [3.9]	39	1.3 [4.1]		
Diurnal cortisol slope						
BWL	49	-0.16 [0.08]	43	-0.16 [0.08]		
DWL[c]	48	-0.17 [0.08]	44	-0.16 [0.07]		
Total cortisol output						
BWL	46	42.0 [25.5]	38	40.0 [23.7]		
DWL[c]	47	49.7 [25.1]	41	41.9 [19.1]		
DLMO, hh:mm						
BWL	15	20:24 [1:04]	9	20:53 [1:32]		
DWL[c]	8	19:54 [0:53]	10	20:18 [1:25]		

Raw means and standard deviations are reported. Models were adjusted for marital status
BWL Bright white light; **CES-D** Center for Epidemiological Studies – Depression; **CWS** Cancer Worry Scale; **DLMO** Dim light melatonin onset; **DWL** Dim white light; **FCS** Fatigue Catastrophizing Scale; **IS** Interdaily Stability; **IV** Intradaily Variability; **MFI** Multidimensional Fatigue inventory; **PSQI** Pittsburgh Sleep Quality Index; **RAND-36** RAND 36-item Health Survey; **SES** Self-efficacy Scale; **STAI-6** State Trait Anxiety Index – short form; **VAS fatigue** Visual Analogue Scale fatigue; **WSAS** Work and Social Adjustment Scale.
[a] **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy
[b] The effect size was calculated based on the t test statistic $(2*t)/(\sqrt{df})$; small .20; moderate .50; large .80.
[c] DWL is reference group. [d] Based on the AIC and BIC criteria, the model with the best fit excluded a random slope and included an autoregressive covariance structure. [e] identity covariance structure

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
			1.25	0.95	.19				0.28	
			-0.01	0.02	.81				-0.10	
			5.65	5.63	.32				0.18	
			0.13	0.55	.82				0.17	

Table A5.5. Mean values and standard deviations per time-point, and between-group differences of the primary and secondary measures for the growth curve models for individuals who used the light therapy during autumn or winter.

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
PRIMARY OUTCOMES						
Fatigue						
VAS fatigue						
BWL	45	5.8 [1.7]	46	4.6 [1.9]	39	4.8 [2.1]
DWL[c]	43	6.6 [1.5]	41	4.8 [2.0]	40	5.2 [1.5]
MFI general fatigue						
BWL	46	15.6 [2.6]	46	12.9 [3.5]	39	13.4 [3.3]
DWL[c]	43	16.6 [2.5]	41	13.5 [3.3]	40	14.3 [3.1]
Restrictions caused by fatigue (WSAS)						
BWL	46	20.3 [7.5]	46	16.5 [7.7]	39	17.3 [8.7]
DWL[c]	43	22.4 [8.5]	41	19.0 [9.3]	39	19.5 [9.4]
SECONDARY OUTCOMES						
Sleep quality (PSQI)[d]						
BWL	46	7.1 [3.6]	46	5.9 [2.9]	39	6.3 [3.1]
DWL[c]	43	7.3 [3.3]	41	5.3 [2.2]	39	6.1 [3.0]
Depression (CES-D)						
BWL	46	17.6 [4.2]	46	16.5 [3.7]	39	16.7 [4.3]
DWL[c]	43	18.9 [5.4]	41	15.9 [4.6]	39	17.2 [3.9]
Anxiety (STAI-6)						
BWL	46	37.9 [10.1]	46	36.4 [10.4]	39	36.7 [10.3]
DWL[c]	43	40.9 [8.3]	41	37.2 [9.1]	39	37.4 [9.5]
Quality of life (RAND-36)						
Physical functioning						
BWL	46	74.8 [19.7]	46	74.5 [19.6]	39	74.4 [20.4]
DWL[c]	43	74.0 [19.9]	41	74.1 [23.3]	39	76.0 [21.1]
Role functioning/physical						
BWL	46	37.0 [33.2]	46	52.7 [41.2]	39	39.1 [38.0]
DWL[c]	43	39.0 [39.5]	41	46.3 [39.7]	39	50.6 [41.9]
Role functioning/emotional						
BWL	46	78.3 [34.6]	46	79.7 [36.2]	39	80.3 [29.3]
DWL[c]	43	68.2 [39.1]	41	78.0 [34.6]	39	70.1 [37.3]

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
	42	4.8 [2.3]	0.22	0.21	.30	-0.02	0.02	.24	0.32	-0.34
	39	5.7 [2.0]								
	42	13.3 [3.3]	-0.03	0.32	.93	0.01	0.03	.86	0.09	-0.06
	39	14.2 [3.7]								
	42	16.8 [9.3]	-0.15	0.54	.78	0.01	0.05	.80	-0.08	-0.01
	39	19.2 [9.3]								
	42	6.2 [3.0]	0.10	0.27	.72	-0.01	0.03	.67	0.22	-0.21
	39	6.3 [2.9]								
	42	17.1 [4.9]	-0.02	0.45	.97	0.00	0.45	.94	0.40	-0.14
	39	17.4 [5.5]								
	42	37.9 [9.2]	0.66	0.97	.50	-0.05	0.10	.60	0.22	-0.01
	38	38.4 [12.0]								
	42	74.4 [24.2]	-0.48	0.33	.15				0.01	-0.21
	38	77.6 [19.2]								
	42	49.4 [41.1]	-0.67	1.00	.51				0.23	-0.22
	38	50.7 [43.7]								
	42	73.8 [37.2]	-0.23	0.91	.81				-0.20	-0.06
	38	73.7 [38.1]								

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Table A5.5. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
Energy						
BWL	46	46.1 [11.8]	46	53.8 [15.5]	39	50.9 [15.0]
DWL[c]	43	36.6 [14.3]	41	47.6 [17.4]	39	45.9 [15.0]
Emotional well-being						
BWL	46	76.2 [13.7]	46	76.6 [15.5]	39	75.2 [16.9]
DWL[c]	43	67.1 [16.2]	41	74.4 [16.6]	39	75.0 [16.3]
Social functioning						
BWL	46	62.5 [16.2]	46	71.2 [16.6]	39	69.2 [18.8]
DWL[c]	43	56.4 [19.0]	41	63.7 [19.1]	39	61.5 [19.3]
Pain						
BWL	46	70.7 [24.8]	46	78.6 [22.5]	39	73.3 [27.1]
DWL[c]	43	70.5 [26.1]	41	71.5 [23.4]	39	72.5 [22.6]
General health						
BWL	46	46.5 [15.5]	46	48.6 [17.9]	39	46.7 [19.7]
DWL[c]	43	47.8 [20.2]	41	51.6 [19.2]	39	52.9 [19.3]
Sleep (actigraphy)						
Sleep efficiency. %						
BWL	44	75.00 [8.25]	41	74.27 [7.89]	39	75.04 [8.26]
DWL[c]	42	73.83 [7.09]	41	73.46 [7.71]	39	74.27 [7.52]
Mid-sleep time. hh:mm						
BWL	44	3:42 [0:43]	41	3:36 [0:46]	39	3:43 [0:48]
DWL[c]	42	3:54 [0:59]	41	3:50 [1:01]	39	3:50 [0:48]
Total sleep time, min						
BWL	44	6:26 [0:54]	41	6:24 [0:52]	39	6:21 [0:55]
DWL[c]	42	6:25 [0:37]	41	6:24 [0:48]	39	6:18 [0:44]
IS [e]						
BWL	43	0.77 [0.10]	40	0.77 [0.09]	38	0.75 [0.09]
DWL[c]	42	0.76 [0.12]	41	0.72 [0.14]	39	0.76 [0.11]
IV						
BWL	43	0.42 [0.11]	40	0.41 [0.11]	38	0.42 [0.13]
DWL[c]	42	0.40 [0.12]	41	0.42 [0.13]	39	0.39 [0.11]

T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
41	54.4 [18.3]	-2.12	1.33	.11	0.19	0.13	.15	-0.17	0.03
38	47.2 [18.2]								
41	75.3 [17.2]	-2.57	1.18	.03	0.24	0.12	.05	-0.41	0.07
38	72.5 [16.9]								
42	72.3 [21.5]	0.51	1.65	.76	-0.03	0.16	.85	0.08	0.03
38	64.1 [22.7]								
42	72.7 [26.4]	0.23	1.64	.89	-0.07	0.16	.67	0.27	-0.25
38	72.0 [24.2]								
41	46.0 [20.2]	-0.61	0.37	.10				-0.06	-0.26
38	53.8 [21.1]								
40	75.63 [9.05]	0.06	0.09	.53				-0.01	0.11
39	73.76 [7.51]								
40	3:44 [0:41]	-14.15	48.95	.77				-0.06	0.04
39	3:53 [0:55]								
40	6:17 [0:57]	141.36	151.97	.35	-18.78	15.08	.22	-0.02	-0.07
39	6:22 [0:49]								
39	0.77 [0.08]	-0.01	0.01	.56	0.00	0.00	.70	0.39	-0.41
39	0.77 [0.10]								
39	0.41 [0.10]	0.01	0.01	.40	0.00	0.00	.42	-0.21	0.12
39	0.41 [0.14]								

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Table A5.5. *(continued)*

	T0[a]		T1[a]		T2[a]	
	n	M [SD]	n	M [SD]	n	M [SD]
Circadian rhythm						
Cortisol Awakening Response						
BWL	27	-0.2 [3.1]	29	0.4 [3.8]		
DWL[c]	31	1.5 [4.6]	29	0.7 [4.3]		
Diurnal cortisol slope						
BWL	35	-0.17 [0.07]	32	-0.19 [0.09]		
DWL[c]	26	-0.18 [0.08]	24	-0.19 [0.08]		
Total cortisol output						
BWL	35	37.4 [16.0]	28	40.3 [25.5]		
DWL[c]	26	47.3 [21.2]	21	40.8 [17.6]		
DLMO, hh:mm						
BWL	20	20:25 [1:01]	15	20:43 [1:27]		
DWL[c]	13	20:33 [1:29]	12	20:40 [1:40]		

Raw means and standard deviations are reported. Models were adjusted for marital status
BWL Bright white light; **CES-D** Center for Epidemiological Studies – Depression; **CWS** Cancer Worry Scale; **DLMO** Dim light melatonin onset; **DWL** Dim white light; **FCS** Fatigue Catastrophizing Scale; **IS** Interdaily Stability; **IV** Intradaily Variability; **MFI** Multidimensional Fatigue inventory; **PSQI** Pittsburgh Sleep Quality Index; **RAND-36** RAND 36-item Health Survey; **SES** Self-efficacy Scale; **STAI-6** State Trait Anxiety Index – short form; **VAS fatigue** Visual Analogue Scale fatigue; **WSAS** Work and Social Adjustment Scale.
[a] **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy
[b] The effect size was calculated based on the t test statistic (2*t)/(√df); small .20; moderate .50; large .80.
[c] DWL is reference group. [d] Based on the AIC and BIC criteria, the model with the best fit excluded a random slope and included an autoregressive covariance structure. [e] identity covariance structure

	T3[a]		Group difference linear time effect			Group difference quadratic time effect			ES[b]	
	n	M [SD]	B	SE	*p*	B	SE	*p*	T0-T1	T1-T3
			1.37	1.32	.30				0.34	
			-0.01	0.03	.76				-0.13	
			10.21	7.22	.16				0.53	
			0.46	0.76	.55				0.17	

APPENDIX 6 PITTSBURGH SLEEP QUALITY INDEX SUBSCALES ANALYSES

INTRODUCTION

The Pittsburgh Sleep Quality Index does not only describe a total score for general sleep quality but also provides scores for seven subscales assessing different aspects of sleep quality: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disruptions, sleep medication, and daily dysfunctioning. We previously showed that fatigue after cancer was associated with subjective sleep quality and daily dysfunctioning[1]. Therefore, we wanted to further investigate whether these aspects of sleep quality were affected by the light therapy intervention.

METHODS

The scores on the subscales of the PSQSI were calculated according to published algorithms. Missing values were replaced by the average score of the completed items of the same scale for each individual provided that at least 50% of the items of a scale had been completed. Subscale scores ranges between 0 (no problems) and 3 (problems). Because of the ordinal character of these outcomes, we used Generalized Estimating Equations to evaluate group differences over time. All models were adjusted for marital status. In case of non-significant group effects, we performed a post-hoc analysis with the exclusion of group to evaluate the time effect.

RESULTS

Figure A6.1 shows the results of the generalized estimating equations per subscale. None of the subscales showed significant differences in change of time between groups indicating that the effect of light therapy was similar in both groups. The post-hoc analyses with the complete samples showed that there was a significant improvement after light therapy on subjective sleep quality, sleep latency, and daily dysfunctioning. This indicates that these aspects of sleep quality improved irrespective of the intensity of light therapy that they used.

DISCUSSION

The results of the subscales of the PSQI showed that BWL showed no superiority to DWL in improving different aspects of sleep quality. When the whole group was evaluated, light therapy did not affect self-reported sleep duration, sleep efficiency, sleep disruptions, and sleep medication use. Light therapy did affect subjective sleep quality, sleep latency, and daily dysfunctioning. This is in line with recent findings that fatigue after cancer was associated with subjective sleep quality and daily dysfunctioning in survivors of (non-)Hodgkin lymphoma[1]. The effect of light therapy on self-reported sleep latency is not in line with the results of the actigraphy assessment (data not shown) in the current study. This indicates that, although the objective time necessary to fall asleep (assessed with actigraphy) did not change, participants

experienced an improvement in the time that they needed to fall asleep (assessed with the self-reported sleep latency scale of the PSQI).

REFERENCES

1. Starreveld DEJ, Habers GEA, Valdimarsdottir HB, Kessels R, Daniels LA, van Leeuwen FE et al (2021): Cancer-related Fatigue in Relation to Chronotype and Sleep Quality in (Non-)Hodgkin Lymphoma Survivors. *Journal of Biological Rhythms*, 36(1): 71-83.

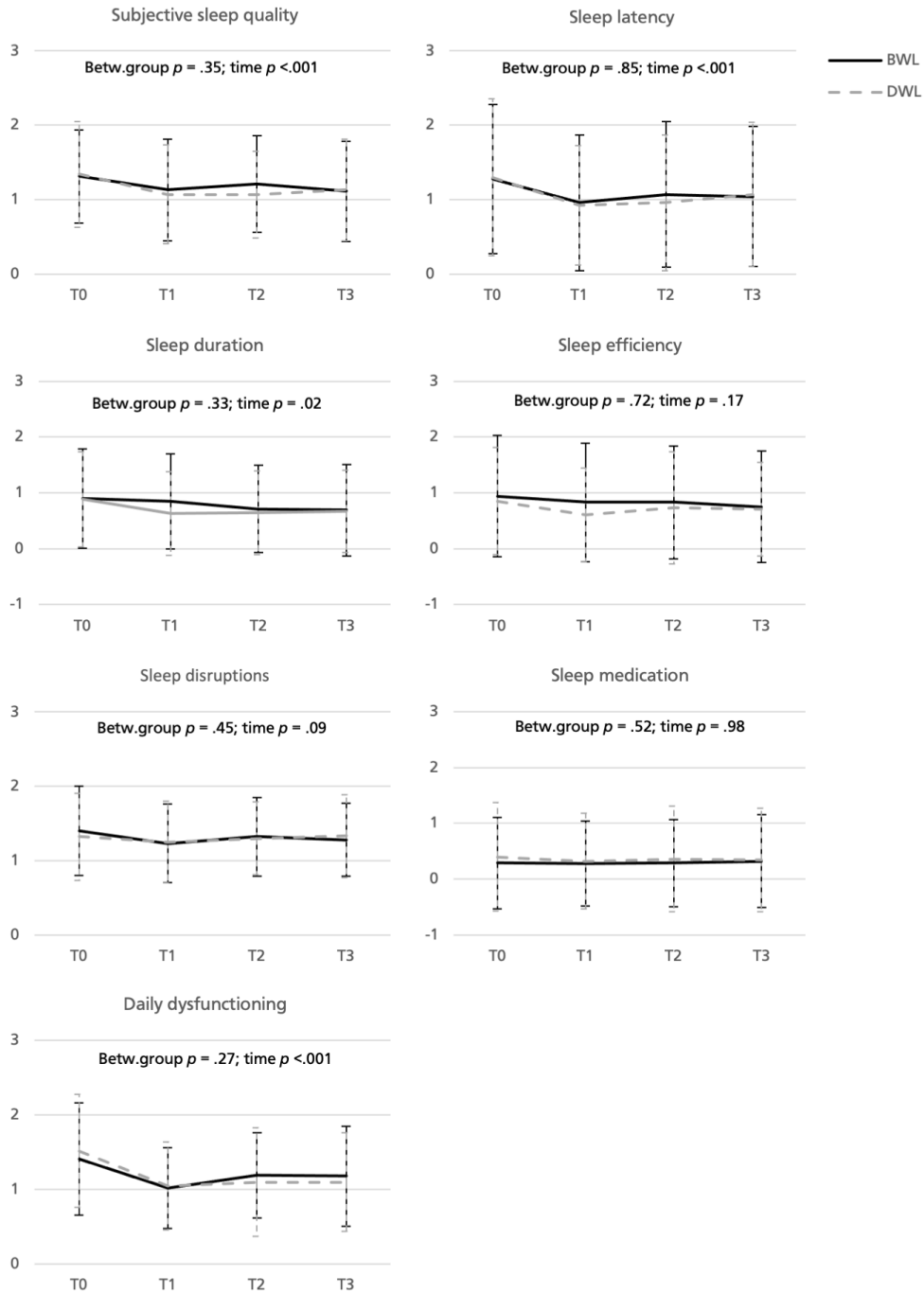

Figure A6.1 Overview of the effect of light therapy on the different subscales of the PSQI.
There were no between group differences on the different aspects of sleep quality (betw.group p-value). In the complete sample, we saw a significant improvement on subjective sleep quality, sleep latency, and daily dysfunctioning (time p-value).