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

Starreveld, D.E.J.

LIGHT THERAPY FOR CANCER-RELATED FATIGUE IN (NON-)HODGKIN LYMPHOMA SURVIVORS

DANIELLE STARREVELD

Cover and chapter intros: Thijs Kelder, Studio Ruwedata (www.studioruwedata.nl)
Layout: Daniëlle Starreveld
Printing: Proefschrift All In One

The cover visualizes a clock. Specifically, a biological clock envisioned by the green leaves around the clock. The yellow circle represents a light source with green lines that represent the radiation of light.

The work presented in this thesis was performed at the Netherlands Cancer Institute, Amsterdam, the Netherlands. The research described in this thesis was supported financially by the Dutch Cancer Society (grant number NKI 2015-7909).

Financial support for printing of this thesis was kindly provided by The Netherlands Cancer Institute.

ISBN: 978-94-93270-43-5

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

PROEFSCHRIFT

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus
prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 24 maart 2022
klokke 15:00 uur

door Daniëlle Elisabeth Jacoba Starreveld
geboren op 25 april 1989,
te Alphen aan den Rijn

Promotor	prof. dr. E.M.A. Bleiker	
Copromotores	prof. dr. ir. F.E. van Leeuwen	Vrije Universiteit Amsterdam
	dr. L.A. Daniels	Amsterdam UMC
Promotiecommissie	prof. dr. C.L. Creutzberg	
	prof. dr. A.W.M. Evers	
	prof. dr. E.J.W. van Someren	Vrije Universiteit Amsterdam
	prof. dr. J.A. Knoop	Amsterdam UMC

CONTENT

CHAPTER 1

GENERAL INTRODUCTION

Cancer-related fatigue in (non-)Hodgkin lymphoma

Hematological cancers represent the fifth most prevalent cancer in the Netherlands[1]. A relatively rare type of hematological cancer is Hodgkin lymphoma (HL) with an absolute incidence of 532 in 2019[2]. This cancer develops in het lymphatic system; more specifically, it is an abnormal multiplication of B-lymphocytes. HL is most often diagnosed in younger individuals (age between 15 and 44 years). In the past decades, treatments for HL changed from large radiotherapy fields to the combination of chemotherapy and radiotherapy with smaller radiotherapy fields. Responses to these improved treatments are good, with a current overall 10-year survival rate of 78 percent[3].

The good prognosis leading to a higher number of survivors caused an increased interest towards the late effects experienced by HL survivors. For example, increased risks to develop secondary cancers and cardio-vascular diseases are reported in this group[4]. In the Netherlands, the BETER consortium (better care after HL: evaluation of long-term treatment effects and screening) offers a healthcare infrastructure aiming to inform, screen, and treat HL survivors for these late effects[5]. In 2021, the BETER consortium included 22 hospitals. Within this consortium, radiation-oncologists, hematologists, epidemiologists, and psychologists work together to formulate treatment guidelines and conduct research to improve care for these survivors. More recently, diffuse large B-cell lymphoma (DLBCL) survivors were added to the BETER-consortium because the late effects in this group are comparable to the late effects reported in HL survivors. DLBCL is the most prevalent hematological cancer with an incidence of 1.548 in 2019[2]. This aggressive non-Hodgkin lymphoma (NHL) is most often diagnosed in individuals 60 years of age or older and has a 10-year survival rate of 45 percent[1, 2, 6].

The screening within the BETER-clinics focuses on somatic and psychological late effects influencing the daily life of HL and DLBCL survivors. One of the symptoms often reported to radiation-oncologists and hematologists is cancer-related fatigue (CRF)[7]. A previous study within the BETER-consortium showed a prevalence of CRF in HL survivors of 41 to 43 percent compared to 23 to 28 percent in the general Dutch population. Moreover, a study with more than 800 NHL survivors (mean survivorship 4.2 years [SD = 2.7]) showed that 61 percent reported clinically relevant and persistent fatigue[8]. The National Comprehensive Cancer Network (NCCN) defines CRF as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning"[9]. Survivors suffering from fatigue report feeling tired despite resting, have difficulties to complete normal activities, and have problems concentrating[10]. It affects the quality of life of these survivors[11] and is often reported in a cluster of symptoms including sleep problems, depression, anxiety, and pain[12-16]. Moreover, higher levels of fatigue are associated with more problems in cognitive functioning[17-19], which are also reported by lymphoma survivors[20].

Etiology of cancer-related fatigue

Despite the high number of cancer survivors that suffer from CRF, relatively little is known about the etiology of CRF. There are several hypotheses for the etiology of CRF, covering demographic, medical, psychosocial, behavioral, and biological factors[21-24]. This section describes the current

knowledge on the influence of these factors on CRF based on four systematic reviews covering information from patients and survivors with different types of cancer[21-24]. If available, specific results for HL are reported separately[25].

Demographic factors

The majority of studies investigating the association between demographic factors and CRF suggest the absence of associations of gender, age, marital status, ethnicity, education, employment, or income to CRF[21-24]. Some studies suggested that fatigue was associated with gender, age, marital status, employment, and income[22]. Yet, there is an inconsistency in these studies as not all of these studies report associations into the same direction[22]. For example, it has been shown that higher levels of fatigue occur in younger patients in breast cancer patients receiving chemotherapy[22] while in HL survivors, it has been shown that higher levels of CRF were reported by older survivors[25].

Medical factors

In general, no associations were found of CRF with disease-related variables, including diagnosis, tumor size, tumor stage, the presence of metastases, and time since diagnosis in cancer survivors[22, 23]. Moreover, no associations were found between CRF and treatment-related variables, including treatment (e.g. chemotherapy, radiotherapy, tamoxifen), time since treatment completion and the length of hospital stay[22, 23]. This is also confirmed in 5-years HL survivors as there were no associations of CRF with HL specific factors or treatment-related variables[25]. There is a significant positive association between CRF and the number of self-reported comorbidities[12].

Psychosocial and behavioral factors

There are consistent findings showing that higher levels of fatigue are related to higher levels of anxiety, depression, sleep problems, dysfunctional coping behavior, lack of social support, and stressful life events[21-23, 26]. Moreover, higher levels of baseline fatigue prior to treatment are associated with higher levels of fatigue at follow-up in HL survivors[25]. It has been shown that higher levels of CRF are associated with lower levels of physical activity and increased body mass index[21-23].

Biological factors

Multiple biological factors have been studied in the context of CRF. For these biological factors, a difference is made between *central fatigue* that originates in the central nervous system and *peripheral fatigue* that reflects the inability of muscles to perform a task[27]. For *central fatigue*, the most studied mechanism is cytokine dysregulation[21, 26-28]. This is based on the principle that inflammatory cytokines can induce fatigue and other changes in behavior[29]. It is proposed that cancer and cancer treatment activate the production of pro-inflammatory cytokines[30, 31] that may persist after treatment as the host deals with persisting pathogenesis and changes in homeostasis[21]. Nonetheless, it should be noted that results on the association between different types of proinflammatory cytokines and CRF are inconclusive[21, 26-28]. Another biological factor linked to central fatigue is a dysregulation of the hypothalamic-pituitary-adrenal (HPA)

axis[21, 26-28]. The HPA-axis is responsible for the production of the hormone cortisol following a daily rhythm and in response to stress. There is some evidence that breast cancer survivors with fatigue had lower cortisol levels during the day and a blunted response to a stressor compared to breast cancer survivors without fatigue[32, 33] suggesting a dysregulation of the HPA axis. Similar results have been shown for women with ovarian cancer and advanced cancer patients[34, 35]. Animal studies suggested that this might be a consequence of chronic inflammation[36]. A third biological factor that may influence central fatigue is circadian rhythm disruption[21, 26-28], which is described in more detail below. Other hypothesized mechanisms related to central fatigue are serotonin dysregulation and vagal afferent nerve function, although these hypotheses are primarily based on animal studies[26, 27]. Hypotheses for *peripheral* mechanism include a muscle metabolism dysregulation caused by adenosine triphosphate dysregulation and contractile properties[26-28]. However, it should be noted that these hypotheses are based on small sample sized (animal) studies[26, 27].

It is important to mention that these biological factors relate to each other, making the pathophysiology of CRF very complex[26, 27]. Cytokine dysregulation seems to play a crucial role as cytokines influence other described mechanisms, including the HPA axis, circadian rhythms, serotonin metabolism and vagal afferent activation, via signaling pathways and feedback loops. The HPA axis regulates cortisol and cytokine production, while the HPA axis itself is also influenced by serotonin. Moreover, cortisol, inflammatory cytokines and serotonin influence circadian rhythms and disrupted circadian rhythms influence the HPA axis.

Circadian rhythms

Circadian rhythms[37] are internally generated rhythms that have a cycle of approximately 24-hours. The name stems from the Latin *circa* (about) and *dies* (day). These rhythms are necessary to optimize physiology and behavior in anticipation on the regular changes in environmental light, temperature, and food availability because of the earth's daily rotation. For example, in anticipation of sleeping, the production of cortisol is decreased and the production of melatonin, a hormone that stimulates sleep, is increased in dim light situations to optimize bodily conditions for sleep (Figure 1). It is essential that these internal rhythms synchronize to the external environment. For example, when we travel to the east or the west, we want our biological clock to adjust to the external environment in that situation. Our biological clock, based in the superchiasmatic nucleus (SCN) situated in the brain, uses signals from the environment to entrain internal circadian rhythms to external circadian rhythms. These entraining signals are called *zeitgebers*. The most important *zeitgeber* is light. Other *zeitgebers* are temperature, food availability and, for humans, social obligations[37].

Disruptions of circadian rhythms and the association with CRF have been studied using different methods. First, actigraphy can be used to assess rest-activity rhythms, i.e. sleep-wake cycles (Figure 2)[38]. An actigraph is a wrist-worn tri-axial accelerometer. Based on movements, each epoch (for example, a period of 60 seconds) is categorized as being asleep or being awake. Together with information on bed times provided by the individual who wore the actigraph, it is possible to calculate sleep and circadian variables[38, 39], e.g. total time in bed, actual sleep time, and mid-sleep (the time between sleep onset and sleep offset). Results of actigraphy studies in patients with cancer showed that patients with higher levels of CRF showed more disruptions

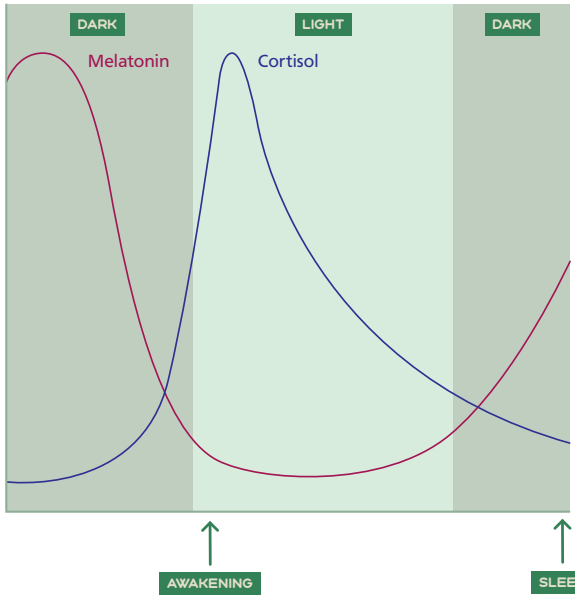


Figure 1. Circadian rhythm of cortisol and melatonin. Cortisol shows a strong increase in the early morning with a decrease during the day that reaches its lowest point during the night. Melatonin shows an increase in the evening in dim light conditions with the highest point during the night and a steep decrease in the early morning.

in their sleep-wake cycle, i.e. they had more awakenings during the night and were less active during the day[40-43].

A second method to study circadian rhythms is via the assessment of the secretion of hormones that follow a circadian rhythm, specifically melatonin and cortisol. Melatonin is the best marker of the internal rhythm in dim light conditions[44]. Its circadian rhythm shows increasing levels during the evening (in dim light conditions) that reaches its top during the night followed by a decrease that reaches its lowest point during the day[44]. To the best of our knowledge, there are currently no published results on the association between melatonin secretion and CRF. Cortisol shows a circadian rhythm with a steep increase after awakening followed by a gradual decline during the day that reaches its lowest point during the night. Besides the lower secretion of cortisol and the smaller response to stressors[32-35], some studies suggested that a disruption in this circadian rhythm is associated with CRF[34, 35, 45]. For example, it is shown that a smaller morning/night ratio of cortisol is associated with higher levels of CRF[34].

A third approach to study circadian rhythms is via self-reported questionnaires that include items on the sleep-wake rhythm. Examples of these questionnaires are the Munich Chronotype Questionnaire (MCTQ)[46], the Morningness Eveningness Questionnare (MEQ)[47], and the Composite Scale of Morningness (CSM)[48]. The outcome of these questionnaires is someone's chronotype, which describes an individual's preference in the timing of sleep and wake, also known as morning or evening types[46]. Morning types, or *larks*, tend to get up early and prefer to complete tasks in the morning, while evening types, or *owls*, tend to wake up later and prefer to complete tasks in the afternoon or evening. Individual differences in chronotype are

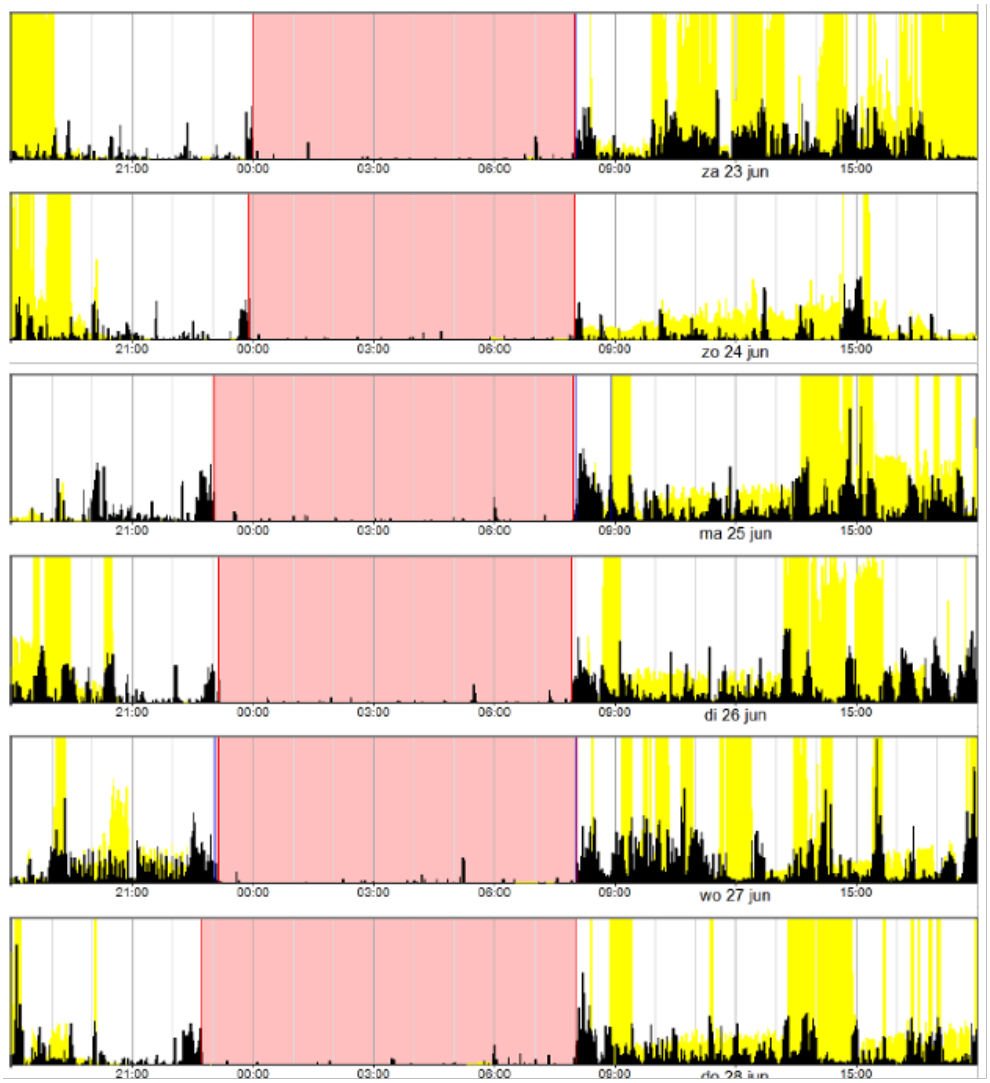


Figure 2. Example of an actigraphy measurement of six days. The black spikes represent activity as measured with the tri-axial accelerometer. The yellow spikes show when the light sensory detected light and at which intensity. The red area is the period during which the participant reported to be asleep. To determine this period, the participant pushed a button on the actigraph. These periods are used to calculate sleep variables like time in bed, sleep onset, sleep offset, got-up time, and sleep efficiency. The activity of the complete days are used to calculate non-parametric outcomes concerning the circadian rhythm like interdaily stability and intradaily variability.

the result of genetic variation (genes affect the temporal relationship between a zeitgeber and the biological clock[49-51]), weaker zeitgeber signals in the current society (the introduction of artificial light increases exposure to light in previously dim light situations), and age (adolescents are more likely to have later chronotypes, which shifts to earlier chronotypes after adolescence)[52]. Some studies showed that evening types reported higher levels of fatigue

compared to morning types in individuals with irritable bowel symptoms[53] and students[54]. As far as we know, the association between chronotype and fatigue in cancer populations has not been studied.

Assessment of cancer-related fatigue

Originally, the general concept of fatigue was conceptualized as a unidimensional construct but increased research interest for fatigue changed this view to a multidimensional concept of fatigue since the 1990s[55]. The first distinction was made into physical and mental components of fatigue[56, 57]. Nowadays, different views exist on the multidimensionality of fatigue. For example, Vercoulen et al. propose four domains: subjective experience of fatigue, reduced concentration, reduced motivation, and reduced physical activity[58]; while Schwartz et al propose three domains: situation-specific fatigue, consequences of fatigue, and response to rest/sleep[59].

The distinction between unidimensional and multidimensional fatigue is also reflected in the number of instruments that are available to measure CRF. Several review studies[60-62] identified a range of 14 up to 40 different questionnaires, although the validity and reliability for most of these questionnaires is questionable. Taken together, these reviews suggest that a 10-point numeric rating scale is the best screening tool for CRF[61, 62]. For the unidimensional construct, the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) fatigue subscale[63] and the Functional Assessment of Cancer Therapy-Fatigue subscale (FACT-F)[64] were suggested as questionnaires with excellent psychometric properties[60-62]. The Multidimensional Fatigue Symptom Inventory short form (MFSI-30)[65] and the Chalder Fatigue Scale (FQ)[66] were highly recommended for the assessment of multiple dimensions of fatigue [60-62].

Another assessment of fatigue recommended for measuring multiple dimensions of CRF is the Multidimensional Fatigue Inventory[67]. This scale aims to measure five dimensions of fatigue, including general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. After the initial validation[67, 68], the questionnaire became one of the most widely used fatigue assessments in Europe[69]. It has been translated and validated in multiple languages[70-83]. However, the original validation study did not only show an acceptable fit for the five-factor structure but also for two four-factor structures. One in which the dimensions of general fatigue and physical fatigue were combined and one in which the general fatigue items were removed[67]. Therefore, the authors suggested that additional research was necessary to investigate the additional value of the separate use of the general fatigue and physical fatigue subscales.

Treatment for cancer-related fatigue

Even though there is a high prevalence of cancer-related fatigue, radiation-oncologists and hematologists of the BETER-consortium have no standard treatment to offer HL and DLBCL survivors suffering from CRF. The NCCN guidelines[84] mention high-level evidence for non-pharmacological interventions, including physical activity, psychosocial interventions, and cognitive behavioral therapy for insomnia, which could be offered to cancer survivors to

reduce CRF. Lower-level evidence is available for pharmacologic treatments, including psychostimulants, for CRF. A recent meta-analysis[85] evaluated which intervention type is most effective in reducing cancer-related fatigue. A total number of 113 studies were included. The majority of the studies (n=69) investigated physical activity (including aerobic, anaerobic, or the combination of aerobic and anaerobic modes of exercise), followed by psychological interventions (n=34; including cognitive behavioral therapy, psychoeducation, or an eclectic method), pharmaceutical interventions (n=14; including paroxetine hydrochloride, modafinil or armodafinil, methylphenidate hydrochloride or dexymethylphenidate, dexamphetamine, or methylprednisolone) and the combination of physical activity and psychosocial interventions (n=10). Results showed that the largest improvement in CRF was seen after physical activity interventions, which are associated with a general weighted moderate effect size of 0.33. Psychological interventions and the combination of physical activity and psychological interventions showed similar improvements, with weighted effect sizes of 0.27 and 0.26, respectively. Pharmaceutical interventions led to significant improvements but these were associated with a smaller weighted effect size of 0.09. Therefore, it was concluded that physicians should prescribe physical activity and psychological interventions to reduce fatigue in patients suffering from CRF.

Despite the high number of studies showing promising results for physical activity and psychological interventions, these type of interventions are still not implemented as standard treatments for CRF. This might be due to limitations of these interventions. For example, fatigue has the characteristic to be a barrier to start physical activity meaning that not all fatigued survivors will be motivated to participate[86]. Moreover, most of the studied interventions are labor intensive, as they require professional guidance during the intervention. Therefore, it is interesting to seek for other interventions that are easy to deliver and have low costs and a low burden to complete. An example of such an intervention is light therapy, which is also mentioned in the NCCN guidelines based on lower-level evidence with consensus that the treatment is appropriate[84].

Light therapy

The history of light therapy is well described by Choukroun and Geoffroy[87]. Briefly, the importance and therapeutic effect of the sun, and thus light, was already mentioned by Hippocrates in his book *On Airs, Waters, Places*[88] at 400 BC. The modern use of light therapy stems from the 1980s when doctor Rosenthal described Seasonal Affective Disorder (SAD) and the antidepressant effect of light therapy on these depressive symptoms during autumn and winter[89]. Since then, many studies followed to test the efficacy of light therapy on reducing depressive symptoms[90, 91] and other symptoms like circadian rhythm disturbances and sleep disorders[92, 93]. While it has been shown to be effective to improve sleep and circadian problems[92, 93], the results for the efficacy of light therapy on mood disorders is promising but less conclusive[90].

The current guidelines on the treatment of SAD prescribe a standard protocol for light therapy[94, 95]. This protocol mentions that individuals should be exposed to bright light of at least 2.500 lux of white, fluorescent light without ultra-violet wavelengths. The preferred starting 'dose' is exposure to a light intensity of 10.000 lux for a duration of 30 minutes in the morning.

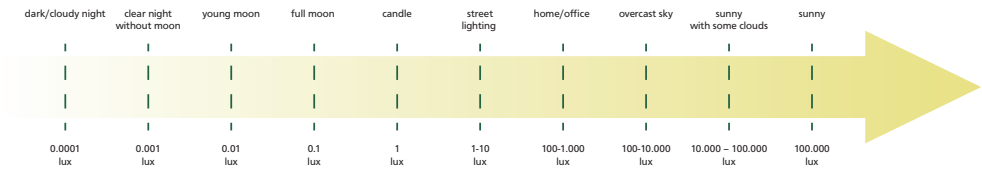


Figure 3. Overview of light intensities for different situations.

Figure 3 shows a comparison of this light intensity to daily situations. Individuals should position the light source closely to their eyes (no more than 50-80 centimeters apart) and the eyes should be open. Based on this protocol, patients with SAD usually show improvements within one week, which can take up to four weeks to achieve a full response[94].

Physiology of light

The exact mechanism of light therapy to improve mood, sleep and circadian rhythm disorders are not completely understood. To understand more about this mechanism it is important to learn more about the information processing of light by the retina and brain, which can be identified in two categories[87]. First, and best known, is *visual* information: light that falls on the retina is transferred to the visual cortex. This is primarily done by rods and cones, which are photoreceptors that transmit their signals via ganglion cells to the optic nerve for further processing in the visual cortex. The second type of information is *non-visual* and results primarily from light information processed by the intrinsically photosensitive retinal ganglion cells (ipRGC)[96, 97]. These cells transmit their signals via the production of melanopsin to non-image forming centers of the brain that are involved in the regulation of pupillary light reflex, sleep, arousal, and circadian rhythms[87, 96-99].

The mechanism of light therapy is attributed to this non-visual information processing. So far, the most studied pathway that explains the effect of light therapy is the influence of light on circadian rhythms[100, 101]. The link between light and circadian rhythms is strong, as light is the most important *zeitgeber* for circadian rhythms[37, 102]. This is the result of a direct association between of the ipRGCs via the retinohypothalamic tract to the superchiasmatic nucleus (SCN)[96, 97]. The SCN is the pacemaker of circadian rhythms, i.e. the human biological clock, that ensures entrainment of circadian rhythms to the environment via the secretion of hormones to signal circadian rhythms to other structures in the body[96, 97, 102]. The most important example is the secretion of melatonin by the pineal gland, which is inhibited in bright light conditions[103]. The effect of light therapy in the morning on melatonin is shown in figure 4. Exposure to light in the morning results in a phase advance of the circadian rhythm, i.e. the biological night, causing someone to feel alert earlier in the morning and sleepy earlier in the night. Light therapy in the evening prolongs the environmental day and therefore delays the biological night, causing someone to feel alert later in the morning and sleepy later in the night.

The rods, cones, and ipRGC have different photo pigments, which makes them most sensitive to light with different wavelengths, i.e. different colors. The rods are most sensitive to light of 492 nm (blue-greenish) and are necessary to process visual information in dim light circumstances[104]. Cones are necessary for distinguishing colors in normal lit situations with different sensitivity peaks for short (S, 420 nm, blue), medium (M, 533 nm, green color) and long (L, 562 nm, red color) wavelengths[104]. The ipRGCs are most sensitive for blue light (around

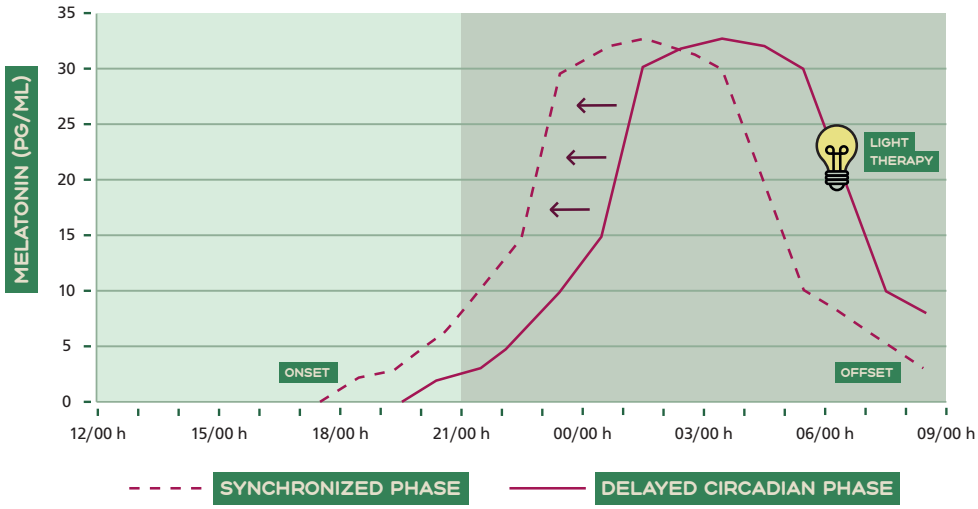


Figure 4. The effect of morning light therapy on the circadian rhythm of melatonin. In this case, the solid line shows a circadian rhythm of someone who has a delayed circadian rhythm, i.e. has problems to fall asleep during the night and difficulties to stay awake in the morning because the biological night is not synchronized to the environmental night. Light therapy in the morning cause a phase advance of light therapy. As a result, the onset of melatonin production is at an earlier time point, inducing sleepiness at an earlier time point.

460 nm) and therefore the circadian response is most strongly affected by blue light[98, 105]. Hence, the type of light used in light therapy is mostly enriched around these wavelengths.

Light therapy in cancer populations

At the start of the study described in this thesis, two pilot studies tested the efficacy of light therapy as a treatment for CRF in cancer populations[106, 107]. The first study was conducted by Ancoli-Israel et al in women with breast cancer undergoing chemotherapy to test the effect of light therapy during treatment[106]. Thirty-nine participants were randomized to a bright white light condition (BWL, intervention)or a dim red light condition (DRL, control). Results showed that the usual increase in CRF during chemotherapy (from baseline to the recovery week after a fourth cycle of chemotherapy) was present in the DRL condition but not in the BWL condition. This indicates that light therapy protected against a deterioration of fatigue during treatment. Secondary analyses with actigraphy data indicated that light therapy prevented circadian rhythm desynchronization[108]. More specifically, the group exposed to DRL showed circadian rhythm deterioration during the first and fourth chemotherapy treatment week, which did not return to baseline during the recovery weeks. However, the group exposed to BWL showed some deterioration of the circadian rhythm during the chemotherapy weeks but also showed statistically significant improvements of the circadian rhythm during the recovery weeks. Moreover, it has been shown that BWL prevented a quality of life deterioration, while individuals exposed to DRL showed lower levels of quality of life after chemotherapy[109].

Based on the positive effects of light therapy in cancer patients receiving treatment, Redd et al investigated the efficacy of light therapy on CRF in survivors of different types of cancer[107].

Thirty-six participants with a mean time since diagnosis of 1.4 years were randomized to a BWL of DRL condition and used light therapy for four consecutive weeks. The results were promising. Both groups showed an equal improvement in fatigue during the first two weeks, but during the last two weeks a clear difference was seen between the two groups. Participants exposed to BWL showed further improvements in fatigue that continued until three weeks post intervention, while the fatigue levels of participants exposed to DRL returned to baseline levels. The effect size of the difference in change of fatigue over time between BWL and DWL was large (d = 0.98). On an individual level, all participants in the BWL condition had fatigue levels below the cut-off score of clinically relevant fatigue, while 55 percent of the participants in the DRL condition still showed clinically relevant fatigue after four weeks of light therapy. A secondary analyses on sleep parameters showed that subjectively reported sleep quality and actigraphy derived sleep efficiency, total sleep time and wake after sleep onset improved for participants in the BWL condition and remained stable in participants exposed to DRL[110].

These first studies[106, 107] showed that light therapy is feasible and potentially effective as a treatment for CRF and symptoms related to CRF like depression, quality of life, sleep quality and sleep disturbances. However, sample sizes of both studies were small and the follow-up time was relatively short (until 3 weeks post intervention). Moreover, the effect of light therapy on biological outcomes, e.g. the circadian rhythms of cortisol and melatonin, has not been described. This information could provide new insights into the mechanism of action of light therapy and the etiology of CRF.

Light therapy and cognitive functioning

CRF is associated with cancer-related cognitive impairments[17-19]. Hence, it is clinically relevant to investigate whether light therapy also leads to improvements in cognitive functioning. Two types of studies can be identified. First, studies that investigate the direct effect of light on someone's cognitive functioning[111-115]. Results of these studies provide information on light settings in which individuals function best, for example, what type of lights in the office leads to the most optimal work environment for employers. Second, studies that investigate long-term exposure to light therapy (daily use of at least two weeks). So far, these studies have been reported for patients with dementia and mild traumatic brain injury with inconclusive results. Some showed positive effects[116-118], while other studies showed no effects[119, 120]. As far as we know, the effect of light therapy on cognitive functioning in cancer populations has not been studied before.

Thesis outline

In this thesis, we report on the SPARKLE study: a multicenter, double blind, randomized controlled trial (RCT) evaluating the effect of light therapy on CRF and related symptoms including sleep quality, psychosocial functioning, and circadian rhythms in HL and DLBCL survivors with CRF. **Chapter 2** describes the study rationale, design and methods of the SPARKLE study. In **Chapter 3**, we report the efficacy of light therapy on improving CRF, sleep quality, depression, anxiety, health-related quality of life, and objectively assessed circadian rhythms of sleep, cortisol, and melatonin. **Chapter 4** describes the efficacy of light therapy on subjective and objective cognitive functioning. **Chapter 5** reports on a cross-sectional study to evaluate the factor

structure and the optimal scoring algorithm of the Multidimensional Fatigue Inventory in the general Dutch population, which has been used as a primary outcome in the SPARKLE study. In **chapter 6**, we investigated the associations of CRF with chronotype and CRF with sleep quality in (non-) Hodgkin lymphoma survivors with and without CRF to learn more about potential working mechanisms of light therapy as a treatment for CRF. This thesis ends with an overall summary and a general discussion of the research and outcomes in **chapter 7**.

REFERENCES

1. Netherlands Comprehensive Cancer Organisation (IKNL). Incidentie hematologische kanker (2021) [January 2021]. Available from: https://www.iknl.nl/kankersoorten/hemato-oncologie/registratie/incidentie.
2. Netherlands Comprehensive Cancer Organisation (IKNL). Cijfers over kanker (2021) [January 2021]. Available from: https://www.cijfersoverkanker.nl/.
3. Favier O, Heutte N, Stamatoullas-Bastard A, Carde P, van't Veer M B, Aleman B M, et al. (2009). Survival after Hodgkin lymphoma. *Cancer*, 115(8):1680-91.
4. Aleman B M, van den Belt-Dusebout A W, Klokman W J, van't Veer M B, Bartelink H, van Leeuwen F E (2003). Long-term cause-specific mortality of patients treated for Hodgkin's lymphoma. *J Clin Oncol*, 21:3431-9.
5. Dekker N, Aleman B, Raemaekers J (2015). The BETER survivorship care initiative for Hodgkin lymphoma; tailored survivorship care for late effects of treatment. *Ned Tijdschr Geneeskd*, 159:A9269-A.
6. Pfreundschuh M, Trümper L, Österborg A, Pettengell R, Trneny M, Imrie K, et al. (2006). CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *The lancet oncology*, 7(5):379-91.
7. Aleman B M, van Leeuwen F E (2007). Are we improving the long-term burden of Hodgkin's lymphoma patients with modern treatment? *Hematol Oncol Clin North Am*, 21(5):961-75.
8. Oerlemans S, Mols F, Issa D E, Pruijt J, Peters W G, Lybeert M, et al. (2013). A high level of fatigue among long-term survivors of non-Hodgkin's lymphoma: results from the longitudinal population-based PROFILES registry in the south of the Netherlands. *Haematologica*, 98(3):479-86.
9. Mock V, Atkinson A, Barsevick A, Cella D, Cimprich B, Cleeland C, et al. (2000). NCCN Practice Guidelines for Cancer-Related Fatigue. *Oncology (Williston Park, NY)*, 14(11A):151-61.
10. Curt G A, Breitbart W, Cella D, Groopman J E, Horning S J, Itri L M, et al. (2000). Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *The oncologist*, 5(5):353-60.
11. Bower J E, Bak K, Berger A, Breitbart W, Escalante C P, Ganz P A, et al. (2014). Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*, 32(17):1840-50.
12. Daniëls L, Oerlemans S, Krol A, Creutzberg C, van de Poll-Franse L (2014). Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. *Br J Cancer*, 110(4):868-74.
13. Agasi-Idenburg S, Thong M, Punt C, Stuiver M, Aaronson N (2017). Comparison of symptom clusters associated with fatigue in older and younger survivors of colorectal cancer. *Support Care Cancer*, 25(2):625-32.
14. Kwekkeboom K L, editor Cancer symptom cluster management. Semin Oncol Nurs; 2016: Elsevier.
15. Barsevick A M (2007). The elusive concept of the symptom cluster. *Oncol Nurs Forum*, 34(5).
16. Gehrman P R, Garland S N, Matura L A, Mao J J P, care s (2017). Insomnia in breast cancer: Independent symptom or symptom cluster? *Palliative & supportive care*, 15(3):369-75.
17. Ganz P A, Kwan L, Castellon S A, Oppenheim A, Bower J E, Silverman D H, et al. (2013). Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. *J Natl Cancer Inst*, 105:791-801.
18. Vardy J L, Dhillon H M, Pond G R, Rourke S B, Bekele T, Renton C, et al. (2015). Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. *J Clin Oncol*, 33(34):4085.
19. Schilder C, Seynaeve C, Linn S, Boogerd W, Beex L, Gundy C, et al. (2012). Self-reported cognitive functioning in postmenopausal breast cancer patients before and during endocrine treatment: findings from the neuropsychological TEAM side-study. *Psycho-Oncology*, 21(5):479-87.
20. Wouters H, Baars J W, Schagen S B (2016). Neurocognitive function of lymphoma patients after treatment with chemotherapy. *Acta Oncol*, 55(9-10):1121-5.
21. Bower J E (2014). Cancer-related fatigue: mechanisms, risk factors, and treatments. *Nature Reviews Clinical Oncology*, 11(10):597-609.
22. Prue G, Rankin J, Allen J, Gracey J, Cramp F (2006). Cancer-related fatigue: a critical appraisal. *Eur J Cancer*, 42(7):846-63.

23. Servaes P, Verhagen C, Bleijenberg G (2002). Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer*, 38(1):27-43.
24. Donovan K A, Stein K D, Lee M, Leach C R, Ilozumba O, Jacobsen P B (2015). Systematic review of the multidimensional fatigue symptom inventory-short form. *Support Care Cancer*, 23(1):191-212.
25. Kreissl S, Mueller H, Goergen H, Mayer A, Brillant C, Behringer K, et al. (2016). Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. *The Lancet Oncology*, 17(10):1453-62.
26. Ryan J L, Carroll J K, Ryan E P, Mustian K M, Fiscella K, Morrow G R (2007). Mechanisms of cancer-related fatigue. *Oncologist*, 12.
27. O'Higgins C, Brady B, O'Connor B, Walsh D, Reilly R (2018). The pathophysiology of cancer-related fatigue: current controversies. *Support Care Cancer*, 26(10):3353-64.
28. Saligan L N, Olson K, Filler K, Larkin D, Cramp F, Sriram Y, et al. (2015). The biology of cancer-related fatigue: a review of the literature. *Support Care Cancer*, 23(8):2461-78.
29. Dantzer R, O'Connor J C, Freund G G, Johnson R W, Kelley K W (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews neuroscience*, 9(1):46-56.
30. Aggarwal B B, Vijayalekshmi R, Sung B (2009). Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. *Clin Cancer Res*, 15(2):425-30.
31. Coussens L M, Werb Z (2002). Inflammation and cancer. *Nature*, 420(6917):860-7.
32. Bower J E, Ganz P A, Aziz N, Fahey J L (2002). Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med*, 64(4):604-11.
33. Bower J E, Ganz P A, Aziz N (2005). Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosom Med*, 67(2):277-80.
34. Weinrib A Z, Sephton S E, DeGeest K, Penedo F, Bender D, Zimmerman B, et al. (2010). Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. *Cancer*, 116(18):4410-9.
35. Innominato P F, Mormont M-C, Rich T A, Waterhouse J, Lévi F A, Bjarnason G A (2009). Circadian disruption, fatigue, and anorexia clustering in advanced cancer patients: implications for innovative therapeutic approaches. *Integr Cancer Ther*, 8(4):361-70.
36. Shanks N, Harbuz M, Jessop D, Perks P, Moore P, Lightman S (1998). Inflammatory disease as chronic stress. *Ann N Y Acad Sci*, 840(1):599-607.
37. Foster R, Kreitzman L (2017). Circadian Rhythms: A 24-hour phenomenon, in Foster R, Kreitzman L (eds): Circadian rhythms: a very short introduction. Oxford, United Kingdom: Oxford University Press. p. 1-12.
38. Ancoli-Israel S, Martin J L, Blackwell T, Buenaver L, Liu L, Meltzer L J, et al. (2015). The SBSM guide to actigraphy monitoring: clinical and research applications. *Behav Sleep Med*, 13(sup1):S4-S38.
39. Van Someren E J, Swaab D F, Colenda C C, Cohen W, McCall W V, Rosenquist P B (1999). Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. *Chronobiol Int*, 16(4):505-18.
40. Mormont M-C, Waterhouse J (2002). Contribution of the rest–activity circadian rhythm to quality of life in cancer patients. *Chronobiol Int*, 19(1):313-23.
41. Payne J K (2011). Altered circadian rhythms and cancer-related fatigue outcomes. *Integr Cancer Ther*, 10(3):221-33.
42. Rich T A (2007). Symptom clusters in cancer patients and their relation to EGFR ligand modulation of the circadian axis. *J Support Oncol*, 5(4):167-74.
43. Innominato P F, Roche V P, Palesh O G, Ulusakarya A, Spiegel D, Lévi F A (2014). The circadian timing system in clinical oncology. *Ann Med*, 46(4):191-207.
44. Cajochen C, Kräuchi K, Wirz-Justice A (2003). Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol*, 15(4):432-7.
45. Schrepf A, Clevenger L, Christensen D, DeGeest K, Bender D, Ahmed A, et al. (2013). Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability. *Brain Behav Immun*, 30:S126-S34.
46. Roenneberg T, Wirz-Justice A, Merrow M (2003). Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms*, 18(1):80-90.
47. Horne J A, Ostberg O (1975). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol*, 4(2):97-110.

48. Smith C S, Reilly C, Midkiff K (1989). Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. *J Appl Psychol*, 74(5):728-38.
49. Jones C R, Campbell S S, Zone S E, Cooper F, DeSano A, Murphy P J, et al. (1999). Familial advanced sleep-phase syndrome: A short-period circadian rhythm variant in humans. *Nat Med*, 5(9):1062-5.
50. Jones S E, Tyrrell J, Wood A R, Beaumont R N, Ruth K S, Tuke M A, et al. (2016). Genome-wide association analyses in 128,266 individuals identifies new morningness and sleep duration loci. *PLoS Genet*, 12(8):e1006125.
51. Xu Y, Padiath Q S, Shapiro R E, Jones C R, Wu S C, Saigoh N, et al. (2005). Functional consequences of a CKIδ mutation causing familial advanced sleep phase syndrome. *Nature*, 434(7033):640-4.
52. Roenneberg T, Pilz L K, Zerbini G, Winnebeck E C J B (2019). Chronotype and Social Jetlag: A (Self-) Critical Review. *Biology*, 8(3):54.
53. Chrobak A A, Nowakowski J, Zwolińska-Wcisło M, Cibor D, Przybylska-Feluś M, Ochyra K, et al. (2018). Associations between chronotype, sleep disturbances and seasonality with fatigue and inflammatory bowel disease symptoms. *Chronobiol Int*, 35(8):1142-52.
54. Martin J S, Hébert M, Ledoux É, Gaudreault M, Laberge L (2012). Relationship of chronotype to sleep, light exposure, and work-related fatigue in student workers. *Chronobiol Int*, 29(3):295-304.
55. Michielsen H J, De Vries J, Van Heck G L, Van de Vijver F J, Sijtsma K J E J o P A (2004). Examination of the dimensionality of fatigue. 20(1):39-48.
56. Grandjean E (1979). Fatigue in industry. *Occup Environ Med*, 36(3):175-86.
57. Rockwell D, Burr B (1977). The tired patient. *The Journal of family practice*, 5(5):853-7.
58. Vercoulen J (1999). The checklist individual strength. *Gedragstherapie*, 32:131-6.
59. Schwartz J E, Jandorf L, Krupp L B (1993). The measurement of fatigue: a new instrument. *J Psychosom Res*, 37(7):753-62.
60. Minton O, Stone P (2009). A systematic review of the scales used for the measurement of cancer-related fatigue (CRF). *Ann Oncol*, 20(1):17-25.
61. Fisher M I, Davies C, Lacy H, Doherty D (2018). Oncology section EDGE task force on cancer: measures of cancer-related fatigue—a systematic review. *Rehabil Oncol*, 36(2):93-105.
62. Seyidova-Khoshknabi D, Davis M P, Walsh D (2011). A systematic review of cancer-related fatigue measurement questionnaires. *American Journal of Hospice and Palliative Medicine®*, 28(2):119-29.
63. Aaronson N K, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N J, et al. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*, 85(5):365-76.
64. Yellen S B, Cella D F, Webster K, Blendowski C, Kaplan E (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*, 13(2):63-74.
65. Stein K D, Martin S C, Hann D M, Jacobsen P B J C p (1998). A multidimensional measure of fatigue for use with cancer patients. *Cancer Pract*, 6(3):143-52.
66. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. (1993). Development of a fatigue scale. *J Psychosom Res*, 37(2):147-53.
67. Smets E, Garssen B, Bonke B d, De Haes J (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 39(3):315-25.
68. Smets E, Garssen B, Cull A, De Haes J (1996). Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer*, 73(2):241.
69. Schwarz R, Krauss O, Hinz A (2003). Fatigue in the general population. *Oncology Research and Treatment*, 26(2):140-4.
70. Wintermann G-B, Rosendahl J, Weidner K, Strauß B, Hinz A, Petrowski K (2018). Fatigue in chronically critically ill patients following intensive care-reliability and validity of the multidimensional fatigue inventory (MFI-20). *Health and quality of life outcomes*, 16(1):37.
71. Buss T, Kruk A, Wiśniewski P, Modlinska A, Janiszewska J, Lichodziejewska-Niemierko M (2014). Psychometric Properties of the Polish Version of the Multidimensional Fatigue Inventory-20 in Cancer Patients. *J Pain Symptom Manage*, 48(4):730-7.
72. Gentile S, Delaroziere J, Favre F, Sambuc R, San Marco J (2003). Validation of the French 'multidimensional fatigue inventory'(MFI 20). *European journal of cancer care*, 12(1):58-64.
73. Song S-W, Kang S-G, Kim K-S, Kim M-J, Kim K-M, Cho D-Y, et al. (2018). Reliability and validity of the Korean version of the multidimensional fatigue inventory (MFI-20): a multicenter, cross-sectional study. *Pain Research and Management*, 2018.

74. Baptista R L R, Biasoli I, Scheliga A, Soares A, Brabo E, Morais J C, et al. (2012). Psychometric properties of the multidimensional fatigue inventory in Brazilian Hodgkin's lymphoma survivors. *J Pain Symptom Manage*, 44(6):908-15.
75. Saffari M, Naderi M K, Piper C N, Koenig H G (2017). Multidimensional Fatigue Inventory in People With Hepatitis B Infection: Cross-cultural Adaptation and Psychometric Evaluation of the Persian Version. *Gastroenterol Nurs*, 40(5):380-92.
76. Chandel P, Sultan A, Khan K A, Choudhary V, Parganiha A (2015). Validation of the Hindi version of the Multidimensional Fatigue Inventory-20 (MFI-20) in Indian cancer patients. *Support Care Cancer*, 23(10):2957-64.
77. Tian J, Hong J-S (2012). Validation of the Chinese version of Multidimensional Fatigue Inventory-20 in Chinese patients with cancer. *Support Care Cancer*, 20(10):2379-83.
78. Chung K-F, Yu B Y-M, Yung K-P, Yeung W-F, Ng T H, Ho F Y-Y (2014). Assessment of fatigue using the Multidimensional Fatigue Inventory in patients with major depressive disorder. *Compr Psychiatry*, 55(7):1671-8.
79. Lin J-M S, Brimmer D J, Maloney E M, Nyarko E, BeLue R, Reeves W C (2009). Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. *Population health metrics*, 7(1):18.
80. Chilcot J, Guirguis A, Friedli K, Almond M, Davenport A, Day C, et al. (2017). Measuring fatigue using the Multidimensional Fatigue Inventory-20: a questionable factor structure in haemodialysis patients. *Nephron*, 136(2):121-6.
81. Goodchild C E, Treharne G J, Booth D A, Kitas G D, Bowman S J (2008). Measuring fatigue among women with Sjogren's syndrome or rheumatoid arthritis: a comparison of the Profile of Fatigue (ProF) and the Multidimensional Fatigue Inventory (MFI). *Musculoskeletal Care*, 6(1):31-48.
82. Meek P M, Nail L M, Barsevick A, Schwartz A L, Stephen S, Whitmer K, et al. (2000). Psychometric testing of fatigue instruments for use with cancer patients. *Nurs Res*, 49(4):181-90.
83. Lundh Hagelin C, Wengström Y, Runesdotter S, Johan Fürst C (2007). The psychometric properties of the Swedish Multidimensional Fatigue Inventory MFI-20 in four different populations. *Acta Oncol*, 46(1):97-104.
84. Berger A M, Mooney K, Aranha O, Banarjee C, Breitbart W S, Carpenter K M, et al. (2020). Cancer-related fatigue, version 1.2021. *NCCN Guidelines*.
85. Mustian K M, Alfano C M, Heckler C, Kleckner A S, Kleckner I R, Leach C R, et al. (2017). Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA oncology*, 3(7):961-8.
86. Craike M J, Hose K, Courneya K S, Harrison S J, Livingston P M (2013). Perceived benefits and barriers to exercise for recently treated patients with multiple myeloma: a qualitative study. *BMC Cancer*, 13(1):1.
87. Choukroun J, Geoffroy P A (2019). Light therapy in mood disorders: a brief history with physiological insights. *Chronobiol Med*, 1:3-8.
88. Hippocrates H ippocrates on Airs, Waters and Places. London: Messrs. Wyman and Sons; 1881.
89. Rosenthal N E, Sack D A, Gillin J C, Lewy A J, Goodwin F K, Davenport Y, et al. (1984). Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry*, 41(1):72-80.
90. Mårtensson B, Pettersson A, Berglund L, Ekselius L (2015). Bright white light therapy in depression: a critical review of the evidence. *J Affect Disord*, 182:1-7.
91. Al-Karawi D, Jubair L (2016). Bright light therapy for nonseasonal depression: meta-analysis of clinical trials. *J Affect Disord*, 198:64-71.
92. Åkerstedt T, Landström U, Byström M, Nordström B, Wibom R (2003). Bright light as a sleepiness prophylactic: a laboratory study of subjective ratings and EEG. *Percept Mot Skills*, 97(3):811-9.
93. van Maanen A, Meijer A M, van der Heijden K B, Oort F J (2016). The effects of light therapy on sleep problems: A systematic review and meta-analysis. *Sleep Med Rev*, 29:52-62.
94. Lam R, Levitt A (1999). Canadian Consensus Guidelines for the treatment of SAD. *A summary of the report of the Canadian Consensus Group on SAD Clinical and Academic Publishing, Vancouver, Canada*.
95. Bauer M, Bschor T, Pfennig A, Whybrow P C, Angst J, Versiani M, et al. (2007). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. *The World Journal of Biological Psychiatry*, 8(2):67-104.

96. Hattar S, Liao H-W, Takao M, Berson D M, Yau K-W (2002). Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science*, 295(5557):1065-70.
97. Berson D M, Dunn F A, Takao M (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science*, 295(5557):1070-3.
98. Lucas R J, Peirson S N, Berson D M, Brown T M, Cooper H M, Czeisler C A, et al. (2014). Measuring and using light in the melanopsin age. *Trends Neurosci*, 37(1):1-9.
99. Schmidt T M, Chen S-K, Hattar S J T i n (2011). Intrinsically photosensitive retinal ganglion cells: many subtypes, diverse functions. *Trends Neurosci*, 34(11):572-80.
100. Tsai J W, Hannibal J, Hagiwara G, Colas D, Ruppert E, Ruby N F, et al. (2009). Melanopsin as a sleep modulator: circadian gating of the direct effects of light on sleep and altered sleep homeostasis in Opn4−/− mice. *PLoS Biol*, 7(6):e1000125.
101. LeGates T A, Fernandez D C, Hattar S (2014). Light as a central modulator of circadian rhythms, sleep and affect. *Nature Reviews Neuroscience*, 15(7):443-54.
102. Blume C, Garbazza C, Spitschan M (2019). Effects of light on human circadian rhythms, sleep and mood. *Somnologie*:1-10.
103. Lewy A J, Wehr T A, Goodwin F K, Newsome D A, Markey S (1980). Light suppresses melatonin secretion in humans. *Science*, 210(4475):1267-9.
104. Bowmaker J K, Dartnall H (1980). Visual pigments of rods and cones in a human retina. *The Journal of physiology*, 298(1):501-11.
105. Brainard G C, Sliney D, Hanifin J P, Glickman G, Byrne B, Greeson J M, et al. (2008). Sensitivity of the human circadian system to short-wavelength (420-nm) light. *J Biol Rhythms*, 23(5):379-86.
106. Ancoli-Israel S, Rissling M, Neikrug A, Trofimenko V, Natarajan L, Parker B A, et al. (2012). Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. *Support Care Cancer*, 20(6):1211-9.
107. Redd W H, Valdimarsdottir H, Wu L M, Winkel G, Byrne E E, Beltre M A, et al. (2014). Systematic light exposure in the treatment of cancer-related fatigue: a preliminary study. *Psychooncology*, 23(12):1431-4.
108. Neikrug A B, Rissling M, Trofimenko V, Liu L, Natarajan L, Lawton S, et al. (2012). Bright light therapy protects women from circadian rhythm desynchronization during chemotherapy for breast cancer. *Behav Sleep Med*, 10(3):202-16.
109. Jeste N, Liu L, Rissling M, Trofimenko V, Natarajan L, Parker B A, et al. (2013). Prevention of quality-of-life deterioration with light therapy is associated with changes in fatigue in women with breast cancer undergoing chemotherapy. *Qual Life Res*, 22(6):1239-44.
110. Wu L M, Amidi A, Valdimarsdottir H, Ancoli-Israel S, Liu L, Winkel G, et al. (2018). The effect of systematic light exposure on sleep in a mixed group of fatigued cancer survivors. *J Clin Sleep Med*, 14(01):31-9.
111. Huiberts L, Smolders K, De Kort Y (2017). Seasonal and time-of-day variations in acute non-image forming effects of illuminance level on performance, physiology, and subjective well-being. *Chronobiol Int*, 34(7):827-44.
112. Smolders K C, De Kort Y A, Cluitmans P J P, Behavior (2012). A higher illuminance induces alertness even during office hours: findings on subjective measures, task performance and heart rate measures. *Physiol Behav*, 107(1):7-16.
113. Gabel V, Maire M, Reichert C F, Chellappa S L, Schmidt C, Hommes V, et al. (2015). Dawn simulation light impacts on different cognitive domains under sleep restriction. *Behav Brain Res*, 281:258-66.
114. Phipps-Nelson J, Redman J R, Dijk D-J, Rajaratnam S M (2003). Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. *Sleep*, 26(6):695-700.
115. Smolders K C, de Kort Y A (2014). Bright light and mental fatigue: Effects on alertness, vitality, performance and physiological arousal. *J Environ Psychol*, 39:77-91.
116. Riemersma-Van Der Lek R F, Swaab D F, Twisk J, Hol E M, Hoogendijk W J, Van Someren E J (2008). Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA*, 299(22):2642-55.
117. Royer M, Ballentine N H, Eslinger P J, Houser K, Mistrick R, Behr R, et al. (2012). Light therapy for seniors in long term care. *J Am Med Dir Assoc*, 13(2):100-2.
118. Killgore W D, Vanuk J R, Shane B R, Weber M, Bajaj S (2020). A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury. *Neurobiol Dis*, 134:104679.

119. Burns A, Allen H, Tomenson B, Duignan D, Byrne J (2009). Bright light therapy for agitation in dementia: a randomized controlled trial. *Int Psychogeriatr*, 21(4):711.
120. Forbes D, Blake C M, Thiessen E J, Peacock S, Hawranik P (2014). Light therapy for improving cognition, activities of daily living, sleep, challenging behaviour, and psychiatric disturbances in dementia. *Cochrane database of systematic reviews*, (2).

CHAPTER 2

LIGHT THERAPY AS A TREATMENT OF CANCER-RELATED FATIGUE IN (NON-)HODGKIN LYMPHOMA SURVIVORS (SPARKLE TRIAL): STUDY PROTOCOL OF A MULTICENTER RANDOMIZED CONTROLLED TRIAL.

BMC Cancer, 2018; 18(1): 880
doi.org/10.1186/s12885-018-4746-2

Daniëlle E.J. Starreveld
Laurien A. Daniels
Heiddis B. Valdimarsdottir
William H. Redd
Jessie de Geus
Sonia Ancoli-Israel
Susan Lutgendorf
Catharina M. Korse
Jacobien M. Kieffer
Flora E. van Leeuwen
Eveline M.A. Bleiker

ABSTRACT

Background

Cancer related fatigue (CRF) is one of the most prevalent and distressing long-term complaints reported by (non-) Hodgkin survivors. To date there has been no standard treatment for CRF in this population. A novel and promising approach to treat CRF is exposure to bright white light (BWL) therapy. Yet, large scale randomized controlled trials (RCT) testing its efficacy in these patients and research on potential mechanisms is lacking. The objective of the current study is to investigate the efficacy of light therapy as a treatment for CRF and to explore potential mechanisms.

Methods/design

In a multicenter, randomized controlled trial we are evaluating the efficacy of two intensities of light therapy in reducing CRF complaints and restrictions caused by CRF in survivors of Hodgkin lymphoma or diffuse large B-cell lymphoma. Secondary outcomes include sleep quality, depression, anxiety, quality of life, cognitive complaints, cancer worries, fatigue catastrophizing, self-efficacy to handle fatigue, biological circadian rhythms of melatonin, cortisol and activity, and biomarkers of inflammation. We will recruit 128 survivors, with fatigue complaints, from academic and general hospitals. Survivors are randomized to either an intervention (exposure to bright white light) or a comparison group (exposure to dim white light). The longitudinal design includes four measurement points at baseline (T0), post-intervention at 3.5 weeks (T1), 3 months post-intervention (T2) and 9 months post-intervention (T3). Each measurement point includes self-reported questionnaires and actigraphy (10 days). T0 and T1 measurements also include collection of blood and saliva samples.

Discussion

Light therapy has the potential to be an effective treatment for CRF in cancer survivors. This study will provide insights on its efficacy and potential mechanisms. If proven to be effective, light therapy will provide an easy to deliver, low-cost and low-burden intervention, introducing a new era in the treatment of CRF.

BACKGROUND

After the introduction of modern radiotherapy and combination chemotherapy, Hodgkin lymphoma (HL) has become the prototype of a curable malignancy with cure rates of 80 to 90%[1]. Also, for selected patients with aggressive non-Hodgkin lymphoma, survival has improved significantly, i.e. the 5-year overall survival of patients with diffuse large B-cell lymphoma (DLBCL) varies from 40 to 85%[2]. Unfortunately, treatment of lymphoma is associated with various late adverse effects, including cancer related fatigue (CRF)[3].

CRF is defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning"[4, 5]. Patients feel tired even after resting, have reduced capacity to carry out normal activities, experience slow physical recovery from tasks, and report diminished concentration[6]. CRF is one of the most frequently reported long-term symptoms in (non-) Hodgkin survivors with prevalence ratings between 25 to 60% compared to 10 to 25% in the general population[7, 8]. CRF significantly affects patients' quality of life[5] and seems to be influenced by symptoms of depression, anxiety, and the presence of comorbid conditions[8].

Currently, there is no standard treatment for CRF. A range of non-pharmacological interventions to treat CRF have been investigated, including physical activity (PA), psycho-education, cognitive-behavior therapy (CBT), CBT with hypnosis (CBTH), mindfulness-based approaches, and a number of complementary and alternative medicine interventions (e.g., acupuncture/acupressure, yoga, music therapy)[5]. Some of these interventions, including PA[9, 10], CBT[11], and CBTH[12], have been associated with large effect sizes. In the case of CBT, these effects remain stable for at least two years[13]. These findings are promising but not without limitations. For example, motivation is essential to complete these interventions while fatigue can reduce the motivation for PA[14]. Also, CBT is labor intensive since it requires professional guidance for several weeks.

A new development in the treatment of CRF is the use of light therapy. During this therapy, patients are asked to expose themselves to bright white light (BWL) for 30 minutes within the first half hour after awakening. Systematic exposure to BWL was originally developed to treat seasonal affective disorder[15] and is currently the treatment of choice for this disorder[16-18] although a recent review provided less conclusive results[19]. Additionally, light therapy has been found to help restore circadian rhythm disturbances and sleep disorders[20, 21].

Several studies have investigated the efficacy of light therapy specifically for CRF. One study randomized breast cancer patients undergoing chemotherapy to either a BWL (n = 23) or a dim red light (DRL; n = 16) condition[22]. Results showed that the usual increase in CRF from baseline to the end of the fourth chemotherapy cycle was seen in women exposed to DRL, while such an increase was not seen in the group exposed to BWL. In addition, circadian rhythms became more synchronized and quality of life was better in the women exposed to BWL compared to women exposed to DRL. Another study used the same design to test the efficacy of light therapy for CRF in cancer survivors[23]. Results showed that fatigue decreased to normal levels in survivors exposed to BWL (n = 18) while survivors exposed to DRL (n = 18) stayed at clinically significant levels of fatigue. These results also showed a significant decrease

in depressive symptoms and better sleep quality in survivors exposed to BWL compared to DRL. More recently, results were published from a larger RCT that included 81 cancer survivors[24]. Survivors exposed to BWL showed greater reductions in fatigue and improvements in mood, depressive symptoms and quality of life compared to survivors exposed to DRL. In summary, these findings support the use of light therapy as a treatment for CRF.

However, the mechanisms that explain the effect of light therapy on CRF have largely remained unexplored. Light is one of the strongest synchronizers of the circadian rhythm system[25]. When it enters the eye, light affects processes in the suprachiasmatic nucleus (SCN), a structure better known as the human master pacemaker of circadian rhythms[26]. Based on this knowledge, several hypotheses about potential mechanisms could be formulated.

The first hypothesis is that light therapy normalizes the sleep-wake cycle. Previous studies showed that sleep-wake cycles, measured with questionnaires as well as objective measurements with actigraphy, were disrupted in patients with cancer after chemotherapy and that this disruption was related to increased CRF[22, 27]. Furthermore, it was shown that light therapy during chemotherapy resulted in sleep-wake cycles that returned to baseline levels after chemotherapy while patients in the comparison condition showed disrupted sleep-wake cycles after four cycles of chemotherapy[27]. Moreover, secondary analysis on objective sleep data collected with actigraphy in cancer survivors with CRF suggested that exposure to bright white light improved the sleep efficiency to normal ranges while this improvement was not seen in the group exposed to dim red light[28].

The second hypothesis is that the mechanism may be related to changes in circadian rhythms. The superchiasmatic nucleus (SCN) is responsible for the production of melatonin, a hormone that is secreted in darkness, which acts as a time-cue for sleep. Melatonin shows a circadian rhythm with rising levels during the evening that reaches the peak during the night followed by a decrease that reaches its lowest point (nadir) in the morning. The SCN also plays a role in the production of cortisol, a glucocorticoid hormone that shows a sharp increase in the first 30 minutes after awakening, followed by a gradual decline over the day that reaches its nadir during the night[29]. Impairments of this rhythmicity, such as the flattened morning-rise and a lower ratio between morning and nocturnal levels of cortisol, have consistently been associated with deteriorations in mood in both healthy and clinical populations and increased CRF in clinical populations[30-32]. Light therapy was proven to be effective in entrainment of the circadian rhythms of melatonin and cortisol[33]. Moreover, improvements in CRF over time were associated with normalization of the circadian cortisol rhythm[34], suggesting that a potential mechanism of light therapy on CRF is via the normalization of the circadian rhythms of these hormones.

A third potential mechanism is the normalizing effect of light therapy on the HPA axis, which may affect inflammatory cytokine activity. There is a wealth of research, both in animals as well as in clinical and healthy human populations, showing strong interconnections between fatigue and inflammation. Consistent associations have been shown between CRF and plasma levels of inflammatory markers such as interleukin-6 and C-reactive protein[35, 36]. There is also a well characterized feedback loop between the HPA axis and inflammation, whereby the HPA axis can down regulate inflammation and is itself up regulated by inflammatory signaling[37].

BWL has been found to normalize HPA axis function[38] raising the possibility that BWL may affect inflammatory cytokine activity either directly or indirectly, e.g., via its normalizing effects on the HPA axis.

The main aim of this double-blind, randomized controlled trial, called 'improving Sleep quality, Psychosocial functioning and cAncer Related fatigue with Light thErapy (SPARKLE)', is to determine the effect of exposure to BWL compared to exposure to dim white light (DWL), on CRF in ≥ 2 years survivors of HL and DLBCL. Additionally, this trial will explore potential mechanisms of light therapy on CRF by investigating the influence of light therapy on factors associated with CRF. More specific, the secondary objectives are:

1. to examine the effect of exposure to BWL compared to DWL on sleep quality and psychological variables (depression, anxiety, cognitive complaints, and quality of life).
2. to investigate whether exposure to BWL, compared to DWL, affects circadian rhythms of cortisol and melatonin, activity, vitamin D concentrations and levels of biomarkers for inflammation markers.
3. to explore whether the effects of exposure to BWL on CRF can be predicted by the effect of BWL on sleep quality, psychological variables, biological and activity circadian rhythms, and inflammation markers.

METHODS

This trial will use a double blind randomized controlled trial design with one intervention group exposed to bright white light and one comparison group exposed to dim white light. The design of the trial and the anticipated flow is shown in Figure 1. This trial (under number NL61017.031.17) has been approved by The Institutional Review Board of The Netherlands Cancer Institute as well as by the review boards of the participating hospitals (see recruitment and randomization). Patient recruitment and data collection started in August 2017.

Participants

The intended study sample will comprise 128 survivors of Hodgkin lymphoma (HL) or diffuse large B-cell lymphoma (DLBCL). Inclusion criteria are: (1) a survivorship of ≥ 2 years; (2) presence of moderate to severe fatigue symptoms since diagnosis of or treatment for HL or DLBCL. The presence of fatigue will be defined by fulfilling at least one of the following criteria: (a) a moderate to severe fatigue score on the general fatigue subscale of the multidimensional fatigue index; (b) a score of ≥ 17 on the Work and Social Adjustment Scale indicating clinical levels of impairments in daily functioning caused by fatigue[39].

Exclusion criteria are: (1) presence of somatic cause for fatigue (defined as (a) New York Heart Association class 3/4 (heart failure), (b) having a COPD gold class 3/4 (lung failure), or (c) having other organ failure that has led to marked limitation of physical activity). Patient can be included if, despite having used stable medication for ≥ 6 months for the somatic cause, fatigue complaints remain; (2) pregnancy (until 3 months postnatal) or lactating; (3) having had extensive surgery in the past 3 months; (4) having a current diagnosis of psychiatric disorder that can hamper participation; (5) having had a diagnosis of and/or treatment for secondary

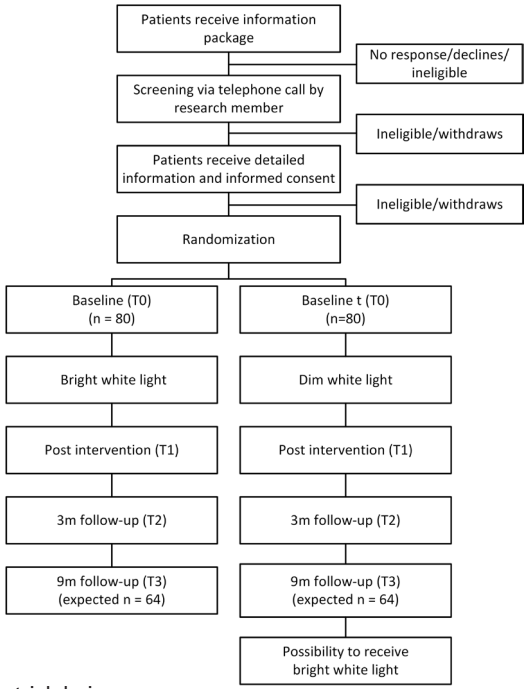


Figure 1. Overview of the trial design

malignancy in the past 12 months; (6) presence of photophobia or other eye diseases that show symptoms of photophobia; (7) current or previous use of light therapy (≥ 1 week); (8) current employment in shift work.

Recruitment

Participants for this study will be recruited via collaborating BETER-clinics. The BETER consortium (Better care after Hodgkin lymphoma: Evaluation of long-Term Treatment Effects and screening) is organising a nationwide infrastructure for survivorship care for lymphoma survivors, to prevent morbidity and mortality from late treatment effects[40]. This consortium identifies and traces 5-year survivors of HL and DLBCL treated in 23 Dutch academic as well as general hospitals. So far, eight BETER-clinics agreed to collaborate with the SPARKLE study: Antoni van Leeuwenhoek, LUMC, Radboudumc, VUmc, UMCU, ErasmusMC, Albert Schweitzer hospital, HagaZiekenhuis, Admiraal de Ruyter hospital.

Survivors (≥ 2 years) of HL or DLBCL who visit their treating physician for follow-up care are screened for CRF symptoms. When CRF symptoms are present and the patient meets the inclusion criteria, the physician will hand out a pamphlet, a response card and a screening questionnaire to the patient. A second strategy to recruit patients is via an evaluation of the BETER screening questionnaire that patients complete for their first BETER-clinic visit. This questionnaire includes a visual analogue scale (VAS) scale from 0 (no fatigue) to 10 (worst imaginable fatigue). If the fatigue score is 4 or higher, patients will be sent the information package.

Patients are asked to return the response card to express their interest in participation. In case of no interest, patients are asked to specify their reason(s) on the response card. If patients are interested, they are asked to complete the screening questionnaire and return this to the SPARKLE research team. Non-responders will receive a reminder three weeks after receiving the information package.

Patients who return the screening questionnaire receive a call from the SPARKLE research team. The aim of this phone call is to provide more information about the study and to screen on inclusion and exclusion criteria. Interested and eligible patients will receive a more detailed patient information letter and an informed consent form. Patients are requested to return a signed informed consent or a no-interest-response-card within two weeks. Non-responders will be called to assess willingness for participation three weeks after sending the patient information letter.

Randomization

Equally distributed across all four seasons, participants are randomized to either an intervention group (n = 64) or a comparison condition (n = 64) using the minimization technique at a 1:1 ratio. Randomization is stratified for diagnosis (HL; DLBCL), time since diagnosis (<5 years; 5-10 years; 11-20 years; >20 years) and gender (male; female). Randomization is outsourced to an independent party, using the randomization programme ALEA. The output determines which lamp (with BWL or with DWL) is offered to each participant. This lamp will be part of the content of a bag offered to the research assistant who visits the participants. In this way, both the research team and the participants are blinded to the allocated condition. The randomization code will only be broken if a patient reports severe adverse side effects as a result of the light intervention.

Description of interventions

Instructions for light therapy are equal in both conditions. All participants self-administer light therapy at home for 30 minutes each morning during a period of 3,5 weeks. Participants start with the light therapy within 30 minutes after waking up and position the light box at a distance of 45 cm and an angle of 45° from their face. During the light therapy participants can engage in other activities such as reading or having breakfast. They are informed not to stare into the light but to keep their eyes open to ensure that light falls on the retina. No instructions for sleep pattern adjustments are provided in the current trial.

Light therapy in both conditions will be administered via a Litebook© Edge (Litebook, Ltc. Medicine Hat, Canada). The Litebook© Edge is a small (15 x 12 x 1 cm), lightweight box designed to be placed on a table. The Litebook© Edge contains 60 premium white light emitting diode (LED) lights which mimic the visible spectrum of sunlight for minimum glare and maximum eye comfort. For purposes of safety, the Litebook© Edge emits no ultraviolet light. The Litebook© Edge devices used in this study were modified to include an integrated meter that allows for adherence monitoring by recording time and duration of on-time on each day.

Intervention group

The intervention group will be exposed to BWL with an intensity of 10.000 lux at a distance of 45 cm. The spectrum of the light in this condition will be enriched around 480 nm wavelengths. Light with this colour has previously been shown to be the effective factor in light therapy as it is associated with melatonin suppression[26].

Comparison group

Participants in the comparison condition will be exposed to dim white light, with an intensity of 10-20 lux at a distance of 45 cm. This light was successfully used as a comparison condition for BWL therapy in Alzheimer´s disease. Similar results are expected in cancer survivors (personal communication with Dr. M.G. Figueiro, November 14, 2016).

Study procedure

All participants complete a battery of self-report questionnaires and wear a wrist actigraph at four different measurement points (T0: baseline; T1: directly after 3,5 weeks of light therapy; T2: 3 months after light therapy; T3: 9 months after light therapy). The first (T0) and second (T1) measurement points include a visit to the hospital to provide participants with materials and instructions, to perform cognitive tests, and to collect blood (during the visit) and saliva (on day 8 and 36) samples. Figure 2 shows a schematic diagram of a participant's timeline.

The research assistant or study coordinator calls the participant after 5 days of light therapy asking for the occurrence of any side effects (headache, nausea, agitated feeling and irritated eyes). In normal cases, these side effects vanish in a few days. Light therapy is terminated when these side effects are still present after 5 days of light therapy. These participants are asked to complete all follow-up assessments.

After 3,5 weeks of light therapy, participants are asked not to use light therapy during the follow-up measurements. No instructions are provided for the use of concomitant care and other interventions.

Study measures

Sociodemographic and clinical data

Information regarding the patients' age, education, marital status, living situation, work status and medication use will be obtained via a questionnaire. Clinical information, including date of diagnosis, tumor characteristics, and treatment history will be abstracted from the BETER-database. This clinical information will be abstracted from the patients' medical record when participants are not included in the BETER-consortium. Current season will be derived from the start date of light therapy.

Outcome measures

The Multidimensional Fatigue Inventory (MFI)[41], a VAS-scale for fatigue[42] and the Work and Social Adjustment Scale (WSAS)[43] are the primary outcome measure of this study. Secondary outcome measures include: Pittsburg Sleep Quality Index (PSQI)[44], wrist actigraphy[45], Center for Epidemiological Studies – Depression scale (CES-D)[46], State-Trait Anxiety Inventory-6 items (STAI-6)[47], Medical outcome studies short form (SF-36)[48], Medical Outcomes Studies Cognitive

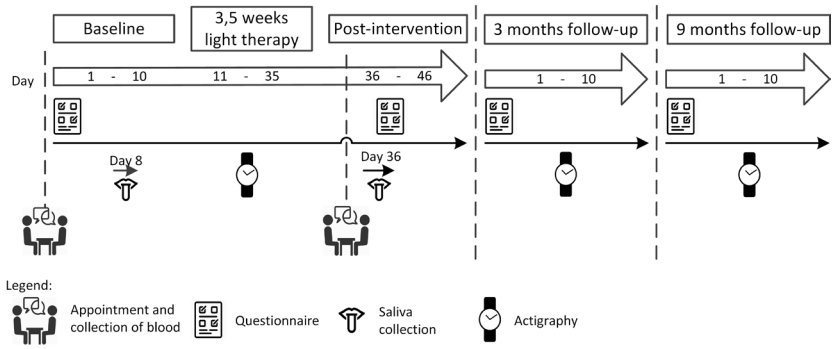


Figure 2. Overview of study procedure

function scale (MOS-CF6)[49], MD Anderson Symptom Inventory (MDASI)[50], Psychomotor Vigilance Task (PVT)[51], 15 words task[52], digit span task[53], cancer worry scale (CWS)[54], fatigue catastrophizing scale (FCS)[55], Self-efficacy scale 28 (SES-28)[56], salivary cortisol and melatonin, and inflammatory biomarkers. Detailed descriptions of these outcome measures are provided in table 1.

A brief self-developed questionnaire will be used to examine the use of alcohol and caffeine, screen time prior to sleeping, solarium, wake-up lights, or the use of other interventions that could impact CRF (including physical exercise, CBT, or other interventions). Additional questions assess participant's experience, compliance, and satisfaction with light therapy. Compliance is also assessed with a light therapy log during light therapy.

Actigraphy

Objective measures of sleep and circadian activity will be monitored with an accelerometer in a microelectromechanical system (MotionWatch8, Camntech, Cambridgeshire, United Kingdom). The MotionWatch8 is a small device, similar in size to a watch, with a tri-axial accelerometer. It has a 4.0 Mbits storage capacity and a waterproof casing. This watch will be worn on the non-dominant wrist for 10 (24-h) days at all measurement points and during light therapy. Output of the MotionWatch8 includes the following sleep parameters: time in bed, time out of bed, sleep onset latency (min), sleep efficiency, total time in bed (min), total sleep time (min), wake after sleep onset (min), number of awakenings, and average awakening time (min). Additionally, output of the MotionWatch8 includes the following circadian activity rhythm variables: interdaily stability (IS), Intra-Daily Variability (IV), Least 5 (L5) average, Most 10 (M10) average, and relative amplitude (RA). In addition, it offers nap analyses for naps during the day and day activity analyses.

An actigraphy log will be used to ensure that the scoring software of the actigraph detects the sleep habits of participants accurately. Based on the guidelines for the use of actigraphy, the following items will be included: bed time, attempted time to fall asleep, wake-up time, out-of-bed time, time of day time naps, times the actigraph was removed, unusual circumstances that might have affected sleep/wake patterns (such as illness)[45].

Table 1. Study outcome measures and corresponding questionnaires

Variable	Questionnaire	Number of items	Type of items	Time frame
PRIMARY OUTCOMES				
Cancer-related fatigue	MFI[41]	20	4-point Likert scale	Past few days
	VAS-scale[42]	1	11-point Likert scale	This moment
Restrictions caused by fatigue	WSAS[43, 57]	5	9-point Likert scale	Influence of fatigue on daily life'
SECONDARY OUTCOMES				
Sleep quality	PSQI[44]	19	4-point Likert scale and open-ended questions	Past month
Depression	CES-D[46, 58]	20	4-point Likert scale	Past week
Anxiety	STAI-6[47]	6	4 point Likert scale	This moment
Quality of life	SF-36[48, 59]	36	Dichotomous 3- to 6-point Likert scale	Past 4 weeks
Cognitive complaints	MOS-CF6[49, 60]	6	6-point Likert scale	Past week
	MDASI[50]	8	11-point Likert scale	Past 24 hours
Cancer worries	CWS[54]	8 + 1	4-point Likert scale	Past week
Fatigue catastrophizing	FCS[55, 61]	10	5-point Likert scale	Current attitude
Self-efficacy	SES-28[56, 62]	7	4-point Likert scale	Current attitude

CES-D Center for Epidemiological Studies – Depression scale; **CWS** Cancer Worry Scale; **FCS** Fatigue catastrophizing Scale; **MDASI** MD Anderson Symptom Inventory; **MFI** Multidimensional Fatigue Inventory; **MOS-CF6** Medical Outcomes Studies Cognitive functioning; **PSQI** Pittsburgh Sleep Quality Index; **SF-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.

	Score range	Psychometric details
	Subscale scores: 4-20; higher scores indicate more fatigue	Subscales: general fatigue, mental fatigue, physical fatigue, reduced motivation, reduced activity. Cronbach's alpha: 0.84.
	0-10; higher scores indicate more fatigue	
	0-40; higher scores indicate higher levels of disability.	Cronbach's alpha: >0 .79.
	Total score: 0-21 Subscale scores: 0-3; higher scores indicate more acute sleep disturbances.	Subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction. Cronbach's alpha: 0.83.
	0-60; higher scores indicate greater depressive symptoms.	Cronbach's alpha: 0.85-0.90
	20-80; higher scores indicate increased anxiety	Cronbach's alpha: 0.83
	Subscale scores: 0-100; higher scores indicates higher levels of functioning/ well-being	Subscales: physical functioning, role limitations due to physical health problems, bodily pain, social functioning, general mental health, role limitations due to emotional problems, vitality, general health perceptions Cronbach's alpha: 0.84
	0-100; higher scores indicated better cognitive functioning	Cronbach's alpha: ≥ 0.89
	0-80; higher score indicates worse or more disturbing cognitive complaints.	
	9-36; higher score indicates more frequent worries about cancer.	Cronbach's alpha: 0.87
	10-40; higher score indicates more catastrophizing	Cronbach's alpha: 0.85
	7-28; higher score indicates higher level of perceived control over fatigue symptoms.	Cronbach's alpha: 0.68-0.77

Biological samples

Salivary cortisol

All participants will be asked to collect saliva to assess cortisol 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. These time points are chosen in line with published guidelines for determination of the *Cortisol Awakening Response* (CAR)[63]. The afternoon and evening samples are used to estimate the *diurnal cortisol slope* and the *area under the curve.*

Saliva will be collected by a passive drool technique into a propylene vial. Participants are not allowed to smoke, engage in vigorous exercise, eat or drink caffeinated drinks or food, and eat protein-rich meal during the sampling period starting 1 hour prior to sampling. Eating and drinking of other nourishments is allowed until 5 minutes prior to sampling. Brushing of teeth is not allowed for 30 minutes before sampling. After sampling, the participant is instructed to record the time that they completed the sample and to refrigerate it. Samples will be returned to the study coordinator by mail after which the samples will be frozen at -80°C to keep samples stable until analysis. Cortisol levels will be determined with an electrochemiluminescensce immunoassay 'ECLIA' on the Cobas®6000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

Salivary melatonin

A subgroup (n = 25 per condition) will be asked to collect five additional saliva samples in the evening to determine the *Dim Light Melatonin Onset* (DLMO). Starting point forthis saliva collection will be 5h prior to usual bedtime followed by one sample every sequential hour. Previous research indicated that these time points provide a reliable measurement for DLMO with at home collected saliva samples[64]. Participants receive the additional instruction to collect these samples in dim light conditions.

A commercial direct saliva melatonin radioimmunoassay (RIA; Bühlmann laboratories, Schönenbuch, Switzerland) will be used to assess melatonin levels in saliva. The DLMO will be determined based on a threshold of 4.0 pg/mL. Previous research indicated that a fixed threshold is the most convenient way to determine DLMO although there is a risk that DLMO cannot be determined in patients with sleep problems as a consequence of low secretion of melatonin[64]. When we address this problem in the current study, an alternative procedure will be used. DLMO will then be defined as the time when melatonin concentration is two SD above the basal mean of three daytime samples[65].

Blood samples

Blood samples are collected to measure biomarkers of inflammation and vitamin D at baseline. During T0 and T1, two tubes of 10 mL of blood will be collected. One of these tubes will be saved in the biobank NKI-AVL. The other will be used to assess vitamin D and the following inflammatory biomarkers in duplicate by ELISA: IL-1RA, hsIL-6, sTNF-RII, and hsCRP. Vitamin D has been associated with current levels of fatigue[66-68]. The before-mentioned biomarkers have previously been associated with fatigue in patients with cancer[35, 69]. The level of these biomarkers, as well as the change in biomarker levels will be used as parameters for the statistical analysis.

Data management

The original signed informed consent forms are stored at the department of the participating institute where the participant is recruited. All participants receive a unique participant number, in order to code their outcome measures without the-risk of harming anonymity. Participants can choose to complete an online or pen-and paper version of the questionnaire. Paper versions of completed questionnaires and a (copy of) the signed informed consent forms are stored at the Division of Psychosocial Research and Epidemiology of the Netherlands Cancer Institute separately. Online completion of questionnaires will take place via an online secured (HTTPS) research tool, called Explora Zorg, which is specifically developed for research in Dutch health care. Each participant has a personal log-in code. Completed paper versions of the questionnaires will be entered in this online system by the research assistant.

The information given online by patients is accessible to the study staff only, via a secured code. This code is known by the principal investigator (EB), the study coordinator (DS), and the research assistant (JG). The principal investigator will safeguard the key to the code. The collected data in this research tool is saved on the secured database of the Netherlands Cancer Institute on a monthly basis.

Blood and saliva samples of all participants are stored at the general clinical laboratory of the Netherlands Cancer Institute. Each sample is coded with a unique participant number. Date and time of sampling are reported on the samples.

Statistical methods

Sample size calculation

The MFI is the primary outcome on which sample size calculations are based. With a sample of 128 patients (n = 64 per group), the study will have an 80% power to detect an Cohen's effect size of 0.5 for the main effect of light therapy on fatigue with a p-value set at 0.05 (power calculation with G*power 3[70]). Cohen's effect size of 0.5 means a 0.5 standard deviation difference on the primary measurement outcome, which is considered to be a clinical meaningful difference[71]. Participants who discontinue light therapy but complete questionnaires will be included in the intention-to-treat analysis.

Statistical analyses

Data will be analysed using the Statistical Package for the Social Sciences (SPSS). Although we endeavour to check all questionnaires upon their return and call participants to complete missing items, some data might still be missing. Missing values will be imputed according to the manual of the questionnaire. In general, descriptive statistics will be computed for the outcome variables, potential covariates and demographic variables. Bivariate analyses will be undertaken to explore associations between outcome and potentially confounding variables (e.g. season, diagnosis, years since diagnosis) using correlations (for continuous variables) and Chi-square tests (for categorical variables).

Group differences in change in fatigue during the trial will be investigated using a mixed effect growth model with random intercept and slope, nested within site (clusters of different hospitals). This approach takes into account the within and between person variability, and deals

adequately with missing data[72]. If baseline differences are identified despite randomisation, these variables will be accounted for in the model. In case of non-ignorable dropout we will correct the model for different patterns of missing values[73]. All analyses will be done on an ´intention to treat´ basis. Additional explorative analyses will be done on a ´per protocol´ basis.

The mixed effect model approach described for change in fatigue will also be used to determine treatment effects of continuous secondary outcome measures. To evaluate between-group differences in categorical secondary outcome measures, we will use generalized estimating equations (GEE) for longitudinal data. This approach accounts for correlated within subject responses, allows for not normally distributed variables and deals adequately with missing data[73-75]. Since there are multiple outcomes, the p-values for each model will be adjusted for multiple comparisons.

Within the intervention group we will explore which variables are predictive for the efficacy of light therapy in reducing fatigue. A mixed effect model for longitudinal data will be used with fatigue as dependent variable and the following independent variables: sleep quality, depression, anxiety, cognitive complaints, quality of life, and biological circadian rhythms. The p-values will be adjusted for multiple testing.

Monitoring

The Institutional Review Board of The Netherlands Cancer Institute did not appoint a data monitoring committee because of the low risk on adverse events. Instead, the investigator submits a summary of the progress of the trial to the accredited METC once a year. Information is provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments. Some study sites require adherence to local monitoring protocols.

DISCUSSION

CRF affects approximately 40 to 60% of long-term survivors treated for (non-) Hodgkin lymphoma. Recently, interest shifted to light therapy as a promising treatment for CRF. Previous studies showed a prevention of increasing levels of CRF in breast cancer patients during chemotherapy and a reduction of fatigue complaints in cancer survivors after exposure to BWL compared to exposure to dim red light. Yet, the patient samples in these studies were small and knowledge of possible mechanisms and long-term effect of light therapy is lacking. This trial investigates the efficacy of light therapy in survivors of HL and DLBCL and explores potential mechanisms explaining its efficacy, including chronobiological and psychosocial pathways.

This trial has several noteworthy strengths, including (1) the randomized controlled trial design; (2) recruitment in multiple centers across the Netherlands; (3) the use of a dim white light comparison condition instead of a dim red light comparison condition to exclude the influence of light color; (4) the use of intention-to-treat analyses; and (5) inclusion of long-term follow-up measurements to investigate the long-term efficacy of light therapy.

There are also several limitations in this trial. First, for practical reasons the duration of light therapy is 3,5 weeks in the current study while previous studies provided light therapy for four weeks. Since light therapy for CRF is an upcoming research field, the duration of light therapy and its efficacy is not yet investigated. Clinical practice suggests that the effect of light therapy is often seen within two weeks. If no effect is seen in this period, than it is unlikely to see a change in the following weeks. For this reason, it is expected that shortening the time period of light therapy with four days will not impact the efficacy of light therapy. Second, a somatic cause for fatigue complaints is an exclusion criterion. Yet, screening does not include assessments of possible somatic factors. Instead, the treating physician judges whether a patient has a somatic cause for fatigue or not. In case of doubt, a team of three experts will be consulted to judge whether someone can be included in the trial. Third, the DLMO is assessed with 5 saliva collections starting 5 hours prior to sleep onset. Recommendations by EUCLOCK (a large European wide research network aiming to investigate the circadian clock in single cells and humans) advices to include a saliva collection until 1 hour after sleep onset. Yet, this would influence someone's sleep pattern and might affect fatigue levels the following day. For this reason, saliva is only collected prior to sleep onset.

In conclusion, new insights suggest the efficacy of light therapy as a treatment for cancer related fatigue. If proven to be effective, light therapy will provide an easy to deliver, low-cost and low-burden intervention, introducing a new era in the treatment of CRF. National implementation of light therapy will be facilitated via close collaboration with the BETER-clinics. Moreover, the investigation of potential mechanisms enriches the CRF literature with possible new suggestions for causative factors of CRF, a symptom that is neither well understood nor treated.

REFERENCES

1. Favier O, Heutte N, Stamatoullas-Bastard A, Carde P, van't Veer M B, Aleman B M, et al. (2009). Survival after Hodgkin lymphoma. *Cancer*, 115(8):1680-91.
2. Pfreundschuh M, Trümper L, Österborg A, Pettengell R, Trneny M, Imrie K, et al. (2006). CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *The lancet oncology*, 7(5):379-91.
3. Aleman B M, van Leeuwen F E (2007). Are we improving the long-term burden of Hodgkin's lymphoma patients with modern treatment? *Hematol Oncol Clin North Am*, 21(5):961-75.
4. Mock V, Atkinson A, Barsevick A, Cella D, Cimprich B, Cleeland C, et al. (2000). NCCN Practice Guidelines for Cancer-Related Fatigue. Oncology (Williston Park, NY), 14(11A):151-61.
5. Bower J E, Bak K, Berger A, Breitbart W, Escalante C P, Ganz P A, et al. (2014). Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*, 32(17):1840-50.
6. Curt G A, Breitbart W, Cella D, Groopman J E, Horning S J, Itri L M, et al. (2000). Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *The oncologist*, 5(5):353-60.
7. Oerlemans S, Mols F, Issa D E, Pruijt J, Peters W G, Lybeert M, et al. (2013). A high level of fatigue among long-term survivors of non-Hodgkin's lymphoma: results from the longitudinal population-based PROFILES registry in the south of the Netherlands. *Haematologica*, 98(3):479-86.
8. Daniëls L, Oerlemans S, Krol A, Creutzberg C, van de Poll-Franse L (2014). Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. *Br J Cancer*, 110(4):868-74.
9. Burnham T R, Wilcox A (2002). Effects of exercise on physiological and psychological variables in cancer survivors. *Med Sci Sports Exerc*, 34(12):1863-7.
10. Milne H M, Wallman K E, Gordon S, Courneya K S (2008). Impact of a combined resistance and aerobic exercise program on motivational variables in breast cancer survivors: a randomized controlled trial. *Ann Behav Med*, 36(2):158-66.
11. Gielissen M F, Verhagen S, Witjes F, Bleijenberg G (2006). Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol*, 24(30):4882-7.
12. Montgomery G H, Kangas M, David D, Hallquist M N, Green S, Bovbjerg D H, et al. (2009). Fatigue during breast cancer radiotherapy: An initial randomized study of cognitive–behavioral therapy plus hypnosis. *Health Psychol*, 28(3):317.
13. Gielissen M, Verhagen C, Bleijenberg G (2007). Cognitive behaviour therapy for fatigued cancer survivors: long-term follow-up. *Br J Cancer*, 97(5):612-8.
14. Craike M J, Hose K, Courneya K S, Harrison S J, Livingston P M (2013). Perceived benefits and barriers to exercise for recently treated patients with multiple myeloma: a qualitative study. *BMC Cancer*, 13(1):1.
15. Rosenthal N E, Sack D A, Gillin J C, Lewy A J, Goodwin F K, Davenport Y, et al. (1984). Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry*, 41(1):72-80.
16. Pail G, Huf W, Pjrek E, Winkler D, Willeit M, Praschak-Rieder N, et al. (2011). Bright-light therapy in the treatment of mood disorders. *Neuropsychobiology*, 64(3):152-62.
17. Terman M, Terman J S (2005). Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS spectrums*, 10(08):647-63.
18. Golden R N, Gaynes B N, Ekstrom R D, Hamer R M, Jacobsen F M, Suppes T, et al. (2005). The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry*, 162(4):656-62.
19. Mårtensson B, Pettersson A, Berglund L, Ekselius L (2015). Bright white light therapy in depression: a critical review of the evidence. *J Affect Disord*, 182:1-7.
20. Åkerstedt T, Landström U, Byström M, Nordström B, Wibom R (2003). Bright light as a sleepiness prophylactic: a laboratory study of subjective ratings and EEG. *Percept Mot Skills*, 97(3):811-9.
21. van Maanen A, Meijer A M, van der Heijden K B, Oort F J (2016). The effects of light therapy on sleep problems: A systematic review and meta-analysis. *Sleep Med Rev*, 29:52-62.

22. Ancoli-Israel S, Rissling M, Neikrug A, Trofimenko V, Natarajan L, Parker B A, et al. (2012). Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. *Support Care Cancer*, 20(6):1211-9.
23. Redd W H, Valdimarsdottir H, Wu L M, Winkel G, Byrne E E, Beltre M A, et al. (2014). Systematic light exposure in the treatment of cancer-related fatigue: a preliminary study. *Psychooncology*, 23(12):1431-4.
24. Johnson J A, Garland S N, Carlson L E, Savard J, Simpson J S A, Ancoli-Israel S, et al. (2017). Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. *J Cancer Surviv*, 12:1-10.
25. Küller R (2002). The influence of light on circarhythms in humans. *J Physiol Anthropol Appl Human Sci,* 21(2):87-91.
26. Lucas R J, Peirson S N, Berson D M, Brown T M, Cooper H M, Czeisler C A, et al. (2014). Measuring and using light in the melanopsin age. *Trends Neurosci*, 37(1):1-9.
27. Neikrug A B, Rissling M, Trofimenko V, Liu L, Natarajan L, Lawton S, et al. (2012). Bright light therapy protects women from circadian rhythm desynchronization during chemotherapy for breast cancer. *Behav Sleep Med*, 10(3):202-16.
28. Wu L M, Amidi A, Valdimarsdottir H, Ancoli-Israel S, Liu L, Winkel G, et al. (2018). The effect of systematic light exposure on sleep in a mixed group of fatigued cancer survivors. *J Clin Sleep Med*, 14(01):31-9.
29. Figueiro M G, Rea M S (2010). The effects of red and blue lights on circadian variations in cortisol, alpha amylase, and melatonin. *Int J Endocrinol*, 2010.
30. Bower J E, Ganz P A, Aziz N (2005). Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosom Med*, 67(2):277-80.
31. Innominato P F, Mormont M-C, Rich T A, Waterhouse J, Lévi F A, Bjarnason G A (2009). Circadian disruption, fatigue, and anorexia clustering in advanced cancer patients: implications for innovative therapeutic approaches. *Integr Cancer Ther*, 8(4):361-70.
32. Weinrib A Z, Sephton S E, DeGeest K, Penedo F, Bender D, Zimmerman B, et al. (2010). Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. *Cancer*, 116(18):4410-9.
33. Anderson J, Glod C, Dai J, Cao Y, Lockley S (2009). Lux vs. wavelength in light treatment of Seasonal Affective Disorder. *Acta Psychiatr Scand*, 120(3):203-12.
34. Schrepf A, Clevenger L, Christensen D, DeGeest K, Bender D, Ahmed A, et al. (2013). Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability. *Brain Behav Immun*, 30:S126-S34.
35. Bower J E, Lamkin D M (2013). Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications. *Brain Behav Immun*, 30:S48-S57.
36. Wang X S, Shi Q, Shah N D, Heijnen C J, Cohen E N, Reuben J M, et al. (2014). Inflammatory markers and development of symptom burden in patients with multiple myeloma during autologous stem cell transplantation. *Clin Cancer Res*, 20(5):1366-74.
37. Powell N, Tarr A, Sheridan J F (2013). Psychosocial stress and inflammation in cancer. *Brain Behav Immun*, 30:S41-S7.
38. Lieverse R, Van Someren E J, Nielen M M, Uitdehaag B M, Smit J H, Hoogendijk W J (2011). Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. *Arch Gen Psychiatry*, 68(1):61-70.
39. Jansson-Fröjmark M (2014). The work and social adjustment scale as a measure of dysfunction in chronic insomnia: reliability and validity. *Behav Cogn Psychother*, 42(02):186-98.
40. Dekker N, Aleman B, Raemaekers J (2015). The BETER survivorship care initiative for Hodgkin lymphoma; tailored survivorship care for late effects of treatment. *Ned Tijdschr Geneeskd*, 159:A9269-A.
41. Smets E, Garssen B, Bonke B d, De Haes J (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 39(3):315-25.
42. Oldenmenger W H, Pleun J, de Klerk C, van der Rijt C C (2013). Cut points on 0–10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review. *J Pain Symptom Manage*, 45(6):1083-93.
43. Mundt J C, Marks I M, Shear M K, Greist J M (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *The British Journal of Psychiatry*, 180(5):461-4.

44. Buysse D J, Reynolds C F, Monk T H, Berman S R, Kupfer D J (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*, 28(2):193-213.
45. Ancoli-Israel S, Martin J L, Blackwell T, Buenaver L, Liu L, Meltzer L J, et al. (2015). The SBSM guide to actigraphy monitoring: clinical and research applications. *Behav Sleep Med*, 13(sup1):S4-S38.
46. Radloff L S (1977). The CES-D scale a self-report depression scale for research in the general population. *Appl Psychol Meas*, 1(3):385-401.
47. van der Bij A K, de Weerd S, Cikot R J, Steegers E A, Braspenning J, CC e (2003). Validation of the dutch short form of the state scale of the Spielberger State-Trait Anxiety Inventory: considerations for usage in screening outcomes. *Public Health Genomics*, 6(2):84-7.
48. Ware Jr J E, Sherbourne C D (1992). The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care*:473-83.
49. Stewart A L, Ware J E, Sherbourne C D, Wells K B (1992). Psychological distress/well-being and cognitive functioning measures, in Stewart AL, Ware JE (eds): Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, NC: Duke University. p. 102-42.
50. Cleeland C S, Mendoza T R, Wang X S, Chou C, Harle M T, Morrissey M, et al. (2000). Assessing symptom distress in cancer patients. *Cancer*, 89(7):1634-46.
51. Dinges D F, Powell J W (1985). Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behavior research methods, instruments, & computers*, 17(6):652-5.
52. Saan R, Deelman B (1986). De 15-woordentest A en B (een voorlopige handleiding). Groningen: Afdeling Neuropsychologie, AZG.
53. Wechsler D. Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV). 2014.
54. Custers J A, van den Berg S W, van Laarhoven H W, Bleiker E M, Gielissen M F, Prins J B (2014). The cancer worry scale: detecting fear of recurrence in breast cancer survivors. *Cancer Nurs*, 37(1):E44-E50.
55. Jacobsen P, Azzarello L, Hann D (1999). Relation of catastrophizing to fatigue severity in women with breast cancer. *Cancer Res Ther Control*, 8:155-64.
56. de Vree B, Van der Werf S, Prins J, Bazelmans H, Vercoulen J, Servaes P, et al. (2002). Meetinstrumenten bij chronische vermoeidheid.
57. Cella M, Sharpe M, Chalder T (2011). Measuring disability in patients with chronic fatigue syndrome: reliability and validity of the Work and Social Adjustment Scale. *J Psychosom Res*, 71(3):124-8.
58. Vodermaier A, Linden W, Siu C (2009). Screening for emotional distress in cancer patients: a systematic review of assessment instruments. *J Natl Cancer Inst*, 101(21):1464-88.
59. Aaronson N K, Muller M, Cohen P D, Essink-Bot M-L, Fekkes M, Sanderman R, et al. (1998). Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*, 51(11):1055-68.
60. Yarlas A, White M, Bjorner J (2013). The development and validation of a revised version of the Medical Outcomes Study Cognitive Functioning Scale (Mos-Cog-R). *Value in Health*, 16(3):A33-A4.
61. Jacobsen P B, Andrykowski M A, Thors C L (2004). Relationship of catastrophizing to fatigue among women receiving treatment for breast cancer. *J Consult Clin Psychol*, 72(2):355.
62. Prins J B, Bleijenberg G, Bazelmans E, Elving L D, de Boo T M, Severens J L, et al. (2001). Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *The Lancet*, 357(9259):841-7.
63. Stalder T, Kirschbaum C, Kudielka B M, Adam E K, Pruessner J C, Wüst S, et al. (2016). Assessment of the cortisol awakening response: expert consensus guidelines. *Psychoneuroendocrinology*, 63:414-32.
64. Keijzer H, Smits M G, Duffy J F, Curfs L M (2014). Why the dim light melatonin onset (DLMO) should be measured before treatment of patients with circadian rhythm sleep disorders. *Sleep Med Rev*, 18(4):333-9.
65. Voultsios A, Kennaway D J, Dawson D (1997). Salivary melatonin as a circadian phase marker: validation and comparison to plasma melatonin. *J Biol Rhythms*, 12(5):457-66.
66. Hoeck A D (2014). Vitamin D3 deficiency results in dysfunctions of immunity with severe fatigue and depression in a variety of diseases. *In Vivo*, 28(1):133-45.
67. Biersack M G, Hajdukiewicz M, Uebelhack R, Franke L, Piazena H, Klaus P, et al. (2016). Sustained increase of 25-hydroxyvitamin D levels in healthy young women during wintertime after three suberythemal UV irradiations—The MUVY Pilot Study. *PLoS One*, 11(7):e0159040.
68. Nowak A, Boesch L, Andres E, Battegay E, Hornemann T, Schmid C, et al. (2016). Effect of vitamin D3 on self-perceived fatigue: A double-blind randomized placebo-controlled trial. *Medicine*, 95(52).

69. Schubert C, Hong S, Natarajan L, Mills P J, Dimsdale J E (2007). The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun*, 21(4):413-27.
70. Faul F, Erdfelder E, Lang A-G, Buchner A (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*, 39(2):175-91.
71. Cohen J Statistical power analysis for the behavioral sciences 2ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
72. Diggle P J, Heagerty P J, Liang K-Y, Zeger S L Analysis of Longitudinal Data. 2 ed. New York, NY: Oxford University Press; 2002.
73. Son H, Friedmann E, Thomas S A (2012). Application of pattern mixture models to address missing data in longitudinal data analysis using SPSS. *Nurs Res*, 61(3):195-203.
74. Ghisletta P, Spini D (2004). An introduction to generalized estimating equations and an application to assess selectivity effects in a longitudinal study on very old individuals. *Journal of Educational and Behavioral Statistics*, 29(4):421-37.
75. Liu I, Agresti A (2005). The analysis of ordered categorical data: An overview and a survey of recent developments. *Test*, 14(1):1-73.

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

Daniëlle E.J. Starreveld
Laurien A. Daniels
Jacobien M. Kieffer
Heiddis B. Valdimarsdottir
Jessie de Geus
Mirthe Lanfermeijer
Eus J.W. van Someren
G. Esther A. Habers
Jos A. Bosch
Cécile P.M. Janus
Dick-Johan van Spronsen
Roel J. de Weijer
Erik W.A. Marijt
Eva de Jongh
Josée M. Zijlstra
Lara H. Böhmer
Margreet Houmes
Marie José Kersten
Catharina M. Korse
Huub H. van Rossum
William H. Redd
Susan Lutgendorf
Sonia Ancoli-Israel
Flora E. van Leeuwen
Eveline M.A. Bleiker

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

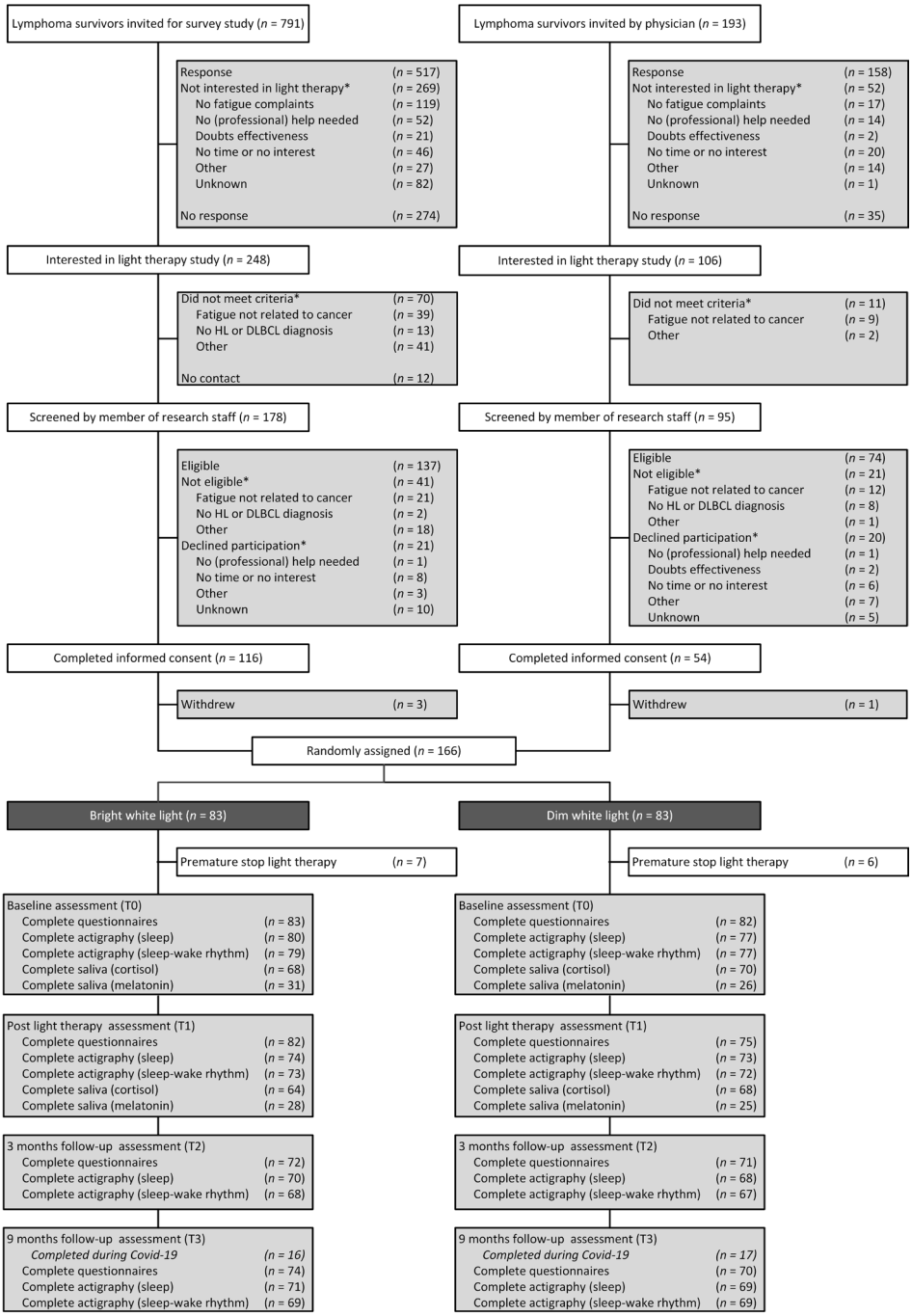


Figure 1: CONSORT diagram.
HL Hodgkin lymphoma; **DLBCL** Diffuse Large B-cell lymphoma
* Patients could provide more than one reason for nonparticipation or could be excluded for more than one reason. No. of missing assessments at T1, T2, and T3 were not necessarily cumulative.

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].

(Continued on next page)

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)		

(Continued on next page)

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).

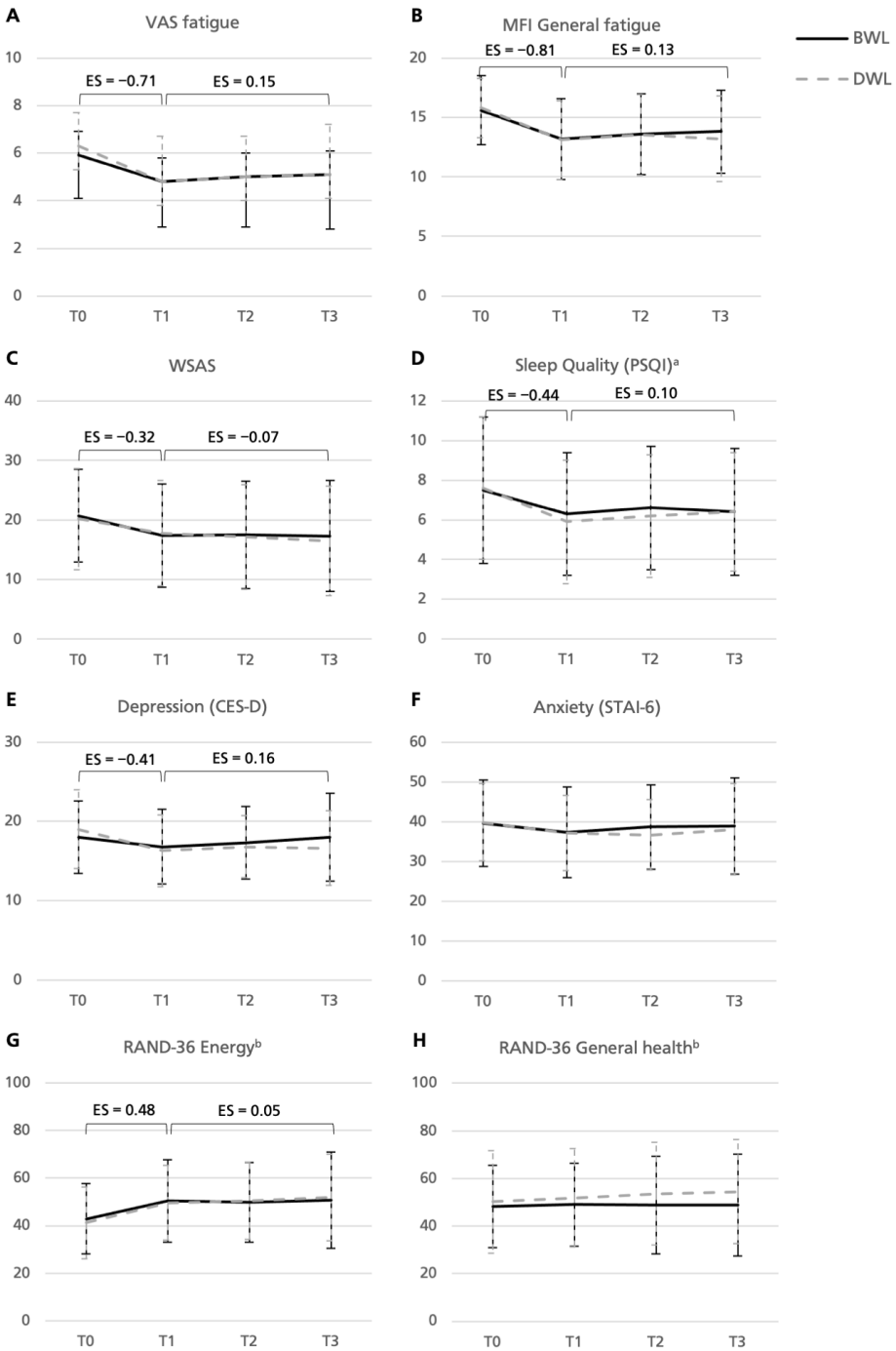


Figure 2 Changes in raw mean levels of primary and secondary self-reported outcomes from baseline to nine months follow-up in groups receiving bright white light therapy (BWL; n = 83) and dim white light therapy (DWL; n = 83).

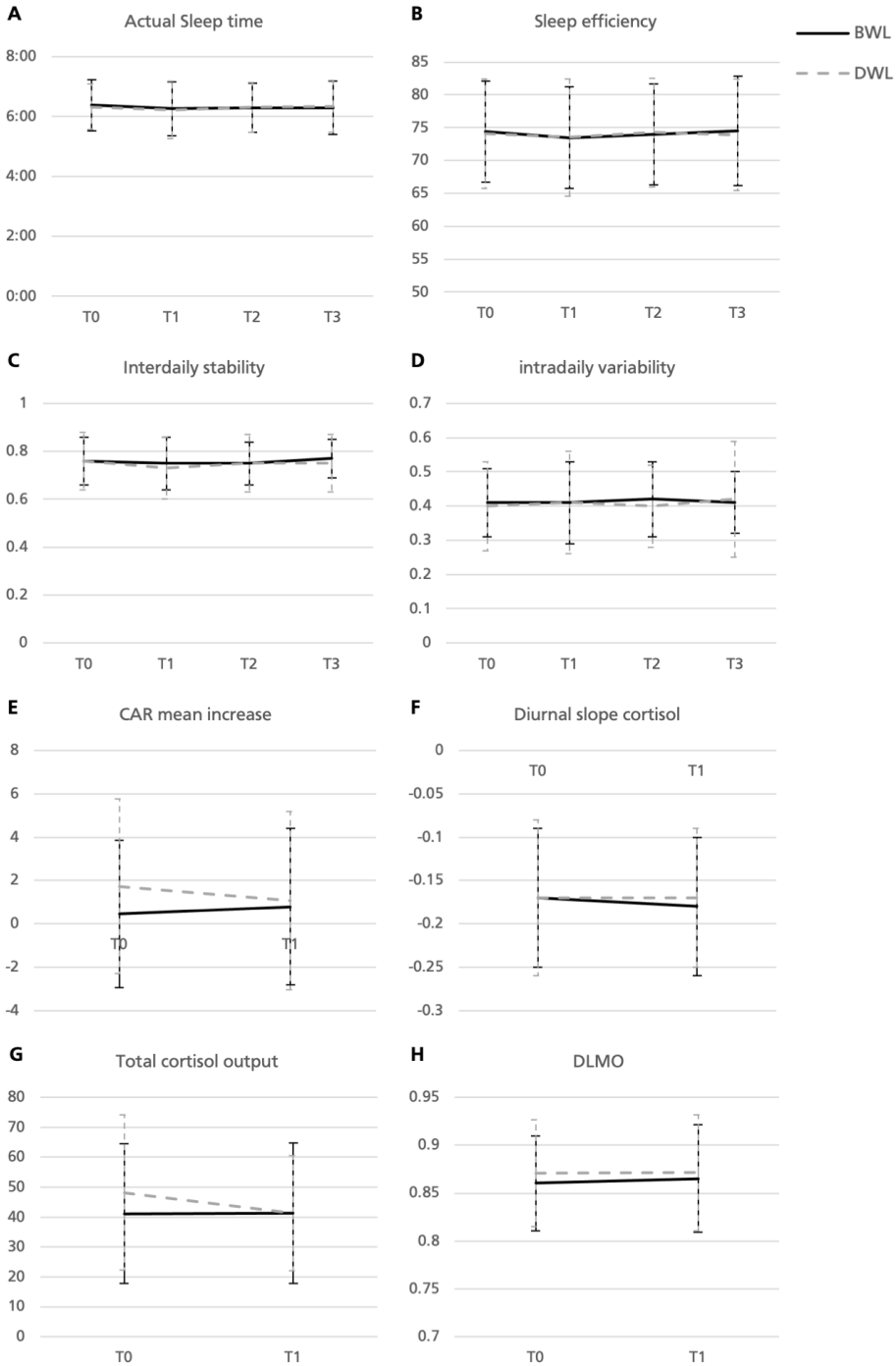


Figure 3. Changes in raw mean levels of actigraphy-derived sleep variables (A, B, C, D) and cortisol and melatonin variables (E, F, G, H) in groups receiving bright white light therapy (BWL; n = 83) and dim white light therapy (DWL; n = 83).

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.

REFERENCES

1. Daniëls L, Oerlemans S, Krol A, Creutzberg C, van de Poll-Franse L (2014). Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. *Br J Cancer*, 110(4):868-74.
2. Oerlemans S, Mols F, Issa D E, Pruijt J, Peters W G, Lybeert M, et al. (2013). A high level of fatigue among long-term survivors of non-Hodgkin's lymphoma: results from the longitudinal population-based PROFILES registry in the south of the Netherlands. *Haematologica*, 98(3):479-86.
3. Bower J E, Bak K, Berger A, Breitbart W, Escalante C P, Ganz P A, et al. (2014). Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*, 32(17):1840-50.
4. Agasi-Idenburg S, Thong M, Punt C, Stuiver M, Aaronson N (2017). Comparison of symptom clusters associated with fatigue in older and younger survivors of colorectal cancer. *Support Care Cancer*, 25(2):625-32.
5. Kwekkeboom K L, editor Cancer symptom cluster management. *Semin Oncol Nurs*; 2016: Elsevier.
6. Barsevick A M (2007). The elusive concept of the symptom cluster. *Oncol Nurs Forum*, 34(5).
7. Gehrman P R, Garland S N, Matura L A, Mao J J P, care s (2017). Insomnia in breast cancer: Independent symptom or symptom cluster? *Palliative & supportive care*, 15(3):369-75.
8. Innominato P F, Roche V P, Palesh O G, Ulusakarya A, Spiegel D, Lévi F A (2014). The circadian timing system in clinical oncology. *Ann Med*, 46(4):191-207.
9. Payne J K (2011). Altered circadian rhythms and cancer-related fatigue outcomes. *Integr Cancer Ther*, 10(3):221-33.
10. Rich T A (2007). Symptom clusters in cancer patients and their relation to EGFR ligand modulation of the circadian axis. *J Support Oncol*, 5(4):167-74.
11. Weinrib A Z, Sephton S E, DeGeest K, Penedo F, Bender D, Zimmerman B, et al. (2010). Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. *Cancer*, 116(18):4410-9.
12. Innominato P F, Mormont M-C, Rich T A, Waterhouse J, Lévi F A, Bjarnason G A (2009). Circadian disruption, fatigue, and anorexia clustering in advanced cancer patients: implications for innovative therapeutic approaches. *Integr Cancer Ther*, 8(4):361-70.
13. Schrepf A, Clevenger L, Christensen D, DeGeest K, Bender D, Ahmed A, et al. (2013). Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability. *Brain Behav Immun*, 30:S126-S34.
14. Pail G, Huf W, Pjrek E, Winkler D, Willeit M, Praschak-Rieder N, et al. (2011). Bright-light therapy in the treatment of mood disorders. *Neuropsychobiology*, 64(3):152-62.
15. Terman M, Terman J S (2005). Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS spectrums*, 10(08):647-63.
16. Golden R N, Gaynes B N, Ekstrom R D, Hamer R M, Jacobsen F M, Suppes T, et al. (2005). The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry*, 162(4):656-62.
17. Åkerstedt T, Landström U, Byström M, Nordström B, Wibom R (2003). Bright light as a sleepiness prophylactic: a laboratory study of subjective ratings and EEG. *Percept Mot Skills*, 97(3):811-9.
18. van Maanen A, Meijer A M, van der Heijden K B, Oort F J (2016). The effects of light therapy on sleep problems: A systematic review and meta-analysis. *Sleep Med Rev*, 29:52-62.
19. Küller R (2002). The influence of light on circarhythms in humans. *J Physiol Anthropol Appl Human Sci*, 21(2):87-91.
20. Lucas R J, Peirson S N, Berson D M, Brown T M, Cooper H M, Czeisler C A, et al. (2014). Measuring and using light in the melanopsin age. *Trends Neurosci*, 37(1):1-9.
21. Schmidt T M, Chen S-K, Hattar S (2011). Intrinsically photosensitive retinal ganglion cells: many subtypes, diverse functions. *Trends Neurosci*, 34(11):572-80.
22. Ancoli-Israel S, Rissling M, Neikrug A, Trofimenko V, Natarajan L, Parker B A, et al. (2012). Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. *Support Care Cancer*, 20(6):1211-9.
23. Redd W H, Valdimarsdottir H, Wu L M, Winkel G, Byrne E E, Beltre M A, et al. (2014). Systematic light exposure in the treatment of cancer-related fatigue: a preliminary study. *Psychooncology*, 23(12):1431-4.

24. Johnson J A, Garland S N, Carlson L E, Savard J, Simpson J S A, Ancoli-Israel S, et al. (2017). Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. *J Cancer Surviv*, 12:1-10.
25. Wu L M, Amidi A, Valdimarsdottir H, Ancoli-Israel S, Liu L, Winkel G, et al. (2018). The effect of systematic light exposure on sleep in a mixed group of fatigued cancer survivors. *J Clin Sleep Med*, 14(01):31-9.
26. Fox R S, Baik S H, McGinty H, Garcia S F, Reid K J, Bovbjerg K, et al. (2020). Feasibility and Preliminary Efficacy of a Bright Light Intervention in Ovarian and Endometrial Cancer Survivors. *Int J Behav Med*:1-13.
27. Garland S N, Johnson J A, Carlson L E, Rash J A, Savard J, Campbell T S (2020). Light therapy for insomnia symptoms in fatigued cancer survivors: a secondary analysis of a randomized controlled trial. *Journal of Psychosocial Oncology Research and Practice*, 2(3):e27.
28. Jeste N, Liu L, Rissling M, Trofimenko V, Natarajan L, Parker B A, et al. (2013). Prevention of quality-of-life deterioration with light therapy is associated with changes in fatigue in women with breast cancer undergoing chemotherapy. *Qual Life Res*, 22(6):1239-44.
29. Neikrug A B, Rissling M, Trofimenko V, Liu L, Natarajan L, Lawton S, et al. (2012). Bright light therapy protects women from circadian rhythm desynchronization during chemotherapy for breast cancer. *Behav Sleep Med*, 10(3):202-16.
30. Starreveld D E J, Daniels L A, Valdimarsdottir H B, Redd W H, de Geus J L, Ancoli-Israel S, et al. (2018). Light therapy as a treatment of cancer-related fatigue in (non-) Hodgkin lymphoma survivors (SPARKLE trial): study protocol of a multicenter randomized controlled trial. *BMC Cancer*, 18(1):880.
31. Starreveld D E J, Habers G E A, Valdimarsdottir H B, Kessels R, Daniëls L A, van Leeuwen F E, et al. (2021). Cancer-related Fatigue in Relation to Chronotype and Sleep Quality in (Non-) Hodgkin Lymphoma Survivors. *J Biol Rhythms*:0748730420987327.
32. Oldenmenger W H, Pleun J, de Klerk C, van der Rijt C C (2013). Cut points on 0–10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review. *J Pain Symptom Manage*, 45(6):1083-93.
33. Smets E, Garssen B, Bonke B d, De Haes J (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 39(3):315-25.
34. Kieffer J M, Starreveld D E J, Boekhout A, Bleiker E M A (2020). A questionable factur structure of the multidimensional fatigue inventory in the general Dutch population. *J Clin Epidemiol*, 137:266-276.
35. Mundt J C, Marks I M, Shear M K, Greist J M (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *The British Journal of Psychiatry*, 180(5):461-4.
36. Buysse D J, Reynolds C F, Monk T H, Berman S R, Kupfer D J (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*, 28(2):193-213.
37. Radloff L S (1977). The CES-D scale a self-report depression scale for research in the general population. *Appl Psychol Meas*, 1(3):385-401.
38. van der Bij A K, de Weerd S, Cikot R J, Steegers E A, Braspenning J C C (2003). Validation of the dutch short form of the state scale of the Spielberger State-Trait Anxiety Inventory: considerations for usage in screening outcomes. *Public Health Genomics*, 6(2):84-7.
39. Hays R D, Sherbourne C D, Mazel R M (1993). The rand 36-item health survey 1.0. *Health Econ*, 2(3):217-27.
40. Van der Zee K, Sanderman R (1993). Het meten van de algemene gezondheidstoestand met de RAND-36: een handleiding. *Groningen: Noordelijk centrum voor gezondheidsvraagstukken*:1-23.
41. Ancoli-Israel S, Martin J L, Blackwell T, Buenaver L, Liu L, Meltzer L J, et al. (2015). The SBSM guide to actigraphy monitoring: clinical and research applications. *Behav Sleep Med*, 13(sup1):S4-S38.
42. Van Someren E J, Swaab D F, Colenda C C, Cohen W, McCall W V, Rosenquist P B (1999). Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. *Chronobiol Int*, 16(4):505-18.
43. Stalder T, Kirschbaum C, Kudielka B M, Adam E K, Pruessner J C, Wüst S, et al. (2016). Assessment of the cortisol awakening response: expert consensus guidelines. *Psychoneuroendocrinology*, 63:414-32.
44. Keijzer H, Smits M G, Duffy J F, Curfs L M (2014). Why the dim light melatonin onset (DLMO) should be measured before treatment of patients with circadian rhythm sleep disorders. *Sleep Med Rev*, 18(4):333-9.
45. Danilenko K V, Verevkin E G, Antyufeev V S, Wirz-Justice A, Cajochen C (2014). The hockey-stick method to estimate evening dim light melatonin onset (DLMO) in humans. *Chronobiol Int*, 31(3):349-55.

46. Schwarz G (1978). Estimating the dimension of a model. *The Annals of Statistics*, 6(2):461-4.
47. Akaike H (1998). Information theory and an extension of the maximum likelihood principle, in Parzen E, Tanabe K, Kitagawa G (eds): Selected papers of hirotugu akaike. New Yotk, NY: Springer. p. 199-213.
48. Cohen J Statistical power analysis for the behavioral sciences 2ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
49. Norman G R, Sloan J A, Wyrwich K W (2003). Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*:582-92.
50. Schwarz R, Krauss O, Hinz A (2003). Fatigue in the general population. *Oncology Research and Treatment*, 26(2):140-4.
51. Khanna D, Pope J E, Khanna P P, Maloney M, Samedi N, Norrie D, et al. (2008). The minimally important difference for the fatigue visual analog scale in patients with rheumatoid arthritis followed in an academic clinical practice. *The Journal of Rheumatology*, 35(12):2339-43.
52. Purcell A, Fleming J, Bennett S, Burmeister B, Haines T (2010). Determining the minimal clinically important difference criteria for the Multidimensional Fatigue Inventory in a radiotherapy population. *Support Care Cancer*, 18(3):307-15.
53. Streiner D L, Norman G R, Cairney J Health measurement scales: a practical guide to their development and use. 5 ed. Oxford, UK: Oxford University Press; 2015.
54. Shechter A, Julian J, Davidson K W, Cheung K, Lee J, Kronish I M (2019). A within-subject comparison of the effect of two putative sham light therapies on mood and fatigue in cancer survivors: Results from a series of N-of-1 trials. *Psychiatry Res*, 279:385-6.
55. Mustian K M, Alfano C M, Heckler C, Kleckner A S, Kleckner I R, Leach C R, et al. (2017). Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA oncology*, 3(7):961-8.
56. Persoon S, Kersten M J, van der Weiden K, Buffart L M, Nollet F, Brug J, et al. (2013). Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. *Cancer Treat Rev*, 39(6):682-90.
57. Gielissen M F, Verhagen S, Witjes F, Bleijenberg G (2006). Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol*, 24(30):4882-7.
58. McCarney R, Warner J, Iliffe S, Van Haselen R, Griffin M, Fisher P (2007). The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol*, 7(1):30.
59. Junior P N A, Barreto C M N, Cubero D d I G, Del Giglio A (2020). The efficacy of placebo for the treatment of cancer-related fatigue: a systematic review and meta-analysis. *Support Care Cancer*, 28(4):1755-64.
60. Servaes P, Verhagen S, Schreuder H B, Veth R P, Bleijenberg G (2003). Fatigue after treatment for malignant and benign bone and soft tissue tumors. *J Pain Symptom Manage*, 26(6):1113-22.
61. Hjermstad M J, Fosså S D, Oldervoll L, Holte H, Jacobsen A B, Loge J H (2005). Fatigue in long-term Hodgkin's Disease survivors: a follow-up study. *J Clin Oncol*, 23(27):6587-95.
62. Johnson J A, Subnis U, Carlson L E, Garland S N, Santos-Iglesias P, Piedalue K-A L, et al. (2020). Effects of a light therapy intervention on diurnal salivary cortisol in fatigued cancer survivors: A secondary analysis of a randomized controlled trial. *J Psychosom Res*, 139:110266.
63. Jones S E, van Hees V T, Mazzotti D R, Marques-Vidal P, Sabia S, van der Spek A, et al. (2019). Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nature communications*, 10(1):1-12.
64. Häusler N, Marques-Vidal P, Haba-Rubio J, Heinzer R (2020). Association between actigraphy-based sleep duration variability and cardiovascular risk factors–Results of a population-based study. *Sleep Med*, 66:286-90.
65. Luik A I, Zuurbier L A, Direk N, Hofman A, Van Someren E J, Tiemeier H (2015). 24-hour activity rhythm and sleep disturbances in depression and anxiety: A population-based study of middle-aged and older persons. *Depress Anxiety*, 32(9):684-92.
66. Rogers V E, Mowbray C, Zhu S, Liu L, Ancoli-Israel S, Barr E A, et al. (2020). Circadian activity rhythms and fatigue of adolescent cancer survivors and healthy controls: a pilot study. *J Clin Sleep Med*, 16(7):1141-7.
67. Lam R, Levitt A (1999). Canadian Consensus Guidelines for the treatment of SAD. A summary of the report of the Canadian Consensus Group on SAD Clinical and Academic Publishing, Vancouver, Canada.

68. Kreissl S, Mueller H, Goergen H, Mayer A, Brillant C, Behringer K, et al. (2016). Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. *The Lancet Oncology*, 17(10):1453-62.
69. Prue G, Rankin J, Allen J, Gracey J, Cramp F (2006). Cancer-related fatigue: a critical appraisal. *Eur J Cancer*, 42(7):846-63.
70. Servaes P, Verhagen C, Bleijenberg G (2002). Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer*, 38(1):27-43.

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

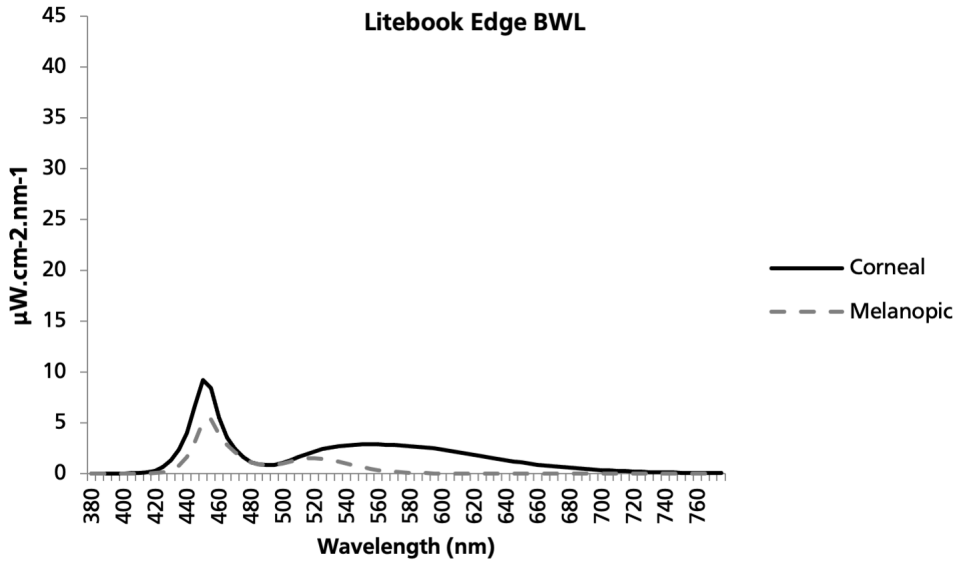


Figure A1.1. Light spectrum of the BWL Litebook Edge.

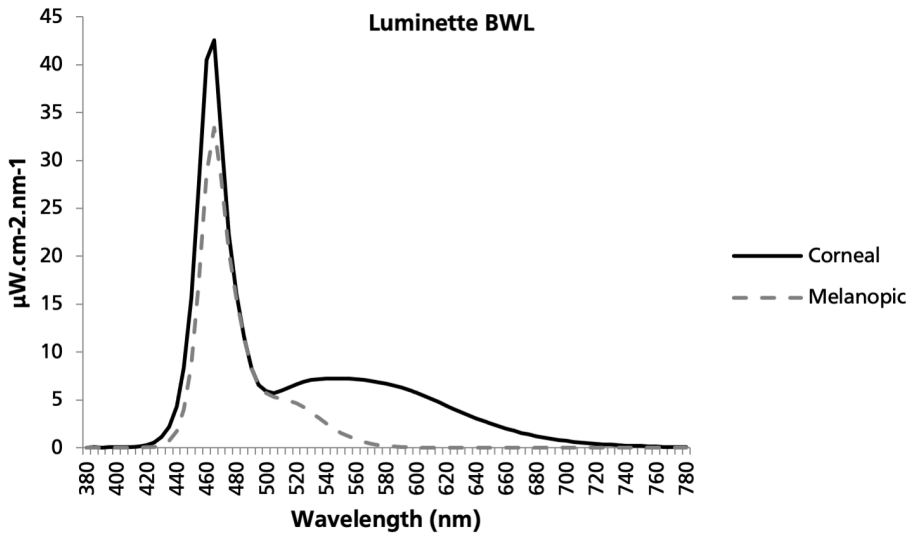


Figure A1.2. Light spectrum of the BWL Luminette glasses

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.

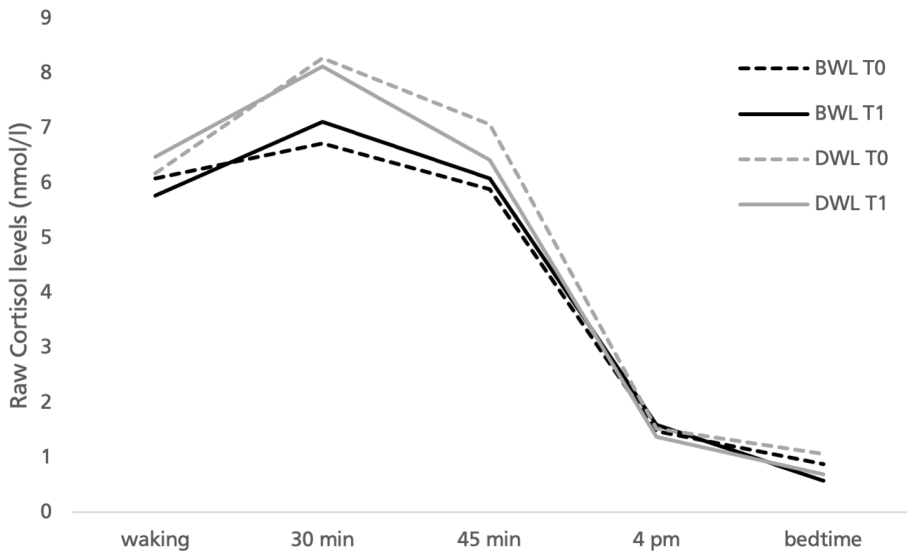


Figure A2.1. Average raw cortisol values for bright white light (BWL) and dim white light (DWL) conditions at each sampling time pre- and post-intervention.

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.

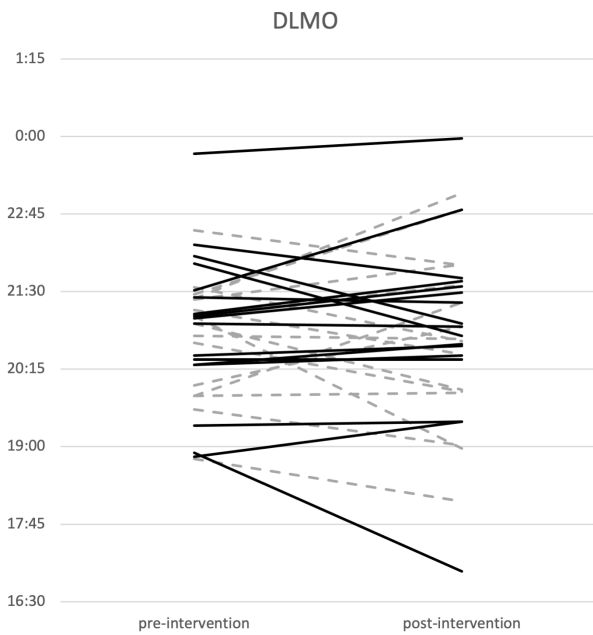


Figure A2.2. Overview of individual changes in DLMO in BWL (black) and DWL (grey) from pre- to post-intervention.

REFERENCES

1. van Faassen M, Bischoff R, Kema I P (2017). Relationship between plasma and salivary melatonin and cortisol investigated by LC-MS/MS. *Clin Chem Lab Med*, 55(9):1340-8.
2. Stalder T, Kirschbaum C, Kudielka B M, Adam E K, Pruessner J C, Wüst S, et al. (2016). Assessment of the cortisol awakening response: expert consensus guidelines. *Psychoneuroendocrinology*, 63:414-32.
3. Wust S, Wolf J, Hellhammer D H, Federenko I, Schommer N, Kirschbaum C (2000). The cortisol awakening response-normal values and confounds. *Noise and health*, 2(7):79.
4. Adam E K, Kumari M (2009). Assessing salivary cortisol in large-scale, epidemiological research. *Psychoneuroendocrinology*, 34(10):1423-36.
5. Pruessner J C, Kirschbaum C, Meinlschmid G, Hellhammer D H (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*, 28(7):916-31.
6. Danilenko K V, Verevkin E G, Antyufeev V S, Wirz-Justice A, Cajochen C (2014). The hockey-stick method to estimate evening dim light melatonin onset (DLMO) in humans. *Chronobiol Int*, 31(3):349-55.
7. Smyth N, Thorn L, Hucklebridge F, Clow A, Evans P (2016). Assessment of the cortisol awakening response: Real-time analysis and curvilinear effects of sample timing inaccuracy. *Psychoneuroendocrinology*, 74:380-6.

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]								

(Continued on next page)

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]								

(Continued on next page)

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]								

(Continued on next page)

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]								

(Continued on next page)

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]								

(Continued on next page)

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]								

(Continued on next page)

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]								

(Continued on next page)

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]								

(Continued on next page)

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]								

(Continued on next page)

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.

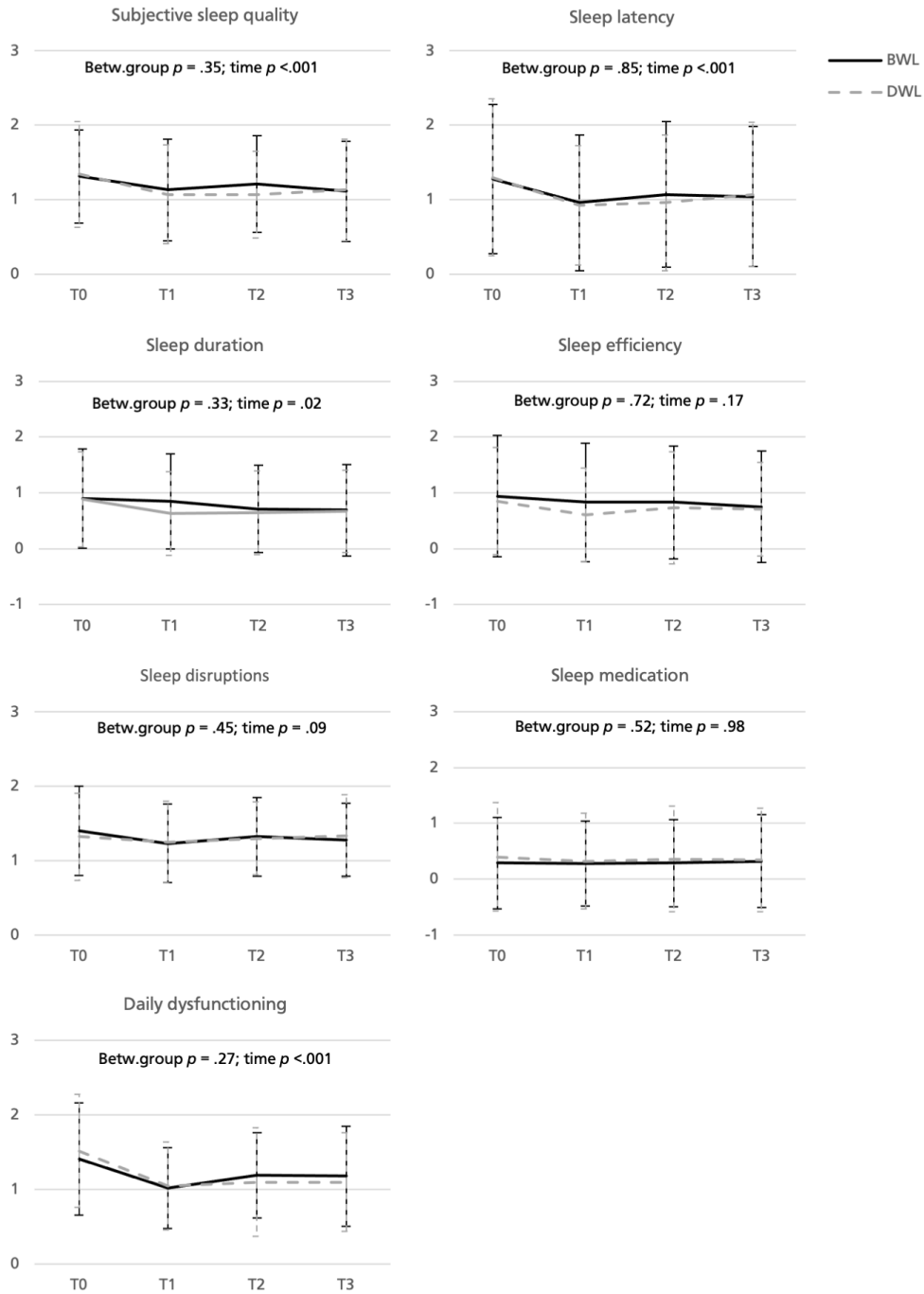


Figure A6.1 Overview of the effect of light therapy on the different subscales of the PSQI.
There were no between group differences on the different aspects of sleep quality (betw.group p-value). In the complete sample, we saw a significant improvement on subjective sleep quality, sleep latency, and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

CHAPTER 4

THE EFFICACY OF LIGHT THERAPY ON COGNITIVE FUNCTIONING OF (NON-)HODGKIN LYMPHOMA SURVIVORS WITH CANCER-RELATED FATIGUE.

Submitted

Daniëlle E.J. Starreveld
Laurien A. Daniels
Jacobien M. Kieffer
Heiddis B. Valdimarsdottir
Ellen van Berlo
Laura C. Mesland
Jessie E. de Geus
Flora E. van Leeuwen
Eveline M.A. Bleiker

ABSTRACT

Objectives

Cancer-related fatigue is associated with cancer-related cognitive impairment. Therefore, this study evaluated short- and long-term effects of light therapy on cognitive complaints and cognitive functioning in fatigued lymphoma survivors.

Methods

Fatigued Hodgkin Lymphoma (HL) and Diffuse Large B-cell Lymphoma (DLBCL) survivors (N = 166; mean survival 13 years) were randomly assigned to receive either bright white light (BWL; intervention) or dim white light (DWL, comparison) therapy for 30 minutes over 25 days. Assessments of fatigue and cognitive complaints (questionnaires) were collected at baseline, post-intervention, and at three and nine months follow-up. Cognitive functioning was assessed with neuropsychological tests at baseline and post-intervention. Differences between groups in changes over time were examined using a mixed-effect modeling approach.

Results

Over one-third of the participants showed cognitive dysfunction at baseline, specifically in verbal memory where deviant scores were observed for immediate recall in 34% and delayed recall in 27% of the participants compared to 16% in the norm population. Neither BWL nor DWL diminished cognitive complaints or improved cognitive functioning (range *p*-values .07 to .80; range effect sizes .04 to .29) in the total group of fatigued survivors nor in the subgroup suffering from cognitive dysfunction.

Conclusion

Approximately one-third of the survivors of HL and DLBCL with cancer-related fatigue experience objectively measured cognitive dysfunctioning. Light therapy does not appear to improve these complaints. Therefore, we suggest that other cognitive rehabilitation interventions should be made available to mitigate cognitive dysfunctioning in these survivors.

INTRODUCTION

Cancer-related cognitive impairment (CRCI) involves cognitive symptoms, such as impairments in short-term and working memory, attention, executive functioning and/or processing speed, reported by patients with non-central nervous system cancers[1]. CRCI includes patient-reported *cognitive complaints* and objectively measured *cognitive decline* assessed by neuropsychological tests. Cognitive complaints are reported by up to 75 percent of cancer survivors that have received chemotherapy[1]. Cognitive decline is shown in 15 to 25 percent of patients treated for breast cancer and in 16 percent of patients treated for lymphoma[2]. As cognitive complaints may also be influenced by additional psychological factors such as fatigue, anxiety, depression, and insomnia[3], this may explain the discrepancy between prevalence rates of subjectively measured cognitive complaints and objectively measured cognitive decline.

Light therapy has been suggested as an effective treatment for cancer-related fatigue. Several studies showed a decline in fatigue after 4 weeks of morning light therapy in survivors of cancer[4, 5]. Moreover, results showed improved sleep quality, sleep-wake cycles, and depression[5-8], which are also associated with CRCI. These effects might be explained by the resynchronizing effect of light on circadian rhythms via stimulation of the suprachiasmatic nucleus (SCN; the biological clock)[9].

Studies on the effect of light on cognitive functioning can be categorized into two groups. First, the effect of short-term exposure to light, i.e. light therapy on 1 or 2 days. Results showed an improvement in alertness and cognitive performance in healthy subjects[10], sleep-deprived healthy subjects[11], and healthy subjects under mental fatigue initiated by demanding tasks[12]. Secondly, a few studies investigated the effect of long-term exposure to light therapy (daily use during at least two consecutive weeks). These studies were limited to patients with dementia and mild traumatic brain injury. Results were inconclusive with some studies showing positive effects on cognitive functioning after light therapy[13-15] and some showing no effects[16, 17].

We recently conducted a double-blind, randomized controlled trial to test the efficacy of light therapy in reducing cancer-related fatigue in chronically fatigued Hodgkin lymphoma (HL) and Diffuse Large B-cell lymphoma (DLBCL) survivors. Results showed that, irrespective of the type of intervention (exposure to bright white light [BWL; intervention group] or dim white light [DWL; comparison group], reduced levels of fatigue were reported. As far as we know, studies measuring the effect of light therapy on cognitive functioning in cancer survivors are lacking. Therefore, the objective of this planned secondary analysis was to evaluate the efficacy of light therapy in diminishing cognitive complaints and improving cognitive functioning in HL and DLBCL survivors with cancer-related fatigue. It was hypothesized that light therapy would diminish cognitive complaints and improve cognitive functioning, especially for survivors who showed cognitive dysfunctioning at baseline.

METHODS

This study was a secondary analysis of a double-blind randomized controlled trial on the efficacy of light therapy on decreasing fatigue in chronically fatigued HL or DLBCL survivors. The study

design and primary results are described in detail elsewhere[18]. The study was executed in accordance with the Declaration of Helsinki and with approval from the institutional review board of the Netherlands Cancer Institute (number NL61017.031.17).

Participants

Survivors were recruited from ten hospitals in the Netherlands between September 2017 and October 2019. Participants were included if they were: (1) aged between 18 and 70 years; (2) diagnosed with HL or DLBCL 2 years before study entry; and (3) experienced moderate to severe fatigue since diagnosis or treatment. Moderate to severe fatigue was defined as a score of the general fatigue subscale of the Multidimensional Fatigue Inventory (MFI)[19] above the 75th percentile compared to age- and sex-matched cancer survivors[20] or a score of 17 or higher on the Work and Social Adjustment Scale[21]. Participants were excluded if there was a somatic cause for fatigue or a (medical) condition that could potentially compromise the effect of light therapy.

Procedure, randomization, and timing of assessments

Survivors were recruited in two separate ways: (1) via referral from their physician, or (2) by showing interest in participating in this clinical study after participation in a survey study on chronotype, sleep quality and fatigue for which they were invited by their treating physician[22]. Eligible survivors received an information brochure and sent a completed screening questionnaire and a response card indicating their interest or reasons for nonparticipation to the research team. Eligibility of interested survivors was confirmed by telephone screening after which eligible survivors received a patient information letter and informed consent.

After signing informed consent, a research assistant not involved in other study procedures randomly assigned participants to the intervention group (BWL) or control group (DWL) at a 1:1 ratio stratified on diagnosis, time since diagnosis, and gender using a minimization technique (randomization software program ALEA; FormVision, Abcoude, the Netherlands). All other members of the research team were blinded to the study arm until the participant completed the final assessment. We told participants that two intensities of light therapy were compared without mentioning the expected absence of an effect of DWL.

Assessments of fatigue and cognitive complaints via questionnaires were at baseline (T0), post-intervention (T1), 3 months post-intervention (T2), and 9 months post-intervention (T3). Neuropsychological tests were completed in person during a visit to the hospital at T0 and T1.

Intervention

Light therapy comprised of exposure to an artificial source of light, which is already widely known for seasonal affective disorder. In line with previous studies on light therapy in cancer survivors[4, 5], the first 37 randomly assigned participants used the Litebook Edge (Litebook, Ltc. Medicine Hat, Canada). This device should have exposed participants in the BWL group to blue-enriched (480 nm) white light of 10.000 lux (app. 1.500 lux at eye level) and the DWL group to blue-enriched (480 nm) white light of 10-20 lux. However, confirmatory spectral measurements indicated that the Litebook Edge exposed participants in the BWL condition to 351 lux at eye level, which is insufficient for light therapy. Therefore, the remaining 127 participants used

Luminette glasses (Lucimed SA, Villers-le-Bouillet, Belgium) for the administration of light therapy, which exposed participants to white light enriched around 468 and 570 nm of 1.500 lux (BWL) or 8 lux (DWL) at eye level. All participants, including Litebook Edge users, were included in the intention-to-treat analyses.

Light therapy was completed in the morning within 30 minutes after wakening for the duration of 30 minutes over 3,5 weeks (25 days). Participants were encouraged to engage in other activities like having breakfast or reading while completing light therapy.

Measures

Sociodemographic information was collected with a screening and baseline questionnaire. Clinical information was abstracted from patients' medical records. A *Visual Analogue Scale* (VAS-fatigue) from 0 (no fatigue) to 10 (worst imaginable fatigue) and the general fatigue subscale of the Multidimensional Fatigue Inventory (MFI)[19] were used to describe fatigue.

Cognitive complaints

Self-reported cognitive complaints were assessed with two questionnaires. The *Medical Outcomes Studies cognitive functioning* (MOS-CF6)[23] was used to assess cognitive complaints. This 6-item scale assesses memory, reasoning and thinking during the past week. Responses are given on a 6-point scale from 'always' to 'never'. The total score is the summation of all responses converted to a 0 (worst cognitive functioning) to 100 (best cognitive functioning) scale.

Eight items of the *MD Anderson Symptom Inventory* (MDASI)[24] were included to assess remembering, concentration, and interference caused by cognitive complaints in daily life. These items were rated on an 11-point scale, ranging from 0 (no complaints) to 10 (worst complaints) during the past 24 hours. Memory and concentration were based on the single items 'remembering' and 'concentration'. The interference caused by cognitive complaints was based on the average of the remaining six items.

Cognitive functioning

Objectively measured cognitive functioning was based on three neuropsychological tasks. Attention and vigilance were assessed with the *psychomotor vigilance task* (PVT)[25]. During this task, participants monitor a black computer screen and push a button when a reaction time counter starts to run on the display. A response with feedback on the reaction time appeared on the screen after pressing the button for 1 second. The time counter was presented with a random inter-stimulus interval ranging from 2 to 10 seconds. The total test time was 5 minutes. Derived variables from the PVT were response speed defined as mean 1/reaction times (1/RT; s) and the number of performance lapses (RTs ≥ 500ms).

The *15 words task*[26] was used to assess verbal learning and retention of information. During a learning phase, a list of 15 words was read aloud to the participants after which the participant was asked to recall all the remembered words. After 15 min, participants were asked for delayed recall of all remembered words and for recognition of the presented words in a list of 30 words. Two parallel versions were used in random order to limit practice effects.

Derived variables from the 15 words task were the total number of correct words during the learning phase (5 trials), free recall, and recognition.

Attention and working memory were assessed with the *digit span task*[27]. Participants listened to a sequence of numerical digits and were asked to recall the sequence in the same order (forward) or reverse order (backward). The number of digits increased from 2 to 9 (forward) or 8 (backward) until the participant was no longer able to recall two sequences with the same number of digits correctly. Derived variables from the digit span task were the total number of correctly repeated sequences (forward and backward).

Statistical analysis

Baseline characteristics of the intervention and control group were compared using independent samples t-test, Mann Whitney, Chi-square, or Fisher's Exact tests. Questionnaire scores were calculated according to published scoring algorithms. Missing values were replaced by the average score of the completed items in the same scale for each individual, provided that ≥ 50% of the items in that scale had been completed.

To evaluate the prevalence of cognitive dysfunctioning at baseline, we compared baseline scores of two neuropsychological tests to a Dutch norm population. Specifically, scores on the 15 words task were compared to sex-, age- and education-matched controls[28] and scores on the digit span task were compared to age-matched controls[27] and transformed to t-scores. A score was classified as deviant when it was at least 1 standard deviation (SD) below the mean of the general population. An individual was categorized as showing cognitive dysfunctioning when at least two subtests had a deviant score. Due to the absence of norm data for the PVT, this task was not included in this analysis.

To evaluate differences in the effect of light therapy on cognitive complaints between the intervention and control group over time (T0-T3), we used a mixed effect modelling approach with a random intercept and a restricted maximum likelihood solution. We used baseline to follow-up analysis to evaluate the effect of light therapy on cognitive functioning between groups (T0-T1). Within each mixed-effect model, the control group was the reference category. Models were adjusted for age, education level, and baseline fatigue. Additionally, models were adjusted for possible baseline differences and, in case of non-ignorable drop-out, for different patterns of missing values. Models with and without correction for baseline differences, different missing data patterns, and different covariance structures (UN, AR1, CS) were compared using the Bayesian Information Criterion (BIC)[29] and the Akaike's Information Criterion (AIC)[30]. Models with lower BIC or AIC values are considered to be better fitting models.

Differences in mean change scores over time between the treatment group and the control group were accompanied by standardized effect sizes (ES) calculated based on the mean scores and pooled standard deviation (SD): $(mean_{T1}\text{-}mean_{T0})/pooled\ SD_{T0\text{-}T1}$ or $(mean_{T3}\text{-}mean_{T1})/pooled\ SD_{T1\text{-}T3}$. Effect sizes of 0.2 were considered small, 0.5 moderate, and 0.8 large[31]. An effect size ≥ .50 was considered clinically relevant[32].

All analyses were conducted on an intention-to-treat (ITT) basis. Additionally, we performed a per-protocol analysis on data from participants who adhered to the light therapy on all 25 days; and three sensitivity analyses on data from patients who (1) showed cognitive

dysfunctioning at baseline; (2) used the Luminette glasses; (3) used light therapy during fall or winter (October to March). All statistical analyses were conducted in SPSS version 25.

RESULTS

Participants

In total, 166 participants signed informed consent and were randomly allocated to either BWL (n = 83) or DWL (n = 83). Table 1 summarizes sociodemographic, clinical and fatigue-related characteristics of the study sample. The mean age of the survivors was 45.7 years (SD = 12.2). More than half of the participants were female (60%). Almost half of the group (47%) had completed college or university.

The majority of the participants (83%) was diagnosed with HL and had received chemotherapy (93%). The mean survival was 12.9 years (SD = 9.9). Baseline levels of fatigue were high with a mean VAS-fatigue score of 6.1 (SD = 1.6) and a mean general fatigue score of 15.7 (SD = 2.7). Except for marital status, all baseline characteristics were balanced between groups.

The completion rates of the questionnaires at baseline assessment T0 (n = 165, 99%), and follow-up assessments T1 (n = 157; 95%), T2 (n = 141; 85%), and T3 (n = 142; 86%) differed between groups at T1 (DWL: 90% *v* BWL: 99%; $p = .03$). There were no differences between groups for the completion rates of the PVT at T0 (n = 159; 96%)and T1 (n = 146; 88%) and the 15 words task and digit span task at T0 (n = 164; 99%) and T1 (n = 154; 93).

Baseline cognitive functioning

Fifty-six participants (34%) showed cognitive dysfunctioning in the number of correctly remembered items during the learning phase and 45 participants (27%) during the recall phase of the 15 words task compared to 16% in the norm groups. For the digit span task, deviant scores on the total number of correctly repeated sequences were seen in 27 participants (17%), on the forward digit span task in 25 participants (15%), and on the backward digit span task in 23 participants (14%) compared to 16% in the norm groups. Overall, 53 participants (32%) had a deviant score on two or more subtests. The percentage of cognitive dysfunctioning at baseline did not differ between groups (data not shown).

Efficacy analyses

Figure 1 shows results of the intention-to-treat analyses corrected for age, education, and baseline fatigue (see appendix Table A1 for details). Correction for marital status and missing data patterns did not improve model fit, and both were omitted from the models. For cognitive complaints, results showed no differences between BWL and DWL over time ($p \geq .10$) nor an overall time effect (appendix Table A2) in both groupscombined ($p \geq .62$). Results were similar for cognitive functioning, as there were no differences between groups over time ($p \geq .07$) nor an overall time effect ($p \geq .05$; see appendix Table A2). These results suggest that cognitive complaints and cognitive functioning were unaffected by light therapy.

The per-protocol analysis including participants who adhered to the complete light therapy protocol (Appendix Table A3) and sensitivity analyses including (1) participants with cognitive

Table 1. Baseline sociodemographic, clinical, fatigue, and light therapy characteristics

	All survivors (n=166)	BWL (n=83)	DWL (n=83)	*p*	N
SOCIODEMOGRAPHIC VARIABLES					
Age, *mean years (SD)*	45.7 (12.2)	46.7 (11.9)	44.8 (12.5)	.30	166
Female, *n (%)*	99 (59.6)	50 (60.2)	49 (59.0)	.87	166
Education, *n (%)*				.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, *n (%)*	130 (78.8)	71 (85.5)	59 (72.0)	.03*	165
Part- or full-time job, *n (%)*	85 (51.5)	42 (50.6)	43 (52.4)	.81	165
CLINICAL VARIABLES					
Diagnosis, *n (%)*				.68	166
HL	138 (83.1)	70 (84.3)	68 (81.9)		
DLBCL	28 (16.9)	13 (15.7)	15 (18.1)		
Time since diagnosis, *mean years (SD)*[a]	12.9 (9.9)	13.0 (9.6)	12.9 (10.3)	.88	166
Treatments received, *n (%)*					
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 (12.1)	8 (10.1)	11 (14.1)	.45	161
Total body irradiation[b]	2 (1.2)	0 (0.0)	2 (2.5)	.24	162
Surgery (splenectomy)[b]	6 (3.7)	3 (3.7)	3 (3.8)	1.0	162
FATIGUE					
VAS-fatigue, *mean (SD)*[c]	6.1 (1.6)	5.9 (1.8)	6.3 (1.4)	.09	164
General fatigue (MFI), *mean (SD)*[d]	15.7 (2.7)	15.6 (2.9)	15.8 (2.5)	.76	165
LIGHT THERAPY CHARACTERISTICS					
Season start light therapy				.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)		
Light therapy device					
Litebook Edge	37 (22.6)	18 (21.7)	19 (23.5)		164
Luminette	127 (77.4)	65 (78.3)	62 (76.5)		164
Premature stop of light therapy	13 (7.8)	7 (8.4%)	6 (7.2)	.77	166

(Continued on next page)

Table 1. *(continued)*

	All survivors (n=166)	BWL (n=83)	DWL (n=83)	*p*	N
Days light therapy use, *mean (SD)*	22.7 (4.4)	22.5 (4.6)	22.9 (4.0)	.52	155
> 25 days[b]	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)		

BWL bright white light; **DWL** dim white light; **SD** standard deviation; **HL** Hodgkin lymphoma; **DLBCL**: Diffuse large B-cell lymphoma; **MFI** Multidimensional Fatigue inventory; **VAS** visual analogue scale; **WSAS** Work and Social Adjustment Scale

* $p < .05$

[a] Based on Mann-Whitney Test. [b] Based on Fisher's Exact Test. [c] Score range 0 - 10, with higher scores reflecting higher levels of fatigue. [d] Score range 4 - 20, with higher scores reflecting higher levels of general fatigue.

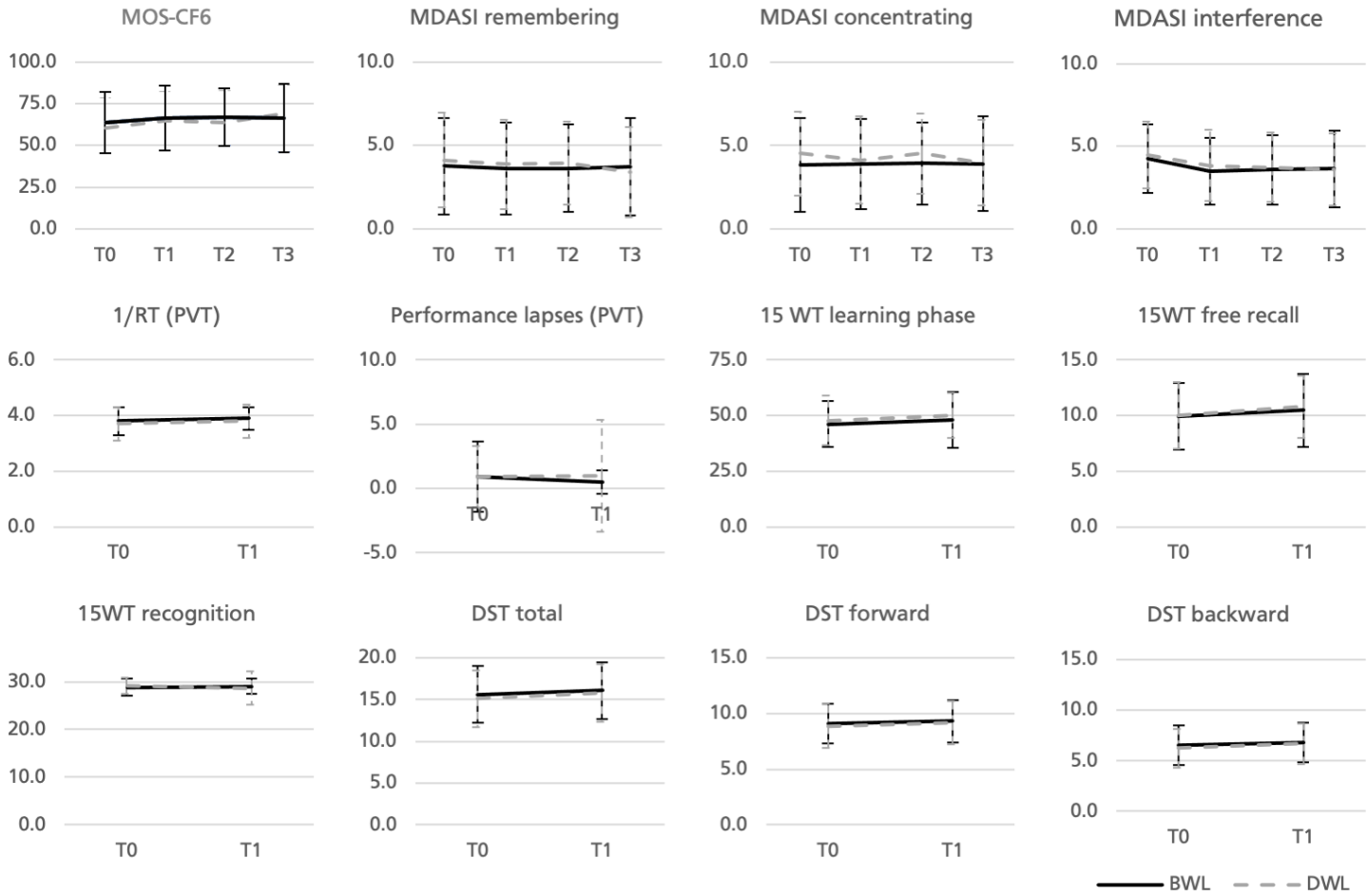
dysfunctioning at baseline (Figure 2 and Appendix Table A4); (2) participants who used the Luminette glasses (appendix Table A5), and (3) participants who used light therapy during fall or winter (appendix Table A6) did not change the conclusions from the intention-to-treat analysis.

DISCUSSION

The results of this double blind, randomized controlled trial, showed that over one-third of long-term HL and DLBCL survivors presenting with chronic cancer-related fatigue experience (objectively assessed) cognitive dysfunctioning. We previously showed that light therapy, irrespective of light intensity, improved fatigue in long-term chronically fatigued lymphoma survivors. The results of the current analyses suggest that light therapy has no effect on cognitive complaints or cognitive functioning in this group. There was no superiority for the effect of exposure to morning BWL compared to DWL on cognitive complaints or cognitive functioning, nor was there an overall improvement irrespective of exposure to BWL or DWL.

Cognitive dysfunctioning was predominantly seen for verbal memory; the prevalence was twice as high in the study population compared to the norm population. The prevalence of problems with attention and working memory was comparable to the norm population. These prevalence rates are in line with previous studies on survivors of different types of cancer[33]. Although normative data for the PVT is lacking, the PVT scores in our sample were comparable to that of the community-based sample of the Wisconsin Sleep Cohort study[34] and are therefore, likely within the normative range.

The finding that light therapy was not effective in our sample as a treatment for CRCI is in line with a previous study on light therapy in individuals with dementia[16] and a Cochrane review[17]. This Cochrane review included 11 trials comprising 499 participants. The pooled data of these studies showed no effect of light therapy on cognitive functioning assessed with a Mini-Mental State Examination. However, our findings contradict studies (not included in the


MOS-CF6
100.0
75.0
50.0
25.0
0.0
T0 T1 T2 T3
MDASI remembering
10.0
5.0
0.0
T0 T1 T2 T3
MDASI concentrating
10.0
5.0
0.0
T0 T1 T2 T3
MDASI interference
10.0
5.0
0.0
T0 T1 T2 T3
1/RT (PVT)
6.0
4.0
2.0
0.0
T0 T1
Performance lapses (PVT)
10.0
5.0
0.0
-5.0
T0 T1
15 WT learning phase
75.0
50.0
25.0
0.0
T0 T1
15WT free recall
15.0
10.0
5.0
0.0
T0 T1
15WT recognition
30.0
20.0
10.0
0.0
T0 T1
DST total
20.0
15.0
10.0
5.0
0.0
T0 T1
DST forward
15.0
10.0
5.0
0.0
T0 T1
DST backward
15.0
10.0
5.0
0.0
T0 T1
BWL
DWL

Left page
Figure 1. Effects of light therapy on cognitive complaints and cognitive functioning in participants exposed to BWL (n=83) and dim white light DWL(n=82). Exact values, p-values, and effect sizes are available in Appendix Table A1.
15WT 15 words task; **BWL** bright white light; **DST** Digit Span Task; **DWL** dim white light; **MDASI** MD Anderson Symptom Inventory; **MOS-CF6** Medical Outcomes Studies – Cognitions; **PVT** Psychomotor Vigilance Task; **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy.

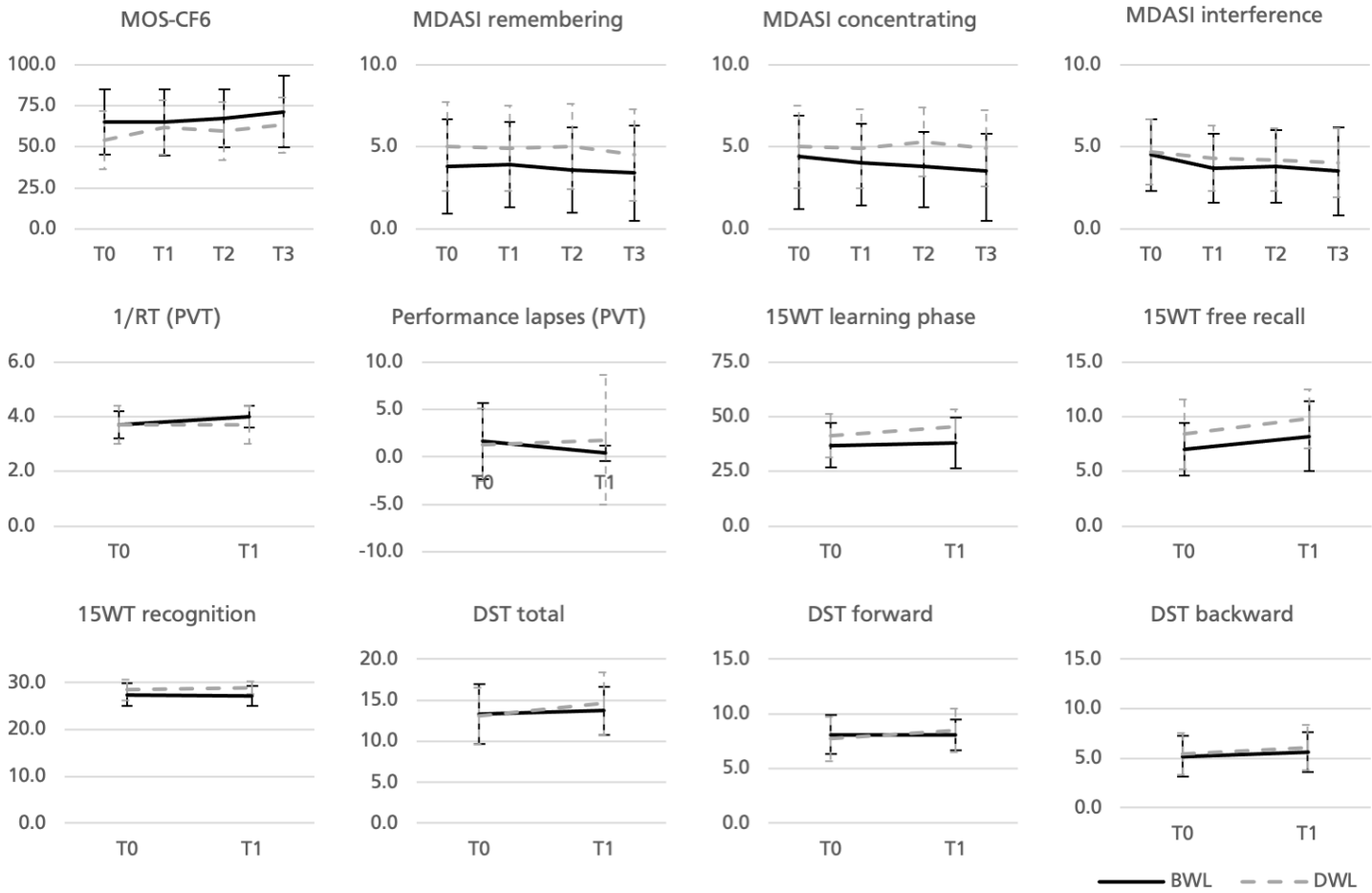
Cochrane review) that show an effect of light therapy on cognitive functioning in seniors[14] and individuals with mild traumatic brain injury[15]. These studies tested comparable light therapy protocols but used monochromatic blue light instead of the polychromatic white light used in the current study. This might explain the differences in results, as blue wavelengths are assumed responsible for the restoring effect of light therapy on the circadian rhythm[9]. However, it is reasonable to expect similar results as the light used in our study was enriched in this blue spectrum. Another study that tested light therapy in individuals with dementia[13] showed a positive effect on cognitive functioning. However, this study included a comparison between whole day bright and dim light in group care facilities for a duration of multiple years and is therefore less comparable to our study design.

Another reason for the contradicting results of the current study compared to previous studies might be related to the characteristics of our study population. The studies showing an effect of light therapy recruited seniors with or without dementia and individuals with brain traumatic brain injury[13-15]. These populations showed cognitive decline in multiple domains, while the cognitive decline in the current sample was limited to a verbal memory. Therefore, the overall cognitive decline in these populations might not be comparable.

Alternatively, the lack of an effect of light therapy on cognitive functioning in HL and DLBCL survivors might be explained by the suggested absence of a disturbed circadian rhythm in our sample. Therefore, we hypothesize that there is no causal relationship between a disturbed circadian rhythm and CRCI in long-term lymphoma survivors. Previous studies found some indications for such an association in advanced cancer patients[35] but also showed indications for different biological mechanisms, for example skeletal muscular and mitochondrial dysfunction, inflammation dysfunction, a dysregulation of cytokine activity, and central nervous system disorders[36]. Light therapy is known for its restorative effect on circadian rhythm. Consequently, a lack of an association between disturbed circadian rhythms and CRCI may explain why light therapy had no effect on cognitive complaints or cognitive functioning. It should be mentioned that alternative mechanism of action, for example stimulation of mood regulation areas, have also been reported for light therapy.

Study limitations

The current study had several strengths, including a randomized controlled double-blind design with a large sample size. However, there are also some limitations. First, as this study described a secondary analysis, participants were not recruited based on cognitive dysfunctioning. Whereas all suffered from cancer related fatigue, only over one-third of the current sample experienced cognitive dysfunctioning. Therefore, we cannot rule out that there was insufficient room for improvement in the total group. However, the sensitivity analysis in survivors who


MOS-CF6
100.0
75.0
50.0
25.0
0.0
T0 T1 T2 T3
MDASI remembering
10.0
5.0
0.0
T0 T1 T2 T3
MDASI concentrating
10.0
5.0
0.0
T0 T1 T2 T3
MDASI interference
10.0
5.0
0.0
T0 T1 T2 T3
1/RT (PVT)
6.0
4.0
2.0
0.0
T0 T1
Performance lapses (PVT)
10.0
5.0
0.0
-5.0
-10.0
T0 T1
15WT learning phase
75.0
50.0
25.0
0.0
T0 T1
15WT free recall
15.0
10.0
5.0
0.0
T0 T1
15WT recognition
30.0
20.0
10.0
0.0
T0 T1
DST total
20.0
15.0
10.0
5.0
0.0
T0 T1
DST forward
15.0
10.0
5.0
0.0
T0 T1
DST backward
15.0
10.0
5.0
0.0
T0 T1
BWL
DWL

Left page
Figure 2. Effects of light therapy on cognitive complaints and cognitive functioning in participants who showed cognitive dysfunctioning at baseline exposed to BWL (n=25) or DWL (n=28). Exact values, p-values, and effect sizes are available in Appendix Table A4.
15WT 15 words task; **BWL** bright white light; **DST** Digit Span Task; **DWL** dim white light; **MDASI** MD Anderson Symptom Inventory; **MOS-CF6** Medical Outcomes Studies – Cognitions; **PVT** Psychomotor Vigilance Task; **T0** baseline; **T1** post intervention; **T2** 3 months after light therapy; **T3** 9 months after light therapy.

experienced cognitive dysfunctioning showed similar results to the complete sample but suffered from insufficient power to detect significant effects. Second, the PVT was originally developed for studies investigating the influence of sleep deprivation or circadian rhythms on sustained attention[25]. Sustained attention shows a circadian rhythm with the highest level of alertness between 10:00 and 14:00 hour[37]. To account for this rhythm, the PVT is normally assessed on multiple time points during the day. We assessed the PVT only once at both measurements points. To limit the effect of the circadian rhythm on cognitive functioning, the neuropsychological tasks were completed at similar times at pre- and post-intervention. A third possible limitation of the study is that the sample was highly educated.

Clinical implications

Over one-third of the survivors of HL and DLBCL showed cognitive dysfunctioning, predominantly in verbal memory. The experience of cognitive dysfunctioning can be very disturbing for survivors and can lead to problems in daily life, for example in people's professional life. Therefore, early identification of those at risk, for example via the Amsterdam Cognition Scan[38], is advised and rehabilitation interventions (e.g. internet-based cognitive rehabilitation[39]) should be available for these survivors.

Conclusions

This study showed that approximately one third of the HL and DLBCL survivors, with an average time since diagnosis of 13 years, experience objectively defined cognitive dysfunctioning. This was specifically seen for the verbal memory domain. Cognitive functioning on attention and working memory was comparable to the norm population. Although previous studies suggested that light therapy improved cognitive functioning in senior individuals, and individuals with dementia and mild traumatic brain injury, the current results suggest that light therapy does not improve cognitive functioning in survivors of HL and DLBCL. Sufficiently powered studies in survivors with confirmed cognitive dysfunctioning are necessary to support our conclusions.

REFERENCES

1. Wefel J S, Vardy J, Ahles T, Schagen S B (2011). International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*, 12(7):703-8.
2. Wouters H, Baars J W, Schagen S B (2016). Neurocognitive function of lymphoma patients after treatment with chemotherapy. *Acta Oncol*, 55(9-10):1121-5.
3. Ganz P A, Kwan L, Castellon S A, Oppenheim A, Bower J E, Silverman D H, et al. (2013). Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. *J Natl Cancer Inst*, 105:791-801.
4. Redd W H, Valdimarsdottir H, Wu L M, Winkel G, Byrne E E, Beltre M A, et al. (2014). Systematic light exposure in the treatment of cancer-related fatigue: a preliminary study. *Psychooncology*, 23(12):1431-4.
5. Johnson J A, Garland S N, Carlson L E, Savard J, Simpson J S A, Ancoli-Israel S, et al. (2017). Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. *J Cancer Surviv*, 12:1-10.
6. Wu L M, Amidi A, Valdimarsdottir H, Ancoli-Israel S, Liu L, Winkel G, et al. (2018). The effect of systematic light exposure on sleep in a mixed group of fatigued cancer survivors. *J Clin Sleep Med*, 14(01):31-9.
7. Fox R S, Baik S H, McGinty H, Garcia S F, Reid K J, Bovbjerg K, et al. (2020). Feasibility and Preliminary Efficacy of a Bright Light Intervention in Ovarian and Endometrial Cancer Survivors. *Int J Behav Med*:1-13.
8. Garland S N, Johnson J A, Carlson L E, Rash J A, Savard J, Campbell T S (2020). Light therapy for insomnia symptoms in fatigued cancer survivors: a secondary analysis of a randomized controlled trial. *J Psychosoc Oncol*, 2(3):e27.
9. Lucas R J, Peirson S N, Berson D M, Brown T M, Cooper H M, Czeisler C A, et al. (2014). Measuring and using light in the melanopsin age. *Trends Neurosci*, 37(1):1-9.
10. Huiberts L, Smolders K, De Kort Y (2017). Seasonal and time-of-day variations in acute non-image forming effects of illuminance level on performance, physiology, and subjective well-being. *Chronobiol Int*, 34(7):827-44.
11. Gabel V, Maire M, Reichert C F, Chellappa S L, Schmidt C, Hommes V, et al. (2015). Dawn simulation light impacts on different cognitive domains under sleep restriction. *Behav Brain Res*, 281:258-66.
12. Smolders K C, de Kort Y A (2014). Bright light and mental fatigue: Effects on alertness, vitality, performance and physiological arousal. *J Environ Psychol*, 39:77-91.
13. Riemersma-Van Der Lek R F, Swaab D F, Twisk J, Hol E M, Hoogendijk W J, Van Someren E J (2008). Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA*, 299(22):2642-55.
14. Royer M, Ballentine N H, Eslinger P J, Houser K, Mistrick R, Behr R, et al. (2012). Light therapy for seniors in long term care. *J Am Med Dir Assoc*, 13(2):100-2.
15. Killgore W D, Vanuk J R, Shane B R, Weber M, Bajaj S (2020). A randomized, double-blind, placebo-controlled trial of blue wavelength light exposure on sleep and recovery of brain structure, function, and cognition following mild traumatic brain injury. *Neurobiol Dis*, 134:104679.
16. Burns A, Allen H, Tomenson B, Duignan D, Byrne J (2009). Bright light therapy for agitation in dementia: a randomized controlled trial. *Int Psychogeriatr*, 21(4):711.
17. Forbes D, Blake C M, Thiessen E J, Peacock S, Hawranik P (2014). Light therapy for improving cognition, activities of daily living, sleep, challenging behaviour, and psychiatric disturbances in dementia. *Cochrane Database Syst Rev*, (2).
18. **Starreveld, DEJ**, Daniels, LA, Kieffer, JM, Valdimarsdottir, HB, van Someren, E, de Geus, JL, Janus CPM, van Spronsen, DJ, Petersen, EJ, Marijt, EWA, de Jongh, E, Zijlstra, JM, Böhmer, LH, Houmes, M, Kersten, MJ, Habers, GEA, Redd, WH, Lutgendorf, S, Ancoli-Israel, S, van Leeuwen FE, and Bleiker, EMA. Efficacy of Light Therapy for Cancer Related Fatigue in (non-)Hodgkin Lymphoma Survivors: Results of a Randomized Controlled Trial. *Cancers*, 2021; 13(19): 4948
19. Smets E, Garssen B, Bonke B d, De Haes J (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 39(3):315-25.
20. Kuhnt S, Ernst J, Singer S, Rueffer J U, Kortmann R-D, Stolzenburg J, et al. (2009). Fatigue in cancer survivors: prevalence and correlates. *Oncol Res Treat*, 32(6):312-7.

21. Mundt J C, Marks I M, Shear M K, Greist J M (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br J Psychiatry*, 180(5):461-4.
22. Starreveld D E J, Habers G E A, Valdimarsdottir H B, Kessels R, Daniëls L A, van Leeuwen F E, et al. (2021). Cancer-related Fatigue in Relation to Chronotype and Sleep Quality in (Non-) Hodgkin Lymphoma Survivors. *J Biol Rhythms*:0748730420987327.
23. Stewart A L, Ware J E, Sherbourne C D, Wells K B (1992). Psychological distress/well-being and cognitive functioning measures, in Stewart AL, Ware JE (eds): Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, NC: Duke University. p. 102-42.
24. Cleeland C S, Mendoza T R, Wang X S, Chou C, Harle M T, Morrissey M, et al. (2000). Assessing symptom distress in cancer patients. *Cancer*, 89(7):1634-46.
25. Dinges D F, Powell J W (1985). Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Methods*, 17(6):652-5.
26. Saan R, Deelman B (1986). De 15-woordentest A en B (een voorlopige handleiding). Groningen: Afdeling Neuropsychologie, AZG.
27. Wechsler D. WAIS-III: Nederlandse bewerking Wechsler adult intelligence scale—Derde Editie. Lisse: Swets & Zeitlinger BV; 2000.
28. Schmand B, Houx P, de Koning I (2012). Normen van psychologische tests voor gebruik in de klinische neuropsychologie. *Sectie Neuropsychologie Nederlands Instituut van Psychologen*.
29. Schwarz G (1978). Estimating the dimension of a model. *The Annals of Statistics*, 6(2):461-4.
30. Akaike H (1998). Information theory and an extension of the maximum likelihood principle, in Parzen E, Tanabe K, Kitagawa G (eds): Selected papers of hirotugu akaike. New Yotk, NY: Springer. p. 199-213.
31. Cohen J Statistical power analysis for the behavioral sciences 2ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
32. Norman G R, Sloan J A, Wyrwich K W (2003). Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*:582-92.
33. Ahles T A, Saykin A J, Furstenberg C T, Cole B, Mott L A, Skalla K, et al. (2002). Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol*, 20(2):485-93.
34. Kim H, Dinges D F, Young T (2007). Sleep-disordered breathing and psychomotor vigilance in a community-based sample. *Sleep*, 30(10):1309-16.
35. Innominato P F, Mormont M-C, Rich T A, Waterhouse J, Lévi F A, Bjarnason G A (2009). Circadian disruption, fatigue, and anorexia clustering in advanced cancer patients: implications for innovative therapeutic approaches. *Integr Cancer Ther*, 8(4):361-70.
36. Lange M, Joly F, Vardy J, Ahles T, Dubois M, Tron L, et al. (2019). Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol*, 30(12):1925-40.
37. Valdez P (2019). Focus: Attention Science: Circadian Rhythms in Attention. *Yale J Biol Med*, 92(1):81.
38. Feenstra H E, Murre J M, Vermeulen I E, Kieffer J M, Schagen S B (2018). Reliability and validity of a self-administered tool for online neuropsychological testing: The Amsterdam Cognition Scan. *J Clin Exp Neuropsychol*, 40(3):253-73.
39. Klaver K, Duijts S, Geusgens C, Aarts M, Ponds R, van der Beek A, et al. (2020). Internet-based cognitive rehabilitation for WORking Cancer survivors (i-WORC): study protocol of a randomized controlled trial. *Trials*, 21(1): 1-12

APPENDIX

Table A1. Mean values and standard deviations per time-point and between-group differences for the mixed-effects models of the outcome measurements.

	T0[a]		T1[a]	
	n	M [SD]	n	M [SD]
COGNITIVE COMPLAINTS				
MOS-CF6				
BWL	83	63.8 [18.2]	82	66.4 [19.5]
DWL[c]	82	60.5 [17.9]	75	64.7 [17.7]
MDASI remembering				
BWL	83	3.8 [2.9]	82	3.6 [2.8]
DWL[c]	82	4.1 [2.8]	75	3.9 [2.7]
MDASI concentrating				
BWL	83	3.8 [2.8]	82	3.9 [2.7]
DWL[c]	82	4.5 [2.5]	75	4.1 [2.6]
MDASI interference				
BWL	83	4.3 [2.1]	82	3.5 [2.0]
DWL[c]	82	4.5 [2.0]	74	3.8 [2.2]
COGNITIVE FUNCTIONING				
1/RT (PVT)[d]				
BWL	80	3.8 [0.5]	74	3.9 [0.4]
DWL[c]	78	3.7 [0.6]	71	3.8 [0.6]
Performance lapses (PVT)[d]				
BWL	80	0.9 [2.7]	74	0.5 [0.9]
DWL[c]	78	0.9 [2.4]	71	1.0 [4.3]
No. correct items learning phase (15WT)				
BWL	83	46.2 [10.4]	79	48.1 [12.6]
DWL[c]	81	47.7 [11.1]	75	50.0 [10.0]
No. correct items free recall (15WT)				
BWL	83	10.0 [3.0]	79	10.5 [3.3]
DWL[c]	81	10.0 [3.0]	75	10.8 [2.8]
No. correct items recognition (15WT)				
BWL	83	28.8 [1.8]	79	29.0 [1.6]
DWL[c]	80	29.1 [1.7]	75	28.7 [3.5]

T2[a]		T3[a]		Linear time effect T0-T3			ES[b]	
n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
72	66.9 [17.2]	73	66.4 [20.4]	-0.41	0.26	.12	0.06	0.19
68	63.8 [18.9]	69	69.3 [16.7]					
72	3.6 [2.6]	73	3.7 [2.9]	0.06	0.04	.10	0.03	0.18
69	4.0 [2.5]	69	3.4 [2.7]					
72	3.9 [2.5]	73	3.9 [2.8]	0.03	0.04	.39	0.17	0.02
69	4.5 [2.4]	69	4.0 [2.6]					
72	3.6 [2.1]	73	3.7 [2.3]	0.03	0.03	.29	0.08	0.19
69	3.7 [2.1]	69	3.6 [2.2]					
				Between-group difference T0-T1				
	N/A		N/A	0.06	0.08	.48	0.10	N/A
	N/A		N/A					
	N/A		N/A	-0.65	0.49	.19	0.18	N/A
	N/A		N/A					
	N/A		N/A	-0.69	1.25	.58	0.06	N/A
	N/A		N/A					
	N/A		N/A	-0.32	0.37	.39	0.10	N/A
	N/A		N/A					
	N/A		N/A	0.83	0.46	.07	0.27	N/A
	N/A		N/A					

(Continued on next page)

Table A1. *(continued)*

	T0[a]		T1[a]	
	n	**M [SD]**	**n**	**M [SD]**
No. correct items digit span task				
BWL	83	15.6 [3.4]	79	16.1 [3.4]
DWL[c]	81	15.1 [3.4]	75	15.8 [3.5]
Forward digit span task				
BWL	83	9.1 [1.8]	79	9.3 [1.9]
DWL[c]	81	8.9 [2.0]	75	9.2 [1.9]
Backward digit span task				
BWL	83	6.5 [1.9]	79	6.8 [2.0]
DWL[c]	81	6.2 [1.9]	75	6.7 [2.0]

Raw means and standard deviations are reported.
BWL Bright white light; **DWL** Dim white light; **MDASI** MD Anderson Symptom Inventory; **MOS-CF6** Medical Outcomes Studies – Cognitions.
[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 mean scores and pooled standard deviation (SD): ($mean_{T1}$-$mean_{T0}$)/pooled $SD_{T0\text{-}T1}$ or ($mean_{T3}$-$mean_{T1}$)/pooled $SD_{T1\text{-}T3}$; small 0.2, moderate 0.5, large 0.8. [c] DWL is the reference group. [d] 1 case excluded because of influential outlier.

	T2[a]		T3[a]		Between-group difference T0-T1			ES[b]	
	n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
		N/A		N/A	-0.38	0.43	.38	0.12	N/A
		N/A		N/A					
		N/A		N/A	-0.08	0.31	.80	0.07	N/A
		N/A		N/A					
		N/A		N/A	-0.27	0.24	.26	0.14	N/A
		N/A		N/A					

Table A2. Mean values and standard deviations per time-point and linear time effects of the outcome measurements for all participants.

	T0[a]		T1[a]	
	n	M [SD]	n	M [SD]
COGNITIVE COMPLAINTS				
MOS-CF6	165	62.2 [18.1]	157	65.6 [18.6]
MDASI remembering	165	4.0 [2.9]	157	3.7 [2.7]
MDASI concentrating	165	4.2 [2.7]	157	4.0 [2.7]
MDASI interference	165	4.4 [2.0]	156	3.7 [2.1]
COGNITIVE FUNCTIONING				
Reaction time (PVT)[c]	158	3.8 [0.5]	145	3.9 [0.5]
Performance lapses (PVT)[c]	158	0.9 [2.6]	145	0.7 [3.1]
No. correct items learning phase (15WT)	164	46.9 [10.7]	154	49.0 [11.4]
No. correct items free recall (15WT)	164	10.0 [3.0]	165	10.6 [3.1]
No. correct items recognition (15WT)	163	29.0 [1.7]	154	28.9 [2.7]
No. correct items digit span task	164	15.3 [3.4]	154	15.9 [3.4]
Forward digit span task	164	9.0 [1.9]	154	9.2 [1.9]
Backward digit span task	164	6.4 [1.9]	154	6.7 [2.0]

Raw means and standard deviations are reported.
15WT 15 words task; **MDASI** MD Anderson Symptom Inventory; **MOS-CF6** Medical Outcomes Studies – Cognitions; **PVT** Psychomotor Vigilance Task.
[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 mean scores and pooled standard deviation (SD): ($mean_{T1}$-$mean_{T0}$)/pooled $SD_{T0\text{-}T1}$ or ($mean_{T3}$-$mean_{T1}$)/pooled $SD_{T1\text{-}T3}$; small 0.2, moderate 0.5, large 0.8. [c] One case excluded because of influential outlier.

	T2[a]		T3[a]		Linear time effect			ES[b]	
	n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
	140	65.4 [18.0]	142	67.8 [18.7]	0.09	0.72	.90	0.18	0.10
	141	3.8 [2.6]	142	3.6 [2.8]	-0.05	0.11	.66	0.08	0.06
	141	4.2 [2.5]	142	3.9 [2.7]	0.03	0.10	.77	0.07	0.01
	141	3.7 [2.1]	142	3.6 [2.2]	0.04	0.07	.62	0.34	0.01
		N/A		N/A	-0.42	0.22	.06	0.14	N/A
		N/A		N/A	0.43	1.33	.74	0.06	N/A
		N/A		N/A	4.86	3.41	.16	0.19	N/A
		N/A		N/A	-0.27	1.00	.79	0.20	N/A
		N/A		N/A	0.19	1.26	.88	0.05	N/A
		N/A		N/A	1.39	1.16	.23	0.20	N/A
		N/A		N/A	0.07	0.85	.93	0.14	N/A
		N/A		N/A	1.32	0.67	.05	0.20	N/A

Table A3. Mean values and standard deviations per time-point and between-group differences for the mixed-effects models of the outcome measurements for participants who used light therapy on at least 25 days.

	T0[a]		T1[a]	
	n	M [SD]	n	M [SD]
COGNITIVE COMPLAINTS				
MOS-CF6				
BWL	33	62.4 [17.5]	33	68.2 [19.6]
DWL[c]	28	61.5 [15.6]	28	64.6 [19.2]
MDASI remembering				
BWL	33	4.3 [3.0]	33	3.7 [3.0]
DWL[c]	28	3.8 [3.0]	28	3.6 [3.0]
MDASI concentrating				
BWL	33	4.3 [2.8]	33	3.7 [2.9]
DWL[c]	28	4.3 [2.7]	28	3.9 [2.8]
MDASI interference				
BWL	33	4.5 [1.9]	33	3.8 [1.9]
DWL[c]	28	4.7 [1.8]	27	4.1 [2.1]
COGNITIVE FUNCTIONING				
1/RT (PVT)[d]				
BWL	32	3.7 [0.5]	30	3.9 [0.4]
DWL[c]	28	3.8 [0.6]	28	3.8 [0.7]
Performance lapses (PVT)[d]				
BWL	32	1.4 [3.5]	30	0.4 [0.8]
DWL[c]	28	1.1 [3.0]	28	1.9 [6.8]
No. correct items learning phase (15WT)				
BWL	33	42.6 [11.0]	33	43.7 [11.9]
DWL[c]	28	46.2 [13.7]	28	50.0 [12.2]
No. correct items free recall (15WT)				
BWL	33	8.8 [3.1]	33	9.2 [3.3]
DWL[c]	28	9.5 [3.5]	28	10.3 [3.0]
No. correct items recognition (15WT)				
BWL	33	28.4 [2.0]	33	28.4 [2.0]
DWL[c]	28	29.2 [1.4]	28	29.4 [1.2]

T2[a]		T3[a]		Linear time effect T0-T3			ES[b]	
n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
31	66.2 [17.7]	31	64.9 [22.2]	-0.37	0.46	.42	0.14	0.30
26	63.8 [21.4]	27	68.0 [19.6]					
31	3.5 [2.7]	31	3.9 [3.0]	-0.04	0.05	.47	0.16	0.04
28	4.0 [3.2]	27	3.7 [3.1]					
31	4.1 [2.5]	31	4.1 [2.8]	-0.02	0.06	.69	0.10	0.04
26	4.3 [2.8]	27	4.0 [3.0]					
31	4.0 [2.2]	31	3.8 [2.3]	0.02	0.05	.64	0.06	0.11
26	3.5 [2.1]	27	3.8 [2.3]					
				Between-group difference T0-T1				
	N/A		N/A	0.23	0.16	.14	0.42	N/A
	N/A		N/A					
	N/A		N/A	-1.72	1.10	.12	0.43	N/A
	N/A		N/A					
	N/A		N/A	-2.65	2.09	.21	0.22	N/A
	N/A		N/A					
	N/A		N/A	-0.54	0.63	.40	0.12	N/A
	N/A		N/A					
	N/A		N/A	-0.11	0.48	.82	0.12	N/A
	N/A		N/A					

(Continued on next page)

Table A3. *(continued)*

	T0[a]		T1[a]	
	n	**M [SD]**	**n**	**M [SD]**
No. correct items digit span task				
BWL	33	14.8 [3.6]	33	15.7 [3.1]
DWL[c]	28	14.9 [4.1]	28	15.1 [3.9]
Forward digit span task				
BWL	33	8.7 [1.8]	33	9.0 [1.7]
DWL[c]	28	8.6 [2.4]	28	8.7 [2.1]
Backward digit span task				
BWL	33	6.2 [2.0]	33	6.6 [2.0]
DWL[c]	28	6.2 [2.2]	28	6.4 [2.2]

Raw means and standard deviations are reported.
BWL Bright white light; **DWL** Dim white light; **MDASI** MD Anderson Symptom Inventory; **MOS-CF6** Medical Outcomes Studies – Cognitions.
[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 mean scores and pooled standard deviation (SD): $(mean_{T1}-mean_{T0})$/pooled SD_{T0-T1} or $(mean_{T3}-mean_{T1})$/pooled SD_{T1-T3}; small 0.2, moderate 0.5, large 0.8. [c] DWL is the reference group. [d] 1 case excluded because of influential outlier.

	T2[a]		T3[a]		Between-group difference T0-T1			ES[b]	
	n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
		N/A		N/A	0.41	0.68	.55	0.17	N/A
		N/A		N/A					
		N/A		N/A	0.22	0.54	.69	0.15	N/A
		N/A		N/A					
		N/A		N/A	0.19	0.34	.58	0.15	N/A
		N/A		N/A					

Table A4: Mean values and standard deviations per time-point and between-group differences for the mixed-effects models of the outcome measurements for participants showed deviant cognitive functioning on baseline.

	T0[a]		T1[a]	
	n	M [SD]	n	M [SD]
COGNITIVE COMPLAINTS				
MOS-CF6				
BWL	25	65.0 [19.9]	24	65.0 [20.1]
DWL[c]	28	54.0 [17.6]	27	61.9 [16.5]
MDASI remembering				
BWL	25	3.8 [2.9]	24	3.9 [2.6]
DWL[c]	28	5.0 [2.7]	27	4.9 [2.6]
MDASI concentrating				
BWL	25	4.4 [3.2]	24	4.0 [2.6]
DWL[c]	28	5.0 [2.5]	27	4.9 [2.4]
MDASI interference				
BWL	25	4.5 [2.2]	24	3.7 [2.1]
DWL[c]	28	4.7 [2.0]	27	4.3 [2.0]
COGNITIVE FUNCTIONING				
1/RT (PVT)[d]				
BWL	25	3.7 [0.5]	23	4.0 [0.4]
DWL[c]	28	3.7 [0.7]	28	3.7 [0.7]
Performance lapses (PVT)[d]				
BWL	25	1.7 [4.0]	23	0.4 [0.8]
DWL[c]	28	1.3 [3.8]	28	1.8 [6.8]
No. correct items learning phase (15WT)				
BWL	25	36.8 [10.1]	24	37.9 [11.5]
DWL[c]	28	41.3 [10.1]	28	45.6 [7.7]
No. correct items free recall (15WT)				
BWL	25	7.0 [2.4]	24	8.2 [3.2]
DWL[c]	28	8.4 [3.2]	28	9.8 [2.7]
No. correct items recognition (15WT)				
BWL	25	27.4 [2.4]	24	27.1 [2.1]
DWL[c]	28	28.4 [2.3]	28	28.9 [1.4]

	T2[a]		T3[a]		Linear time effect T0-T3			ES[b]	
	n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
	20	67.3 [17.5]	21	71.3 [21.9]	0.46	0.41	.27	0.39	0.33
	25	59.6 [17.5]	26	63.2 [16.7]					
	20	3.6 [2.6]	21	3.4 [2.9]	-0.03	0.07	.65	0.04	0.07
	25	5.0 [2.6]	26	4.5 [2.8]					
	20	3.8 [2.5]	21	3.5 [3.0]	-0.14	0.07	.05	0.15	0.24
	25	5.3 [2.1]	26	4.9 [2.3]					
	20	3.8 [2.2]	21	3.5 [2.7]	-0.07	0.06	.20	0.28	0.04
	25	4.2 [1.9]	26	4.0 [2.1]					
					Between-group difference T0-T1				
		N/A		N/A	0.25	0.20	.20	0.43	N/A
		N/A		N/A					
		N/A		N/A	-2.26	1.28	.09	0.41	N/A
		N/A		N/A					
		N/A		N/A	-3.28	2.42	.18	0.32	N/A
		N/A		N/A					
		N/A		N/A	-0.20	0.70	.78	0.09	N/A
		N/A		N/A					
		N/A		N/A	0.27	0.55	.62	0.11	N/A
		N/A		N/A					

(Continued on next page)

Table A4. *(continued)*

	T0[a]		T1[a]	
	n	**M [SD]**	**n**	**M [SD]**
No. correct items digit span task				
BWL	25	13.3 [3.7]	24	13.7 [2.9]
DWL[c]	28	13.1 [3.4]	28	14.6 [3.8]
Forward digit span task				
BWL	25	8.1 [1.8]	24	8.1 [1.4]
DWL[c]	28	7.7 [2.0]	28	8.5 [2.0]
Backward digit span task				
BWL	25	5.2 [2.1]	24	5.6 [2.0]
DWL[c]	28	5.4 [2.1]	28	6.1 [2.3]

Raw means and standard deviations are reported.
BWL Bright white light; **DWL** Dim white light; **MDASI** MD Anderson Symptom Inventory; **MOS-CF6** Medical Outcomes Studies – Cognitions.
[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 mean scores and pooled standard deviation (SD): $(mean_{T1}-mean_{T0})/pooled\ SD_{T0\text{-}T1}$ or $(mean_{T3}-mean_{T1})/pooled\ SD_{T1\text{-}T3}$; small 0.2, moderate 0.5, large 0.8. [c] DWL is the reference group. [d] 1 case excluded because of influential outlier.

	T2[a]		T3[a]		Between-group difference T0-T1			ES[b]	
	n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
		N/A		N/A	-0.93	0.76	.22	0.30	N/A
		N/A		N/A					
		N/A		N/A	-0.72	0.57	.22	0.40	N/A
		N/A		N/A					
		N/A		N/A	-0.21	0.40	.60	0.15	N/A
		N/A		N/A					

Table A5. Mean values and standard deviations per time-point and between-group differences for the mixed-effects models of the outcome measurements for Luminette Glasses users only.

	T0[a]		T1[a]	
	n	M [SD]	n	M [SD]
COGNITIVE COMPLAINTS				
MOS-CF6				
BWL	65	62.9 [17.8]	64	65.9 [19.4]
DWL[c]	62	60.6 [16.1]	58	64.0 [16.3]
MDASI remembering				
BWL	65	3.9 [2.8]	64	3.8 [2.7]
DWL[c]	62	4.3 [2.8]	58	3.8 [2.6]
MDASI concentrating				
BWL	65	4.0 [2.7]	64	4.1 [2.7]
DWL[c]	62	4.6 [2.4]	58	4.2 [2.5]
MDASI interference				
BWL	65	4.4 [1.9]	64	3.6 [1.9]
DWL[c]	62	4.5 [1.9]	57	3.9 [2.0]
COGNITIVE FUNCTIONING				
1/RT (PVT)[d]				
BWL	62	3.8 [0.5]	57	3.9 [0.4]
DWL[c]	59	3.7 [0.5]	54	3.8 [0.6]
Performance lapses (PVT)[d]				
BWL	62	1.1 [3.0]	57	0.5 [0.9]
DWL[c]	59	0.8 [2.2]	54	1.0 [4.9]
No. correct items learning phase (15WT)				
BWL	65	46.6 [10.3]	61	48.7 [11.9]
DWL[c]	62	48.6 [11.1]	57	49.8 [10.4]
No. correct items free recall (15WT)				
BWL	65	10.2 [2.9]	61	10.7 [3.0]
DWL[c]	62	10.3 [3.0]	57	11.0 [2.7]
No. correct items recognition (15WT)				
BWL	65	29.0 [1.7]	61	29.1 [1.6]
DWL[c]	61	29.3 [1.1]	57	28.7 [4.0]
No. correct items digit span task				
BWL	65	15.5 [3.5]	61	16.2 [3.6]
DWL[c]	62	15.1 [3.6]	57	15.9 [3.7]

	T2[a]		T3[a]		Linear time effect T0-T3			ES[b]	
	n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
	55	65.5 [16.6]	57	65.2 [20.5]	-0.49	0.30	.11	0.02	0.29
	52	61.9 [17.3]	54	69.6 [15.7]					
	55	3.6 [2.5]	57	3.8 [2.9]	0.05	0.04	.30	0.08	0.09
	53	4.0 [2.3]	54	3.6 [2.6]					
	55	4.0 [2.3]	57	4.1 [2.7]	0.04	0.04	.42	0.19	0.02
	53	4.5 [2.2]	54	4.0 [2.5]					
	55	3.7 [1.9]	57	3.7 [2.1]	0.03	0.03	.28	0.11	0.25
	53	3.8 [1.9]	54	3.5 [2.0]					
					Between-group difference T0-T1				
		N/A		N/A	0.06	0.09	.49	0.15	N/A
		N/A		N/A					
		N/A		N/A	-0.84	0.61	.17	0.29	N/A
		N/A		N/A					
		N/A		N/A	-0.83	1.33	.54	0.07	N/A
		N/A		N/A					
		N/A		N/A	-0.23	0.41	.57	0.09	N/A
		N/A		N/A					
		N/A		N/A	1.05	0.55	.06	0.33	N/A
		N/A		N/A					
		N/A		N/A	-0.40	0.45	.37	0.07	N/A
		N/A		N/A					

(Continued on next page)

Table A5. *(continued)*

	T0[a]		T1[a]	
	n	M [SD]	n	M [SD]
Forward digit span task				
BWL	65	8.9 [1.8]	61	9.4 [2.0]
DWL[c]	62	8.9 [2.1]	57	9.2 [2.0]
Backward digit span task				
BWL	65	6.6 [2.0]	61	6.8 [2.1]
DWL[c]	62	6.2 [2.0]	57	6.8 [2.2]

Raw means and standard deviations are reported.
BWL Bright white light; **DWL** Dim white light; **MDASI** MD Anderson Symptom Inventory; **MOS-CF6** Medical Outcomes Studies – Cognitions.
[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 mean scores and pooled standard deviation (SD): ($mean_{T1}$-$mean_{T0}$)/pooled $SD_{T0\text{-}T1}$ or ($mean_{T3}$-$mean_{T1}$)/pooled $SD_{T1\text{-}T3}$; small 0.2, moderate 0.5, large 0.8. [c] DWL is the reference group. [d] 1 case excluded because of influential outlier.

	T2[a]		T3[a]		Between-group difference T0-T1			ES[b]	
	n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
		N/A		N/A	0.02	0.35	.95	0.08	N/A
		N/A		N/A					
		N/A		N/A	-0.40	0.26	.12	0.19	N/A
		N/A		N/A					

Table A6. Mean values and standard deviations per time-point and between-group differences for the mixed-effects models of the outcome measurements for participants who used light therapy during fall or winter.

	T0[a]		T1[a]	
	n	M [SD]	n	M [SD]
COGNITIVE COMPLAINTS				
MOS-CF6				
BWL	46	62.4 [16.7]	46	65.9 [18.0]
DWL[c]	43	57.1 [18.6]	41	62.4 [19.0]
MDASI remembering				
BWL	46	4.0 [2.9]	46	3.8 [2.7]
DWL[c]	43	4.2 [2.8]	41	4.0 [2.6]
MDASI concentrating				
BWL	46	3.8 [2.6]	46	3.9 [2.5]
DWL[c]	43	5.0 [2.5]	43	4.5 [2.6]
MDASI interference				
BWL	46	3.9 [1.9]	46	3.1 [2.0]
DWL[c]	43	5.0 [2.0]	40	4.1 [2.1]
COGNITIVE FUNCTIONING				
1/RT (PVT)[d]				
BWL	43	3.9 [0.4]	39	3.9 [0.4]
DWL[c]	42	3.7 [0.6]	38	3.7 [0.6]
Performance lapses (PVT)[d]				
BWL	43	0.8 [2.1]	39	0.5 [1.0]
DWL[c]	42	1.0 [2.6]	38	1.5 [5.8]
No. correct items learning phase (15WT)				
BWL	46	45.7 [10.0]	44	49.2 [12.5]
DWL[c]	43	48.8 [11.3]	42	50.6 [10.4]
No. correct items free recall (15WT)				
BWL	46	9.9 [2.9]	44	10.6 [3.5]
DWL[c]	43	10.3 [3.1]	42	11.0 [2.6]
No. correct items recognition (15WT)				
BWL	46	28.6 [2.0]	44	29.1 [1.5]
DWL[c]	43	29.2 [1.1]	42	28.6 [4.2]

	T2[a]		T3[a]		Linear time effect T0-T3			ES[b]	
	n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
	39	66.4 [17.1]	41	68.8 [16.6]	-0.22	0.35	.54	0.06	0.04
	39	58.9 [20.7]	38	66.1 [18.6]					
	39	3.7 [2.8]	41	3.6 [2.9]	0.08	0.06	.14	0.03	0.20
	39	4.1 [2.7]	38	3.3 [3.1]					
	39	3.9 [2.5]	41	3.7 [2.8]	0.02	0.05	.74	0.22	0.09
	39	5.1 [2.4]	38	4.5 [2.6]					
	39	3.3 [1.8]	41	3.1 [2.1]	-0.01	0.04	.89	0.06	0.09
	39	4.2 [2.1]	38	4.0 [2.2]					
					Between-group difference T0-T1				
		N/A		N/A	0.03	0.10	.78	0.05	N/A
		N/A		N/A					
		N/A		N/A	-0.70	1.08	.52	0.28	N/A
		N/A		N/A					
		N/A		N/A	1.51	1.72	.38	0.16	N/A
		N/A		N/A					
		N/A		N/A	-0.09	0.49	.85	0.00	N/A
		N/A		N/A					
		N/A		N/A	1.46	0.74	.05	0.43	N/A
		N/A		N/A					

(Continued on next page)

Table A6. *(continued)*

	T0[a]		T1[a]	
	n	**M [SD]**	**n**	**M [SD]**
No. correct items digit span task				
BWL	46	15.8 [3.1]	44	16.2 [3.3]
DWL[c]	43	14.9 [3.6]	42	15.9 [3.7]
Forward digit span task				
BWL	46	9.3 [1.6]	44	9.3 [1.9]
DWL[c]	43	8.8 [2.1]	42	9.2 [2.0]
Backward digit span task				
BWL	46	6.5 [1.8]	44	6.9 [1.8]
DWL[c]	43	6.2 [2.1]	42	6.6 [2.1]

Raw means and standard deviations are reported.
BWL Bright white light; **DWL** Dim white light; **MDASI** MD Anderson Symptom Inventory; **MOS-CF6** Medical Outcomes Studies – Cognitions.
[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 mean scores and pooled standard deviation (SD): $(mean_{T1}-mean_{T0})$/pooled SD_{T0-T1} or $(mean_{T3}-mean_{T1})$/pooled SD_{T1-T3}; small 0.2, moderate 0.5, large 0.8. [c] DWL is the reference group. [d] One case excluded because of influential outlier. For 1/RT. no random intercept was included in the model because convergence could not be reached for the model including a random intercept.

	T2[a]		T3[a]		Between-group difference T0-T1			ES[b]	
	n	M [SD]	n	M [SD]	B	SE	*p*	T0-T1	T1-T3
		N/A		N/A	-0.61	0.57	.28	0.20	N/A
		N/A		N/A					
		N/A		N/A	-0.62	0.43	.15	0.27	N/A
		N/A		N/A					
		N/A		N/A	0.02	0.29	.95	0.08	N/A
		N/A		N/A					

CHAPTER 5

A QUESTIONABLE FACTOR STRUCTURE OF THE MULTIDIMENSIONAL FATIGUE INVENTORY IN THE GENERAL DUTCH POPULATION

Journal of Clinical Epidemiology, 2021; 137: 266-276
doi.org/10.1016/j.jclinepi.2021.05.005

Jacobien M. Kieffer*
Daniëlle E.J. Starreveld*
Annelies Boekhout
Eveline M.A. Bleiker

* both authors contributed equally to this manuscript.

ABSTRACT

Objective

One of the most commonly used tools to measure fatigue is the Multidimensional Fatigue Inventory (MFI). Studies into the scale structure of the MFI show discrepant findings. The objective of this study was to investigate the scale structure of the MFI in the general Dutch population.

Study design and Setting

Using data from a Dutch probability-based internet panel (n=2512), the original 5-factor model, a 4-factor, and a 5- and 4-bifactor model of the MFI were tested with confirmatory factor analyses. Additional models were investigated using exploratory factor analysis (EFA).

Results

Results neither confirmed a 5-factor (RMSEA = 0.120, CFI = 0.933, TLI = 0.920) nor a 4-factor model (RMSEA = 0.122, CFI = 0.928, TLI = 0.917). The two bi-factor models also showed a poor fit (bi-4-factor: RMSEA = 0.151, CFI = 0.895, TLI = 0.873; bi-5-factor: RMSEA = 0.153, CFI = 0.894, TLI = 0.871). EFA did not support an alternative model but seemed to show robustness in the loading of the original *general fatigue* items.

Conclusion

Our results did not provide empirical support for a four or five (bi-)factor structure of the MFI, nor for an alternative model. The most reliable scale of the MFI seems to be the *general fatigue* scale that could be used as a general indicator of fatigue.

INTRODUCTION

Fatigue is a symptom that is familiar to almost all individuals. There is a high prevalence of fatigue in both the normal population[1] and in individuals with (chronic) illnesses, i.e. cancer[2]. However, there is a lack of consensus on the definition and multidimensionality of fatigue. For example, a general definition of fatigue is: "overwhelming sense of tiredness, lack of energy, and a feeling of exhaustion, associated with impaired physical and/or cognitive functioning; which needs to be distinguished from symptoms of depression"[3]. This general definition ignores the current discussion on the dimensionality of fatigue. Some authors propose that fatigue can be distinguished in mental and physical fatigue[4], while others propose more than two dimensions, e.g. the EORTC-FA12[5] measures three dimensions (physical, emotional and cognitive fatigue)[5, 6]. Due to the lack of consensus on the multidimensionality of fatigue, a gold standard to measure fatigue is missing.

One of the most commonly used questionnaires for fatigue in Europe is the Multidimensional Fatigue Inventory (MFI)[7]. It was developed by Smets and colleagues[6] to meet the need for a brief questionnaire that excludes somatic items (such as headache) and measures multiple dimensions of fatigue. A priori defined dimensions based on literature and patient interviews (n = 12) included: general fatigue (general remarks that reflects an individual's functioning), physical fatigue (feeling of tiredness), reduced activity (often co-occurring with fatigue), reduced motivation (to start with new activities), and mental fatigue (cognitive symptoms related to fatigue)[6]. These dimensions were confirmed in samples of radiotherapy patients (n = 111), chronic fatigued patients (n = 357), psychology students (n = 481), medical students (n = 158), and army recruits (n = 316), using confirmatory factor analyses[6, 8].

The original validation of the MFI provided evidence for the five dimensions of fatigue[6, 8]. Several studies investigated the psychometric properties of the MFI. Only two studies[8, 9] identified the originally proposed factor structure. Most studies reported different factor structures such as a three[10-12], a four[13-16] or a five-factor structure with different item loadings compared to the original factor structure[17-21]. Multiple studies have presented a combination of the general and physical fatigue scales[6, 11, 13-17, 19, 20, 22] (see Table 1). Originally, Smets et al.[6] also reported a four factor model in which the general and physical fatigue scales were combined, but chose a 5-factor model because the separate scales of general and physical fatigue might provide additional information for other constructs associated with fatigue.

Considering these discrepant findings, the objective of this study was to further investigate the factor structure of the MFI in the general Dutch population with the aim of generating an optimal scoring algorithm. Therefore, we investigated the original five factor structure, and the alternative four factor structure (general fatigue and physical fatigue combined), and two bi-factor models, in which both the 4- and 5-factor models are modeled as hierarchical structures that include a general factor and specific domain factors.

Table 1. Overview of validation studies of the MFI.

Language	Ref	Population
Dutch	[5]	Patients with: cancer treated with RT (n=111), chronic fatigue syndrome (n=395 psychology students (n=481), medical students (n=158), junior physicians (before and after first practical training; n=46), and army recruits(n=160 and n=156 after military training)
	[11]	Patients with cancer receiving RT (n=141)
	[16]	Patients with Parkinson's disease (n=153)
German	[13]	Chronically critically ill patients (post-acute ICU) (n=113)
Polish	[14]	Patients with cancer (n=340)
French	[18]	Patients with thyroid disease (n=225)
Korean	[19]	Outpatients visiting university hospital (n=595)
Brazilian-Portuguese	[20]	Survivors of Hodgkin lymphoma (n=200)
Persian	[17]	Patients with chronic hepatitis B (n=297)
Hindi	[12]	Patients with cancer (n=200)
Chinese	[15]	Patients with cancer prior to CT and last week CT (n=385)
	[21]	Patients with major depression (n=137)
English	[22]	US adult population (CFS-like n=292; chronically unwell n=269; well n=222)
	[42]	Patients treated with dialysis (n=470)
	[23]	Patients with Sjogren's syndrome (n=34) or rheaumatoid arthritis (n=48)
	[24]	Patients with cancer (n=210)
Swedish	[25]	Cancer patients receiving RT (n=100); palliative cancer patients (n=284); outpatients at a medical clinic (n=145); hospital staff (n=220)

GF general fatigue; **PF** physical fatigue; **MF** mental fatigue; **RA** reduced activity; **RM** reduced motivation; **CFA** confirmatory factor analysis; **PCA** principal components analysis; **RT** radiotherapy; **ICU** intensive care unit; **CT** chemotherapy; **CFS**: Chronic Fatigue Syndrome.

	Factor structure	Factor analysis	Remarks
	5 (GF, PF, MF, RA, RM)	CFA	Original validation study, participants completed 24 items.
	5 (Original GF, PF, MF, RA, RM)	CFA	
	4 (GF and PF combined, MF, RA, RM)	PCA	Correlations between scales, total score might be more valid as a general fatigue score.
	3 (GF, PF, RM)	CFA	MFI is not reliable in this sample, too many irrelevant items for individuals on the post-acute ICU
	3 (PF, MF, RM)	PCA	No good fit to model A: fatigue as a unidimensional factor or model B: original 5 factor structure. Model C is result of post-hoc modifications
	4 (GF and PF combined, MF, RA, RM)	PCA, varimax	
	4 (GF and PF combined, MF, RA [negative phrased], RM [positively phrased])	PCA, varimax	
	5 (GF and PF combined, MF, RM (separated over two factors), RA)	Principal axis factoring, Varimax	
	4 (PF, RA, MF, RM)	PCA	
	5 (Original GF, PF, MF, RA, RM)	CFA	Insignificant correlations between scales
	3 (spiritual fatigue, PF, MF)	Exploratory, Varimax	
	5 (physical and mental energy, lack of physical and mental energy, MF, RA, activity planning)	PCA, Varimax	Lower internal consistency compared to patients with cancer, fatigue symptoms and Parkinson's disease.
	5 (PF, MF, RA, RM, general/reduced motivation)	PCA, Varimax	All scales discriminated between groups
	No reliable factor model was confirmed	CFA	Poor model fit to 5-factor, 1-factor, and bi-factor model
	5 (GF and PF combined, MF, RA, RM separated over two factors)	PCA, Varimax	
	5 factor structure was obtained but item loadings were not those proposed and dual loadings were seen.	PCA, Varimax	
	5 (GF, PF, MF, RA, RM)	Cronbach's alpha	

METHODS

Data source

Data collection for this paper was conducted by CentERdata, an institute for online data collection and research located at Tilburg University, the Netherlands (www.centerdata.nl). This institute coordinates the LISS (Longitudinal Internet Studies for the Social Sciences) panel[23, 24]. This internet panel is a probability sample of households drawn from the population register by Statistics Netherlands. Approximately 5000 households, representative of the Dutch-speaking population living in the Netherlands, are included in this panel. Households without internet-access are loaned equipment to provide internet-access. Panel members receive a monthly invitation to complete an online questionnaire, which will take 15 to 30 minutes in total. This questionnaire is completed by one member of the household. Panel members are paid for each completed questionnaire. A full description of the recruitment of (new) panel members is described in further detail elsewhere[24].

In December 2017, CentERdata invited 3.590 randomly selected panel members to complete an online questionnaire that included questions on lifestyle (smoking, drinking), chronic disorders, cancer specific health-related quality of life (EORTC-QLQ-C30), and the MFI. These panel members were aged 16 years or older with an oversampling of 18 to 34 years and 75 years and older. After invitation, 2.544 (70.9%) individuals started with the questionnaire battery and 2512 individuals completed the battery including the MFI (70.0%). Our analyses are based on the sample that completed the total battery. Compared to non-responders, responders were older, more often married, and more often retired (Table 2).

Ethics statement

In the Netherlands, ethical approval for questionnaire research in the general population is not required. Data collection abides the European "General Data Protection Regulation (GDPR)". All participants gave double consent: first to participate in the LISS panel and second to receive monthly questionnaires.

Measurements

The original Dutch version of the MFI[6] was used to measure fatigue. It contains five scales; general fatigue (items 1, 5, 12, 16), mental fatigue (items 7, 11, 13, 19), physical fatigue (items 2, 8, 14, 20), reduced motivation (items 4, 9, 15, 18) and reduced activity (items 3, 6, 10, 17). Items are scored on a 5-point scale on which the participant expressed the degree to which the statement applied to him or her (from agreement "yes, that is true" to disagreement "no, that is not true") in the previous days. Item scores are summed to create a sum score for each scale, ranging between 4 (best condition) and 20 (worst condition). Higher scores indicate more fatigue.

An additional 10-point Visual Analogue Scale (VAS) for fatigue was included. Participants were asked "if you had to mark your fatigue with a score on a scale from 1 (no fatigue at all) to 10 (worst imaginable fatigue), which score would you give your fatigue?"

Statistical analysis

Descriptive statistics were used to report the sociodemographic characteristics of the sample. Pearson correlation analyses were used to calculate the correlation between the scales of the original 5-factor structure and the VAS-fatigue score.

We evaluated the 4- and 5-factor model using confirmatory factor analysis (CFA) using the lavaan package in R[26] and the semTools package[27]. We also modeled the 4- and the 5-factor model as hierarchical structures including a general factor and specific domain factors[28]. This evaluated whether item variation in the MFI reflects variation in a single unidimensional construct or if a questionnaire is multidimensional and scales are needed[29]. This bi-factor model allows items to simultaneously load on a general factor, in our case fatigue, and on a secondary factor of a specific fatigue domain. These specific domain factors account for the residual variance between the items once the contribution to the general factor has been partialed out. All domain factors are uncorrelated and have the same conceptual footing because they all contribute to the general factor[28]. We used the diagonally weighted least squares estimator (DWLS) with the mean- and variance adjustment procedure[30]. A mean- and variance-adjusted scaled chi square was calculated for each model. This is the standard (normal-theory) chi square statistic divided by a scaling correction to better approximate a chi square under non-normality[31]. We also reported the comparative fit index (CFI) and the Tucker-Lewis Index (TLI) (for both, values ≥ 0.97 indicate a good fit, and between 0.95 and 0.97 an acceptable fit), and the Root Mean Square Error of Approximation (RMSEA) (values < 0.05 indicating a good fit, and between 0.05 and 0.08 an acceptable fit)[32]. Because these goodness-of-fit statistics are derived from the models using the chi squared test, they too are scaled and become robust to non-normality[33]. All standardized factor loadings were required to be greater than 0.4 and statistically significant[34].

In case of poor model fit, rather than relying on modification indices, we subsequently carried out exploratory factor analyses (EFA). We evaluated models from one- to six factors using EFA with Geomin rotation and diagonally weighted least squares estimator (DWLS) in Mplus[35-37]. We again used the scaled CFI, TLI, and RMSEA as indicators of model fit. All standardized factor loadings were required to be greater than 0.4 and statistically significant. Items were considered unstable if cross-loadings were significant on another factor with a difference between the two highest loadings being smaller than 0.2[34]. We used the Kaiser criterion and scree plot to determine the number of factors that would yield the best solution[38].

RESULTS

Table 2 summarizes the sociodemographic and clinical characteristics of the respondents. In total, 1165 men (46.4%) and 1347 women (53.6%) with a mean age of 52.1 years (standard deviation (SD) = 18.5) completed the questionnaire. Forty percent of the responders reported no comorbidities. The top six of comorbid diseases in the past 12 months were: back pain (28.9%), high blood pressure (20.1%), arthrosis (17.7%), cancer (9.5%), asthma/chronic bronchitis/COPD (8.7%), and heart disease (8.0%). Depression was reported by 5.9 percent of the participants.

Table 2. Sociodemographic and clinical characteristics and fatigue scores on the MFI for the total sample (n=2512).

	Responders (n=2512)	Non-responders (n=1078)[a]
Age in years (M, SD)	52.1 (18.5)	39.3 (16.3)
Sex		
Male	1165 (46.4)	469 (43.5)
Female	1347 (53.6)	609 (56.5)
Living situation		
Married (n, %)	1262 (50.2)	436 (40.4)
Not married (n, %)	1250 (49.8)	642 (59.6)
Education		
Primary education (n, %)	186 (7.4)	79 (7.4)
High school and vocational education (n, %)	1407 (56.1)	576 (53.7)
College and university (n, %)	915 (36.5)	417 (38.9)
Missing (n)	4	6
Employment		
Paid job / self-employed (n, %)	1194 (47.5)	661 (61.3)
Unemployed (n, %)	349 (13.9)	115 (10.7)
Student (n, %)	218 (8.7)	195 (18.1)
Retired (n, %)	636 (25.3)	67 (6.2)
Work disabled (n, %)	98 (3.9)	30 (2.8)
Other (n, %)	17 (0.7)	10 (0.9)
Self-reported comorbidities[b] (in past 12 months)		
0 (n, %)	914 (39.7)	
1 (n, %)	659 (28.6)	
≥2 (n, %)	732 (31.8)	
Missing[c]	207	
Fatigue		
General fatigue (M, SD)	9.8 (4.4)	
Physical fatigue (M, SD)	8.8 (4.2)	
Reduced activity (M, SD)	9.3 (3.9)	
Reduced motivation (M, SD)	8.7 (3.6)	
Mental fatigue (M, SD)	8.3 (3.7)	
Sum score (M, SD)	44.9 (16.7)	
VAS (M, SD)	4.1 (2.3)	

The reported percentages refer to valid cases.
M Mean**; SD** standard deviation
[a] Responders differed significantly from non-responders on age, living situation, and employment (all p <.001). [b] Comorbidities as measured by an adapted version of the Self-Administered Comorbidity Measure[25], including heart disease, stroke, high blood pressure, lung disease, diabetes mellitus, gastric ulcer, kidney disease, liver disease, anemia or other blood disease, thyroid disease, depression, arthrosis, back pain, rheumatoid arthritis, and other medical conditions. [c] Data of 207 responders was missing because the labels 'yes' or 'no' were not shown to responders who completed the questionnaire on their smartphone. This data was considered unreliable and not included.

The responses to the individual items of the MFI are depicted in Table 3 and show that the majority of the participants reported none to mild fatigue. Based on the VAS-fatigue, 49% of the participants reported mild fatigue (VAS 3 or lower), 31% reported moderate fatigue (VAS 4 to 6), and 20% reported severe fatigue (VAS 7 or higher)[39].

We found a strong correlation between the VAS score and general fatigue (r = 0.77). Moderate correlations were found between the VAS and the remaining scales (range: r = 0.52 to 0.65).

Confirmatory Factor Analyses (CFA)

Standardized factor loadings for the original 5-factor model and the 4-factor model are presented in Appendix Table A1 and A2. Although, both the original 5-factor model, and the 4-factor model revealed statistically significant standardized factor loadings greater than 0.4 on all factors, both model showed a poor model fit according the fit indices (Table 4). We also observed high correlations between the factors in the original 5-factor model (ranging between 0.63-0.97; Table 5), with the highest correlations being between the general and physical fatigue scale (r = 0.92) and the reduced motivation and reduced activity scale (r = 0.97). Similarly, for the 4-factor model with general and physical fatigue forming one factor, high correlations were observed between factors (ranging between 0.69-0.97; Table 5), with the highest correlations again being between the reduced motivation and reduced activity scale.

When modeling these models as hierarchical structures including a general factor and specific domain factors, we found a poor fit for both bi-factor models (Table 4). Additionally, results showed small non-significant factor loadings of items 6 on RA (p = 0.458), and of item 9 on RM (p = 0.511), and negative residual variances for items 1, 2, 7, and 19 when modeling the hierarchical 5-Factor Model. Similarly, results showed small non-significant factor loading of items 6 on RA (p = 0.121), and of item 9 on RM (p = 0.938), and negative residual variances for items 1, 3, 4, and 7 when modeling the hierarchical 4-factor model. This indicates identification problems suggesting the inappropriateness of both models for this data.

Exploratory Factor Analyses (EFA)

Due to the lack of evidence of an adequate model from the CFA, we further investigated the scale structure of the MFI using exploratory factor analyses (EFA). EFA identified a 4-factor solution, reflecting one factor combining physical and general fatigue, a mental fatigue factor, and two factors both having a combination of reduced activity and reduced motivation indicators. Table 6 shows the standardized factor loading per indicator, with the largest loading in bold. Model fit was poor to moderate (CFI = 0.965 and TLI = 0.943, RMSEA = 0.101). Factor

Table 3. Distribution of responses on the single items of the MFI in the total sample (N = 2512).

		N (%)				
		1 Yes, this is true	2	3	4	5 No, this is not true
General Fatigue						
1	I feel fit	1049 (41.8)	637 (25.4)	443 (17.6)	221 (8.8)	162 (6.4)
5	I feel tired	246 (9.8)	478 (19.0)	519 (20.7)	543 (21.6)	726 (28.9)
12	I feel rested	559 (22.3)	708 (28.2)	608 (24.2)	418 (16.6)	219 (8.7)
16	I tire easily	209 (8.3)	374 (14.9)	518 (20.6)	584 (23.2)	827 (32.9)
Physical Fatigue						
2	Physically I feel only able to do a little	139 (5.5)	216 (8.6)	333 (13.3)	457 (18.2)	1367 (54.4)
8	Physically I can take on a lot	870 (34.6)	786 (31.3)	464 (18.5)	238 (9.5)	154 (6.1)
14	Physically I feel I am in a bad condition	160 (6.4)	253 (10.1)	466 (18.6)	587 (23.4)	1046 (41.6)
20	Physically I feel I am in an excellent condition	643 (25.6)	748 (29.8)	519 (20.7)	326 (13.0)	276 (11.0)
Reduced Activity						
3	I feel very active	654 (26.0)	789 (31.4)	597 (23.8)	308 (12.3)	164 (6.5)
6	I think I do a lot in a day	664 (26.4)	665 (26.5)	658 (26.2)	303 (12.1)	222 (8.8)
10	I think I do very little in a day	144 (5.7)	308 (12.3)	481 (19.1)	571 (22.7)	1008 (40.1)
17	I get little done	116 (4.6)	251 (10.0)	491 (19.5)	629 (25.0)	1025 (40.8)
Reduced Motivation						
4	I feel like doing all sorts of nice things	922 (36.7)	781 (31.1)	497 (19.8)	209 (8.3)	103 (4.1)
9	I dread having to do things	133 (5.3)	290 (11.5)	463 (18.4)	655 (26.1)	971 (38.7)
15	I have a lot of plans	681 (27.1)	750 (29.9)	717 (28.5)	250 (10.0)	114 (4.5)
18	I don't feel like doing anything	100 (4.0)	248 (9.9)	488 (19.4)	602 (24.0)	1074 (42.8)
Mental Fatigue						
7	When I am doing something, I can keep my thoughts on it	1243 (49.5)	688 (27.4)	363 (14.5)	150 (6.0)	68 (2.7)
11	I can concentrate well	1084 (43.2)	724 (28.8)	476 (18.9)	173 (6.9)	55 (2.2)
13	My thoughts easily wander	143 (5.7)	255 (10.2)	432 (17.2)	647 (25.8)	1035 (41.2)
19	It takes a lot of effort to concentrate on things	156 (6.2)	338 (13.5)	515 (20.5)	637 (25.4)	866 (34.5)

MFI Multidimensional Fatigue Inventory

Table 4: Scaled fit indices; Confirmatory factor analyses and Bi-factor analyses on the MFI.

	Original 5-Factor Model	5-BI Factor Model	4-Factor Model	4-BI Factor Model
CFI	0.933	0.895	0.928	0.894
TLI	0.920	0.873	0.917	0.871
RMSEA	0.120	0.151	0.122	0.153

4-Factor Model, model consisting of 20 indicators and four factors: general and physical fatigue combined, reduced activity, reduced motivation, and mental fatigue; 5-Factor Model, model consisting of 20 indicators and five factors: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue; Bi-factor model, a hierarchical structure that includes a general factor and specific domain factors.
CFI comparative fit index; **MFI** Multidimensional Fatigue Inventory; **RMSEA** root mean square error of approximation; **TLI** Tucker-Lewis Index.

Table 5. Between-factor correlations of the Multidimensional Fatigue Inventory

Original 5-Factor model

	GF	PF	MF	RA	RM
GF	1				
PF	0.920	1			
MF	0.719	0.625	1		
RA	0.824	0.878	0.704	1	
RM	0.818	0.825	0.756	0.966	1

4-Factor Model

	GPF	MF	RA	RM
GPF	1			
MF	0.692	1		
RA	0.869	0.704	1	
RM	0.838	0.756	0.966	1

4-Factor Model, model consisting of 20 indicators and four factors: general and physical fatigue combined (GPF), reduced activity (RA), reduced motivation(RM), and mental fatigue (MF); 5-Factor Model, model consisting of 20 indicators and five factors: general fatigue (GF), physical fatigue (PF), reduced activity (RA), reduced motivation(RM), and mental fatigue (MF).

Table 6. Single item (cross-)loadings on the four factor solution of Exploratory Factor Analyses.

			F1	F2	F3	F4
General Fatigue						
1	I feel fit	POS	0,620	**0,878**	0,359	0,583
5	I feel tired	NEG	0,321	**0,801**	0,551	0,448
12	I feel rested	POS	0,506	**0,763**	0,547	0,434
16	I tire easily	NEG	0,418	**0,836**	0,518	0,615
Physical Fatigue						
2	Physically I feel only able to do a little	NEG	0,456	**0,743**	0,331	**0,659**
8	Physically I can take on a lot	POS	*0,654*	**0,747**	0,229	0,639
14	Physically I feel I am in a bad condition	NEG	0,444	**0,777**	0,281	**0,649**
20	Physically I feel I am in an excellent condition	POS	0,636	**0,845**	0,236	0,601
Reduced Activity						
3	I feel very active	POS	**0,818**	0,694	0,323	0,599
6	I think I do a lot in a day	POS	*0,557*	0,300	0,069	**0,643**
10	I think I do very little in a day	NEG	0,512	0,473	0,246	**0,853**
17	I get little done	NEG	0,534	0,616	0,414	**0,852**
Reduced Motivation						
4	I feel like doing all sorts of nice things	POS	**0,802**	0,510	0,292	0,533
9	I dread having to do things	NEG	0,454	0,598	0,469	**0,694**
15	I have a lot of plans	POS	**0,691**	0,375	0,226	0,475
18	I don't feel like doing anything	NEG	0,609	0,600	0,457	**0,795**
Mental Fatigue						
7	When I am doing something, I can keep my thoughts on it	POS	*0,526*	0,370	**0,726**	0,432
11	I can concentrate well	POS	0,571	0,456	**0,820**	0,452
13	My thoughts easily wander	NEG	0,360	0,457	**0,736**	**0,546**
19	It takes a lot of effort to concentrate on things	NEG	0,362	0,440	**0,696**	**0,584**

F factor

correlations were low to moderate, ranging from 0.23 to 0.58. Although items loaded significantly on their factors, half of the items of the MFI cross-loaded significantly on other factors (see Table 6), indicating that these items are unstable. The only items appearing to be more robust in their loading are the original general fatigue items. When evaluating the factor loadings in bold, and taking the cross loading into account, we found that eight out of 10 negatively worded items (bold grey in Table 6) tended to cluster together on Factor 4. Although less pronounced, a similar trend was found for the positively worded items (bold italic grey in Table 6), of which six out of 10 tended to cluster on factor 1 (see Table 6).

DISCUSSION

The MFI has been used in numerous studies to measure multiple dimensions of fatigue, but consensus about its scale structure or scoring procedure is lacking. In this study, we were unable to replicate the original 5-factor model as proposed by Smets et al.[6], nor was there support for a 4-factor model (combining general and physical fatigue). Adding a general factor to the 5-factor and 4-factor model (i.e. creating a bi-factor model) also did not yield satisfactory results. With additional explorative analyses, we were unsuccessful in identifying an alternative model.

Most other similarly conducted studies have not demonstrated empirical support for the original 5-factor structure of the MFI. Instead, models with different structures were found[10-21]. Chilcot et al.[40], also evaluated the bi- factor structure of the 5 factor model and like us, were unable to confirm it. Similar to the results of Smets et al.[8], we found correlations between the original five factors to be high. This generally indicates an overlap in variation, and brings into question whether these factors are unique and truly represent distinct domains of fatigue. We found one of the largest correlations between general and physical fatigue. Other studies found similar results where the physical and general aspects of fatigue could not be distinguished as separate domains[13-15, 17, 20].

In our study, we tested various factor structures for the MFI, but to no avail. Although results were highly inconsistent, other studies were able to find evidence for certain factor structures of the MFI. We have conducted our analyses on data from a sample of the general Dutch population. We argue that the factor structures found in other studies might be sample specific (i.e., cancer, thyroid disease, Sjogren's syndrome, rheaumatoid arthritis, Parkinson's disease, major depression, post-polio syndrome, chronic hepatitis B, dialysis patients [Table 1]), although no consistent factor structure was proposed. In addition to the use of a heterogeneous sample from the general Dutch population, our study has by far the largest sample size. The sample sizes in most other studies were relatively small for these kinds of factor analytical approaches (Table 1). Rule of thumb dictates a bare minimum of five respondents per parameter estimated to conduct factor analysis[41]. For evaluating the original 5-factor structure of the MFI, this would require a minimum of 350 respondents. If we could assume that the items of the MFI are reliable indicators of the underlying constructs, then a smaller sample size might do. However, in the case of the MFI we would argue that the sparse data might have led to unjust inferences in the past.

The current discussion on the definition and dimensionality of fatigue might also explain the lack of evidence for a robust factor structure and discrepant findings in the literature. Originally, fatigue was originally seen as a unidimensional construct but increased research has suggested a multidimensional construct of fatigue[42]. Michielsen and colleagues[42], showed that four different fatigue assessments claiming to measure one, two or five dimensions of fatigue (excluding the MFI) all measured one unidimensional concept of fatigue. This raises questions about whether the MFI covers the concept it intends to measure. Besides the general fatigue domain, the other domains may reflect constructs that can be, but may not necessarily be influenced by fatigue (i.e., the physical fatigue domain rather represents physical functioning and the mental fatigue domain, cognitive functioning). We also found that the general fatigue scale correlates highly with the VAS scale measuring fatigue, supporting the idea that the other

scales of the MFI might measure concepts related to or influenced by fatigue instead of fatigue itself. However, it is important to note that the suggested unidimensionality of fatigue might be instrument-specific. Validation studies for other instruments were able to replicate different dimensions of fatigue. For example, the three dimension of fatigue assessed with the EORTC-FA12 have been successfully replicated in the general German population[43] and young adults with cancer[44].

The above pertains to a conceptual approximation of the problem with the MFI. However, (part of) the problem may lie in the semantics of the items. When developing an instrument, the intention is to develop scales that resemble unidimensional constructs. The argument for including both positively and negatively worded items is to prevent response bias, i.e. to avoid a respondents' tendency to agree (acquiescence) or disagree (counter-acquiscence) with a question despite its content[45]. Although this response tendency can have an effect on the validity of a questionnaire, reversing items can also lead to mistakes and confusion and may be an even bigger threat to the validity[46]. One study showed that using the original twenty items of the MFI, with 10 positively and 10 negatively worded items, did not prevent response bias. Instead, it facilitated more mistakes than when items were posed in the same direction[47]. Moreover, the reverse wording of items in a questionnaire may inadvertently lead to two distinct factors: one for positive, and one for negative items, purely based on semantics[47]. This was also seen in our exploratory analysis, again with the exception of the general fatigue items. Other studies found similar trends[16-18]. This can be a methodological artefact, or these positively and negatively worded items may simply mirror two separate constructs on different continua. Nevertheless, this is an unintended and unwanted effect of the MFI.

In conclusion, our results did not provide empirical support for the two hypothesised measurement models for the MFI, nor for an alternative model in a large sample of the general Dutch population. Results did indicate that the general fatigue scale could be a good measure of fatigue. Nevertheless, the conceptual and structural issues surrounding the MFI which have been raised in this paper warrant considerable cognisance and caution when choosing a (multidimensional) questionnaire to measure fatigue.

REFERENCES

1. Nielen MMJ B-v D M, Schermer TRJ. Incidentie en prevalentie van gezondheidsproblemen in de Nederlandse huisartsenpraktijk in 2017. (2019) [20-06-2019]. Available from: www.nivel.nl/nl/nivel-zorgregistraties-eerste-lijn/incidenties-en-prevalenties
2. Daniëls L A, Oerlemans S, Krol A D, van de Poll-Franse L V, Creutzberg C L (2013). Persisting fatigue in Hodgkin lymphoma survivors: a systematic review. *Ann Hematol*, 92(8):1023-32.
3. Shen J, Barbera J, Shapiro C M (2006). Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Med. Rev.*, 10(1):63-76.
4. Hann D, Jacobsen P, Azzarello L, Martin S, Curran S, Fields K, et al. (1998). Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res*, 7(4):301-10.
5. Weis J, Tomaszewski K A, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. (2017). International psychometric validation of an EORTC quality of life module measuring cancer related fatigue (EORTC QLQ-FA12). *J Natl Cancer Inst*, 109(5).
6. Smets E M, Garssen B, Bonke B, De Haes J C (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 39(3):315-25.
7. Schwarz R, Krauss O, Hinz A (2003). Fatigue in the general population. *Onkologie*, 26(2):140-4.
8. Smets E M, Garssen B, Cull A, de Haes J C (1996). Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer*, 73(2):241-5.
9. Chandel P, Sultan A, Khan K A, Choudhary V, Parganiha A (2015). Validation of the Hindi version of the Multidimensional Fatigue Inventory-20 (MFI-20) in Indian cancer patients. *Support Care Cancer*, 23(10):2957-64.
10. Wintermann G-B, Rosendahl J, Weidner K, Strauß B, Hinz A, Petrowski K J H, et al. (2018). Fatigue in chronically critically ill patients following intensive care - reliability and validity of the multidimensional fatigue inventory (MFI-20). *Health Qual. Life Outcomes*, 16(1):37.
11. Buss T, Kruk A, Wisniewski P, Modlinska A, Janiszewska J, Lichodziejewska-Niemierko M (2014). Psychometric properties of the Polish version of the Multidimensional Fatigue Inventory-20 in cancer patients. *J Pain Symptom Manage*, 48(4):730-7.
12. Tian J, Hong J S (2012). Validation of the Chinese version of Multidimensional Fatigue Inventory-20 in Chinese patients with cancer. *Support Care Cancer*, 20(10):2379-83.
13. Elbers R G, van Wegen E E, Verhoef J, Kwakkel G (2012). Reliability and structural validity of the Multidimensional Fatigue Inventory (MFI) in patients with idiopathic Parkinson's disease. *Parkinsonism Relat Disord*, 18(5):532-6.
14. Saffari M, Naderi M K, Piper C N, Koenig H G (2017). Multidimensional Fatigue Inventory in People With Hepatitis B Infection: Cross-cultural Adaptation and Psychometric Evaluation of the Persian Version. *Gastroenterol Nurs*, 40(5):380-92.
15. Gentile S, Delaroziere J C, Favre F, Sambuc R, San Marco J L (2003). Validation of the French 'multidimensional fatigue inventory' (MFI 20). *Eur J Cancer Care (Engl)*, 12(1):58-64.
16. Song S W, Kang S G, Kim K S, Kim M J, Kim K M, Cho D Y, et al. (2018). Reliability and Validity of the Korean Version of the Multidimensional Fatigue Inventory (MFI-20): A Multicenter, Cross-Sectional Study. *Pain Res Manag*, 2018:3152142.
17. Baptista R L, Biasoli I, Scheliga A, Soares A, Brabo E, Morais J C, et al. (2012). Psychometric properties of the multidimensional fatigue inventory in Brazilian Hodgkin's lymphoma survivors. *J Pain Symptom Manage*, 44(6):908-15.
18. Chung K F, Yu B Y, Yung K P, Yeung W F, Ng T H, Ho F Y (2014). Assessment of fatigue using the Multidimensional Fatigue Inventory in patients with major depressive disorder. *Compr Psychiatry*, 55(7):1671-8.
19. Lin J M, Brimmer D J, Maloney E M, Nyarko E, Belue R, Reeves W C (2009). Further validation of the Multidimensional Fatigue Inventory in a US adult population sample. *Popul. Health Metr.*, 7:18.
20. Goodchild C E, Treharne G J, Booth D A, Kitas G D, Bowman S J (2008). Measuring fatigue among women with Sjogren's syndrome or rheumatoid arthritis: a comparison of the Profile of Fatigue (ProF) and the Multidimensional Fatigue Inventory (MFI). *Musculoskeletal Care*, 6(1):31-48.
21. Meek P M, Nail L M, Barsevick A, Schwartz A L, Stephen S, Whitmer K, et al. (2000). Psychometric testing of fatigue instruments for use with cancer patients. *Nurs Res*, 49(4):181-90.
22. Hagelin C L, Wengstrom Y, Runesdotter S, Furst C J (2007). The psychometric properties of the Swedish Multidimensional Fatigue Inventory MFI-20 in four different populations. *Acta Oncol*,

46(1):97-104.
23. van de Poll-Franse L V, Horevoorts N, van Eenbergen M, Denollet J, Roukema J A, Aaronson N K, et al. (2011). The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer*, 47(14):2188-94.
24. Scherpenzeel A, Das M (2010). "True" Longitudinal and Probability-Based Internet Panels: Evidence From the Netherlands., in Das M, Ester P, Kasmirek L (eds): Social and Behavioral Research and the Internet: Advances in Applied Methods and Research Strategies. 109. Boca Raton: Taylor & Francis. p. 77-104.
25. Sangha O, Stucki G, Liang M H, Fossel A H, Katz J N (2003). The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Care Res (Hoboken)*, 49(2):156-63.
26. Rosseel Y (2012). Lavaan: An R package for structural equation modeling and more. *J. Stat. Softw.*, 48(2):1-36.
27. Jorgensen T D, Pornprasertmanit S, Schoemann A, Rosseel Y. semTools: Useful tools for structural equation modeling (2020) [Available from: https://CRANR-projectorg/package=semTools.
28. Reise S P, Moore T M, Haviland M G (2010). Bifactor Models and Rotations: Exploring the Extent to which Multidimensional Data Yield Univocal Scale Scores. *J Pers Assess*, 92(6):544-59.
29. Reise S P, Morizot J, Hays R D (2007). The role of the bifactor model in resolving dimensionality issues in health outcomes measures. *Qual Life Res*, 16 Suppl 1:19-31.
30. Muthén B, Asparouhov T (2002). Latent variable analysis with categorical outcomes: Multiple-group and growth modeling in Mplus. *Mplus web notes*, 4(5):1-22.
31. Satorra A (2000). Scaled and adjusted restricted tests in multi-sample analysis of moment structures, in Heijmans DDH, Pollock DS, Satorra A (eds): Innovations in multivariate statistical analysis: A Festschrift for Heinz Neudecker Dordrecht: Kluwer Academic Publishers. p. 233-47.
32. Schermelleh-Engel K, Moosbrugger H, Müller H (2003). Evaluating the fit of structural equation models: Tests of significance and descriptive goodness-of-fit measures. *Methods of psychological research online*, 8(2):23-74.
33. Satorra A, Bentler P M (1994). Corrections to test statistics and standard errors in covariance structure analysis, in Von Eye A, Clogg CC (eds): Latent variable analysis: Applications to developmental research. Thousand Oaks, Ca: Sage. p. 399 - 419.
34. Ferguson E, Cox T (1993). Exploratory Factor Analysis: A Users'Guide. *Int. J. Sel. Assess.*, 1(2):84-94.
35. Muthén L, Muthén B O Mplus User's Guide. 6 ed. Los Angeles, CA: Muthén & Muthén; 2010.
36. Muthén B, du Toit S, Spisic D (1997). Robust interference using weighted least squares and quadratic estimating equations in the latent variable modeling with categorical and continuous outcomes. Unpublished manuscript, University of California, Los Angeles, USA.
37. Flora D B, Curran P J (2004). An empirical evaluation of alternative methods of estimation for confirmatory factor analysis with ordinal data. *Psychol Methods*, 9(4):466.
38. Cattell R B, Vogelmann S (1977). A comprehensive trial of the scree and KG criteria for determining the number of factors. *Multivariate Behavioral Research*, 12(3):289-325.
39. Oldenmenger W H, Pleun J, de Klerk C, van der Rijt C C (2013). Cut points on 0–10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review. *J Pain Symptom Manage*, 45(6):1083-93.
40. Chilcot J, Guirguis A, Friedli K, Almond M, Davenport A, Day C, et al. (2017). Measuring Fatigue Using the Multidimensional Fatigue Inventory-20: A Questionable Factor Structure in Haemodialysis Patients. *Nephron*, 136(2):121-6.
41. Bentler P M, Chou C-P (1987). Practical issues in structural modeling. *Sociological methods & research*, 16(1):78-117.
42. Michielsen H J, De Vries J, Van Heck G L, Van de Vijver F J, Sijtsma K (2004). Examination of the dimensionality of fatigue. *Eur. J. Psychol. Assess*, 20(1):39-48.
43. Hinz A, Weis J, Brähler E, Mehnert A (2018). Fatigue in the general population: German normative values of the EORTC QLQ-FA12. *Qual Life Res*, 27(10):2681-9.
44. Friedrich M, Nowe E, Hofmeister D, Kuhnt S, Leuteritz K, Sender A, et al. (2018). Psychometric properties of the fatigue questionnaire EORTC QLQ-FA12 and proposal of a cut-off value for young adults with cancer. *Health Qual. Life Outcomes*, 16(1):1-11.
45. Rammstedt B, Danner D, Bosnjak M (2017). Acquiescence response styles: A multilevel model explaining individual-level and country-level differences. *Pers. Individ*, 107:190-4.

46. Schriesheim C A, Hill K D (1981). Controlling Acquiescence Response Bias by Item Reversals: The Effect on Questionnaire Validity. *Educ Psychol Meas*, 41(4):1101-14.
47. van Sonderen E, Sanderman R, Coyne J C (2013). Ineffectiveness of reverse wording of questionnaire items: let's learn from cows in the rain. *PLoS ONE*, 8(7):e68967.

APPENDIX

Table A1. Single item Standardized factor loadings for the five factor model.

		GF	PF	MF	RA	RM
General Fatigue						
1	I feel fit	0.927	0.000	0.000	0.000	0.000
5	I feel tired	0.788	0.000	0.000	0.000	0.000
12	I feel rested	0.810	0.000	0.000	0.000	0.000
16	I tire easily	0.876	0.000	0.000	0.000	0.000
Physical Fatigue						
2	Physically I feel only able to do a little	0.000	0.807	0.000	0.000	0.000
8	Physically I can take on a lot	0.000	0.846	0.000	0.000	0.000
14	Physically I feel I am in a bad condition	0.000	0.811	0.000	0.000	0.000
20	Physically I feel I am in an excellent condition	0.000	0.890	0.000	0.000	0.000
Mental Fatigue						
7	When I am doing something, I can keep my thoughts on it	0.000	0.000	0.786	0.000	0.000
11	I can concentrate well	0.000	0.000	0.877	0.000	0.000
13	My thoughts easily wander	0.000	0.000	0.810	0.000	0.000
19	It takes a lot of effort to concentrate on things	0.000	0.000	0.806	0.000	0.000
Reduced Activity						
3	I feel very active	0.000	0.000	0.000	0.880	0.000
6	I think I do a lot in a day	0.000	0.000	0.000	0.563	0.000
10	I think I do very little in a day	0.000	0.000	0.000	0.749	0.000
17	I get little done	0.000	0.000	0.000	0.856	0.000
Reduced Motivation						
4	I feel like doing all sorts of nice things	0.000	0.000	0.000	0.000	0.756
9	I dread having to do things	0.000	0.000	0.000	0.000	0.782
15	I have a lot of plans	0.000	0.000	0.000	0.000	0.615
18	I don't feel like doing anything	0.000	0.000	0.000	0.000	0.859

GF general fatigue **PF** physical fatigue; **MF** Mental fatigue; **RA** Reduced Activity; **RM** Reduced Motivation.

Table A2. Single item standardized factor loadings for the four factor model.

		GPF	MF	RA	RM
General Fatigue					
1	I feel fit	0.900	0.000	0.000	0.000
5	I feel tired	0.776	0.000	0.000	0.000
12	I feel rested	0.796	0.000	0.000	0.000
16	I tire easily	0.858	0.000	0.000	0.000
Physical Fatigue					
2	Physically I feel only able to do a little	0.790	0.000	0.000	0.000
8	Physically I can take on a lot	0.831	0.000	0.000	0.000
14	Physically I feel I am in a bad condition	0.794	0.000	0.000	0.000
20	Physically I feel I am in an excellent condition	0.870	0.000	0.000	0.000
Mental Fatigue					
7	When I am doing something, I can keep my thoughts on it	0.000	0.787	0.000	0.000
11	I can concentrate well	0.000	0.877	0.000	0.000
13	My thoughts easily wander	0.000	0.810	0.000	0.000
19	It takes a lot of effort to concentrate on things	0.000	0.806	0.000	0.000
Reduced Activity					
3	I feel very active	0.000	0.000	0.881	0.000
6	I think I do a lot in a day	0.000	0.000	0.563	0.000
10	I think I do very little in a day	0.000	0.000	0.749	0.000
17	I get little done	0.000	0.000	0.856	0.000
Reduced Motivation					
4	I feel like doing all sorts of nice things	0.000	0.000	0.000	0.756
9	I dread having to do things	0.000	0.000	0.000	0.782
15	I have a lot of plans	0.000	0.000	0.000	0.615
18	I don't feel like doing anything	0.000	0.000	0.000	0.859

GPF combined scale of general fatigue and physical fatigue; **MF** Mental fatigue; **RA** Reduced Activity; **RM** Reduced Motivation.

CHAPTER 6

CANCER-RELATED FATIGUE IN RELATION TO CHRONOTYPE AND SLEEP QUALITY IN (NON-)HODGKIN LYMPHOMA SURVIVORS.

Journal of Biological Rhythms, 2021; 36(1): 71-83.
doi.org/10.1177%2F0748730420987327

Danielle E.J. Starreveld
G. Esther A. Habers
Heiddis B. Valdimarsdottir
Rob Kessels
Laurien A. Daniëls
Flora E. van Leeuwen
Eveline M.A. Bleiker

ABSTRACT

Cancer-related fatigue has been related to circadian disruptions and lower levels of sleep quality. However, it is unknown whether the circadian phase, which is associated with chronotype and timing of sleep, is related to fatigue after cancer. The aims of this study were to investigate the associations between 1) chronotype and cancer-related fatigue and 2) sleep quality and cancer-related fatigue. In this cross-sectional questionnaire study, 458 (non-)Hodgkin lymphoma survivors (n=231 female, mean age 49.7 years) completed a VAS fatigue-scale from 0 (no fatigue) to 10 (worst imaginable fatigue), the Munich Chronotype Questionnaire (MCTQ), and the Pittsburgh Sleep Quality Index (PSQI) between October 2018 and July 2019. A hierarchical linear regression analysis was used to evaluate the associations between the dependent variable fatigue and chronotype (based on early, intermediate, or late average midsleep) in model 1, and fatigue and sleep quality in model 2. The results showed no indications for an association between chronotype and fatigue (all *p*-values ≥ .50). There were associations between two (out of seven) aspects of sleep quality and fatigue: subjective sleep quality ($p < .001$) and daily dysfunctioning ($p < .001$). Therefore, it is more likely that fatigue is associated with self-reported sleep quality rather than with chronotype. However, experimental studies with objective, physiological data on circadian phase and sleep quality are necessary to confirm the conclusions of this cross-sectional study.

BACKGROUND

Cancer-related fatigue is one of the most frequently reported complaints in cancer survivors[1] with a prevalence between 25 and 60 percent in (non-)Hodgkin lymphoma survivors[2, 3]. The National Comprehensive Cancer Network (NCCN) defined cancer-related fatigue as "a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning"[4]. The etiology of fatigue after cancer is still unknown but it is likely that multiple factors ranging from cognitive, emotional, psychosocial and somatic factors are involved[5].

One proposed underlying cancer-related fatigue mechanism is circadian rhythm disruption. Several studies, based on objective and subjective measurements, showed an association between circadian disruptions and fatigue, sleep disturbances, depression, and cognitive impairment[6-8]. These circadian disruptions in patients treated for cancer include a smaller amplitude of the rest-activity patterns (i.e. more sleep disruptions during the night and less activity during the day) and a flatter slope of the circadian rhythm of cortisol. This dampened rest-activity pattern was correlated with higher levels of fatigue in patients with metastatic colorectal cancer[9]. Additionally, a flatter cortisol slope was found for individuals with fatigue after cancer[10, 11].

Yet, these results do not provide insight into the timing (i.e. phase advanced or phase delayed) of the circadian rhythm and its association with fatigue after cancer. Chronotype can be used as a marker of the circadian phase and is based on the timing of the sleep-wake cycle[12]. It is defined as the mid-point between sleep onset and awakening on days when no alarm clock is used. Individual differences between chronotypes exist due to genetic variance, age, and environment[12]. Some individuals are more prone to be active in the morning, so called 'larks', and some individuals work better in the evening, so called 'owls'. Several studies showed an association between later chronotypes (the owls) and negative health outcomes like depression[13], bipolar disorders[14], obesity[15], and seasonal affective disorder[16]. It is also shown that a later chronotype is related to fatigue in individuals with irritable bowel symptoms[17] and students[18]. However, the causal relationship between chronotype and negative health outcomes remains unclear. One explanation might be the misalignment between the circadian clock and social obligations. For example, extremely late evening types experience a need to sleep around 3 o'clock in the morning. Yet, society obligates these individuals to set an early alarm, creating a sleep debt during the week. This phenomenon is also known as a *social jet lag*[12].

On the other hand, circadian rhythm disruptions have been associated with lower levels of sleep quality in cancer patients[19]. Sleep disturbances and sleep disorders are well studied in patients treated for cancer and prevalence rates up to 62% have been reported in patients with cancer compared to 30% in healthy volunteers. This prevalence remains higher in patients treated for cancer compared to healthy volunteers up to 18 months after diagnosis[20]. Several studies showed an association between poorer sleep quality and increased levels of fatigue in patients treated for cancer[21, 22]. Related to chronotype, several studies in other populations showed that evening types had worse sleep quality[14, 15, 18].

The reason to study the associations between chronotype and cancer-related fatigue and sleep quality and cancer-related fatigue is threefold. First, studies in other populations showed associations between eveningness and fatigue[14, 15, 17, 18] suggesting that this association might also be present in other populations. Second, it provides information on the potential working mechanism of morning light therapy as a treatment for fatigue after cancer[23-25] . As morning light therapy advances the circadian phase, which is associated with chronotype[26], a later chronotype might be associated with fatigue. Alternatively, light therapy has been shown to improve sleep quality[27], which might be the working mechanism of light therapy for decreasing fatigue. Third, a description of chronotypes in cancer survivors with cancer-related fatigue provides information on the optimal timing of light therapy (e.g. when cancer survivors with fatigue are more often morning types, morning light therapy will shift them even earlier which is not desired). Therefore, the current study aimed to explore the associations between 1) chronotype and fatigue after cancer and 2) sleep quality and fatigue after cancer. It was expected that survivors with moderate to severe fatigue would show a delayed chronotype, i.e. being an evening type, and report poorer sleep quality compared to survivors with no to mild fatigue. If this is the case, light therapy in the morning might decrease symptoms of fatigue after cancer.

METHODS

Study participants

For this cross-sectional study, individuals were invited to participate in the study if they met the following inclusion criteria: (1) diagnosis of Hodgkin Lymphoma (HL) or Diffuse Large B-cell Lymphoma (DLBCL) at least 2 years ago; (2) no treatment for cancer in the past 12 months; (3) sufficient knowledge of the Dutch language. Individuals were excluded if they reported to work in nightshifts.

Procedure

The hematologist or radiation oncologist in seven hospitals in the Netherlands (Admiraal de Ruyter hospital, Albert Schweitzer hospital, Amsterdam UMC [location AMC], Erasmus MC, Haga hospital, Leiden University Medical Center, University Medical Center Utrecht) identified eligible participants. Based on the inclusion criteria, a total number of 761 eligible survivors were identified. These individuals received an information package from their treating physician, including an invitation letter, a patient information letter with informed consent, our questionnaire, and a return envelope. The package also included additional information on a clinical trial testing light therapy as a treatment for fatigue after cancer (SPARKLE study)[28] . Participants with fatigue could request more information about this clinical trial via a response card. All participants returned a signed informed consent form and the completed questionnaire by mail to the study coordinator.

Additionally, Hematon (the patient organization of lymphoma patients in the Netherlands) included a message in their monthly newsletter to their members (> 4300 members) to inform them about the study. This message included a link to an online version of the questionnaire.

Only those responders who expressed interest and left contact details were contacted for further screening for eligibility in the SPARKLE study. No contact details were available for responders who completed the survey but were not interested in the SPARKLE study.

Study procedures conformed to the Declaration of Helsinki. Ethical approval for the study was obtained from the Institutional Review board of the Netherlands Cancer Institute (under number NL61017.031.17). Questionnaires were completed between October 2018 and July 2019.

Measurements

Sociodemographic data included self-reported age, gender, education, marital status, living situation, and work status. Clinical data, including diagnosis, date of diagnosis (month and year), treatment history, height, and weight were also obtained via self-report. Height and weight were used to calculate BMI, which was categorized into normal (18.5 – 24.9), overweight (25-30), and obese (> 30). There were only two underweight cases (BMI <1 8.5) who were included in the normal category. Comorbidities were assessed by an adapted version of the Self-Administered Comorbidity Measure[29].

The *Munich Chronotype Questionnaire* (MCTQ)[30] was used to measure sleep timing on work days and work-free days. Fourteen items cover bedtime, sleep time, sleep latency, wake time, sleep inertia, alarm clock use, and light exposure on workdays and work-free days. Based on the completed items of the MCTQ, sleep onset was calculated as the sum of the time to get ready to fall asleep (preparation time) and the minutes needed to fall asleep (sleep latency). Sleep duration was calculated as the difference between sleep onset and sleep offset. Total time in bed was calculated as the difference between bedtime and the time someone gets out of bed. Average midsleep (aMS) was calculated as the midpoint between sleep onset and sleep offset on all days of the week. aMS was used as in indicator for chronotype[31] and categorized in five categories: moderate to extremely early (aMS before 2:00 h) slightly early (aMS between 2:00 h and 3:00 h), intermediate (aMS between 3:00 h and 4:00 h), slightly late (aMD between 4:00 h and 5:00 h) and extremely late (aMS of 5:00 h or later) aMS based on the distribution of chronotype in the population of the Munich Chronotype Questionnaire[12]. Social jetlag was calculated as the difference of the midpoint between sleep onset and sleep offset on workdays and free days. Employment was categorized in three categories: unemployed (0 workdays), employed part time (1 to 4 workdays), and employed fulltime (4 or more workdays).

A *VAS-scale* ranging from 0 (no fatigue) to 10 (worst imaginable fatigue) was used to assess fatigue. Based on the VAS score, fatigue was categorized as no to mild fatigue (VAS-scores ≤ 3), moderate fatigue (VAS range from 4 to 7), or severe fatigue (VAS ≥ 7)[32].

Fatigue was described in more detail by the general fatigue score of the Multidimensional Fatigue Inventory (MFI)[33]. Originally, the MFI measures five domains of fatigue (general fatigue, mental fatigue, physical fatigue, reduced motivation, and reduced activity) but Kieffer et al.[34] showed that this factor structure is questionable. The general fatigue subscale is the most stable measurement for fatigue and was therefore included in our analysis. In addition, the relationship between fatigue and cancer or its treatment was assessed by asking the following question: "Have you experienced persistent fatigue since the diagnosis of and/or treatment for cancer?" which was answered with "yes" or "no".

The *Pittsburgh Sleep Quality Index* (PSQI)[35] was included to assess sleep quality. This 19-item questionnaire measures various aspects of sleep patterns and sleep quality including seven subscales: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disruptions, use of sleep medication and daily dysfunctioning. Questions one to four cover bedtime, sleep inertia, get-up time and sleep duration and were derived from the MCTQ to avoid repetition in the questionnaire. Scores on the subscales range between 0 (no difficulty) to 3 (severe difficulty) and were included as categorical variables (score 0, 1, 2, or 3) in the hierarchical regression model. The complete score ranges between 0 (good sleep quality) to 21 (worse sleep quality) and was used for descriptive purposes only.

Statistical analyses

Sociodemographic, clinical, fatigue, and sleep characteristics of the study population were described using descriptive statistics for the entire sample and, separately, for survivors with no to mild, moderate, or severe fatigue after cancer. Differences between groups for continuous variables were tested with one-way ANOVA's and Bonferroni post-hoc procedures. For non-normal distributions or unequal variances, Kruskall-Wallis tests were used. Chi-square tests were used to study group differences for categorical variables. Fisher's Exact tests were used when the cross table included one or more cells with less than five observations. Bonferroni corrected p-values were used to correct for multiple testing (see footnote under Table 2).

Pearson correlation analysis were used to test bivariate associations between chronotype, sleep quality and fatigue. A hierarchical linear regression analysis was used to evaluate the association between fatigue and average midsleep and fatigue and sleep quality. In the first model, the continuous score of the VAS-fatigue was used as the dependent variable and aMS as independent variable. For the regression analyses, we combined the categories 'slightly morning' and 'moderate to extreme morning' into morning type and 'slightly evening' and 'moderate to extreme evening' into evening type to reduce potential bias by the small number of extreme types. In the second model, the seven sleep quality subscales of the PSQI were added as categorical independent variables to the first model. Both models included age (years), time since diagnosis (years), and comorbidities (number) as continuous factors and sex (male: yes/no), BMI (overweight: yes/no; obese: yes/no), marital status (married or living together: yes/no), education (college or university: yes/no), diagnosis (non-Hodgkin lymphoma: yes/no), part-time employment (yes/no), and fulltime employment (yes/no) as categorical factors to control for their effects on fatigue or chronotype[12]. There were no treatment variables included in the regression models because previous studies showed that treatment had no effect on fatigue scores in survivors of HL[36]. Bonferroni corrected p-values were used to correct for multiple testing (see footnote under Table 3).

Missing values in the 19 variables included in the hierarchical regression were imputed. First, single imputation was used on two items of the MCTQ based on the following imputation rules: 1) Missing 'preparation time to go to sleep' was copied from 'bedtime'; and 2) 'Sleep latency' was copied from 'sleep latency' of the other day (work or free day) if available. After this single imputation, multiple imputation[37] was used to create and analyze 10 multiply imputed datasets. Incomplete variables were imputed under fully conditional specifications, using the default settings of the Mice 3.7 package[38], in R version 3.6.1[39]. All 19 variables included in the

regression were used in the imputation model as well as all auxiliary variables used to create the PSQI subscales and all MFI items. The parameters of substantive interest were estimated in each imputed dataset separately, and combined using Rubin's rules. For comparison, we also performed the analysis on the subset of complete cases. All statistical analyses were performed using SPSS version 25.0 or R version 3.6.1.

RESULTS

Participants

Of the 761 eligible participants who were invited through the hospitals, 430 returned a questionnaire on paper (response rate of 57%). Recruitment via the newsletter of the patient federation Hematon led to 91 online responses. In total, 521 questionnaires were returned. From the online reactions, 37 of the 91 participants completed less than 70% of the questionnaire and were excluded from analyses. Twenty-six participants were excluded from analyses due to shiftwork, leading to an analytic sample of 458 participants.

The mean age of the analytic sample was 49.7 years (SD = 12.3), with 231 females (50%). The majority (71%) was diagnosed with Hodgkin lymphoma. The mean time since diagnosis was 12.0 years (SD = 9.7). Ninety-three percent of the participants received chemotherapy, 60 percent received radiotherapy and 25 percent received other treatments. The majority (68%) reported at least one comorbidity. See Table 1 for more details.

Fatigue

Based on the VAS-fatigue scale, 134 survivors (29%) reported to experience no to mild fatigue, 171 survivors (37%) reported moderate fatigue and 133 (29%) reported severe fatigue since diagnosis or treatment for cancer (20 survivors [4%] did not complete the VAS-fatigue scale). General fatigue (MFI) and the proportion of individuals that report fatigue since cancer were higher in the moderately and severely fatigued group than in the no to mild fatigued group.

Bedtime information

Bedtime information on free days per group is shown in Table 2 for the entire sample and, separately, for groups based on the VAS-fatigue. There were no differences for sleep onset, wake-up time, and sleep duration between groups. However, there was a significant difference in total time spent in bed, which was increased in survivors with severe fatigue (9:35 hrs.) compared to survivors with moderate fatigue (9:12 hrs.), who stayed longer in bed compared to survivors without fatigue (8:48 hrs.). This difference in total time spent in bed can be explained by the finding that moderately and severely fatigued survivors had a statistically significant earlier bed time (36 and 25 minutes, respectively) compared to no-fatigued survivors and tended to have a longer sleep inertia. There were no differences in average midsleep between groups, probably explained by comparable sleep onset and wake-up times between groups.

Based on the average midsleep, 145 survivors (32%) were classified as morning types (M = 2:26; SD = 0:29), 211 survivors (46%) as intermediate types (M = 3:26; SD = 0:17), and 87 (19%)

Table 1. Sociodemographic, clinical and fatigue characteristics for all survivors and for survivors with no, moderate, or severe fatigue separately.

	No. (%)						
	Total (n=458)	**No fatigue (n=134)**	**Moderate fatigue (n=171)**	**Severe fatigue (n=133)**	***p*- value**	**Post-hoc**	**Missing (%)**
Age in years					.002**	N> M,S	1.5
Mean	49.7	52.6	47.9	48.4			
SD	12.3	11.7	12.0	12.9			
20-35 years	71 (16)	14 (11)	29 (18)	27 (21)	.005**		
36-50 years	147 (32)	32 (24)	66 (40)	42 (32)			
51-65 years	186 (41)	67 (50)	58 (35)	52 (40)			
65-75 years	47 (10)	20 (15)	13 (8)	11 (8)			
Sex							
Female	231 (50)	47 (35)	91 (55)	85 (64)	<.001***		1.1
Male	222 (49)	87 (65)	76 (46)	47 (36)			
BMI (SD)					.12		2.2
Mean	26.1	25.3	26.5	25.9			
SD	4.6	4.3	4.8	4.5			
16.5-25[a]	207 (45)	73 (56)	71 (43)	60 (46)	.25		
25-30	171 (37)	40 (31)	67 (40)	52 (39)			
>30	90 (15)	18 (14)	28 (17)	20 (15)			
Living situation							
Married	340 (74)	107 (80)	132 (79)	87 (67)	.02*		1.5
Education[b]							
None/Primary education	7 (2)	1 (1)	2 (1)	4 (3)	.70		1.5
High school and vocational education	229 (50)	66 (50)	86 (52)	65 (50)			
College and university	215 (47)	66 (50)	79 (47)	62 (47)			
Number of working days					.001**	N>S	1.1
Mean	2.9	3.4	2.9	2.5			
SD	2.1	2.1	2.1	2.2			
Employment status							
Unemployed	126 (29)	28 (21)	47 (28)	51 (39)	.01		1.1
Employed part-time	84 (19)	23 (17)	37 (22)	24 (18)			
Employed fulltime	223 (52)	83 (62)	83 (50)	57 (43)			

(Continued on next page)

Table 1. *(continued)*

	No. (%)						
	Total (n=458)	**No fatigue (n=134)**	**Moderate fatigue (n=171)**	**Severe fatigue (n=133)**	***p*- value**	**Post-hoc**	**Missing (%)**
Diagnosis[b]							
HL	324 (71)	92 (70)	122 (72)	94 (71)	.26		1.0
DLBCL	74 (16)	27 (21)	28 (17)	17 (13)			
Aggressive NHL	14 (3)	1 (1)	6 (4)	6 (5)			
Low grade NHL	8 (2)	1 (1)	2 (1)	5 (4)			
NHL, unknown origin	26 (6)	10 (8)	8 (5)	7 (5)			
Other	8 (2)	1 (1)	3 (2)	4 (3)			
Time since diagnosis in years					.56		2.2
Mean	12.0	11.6	12.5	11.3			
SD	9.7	9.3	9.8	9.5			
0-5 years	126 (28)	39 (30)	44 (27)	40 (30)	.95		
6-15 years	184 (40)	53 (40)	68 (41)	54 (41)			
> 15 years	138 (30)	40 (30)	53 (32)	38 (29)			
Treatment							
Chemotherapy	424 (93)	127 (96)	155 (91)	122 (92)	.32		0.4
Radiotherapy	276 (60)	84 (63)	104 (61)	76 (57)	.59		0.4
Other treatments[c]	112 (25)	33 (25)	39 (23)	35 (26)	.79		0.4
Self-reported comorbidities (in past 12 months)							
0	137 (30)	59 (45)	43 (26)	30 (23)	<.001***		2.8
1	126 (28)	38 (29)	51 (31)	34 (26)			
≥2	182 (40)	35 (27)	72 (43)	65 (50)			
Fatigue							
General fatigue					<.001***	N<M<S	0
Mean	12.7	7.9	14.0	16.3			
SD	4.7	3.2	3.4	2.9			
Cancer-related fatigue (yes)	300 (66)	28 (21)	133 (79)	127 (96)	<.001***		1.1

SD standard deviation; **N** no fatigue; **M** moderate fatigue; **S** severe fatigue; **HL** Hodgkin lymphoma; **DLBCL** diffuse large B-cell lymphoma; **NHL** Non-Hodgkin lymphoma.
[a] Two underweight cases (BMI between 16.5 and 18.5) were included in the normal BMI category.
[b] Fisher's Exact Test reported. [c] Other treatments include stem cell transplantation, surgery, immunotherapy or wait and see. * <.05, ** <.01, *** <.001

as evening types (M = 4:31; SD = 0:36). For 15 survivors (3%) aMS could not be calculated due to missing data.

Bedtime information, sleep quality and fatigue

Figure 1 shows a schematic overview of bivariate Pearson correlations between chronotype, sleep quality and fatigue. Chronotype was significantly associated with two aspects of sleep quality: sleep latency (r = .21; p < .001) and sleep duration (r = .14; p < .01). With the exception of chronotype (r = .02; p = .62) and sleep duration (r = .04; p = .42), all subscales of sleep quality were significantly associated with fatigue (r_{range} = .20 to .59; all p *values* < .001).

Table 3 shows the results of the hierarchical linear regression model after multiple imputation. Model 1 (R^2= .18; 95% CI = 0.12 - 0.25) shows significant associations between fatigue after cancer and age (B = −0.06; p < .001), and comorbidities (B = 0.40; p < .001). These associations can be interpreted as follows: an increase of 10 years of age was associated with a decrease of 0.6 point in the VAS fatigue scale; an increase of one comorbidity is associated with an increase of 0.40 points on the VAS-fatigue. No association was found between fatigue and intermediate aMS (B = 0.12; p = .67) or late aMS (B = −0.03; p = 0.90) compared to early aMS.

After inclusion of sleep quality variables, model 2 (R^2 = .51, 95% CI = 0.44 - 0.57) shows significant associations between fatigue and subjective sleep quality ($B_{fairly\ good}$ = 0.87; $B_{fairly\ bad}$ = 1.47; $B_{very\ bad}$ = 2.80; for all $p \leq .001$) and between fatigue and daily dysfunctioning ($B_{some\ dysfunctioning}$ = 2.15; $B_{quite\ a\ bit\ dysfunctioning}$ = 3.09; $B_{severe\ dysfunctioning}$ = 3.28; all p *values* < .001). These associations can be interpreted as follows: the influence of subjective sleep quality ranged from an increase of 0.85 points ('fairly good sleep quality') to 2.82 points ('very bad sleep quality') on the VAS fatigue relative to individuals who report their subjective sleep quality to be 'very good'; the influence of daily dysfunctioning ranged from an increase of 2.03 points ('some dysfunctioning) to 3.28 points ('severe dysfunctioning') on the VAS-fatigue compared to 'no problems'in daily dysfunctioning. Compared to model 1, the associations between fatigue and age and fatigue and comorbidities were no longer significant.

Potential multicollinearity issues of the sleep quality variables were evaluated by inspecting the variance inflation factor (VIF) and tolerance values of the second model applied on complete cases only. Two indicator (dummy) variables of the sleep disruption scale showed VIF (>3.5) and tolerance (<0.2) values that indicated a potential collinearity problems. However, these variables represent answer categories of the same categorical variable (sleep disruption) where the proportion of cases in the reference category is relatively small (5.4%), which causes the VIF to be larger. This was not the case for the other PSQI subscales where the proportion of cases in the reference categories were larger. The relatively large VIF of the dummy variables of the sleep disruption scale did not affect the other variables in the model and can therefore safely be ignored. There were no collinearity problems between subscales of the PSQI.

Similar results were obtained when the analysis was performed on the complete cases only (n=379; see Appendix Table A1). There was one difference: sleep duration answer "5-6 hours" ($B_{imputed}$ = −1.00, p = .01; $B_{complete\ cases}$ = −1.41, p = .001) was significant in the complete cases analysis. Since confidence intervals were smaller for the imputed data analysis, these results were preferred.

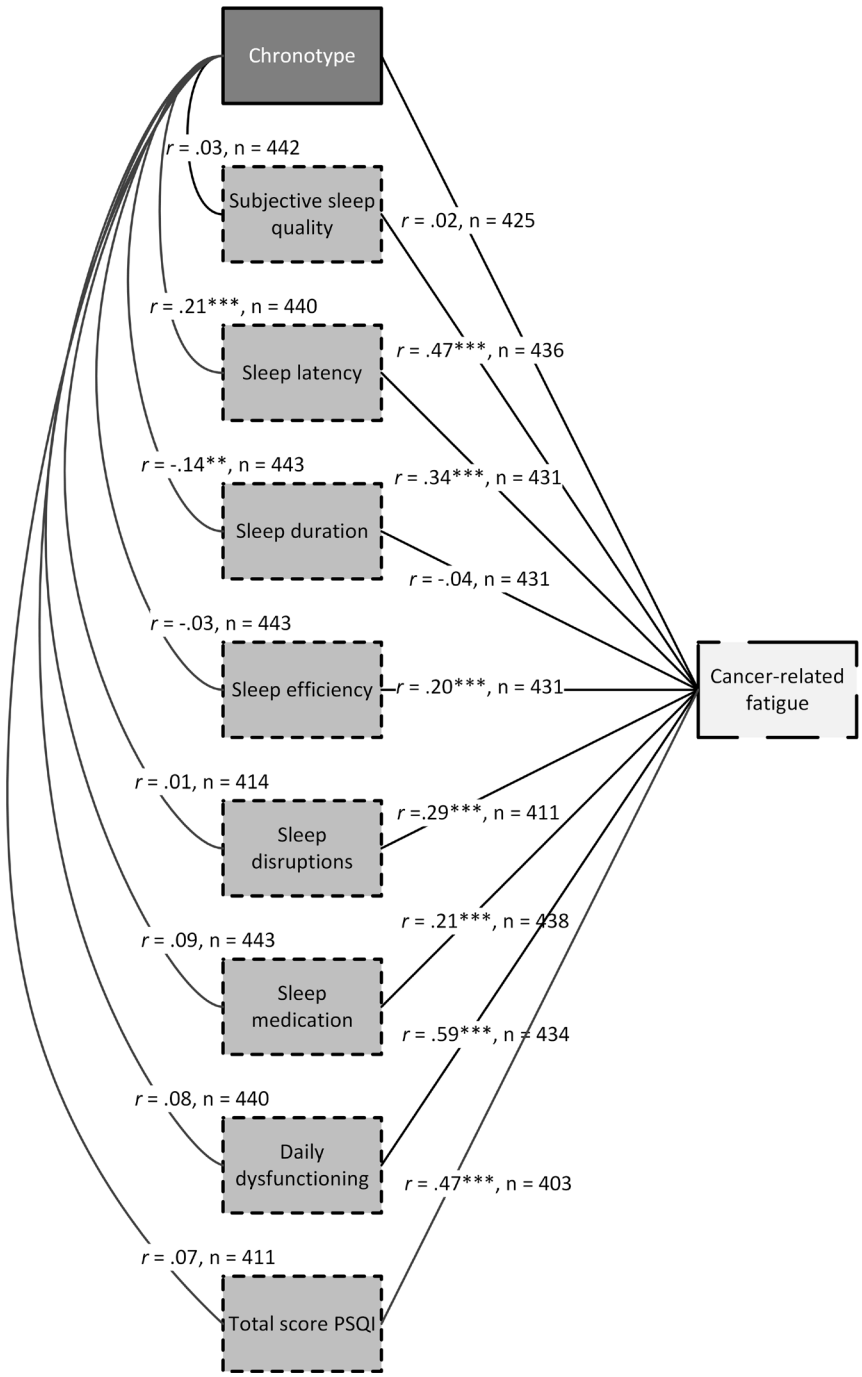


Figure 1 Schematic overview of bivariate Pearson correlations between chronotype, sleep quality, and cancer-related fatigue based on complete cases only.
PSQI Pittsburgh Sleep Quality Index; ** < .01, *** < .001

Table 2: Mean (SD) bedtime and sleep quality information for all survivors and for survivors with no, moderate, or severe fatigue separately.

	Total (n=458)	No fatigue (n=134)	Moderate fatigue (n=171)
BED TIME[a]			
Basic variables			
I go to bed at ... o'clock	23:03 (0:59)	23:23 (0:59)	22:59 (0:58)
I get ready to fall asleep at ... o'clock	23:25 (0:55)	23:37 (0:56)	23:26 (0:50)
I need ... minutes to fall asleep‡	17 (22)	11 (13)	17 (19)
I wake up at ... o'clock[b]	7:43 (1:25)	7:49 (1:10)	7:39 (1:24)
After ... minutes I get up	32 (56)	22 (32)	33 (51)
Hours spent outside[b]	2:38 (1:49)	3:17 (2:14)	2:20 (1:29)
Calculated variables			
Sleep onset	23:42 (0:59)	23:48 (0:59)	23:43 (0:54)
Sleep duration[b]	8:00 (1:28)	8:01 (1:07)	7:55 (1:32)
Total time in bed	9:10 (1:18)	8:48 (1:03)	9:12 (1:21)
Average midsleep	3:19 (0:51)	3:18 (0:48)	3:19 (0:47)
Moderate/extreme early, n (%)[c]	21 (5)	4 (3)	7 (4)
Slightly early, n (%)	124 (27)	42 (32)	44 (27)
Intermediate, n (%)	211 (46)	64 (48)	78 (48)
Slightly late, n (%)	75 (16)	20 (15)	30 (19)
Moderate/extreme late, n (%)	12 (3)	3 (2)	3 (2)
Social jetlag	0:44 (0:43)	0:51 (0:45)	0:41 (0:41)
SLEEP QUALITY[a]			
Subjective sleep quality[b]	1.1 (0.7)	0.6 (0.6)	1.2 (0.6)
Sleep latency	1.0 (0.9)	0.5 (0.8)	1.0 (0.9)
Sleep duration	0.4 (0.8)	0.5 (0.8)	0.4 (0.8)
Sleep efficiency[b]	0.4 (0.7)	0.1 (0.4)	0.5 (0.9)
Sleep disruptions[b]	1.3 (0.6)	1.1 (0.5)	1.3 (0.5)
Sleep medication[b]	0.3 (0.8)	0.1 (0.4)	0.3 (0.8)
Daily dysfunctioning[b]	1.1 (0.8)	0.4 (0.6)	1.2 (0.7)
Total score[b]	5.4 (3.3)	3.4 (2.2)	5.8 (3.2)

The 24-hour clock notation is used for questions regarding time (22:30 is half past 10 p.m.) and duration (0:30 is 30 minutes, i.e. 0,5 hours).
SD standard deviation; **N** no fatigue; **M** moderate fatigue; **S** severe fatigue.
[a] Bonferroni corrected p-value of 0.004 (0.05/12) or less was considered to be statistically significant for bedtime variables. A Bonferroni corrected p-value of 0.006 (0.05/8) or less was considered to be statistically significant for sleep quality variables. [b] Kruskal-Wallis test reported. [c] Fisher's Exact Test reported.
* < .004 for bedtime variables or < .006 for sleep quality variables

Severe fatigue (n=133)	*p*-value	Post-hoc comparison	Missing (%)
22:48 (0:57)	<.001*	N > M, S	0.9
23:14 (0:57)	.004*	N > S	1.1
24 (31)	<.001*	N, M < S	1.7
7:45 (1:36)	.86		1.5
39 (60)	.006		2.6
2:17 (1:34)	<.001*	N > M, S	10.9
23:36 (1:06)	.29		1.3
8:09 (1:41)	.05		2.0
9:35 (1:21)	<.001*	N < M < S	1.7
3:22 (0:58)	.76		3.3
9 (7)	.74		3.3
31 (24)			
62 (48)			
23 (18)			
5 (4)			
0:40 (0:44)	.06		2.2
1.4 (0.8)	<.001*	N < M < S	0.4
1.3 (1.0)	<.001*	N < M < S	1.7
0.4 (0.8)	.51		2.0
0.4 (0.8)	<.001*	N < M, S	2.0
1.5 (0.7)	<.001*	N < M < S	6.8
0.4 (0.9)	<.001*	N < M, S	0
1.6 (0.8)	<.001*	N < M < S	0.9
6.8 (3.4)	<.001*	N < M < S	9.0

Table 3 Linear model of independent variables on the continuous value of the VAS-fatigue with imputed data (n = 458).

	Model 1[a]				
			95% CI		
	B	(SE)	Lower	Upper	*p*
Constant	7.88	0.65	6.59	9.16	
Intermediate aMS	0.14	0.25	-0.35	0.63	.58
Late aMS	-0.01	0.33	-0.66	0.63	.97
Age	-0.06	0.01	-0.08	-0.04	<.001*
Male	-0.64	0.24	-1.12	0.16	.01
BMI: overweight	0.34	0.25	-0.15	0.83	.17
BMI: obese	0.35	0.33	-0.31	1.00	.30
Married	-0.27	0.26	-0.77	0.24	.30
College or university	0.15	0.24	-0.31	0.62	.52
NHL	0.32	0.28	-0.23	0.86	.25
Time since diagnosis	0.00	0.01	-0.03	0.03	.99
Comorbidities	0.40	0.08	0.25	0.55	<.001*
Part-time employment	-0.94	0.35	-1.62	-0.25	.01
Fulltime employment	-0.88	0.32	-1.50	-0.25	.006

	Model 2[a]				
			95% CI		
	B	(SE)	Lower	Upper	*p*
Constant	3.72	0.69	2.38	5.07	
Intermediate aMS	-0.02	0.21	-0.43	0.40	.94
Late aMS	-0.34	0.29	-0.92	0.23	.24
Age	-0.03	0.01	-0.04	-0.01	.01
Male	-0.46	0.21	-0.87	-.06	.03
BMI: overweight	0.26	0.20	-0.14	0.65	.21
BMI: obese	0.18	0.27	-0.36	0.72	.51
Married	0.18	0.21	-0.24	0.60	.40
College or university	-0.16	0.20	-0.55	0.22	.41
NHL	0.04	0.22	-0.40	0.48	.85
Time since diagnosis	0.00	0.01	-0.02	0.02	.72
Comorbidities	0.05	0.07	-0.08	0.18	.45
Part-time employment	-0.49	0.30	-1.07	0.10	.10
Fulltime employment	-0.23	0.28	-0.77	0.32	.43
Subjective sleep quality 1	0.89	0.26	0.38	1.39	.001*
Subjective sleep quality 2	1.47	0.35	0.78	2.15	<.001*
Subjective sleep quality 3	2.80	0.68	1.47	4.14	<.001*
Sleep latency 1	0.19	0.23	-0.27	0.64	.42
Sleep latency 2	0.43	0.30	-0.15	1.01	.14
Sleep latency 3	-0.08	0.46	-0.84	0.99	.87
Sleep duration 1	-0.26	0.25	-0.76	0.23	.30
Sleep duration 2	-1.00	0.40	-1.78	-0.21	.01
Sleep duration 3	-1.08	0.61	-2.28	0.13	.08
Sleep efficiency 1	0.02	0.29	-0.54	0.58	.95
Sleep efficiency 2	1.00	0.48	0.05	1.95	.04
Sleep efficiency 3	1.14	0.71	0.25	2.53	.11
Sleep disruptions 1	-0.50	0.40	-1.29	0.29	.21
Sleep disruptions 2	-0.50	0.46	-1.40	0.39	.27
Sleep disruptions 3	0.42	0.79	-1.14	1.97	.60
Sleep medication 1	-0.03	0.60	-1.21	1.15	.96
Sleep medication 2	-0.06	0.55	-1.13	1.02	.92
Sleep medication 3	0.42	0.40	-0.37	1.22	.30

(Continued on next page)

Table 3 *(continued)*

	Model 1[a]				
			95% CI		
	B	(SE)	Lower	Upper	*p*

aMS average midsleep; **BMI** Body Mass Index; **NHL** Non-Hodgkin lymphoma; **CT** chemotherapy; **RT** radiotherapy; * <.0038 (model 1) or <.0015 (model 2)
[a] For model 1, a Bonferroni corrected p-value of 0.0038 (0.05/13) was used. For model 2, a Bonferroni corrected p-value of 0.0015 (0.05/34) was used.
Intermediate aMS: intermediate aMS (1) vs early aMS (0) and late aMS (0)
Late aMS: late aMS (1) vs early aMS (0) and intermediate aMS (0)
Age: included as continuous variables in years
Male: male (1) vs female (0)
BMI overweight: BMI overweight (1) vs BMI healthy (0) and BMI obese (0)
BMI obese: BMI obese (1) vs BMI healthy (0) and BMI overweight (0)
Married: married or living together (1) vs single, widow or divorced (0)
College or university: college or university (1) vs primary education, high school/vocational education (0)
NHL: non-Hodgkin lymphoma (1) vs Hodgkin lymphoma (0)
Time since diagnosis: included as continuous variable in years
Comorbidities: included as continuous variable in number of self-reported comorbidities.
Part time employment: part time employed (1) vs no employment (0) or fulltime employment (0)
Fulltime employment: fulltime employed (1) vs no employment (0) or part time employment (0)
Subjective sleep quality: reference category is good subjective sleep quality (0)
Sleep latency: reference category is no problems (0)
Sleep duration: reference category is more than 7 hours (0)
Sleep efficiency: reference category is more than 85% (0)
Sleep disruptions: reference category is no disruptions (0)
Sleep medication: reference category is no sleep medication (0)
Daily dysfunctioning: reference category is no dysfunctioning (0)

DISCUSSION

The aim of this study was to investigate the associations between chronotype and cancer-related fatigue and between sleep quality and cancer-related fatigue. Contrary to our hypothesis, the results do not support an association between chronotype and fatigue, measured by average midsleep. There were associations between two aspects of sleep quality and fatigue, specifically subjective sleep quality and daily dysfunctioning, indicating that a higher level of fatigue is associated with lower levels of self-reported sleep quality. Interestingly, we showed that fatigued survivors have comparable self-reported actual sleep times to those with no to mild fatigue but spend a longer time in bed trying to fall asleep. Additionally, our results showed that survivors who are younger or have more comorbidities reported higher levels of fatigue after cancer. These associations attenuated when sleep quality was taken into account.

Previous studies on the association between chronotype and fatigue in other populations showed mixed results. One study showed that morning type individuals with irritable bowel symptoms reported less fatigue compared to evening types while this association was absent in healthy controls[17]. Another study showed increased levels of chronic work-related fatigue

	Model 2[a]				
			95% CI		
	B	(SE)	Lower	Upper	*p*
Daily dysfunctioning 1	2.15	0.23	1.70	2.60	<.001*
Daily dysfunctioning 2	3.09	0.28	2.53	3.64	<.001*
Daily dysfunctioning 3	3.28	0.50	2.31	4.26	<.001*

in evening type student-workers compared to morning and intermediate types[18]. However, in line with the current results, a recent study in patients with rheumatoid arthritis showed no association between chronotype and fatigue while these patients reported a 23 minutes earlier chronotype compared to the general population[40].

One explanation for these mixed results might be the use of different questionnaires to assess chronotype. The MCTQ assesses actual sleep times, but other questionnaires like the Morningness Eveningness Questionnaire (MEQ)[41] and Composite Scale of Morningness (CSM)[42] use preferred sleep times in ideal circumstances and statements to determine chronotype. The advantage of the MEQ and Composite Scale of Morningness is the cut-off score to determine chronotype. For the MCTQ, this determination is more arbitrarily as there are no cut-off times to determine chronotype. To address the issue of mixed results, it is important to replicate the previous findings based on self-reported information with an objective assessment of circadian phase. Until now, this was difficult for large-scaled studies because the golden standard for this assessment is the assessment of Dim Light Melatonin Onset (DLMO). This procedure is very time-consuming. However, the BodyTime assay was introduced recently[43]. This assay determines the circadian phase based on a single blood sample, which makes it more suitable for large-scaled studies.

Although the current results did not provide evidence for an association between chronotype and fatigue after cancer, our results do not contradict previous studies on circadian disruptions in cancer survivors[6-9]. The primary focus of the current study was to investigate whether the timing of actual sleep time, defined as chronotype, differed between survivors of cancer with and without fatigue. The studies on circadian disruptions looked more broadly at disruptions in rest-activity patterns (for example lying awake during the night and taking naps during the day to compensate) and showed that these disruptions were associated with cancer side effects like fatigue, sleep disturbances, depression, and cognitive impairment. Our results suggest a disturbed circadian rhythm in cancer patients with severe fatigue when we have a closer look to their sleep times. Results showed that survivors with moderate to severe fatigue tend to spend more time in bed before they fall asleep. One possible explanation is that fatigued survivors go to bed too early with respect to their circadian sleep drive. In other words, they might feel tired while their circadian rhythm is not yet set to sleep. Moreover, moderately and severely fatigued survivors reported more sleep disruptions compared to survivors without fatigue complaints.

Study strengths and limitations

As far as we know, the current study is the first to explore a potential association between circadian phase, defined as chronotype, and fatigue in cancer survivors. It is important to study this association as it provides more information on the optimal timing of light therapy as a treatment for fatigue after cancer. The results of this correlational study did not provide direct evidence that a delayed circadian phase is associated with fatigue after cancer. However, the results of the sleep times do not rule out that light therapy in the morning will improve fatigue in patients with a delayed circadian phase since moderate to severe fatigued survivors tend to take longer to get up in the morning and spend less time outside during the day. This suggests that they do not get early morning light, which is helpful to advance the circadian rhythm and will prepare them to fall asleep at an earlier time that might improve fatigue. Alternatively, light therapy might be able to improve fatigue by improving sleep quality, which was associated with cancer-related fatigue in our study. A recent study suggested an improvement of sleep quality after light therapy[27].

A second strength of this study was the use of average midsleep as an indicator for circadian phase instead of the original indicator of chronotype from the MCTQ. Originally, someone's chronotype is based on the calculation of the midpoint between sleep onset and offset on free days when no alarm clock is used, corrected for sleep debt during the week, the *mid-sleep on free days sleep corrected* (MSFsc). However, recent results showed a stronger association between DLMO and aMS[31] compared to the association between DLMO and MSFsc[44]. For this reason, aMS was used.

There are also several limitations. First, this survey study was also used to recruit participants for a clinical trial to study the efficacy of light therapy as a treatment for fatigue after cancer. The possibility of participation in a trial to decrease fatigue could have been an additional reason to return a completed questionnaire for those suffering from fatigue. This might explain the high prevalence of 70% of fatigue in responders compared to 40 to 60 percent reported in literature[2, 3]. Moreover, our sample included only survivors of (non-)Hodgkin lymphoma, possibly reducing its generalizability to other populations of cancer survivors.

Second, all data were self-reported by the participants. Clinical variables (diagnosis, time since diagnosis, etc.) could not be verified. Also, we made a crude categorization of employment status based on the self-reported number of working days. We had no information on working hours. Consequently, survivors who were part time employed could have been wrongly categorized as fulltime employment. Moreover, previous studies showed that there is a discrepancy between subjective and objectively measured sleep information[45]. Therefore, future studies should include objective measurements like the DLMO, BodyTime assay, or actigraphy to investigate the association between chronotype, sleep, and fatigue.

Third, the cross-sectional study design implies that our conclusions are based on associations. It is not possible to draw conclusions on the chronological order of the investigated variables in relation to cancer-related fatigue. This is relevant because it is likely that some variables are an effect of fatigue rather than a causal factor, for example daily dysfunctioning. Longitudinal studies are necessary to provide more insight into the causality of associations found in the current study.

Future research

Some of our findings give rise to interesting future research. First, the attenuated associations between fatigue and age and fatigue and comorbidities when sleep quality was added to the model suggest that sleep quality mediates these associations. The current study focused on the relationship between chronotype and cancer-related fatigue and sleep quality and cancer-related fatigue. Therefore, we did not perform mediation analyses to test this hypothesis. It is our recommendation that future research investigates a potential mediating effect of sleep quality while investigating factors that are associated with fatigue after cancer. Second, studies could investigate whether interventions aiming to improve sleep quality are more beneficial as a treatment for fatigue after cancer compared to interventions aiming to improve circadian phase.

Clinical implications

This study suggests that fatigue after cancer is associated with subjective sleep quality and not with chronotype. For this reason, clinicians should not only focus on a patient's timing of sleep and duration but also on the sleep quality reported by survivors of cancer. To do this, clinicians can ask questions like "How would you rate your sleep quality in the previous month: very good, fairly good, fairly bad or very bad?" and "How often do you have trouble to stay awake while driving, eating meals or engaging in social activities?" When a patient reports fairly bad or very bad sleep quality and problems to stay awake, further investigation of the sleep pattern and fatigue is necessary to determine the clinical significance of the fatigue. In case of clinical significant fatigue, patients should be referred for treatment (for example refer to cognitive behavioral therapy[46] or receive sleep hygiene information).

Conclusions

The current study aimed to provide more insight into cancer-related fatigue by investigating associations between 1) fatigue and chronotype and 2) fatigue and sleep quality. As fatigue levels were related to sleep quality but not to chronotype, the results suggest that it is likely that fatigue is associated with disrupted sleep rather than circadian phase. More objectively measured circadian and sleep aspects are necessary to confirm this conclusion.

REFERENCES

1. Mortimer J E, Barsevick A M, Bennett C L, Berger A M, Cleeland C, DeVader S R, et al. (2010). Studying cancer-related fatigue: report of the NCCN scientific research committee. *J Natl Compr Canc Netw*, 8(12):1331-9.
2. Oerlemans S, Mols F, Issa D E, Pruijt J, Peters W G, Lybeert M, et al. (2013). A high level of fatigue among long-term survivors of non-Hodgkin's lymphoma: results from the longitudinal population-based PROFILES registry in the south of the Netherlands. *Haematologica*, 98(3):479-86.
3. Daniëls L, Oerlemans S, Krol A, Creutzberg C, van de Poll-Franse L (2014). Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. *Br J Cancer*, 110(4):868-74.
4. Mock V, Atkinson A, Barsevick A, Cella D, Cimprich B, Cleeland C, et al. (2000). NCCN Practice Guidelines for Cancer-Related Fatigue. Oncology (Williston Park, NY), 14(11A):151-61.
5. O'Higgins C, Brady B, O'Connor B, Walsh D, Reilly R (2018). The pathophysiology of cancer-related fatigue: current controversies. *Support Care Cancer*, 26(10):3353-64.
6. Innominato P F, Roche V P, Palesh O G, Ulusakarya A, Spiegel D, Lévi F A (2014). The circadian timing system in clinical oncology. *Ann Med*, 46(4):191-207.
7. Payne J K (2011). Altered circadian rhythms and cancer-related fatigue outcomes. *Integr Cancer Ther*, 10(3):221-33.
8. Rich T A (2007). Symptom clusters in cancer patients and their relation to EGFR ligand modulation of the circadian axis. *J Support Oncol*, 5(4):167-74.
9. Mormont M-C, Waterhouse J (2002). Contribution of the rest–activity circadian rhythm to quality of life in cancer patients. *Chronobiol Int*, 19(1):313-23.
10. Schrepf A, Clevenger L, Christensen D, DeGeest K, Bender D, Ahmed A, et al. (2013). Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability. *Brain Behav Immun*, 30:S126-S34.
11. Schmidt M E, Semik J, Habermann N, Wiskemann J, Ulrich C M, Steindorf K (2016). Cancer-related fatigue shows a stable association with diurnal cortisol dysregulation in breast cancer patients. *Brain Behav Immun*, 52:98-105.
12. Roenneberg T, Pilz L K, Zerbini G, Winnebeck E C (2019). Chronotype and Social Jetlag: A (Self-) Critical Review. *Biology*, 8(3):54.
13. Levandovski R, Dantas G, Fernandes L C, Caumo W, Torres I, Roenneberg T, et al. (2011). Depression scores associate with chronotype and social jetlag in a rural population. *Chronobiol Int*, 28(9):771-8.
14. Caruso D, Meyrel M, Krane-Gartiser K, Benard V, Benizri C, Brochard H, et al. (2020). Eveningness and poor sleep quality contribute to depressive residual symptoms and behavioral inhibition in patients with bipolar disorder. *Chronobiol Int*, 37(1):101-10.
15. Soreca I, Fagiolini A, Frank E, Goodpaster B H, Kupfer D J (2009). Chronotype and body composition in bipolar disorder. *Chronobiol Int*, 26(4):780-8.
16. Lewy A J, Lefler B J, Emens J S, Bauer V K (2006). The circadian basis of winter depression. *PNAS*, 103(19):7414-9.
17. Chrobak A A, Nowakowski J, Zwolińska-Wcisło M, Cibor D, Przybylska-Feluś M, Ochyra K, et al. (2018). Associations between chronotype, sleep disturbances and seasonality with fatigue and inflammatory bowel disease symptoms. *Chronobiol Int*, 35(8):1142-52.
18. Martin J S, Hébert M, Ledoux É, Gaudreault M, Laberge L (2012). Relationship of chronotype to sleep, light exposure, and work-related fatigue in student workers. *Chronobiol Int*, 29(3):295-304.
19. Ancoli-Israel S, Liu L, Marler M R, Parker B A, Jones V, Sadler G R, et al. (2006). Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. *Support Care Cancer*, 14(3):201-9.
20. Anderson K O, Getto C J, Mendoza T R, Palmer S N, Wang X S, Reyes-Gibby C C, et al. (2003). Fatigue and sleep disturbance in patients with cancer, patients with clinical depression, and community-dwelling adults. *J Pain Symptom Manage*, 25(4):307-18.
21. Coles T, Tan X, Bennett A V, Sanoff H K, Basch E, Jensen R E, et al. (2018). Sleep quality in individuals diagnosed with colorectal cancer: Factors associated with sleep disturbance as patients transition off treatment. *Psychooncology*, 27(3):1050-6.
22. Fortmann J, Fisher A, Hough R, Gregory A, Pugh G (2018). Sleep quality, fatigue, and quality of life among teenage and young adult cancer survivors. *J. Adolesc. Young Adult Oncol.*, 7(4):465-71.

23. Ancoli-Israel S, Rissling M, Neikrug A, Trofimenko V, Natarajan L, Parker B A, et al. (2012). Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. *Support Care Cancer*, 20(6):1211-9.
24. Redd W H, Valdimarsdottir H, Wu L M, Winkel G, Byrne E E, Beltre M A, et al. (2014). Systematic light exposure in the treatment of cancer-related fatigue: a preliminary study. *Psychooncology*, 23(12):1431-4.
25. Johnson J A, Garland S N, Carlson L E, Savard J, Simpson J S A, Ancoli-Israel S, et al. (2017). Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. *J Cancer Surviv*, 12:1-10.
26. Lewy A J, Bauer V K, Cutler N L, Sack R L, Ahmed S, Thomas K H, et al. (1998). Morning vs evening light treatment of patients with winter depression. *Arch Gen Psychiatry*, 55(10):890-6.
27. Wams E J, Woelders T, Marring I, van Rosmalen L, Beersma D G, Gordijn M C, et al. (2017). Linking light exposure and subsequent sleep: A field polysomnography study in humans. *Sleep*, 40(12):zsx165.
28. Starreveld D E J, Daniels L A, Valdimarsdottir H B, Redd W H, de Geus J L, Ancoli-Israel S, et al. (2018). Light therapy as a treatment of cancer-related fatigue in (non-) Hodgkin lymphoma survivors (SPARKLE trial): study protocol of a multicenter randomized controlled trial. *BMC Cancer*, 18(1):880.
29. Sangha O, Stucki G, Liang M H, Fossel A H, Katz J N (2003). The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Care Res (Hoboken)*, 49(2):156-63.
30. Roenneberg T, Wirz-Justice A, Merrow M (2003). Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms*, 18(1):80-90.
31. Kantermann T, Burgess H J (2017). Average mid-sleep time as a proxy for circadian phase. *PsyCh journal*, 6(4):290-1.
32. Oldenmenger W H, Pleun J, de Klerk C, van der Rijt C C (2013). Cut points on 0–10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review. *J Pain Symptom Manage*, 45(6):1083-93.
33. Smets E, Garssen B, Bonke B d, De Haes J (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 39(3):315-25.
34. Kieffer J M, Starreveld D E J, Boekhout A, Bleiker E M A (2021). A questionable factor structure of the multidimensional fatigue inventory in the general Dutch population. *J Clin Epidemiol*, 137:266-76.
35. Buysse D J, Reynolds C F, Monk T H, Berman S R, Kupfer D J (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*, 28(2):193-213.
36. Kreissl S, Mueller H, Goergen H, Mayer A, Brillant C, Behringer K, et al. (2016). Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. *Lancet Oncol.*, 17(10):1453-62.
37. Rubin D B Multiple imputation for nonresponse in surveys. Hoboken, New Jersey: John Wiley & Sons; 1987.
38. van Buuren S, Groothuis-Oudshoorn K (2011). Mice: multivariate imputation by chained equations in R. *J. Stat. Softw.*, 45(3):1–67.
39. R Core Team. R: A language and environment for statistical computing. 3.6.1 ed. Vienna, Austria: R Foundation for Statistical Computing; 2013.
40. Habers G E A, van der Helm-van A H M, Veldhuijzen D S, Allaart C F, Vreugdenhil E, Starreveld D E J, et al. (2021). Earlier chronotype in patients with rheumatoid arthritis. *Clin Rheumatol*, 40:2185-92.
41. Horne J A, Ostberg O (1975). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol*, 4(2):97-110.
42. Smith C S, Reilly C, Midkiff K (1989). Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. *J Appl Psychol*, 74(5):728-38.
43. Wittenbrink N, Ananthasubramaniam B, Münch M, Koller B, Maier B, Weschke C, et al. (2018). High-accuracy determination of internal circadian time from a single blood sample. *The Journal of clinical investigation*, 128(9):3826-39.
44. Kantermann T, Sung H, Burgess H J (2015). Comparing the morningness-eveningness questionnaire and munich chronotype questionnaire to the dim light melatonin onset. *J Biol Rhythms*, 30(5):449-53.
45. Landry G J, Best J R, Liu-Ambrose T (2015). Measuring sleep quality in older adults: a comparison using subjective and objective methods. *Front Aging Neurosci*, 7:166.
46. Gielissen M F, Verhagen S, Witjes F, Bleijenberg G (2006). Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol*, 24(30):4882-7.

APPENDIX

Table A1. Linear model of independent variables on the continuous value of the VAS-fatigue on complete cases (N=379)

	Model 1[a]				
			95% CI		
	B	(SE)	Lower	Upper	*p*
Constant	7.69	0.71	6.29	9.09	
Intermediate aMS	0.25	0.27	-0.29	0.79	.36
Late aMS	0.09	0.36	-0.63	0.80	.81
Age	-0.06	0.01	-0.08	-0.04	<.001*
Male	-0.48	0.27	-1.01	0.06	.08
BMI: overweight	0.40	0.27	-0.13	0.94	.14
BMI: obese	0.40	0.38	-0.34	1.14	.29
Married	-0.44	0.30	-1.03	0.14	.14
College or university	0.21	0.26	-0.30	0.71	.43
NHL	0.25	0.31	-0.35	0.85	.42
Time since diagnosis	0.00	0.01	-0.03	0.03	.83
Comorbidities	0.39	0.09	0.22	0.55	<.001*
Part time employment	-0.66	0.38	-1.42	0.09	.09
Fulltime employment	-0.89	0.35	-1.57	-0.21	.01

	Model 2[a]				
			95% CI		
	B	(SE)	Lower	Upper	*p*
Constant	3.50	0.74	2.05	4.95	
Intermediate aMS	0.05	0.23	-0.39	0.50	.82
Late aMS	-0.19	0.31	-0.80	0.42	.54
Age	-0.02	0.01	-0.04	0.00	.05
Male	-0.38	0.23	-0.83	0.07	.10
BMI: overweight	0.22	0.22	-0.20	0.65	.30
BMI: obese	0.25	0.30	-0.34	0.84	.41
Married	0.14	0.25	-0.34	0.62	.57
College or university	-0.12	0.21	-0.53	0.30	.58
NHL	-0.03	0.25	-0.52	0.46	.91
Time since diagnosis	0.00	0.01	-0.02	0.02	.95
Comorbidities	0.05	0.07	-0.10	0.20	.49
Part time employment	-0.40	0.33	-1.04	0.24	.22
Fulltime employment	-0.23	0.29	-0.81	0.35	.43
Subjective sleep quality 1	0.89	0.28	0.35	1.44	.001*
Subjective sleep quality 2	1.39	0.39	0.63	2.15	<.001*
Subjective sleep quality 3	2.93	0.75	1.45	4.41	<.001*
Sleep latency 1	0.19	0.24	-0.29	0.67	.44
Sleep latency 2	0.46	0.33	-0.19	1.10	.16
Sleep latency 3	0.29	0.51	-0.71	1.29	.57
Sleep duration 1	-0.13	0.29	-0.69	0.43	.64
Sleep duration 2	-1.41	0.43	-2.25	-0.58	.001*
Sleep duration 3	-1.89	0.90	-3.65	-0.11	.04
Sleep efficiency 1	0.06	0.30	-0.54	0.66	.85
Sleep efficiency 2	0.67	0.56	-0.44	1.77	.24
Sleep efficiency 3	2.05	0.90	0.28	3.81	.02
Sleep disruptions 1	-0.59	0.44	-1.45	0.27	.18
Sleep disruptions 2	-0.67	0.51	-1.66	0.33	.19
Sleep disruptions 3	0.65	0.86	-1.03	2.34	.45
Sleep medication 1	-0.18	0.61	-1.38	1.03	.78
Sleep medication 2	-0.29	0.64	-1.55	0.97	.65
Sleep medication 3	0.53	0.45	-0.36	1.41	.24

(Continued on next page)

Table A1. *(continued)*

	Model 1[a]				
			95% CI		
	B	(SE)	Lower	Upper	*p*
R^2 = .17					

aMS average midsleep; **BMI** Body Mass Index; **NHL** Non-Hodgkin lymphoma; * <.0038 (model 1) or <.0015 (model 2)

[a] For model 1, a Bonferroni corrected p-value of 0.0038 (0.05/13) was used. For model 2, a Bonferroni corrected p-value of 0.0015 (0.05/34) was used.

Intermediate aMS: intermediate aMS (1) vs early aMS (0) and late aMS (0)
Late aMS: late aMS (1) vs early aMS (0) and intermediate aMS (0)
Age: included as continuous variables in years
Male: male (1) vs female (0)
BMI overweight: BMI overweight (1) vs BMI healthy (0) and BMI obese (0)
BMI obese: BMI obese (1) vs BMI healthy (0) and BMI overweight (0)
Married: married or living together (1) vs single, widow or divorced (0)
College or university: college or university (1) vs primary education, high school/vocational education (0)
NHL: non-Hodgkin lymphoma (1) vs Hodgkin lymphoma (0)
Time since diagnosis: included as continuous variable in years
Comorbidities: included as continuous variable in number of self-reported comorbidities.
Part time employment: part time employed (1) vs no employment (0) or fulltime employment (0)
Fulltime employment: fulltime employed (1) vs no employment (0) or part time employment (0)
Subjective sleep quality: reference category is good subjective sleep quality (0)
Sleep latency: reference category is no problems (0)
Sleep duration: reference category is more than 7 hours (0)
Sleep efficiency: reference category is more than 85% (0)
Sleep disruptions: reference category is no disruptions (0)
Sleep medication: reference category is no sleep medication (0)
Daily dysfunctioning: reference category is no dysfunctioning (0)

	Model 2[a]				
			95% CI		
	B	(SE)	Lower	Upper	*p*
Daily dysfunctioning 1	2.32	0.25	1.82	2.81	<.001*
Daily dysfunctioning 2	3.31	0.31	2.70	3.91	<.001*
Daily dysfunctioning 3	3.20	0.57	2.08	4.32	<.001*

R^2 = .52

Δ R^2 = .35, p <.001

CHAPTER 7

SUMMARY AND GENERAL DISCUSSION

The studies in this thesis report on the outcomes of a double blind, randomized controlled trial (RCT) of light therapy in Hodgkin Lymphoma (HL) and Diffuse Large B-cell lymphoma (DLBCL) survivors with persistent moderate to severe fatigue since diagnosis. We evaluated the short- and long-term efficacy of light therapy on improving fatigue after cancer and associated symptoms including sleep quality, depression, anxiety, quality of life, cognitive complaints, cognitive functioning, and circadian rhythms of sleep-wake cycles, melatonin, and cortisol. In addition, we described a psychometric evaluation of one of the primary outcomes, the Multidimensional Fatigue Inventory (MFI) in the general Dutch population. We also reported on the associations of chronotype with cancer-related fatigue (CRF) and sleep quality with CRF. This chapter summarizes our main findings in part 1. In part 2, we discuss our results with respect to the current literature and report on methodological considerations, overall conclusions, clinical implications, and implications for future research.

PART 1: SUMMARY

Chapter 1 introduces the need for an effective treatment for cancer-related fatigue for HL and DLBCL survivors. In the Netherlands, the BETER consortium offers a healthcare infrastructure for survivorship care after a HL and DLBCL diagnosis. Within this consortium, survivors are informed about late adverse effects of treatment and offered screening and timely treatment. Cancer-related fatigue (CRF) is one of the most reported symptoms by HL and DLBCL survivors to radiation-oncologists and hematologists in this consortium. The prevalence rates range between 41 to 61 percent compared to a prevalence of moderate to severe fatigue of 23 to 28 percent in the general Dutch population. Although the etiology of CRF is unknown, it is suggested that CRF results from multiple factors covering demographic, medical, psychosocial, behavioral, and biological factors. An example of a biological factor is circadian rhythm disruptions. Despite its high prevalence, evidence-based treatments for CRF are limited (i.e. cognitive behavioral therapy or physical exercise) and are not effective for all survivors suffering from CRF (these therapies require a high motivation from patients). Therefore, it is important to investigate alternative treatments, for example light therapy. When the research described in this thesis started, two pilot studies in breast cancer patients receiving chemotherapy (n = 39) and cancer survivors (n = 36) showed promising effect of light therapy as a treatment for CRF. Moreover, secondary analyses indicated that light therapy affected symptoms associated with CRF including circadian sleep-wake cycles and quality of life. Therefore, it was hypothesized that light therapy reduced fatigue through a restorative effect on circadian rhythms. Despite the positive effects in these pilot studies, there were limitations including small sample sizes and short follow up times (up to three weeks post-intervention) and questions remained about the mechanisms of action that explain the positive effect of light therapy. Hence, replication of these results in a sufficiently powered randomized controlled trial and the investigation of possible mechanisms of action were necessary.

Chapter 2 describes the rationale and design of the SPARKLE study, where we aimed to examine the efficacy of light therapy on improving CRF. Participants were recruited from 10 community and academic hospitals. Eligible survivors were randomly assigned to exposure

to bright white light (BWL; intervention) or exposure to dim white light (DWL; control). Participants were instructed to use light therapy within 30 minutes after awakening for a duration of 30 minutes on 25 consecutive days. Primary outcomes included fatigue and work and social adjustments caused by this fatigue. Secondary outcomes included depression, anxiety, quality of life, sleep quality, circadian rhythms of sleep-wake cycles, melatonin, cortisol, cognitive complaints and cognitive functioning. Outcome measures were assessed at baseline (T0), immediate post-intervention (T1), and at three (T2) and nine (T3) months follow-up. Survivors in the DWL group were offered BWL after completion of the T3 assessment. Based on this study design, it was possible to replicate the promising effect of light therapy on CRF in a sufficiently powered trial, investigate the long-term effect of light therapy on CRF and explore potential mechanisms of action.

Chapter 3 reports the findings of the SPARKLE study. In total, 166 HL and DLBCL survivors with a mean age of 46 and a mean survivorship of 13 years participated. Compliance rates were high with a mean use of light therapy of 23 days. 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 three aspects of quality of life (role limitations due to physical functioning, energy, and social functioning). Light therapy had no effect on anxiety, sleep-wake cycles (determined with actigraphy), and cortisol and melatonin levels. Subgroup analyses on participants who used: 1) light therapy on all 25 treatment days (n = 56); 2) Luminette glasses (n = 127); or 3) light therapy during autumn or winter (n = 88) showed similar results and did not change our conclusions. At the individual patient level, 35 to 63 percent of the survivors showed a clinically relevant reduction of fatigue at T1, irrespective of condition. This study demonstrates that BWL was not superior in reducing fatigue compared to DWL. Instead, both groups showed reduced fatigue levels. Future research is necessary to investigate which elements of the study protocol led to these condition-independent improvements.

Chapter 4 presents the effect of light therapy on cognitive complaints and cognitive functioning in long-term HL and DLBCL survivors with CRF. Over one-third of the participants showed cognitive dysfunction at baseline, specifically in verbal memory where deviant scores were observed for immediate recall in 34% and delayed recall in 27% of the participants compared to 16% in the norm population. Neither BWL nor DWL diminished cognitive complaints or improved cognitive functioning (range *p*-values .07 to .80; range effect sizes .04 to .29) in the total group of fatigued survivors nor in the subgroup suffering from cognitive dysfunction. These results indicate that approximately one-third of long-term HL and DLBCL survivors experience cognitive dysfunctioning. Light therapy does not appear to improve these complaints. Therefore, we suggest that other cognitive rehabilitation interventions should be made available to mitigate cognitive dysfunctioning in these survivors.

Chapter 5 presents the results of a psychometric evaluation of the Multidimensional Fatigue Inventory (MFI), which was one of the primary outcomes of the SPARKLE study. The original validation study suggested that the MFI measures five domains of fatigue, i.e. *general fatigue*, *physical fatigue*, *reduced activity*, *reduced motivation*, and *mental fatigue*, although

two four-factor structures also showed acceptable fit. Further validation studies showed inconclusive results on the factor structure of the MFI. The aim of this psychometric evaluation was to investigate the scale structure of the MFI in the general Dutch population (n = 2512). The results of a confirmatory factor analysis did not provide support for the original 5-factor structure (RMSEA = 0.120, CFI = 0.933, TLI = 0.920). Moreover, we were unable to replicate a four-factor structure that combined the general fatigue and physical fatigue subscales (RMSEA = 0.122, CFI = 0.928, TLI = 0.917). Adding a general factor to the five- and four-factor model to create a bi-factor model also did not show acceptable model fit (bi-4-factor: RMSEA = 0.151, CFI = 0.895, TLI = 0.873; bi-5-factor: RMSEA = 0.153, CFI = 0.894, TLI = 0.871). Exploratory factor analyses provided no alternative models with an acceptable model fit but seemed to show robustness in the loading of the original *general fatigue* items. These results did not provide empirical support for a four or five (bi-)factor structure of the MFI, nor for an alternative model. We propose that the most reliable scale of the MFI seems to be the *general fatigue* scale. This scale could be used as a general indicator of fatigue.

Chapter 6 reports on the results of a survey study, which was part of the recruitment for the SPARKLE study. Hence, it was completed by (non-)Hodgkin lymphoma survivors with and without fatigue. The rationale for this study was based on the ability of light to align internal circadian rhythms to external rhythm. Although several studies showed that circadian disruptions in the sleep-wake cycle (more awakenings during the night and more naps during the day) are associated with CRF in patients with cancer, it is unclear whether the timing of this rhythm is misaligned from the external rhythm in cancer survivors with CRF. Therefore, we investigated the associations of chronotype (someone's preference in the timing of sleep and wake, i.e. a morning or an evening type) with CRF, and sleep quality with CRF in a survey study. It was hypothesized that evening types would report higher levels of cancer-related fatigue compared to morning types. A total number of 458 survivors (50% female) with a mean age of 50 years completed a VAS fatigue-scale from 0 (no fatigue) to 10 (worst imaginable fatigue), the Munich Chronotype Questionnaire (MCTQ), and the Pittsburgh Sleep Quality Index (PSQI) between October 2018 and July 2019. The majority was diagnosed with a HL (71%) and the mean time since diagnosis was 12 years. Sixty-six percent of our sample reported moderate to severe fatigue. There was no statistically significant difference for average midsleep time, i.e. the midpoint between sleep onset and sleep offset that was used to determine chronotype, between survivors with and without fatigue symptoms. A hierarchical linear regression analysis was used to evaluate the associations between fatigue and chronotype (based on early, intermediate, or late average midsleep) in model 1, and fatigue and sleep quality in model 2. The results showed no indications for an association between chronotype and fatigue (all p-values ≥ .50). There were associations between two (out of seven) aspects of sleep quality and fatigue: subjective sleep quality ($p < .001$) and daily dysfunctioning ($p < .001$). Therefore, it is more likely that CRF in long-term HL and DLBCL survivors is associated with self-reported sleep quality rather than with chronotype.

PART 2: GENERAL DISCUSSION

This section describes a general discussion of the studies presented in this thesis. It is divided in two different parts. The first part covers light therapy for CRF and related symptoms. The second part covers circadian rhythms and CRF. The buildup of each part is as follows: first, we discuss our findings in the context of the current literature; thereafter follows a discussion of methodological limitations and an overview of overall conclusions; and finally, we reflect on the clinical implications and provide suggestions for future research.

LIGHT THERAPY FOR CANCER RELATED FATIGUE

Comparison with the literature

The rational for the SPARKLE study was based on two pilot studies from Ancoli-Israel et al.[1] in patients with breast cancer and Redd et al.[2] in cancer survivors that showed promising effects of light therapy as a treatment for CRF. Since then, several studies[3-13] on the effect of light therapy in cancer populations have been published. The sections below provide an overview of the results of these studies. First, studies that investigated the use of light therapy for CRF in cancer survivors with fatigue complaints are mentioned. Second, light therapy for cancer survivors with other symptoms are evaluated. Finally, light therapy for patients with cancer while receiving treatment are described. An overview of these studies is provided in Table 1.

Light therapy for cancer survivors with cancer-related fatigue

Two studies investigated the use of light therapy for cancer survivors with CRF as a treatment to reduce fatigue. The first study by Redd et al.[2] randomly assigned 36 survivors to exposure to BWL or dim red light (DRL) and used the FACIT-fatigue as primary outcome. The results showed superiority of BWL over DRL with an effect size of 0.98. The second study by Johnson et al. studied light therapy in 81 cancer survivorswho met ICD-10 criteria for CRF and compared exposure to BWL or DRL in a RCT[4]. Results showed superiority of BWL over DRL for reducing fatigue symptoms with an effect size of 0.30, indicating that the group exposed to BWL had a 17 percent larger reduction in fatigue complaints compared to participants exposed to DRL.

Our results showed no superiority of BWL over DWL on reducing fatigue but indicated that both groups, irrespective of light intensity, reported reduced fatigue (based on a VAS-scale for fatigue and the general fatigue subscale of the MFI) after completion of the light therapy protocol (**chapter 3**). This was an unexpected finding because both Redd et al.[2] and Johnson et al.[4] reported superiority of BWL. However, it is important to notice that Johnson et al. only observed superiority of BWL for the total score of the Multidimensional Fatigue Symptom Inventory - short form (MFSI-SF)[14]. In line with our results, Johnson et al.[4] showed no differences between survivors exposed to BWL or DRL for the effect of light therapy on the five domains of fatigue assessed with the MFSI-sf (general, physical, emotional, and mental fatigue, and vigor). The total group, irrespective of light intensity, reported clinically relevant improvements on general, physical, emotional, and mental fatigue. No effect was observed for vigor. This indicates that the only study showing a convincing superiority of BWL over DRL

Table 1. Overview of studies on the effect of light therapy in cancer populations

Study[a]	Study type[b]	Participants	Light therapy characteristics
CANCER SURVIVORS WITH CRF			
Redd et al. (2014)[2]	PS	Breast, gynecologic, and hematological cancer survivors Mean survivorship: 17 months	BWL (n=18) vs DRL (n=18) Litebook 1.2 30 min within 30 min upon waking, 4 weeks
Wu et al. (2018)[3]			BWL (n=25) vs DRL (n=19)
Johnson et al. (2017)[4]	RCT	Cancer survivors Mean survivorship: 28 months	BWL (n=42) vs DRL (n=39) Litebook Elite 30 min within 30 min upon waking, 4 weeks
Garland et al. (2020)[5]			
Johnson et al. (2020)[6]			
CANCER SURVIVORS WITH SYMPTOMS OTHER THAN FATIGUE			
Kronish et al. (2019)[7]	PT	Cancer survivors with at least mild depressive symptoms Mean survivorship: N/A	BWL vs DRL N=8 Litebook Advantage 30 min each morning, 3 weeks of BWL or DRL, crossover across 12 weeks

Outcome	Instrument	Conclusion
Fatigue	FACIT-fatigue	• BWL showed superiority over DRL for reducing fatigue (effect size Cohen's *d* = 0.98). • DRL did not reduce fatigue.
Sleep-wake cycles	Wrist actigraphy	• BWL showed superiority over DRL for improving sleep efficiency (partial η^2 = 0.28). • No effect on total sleep time and wake after sleep onset.
Sleep quality	PSQI	• No effect on sleep quality.
Fatigue	MFSI-SF	Total score: • BWL showed superiority over DRL for reducing fatigue (effect size Cohen's *d* = 0.30). • DRL did reduce fatigue (effect size Cohen's *d* = 0.93 compared to *d* = 1.20 in BWL). Subscales: • Improvements on general, physical, emotional, and mental fatigu over time in both groups. • No effect on vigor.
Mood	POMS-SF	• Improvement of mood disturbance over time in both groups.
Depression	CES-D	• Reduction of depressive symptoms over time in both groups.
Quality of Life	FACT-G	• Improvements of QoL over time in both groups.
Insomnia	ISI	• BWL showed superiority over DRL for improving insomnia.
Sleep quality	PSQI	• Improvements of sleep quality over time in both groups.
Sleep-wake cycles	Wrist actigraphy	• No effect on sleep onset latency, wake after sleep onset, sleep efficiency, and total sleep time.
Cortisol	Diurnal slope	• Increased cortisol slopes over time in both groups.
	Total cortisol output	• Increased cortisol output over time in both groups.
Depression	VAS-depression (daily)	• Two individuals reported a decrease, five reported no difference and one reported an increase of depressive symptoms after BWL compared to DRL.
Fatigue	VAS-fatigue (daily)	• One individual reported a decrease, six reported no differences, and one reported an increase of fatigue after BWL compared to DRL.

(Continued on next page)

Table 1. *(continued)*

Study[a]	Study type[b]	Participants	Light therapy characteristics
Fox et al. (2020)[8]	FS	Ovarian and gynecologic cancer survivors with sleep disturbances Mean survivorship: N/A	Green BL (n=10) vs DRL (n=11) Re-Timer 45 min upon waking, 4 weeks
Rogers et al. (2020)[9]	FS	Adolescent cancer survivors Mean survivorship: 12 months	BWL (n=8) Litebook Elite 30 min upon waking, 4 weeks
PATIENTS WITH CANCER WHILE RECEIVING CANCER TREATMENT			
Ancoli-Israel et al. (2012)[1]	PS	Breast cancer patients receiving 4 cycles of chemotherapy	BWL (n=23) vs. DRL (n=16) Litebook 1.2 30 min upon waking, 8-12 weeks (4 cycles of chemotherapy)
Neikrug et al. (2012)[10]			
Jeste et al. (2013)[11]			

Outcome	Instrument	Conclusion
Sleep-wake cycles	Wrist actigraphy	• Tendency for superiority of BL over DRL on number of nighttime wakenings. • Tendency for an increase of total sleep time over time in both groups. • No effect on time in bed, sleep onset latency, wake after sleep onset, sleep efficiency.
Sleep quality	PSQI	• Tendency for superiority of BL over DRL on improving sleep quality.
Quality of life	FACT-G	• No effect on quality of life.
Fatigue	FACIT-fatigue	• Improvements of fatigue over time in both groups.
Cognitive function	FACT-Cognitive Function	• Tendency for superiority of BL over DRL on the comments from others subscale.
Depression	PROMIS-Depression Item Bank	• Tendency for superiority of BL over DRL on depressive symptoms.
Diurnal cortisol	Saliva	• No effect on cortisol.
Melatonin	Urine	• No effect on melatonin.
Sleep-wake cycles	Wrist actigraphy	• No effect on acrophase, amplitude, *F*-statistic, MESOR.
Fatigue	MFSI-SF	Total score: • BWL prevented the increase of fatigue that was seen after DRL. • Changes in fatigue were unrelated to changes in sleep or circadian rhythms. Subscales: • Both groups showed worse scores on general, physical, or mental subscales. • No change on the vigor subscale.
Sleep-wake cycles	Wrist actigraphy	• Both groups showed a dampened and less robust circadian rhythm during chemotherapy weeks compared to baseline. • The circadian rhythm returned to baseline or improved during the recovery week in the BWL group. This was not seen in the DRL group. • No effect on acrophase (time of day of the peak of the circadian rhythm, which is indicative for a phase advance or delay).
Quality of life	FACT-B	• No significant differences on change in QoL over time between groups. • The DRL group showed significantly lower QoL during chemotherapy weeks compared to baseline.

(Continued on next page)

Table 1. *(continued)*

Study[a]	Study type[b]	Participants	Light therapy characteristics
Valdimarsdottir et al. (2018)[12]	RCT	Patients with multiple myeloma during autologous stem cell transplantation hospitalization	BWL (n=23) vs DWL (n=21) Acuity Brands Programmed environmental illumination of hospital rooms between 7 and 10 AM
Crabtree et al. (2020)[13]	FS	AYA's undergoing cancer treatment	BWL (n=26) vs DRL (n=25) Litebook Advantage 30 min within 1 h upon waking, 8 weeks

AYA adolescents and young adults; **BL** bright light; **BWL** bright white light; **CES-D** Center for Epidemiologic Studies-Depression scale; **DRL** dim red light; **FACIT-fatigue** Functional Assessment of Chronic Illness Therapy-Fatigue; **FACT-B** Functional Assessment of Cancer Therapy-Breast; **FACT-G** Functional Assessment of Cancer Therapy-General; **FOSQ** Functional outcomes of Sleep Questionnaire; **ISI** Insomnia Severity Index **MFS** Multidimensional Fatigue Scale; **MFSI-SF** Multidimensional Fatigue Symptom Inventory-Short Form; **POMS-SF** Profile of Mood States-Short Form; **PROMIS** Patient-Reported Outcome Measurement Information System; **PSQI** Pittsburgh Sleep Quality Index; **VAS** Visual Analogue Scale.
[a] Authors in italics reported secondary analyses of the primary studies reported by the authors in normal font. [b] **FS** feasibility study; **PS** pilot study; **PT** personalized (within-subjects) trials; **RCT** Randomized controlled trial

was the pilot study by Redd et al.[2]. Both RCTs that followed after this pilot study showed that reductions of fatigue were also observed after exposure to a control condition.

It is relevant to have a closer look at the clinical importance of the positive effects observed after light therapy. Redd et al.[2] reported a clinically important distinction between survivors exposed to BWL compared to DRL since none of the cancer survivors experienced clinical levels of fatigue after exposure to BWL, while 55 percent of the survivors exposed to DRL still experienced CRF. The effect size of this difference was 0.98. Johnson et al.[4] reported a smaller effect size of 0.30 for the superiority of BWL on the total score of the MFSI-sf. Our results showed an effect size of 0.81 for general fatigue in all participants, irrespective of condition, at post intervention, which corresponds to clinical significant benefits for 60 to 63 percent in the BWL and DWL group, respectively (**chapter 3**). This is in line with effect sizes of 0.96 and 0.76 on general fatigue in BWL and DRL, respectively, reported by Johnson et al.[4]. The effect sizes of our study and the study by Johnson et al. suggest clinically relevant improvements in both groups

Outcome	Instrument	Conclusion
Quality of life	FOSQ	• Significant deterioration in sleepiness-related QoL in DRL compared to no change in BWL. • Changes in sleepiness-related QoL were related to changes in fatigue.
Depression	CES-D	• No significant differences on change in depression over time between groups. • The DRL showed significantly more depressive symptoms during chemotherapy weeks compared to baseline.
Depression	CES-D	• BWL prevented the increase of depressive symptoms that was seen after DRL ($\eta^2 = 0.08$).
Fatigue	PedsQL MFS	Total score: • BWL showed larger reductions of fatigue than the reduction seen after DRL. Subscales: • BWL showed a reductions on cognitive fatigue, which was not seen after DRL. • Both groups showed reductions on general and sleep/rest fatigue.

as effect sizes of 0.50 or larger are considered clinically relevant[15]. Moreover, these numbers are comparable to clinically significant improvements resulting from cognitive behavioral therapy (clinical improvement in 54 percent)[16] and physical exercise ($d = 0.53$)[17]. This suggests that all light therapies, either BWL, DWL, or DRL, led to clinically relevant improvements of fatigue in cancer survivors with CRF.

Our results further showed that both groups, irrespective of condition, showed improvements on subjectively reported sleep quality, depression, and three aspects of quality of life (**chapter 3**). No effects were observed for anxiety and other aspects of quality of life, nor for objectively assessed sleep-wake cycles and circadian rhythms of melatonin and cortisol (**chapter 3**). These results are partially in line with previous results. The pilot study[3] suggested that light therapy had no effect on subjective sleep quality but the RCT[5] showed, in line with our results, that both groups improved on subjective sleep quality over time. Moreover, results of the RCT[4] showed that both types of light therapy (BWL and DRL) led to improvements on depression and quality of life.

Light therapy is known for its entraining effect on circadian rhythms to the environmental rhythm (e.g. light-dark cycle). Redd et al.[2] suggested that the positive effect of light therapy might results from the entrainment of circadian activity rhythms. A secondary analysis of this study[3] suggested that BWL improved sleep efficiency in cancer survivors. However, this effect was small, clinically irrelevant and not replicated by our RCT (**chapter 3)** nor the RCT by Johnson et al.[5]. In fact, both RCTs showed no effect of light therapy on actigraphy derived sleep-wake cycles. We further investigated this hypothesis by looking at neuroendocrine correlates of the circadian rhythm (melatonin and cortisol). Our results showed that there was no effect on these

outcomes (**chapter 3**). This is partly in line with a secondary analysis of the RCT by Johnson et al.[6] showing that the diurnal cortisol slope and the total cortisol slope increased after completion of the light therapy in both groups (d = 0.57 and d = 0.49, respectively). This increase was not a mediator for the relationship between light therapy and fatigue levels.

Light therapy for cancer survivors with symptoms other than fatigue

Studies on light therapy in cancer survivors were not limited to CRF as an outcome. Three studies tested the efficacy for other symptoms in studies with small sample sizes.

First, Kronish et al.[7] used a different approach to study the efficacy of light therapy in cancer survivors with at least mild depressive symptoms. They used a crossover within-subject design for nine cancer survivors who were exposed to either BWL or DRL. The results of this study showed that the effect of light therapy is heterogeneous. Some survivors reported a decrease, the majority showed no difference, and some an increase on depression and fatigue after exposure to BWL compared to exposure to DRL. Whether depression and fatigue decreased during the study irrespective of condition was not reported.

Second, Fox et al.[8] studied the feasibility and preliminary efficacy of light therapy in ovarian and endometrial cancer survivors with sleep disturbances. Although not statistically significant, results showed a tendency towards superiority for green bright light (GBL) over DRL on the number of nighttime awakenings (actigraphy), subjective sleep quality, and depression. Furthermore, in line with our results, the results showed a statistically significant clinically relevant improvement (d = 1.19) of fatigue in all participants, irrespective of light condition. There was a tendency for a significant increase of total sleep time over time in both groups. No effects were found for other actigraphy-derived variables, quality of life, and cortisol and melatonin concentrations.

The study by Fox et al.[8] is the only study that also reported the effect of light therapy on subjectively assessed cognitive functioning, namely: perceived cognitive impairment, impact of perceived cognitive impairment on quality of life, comments from others, and perceived cognitive abilities. There was a nearly significant superiority of DRL over GBL for the comments from others domain since scores worsened in the GBL group and remained stable in the DRL group. However, the change in the GBL group was very small. No effects were found on the other domains. In **chapter 4**, we reported the effect of light therapy on cognitive impairment (assessed with questionnaires) and cognitive functioning (based on neuropsychological tests). Our results showed that light therapy, irrespective of light intensity, had no effect on these outcomes.

An important limitation of our study (**chapter 4**) and the study by Fox et al.[8] is that the samples were not recruited based on the presence of cognitive dysfunctioning but on the presence of sleep disturbances or CRF, respectively. A closer inspection of the baseline values in our study indicated that one-third of the survivors with CRF experienced cognitive dysfunctioning (**chapter 4**), which reduces the power of our study. The results of a sensitivity analysis in these survivors were in line with the intention-to-treat analyses, showing that light therapy had no effect on cognitive complaints or cognitive functioning (range p-values .05 to .78; range effect sizes .04 to .43). Based on these two studies, we suggest that light therapy is probably not effective for reducing cognitive complaints or improving cognitive functioning.

However, replication of these results in a sufficiently powered study in a sample with objectively assessed cognitive dysfunctioning at baseline is necessary to confirm this conclusion.

Finally, Rogers et al.[9] examined the feasibility of light therapy to improve circadian rhythms in eight adolescent cancer survivors. This was a convenience sample not selected on circadian disruptions a priori because the study primarily focused on the acceptability and adverse events and secondarily studied the effect of light therapy on circadian activity rhythms. The results showed that participants did not report an increased number of adverse events compared to healthy adolescents with no history of cancer. Moreover, there was no effect of light therapy on circadian activity rhythms. This might result from the selection of the sample, as the circadian activity rhythms of the participants were comparable to a healthy control group leaving small to no room for improvement.

Light therapy for patients with cancer while receiving cancer treatment

The interest for light therapy as a treatment for CRF stems from the pilot study of Ancoli-Israel et al.[1] that showed promising results. Exposure to BWL prevented the increase of fatigue and deterioration of circadian activity rhythms and quality of life compared to DRL in breast cancer patients receiving chemotherapy[1, 10, 11]. Since then, two more studies investigated the effect of light therapy in patients with cancer while receiving cancer treatment.

Valdimarsdottir et al.[12] investigated the effect of programmed environmental illumination of hospitals room on depressive symptoms in forty-four patients with multiple myeloma scheduled for autologous stem cell transplant. The results showed a significant difference between groups indicating that patients exposed to BWL showed a smaller increase of depressive symptoms during hospitalization compared to patients exposed to DWL.

Crabtree et al.[13] studied the acceptability and feasibility of light therapy to reduce fatigue in adolescent and young adults receiving treatment for cancer. Fifty-one participants with newly diagnosed solid tumors, including lymphoma, were randomized to BWL or DRL. Results showed that there were no differences between individuals exposed to BWL or DWL concerning the side effects reported due to light therapy and treatment of cancer. Moreover, results of self-reported fatigue showed that there were significant differences between groups for the effect of light therapy on cognitive fatigue and total fatigue, with larger reductions of fatigue after BWL compared to DRL. Improvements on general fatigue and sleep/rest fatigue were reported in both groups.

Summary of light therapy studies in cancer populations

In general, research on light therapy for cancer populations is limited. The majority of the published studies are pilot studies with methodological limitations, for example small sample sizes. Studies that primarily focused on light therapy for cancer survivors with CRF[2, 4] concluded superiority of exposure to BWL compared to DRL on fatigue, although a closer inspection of the RCT by Johnson et al.[4] indicates that both types of light therapy led to clinically relevant reductions in multiple domains of fatigue in cancer survivors with CRF. Moreover, light therapy, irrespective of condition, led to improvements on subjectively reported sleep quality, depression, and quality of life. It is unlikely that these positive effects result from an entrainment

of circadian rhythms as no effects were observed for light therapy on circadian rhythms of sleep-wake cycles, cortisol and melatonin.

Studies that included cancer survivors with symptoms other than CRF, also reported a reduction of fatigue after light therapy, irrespective of condition[8]. Moreover, results on the primary outcomes of these studies, including depressive symptoms or sleep disturbances were inconclusive. One study suggested superiority of exposure to BWL for the number of night time awakening, subjective sleep quality, and depression[8]. However, another study showed no effect on objectively assessed sleep-wake cycles[9]. This might be explained by individual differences on the effect of light therapy that was reported after a within-subject comparison of exposure to BWL and DRL[7].

Studies that investigated the use of light therapy in patients with cancer while receiving treatment seem more promising since all of them reported lower levels of fatigue and depression and better quality of life after exposure to BWL compared to DRL[1, 10-13]. One pilot study showed that exposure to BWL maintained the circadian rhythm at baseline while the group exposed to DRL showed deterioration of the circadian activity rhythm[10].

Unexpected improvement of fatigue irrespective of light intensity

Contrary to the results of Redd et al.[2], our study, as well as the RCT reported by Johnson et al.[4], reported clinically relevant improvements of fatigue after light therapy, irrespective of light intensity. There are multiple explanations for this improvement in both groups. First, the positive effect of light therapy on self-reported outcomes in both groups might be the consequence of non-specific treatment effects, i.e. the Hawthorne effect. The Hawthorne effect describes changes in the behavior and/or reporting by a participant simply because the participant is observed[18]. Examples of potential non-specific treatment effects in the SPARKLE study are positive attention from the research team, increased awareness that CRF is a common symptom, increased physical activity, and increased awareness on someone's sleep-wake cycle by the completion of a sleep diary for 10 days, which were all reported by the participants. Some participants also reported to enjoy the 30 minutes of "quiet time" in the morning while completing light therapy. These effects might resemble effective components of (internet-based) cognitive behavioral therapy (CBT) and mindfulness-based CBT (MBCT), which are shown to be effective as a treatment for CRF[16, 19, 20]. One module of CBT addresses the importance of a regular sleep-wake cycle and includes an assignment to track someone's sleep-wake rhythm for several days to gain insight into this rhythm. This assignment unintentionally became part of the study design of the SPARKLE study when we asked participants to complete a sleep diary for 10 days during each measurement point. Moreover, the 30 minutes of quiet time might resemble an assignment of MBCT. A closer evaluation of MBCT showed that an increase on *sense of control* was the most important working mechanism[21], which is in line with personal comments by some participants mentioning that they experienced an increased capability to change their fatigue.

Second, the improvement of fatigue in the DWL group can be the result of a placebo response, which could be the case for the BWL group as well. Placebo responses to treatments for CRF have been reported and a recent meta-analysis based on 29 studies showed that 29 percent (with a range between 3 to 77 percent[22, 23]) of the participants showed a decrease in

fatigue after placebo treatment in patients with cancer and cancer survivors[24]. The included studies mostly investigated pharmacological treatment for CRF compared to placebo pills, but other placebo treatments were sham acupuncture (n = 3), control telephone calls (n = 1), sesame seed oil injections (n = 1), and sham infrared laser (n = 1). Hoenemeyer et al.[25] showed that this placebo response also occurs when it is clearly mentioned to participants that they receive placebo pills. Twenty-nine percent of the participants who received open-label placebo pills reported clinically relevant and statistically significant improvements with a moderate effect size (*d* = 0.63) compared to treatment as usual. This effect remained stable during a follow-up period of three weeks. Another meta-analyses on the effect of placebo treatment for insomnia symptoms showed that participants who received a placebo treatment (pharmacological and psychological) reported significant changes in self-reported sleep outcomes but not in objective outcomes[26].

To the best of our knowledge, a placebo response for light therapy has not been described but the findings of the SPARKLE study suggest this might be the case. Both BWL and DWL led to improvements in self-reported outcomes with effect sizes comparable to those found after open-label placebo pills treatment[25] in the absence of a response on objectively assessed circadian rhythms of sleep-wake cycles, cortisol, and melatonin. However, we should be careful to conclude that light therapy in the SPARKLE study did not elicit a biological response. We primarily focused on the assumption that light therapy works via entrainment of circadian rhythms because light is the most important *zeitgeber* for the circadian rhythm. Nonetheless, it has been shown that the intrinsically photosensitive retinal ganglion cells responsible for this biological response are not only connected to the superchiasmatic nucleus but also to other brain regions involved in sleep regulation, cognitive functioning, and mood[27]. For example, a recent study[28] showed that sleep quality measured with polysomnography was associated with light exposure on the preceding day in healthy participants. These results suggested that light exposure not only affects circadian driven aspects of sleep but also homeostatic sleep pressure. The homeostatic sleep pressure was not assessed in the SPARKLE study. Therefore, there might be other mechanisms of action, independent from circadian entrainment, explaining the effect of light therapy that have not been studied in the SPARKLE study.

Finally, the positive effect of light therapy in both groups might not be related to light therapy or study participation but could simply be the consequence of a natural improvement of fatigue. Although we did not include a waiting list control condition to test this hypothesis, we believe that the chance of spontaneous natural improvement of CRF in our participants is very small. The mean time since diagnosis of our sample was almost 13 years, indicating that these survivors suffered from CRF for many years. A natural improvement of CRF is likely to occur in the first two years after diagnosis but stable levels, or even increasing levels, are reported after this period[29]. Specifically, two longitudinal studies in long-term cancer survivors showed that fatigue levels remained stable during follow-up[30, 31]. Therefore, we expect that a spontaneous improvement of fatigue in our sample during a period of 3,5 weeks is unlikely.

Methodological limitations

Our intervention study had several methodological strengths, including the double-blind, randomized controlled design, the assessment of self-reported, behavioral, and biological

outcomes, a large sample size, multicenter participation, and a relatively long follow-up period of nine months. However, there were also some methodological limitations concerning the light therapy characteristics, the assessment of fatigue, and the assessment of melatonin and cortisol.

Light therapy characteristics

Light therapy protocol

The first study in breast cancer patients receiving chemotherapy instructed participants to use light therapy for 30 minutes in the morning, upon awakening, during the first four cycles of chemotherapy (approximately eight to twelve weeks)[1, 10]. These instructions were based on the guidelines for light therapy for seasonal affective disorder (SAD)[32, 33]. The studies that followed used similar instructions, although the duration was shortened to four weeks (28 days)[2, 4, 8, 9] or three weeks[7] in cancer survivors. Only the Instructions for the study by Valdimarsdottir et al.[12] differed as light sources were on between 7 AM and 9 AM while the participant was hospitalized for autologous stem cell transplant. Although this seems like a much longer time frame, the authors made this choice to ensure that participants were exposed to light therapy for at least 30 minutes each morning as participants were allowed to leave their room. In line with these studies, we instructed participants to use light therapy for 30 minutes within half an hour after wakening. Only the duration of light therapy was slightly shorter (25 days). We preferred this duration, as we wanted to collect saliva at the end of a workweek (i.e. on Friday) to decrease the circadian shift effect due to changing sleep-wake rhythms on weekend days compared to weekdays. The shorter duration of light therapy could potentially explain the lack of superiority of BWL over DWL. However, we believe this is unlikely, as the guideline of light therapy for SAD describe that light therapy usually shows improvements within the first two weeks with a full clinical response after four weeks[33]. Therefore, the duration of 25 days should have been enough to elicit an initial clinical response.

Compliance to light therapy

A compliance rate of 47 to 49 percent was reported in adult patients receiving chemotherapy[1], which was slightly smaller than the compliance rate of 57% reported in AYA's receiving cancer treatment. In adult cancer survivors[3, 4, 8], the compliance rate ranged from 67 to 95 percent compared to 61 percent in adolescent cancer survivors[9]. The subjective report of compliance in the SPARKLE study showed that light therapy was used on 91 percent of the required days. Hence, the compliance rate in our study was high compared to previous studies. When we look at the compliance on an individual basis, we see that 37 percent of the participants completed light therapy on all 25 treatment days. The majority, 56 percent, used light therapy for 14 to 24 days. Based on the light therapy guidelines for seasonal affective disorder[32], we expect that these individuals would have experienced a first response to the light therapy but might not have reached a full response. We did not include an objective measurement of light exposure in our study. Therefore, we could not confirm the compliance to light therapy nor correct for daily light exposure. However, sensitivity analyses corrected for season did not change the conclusions.

Spectral aspects of light therapy

Most studies that investigated light therapy in cancer populations used a light therapy device from the Litebook Company (i.e. *Litebook 1.2*[1, 2], *Litebook Elite*[4, 9], or *Litebook Advantage*[7, 13]). One study used light therapy glasses, i.e. the *Re-Timer*[8] and one study used lights from *Acuity Brands*[12] that could be placed in hospital rooms. The first 37 participants of the SPARKLE study used of *Litebook Edge*. However, spectral measurements established a light spectrum enriched around 450 nm of 351 lux at eye level for the device used in the BWL condition. This is comparable to office lighting and not sufficient for light therapy. Therefore, we changed to *Luminette glasses*. Table 2 gives an overview of the technical aspects of these devices.

Table 2: Overview of technical aspects of light therapy devices[a].

Light source	Condition	LEDs	Light intensity	Peak light spectrum
Litebook 1.2	BWL	60, white	1.350 lux	464 nm and 564 nm
	DRL	60, red	< 50 lux	N/A
Litebook Elite	BWL	25, white	1.250 - 1.500 lux	465 nm
	DRL	25, red	< 400 lux	633 nm
Litebook Advantage	BWL	24, red	10.000 lux	N/A
	DRL	24, red	N/A	N/A
Re-Timer	BGL	4, red	506 lux	N/A
	DRL	4, red	N/A	N/A
Acuity Brands	BWL	N/A	1.300 lux	N/A
	DWL	N/A	90 lux	N/A
Litebook Edge	BWL	15, white	10.000 lux	480 nm
	DWL	15, white	< 20 lux	480 nm
Luminette glasses	BWL	8, white	1.013 lux	465 nm
	DWL	8, white	8 lux	465 nm

LED light-emitting diode, **BWL** bright white light, **DRL** dim red light, **BGL** bright green light, **DWL** dim white light, **nm** nanometer

[a] These technical aspects were retrieved from the methodological sections of the studies using these devices. The technical aspects of the Luminette glasses used in our study are based on spectrometric measurements.

Based on the details of the light spectra used in the different studies, we want to address three issues. First, there appears to be a difference of the intensity of the *Litebook Advantage* (10.000 lux) compared to the *Litebook 1.2* and *Litebook Elite* (1.250 to 1.500 lux). However, it is very likely that the intensity of the *Litebook Advantage* is the intensity reported by the distributor, which is described as an equivalent of 1.500 lux at eye level. Second, the guidelines for light therapy use in seasonal affective disorders propose that the starting "dose" for light therapy is 10.000 lux for 30 to 40 minutes a day. An alternative dose is exposure to 2.500 lux for 2 hours a day[33]. This indicates that the intensity of light therapy used in the described trials might have been too low or the duration too short. However, we suspect that the guidelines mean that light therapy devices used for light therapy should elicit an intensity of 10.000 lux, which is equivalent to 1.500 lux at eye level. If this is the case, than the light therapy protocols in these

studies follow the guidelines. Third, the description of the light spectra lacks details in most studies. Most details were mentioned by Johnson et al.[4] who described the peak wavelength and intensity of both conditions, while other studies[9, 13] only reported the intensity of the BWL condition without details on the peak wavelength or the light spectrum of the DRL condition. There is also an example of different light spectrum reports within the same research team, as Ancoli-Israel et al.[1] reported no information on the BWL condition, Neikrug et al.[10] mentioned an intensity of 1.500 lux, while Jeste et al.[11] described an intensity of 10.000 lux. Therefore, we want to underline the importance of a standard description based on standardized estimations of light spectra in light therapy studies. In our study, we used the Irradiance Toolbox by Lucas et al. to describe light spectra[34]. More recently, the International Commission on Illumination (CIE) introduced an Equivalent Daylight Illuminance Toolbox that can be used to convert light spectra into absolute α-opic irradiance in mW/m^2, which is in line with the seven units of the basic International System of Units (SI units)[35]. More details on minimum reporting guidelines for light exposure are reported by Spitschan et al.[36].

There were differences between the light spectra of the control conditions used in the studies on light therapy in cancer patients or cancer survivors. Most studies used DRL with intensities of less than 50 lux[1, 2] or 400 lux[4], or intensities were not reported[8, 9, 13]. In the SPARKLE study, we used DWL with an intensity of less than 20 lux. This light might have been able to elicit a biological response. Nonetheless, several studies showed that polychromatic light, as used in the SPARKLE trial, needed an intensity of 393 lux or higher to induce an effect on circadian rhythms[37, 38]. This is supported by the study of Valdimarsdottir et al.[12] that showed significant differences in individuals exposed to BWL (1.300 lux) and DWL (90 lux). Moreover, one study[39] compared the effect of dim white light (50 lux, 460 nm) and dim red light (50 lux, 633 nm) on mood and fatigue in a within-subjects design. The results, based on five cancer survivors who completed primary cancer treatment, showed that two participants had significantly lower fatigue symptoms after DRL while this was not seen after exposure to DWL. The remaining participants showed no differences of the effects of exposure to DRL or DWL. These results suggests that the between group differences in the SPARKLE study could be similar or even larger compared to previous studies using DRL.

Assessment of cancer-related fatigue

Different instruments were used to assess fatigue in studies investigating the efficacy of light therapy as a treatment for CRF. Redd et al.[2] used the FACIT-fatigue[40], Johnson et al.[4] the MFSI-SF[14] and we used the MFI[41] as one of the primary outcomes. We decided to use the MFI for four reasons. First, this scale measures five different domains of fatigue and therefore, it was possible to investigate whether light therapy has an effect on some aspects of fatigue and not on other domains of fatigue. Second, the MFI has been widely used to assess CRF[42]. Third, several review studies suggested that the MFI is a valid and reliable assessment for CRF with acceptable psychometric properties[43-46]. Finally, norm data from a German population was available to determine the clinical significance of fatigue in eligible HL and DLBCL survivors[42].

While the SPARKLE study was ongoing, we wanted to publish norm data of the MFI from a Dutch population and had a closer look into the validation studies of the MFI. At that moment, we realized that replication of the original five-factor structure was scarce and decided to

perform a psychometric evaluation of the MFI. The results of our confirmatory factor analyses, reported in **chapter 5**, showed no empirical support for the original 5-factor structure of the MFI, nor for the alternative 4-factor structure reported in the original validation study or a bi-5-factor and bi-4-factor structure that also included a general factor for fatigue. We performed additional exploratory factor analyses to examine whether an alternative factor structure could describe the different dimensions of fatigue assessed with the MFI. The results showed no reliable and valid alternative factor structure. Therefore, we suggest that results of the subscales of the MFI should be interpreted with caution. It is preferred that conclusions are based on the general fatigue subscale as this subscale showed the most robust results and the highest correlations with a visual analogue scale from 0 (no fatigue) to 10 (worst imaginable fatigue).

Consequently, we only reported results of the MFI general fatigue scale in our studies. This could potentially explain why we were unable to detect superiority of BWL over DWL because Redd et al. and Johnson et al. showed superiority of BWL over DRL for the total fatigue score from the FACIT-fatigue and the MFSI-SF. The results on the general fatigue scales in both RCTs were conclusive, showing improvements over time in both groups. When we repeated our analysis for the total score of the MFI and the remaining scales of the MFI (unpublished), we were still unable to detect statistically significant differences in change over time between BWL and DWL. An improvement over time was seen in the total group, irrespective of light intensity, for the total score of the MFI and physical fatigue, reduced activity and reduced motivation. No effect was seen on mental fatigue, which contradicts the finding of Johnson et al. where mental fatigue improved in both groups.

Another aspect of the fatigue instruments used in these studies is whether fatigue was assessed as a unidimensional or a multidimensional construct. The FACIT-fatigue measures fatigue as a unidimensional construct. The MFSI-SF measures multiple dimensions of fatigue. The MFI aims to assess five dimensions of fatigue but the lack of a reproducible factor structure and the presence of high correlations between the original factors (**chapter 5**) suggests that the MFI might not be successful in the assessment of different dimensions of fatigue. The correlations between factors indicate an overlap in variation, which makes it questionable that these factors represent unique domains of fatigue. Instead, it might be that the MFI measures a unidimensional general fatigue dimension and that the other scales cover other constructs that can, but may not necessarily be, influenced by fatigue. For example, the mental fatigue domain covers cognitive functioning and physical fatigue covers physical functioning. Therefore, we only reported the results of general fatigue and considered this a unidimensional assessment of fatigue. Remarkably, Johnson[47] reported that results from the FACIT-fatigue in their RCT showed no significant difference between groups but improvements over time for the total sample. Taken together, the inconsistency for the superiority of BWL compared to a comparison condition is also not explained by the choice to assess fatigue as a unidimensional or multidimensional construct.

It is important to note two important methodological aspects when interpreting the lack of a factor structure in our psychometric evaluation of the MFI while other studies were able to identify certain factor structures. First, the samples used to examine the factor structure of the MFI. Our study was conducted in a sample of the Dutch general population, while other

studies tested the factor structure in samples of patients with somatic disorders. Consequently, the reported factor structures might be sample specific. Second, the sample size should be considered. A rule of thumb states that at least five participants per estimated parameter need to be included to perform confirmatory factor analysis[48]. This means that at least 350 participants are necessary to confirm the factor structure of the MFI. Our study included the largest sample size so far for a confirmatory factor analysis of the MFI (n = 2512). Most of the validation studies in the past did not reach this bare minimum, which might have led to unjustified conclusions in the past.

Assessment of melatonin and cortisol

One of the strengths of our study is the inclusion of the assessment of circadian rhythms of melatonin and cortisol. It is known that these neuroendocrine correlates of the circadian rhythm are affected by multiple factors, e.g. drinking of caffeinated drinks, eating bananas or chocolate. Moreover, it is important for the determination of the dim light melatonin onset (DLMO) that the evening saliva samples were collected in dim light situations. Therefore, we planned to collect the melatonin samples only during autumn and winter and asked participants to close the curtains during the collection of these samples. Despite our efforts, 15 out of 57 participants collected evening saliva samples for DLMO determination in the spring or the summer. These participants were asked to wear orange glasses to block blue light during the evening sample collection. Although we provided clear instructions, we don't know whether all participants followed these instructions. Some participants self-reported that they did not comply with some of the instructions and were removed from the analyses. Specifically for the DLMO, non-adherence to the dim light saliva collection could have masked a true effect of light therapy.

Overall conclusions

The following conclusions can be drawn from the light therapy study presented in this thesis:

- There is insufficient evidence to recommend light therapy as a treatment for cancer-related fatigue in long-term cancer survivors.
  - There was no superiority for exposure to BWL compared to DWL on reducing fatigue in long-term HL and DLBCL survivors with chronic-cancer related fatigue (**chapter 3**).
  - Both groups, irrespective of light intensity, showed clinically relevant improvements of fatigue (**chapter 3**).
  - Both groups, irrespective of light intensity, showed improvements on subjective sleep quality, depression and some aspects of quality of life (i.e. role limitations due to physical functioning, energy, and social functioning) (**chapter 3**).
  - Light therapy had no effect on objectively assessed circadian activity rhythms (**chapter 3**).
  - Light therapy had no effect on the circadian rhythms of cortisol and melatonin (**chapter 3**).
- One-third of long-term HL and DLBCL survivors with persistent fatigue experience cognitive dysfunctioning.

- Cognitive dysfunctioning especially occurs in the verbal memory domain (**chapter 4**).
- Light therapy had no effect on cognitive complaints and cognitive functioning in long-term HL and DLBCL survivors with chronic cancer-related fatigue (**chapter 4**).

❖ The multidimensional fatigue inventory has a questionable factor structure.

- A psychometric evaluation of the Multidimensional Fatigue Inventory in the Dutch general population (n = 2512) did not confirm the original 5-factor structure, nor an alternative 4-factor nor a 5- and 4-bifactor model (**chapter 5**).
- The lack of a clear factor structure makes it questionable whether the MFI measures multiple dimensions of fatigue (**chapter 5**).
- The conceptual and structural issues with the MFI question whether conclusions based on the five scales of the MFI are reliable (**chapter 5**).
- The *general fatigue* scale showed robust loadings and showed the highest correlation with a fatigue rating from 0 (no fatigue) to 10 (worst fatigue) suggesting that the *general fatigue* scale could be a good measure to assess fatigue (**chapter 5**).

Clinical implications

The guidelines of the National Comprehensive Cancer Network (NCCN) currently recommend the use of light therapy for CRF in cancer survivors. This recommendation is based on lower-level evidence from the pilot study by Redd et al.[2] and the RCT by Johnson et al.[4] and uniform consensus that the intervention is appropriate. The study described in this thesis does not support this recommendation for long-term cancer survivors. However, there was a clinically relevant and statistically significant improvement for fatigue in approximately sixty percent of our participants, irrespective of light intensity, which should not be ignored as these survivors suffered from fatigue for an average duration of 13 years. For some participants, this effect was life changing, as can be seen in the comment of one participant describing how light therapy influenced her life nine months after light therapy use:

> *"I can't describe the feeling that I got my life back. No longer a walking zombie. Sleeping for max. 2 to 3 hours a night is over. During the last 10 years, my life was disrupted because of insomnia. Continuously fatigued. Now, people in my environment see a sparkle in my eyes. They see changes in my behavior. I also feel this. I am more active. More outgoing. Enjoying trips and vacations. I can go on for hours. The light therapy was offered to me at the right time in my life. It felt like a complete reset. Shortly, I feel reborn. I became a new human."*
> (Female participant, 58 years, 9 years since DLBCL diagnosis, exposed to DWL)

At this moment, it remains unclear what caused this positive effect reported by the majority of the participants. Therefore, the interpretation of these results for clinical implications can be twofold. On the one hand, we can conclude that we cannot advice the radiation-oncologists and hematologists of the BETER consortium to prescribe light therapy as a treatment for CRF. Within our RCT, we compared a biologically active light intensity with a light intensity

that is currently considered to be biologically inactive. As there were no differences between individuals exposed to the intervention or the control light, there is no proof for the efficacy of light therapy. Instead, the improvement might be caused by other factors, for example life style changes, the Hawthorne effect or a placebo response. Therefore, it is necessary to further investigate which elements of the light therapy study protocol are responsible for the clinical relevant improvements before implementation of light therapy as a treatment for cancer survivors with CRF.

On the other hand, one could argue that light therapy could be made available for cancer survivors with CRF. As described by Kaptchuk and Miller[49], the goal of medicine is to heal. This includes curation, controlling a disease, and *relieving* symptoms. The results described in this thesis suggest that light therapy is able to relieve fatigue in a substantial part of cancer survivors that are suffering. Moreover, it is easy to deliver and requires almost no supervision from clinical staff. As the mechanisms of action are currently unclear, and a placebo response cannot be excluded, light therapy could be implemented according to the recommendations for implementation of placebo treatments in clinical practice[50]. These recommendations mention that placebo effects should be optimally used in clinical practice while informing patients optimally about placebo effects. For light therapy, this would mean that physicians acknowledge that the positive effects for light therapy are not yet understood and might stem from placebo effects. If a patient remains enthusiastic about light therapy, they could try if it works for them. Expectations play an important role in placebo effects[50]. Hence, we advise to only offer light therapy to cancer survivors who have a positive attitude towards it. Previous studies showed that the prescription of an open-label placebo treatment in cancer survivors with CRF[25], irritable bowel syndrome[51], chronic pain[52, 53], and migraine[54] led to reduced symptoms.

However, while our study was ongoing, the evaluation of an internet-based cognitive behavioral therapy (ICBT) for CRF was published[19]. Severely fatigued breast cancer survivors were randomized to ICBT or care a usual (CAU; mean time since diagnosis of 44 and 39 months, respectively). Results showed that survivors randomized to ICBT reported significantly reduced fatigue levels compared to survivors who received CAU with an effect size of 1.0. On an individual level, 73% of the survivors in the ICBT group reported a clinically relevant reduction compared to 27% of the survivors in the CAU group. Therefore, it can be suggested that this internet-based function was as successful (or even more successful) that the face-to-face version of CBT for CRF, which led to a clinical improvement in 54% of the participants[55]. Moreover, the internet-based version has additional advantages, for example lower costs and it is easier accessible for survivors. Therefore, it might be more interesting for the radiation-oncologists and hematologists of the BETER-consortium to explore the efficacy and implementation of ICBT for CRF in clinical practice.

Another important clinical finding described in this thesis is the finding that approximately one-third of the long-term HL and DLBCL survivors with persistent CRF experienced cognitive dysfunctioning, predominantly in the verbal memory domain. This can be very disturbing for survivors as it can influence their daily life, e.g. they might have trouble in their professional life. Therefore, physicians of the BETER consortium should be aware of these problems. Survivors

might benefit from early detection, for example via the Amsterdam Cognition Scan[56], and referral to cognitive rehabilitations programs, e.g. internet-based cognitive rehabilitation[57].

Directions for future research

Multiple questions for the use of light therapy as a treatment of CRF remain. For example, it could be further investigated which elements of light therapy study protocols are responsible for the clinically relevant improvements observed in a small majority of our participants. The section "Unexpected improvement of fatigue irrespective of light intensity" gives an overview of potential elements, including non-specific treatment effects or a placebo response. Moreover, the dataset collected during this project can be used to further investigate several research questions. First, actigraphy data collected during the day can be used to investigate whether the positive effect of light therapy was associated with increased physical activity during the intervention. Second, exploratory analyses can be performed to investigate individual differences between individuals who experienced reduced fatigue levels after light therapy, irrespective of condition, compared to survivors who did not experience this effect. Third, blood samples collected at baseline and post intervention can be used to investigate the influence of light therapy in inflammatory biomarkers related to CRF. These blood samples can also be used to investigate associations between a response to light therapy and the genetic profile, for example with clock genes.

It is a difficult issue to investigate whether a placebo response led to the positive effects observed in our light therapy trial, as there are still gaps in our knowledge on the mechanisms of action for light therapy. The literature describes several control conditions for light therapy trials, including DRL, DWL, negative ions at a low or high flow rate, or the use of a deactivated negative air ionizer[58]. We choose to use white light with a low intensity as a control condition because we assumed the lower intensity would cause no, or a very limited, biological response. However, we cannot rule out that the DWL had some biological effects. Therefore, future studies should investigate whether the DWL spectrum of our study had any biological effects. More fundamental research on the projections of intrinsically photosensitive retinal ganglion cells might unravel pathways sensitive for blue-enriched white light of low intensities. This research should not be limited to circadian responses but should also investigate projections to other brain regions (for example emotion regulation and sleep regulation). New insights into these pathways will make it easier to determine the characteristics of a true placebo light therapy.

On a more general level, it would be interesting to explore whether the combination of light therapy with other treatments for CRF, for example ICBT, leads to additive treatment effects. For example, in insomnia patients it has been shown that the combination of chronobiologic treatment, e.g. light therapy, and internet-based CBT for insomnia (ICBTI) led to a longer sustained effect of ICBTI[59]. The design of a similar study in breast cancer patients receiving chemotherapy was recently published by Bean et al.[60] and data collection is ongoing. To the best of our knowledge, this is currently not under investigation in cancer survivors. An alternative approach might be a design in which participants first complete four weeks of light therapy followed by a physical exercise or CBT intervention based on the hypothesis that an initial response to light therapy might increase motivation to participate in these interventions.

The discussion on light therapy studies in cancer populations in this chapter described a discrepancy for the effect of light therapy in cancer survivors compared to patients with cancer receiving treatment. The evidence for superiority of BWL over a control condition in the treatment of CRF in cancer survivors is not convincing. However, several studies in patients with cancer receiving treatment suggest a protective effect of BWL compared to DRL for the increase of negative symptoms like fatigue and depression and desynchronization of circadian rhythms during treatment. As these studies had methodological limitations, we would advice to perform a RCT to test the protective effect of light therapy for the occurrence of fatigue and related symptoms in patients with cancer undergoing treatment. This trial should include long-term follow-up assessments to investigate whether this initial intervention prevents the occurrence or reduces the levels of these symptoms in cancer survivors.

The results of our critical evaluation of the psychometric properties of the MFI shows the importance of psychometric evaluations of scales that have been widely used in research. Even though multiple review studies mentioned the MFI as a valid and reliable scale to measure multiple dimensions of fatigue, our results suggest otherwise. Based on the lack of a clear distinction between multiple dimensions of fatigue, we suggest that results from the MFI should be interpreted with caution. The general fatigue subscale seems to be the most reliable scale. For future studies, we would advice to primarily use a valid and reliable assessment of the unidimensional concept of fatigue. This advice is in line with previous recommendations[61, 62]. Moreover, it is questionable whether it is clinically relevant to distinguish different dimensions of fatigue[45]. In case of specific hypotheses on subdomains of fatigue, a multidimensional assessment of fatigue can be added. This recommendation is in line with current guidelines of an independent working group, the ASCPRO (assessing symptoms of cancer using patient-reported outcomes)[63]

CIRCADIAN RHYTHMS AND CANCER RELATED FATIGUE

Comparison with the literature

The studies described in this thesis strongly focused on the effect of light on circadian rhythms. This was based on the rationale that light is the most strongest *zeitgeber* for circadian rhythms and the findings that higher levels of CRF are consistently associated with disruptions in circadian rhythms in patients with cancer[64-69]. Studies based on circadian activity rhythms, assessed with actigraphy, concluded that patients with cancer with higher levels of fatigue showed less daytime activity, more daytime sleep, and night awakenings. Studies that investigated the association between neuroendocrine correlates of circadian rhythms and fatigue after cancer showed that a flatter diurnal slope was associated with higher levels of CRF[70, 71]. However, when we started this study, it was unclear whether a misalignment between the environmental rhythm and endogenous circadian rhythms is associated with CRF. We hypothesized that the endogenous circadian rhythms of cancer survivors with CRF might be delayed compared to the environmental rhythm.

To test this hypothesis, we performed a survey study in which we compared the chronotype and sleep quality of long-term HL and DLBCL survivors with and without CRF (**chapter 6**). Our results showed that there was no association between chronotype and CRF, suggesting that the

preference for morningness or eveningness did not differ between survivors with and without fatigue. Our results are in line with the finding that chronotype was not associated with fatigue in patients with rheumatoid arthritis[72]. However, our results contradict a previous study that reported that breast cancer survivors who reported to be an evening type suffered from higher levels of fatigue compared to survivors who reported to be a morning type[73]. Studies in other populations also showed that evening types reported higher levels of fatigue compared to morning types (e.g.in individuals with irritable bowel symptoms[74] and students[75]).

Since chronotype is not only correlated with circadian phase but also with the homeostatic sleep drive, we also assessed sleep quality in the survey study. Results showed that two aspects of sleep quality, i.e. subjective sleep quality and daily dysfunctioning, were associated with CRF (i.e. worse scores on these aspects were associated with higher levels of fatigue). These findings are in line with the baseline values of the objective assessment of circadian sleep-wake cycles in the light therapy study (**chapter 3**) suggesting that cancer survivors with CRF showed disrupted sleep patterns compared to healthy populations, while circadian variables were within the normal range[76-78].

Remarkably, the number of studies on the association between circadian disruptions and CRF in long-term cancer survivors (at least two years after diagnosis) is very limited. To the best of our knowledge, only two recent studies are available[79-81]. One study compared circadian activity rhythms, assessed with actigraphy, between 15 breast cancer survivors (5 years post-diagnosis) to 13 age and BMI-matched healthy controls[79, 80]. Results showed no differences in the timing of the sleep-wake cycle between both group but there were differences between groups for activity levels. Breast cancer survivors showed lower activity levels during the total 24-hour cycle compared to healthy controls. There was no report on the association between circadian activity rhythms and fatigue. The other study assessed circadian activity rhythms with actigraphy in 29 adolescents within 5 years after cancer treatment and 30 healthy controls[81]. There were no differences between survivors and healthy controls on circadian activity rhythms and fatigue scores between adolescent cancer survivors and healthy controls. Notably, there was an association between circadian activity disruptions and fatigue in early survivors, which was not seen in long-term survivors, suggesting that disruptions in circadian activity rhythms experienced shortly after treatment recovered within the first 5 years after treatment for adolescent cancer.

Taken together, disruptions in circadian rhythms have been associated with fatigue in patients with cancer. However, studies on this association in cancer survivors are scarce and suggest the absence of an association between disruptions in circadian rhythms and CRF in long-term cancer survivors. Replication of these results is necessary in sufficiently powered studies including objective assessments of circadian rhythms.

Methodological considerations

This survey study (**chapter 6**) had several strengths, including the large sample size, multicenter participation and the use of average midsleep as an indicator for chronotype instead of the original indicator of chronotype from the Munich Chronotype Questionnaire (MCTQ). However, several methodological issues need to be considered when interpreting the results.

The inconclusive results on the association between chronotype and fatigue in the studies described above might result from the use of different questionnaires to assess someone's chronotype. The two studies that showed no association between chronotype and fatigue, including our study, used the MCTQ[82]. This questionnaire assesses actual sleep times on work and free days to determine chronotype. The studies suggesting an association between chronotype and fatigue used other questionnaires, for example the Morningness Eveningness Questionnaire (MEQ)[83] or the Composite Scale of Morningness (SCM)[84]. An advantage of these questionnaires is the availability of cutoff scores to determine someone's chronotype. These cutoff scores are not available for the MCTQ and therefore the categorization of morning type and evening type might seem more arbitrarily. A disadvantage of the MEQ and CSM is that chronotype is based on preferred sleep times in ideal circumstances and statements. Therefore, we preferred to use the MCTQ as we aimed to describe actual sleeping patterns from cancer survivors with and without CRF.

Additionally, our results are based on self-reported data from a cross-sectional survey study. Self-reported sleep times are also influenced by work and social obligations. Therefore, the absence of an association between circadian rhythm disruptions and CRF needs to be confirmed with objective measurements of circadian rhythms, e.g. actigraphy assessments or the DLMO. The baseline actigraphy results of the light therapy study seem to confirm this conclusion but this was based on a comparison of published outcomes in the general population. To draw robust conclusions, it is necessary to perform statistical tests on this comparison.

Overall conclusions

- ❖ It is unlikely that circadian disruptions are associated with cancer-related fatigue in long-term cancer survivors.
  - There was no relationship between chronotype and cancer-related fatigue in long-term (non-)Hodgkin lymphoma survivors (**chapter 6**).
  - Two aspects of sleep quality, i.e. subjective sleep quality and daily dysfunctioning, were associated with cancer-related fatigue in long-term (non-)Hodgkin lymphoma survivors (**chapter 6**).
  - Baseline levels of actigraphy-derived sleep-wake cycles in participants of the SPARKLE study suggested the presence of sleep problems and the absence of circadian disruptions when compared to the general population (**chapter 3**).

Clinical implications

The aim of our survey study was to learn more about the association between sleep times and CRF. This information is valuable to determine the most optimal timing of light therapy. If the results would show that survivors with CRF showed an advanced sleep-wake rhythm compared to survivors without CRF, i.e. going to bed at 21:00 h and waking up at 5:00, than light therapy in the evening would be most effective because this will delay the sleep-wake cycle. On the other hand, if the results would show that survivors with CRF showed a delayed sleep-wake rhythm compared to survivors without CRF, i.e. going to bed at 1:00 h and waking up at 9:00 h, than light therapy in the morning would be most effective because this would advance the sleep-wake cycle.

However, the results described in this thesis showed no indications for a relationship between the timing of the circadian sleep-wake cycle and CRF in long-term HL and DLBCL survivors. There was an association between sleep quality and CRF, indicating that survivors with a lower sleep quality suffered from higher levels of fatigue. Therefore, survivors with CRF might benefit most from a closer inspection of sleep problems and interventions aiming to improve sleep quality, e.g. CBT.

Directions for future research

Disruptions in circadian rhythms have been associated with fatigue in patients with cancer. However, the number of studies on this association in cancer survivors are limited and mostly focus on patients with cancer while receiving treatment. We performed a survey study to investigate the association of chronotype, which correlates to endogenous circadian rhythms, and cancer-related fatigue. Although we found no association between chronotype and CRF in long-term HL and DLBCL survivors, a closer inspection of the bed times showed differences between survivors with and without fatigue. Survivors with severe fatigue tended to go to bed at an earlier time compared to non-fatigued survivors (22:48 h and 23:23 h, respectively) and needed more time to fall asleep (24 min and 11 min, respectively). Moreover, moderately to severely fatigued survivors tended to use more time to get up in the morning and spend less time outside during the day. Consequently, we cannot rule out that survivors with fatigue go to bed too early with respect to their circadian sleep drive. This hypothesis could not be investigated in this survey study but can be studied if future research includes objective assessments, for example, actigraphy assessments or determinations of the DLMO from saliva or with the BodyTime assay[85]. These studies are necessary to draw firm conclusions about the association between circadian disruptions and CRF in cancer survivors.

Additionally, it is interesting to further investigate the longitudinal influence of cancer and cancer treatment on circadian disruptions and the association between circadian disruptions and CRF. As mentioned above, the association between circadian rhythm disruptions and CRF has been consistently shown for patients with cancer while receiving treatment but not for cancer survivors. The same discrepancy has been described above for studies on light therapy. Several studies suggest superiority of BWL compared to DRL in patients with cancer while receiving treatment but not for cancer survivors with CRF. Therefore, we hypothesize that biological changes during cancer treatment, i.e. circadian disruptions, might be responsible for negative health outcomes, including fatigue, sleep problems, depression, and diminished quality of life. In cancer survivors, these underlying biological causes might no longer be present. Instead, behavioral and mental adaptations might be responsible for maintaining these negative outcomes. One approach to study this is by using patient reported outcomes (PROMS) used in clinical practice and biobank blood samples. These blood samples could be used to determine changes in dim light melatonin onset, which can be determined with the BodyTime assay[85]. Within such a cohort, researchers could also investigate the course of CRF and determine whether maladaptive behavior and/or cognitions are responsible for the shift from acute fatigue to chronic fatigue.

For the methodology of future studies investigating the association between circadian disruptions and CRF, it is important to formulate guidelines describing the most optimal

procedure to identify individuals with clinically relevant circadian disruptions for scientific purposes. Currently, actigraphy and DLMO are used in clinical practice to determine whether someone's circadian activity rhythm or endogenous circadian rhythm are not entrained to environmental rhythm. However, for scientific purposes, there are no clear guidelines how clinically relevant circadian disruptions can be determined in large datasets. A first step in this process might be to publish norm data per gender and age group for actigraphy-derived variables. These are currently not available although large datasets, for example from the UK Biobank[76], exist.

CONCLUSIONS

In view of the high prevalence of CRF in long-term HL and DLBCL survivors, we evaluated the efficacy of light therapy to reduce this symptom. Although there was no superiority of exposure to BWL compared to DWL, both groups, irrespective of light intensity, showed clinically relevant improvements. Therefore, we recommend future studies to investigate which elements of the current study protocol were responsible for this positive effect before the implementation of light therapy in clinical practice. Moreover, the effect of light therapy on circadian rhythms was evaluated. The results showed no effect of light therapy on circadian activity rhythms or neuroendocrine correlates of the circadian system (melatonin and cortisol). This might be explained by the lack of an association between circadian rhythm disturbances and CRF in long-term cancer survivors. Future studies should investigate whether circadian rhythm disruptions are an initial cause of CRF that play no, or only a limited, role in the maintenance of this symptom. Furthermore, one-third of the long-term HL and DLBCL survivors with CRF suffers from cognitive dysfunctioning, specifically in verbal memory. Physicians should be aware of these symptoms and might refer their patients to specialized neuropsychologist for further screening and treatment of these complaints.

REFERENCES

1. Ancoli-Israel S, Rissling M, Neikrug A, Trofimenko V, Natarajan L, Parker B A, et al. (2012). Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. *Support Care Cancer*, 20(6):1211-9.
2. Redd W H, Valdimarsdottir H, Wu L M, Winkel G, Byrne E E, Beltre M A, et al. (2014). Systematic light exposure in the treatment of cancer-related fatigue: a preliminary study. *Psychooncology*, 23(12):1431-4.
3. Wu L M, Amidi A, Valdimarsdottir H, Ancoli-Israel S, Liu L, Winkel G, et al. (2018). The effect of systematic light exposure on sleep in a mixed group of fatigued cancer survivors. *J Clin Sleep Med*, 14(01):31-9.
4. Johnson J A, Garland S N, Carlson L E, Savard J, Simpson J S A, Ancoli-Israel S, et al. (2017). Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. *J Cancer Surviv*, 12:1-10.
5. Garland S N, Johnson J A, Carlson L E, Rash J A, Savard J, Campbell T S (2020). Light therapy for insomnia symptoms in fatigued cancer survivors: a secondary analysis of a randomized controlled trial. *J. Psychosoc. Oncol.*, 2(3):e27.
6. Johnson J A, Subnis U, Carlson L E, Garland S N, Santos-Iglesias P, Piedalue K-A L, et al. (2020). Effects of a light therapy intervention on diurnal salivary cortisol in fatigued cancer survivors: A secondary analysis of a randomized controlled trial. *J Psychosom Res*, 139:110266.
7. Kronish I M, Cheung Y K, Julian J, Parsons F, Lee J, Yoon S, et al., editors. Clinical Usefulness of Bright White Light Therapy for Depressive Symptoms in Cancer Survivors: Results from a Series of Personalized (N-of-1) Trials. Healthcare; 2020: Multidisciplinary Digital Publishing Institute.
8. Fox R S, Baik S H, McGinty H, Garcia S F, Reid K J, Bovbjerg K, et al. (2020). Feasibility and Preliminary Efficacy of a Bright Light Intervention in Ovarian and Endometrial Cancer Survivors. *Int J Behav Med*:1-13.
9. Rogers V E, Mowbray C, Rahmaty Z, Hinds P S (2020). A Morning Bright Light Therapy Intervention to Improve Circadian Health in Adolescent Cancer Survivors: Methods and Preliminary Feasibility. *J Pediatr Oncol Nurs*:1043454220975457.
10. Neikrug A B, Rissling M, Trofimenko V, Liu L, Natarajan L, Lawton S, et al. (2012). Bright light therapy protects women from circadian rhythm desynchronization during chemotherapy for breast cancer. *Behav Sleep Med*, 10(3):202-16.
11. Jeste N, Liu L, Rissling M, Trofimenko V, Natarajan L, Parker B A, et al. (2013). Prevention of quality-of-life deterioration with light therapy is associated with changes in fatigue in women with breast cancer undergoing chemotherapy. *Qual Life Res*, 22(6):1239-44.
12. Valdimarsdottir H B, Figueiro M G, Holden W, Lutgendorf S, Wu L M, Ancoli-Israel S, et al. (2018). Programmed environmental illumination during autologous stem cell transplantation hospitalization for the treatment of multiple myeloma reduces severity of depression: A preliminary randomized controlled trial. *Cancer medicine*, 7(9):4345-53.
13. Crabtree V M, LaRosa K N, MacArthur E, Russell K, Wang F, Zhang H, et al. (2020). Feasibility and Acceptability of Light Therapy to Reduce Fatigue in Adolescents and Young Adults Receiving Cancer-Directed Therapy. *Behav Sleep Med*:1-13.
14. Stein K D, Jacobsen P B, Blanchard C M, Thors C (2004). Further validation of the multidimensional fatigue symptom inventory-short form. *J Pain Symptom Manage*, 27(1):14-23.
15. Norman G R, Sloan J A, Wyrwich K W (2003). Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*:582-92.
16. Gielissen M F, Verhagen S, Witjes F, Bleijenberg G (2006). Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol*, 24(30):4882-7.
17. Persoon S, Kersten M J, van der Weiden K, Buffart L M, Nollet F, Brug J, et al. (2013). Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: a systematic review and meta-analysis. *Cancer Treat Rev*, 39(6):682-90.
18. McCarney R, Warner J, Iliffe S, Van Haselen R, Griffin M, Fisher P (2007). The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol*, 7(1):30.
19. Abrahams H J, Gielissen M F, Donders R R, Goedendorp M M, van der Wouw A J, Verhagen C A, et al. (2017). The efficacy of internet-based cognitive behavioral therapy for severely fatigued survivors of breast cancer compared with care as usual: a randomized controlled trial. *Cancer*, 123(19):3825-34.

20. Bruggeman-Everts F Z, Wolvers M D, Van de Schoot R, Vollenbroek-Hutten M M, Van der Lee M L (2017). Effectiveness of two web-based interventions for chronic cancer-related fatigue compared to an active control condition: results of the "Fitter na kanker" randomized controlled trial. *J Med Internet Res*, 19(10):e336.
21. Bruggeman-Everts F, Van der Lee M, Wolvers M, Van de Schoot R (2019). Understanding change in online mindfulness-based cognitive therapy for chronic cancer-related fatigue. *Evaluation of two different Web-based interventions for chronic cancer-related fatigue*:159.
22. Stockler M R, O'Connell R, Nowak A K, Goldstein D, Turner J, Wilcken N R, et al. (2007). Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. *The lancet oncology*, 8(7):603-12.
23. Spathis A, Fife K, Blackhall F, Dutton S, Bahadori R, Wharton R, et al. (2014). Modafinil for the treatment of fatigue in lung cancer: results of a placebo-controlled, double-blind, randomized trial. *J Clin Oncol*, 32(18):1882-8.
24. Junior P N A, Barreto C M N, Cubero D d I G, Del Giglio A (2020). The efficacy of placebo for the treatment of cancer-related fatigue: a systematic review and meta-analysis. *Support Care Cancer*, 28(4):1755-64.
25. Hoenemeyer T W, Kaptchuk T J, Mehta T S, Fontaine K R (2018). Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. *Sci Rep*, 8(1):1-8.
26. Yeung V, Sharpe L, Glozier N, Hackett M L, Colagiuri B (2018). A systematic review and meta-analysis of placebo versus no treatment for insomnia symptoms. *Sleep Med Rev*, 38:17-27.
27. Schmidt T M, Chen S-K, Hattar S (2011). Intrinsically photosensitive retinal ganglion cells: many subtypes, diverse functions. *Trends Neurosci*, 34(11):572-80.
28. Wams E J, Woelders T, Marring I, van Rosmalen L, Beersma D G, Gordijn M C, et al. (2017). Linking light exposure and subsequent sleep: A field polysomnography study in humans. *Sleep*, 40(12):zsx165.
29. Abrahams H, Gielissen M, Schmits I, Verhagen C, Rovers M, Knoop H (2016). Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. *Ann Oncol*, 27(6):965-74.
30. Servaes P, Verhagen S, Schreuder H B, Veth R P, Bleijenberg G (2003). Fatigue after treatment for malignant and benign bone and soft tissue tumors. *J Pain Symptom Manage*, 26(6):1113-22.
31. Hjermstad M J, Fosså S D, Oldervoll L, Holte H, Jacobsen A B, Loge J H (2005). Fatigue in long-term Hodgkin's Disease survivors: a follow-up study. *J Clin Oncol*, 23(27):6587-95.
32. Lam R, Levitt A (1999). Canadian Consensus Guidelines for the treatment of SAD. A summary of the report of the Canadian Consensus Group on SAD Clinical and Academic Publishing, Vancouver, Canada.
33. Bauer M, Bschor T, Pfennig A, Whybrow P C, Angst J, Versiani M, et al. (2007). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. *World J. Biol. Psychiatry*, 8(2):67-104.
34. Lucas R J, Peirson S N, Berson D, Brown T, Cooper H, Czeisler C A, et al. Irradiance toolbox. Oxford; 2013.
35. CIE S (2018). 026/E: 2018 CIE System for Metrology of Optical Radiation for ipRGC-Influenced Responses to Light. CIE, Vienna.
36. Spitschan M, Stefani O, Blattner P, Gronfier C, Lockley S W, Lucas R J (2019). How to report light exposure in human chronobiology and sleep research experiments. *Clocks & sleep*, 1(3):280-9.
37. Aoki H, Yamada N, Ozeki Y, Yamane H, Kato N (1998). Minimum light intensity required to suppress nocturnal melatonin concentration in human saliva. *Neurosci Lett*, 252(2):91-4.
38. Figueiro M, Nagare R, Price L (2018). Non-visual effects of light: How to use light to promote circadian entrainment and elicit alertness. *Light. Res. Technol.*, 50(1):38-62.
39. Shechter A, Julian J, Davidson K W, Cheung K, Lee J, Kronish I M (2019). A within-subject comparison of the effect of two putative sham light therapies on mood and fatigue in cancer survivors: Results from a series of N-of-1 trials. *Psychiatry Res*, 279:385-6.
40. Cella D (2013). The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale: Summary of development and validation.
41. Smets E, Garssen B, Bonke B d, De Haes J (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*, 39(3):315-25.
42. Schwarz R, Krauss O, Hinz A (2003). Fatigue in the general population. *Oncology Research and Treatment*, 26(2):140-4.

43. Fisher M I, Davies C, Lacy H, Doherty D (2018). Oncology section EDGE task force on cancer: measures of cancer-related fatigue—a systematic review. *Rehabil Oncol*, 36(2):93-105.
44. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V (2003). Assessment and management of cancer-related fatigue in adults. *The lancet*, 362(9384):640-50.
45. Minton O, Stone P (2009). A systematic review of the scales used for the measurement of cancer-related fatigue (CRF). *Ann Oncol*, 20(1):17-25.
46. Seyidova-Khoshknabi D, Davis M P, Walsh D (2011). A systematic review of cancer-related fatigue measurement questionnaires. *American Journal of Hospice and Palliative Medicine®*, 28(2):119-29.
47. Johnson J. Light Therapy for Post-Treatment Cancer-Related Fatigue: An Investigation of Impact on Psychological Outcomes and Biological Mechanisms 2016.
48. Bentler P M, Chou C-P (1987). Practical issues in structural modeling. *Sociological methods & research*, 16(1):78-117.
49. Kaptchuk T J, Miller F G (2015). Placebo effects in medicine. *N Engl J Med*, 373(1):8-9.
50. Evers A W, Colloca L, Blease C, Annoni M, Atlas L Y, Benedetti F, et al. (2018). Implications of placebo and nocebo effects for clinical practice: expert consensus. *Psychother Psychosom*, 87(4):204-10.
51. Kaptchuk T J, Friedlander E, Kelley J M, Sanchez M N, Kokkotou E, Singer J P, et al. (2010). Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One*, 5(12):e15591.
52. Carvalho C, Caetano J M, Cunha L, Rebouta P, Kaptchuk T J, Kirsch I (2016). Open-label placebo treatment in chronic low back pain: a randomized controlled trial. *Pain*, 157(12):2766.
53. Locher C, Nascimento A F, Kirsch I, Kossowsky J, Meyer A, Gaab J (2017). Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain*, 158(12):2320-8.
54. Kam-Hansen S, Jakubowski M, Kelley J M, Kirsch I, Hoaglin D C, Kaptchuk T J, et al. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci Transl Med*, 6(218):218ra5-ra5.
55. Gielissen M, Verhagen C, Bleijenberg G (2007). Cognitive behaviour therapy for fatigued cancer survivors: long-term follow-up. *Br J Cancer*, 97(5):612-8.
56. Feenstra H E, Murre J M, Vermeulen I E, Kieffer J M, Schagen S B (2018). Reliability and validity of a self-administered tool for online neuropsychological testing: The Amsterdam Cognition Scan. *J Clin Exp Neuropsychol*, 40(3):253-73.
57. Klaver K, Duijts S, Geusgens C, Aarts M, Ponds R, van der Beek A, et al. (2020). Internet-based cognitive rehabilitation for WORking Cancer survivors (i-WORC): study protocol of a randomized controlled trial. *Trials*, 21(1): 1-12
58. Mårtensson B, Pettersson A, Berglund L, Ekselius L (2015). Bright white light therapy in depression: a critical review of the evidence. *J Affect Disord*, 182:1-7.
59. Dekker K, Benjamins J S, Maksimovic T, Filardi M, Hofman W F, Van Straten A, et al. (2020). Combined internet-based cognitive-behavioral and chronobiological intervention for insomnia: a randomized controlled trial. *Psychother Psychosom*, 89(2):117-8.
60. Bean H R, Stafford L, Little R, Diggens J, Ftanou M, Alexander M, et al. (2020). Light-enhanced cognitive behavioural therapy for sleep and fatigue: study protocol for a randomised controlled trial during chemotherapy for breast cancer. *Trials*, 21:1-14.
61. Michielsen H J, De Vries J, Van Heck G L, Van de Vijver F J, Sijtsma K (2004). Examination of the dimensionality of fatigue. *Eur J Psychol Assess*, 20(1):39-48.
62. Lai J-S, Crane P K, Cella D (2006). Factor analysis techniques for assessing sufficient unidimensionality of cancer related fatigue. *Qual Life Res*, 15(7):1179-90.
63. Barsevick A M, Cleeland C S, Manning D C, O'Mara A M, Reeve B B, Scott J A, et al. (2010). ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. *J Pain Symptom Manage*, 39(6):1086-99.
64. Rich T A (2007). Symptom clusters in cancer patients and their relation to EGFR ligand modulation of the circadian axis. *J Support Oncol*, 5(4):167-74.
65. Payne J K (2011). Altered circadian rhythms and cancer-related fatigue outcomes. *Integr Cancer Ther*, 10(3):221-33.
66. Innominato P F, Roche V P, Palesh O G, Ulusakarya A, Spiegel D, Lévi F A (2014). The circadian timing system in clinical oncology. *Ann Med*, 46(4):191-207.
67. Mormont M-C, Waterhouse J (2002). Contribution of the rest–activity circadian rhythm to quality of life in cancer patients. *Chronobiol Int*, 19(1):313-23.

68. Schrepf A, Clevenger L, Christensen D, DeGeest K, Bender D, Ahmed A, et al. (2013). Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: relationships with depression, fatigue, and disability. *Brain Behav Immun*, 30:S126-S34.
69. Schmidt M E, Semik J, Habermann N, Wiskemann J, Ulrich C M, Steindorf K (2016). Cancer-related fatigue shows a stable association with diurnal cortisol dysregulation in breast cancer patients. *Brain Behav Immun*, 52:98-105.
70. Weinrib A Z, Sephton S E, DeGeest K, Penedo F, Bender D, Zimmerman B, et al. (2010). Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. *Cancer*, 116(18):4410-9.
71. Innominato P F, Mormont M-C, Rich T A, Waterhouse J, Lévi F A, Bjarnason G A (2009). Circadian disruption, fatigue, and anorexia clustering in advanced cancer patients: implications for innovative therapeutic approaches. *Integr Cancer Ther*, 8(4):361-70.
72. Habers G E A, van der Helm-van A H M, Veldhuijzen D S, Allaart C F, Vreugdenhil E, Starreveld D E J, et al. (2021). Earlier chronotype in patients with rheumatoid arthritis. *Clin Rheumatol*, 40:2185-92.
73. Palesh O, Packer M M, George H, Koopman C, Innominato P F. Associations between morning–evening chronotype, fatigue, and QOL in breast cancer survivors. *J. Clin. Oncol*; 2016.
74. Chrobak A A, Nowakowski J, Zwolińska-Wcisło M, Cibor D, Przybylska-Feluś M, Ochyra K, et al. (2018). Associations between chronotype, sleep disturbances and seasonality with fatigue and inflammatory bowel disease symptoms. *Chronobiol Int*, 35(8):1142-52.
75. Martin J S, Hébert M, Ledoux É, Gaudreault M, Laberge L (2012). Relationship of chronotype to sleep, light exposure, and work-related fatigue in student workers. *Chronobiol Int*, 29(3):295-304.
76. Jones S E, van Hees V T, Mazzotti D R, Marques-Vidal P, Sabia S, van der Spek A, et al. (2019). Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nat. Commun.*, 10(1):1-12.
77. Häusler N, Marques-Vidal P, Haba-Rubio J, Heinzer R (2020). Association between actigraphy-based sleep duration variability and cardiovascular risk factors–Results of a population-based study. *Sleep Med*, 66:286-90.
78. Luik A I, Zuurbier L A, Direk N, Hofman A, Van Someren E J, Tiemeier H (2015). 24-hour activity rhythm and sleep disturbances in depression and anxiety: A population-based study of middle-aged and older persons. *Depress Anxiety*, 32(9):684-92.
79. Roveda E, Bruno E, Galasso L, Mulè A, Castelli L, Villarini A, et al. (2019). Rest-activity circadian rhythm in breast cancer survivors at 5 years after the primary diagnosis. *Chronobiol Int*, 36(8):1156-65.
80. Galasso L, Montaruli A, Mulè A, Castelli L, Bruno E, Pasanisi P, et al. (2020). Rest-activity rhythm in breast cancer survivors: an update based on non-parametric indices. *Chronobiol Int*, 37(6):946-51.
81. Rogers V E, Mowbray C, Zhu S, Liu L, Ancoli-Israel S, Barr E A, et al. (2020). Circadian activity rhythms and fatigue of adolescent cancer survivors and healthy controls: a pilot study. *J Clin Sleep Med*, 16(7):1141-7.
82. Roenneberg T, Wirz-Justice A, Merrow M (2003). Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms*, 18(1):80-90.
83. Horne J A, Ostberg O (1975). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol*, 4(2):97-110.
84. Smith C S, Reilly C, Midkiff K (1989). Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. *J Appl Psychol*, 74(5):728-38.
85. Wittenbrink N, Ananthasubramaniam B, Münch M, Koller B, Maier B, Weschke C, et al. (2018). High-accuracy determination of internal circadian time from a single blood sample. *J. Clin. Investig.*, 128(9):3826-39.

APPENDICES

SAMENVATTING (SUMMARY IN DUTCH)

De studies die beschreven zijn in dit proefschrift presenteren de resultaten van een dubbelblind, gerandomiseerde gecontroleerde studie naar het gebruik van lichttherapie door mensen die in het verleden een Hodgkin lymfoom (HL) of een diffuus grootcellig B-cel lymfoom hadden (DLBCL). Deze studies evalueerden het korte en lange termijneffect van lichttherapie op vermoeidheid na kanker en symptomen die hiermee in verband staan, zoals slaap kwaliteit, depressie, angst, kwaliteit van leven, cognitieve klachten, cognitief functioneren en circadiane ritmes van slaap-waak patronen, melatonine en cortisol. Daarnaast hebben we een psychometrische evaluatie uitgevoerd van één van de primaire uitkomstmaten, de Multidimensionele Vermoeidheids Index, in de algemene Nederlandse populatie. Als laatste hebben we de verbanden tussen kanker-gerelateerde vermoeidheid en chronotype en kanker-gerelateerde vermoeidheid en slaap kwaliteit beschreven. Dit hoofdstuk is een samenvatting van de belangrijkste uitkomsten.

In **hoofdstuk 1** wordt het belang voor een effectieve behandeling voor kanker-gerelateerde vermoeidheid na een HL- of DLBCL-diagnose geïntroduceerd. In Nederland biedt het BETER consortium een infrastructuur voor gezondheidszorg na een HL- of DLBCL-diagnose. Binnen deze gezondheidszorg worden overlevenden geïnformeerd over lange termijneffecten van hun behandeling en krijgen ze screening en tijdige behandeling voor deze effecten aangeboden. Vermoeidheid na kanker is één van de meest gehoorde symptomen die overlevenden binnen dit consortium rapporteren bij hun hematoloog of radiotherapeut. De prevalentie van vermoeidheid na kanker ligt tussen 41 en 61 procent in deze groep wat vergeleken kan worden met een prevalentie van matige tot ernstige vermoeidheid tussen 23 en 28 procent in de algemene Nederlandse populatie. Hoewel er nog veel onduidelijk is over de etiologie van vermoeidheid na kanker, bestaat er het idee dat deze vermoeidheid veroorzaakt wordt door een combinatie van meerdere factoren waaronder demografische, medische, psychosociale, gedrag en biologische factoren. Een voorbeeld van een biologische factor is een verstoring van het circadiane ritme. Ondanks de hoge prevalentie van vermoeidheid na kanker, zijn er weinig op bewijs gebaseerde behandelingen (i.e. cognitieve gedragstherapie voor vermoeidheid na kanker of fysieke activiteit) en zijn deze behandelingen niet voor iedereen effectief (een hoge motivatie is vereist). Om deze redenen is het belangrijk om alternatieve behandelingen voor vermoeidheid na kanker te onderzoeken, bijvoorbeeld lichttherapie. Toen het onderzoek beschreven in dit proefschrift startte, beschreef de literatuur twee pilotstudies in borstkanker patiënten die chemotherapie ontvingen (n = 39) en overlevenden van kanker (n = 36) die veelbelovende resultaten lieten zien. Secundaire analyses van deze studies suggereerden daarnaast dat lichttherapie symptomen die in verband staan met vermoeidheid na kanker, zoals circadiane slaap-waak patronen en kwaliteit van leven, verbeterden. Hierdoor werd de hypothese geformuleerd dat lichttherapie vermoeidheid na kanker kan verminderen door het corrigerende effect op het circadiane ritme. Echter, deze pilotstudies hadden een aantal beperkingen waaronder een kleine groep deelnemers en korte termijn vervolgmetingen (tot 3 weken na de lichttherapie) en roepen vragen op over de mechanismen die dit effect kunnen verklaren. Zodoende is het nodig om deze positieve resultaten te repliceren in een gerandomiseerd gecontroleerde studie met voldoende deelnemers en mogelijke mechanismen die dit positieve effect kunnen verklaren verder uit te zoeken.

Hoofdstuk 2 beschrijft de opzet van de SPARKLE-studie. Het primaire doel van de SPARKLE-studie was om de effectiviteit van lichttherapie voor vermoeidheid na kanker na een HL- of DLBCL-diagnose te onderzoeken. Deelnemers werden geworven in tien verschillende academische en perifere ziekenhuizen. Potentiele deelnemers werden willekeurig toegewezen aan blootstelling aan fel wit licht (BWL; de interventie) of zwak wit licht (DWL; de controle). Deelnemers werden geïnstrueerd om deze lichttherapie te volgen binnen een half uur nadat zij wakker werden voor de duur van 30 minuten gedurende 25 aaneengesloten dagen. Primaire uitkomstmaten waren vermoeidheid en werk en sociale aanpassingen veroorzaakt door vermoeidheid. Secundaire uitkomstmaten waren depressie, angst, kwaliteit van leven, slaap kwaliteit, circadiane ritmes van slaap-waak patronen, cortisol en melatonine, cognitieve klachten en cognitief functioneren. Deze uitkomstmaten werden gemeten voorafgaand aan de lichttherapie (T0), direct na lichttherapie (T1), 3 maanden na lichttherapie (T2) en 9 maanden na lichttherapie (T3). Deelnemers die blootgesteld waren aan DWL kregen na het beantwoorden van T3 de mogelijkheid om alsnog BWL te volgen. Op basis van deze studie opzet was het mogelijk om de veelbelovende effecten uit de pilotstudies verder te onderzoeken in een studie met voldoende deelnemers. Daarnaast was het mogelijk om de lange termijneffecten en mogelijke mechanismen die dit positieve effect kunnen verklaren verder uit te zoeken.

In **hoofdstuk 3** worden de resultaten van de SPARKLE-studie beschreven. In totaal deden er 166 overlevenden van HL of DLBCL mee. Zij hadden een gemiddelde leeftijd van 46 jaar en de gemiddelde tijd tussen diagnose en deelname was 13 jaar. De naleving van lichttherapie was hoog met een gemiddeld gebruik van lichttherapie gedurende 23 dagen. Er waren geen verschillen in het effect van lichttherapie op vermoeidheid tussen deelnemers blootgesteld aan BWL of DWL. Beide groepen, dus ongeacht lichtintensiteit, lieten een significante ($p < .001$) verbetering zien van vermoeidheid gedurende de interventie wat maar iets afnam gedurende de vervolgmetingen ($ES_{T0\text{-}T1} = -0.71$; $ES_{T1\text{-}T3} = 0.15$). Vergelijkbare resultaten werden gevonden voor depressie, slaap kwaliteit en drie aspecten van kwaliteit van leven (rol beperkingen door fysieke functioneren, energie en sociaal functioneren). Lichttherapie had geen effect op angst, slaap-waak ritmes (gemeten met actigrafie) en cortisol en melatonine niveaus. Subgroep analyses van deelnemers die lichttherapie gebruikten: 1) op alle 25 behandeling dagen (n = 56); 2) via de Luminette brillen (n = 127); of 3) in de herfst/winter (n = 88) lieten vergelijkbare uitkomsten zien waardoor onze conclusies niet veranderden. Op het individuele niveau zagen we dat 35 tot 63 procent een klinisch relevante verbetering van vermoeidheid ervaarde, ongeacht de lichttherapie waar ze aan blootgesteld waren. Deze resultaten laten zien dat BWL niet superieur is in het verminderen van vermoeidheid na kanker ten opzichte van DWL. In plaats daarvan lieten deelnemers in beide groepen een verbetering zien. Aanvullend onderzoek is nodig om te bepalen welke onderdelen van het studieprotocol geleid hebben tot de conditie-onafhankelijke verbeteringen.

Hoofdstuk 4 presenteert de effecten van lichttherapie op cognitieve klachten en cognitief functioneren in lange termijn overlevenden van een HL of DLBCL met klinisch relevante vermoeidheid. Ongeveer een derde van de deelnemers liet cognitief disfunctioneren zien op baseline. Dit werd met name gezien in het verbale geheugen waar afwijkende scores gezien werden bij 34% voor directe herinnering en bij 27% voor verlate herinnering ten opzichte van

16% in een norm populatie. Zowel BWL als DWL had geen effect op cognitieve klachten of op cognitief functioneren (range *p*-waarden tussen .07 en .80; range effect grootte tussen .04 en .29). Ook werd er geen effect gezien in de totale groep of in de subgroep die cognitief disfunctioneren ervaarde op baseline. Deze resultaten laten zien dat ongeveer een derde van de HL en DLBCL overlevenden met vermoeidheid na kanker problemen ervaart met cognitief functioneren. Lichttherapie lijkt hier geen succesvolle behandeling voor te zijn. Daarom stellen wij voor dat andere cognitieve revalidatie trajecten beschikbaar gesteld moeten worden om het cognitief functioneren van deze mensen te verbeteren.

In **hoofdstuk 5** wordt een psychometrische evaluatie van de Multidimensionele Vermoeidheids Index (MFI) beschreven. De MFI was één van de primaire uitkomstmaten van de SPARKLE-studie. De originele validatie studie van de MFI concludeerde dat de MFI vijf dimensies van vermoeidheid meet: *algemene vermoeidheid, fysieke vermoeidheid, verminderde activiteit, verminderde motivatie* en *mentale vermoeidheid*. Desondanks waren er ook aanwijzingen voor twee modellen waarin vier dimensies van vermoeidheid gemeten worden. Aanvullende validatie studies geven geen uitsluitsel over de factor structuur van de MFI. Daarom was het doel van deze studie om de factor structuur van de MFI verder te onderzoeken in de algemene Nederlandse populatie (n = 2512). De resultaten van een confirmatieve factor analyse ondersteunde het oorspronkelijke vijf factor model niet (RMSEA = 0.120, CFI = 0.933, TLI = 0.920). Ook was het niet mogelijk om een alternatief vier factor model waarin algemene vermoeidheid en fysieke vermoeidheid gecombineerd werden te bevestigen (RMSEA = 0.122, CFI = 0.928, TLI = 0.917). Na het toevoegen van een algemene factor aan dit vijf of vier factor model om een bi-factor model te creëren werd er nog steeds geen acceptabele factor structuur gevonden (bi-4-factor: RMSEA = 0.151, CFI = 0.895, TLI = 0.873; bi-5-factor: RMSEA = 0.153, CFI = 0.894, TLI = 0.871). Exploratieve factor analyse bood geen alternatieve modellen met een acceptabele factor structuur, hoewel het wel de robuustheid van de items van de *algemene vermoeidheid* schaal liet zien. Deze resultaten geven aan dat er geen empirisch bewijs is voor een vijf of vier (bi-)factor structuur van de MFI of voor een alternatief model. Wij stellen dat de *algemene vermoeidheid* sub schaal de meest betrouwbare uitkomstmaat van de MFI is. Deze schaal kan gebruikt worden als een indicator voor vermoeidheid.

In **hoofdstuk 6** worden de resultaten van een vragenlijst studie die onderdeel was van de werving van de lichttherapie studie beschreven. Hierdoor is deze vragenlijst beantwoord voor HL- en DLBCL-overlevenden met en zonder vermoeidheid na kanker. De rationale voor dit onderzoek is gebaseerd op het vermogen van licht om interne circadiane ritmes bij te stellen aan externe circadiane ritmes. Hoewel verschillende onderzoeken hebben laten zien dat verstoringen in het interne circadiane ritme (meer wakker worden gedurende de nacht en meer dutjes doen overdag) een relatie hebben met vermoeidheid in patiënten met kanker, is het nog onduidelijk is dit ook komt doordat de timing van het interne circadiane ritme afwijkend is van het externe circadiane ritme. Om die reden hebben wij onderzocht of er een relatie is tussen chronotype (iemands voorkeur in de timing van het slaap-waakpatroon, bijvoorbeeld of iemand een ochtend- of een avondmens is) en vermoeidheid na kanker. In deze vragenlijst studie hebben we verder nog onderzocht wat het verband is tussen slaap kwaliteit en vermoeidheid na kanker. De hypothese was dat avondmensen hogere vermoeidheidsscores

zouden hebben ten opzichte van ochtendmensen. In totaal hebben 458 overlevenden (50% vrouw) met een gemiddelde leeftijd van 50 jaar deelgenomen. Zij vulden een VAS vermoeidheidsschaal van 0 (geen vermoeidheid) tot 10 (ergst voorstelbare vermoeidheid), de Munich Chronotype Questionnaire en de Pittsburgh Sleep Quality Index in tussen oktober 2018 en juli 2019. De meerderheid was gediagnosticeerd met een HL (71%) en de gemiddelde tijd sinds diagnose was 12 jaar. Zessenzestig procent van de deelnemers rapporteerde matige tot ernstige vermoeidheid. Er was geen statistisch significant verschil voor het gemiddelde midsleep tijdstip, i.e. het tijdstip tussen het in slaap vallen en het wakker worden wat gebruikt wordt om chronotype te bepalen, tussen deelnemers met en zonder vermoeidheid. Een hiërarchische lineaire regressie werd gebruikt om de verbanden tussen vermoeidheid na kanker en chronotype (gebaseerd op vroeg, gemiddeld en laat chronotype; model 1) en vermoeidheid na kanker en slaap kwaliteit (model 2) te onderzoeken. De resultaten lieten zien dat er geen verband was tussen vermoeidheid na kanker en chronotype (alle p-waarden ≥ .50). Er waren wel verbanden tussen vermoeidheid na kanker en twee (van de zeven) aspecten van slaap kwaliteit: subjectieve slaap kwaliteit ($p < .001$) en dagelijks disfunctioneren ($p < .001$). Daarom is het waarschijnlijker dat vermoeidheid na kanker in verband staat met iemands slaap kwaliteit dan met iemands chronotype.

Hoofdstuk 7 beschrijft de belangrijkste bevindingen van de studies die beschreven zijn in dit proefschrift, vergelijkt deze bevindingen met de huidige literatuur en bespreekt methodologische beperkingen en ideeën voor toekomstig onderzoek. Op basis van de huidige literatuur concluderen we dat er onvoldoende bewijs is voor de effectiviteit van lichttherapie voor vermoeidheid na kanker in (lange termijn) overlevenden van kanker. Er zijn wel suggesties dat lichttherapie effectief kan zijn om vermoeidheid laag te houden in patiënten die behandeld worden voor kanker. Eenzelfde scheiding is te zien in de literatuur over het verband tussen circadiane ritmes en vermoeidheid: voor patiënten met kanker laten verschillende studies zien dat een verstoring in het circadiane ritme in verband staan met hogere niveaus van vermoeidheid, maar de (beperkte) studies in overlevenden van kanker bieden geen bewijs voor dit verband. Dit suggereert dat vermoeidheid tijdens kanker een gevolg kan zijn van deze biologische factor, maar dat na genezing andere factoren een belangrijkere rol spelen in het behoud van deze vermoeidheidsklachten. Methodologische beperkingen van de beschreven studies hebben te maken met het lichttherapie protocol, de naleving van de lichttherapie, eigenschappen van de lichttherapie en de meting van vermoeidheid, cortisol, melatonine en chronotype. Toekomstig onderzoek kan meer duidelijkheid schetsen over welke onderdelen van het huidige studieprotocol verantwoordelijk zijn voor de geobserveerde, klinisch relevante verbetering in een gedeelte van de deelnemers. Dit zou kunnen komen door non-specifieke behandel effecten of er is sprake van een placebo reactie. Ook kan er gekeken worden of een combinatie van cognitieve gedragstherapie voor vermoeidheid na kanker en lichttherapie leidt tot additieve behandelingseffecten. Daarnaast kan verder onderzocht worden tot wanneer circadiane verstoringen een invloed hebben op vermoeidheid tijdens of na kanker en welke factoren een rol spelen in het behoud van de vermoeidheidsklachten na genezing.

A

PUBLICATIONS

List of publications

Starreveld, DEJ, Daniels, LA, Kieffer, JM, Valdimarsdottir, HB, van Someren, E, de Geus, JL, Janus CPM, van Spronsen, DJ, Petersen, EJ, Marijt, EWA, de Jongh, E, Zijlstra, JM, Böhmer, LH, Houmes, M, Kersten, MJ, Habers, GEA, Redd, WH, Lutgendorf, S, Ancoli-Israel, S, van Leeuwen FE, and Bleiker, EMA. Efficacy of Light Therapy for Cancer Related Fatigue in (non-)Hodgkin Lymphoma Survivors: Results of a Randomized Controlled Trial. *Cancers*, 2021; 13(19): 4948

Kieffer, JM*, **Starreveld, DEJ***, Boekhout, A, and Bleiker EMA. A questionable factor structure of the multidimensional fatigue inventory in the general Dutch population. *Journal of Clinical Epidemiology*, 2021; 137: 266-276.

Starreveld, DEJ, Habers, GEA, Valdimarsdottir, HB, Kessels R, Daniëls LA, van Leeuwen FE, and Bleiker EMA. Cancer-related fatigue in relation to chronotype and sleep quality in (non-) Hodgkin lymphoma survivors. *Journal of Biological Rhythms*, 2021; 36(1): 71-83.

Habers, GEA, van der Helm-van Mil, AHM, Veldhuijzen, DS, Allaart, CF, Vreugdenhil, E, **Starreveld, DEJ**, Huizinga, TWJ, and Evers, AWM. Earlier sleep-wake timing in patients with rheumatoid arthritis. *Clinical Rheumatology*, 2021; 40(6): 2185-2192.

Meesters, Y, **Starreveld, DEJ**, Verwijk, E, Spaans, HP, and Gordijn, MC. Chronotherapy Network Netherlands (CNN). *Journal of Biological Rhythms,* 2020; 35(3):317-319.

Starreveld, DEJ, Daniels, LA, Valdimarsdottir, HB, Redd, WH, de Geus, JL, Ancoli-Israel, S, Lutgendorf, S, Korse, CM, Kieffer, JM, van Leeuwen, FE, and Bleiker, EMA. Light therapy as a treatment of cancer-related fatigue in (non-) Hodgkin lymphoma survivors (SPARKLE trial): study protocol of a multicenter randomized controlled trial. *BMC Cancer,* 2018; 18(1):1-11.

Starreveld, DEJ, Markovitz, SE, van Breukelen, G, and Peters, ML. The course of fear of cancer recurrence: Different patterns by age in breast cancer survivors. *Psycho-Oncology,* 2018; *27*(1): 295-301.

Starreveld, DEJ. The Need for Psychosocial interventions in oncology Care. *Maastricht Student Journal of Psychology and Neuroscience*, 2015; 4(1):75-88.

Manuscripts in preparation or submitted

Starreveld, DEJ, Daniels, LA, Kieffer, JM, Valdimarsdottir, HB, de Geus, JL, van Berlo, E, Mesland, L, van Leeuwen FE, and Bleiker EMA. The efficacy of light therapy on cognitive functioning of (non-) Hodgkin lymphoma survivors with cancer-related fatigue. [*submitted*].

* Both authors contributed equally to the manuscript

DANKWOORD

Dat mijn naam op de kaft van dit proefschrift staat, doet veel mensen die betrokken zijn geweest bij dit project te kort. Daarom wil ik hier graag een aantal mensen bedanken.

Als eerste de deelnemers aan de studies die beschreven zijn in dit proefschrift. Zonder jullie verhalen en motivatie om deze te delen had ik nergens over kunnen schrijven.

Dan mijn (co-)promotoren. Prof. dr. E.M.A. Bleiker, beste Eveline, ik heb je vaak omschreven als mijn "moeder in de wetenschap". Dat ik me het SPARKLE-project zo eigen mocht maken, is het grootste cadeau dat je me gegeven hebt. Prof. dr. ir. F.E. van Leeuwen, beste Floor, jouw praktische tips en kritische vragen hebben ons onderzoek naar een hoger niveau getild. Dr. L.A. Daniels, beste Laurien, hoe leuk is het dat jij als oude bekende mijn copromotor bent. Dankzij jouw ervaring in de kliniek vergat ik nooit om na te denken over klinische implicaties van onze studies.

Een onderzoek uitvoeren in tien verschillende ziekenhuizen kan niet zonder de hulp van artsen, research medewerkers, verpleegkundigen, lab medewerkers, secretaresses en baliemedewerkers in deze ziekenhuizen. Ik kan jullie niet allemaal bij naam noemen, maar iedereen van het Admiraal de Ruyter ziekenhuis, Albert Schweitzer ziekenhuis, Amsterdam UMC, Antoni van Leeuwenhoek ziekenhuis, Erasmus MC, HagaZiekenhuis, LUMC, Radboudumc en het UMCU: bedankt voor jullie hulp om de SPARKLE-studie tot een succes te maken.

Jessie, jij hebt een groot deel van de data voor dit onderzoek verzameld. Ik neem een petje af voor al het werk dat je gedaan hebt.

Voor de randomisatie heb je onafhankelijke mensen nodig. Danielle, Karin, Jacqueline, Pernilla en Viviana, bedankt dat jullie dit voor ons deden.

Jacobien, bedankt dat ik je altijd lastig mocht vallen met mijn statistiek vragen.

Tiny en Els, ik zou niet weten wat ik had moeten doen zonder jullie ondersteuning bij het verzamelen en opslaan van speeksel en bloed. Huub en Mirthe, bedankt voor jullie hulp bij de analyses van het speeksel. Mirthe, ontzettend bedankt voor alle uren die je hiervoor in het lab doorbracht.

Ellen en Laura, dank voor jullie hulp met de analyses van de cognitieve data. Het heeft een mooi artikel opgeleverd!

In de afgelopen vijf jaar heb ik ontzettend veel mogen leren van verschillende experts. Eus, in het begin klopten Eveline en ik bij jou aan met veel vragen. Jouw tips destijds vormden de basis voor onze actigrafie meting. Ook introduceerde je me bij Chronotherapie Netwerk Nederland. Esmee, Harm-Pieter, Lisette, Marijke, en Ybe, bedankt dat ik CNN als platform mocht gebruiken om de SPARKLE-studie van begin tot eind te bespreken.

The ALECCS consortium: Heiddis, Bill, Lisa, Ali, Susan, and Sonia, it was such a pleasure to meet you all in different places of the world to discuss our research. Heiddis, thank you for our weekly meetings to discuss our results.

Natuurlijk is je werk een stuk leuker als je gezellige collega's om je heen hebt. Anne-Marthe Kroon, ik krijg een lach op mijn gezicht als ik terugdenk aan de ontzettend gezellige tijd op onze kamer. Melanie, Hester, Emmie, Vera, Silvie, Vivian, Kete, Barbara, Lara en Suzanne ook bij jullie alleen maar fijne herinneringen. Of het nu over werk of privézaken ging, het was altijd

fijn om weer even bij te praten. Jacqueline, Rianne en Ellen, samen waren we onderdeel van de Bleiker-werkgroep. Bedankt voor alle (digitale) koffie-momentjes en de gezamenlijke lunches.

DanielA, mijn kamergenootje van begin tot dat Corona dat toe liet. Lief en leed hebben we gedeeld. Chocolade hebben we gedeeld. Kennis hebben we gedeeld. Bedankt voor de fijne tijd die we samen hadden en bedankt voor je relativering wanneer die nodig was.

Marloes, freundin, allebei verhuisden we van Maastricht naar de Randstad. Nu allebei aan het promoveren. Ik ben blij dat ik de afgelopen jaren hoogte- en dieptepunten met je kon delen, maar nog blijer ben ik met onze leuke uitstapjes samen.

Lieve Stefan, je was verbaasd dat ik je zou noemen in mijn dankwoord, maar voor mij is dat niet meer dan logisch. De afgelopen jaren heb je me zo veel geholpen. Je bood een luisterend oor en voelde haarfijn aan wanneer ik een wandeling met jou en Bowy of een dosis hondenfilmpjes nodig had om een lach op mijn gezicht te toveren. Bedankt dat je er altijd bent als het nodig is. En omdat belofte schuld maakt: gotta catch 'em all.

Lieve papa en mama, Jeroen, Edwin en Kiki. Hier is het dan eindelijk: mijn proefschrift. De afgelopen jaren heb ik geprobeerd om uit te leggen waar ik mee bezig was, maar alles was toch een ver-van-jullie-bed show. Dat maakt ook helemaal niet uit. Wat wel uitmaakt, is dat ik het zonder jullie niet had gekund.

A

CURRICULUM VITAE

Daniëlle Starreveld was born on 25th of April 1989 in Alphen aan den Rijn, the Netherlands. In 2007, she completed secondary school at the Scala College in Alphen aan den Rijn. She completed an in-service training for radiation technologist at the Leiden University Medical Center and Erasmus Medical Center in 2010. In 2011, she started her Bachelor in Psychology at Maastricht University. During this time, she completed the Honors Program, followed electives at Örebro University in Sweden and wrote her bachelor thesis at the Center of Health and Medical Psychology (CHAMP, Örebro University). She graduated her Bachelor, cum laude, in 2014 and started with a research master in Clinical and Cognitive Neuroscience (specialization psychopathology) at Maastricht University. She completed her research internship at the department of pain treatment at the Netherlands Cancer Institute after which she graduated in 2016. Since 2016, she worked as a PhD student at the department of Psychosocial Research and Epidemiology of the Netherlands Cancer Institute. The research was performed under the supervision of prof. dr. Eveline M.A. Bleiker, prof. dr. ir. Floor van Leeuwen, and dr. Laurien A. Daniels. During this time, she was a member of the student council of the Graduate School Oncology Amsterdam and the scientific committee of the Dutch Association of Psycho-Oncology. Between March 2021 and February 2022, she worked as coordinator of the Dutch sleep register at the Netherlands Institute of Neuroscience. Currently she works as a junior Advisor at the Federatie Medisch Specialisten.