Sleep Medicine 134 (2025) 106740

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Longitudinal investigation of sleep and circadian rest-activity rhythms in non-small cell lung cancer patients during immunotherapy and associations with fatigue, depression, and perceived stress

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ARTICLE INFO

Keywords:
Sleep
Circadian rest-activity rhythms
Cancer patients
Immune check point inhibitors
Fatigue
Depression
Stress

ABSTRACT

Background: Patients with advanced non-small cell lung cancer (NSCLC) face poor prognosis. However, new therapies like immune checkpoint inhibitors (ICIs) have improved survival. Nevertheless, ICIs act through immune activation – a proposed underlying mechanism of frequently reported symptoms such as sleep and circadian disturbances. The objective of this study was to longitudinally investigate sleep and circadian rest-activity rhythms and associations with psychological symptoms in NSCLC during ICI treatment.
Methods: Newly diagnosed NSCLC patients were included in this prospective study, assessing insomnia severity, total sleep time, circadian rest-activity rhythms, and psychological symptoms (fatigue, depression, and stress) during the first five months of ICI treatment, using validated questionnaires, sleep diaries and actigraphy.
Results: Forty-nine patients were included. Prior to treatment, patients slept on average 5.8 hours/night and 49 % reported clinical levels of insomnia. Spontaneous improvements in insomnia severity and total sleep time were observed, along with marginal but non-significant improvements in circadian rest-activity rhythm robustness. Insomnia severity was significantly associated with higher levels of fatigue ($p = .004$), depression ($p = .007$), and perceived stress ($p = .033$). Moreover, lower circadian rest-activity robustness was associated with more fatigue ($p = .021$). At baseline, mean levels of fatigue, depression, and perceived stress were below clinical levels and declined further over time.
Conclusion: Sleep disturbances, circadian disruption, and psychological symptom burden in NSCLC patients were greatest prior to and shortly after initiation of ICI treatment, with gradual improvement over the first five months. However, inter-individual differences in sleep and circadian disturbances were evident and linked to psychological symptoms.

1. Introduction

Lung cancer is currently the most common cancer worldwide and the leading cause of cancer-related deaths [1]. Non-small cell lung cancer (NSCLC) represents over 80 % of lung cancer cases and are primarily diagnosed at advanced stages [2,3], limiting treatment options to primarily focusing on the prolongation of patient survival [4]. In the early 2000s, chemotherapy was the most common anti-cancer treatment [5]. However, in around 2010, modern checkpoint inhibitors were introduced to cancer care [6],and since then the treatment landscape has

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https://doi.org/10.1016/j.sleep.2025.106740
Received 10 April 2025; Received in revised form 16 July 2025; Accepted 8 August 2025
Available online 10 August 2025
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shifted towards targeted therapies and immunotherapies employing checkpoint inhibitors (ICIs). ICIs have shown notable improvements in survival rates for various cancers, including NSCLC. In particular, Programmed Cell Death Protein 1 (PD-1) and Programmed Cell Death Ligand 1 (PD-L1) inhibitors have shown impressive clinical responses [7]. Despite these advances, patient outcomes remain suboptimal, and durable benefits with manageable toxicity can so far only be achieved for a minority of patients [8,9]. The mechanism underlying ICIs involves strengthening the immune system's attack on tumors by obstructing negative regulatory signals (checkpoint inhibition) on T-cells [10]. Although this augmentation in antitumor immunity is promising, it introduces an elevated risk of triggering autoimmunity. Consequently, patients may experience immune-related adverse effects that can manifest across multiple organs [11,12]. Thus, treatment with ICIs represents a shift in the profile of anticipated side-effects, and much remains to be learned about these side-effects and eventually how they may relate to the continuation of treatment, which, in turn, is important for prognosis.

While immune-related adverse events of a primarily physiological nature, such as immune-related diarrhea and colitis have received some attention [13], sleep, circadian rhythms and psychological symptoms related to ICIs remain underexplored. However, the immune system is closely and bi-directionally linked to the circadian system, and to sleep regulation, where inflammatory cytokine release has been found to disrupt biobehavioral rhythms, and in turn increase inflammation [14]. Moreover, both disruption of the circadian system and changes in behavioral rhythms are hypothesized to be related to cancer- and cancer treatment-related symptoms such as fatigue, depression, and stress [15].

Indeed, several studies have reported high prevalence of sleep and circadian disturbances among cancer patients during traditional treatments such as chemotherapy [16,17]. These symptoms are inherently burdensome but may also contribute to the exacerbation of comorbid psychological symptoms. Notably, cancer patients experiencing insomnia (i.e., difficulties falling asleep and/or maintaining sleep) [18], tend to report elevated levels of depressive symptoms and fatigue compared to those without insomnia [17]. Moreover, sleep and circadian rhythm dysregulation have been bidirectionally associated with cancer prognosis [19], underscoring the clinical relevance of these symptoms in patients with advanced NSCLC facing poor prognosis.

As previously described a trans-diagnostic mechanism involved in both sleep and circadian disturbances [20], fatigue, and depression [15], as well as stress [21] is inflammation. Since inflammation arises from immune activation [22], which is the core mechanism of immunotherapy [23], we hypothesize that immune activation induced by ICIs could negatively impact sleep and circadian rhythms, and worsen fatigue, depression, and stress in cancer patients undergoing immunotherapy. Apart from their negative impact on quality of life [24], symptom burden plays a critical role in determining patient eligibility for both the initiation and continuation of immunotherapy [25]. Consequently, a deeper understanding of possible symptom patterns during these new anti-cancer treatments, and potential modifiable factors underlying these symptoms could assist clinicians in implementing timely interventions.

Although overlapping and interrelated, sleep and circadian outcomes reflect distinct constructs that may not always be correlated. While sleep-related measures such as sleep duration or insomnia symptoms primarily capture the quantity [26] and subjective quality of sleep [18], circadian metrics such as rhythm robustness and timing offer insights into the temporal patterns within and across days [27]. Therefore, a multimodal and longitudinal approach is essential to capture nuances in sleep and circadian markers, as well as their association with psychological and behavioral symptoms during immunotherapy. Such insights may help clinicians prevent premature treatment discontinuation, improve quality of life, and possibly even improve prognosis.

Against this background, the primary aim of this study was to prospectively examine the severity and trajectory of insomnia, sleep duration and circadian rest-activity disruption in newly diagnosed, treatment-naïve NSCLC patients undergoing treatment with ICIs, and examine associations with psychological symptoms of fatigue, depression, and perceived stress. We hypothesized that immune activation induced by ICIs would negatively impact sleep and circadian rhythms, and in turn worsen fatigue, depression, and stress during the 5-month study period. We also hypothesized that sleep and circadian parameters would show different patterns and associations with psychological symptoms.

2. Materials and methods

2.1. Patients

Newly diagnosed, advanced NSCLC patients referred to the Department of Oncology at Aarhus University Hospital between September 2019 and December 2021 were invited to participate in this prospective, longitudinal study. To ensure a homogeneous sample in terms of cancer stage, treatment status and treatment options, we included only newly diagnosed, treatment naïve patients, with advanced non-curable cancer stage (III and IV), who were referred for standard first line treatment. According to standardized Danish protocol [28] this patient group is offered the same treatment modality, i.e., palliative pembrolizumab (ICI) as either a monotherapy or in combination with chemotherapy, with the alternative of no systemic anti-cancer treatment at all. Thus, eligibility criteria were: Age $\geq$18 years, newly diagnosed with a histologically and cytologically confirmed advanced non-curable NSCLC, no prior anti-cancer-treatment, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 [29], no brain metastases, and clinically eligible (performance status 0–2) to initiate first line treatment with the ICI pembrolizumab. Pembrolizumab was administered every three weeks, either as monotherapy (cancer cell proliferation rate $>$50 %) or combined with chemotherapy (cancer cell proliferation rate $<$50 %) [28].

2.2. Recruitment and study procedure

This study was preregistered (Clinical Trail ID NCT04070651) and approved by the Regional Research Ethics Committee (JNR 1-10-72-86-19). According to Danish law [30], the total diagnostic pathway, from referral to a hospital due to suspected lung cancer to confirmed diagnosis, must not exceed 30 days. Furthermore, newly diagnosed patients are required to initiate treatment within 11 days of receiving their diagnosis. In this study, eligible patients were introduced to the study at their first consultation with an oncologist following recent diagnosis. Patients who consented to participate, were enrolled prior to treatment initiation, and followed the study procedures and assessment timepoints as shown in Fig. 1. Participants were not incentivized to participate nor compensated, and they were informed that declining participation would not affect their treatment or care.

At inclusion and prior to treatment initiation, patients were asked to begin wearing an actigraphy watch (to be worn throughout the five-month study period), complete questionnaires, and fill out a five-day sleep diary. These measures, described in detail below, were repeated throughout the study.

2.3. Measures and data processing

Questionnaires were administered using the Research Electronic Data Capture (REDCap) system [31]. Sleep duration (Total Sleep Time) were collected from sleep diaries, and circadian rest-activity data assessed by wrist actigraphy. Measures are described in detail below.

Sociodemographic and clinical characteristics. Sociodemographic information on age, gender, ethnicity, educational level, marital status, and occupation was collected using questionnaires. Clinical characteristics were obtained from medical records and included cancer

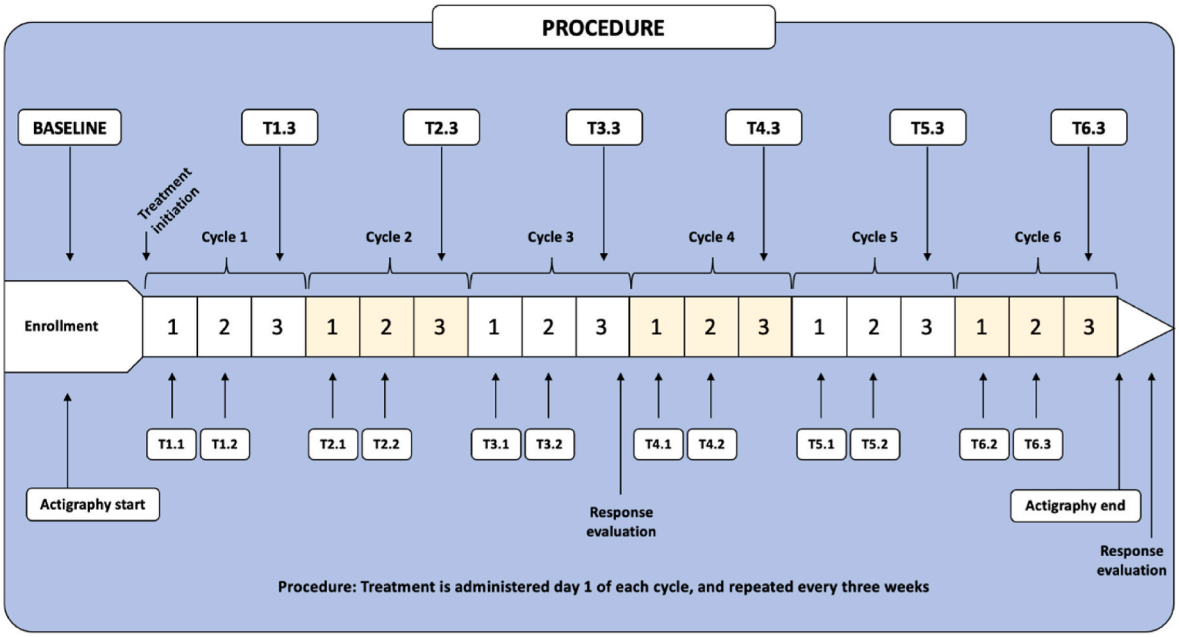

Fig. 1. Flowchart of study procedure
Fig. 1: Objective circadian activity rhythms were assessed continuously by actigraphy, and insomnia severity assessed at all time points, corresponding to weekly assessments over a period of five months (T1.1, T1.2, T1.3, T2.1 etc.), ending with patient's second treatment evaluation with a Computer Tomography scan (CT-scan) at the end of the sixth cycle (T6.3). Assessment of psychological symptoms together with five days of sleep diary were obtained every three weeks corresponding to every treatment cycle (T1.3, T2.3, T3.3 etc.).

diagnosis, stage, performance status, smoking status, and treatment regimen.

Insomnia severity. Insomnia severity was assessed with the 7-item Insomnia Severity Index (ISI) [32] on a weekly basis, with items rated on five-point Likert scales (0 = Not at all, 4 = Extremely) providing a global index of insomnia severity (range: 0–28). Higher levels correspond to greater insomnia severity. ISI has demonstrated good psychometric properties in cancer populations [33,34].

Total sleep time. Patients completed the Consensus Sleep Diary [35] over a 5-day period at the end of every treatment cycle. Diary data were used to calculate 5-day averages of TST [36].

Circadian rest-activity rhythms. Circadian rest-activity rhythms were obtained from actigraphy (ActTrust wrist actimeter by Condor Instruments, Brazil). The approximate 24-h variation in both biological [37],behavioral [38], and cognitive functions [39], that we call circadian rhythms serves as a cue for the homeostatic condition of the human organism [40]. One way of capturing the circadian rhythm of the biological clock, is by using a behavioral proxy, such as circadian rest-activity rhythms as measured by actigraphy. Actigraphy has the advantage of recording rest-activity rhythms in naturalistic settings, and over prolonged periods of time, improving both ecological validity as well as data validity [41]. Moreover, actigraphy is well-suited to studying circadian rest-activity rhythmicity in cancer populations [42]. The actigraph (ActTrust) in this study was worn on patient's non-dominant wrist continuously and at all times throughout the five months, including during showers and other activities. To ensure compliance, monitor battery status, and prevent potential issues, the first author maintained weekly contact with participants. The ActTrust device, with a battery life of three months, required only one 2-h recharge during the five-month period, which was scheduled to coincide with a hospital treatment visit. The ActTrust was configured to collect activity data at 60 s epochs using Proportional Integrating Mode (PIM). Data were binned into one-week periods to investigate fluctuations between and within each treatment cycle, corresponding to the weekly sleep measurements. Due to national guidelines requiring the earliest treatment onset possible, baseline recordings ranged from 1 to 7 days. A minimum of three days of recording were accepted as sufficient for this period. The Circadian Function Index (CFI) was used to measure robustness of the circadian rest-activity rhythm and calculated using ActStudio Software (version 1.0.25, 2022, Condor Instruments, Brazil). The CFI is a non-parametric method incorporating multiple parameters such as intra-daily variability (IV), inter-daily stability (IS) and relative amplitude (RA). Hence, the CFI reflects the overall strength and regularity of the rest-activity rhythm across time, which was our aim when collecting longitudinal and continuous actigraphy data. CFI has high sensitivity, specificity, and accuracy in differentiating activity from rest compared to Temperature, Activity, or Position (TAP) alone, or one-dimensional circadian variables such as auto-correlation indexes [43]. The score range of CFI is 0–1, with higher scores indicating more robust circadian rest-activity rhythms. In this study, the CFI was used to investigate rhythm robustness over time and explore if robustness would predict psychological symptoms across time. Note that no established cut-off currently exists for CFI [44].

Fatigue. Cancer-related fatigue was assessed using the general score of the 30-item Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), which measures five dimensions of fatigue with each item rated on a 5-point scale (0 = Not all; 4 = Extremely). Higher scores indicate worse fatigue [45]. The MFSI has been validated in cancer populations [45,46].

Depressive symptoms. Depressive symptoms were assessed using the 8-item Patient-Reported Outcome Measurement Information System (PROMIS) Depression 8b Short Form. It captures affective aspects of depression on five-point rating scales (1 = never; 5 = Always) [47]. A total raw score was calculated, with higher scores indicating worse symptoms [48].

Stress. Stress was measured with the 10-item Perceived Stress Scale (PSS-10), assessing stress-related feelings and thoughts on 5-point Likert scales (0 = Never; 4 = Very often), with higher scores indicating higher

levels of perceived stress [49]. The PSS-10 has demonstrated good psychometric properties in clinical samples [50].

2.4. Analytic strategy

Data processing and analyses were performed in SPSS version 21 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp) and STATA/SE 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX)

Descriptive statistics were calculated for all measures, followed by statistical trajectory models (growth-curve models) in three steps. First, change over time in ISI, TST, CFI, fatigue, depression, and stress (i.e., main effects of time) were estimated using mixed linear models fitted with restricted maximum likelihood estimation (REML) with random intercepts and slopes to meet the theoretical assumptions of inter-individual variation in baseline levels and trajectories over time [51]. The random coefficients were assumed to be correlated, and thus, modelled with an unstructured covariance matrix. The Kenward-Roger method was used to calculate degrees of freedom [52].

Second, we explored associations between individuals' sleep (ISI, TST) and circadian markers (CFI), and psychological symptoms using mixed linear models fitted with REML with random intercepts and modelled with an unstructured covariance matrix. The respective associations were adjusted for the other psychological symptoms. These models, known as within-person variation models, estimate the degree of association between two time-varying variables in a series.

Third, to explore temporal dynamics, the causal predictive value of sleep and circadian parameters (ISI, TST, CFI) on the psychological symptoms (fatigue, depression, stress) were tested using lagged variables in mixed linear models [53], fitted with REML with random intercepts and modelled with an unstructured covariance matrix. Sleep and circadian parameters were lagged according to intervals between treatment cycles, offering a time-dependent relationship e.g., between sleep during treatment cycle 1 and fatigue during cycle 2. This mixed linear model took into account all time points across the five months in one model, portraying a longitudinal association. Thus, this model tested the association of the average value at one time point with the averaged value at a later time point across the five months [53].

3. Results

3.1. Study sample

Of 65 eligible patients, 49 (75,4 %) consented to enrollment and 31 completed five months of data collection. Participant inclusion and retention are shown in Fig. 2.

3.2. Patient characteristics

Baseline demographic and clinical characteristics are summarized in

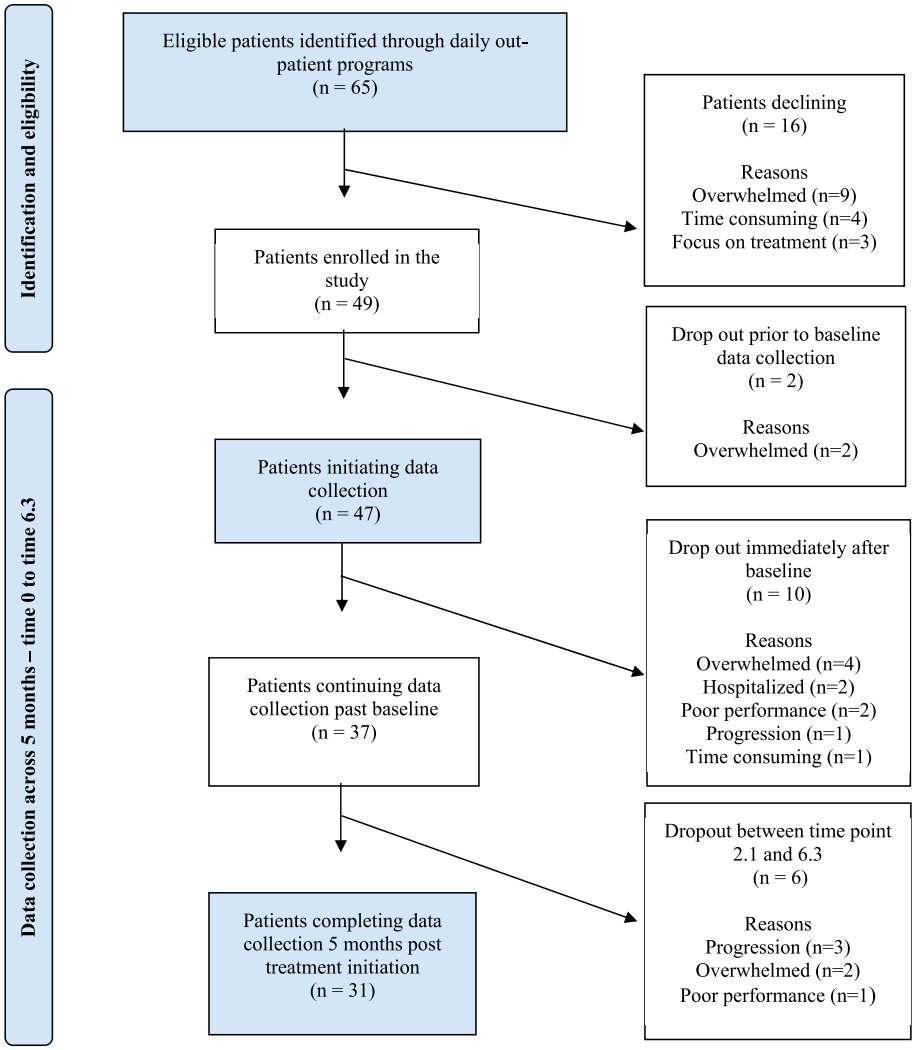

Fig. 2. Flow Diagram of identification, inclusion, and dropout of patients.

Table 1
Demographic and baseline clinical characteristics of participants (n = 47).

Demographic characteristics		Mean (SD)	n (%)
Age	At baseline (years)	69.1 (9.74)	
Gender	Femaletcp		28 (59.5)
	Male		18 (38.3)
	Other		1 (2.1)
Ethnicity	Caucasian		47 (100)
Education	Short		29 (61.7)
	Medium		17 (36.2)
	Long		1(2.1)
Marital status	Married or cohabiting		35 (74.5)
	Never married		0 (0)
	Divorced/separated		3 (6.4)
	widowed		9 (19.1)
Occupational status	Occupationally engaged		11 (23.4)
	Retirement		33 (70.2)
	Sick leave or unemployed		3 (6.4)
Clinical Characteristics			
Smoking	Current smoker		10 (21.2)
	Former smoker		37 (78.7)
Cancer stage	Stage III		5 (10.6)
	Stage IV		41 (87.2)
	Missing		1 (2.1)
Treatment regimen	Pembrolizumab		37 (78.7)
	Pembrolizumab + chemotherapy		10 (21.3)
EORTC Performance status at baseline	Performance 0		17 (36.2)
	Performance 1		25 (53.2)
	Performance 2		5 (10.6)

Educational level: Short (8–13 years: primary and secondary school, high school or similar). Medium (16 years: vocational training, internships and, college and university bachelor's level). Long (18+ years, University master's level or more). European Organization for Research and Treatment of Cancer (EORTC).

Table 1. The majority were women (59.5 %), married or cohabiting (74.5 %), had short education (high school or shorter) (61.7 %), and were retired at the time of diagnosis (70.2 %). All were current or former smokers. At diagnosis 87.2 % had stage IV cancer, and the remaining had non-curable stage III. This meant that all participants had advanced non-curable disease. 78.7 % were referred to pembrolizumab as monotherapy, while the remaining group were prescribed pembrolizumab in combination with chemotherapy.

3.3. Dropout analyses

During the first treatment cycle, 10 patients (21 %) dropped out. Baseline levels showed mean differences favoring completers over dropouts, with higher TST (mean difference = 1.19, SE = .88, p = .19), more robust circadian function (CFI) (mean difference = .08, SE = .05, p = .13), and lower depression scores (mean difference = −1.44, SE = 2.53, p = .57). Conversely, completers had marginally higher insomnia severity (mean difference = .11, SE = 2.15, p = .96), fatigue (mean difference = .53, SE = 2.02, p = .79), and stress levels (mean difference = .06, SE = 2.90, p = .85). However, sample sizes were small and varied across outcomes analyzed (n = 20 to 47), and none of the differences reached statistical significance.

3.4. Descriptive statistics of ISI, TST, CFI and psychological measures

By visual inspection of the descriptive statistics, trends towards improvements in all outcomes, were observed from baseline to 18 weeks post treatment initiation (Table 2). Grouping the sleep parameters by clinical cut-offs, we found that, almost half (48.9 %) experienced clinical levels of insomnia (ISI≥10) [54], dropping to approximately one in four (23.3 %) at 18 weeks post treatment. At baseline two thirds (67.7 %) slept 7 h or less. This number appeared relatively stable over time. The percentage of patients with clinical insomnia and TST below 7 h was not higher in those who dropped out during the first treatment cycle compared with the main sample. No established cut-off currently exists for CFI [44], but CFI remained relatively stable with a tendency towards increased robustness.

3.5. ISI, TST and CFI and psychological symptoms – main effects and associations

The results from the mixed linear models are presented in Table 3.

Main effects of time. Statistically significant main effects of time were found for ISI (b = −.216, p= <.001), TST (b = .036, p = .006), and stress (b = −.147, p = .004), all showing improvements over time. This means that a one unit increase in time (one week), showed a decrease of .216 points on the ISI. Over the 19-week period, this corresponded to an average decrease of 4.10 points in insomnia severity, an increase of .68 h in TST, and a decrease in perceived stress of 2.79 points. For all three measures the random effects models showed statistically significant variation in both intercept and slopes, except for TST slope. Improvements in CFI, fatigue and depression did not reach statistically significance. In a sensitivity analysis omitting patients receiving chemotherapy in combination with ICIs, our findings remained significant.

Insomnia severity and associations with psychological symptoms. Statistically significant associations were found between insomnia severity and severity of psychological symptoms, with higher ISI scores (i.e., more insomnia) being associated with higher scores on

Table 2
Descriptive statistics of cancer-related symptom at three selected anchor points: Baseline, 9- and 18-weeks post treatment initiation, for a descriptive overview.

	Baseline			9 Weeks			18 Weeks			
	n	%	Mean (SD)	n	%	Mean (SD)	n	%	Mean (SD)	Scoring range
Insomnia Severity Index	47	100	9.38 (5.97)	34	100	7.5 (5.58)	30	100	5.97 (4.34)	0–28
≥10 clinical insomnia	23	48.9		10	29.4		7	23.3		
# With clinical insomnia who dropped out (n = 16)	5	31.3		1	6.3		0	0		
Total Sleep Time (hours)	31	100	5.84 (1.84)	29	100	6.67 (1.26)	22	100	6.54 (1.14)	0–24
<7 h	21	67.7		16	55.2		15	68.2		
<7 h in who dropped out (n = 16)	6	19.4		1	3.4		0	0		
Circadian Function Index	23		.63 (.11)	18		.63 (.09)	11		.68 (.06)	0–1
Fatigue	39		5.95 (4.49)	31		5.10 (4.71)	27		4.63 (4.52)	0–24
Depression	38		13.95 (5.21)	31		12.58 (5.00)	27		12.74 (5.01)	8–40
Stress	38		11.68 (5.97)	31		9.81 (6.26)	27		8.37 (5.54)	0–40

Assessments of sleep (Insomnia Severity Index) and circadian rest-activity rhythm robustness (Circadian Function Index) were undertaken weekly over a period of five months, and assessment of psychological symptoms together with sleep diaries (Total Sleep Time) were obtained every three weeks corresponding to every treatment cycle, but here presented at three selected anchor points for overview. Fatigue was assessed with the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) general scale, depressive symptoms with the 8-item Patient-Reported Outcome Measurement Information System (PROMIS) 8b Short Form, and stress with the 10-item Perceived Stress Scale (PSS-10).

Table 3
Results from mixed linear models. Top section presents main effects of time for sleep and circadian outcomes as well as psychological symptoms. Second, third and fourth section reports associations between sleep outcomes (ISI, TST), CFI and psychological symptoms, respectively. Each row represents a distinct model.

		Fixed effects				Adjusted	
	n	b	95 % CI	*p*	b	95 % CI	*p*
Main effects of time							
Insomnia Severity	47	−.22	(-.32, −.12)	**< .001**	–	–	–
Total Sleep Time (hours)	37	.04	(.01, .06)	**.006**	–	–	–
Circadian Function	38	−.001	(-.004, .002)	.55	–	–	–
Fatigue	40	−.02	(-.14, .01)	.75	–	–	–
Depression	39	−.07	(-.14, .01)	.07	–	–	–
Stress	39	−.15	(-.24, −.05)	**.004**	–	–	–
Insomnia Severity (ISI)							
Fatigue	40	.30	(.10, .495)	**.004**	.24	(.45, .44)	**.02**
Depression	39	.18	(.05, .295)	**.007**	.07	(-.05, .19)	.23
Stress	39	.19	(.02, .360)	**.03**	.05	(-.11, .22)	.52
Total Sleep Time (TST)(hours)							
Fatigue	35	−.11	(-.67, .448)	.68	−.06	(-.59, .47)	.83
Depression	35	−.28	(-.88, .329)	.36	−.25	(-.72, .22)	.28
Stress	35	−.01	(-.68, .661)	.98	.15	(-.41, .70)	.60
Circadian function (CFI)							
Fatigue	31	−15.58	(-28.43, −2.74)	**.02**	−15.92	(-27.85, −3.99)	**.01**
Depression	30	6.53	(-7.88, 20.94)	.30	8.78	(-4.71, 22.26)	.16
Stress	30	−.75	(-15.74, 14.24)	.91	−.60	(-15.23, 14.03)	.92

P-values in bold indicate statistical significance at the .05 level. Adjusted models include the other psychological variables (fatigue, depression, and stress). Fatigue was assessed with the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). Depressive symptoms were assessed with the 8-item Patient-Reported Outcome Measurement Information System (PROMIS) 8b Short Form. Stress was assessed with the 10-item Perceived Stress Scale (PSS-10).

fatigue (b = .30, p = .004), depression (b = .175, p = .007), and stress (b = .118, p = .033). Associations between ISI and fatigue remained statistically significant after adjusting for the other psychological variables (depression and stress). This was not the case for the association between ISI and depression and ISI and stress.

Total sleep time and associations with psychological symptoms. No statistically significant associations were found between TST and the psychological symptoms.

Circadian Function Index and associations with psychological symptoms. More robust circadian rest-activity rhythm (CFI) was statistically significantly associated with reductions in fatigue (b = −15.58, p = .021), but not depression or stress. This association remained statistically significant after adjusting for depression and stress.

3.6. Time-lagged analyses

In order to investigate temporal dynamics of the above associations across time (Table 4), we used time-lagged mixed linear models. Sleep and circadian parameters at a previous treatment cycle did not show any statistically significant associations with levels of psychological symptoms at the following cycle. Thus, these analyses did not demonstrate any potential causal effect or order to the manifestation of the symptoms across the five months. However, when examining the reverse direction, higher levels of perceived stress during the previous treatment cycle predicted reduced TST at the following treatment cycle (b = −.071, p < .001). This mixed linear model takes into account all time points across the five months in one model, thus, portraying a longitudinal association [53]. This means that on average across the study period, a one unit increase in perceived stress was significantly associated with a lower TST (b = −.071) at the next time point.

4. Discussion

Summary and discussion of main findings. To our knowledge, this is the first detailed prospective investigation of trajectories, using a multimodal approach to sleep and circadian activity rhythms during

Table 4
Results from mixed linear models produced with time-lags to explore temporal dynamics between sleep and circadian outcomes (ISI, TST, CFI) and psychological symptoms, as well as the reversed direction. Each row represents a distinct model.

		Hypothesized direction				Reversed direction	
	n	b	95 % CI	*p*	b	95 % CI	*p*
Insomnia Severity (ISI)							
Fatigue	34	.08	(-.03, .19)	.14	.07	(-.09, .23)	.39
Depression	34	.05	(-.05, .16)	.31	.13	(-.04, .30)	.13
Stress	34	.06	(-.05, .16)	.30	.05	(-.10, .20)	.51
Total Sleep Time (TST)(hours)							
Fatigue	30	.07	(-.44, .57)	.80	−.01	(-.05, .03)	.66
Depression	30	−.37	(-.82, .08)	.11	−.03	(-.07, .01)	.11
Stress	30	−.14	(-.64, .37)	.60	−.07	(-.11, −.04)	**< .001**
Circadian function (CFI)							
Fatigue	25	−1.32	(-10.01, 7.36)	.77	−.001	(-.005, .002)	.45
Depression	25	−5.48	(-14.01, 3.05)	.21	.002	(-.003, .005)	.59
Stress	26	−3.07	(-13.30, 7.16)	.56	−.001	(-.004, .002)	.47

P-values in bold indicate statistical significance at the .05 level. Fatigue was assessed with the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). Depressive symptoms were assessed with the 8-item Patient-Reported Outcome Measurement Information System (PROMIS) 8b Short Form. Stress was assessed with the 10-item Perceived Stress Scale (PSS-10).

treatment with ICIs in advanced NSCLC patients. We found that patients generally experienced reductions in insomnia severity, increased TST, and a trend towards improved robustness of the circadian rest-activity rhythm together with reductions in fatigue, depression, and stress during the first five months of treatment. This improvement could potentially be related to decreased distress following the initiation of cancer care [55] and/or reduced symptom burden [56,57],both of which have been found to occur shortly after initiation of anti-cancer treatment [55–57]. However, some studies are more equivocal indicating that symptom burden may vary depending on demographic predictors, cancer site, and prognosis [56,58].

Mean baseline levels of insomnia (9.4 on the ISI) were just below the established cut-off of 10 for clinical levels of insomnia [54]. However, exploring the proportion of patients with clinical insomnia, almost half (48.9 %) reported clinical insomnia at baseline, similar to levels found in other samples of cancer patients [59,60], including lung cancer [61]. In the present study, this number declined to less than one in four (23.3 %) during treatment. It is important to note that sleep disturbances in cancer patients can occur prior to cancer diagnosis [62] and treatment initiation [63], potentially driven by both biological and psychological factors, such as tumor-induced inflammation [64,65] and/or psychological distress related to the cancer diagnosis [66]. In comparison, approximately 10 % of the general population meets criteria for clinical insomnia, with another 20 % reporting insomnia symptoms [67]. Given that all participants were recently diagnosed and began ICI treatment no longer than 11 days after, it is likely that a proportion of the 48.9 % of participants who reported clinical insomnia at baseline already had those symptoms prior to diagnosis. However, because we did not assess insomnia onset prior to diagnosis, the temporal link between insomnia and the initiation of immunotherapy remains uncertain. This highlights the need for prospective studies that assess sleep disturbances beginning at the point of diagnostic workup. Taken together, our results highlight that sleep and circadian disturbances across the cancer trajectory should be an important clinical target. Moreover, contributing factors to these disturbances are likely multifactorial and should be assessed and addressed in the context of bio-psycho-social paradigm [68], and in the context of both prevention efforts and treatments.

Regarding the proposed effect of treatments, previous prospective studies of insomnia during chemotherapy have revealed both stable [59,69], increased [70], and reduced levels of insomnia over time [71]. Despite the hypothesized link between sleep disruption and immune activation by ICIs [20,72], we did not find increased insomnia severity over the course of treatment with ICIs. Research in this area is limited. However, our findings are in line with a recent prospective study of sleep in lung cancer patients measured before and nine months after treatment initiation, reporting no statistically significant independent impact of immunotherapy on sleep problems [73]. These findings are also in agreement with several Phase 3 studies, where insomnia during immunotherapy was not found to be more prevalent than in patients undergoing chemotherapy [74].

Regarding sleep duration, in our study we found an increase in average TST from 5.84 h at baseline to 6.54 h at week 18, which is closer to the 7 h of sleep recommended for this age group [26], but no statistically significant associations with psychological symptoms were found.

With respect to circadian rest-activity rhythms, no established cut-off currently exists for CFI [44]. Furthermore, calculating cut-off values for clinical symptoms based on a small sample size is generally not recommended, as it can lead to biased, and non-generalizable thresholds [75,76]. However, to support comparisons in future studies, we report CFI medians from our data. No statistically significant main effect of time was found for CFI, so we report the baseline median CFI (M = .65), and the range of the 18 other time points (Mean range = .60–.69). Other studies have found the dichotomy index (I < O) a useful measure of clinical outcomes in cancer [77,78]. The dichotomy index is a different measure of rest-activity rhythms, yet also derived from actigraphy. This unidimensional measure that calculates the percentage of daytime activity counts that exceed nighttime counts [79], could be relevant to explore in future analyses.

In our study insomnia severity was the most salient predictor, with higher levels of insomnia severity being statistically significantly associated with higher levels of fatigue, depression, and stress across the five treatment months. These findings are in concordance with previous results from studies on chemotherapy where insomnia has been associated with increased levels of fatigue and depression [60,80]. We also found that a more robust circadian rest-activity rhythms (higher CFI) was significantly predictive of lower levels of fatigue, which is in agreement with the circadian disruption hypothesis [15], and with studies showing that circadian-driven interventions (e.g., light therapy) may improve fatigue in cancer populations [81,82].

Results from the time-lagged mixed linear models failed to find any statistically significant time-dependent associations of sleep and circadian parameters with psychological symptoms. However, analyses of the reverse direction revealed that higher levels of perceived stress were associated with shorter TST at the following treatment cycle. This indicates that stress and worry may counteract the otherwise positive development of TST over time during the treatment period. However, no similar relation was seen for insomnia, suggesting a potential spurious finding for this sample. Nevertheless, some studies have reported a bidirectional relationship between stress and sleep disturbances, observed both at the cellular level [83], and through self-reported measures in lung cancer patients [84].

Regarding the psychological symptoms assessed in the present study, the reported levels were generally low. In fact, fatigue assessed with the MFSI-SF showed baseline levels similar to those observed in the general population [85]. This is inconsistent with results from a systematic review of the MFSI-SF showing that patients samples generally report more fatigue [86]. The review, however, included populations receiving mixed treatment regimens, preventing us from drawing conclusions about the tolerability of ICI treatment. While no cut off has been established for the PROMIS depression scale, a raw score cut off of 17, reflecting mild depressive symptoms, has been proposed for cancer patients based on depression levels detected through clinical interviews for DSM-IV [48]. Mean depressive symptom scores in our sample did not exceed this cut-off. Baseline levels of perceived stress in our sample was 11.7 corresponding to normative data in a healthy elderly population [87]. This level declined marginally to 8.4. In sum, these results suggest that our patient sample did not generally report clinical levels of fatigue, depression, or stress, and that ICI treatment in this sample was well-tolerated. In fact, improvements in symptoms were reported across the five months of treatment.

Strengths and limitations. To the best of our knowledge, this is the first study to offer a detailed longitudinal assessment of sleep, circadian rest-activity rhythms and psychological outcomes during treatment with ICIs, and specifically investigate treatment-naïve lung cancer patients. Second, we used validated sleep and psychological measures and multimodal approaches to assessing sleep and circadian rest-activity rhythms. Data were collected prospectively, with dense data collection allowing us to detect weekly fluctuations across a 5-month period. Despite being a small sample, all eligible patients were invited to participate, and the high inclusion rate (75,4 %) increases the representativeness of our sample. Furthermore, our sample was representative in relation to the age and gender distribution of lung cancer patients in general [3,88], although the small sample size did not allow for sex or gender specific analyses.

Some limitations should also be mentioned. First, patients were sampled from only one cancer center and the sample size was small, increasing the risk of Type II errors in our analyses [89]. Second, we had a 21 % dropout-rate during the first treatment cycle, due to hospitalization, progression, poor performance and distress, which prevented us from continuing data collection (Fig. 2). Although baseline levels of sleep parameters, CFI and psychological symptoms revealed no

statistically significant differences between patients who dropped out and those who continued to participate, dropout during treatment may still have influenced our results, as patient trajectories were incomplete and, hence, given less weight in the final analyses. Third, the present study was primarily exploratory, thus, analyses were not corrected for multiple testing, which could have inflated the probability of Type I errors [90]. To reduce multiple testing and the associated risk of chance findings, we did not explore all sleep diary outcomes. Sleep efficiency (SE) has previously been associated with psychological symptoms in lung cancer [84]. While a post hoc mixed linear model analysis showed a statistically significant improvement in SE across time, no associations were observed between SE and the psychological symptoms (see Supplemental materials, A1). Finally, the present sample (n = 47) included patients receiving immunotherapy as a monotherapy (n = 37) or in combination with chemotherapy (n = 10). This heterogeneity could potentially affect results. However, in sensitivity analyses where we undertook the same multi-level models excluding patients receiving chemotherapy, the main effects of time, as well as the within-person variation models, all remained statistically significant.

Future perspectives. The aim of the present study was to explore trajectories of a multimodal approach to sleep and circadian rest-activity rhythms and their associations with important psychological symptoms in lung cancer patients undergoing treatment with ICI. Despite currently being the most common cancer worldwide, lung cancer patients have received less attention and funding compared with other cancer populations [91]. Curable treatment options are limited [2,3] and a preference for quality of life over length of life has been found in elderly patients with declining physical status when considering difficult treatment decisions [24]. Thus, being able to predict and manage sleep and circadian irregularities may be especially important in this patient group. Improvements in symptom severity were seen across the first five months of treatment with ICIs. If these findings are replicated, they could potentially assist clinicians in determining whether symptoms presented at pre-treatment are indicative of future symptom burden, or if they are more likely to diminish. This, in turn, would help to inform decision-making regarding a patients' eligibility for treatment. Furthermore, as a substantial subset of patients reported clinical levels of insomnia, and because insomnia was the most salient predictor of other psychological symptoms, targeting insomnia in this subgroup should be prioritized. Cognitive behavioral therapy for insomnia (CBT-I) has been shown to be effective in cancer survivors [92], with concurrent beneficial effects on depressive symptoms [93]. However, studies on the effect of CBT-I during cancer treatment are scarce. Likewise, given the observed link between circadian rest-activity rhythms and fatigue, circadian-driven interventions including light therapy and other multimodal behavioral interventions [15] may be relevant both during and after treatment.

5. Conclusions

In sum, this prospective study showed that clinical levels of insomnia were present in half of the patients (48.9 %) prior to treatment with ICIs. Spontaneous recovery was observed during the first five months of treatment in insomnia symptoms and TST, while CFI remained relatively stable with a tendency towards increased robustness. Overall, these findings suggest that the first five months of treatment with ICIs are generally well-tolerated with respect to the symptoms investigated in this study, and treatment initiation may even improve symptoms by relieving distress and/or alleviating cancer burden. However, sleep and circadian outcomes may play a role in cancer-related symptoms for a subgroup of patients and targeting sleep and circadian outcomes require distinct interventions. If replicated, these results could aid clinical decision-making regarding patients' eligibility for treatment, and direct clinical attention to inter-individual differences in symptom patterns in order to identify specific individuals likely to be in need of intervention.

CRediT authorship contribution statement

Louise Strøm: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Robert Zachariae:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Formal analysis, Conceptualization. **Lisa M. Wu:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Formal analysis, Conceptualization. **Peter Meldgaard:** Writing – review & editing, Validation, Supervision, Resources, Investigation, Data curation, Conceptualization. **Sonia Ancoli-Israel:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Conceptualization. **Mats Lekander:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Conceptualization. **Daniel Mroczek:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Formal analysis. **Ali Amidi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Formal analysis, Conceptualization.

Patient consent statement

Eligible patients were introduced to the study at their first consultation with an oncologist. Informed consent was obtained prior to any data collection. Participants were not incentivized to participate, nor compensated, and they were informed that declining participation would not affect their treatment or care.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request since national laws and guidelines on data availability does not allow publication of confidential patient data.

Ethical approval statement

This study was preregistered and approved by the Regional Research Ethics Committee (JNR 1-10-72-86-19, June 11th, 2019), ensuring compliance with relevant laws and guidelines, and privacy rights for all participants.

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Clinical trial registration

This study was preregistered (Clinical Trail ID NCT04070651).

Funding sources

Lisa Marie Wu's effort was supported by the European University of Brain and Technology (NeurotechEU grant 101004080) funded by the Erasmus^{+} Programme of the European Union.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Lisa Maria Wu reports financial support was provided by European Union. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to extend our sincere gratitude to the staff at the Department of Oncology in Aarhus Denmark, for their invaluable collaboration on this study, with respect to identifying patients and for supporting this longitudinal data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2025.106740.

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