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

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## CHAPTER 6

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

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## 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  $\geq .50$ ). 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<sup>1</sup> with a prevalence between 25 and 60 percent in (non-)Hodgkin lymphoma survivors<sup>2, 3</sup>. 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”<sup>4</sup>. 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<sup>5</sup>.

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<sup>6-8</sup>. 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<sup>9</sup>. Additionally, a flatter cortisol slope was found for individuals with fatigue after cancer<sup>10, 11</sup>.

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<sup>12</sup>. 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<sup>12</sup>. 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<sup>13</sup>, bipolar disorders<sup>14</sup>, obesity<sup>15</sup>, and seasonal affective disorder<sup>16</sup>. It is also shown that a later chronotype is related to fatigue in individuals with irritable bowel symptoms<sup>17</sup> and students<sup>18</sup>. 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*<sup>12</sup>.

On the other hand, circadian rhythm disruptions have been associated with lower levels of sleep quality in cancer patients<sup>19</sup>. 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<sup>20</sup>. Several studies showed an association between poorer sleep quality and increased levels of fatigue in patients treated for cancer<sup>21, 22</sup>. Related to chronotype, several studies in other populations showed that evening types had worse sleep quality<sup>14, 15, 18</sup>.

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<sup>14, 15, 17, 18</sup> 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<sup>23-25</sup>. As morning light therapy advances the circadian phase, which is associated with chronotype<sup>26</sup>, a later chronotype might be associated with fatigue. Alternatively, light therapy has been shown to improve sleep quality<sup>27</sup>, 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)<sup>28</sup>. 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<sup>29</sup>.

The *Munich Chronotype Questionnaire* (MCTQ)<sup>30</sup> 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 an indicator for chronotype<sup>31</sup> 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 (aMS 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<sup>12</sup>. 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)<sup>32</sup>.

Fatigue was described in more detail by the general fatigue score of the Multidimensional Fatigue Inventory (MFI)<sup>33</sup>. Originally, the MFI measures five domains of fatigue (general fatigue, mental fatigue, physical fatigue, reduced motivation, and reduced activity) but Kieffer et al.<sup>34</sup> 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)<sup>35</sup> 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, Kruskal-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<sup>12</sup>. 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<sup>36</sup>. 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<sup>37</sup> 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<sup>38</sup>, in R version 3.6.1<sup>39</sup>. 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. (%)				p- value	Post-hoc	Missing (%)
	Total (n=458)	No fatigue (n=134)	Moderate fatigue (n=171)	Severe fatigue (n=133)			
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 <sup>a</sup>	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 <sup>b</sup>							
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. (%)				p- value	Post-hoc	Missing (%)
	Total (n=458)	No fatigue (n=134)	Moderate fatigue (n=171)	Severe fatigue (n=133)			
<b>Diagnosis<sup>b</sup></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)			
<b>Time since diagnosis in years</b>							
Mean	12.0	11.6	12.5	11.3	.56		2.2
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)			
<b>Treatment</b>							
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 <sup>c</sup>	112 (25)	33 (25)	39 (23)	35 (26)	.79		0.4
<b>Self-reported comorbidities (in past 12 months)</b>							
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)			
<b>Fatigue</b>							
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.

<sup>a</sup> Two underweight cases (BMI between 16.5 and 18.5) were included in the normal BMI category.

<sup>b</sup> Fisher's Exact Test reported. <sup>c</sup> 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

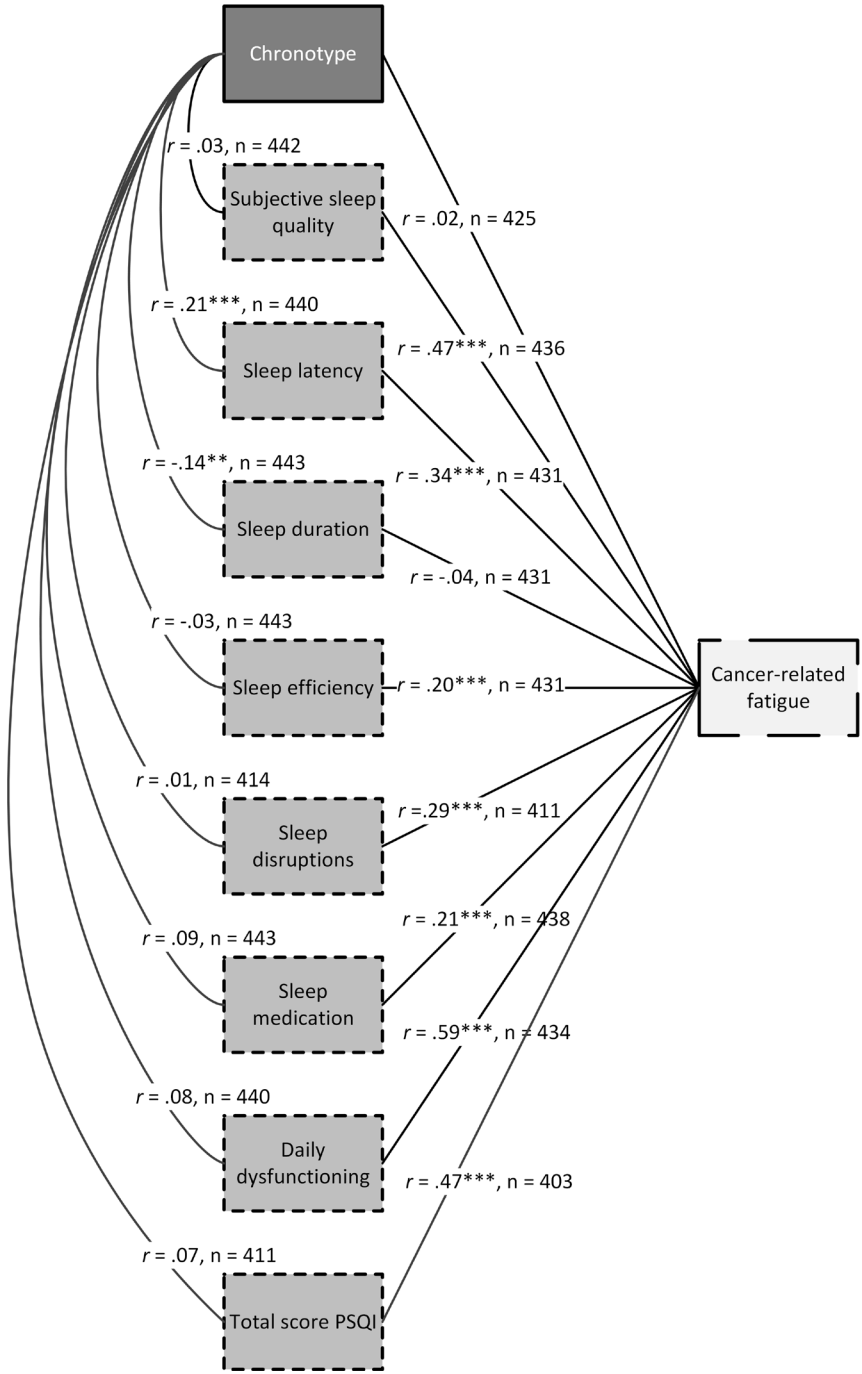
Figure 1 shows a schematic overview of bivariate Pearson correlations between chronotype, sleep quality and fatigue. Chronotype was significantly associated with two aspects of sleep quality: sleep latency ( $r = .21$ ;  $p < .001$ ) and sleep duration ( $r = .14$ ;  $p < .01$ ). With the exception of chronotype ( $r = .02$ ;  $p = .62$ ) and sleep duration ( $r = .04$ ;  $p = .42$ ), all subscales of sleep quality were significantly associated with fatigue ( $r_{\text{range}} = .20$  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 ( $B_{\text{fairly good}} = 0.87$ ;  $B_{\text{fairly bad}} = 1.47$ ;  $B_{\text{very bad}} = 2.80$ ; for all  $p \leq .001$ ) and between fatigue and daily dysfunctioning ( $B_{\text{some dysfunctioning}} = 2.15$ ;  $B_{\text{quite a bit dysfunctioning}} = 3.09$ ;  $B_{\text{severe dysfunctioning}} = 3.28$ ; 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" ( $B_{\text{imputed}} = -1.00$ ,  $p = .01$ ;  $B_{\text{complete cases}} = -1.41$ ,  $p = .001$ ) 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.

	<b>Total (n=458)</b>	<b>No fatigue (n=134)</b>	<b>Moderate fatigue (n=171)</b>
<b>BED TIME<sup>a</sup></b>			
<i>Basic variables</i>			
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 <sup>‡</sup>	17 (22)	11 (13)	17 (19)
I wake up at ... o'clock <sup>b</sup>	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 <sup>b</sup>	2:38 (1:49)	3:17 (2:14)	2:20 (1:29)
<i>Calculated variables</i>			
Sleep onset	23:42 (0:59)	23:48 (0:59)	23:43 (0:54)
Sleep duration <sup>b</sup>	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 (%) <sup>c</sup>	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)
<b>SLEEP QUALITY<sup>a</sup></b>			
Subjective sleep quality <sup>b</sup>	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 <sup>b</sup>	0.4 (0.7)	0.1 (0.4)	0.5 (0.9)
Sleep disruptions <sup>b</sup>	1.3 (0.6)	1.1 (0.5)	1.3 (0.5)
Sleep medication <sup>b</sup>	0.3 (0.8)	0.1 (0.4)	0.3 (0.8)
Daily dysfunctioning <sup>b</sup>	1.1 (0.8)	0.4 (0.6)	1.2 (0.7)
Total score <sup>b</sup>	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.

<sup>a</sup> 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. <sup>b</sup> Kruskal-Wallis test reported. <sup>c</sup> 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).

<b>Model 1<sup>a</sup></b>					
	<i>B</i>	(SE)	95% CI		<i>p</i>
			Lower	Upper	
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 <sup>a</sup>					
	B	(SE)	95% CI		p
			Lower	Upper	
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 <sup>a</sup>					
	<i>B</i>	(SE)	95% CI		<i>p</i>
			Lower	Upper	

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

<sup>a</sup> 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<sup>17</sup>. Another study showed increased levels of chronic work-related fatigue

Model 2 <sup>a</sup>					
	<i>B</i>	(SE)	95% CI		<i>p</i>
			Lower	Upper	
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<sup>18</sup>. 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<sup>40</sup>.

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)<sup>41</sup> and Composite Scale of Morningness (CSM)<sup>42</sup> 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<sup>43</sup>. 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<sup>6-9</sup>. 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<sup>27</sup>.

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<sup>31</sup> compared to the association between DLMO and MSFsc<sup>44</sup>. 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<sup>2, 3</sup>. 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<sup>45</sup>. 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<sup>46</sup> 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.

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## APPENDIX

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

	Model 1 <sup>a</sup>				
	<i>B</i>	(SE)	95% CI		<i>p</i>
			Lower	Upper	
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 <sup>a</sup>					
	B	(SE)	95% CI		p
			Lower	Upper	
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 <sup>a</sup>				
B	(SE)	95% CI		p
		Lower	Upper	

R<sup>2</sup> = .17

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

<sup>a</sup> 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)

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**Model 2<sup>a</sup>**

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	<i>B</i>	(SE)	95% CI		<i>p</i>
			Lower	Upper	
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*

$R^2 = .52$

$\Delta R^2 = .35, p <.001$

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