Comprehensive assessment of sleep in newly diagnosed pediatric brain tumor patients

Eva Hooft van Huijsduijnen[1], Marita Partanen[1], MA Grootenhuis[1], Eelco Hoving[1], Myrthe Nuijts[2], and Raphaële Van Litsenburg[1]

[1]Prinses Maxima Centrum voor Kinderoncologie
[2]Universitair Medisch Centrum Utrecht

June 25, 2022

Abstract

Background. Children with a brain tumor are at risk of developing sleep problems. It remains unclear whether these problems arise at an early or later stage, and insights can facilitate timely interventions. The aim of this study is to examine sleep problems and contributing factors shortly after diagnosis. *Methods.* Children 6-16 years with a newly diagnosed ([?]3 months) primary brain tumor were recruited for a prospective study. Sleep was measured using actigraphy and questionnaires (PROMIS Sleep Disturbance and Sleep Related Impairment, self- and parent-reports). Prevalence of clinical sleep problems were established using PROMIS cut-off scores. Mean PROMIS scores, prevalence of sleep problems and actigraphic outcomes were compared to norms (t-test, chi-square, linear regression). Demographic and medical risk factors were explored with multivariable linear regression models. *Results.* Sixty-nine children (68% male, mean age 11.6±2.8 years, 53±28 days after diagnosis) participated. Parents reported more sleep disturbances (mean T=53.7, $P<.01$) compared to norms. Rates of self- and parent-reported severe sleep disturbances were elevated (11% versus 5% in norms, $P<.04$). Parents also reported higher rates of moderate sleep disturbance (31%) and sleep related impairment (42%) than norms (25%, $P<.03$). Actigraphic outcomes did not differ from norms. Only shorter time since diagnosis was identified as independent risk factor (self-reported sleep disturbances, B=-.11, 95%CI -0.19;-0.03). *Conclusions.* Sleep problems are more frequently reported by children and parents shortly after pediatric brain tumor diagnosis, compared to healthy controls. Attention for sleep around brain tumor diagnosis is important, as sleep is vital for recovery and health-related quality of life.

Introduction

Sleep problems are known to be highly prevalent in pediatric cancer patients and can be caused by biological and/or psychosocial factors such as treatment toxicity, pain, and anxiety[1,2]. In the short term, sleep problems can lead to distress, cognitive problems, and lower quality of life in pediatric cancer patients[2-6]. In the long term, it is clear from studies in the general population, that sleep problems are associated with obesity, cardiovascular disease and lower life expectancy[2]. Sleep also plays a critical role in neuroimmune function and neuronal recovery in pediatric cancer patients. Moreover, fragmented sleep has increasingly been linked to tumor growth in mice[7-9]. Children with a brain tumor are especially prone to develop sleep problems. Neurosurgery, hydrocephalus, cranial radiation therapy and hypothalamic damage may further contribute to the onset of disturbances in sleeping patterns[1,10,11].

Currently, little is known about the prevalence and extent of sleep problems in children with a newly diagnosed brain tumor. Previous studies have mainly focused on patients with all types of cancer diagnoses, causing heterogeneity, or included only patients with hematologic malignancies, the most common type of pediatric cancer[12]. In addition, most studies focus on sleep at the end of treatment or further into survivorship. Multiple physical, psychological, and therapeutic factors related to the period around diagnosis may impact sleep,

such as high levels of distress or the requirement of one or multiple hospitalizations, which are characterized by frequent nightly awakenings[13,14]. Poor sleeping habits and maladaptive strategies may emerge in this period and persist over the course of the disease. Lastly, sleep is most often assessed by questionnaires only, which provide information on sleep behaviors and consequences of disrupted sleep. However, questionnaires do not measure sleep duration and sleep efficiency, and do not correlate well with polysomnography, the gold standard for measuring sleep[15]. Some questionnaire studies only assess parent-reported sleep[16,17], and this inherently poses some reporting bias. Using several modes of sleep assessment is important as it provides complementary information and contributes to our understanding of sleep[15,17,18].

Sleep in the early phases of treatment in pediatric brain tumor patients has thus far not been studied comprehensively, even though this has been strongly recommended by researchers and clinicians[6,7,19]. Identifying which children are at risk to develop sleep problems is important, in order to provide effective, targeted sleep interventions in a timely manner, with the aim to improve long-term negative health outcomes associated with poor sleep. In adult cancer patients, treatment of sleep problems by using non-pharmacological interventions such as cognitive behavioural therapy has shown favorable results[20,21]. In contrast, in children with central nervous system tumors, a multicomponent sleep intervention consisting of cognitive and behavioral interventions modestly improved sleep outcomes[22]. Therefore, more insight into disrupted sleep and contributing factors in the earliest phase after brain tumor diagnosis is needed.

We performed a prospective, observational study into sleep shortly after primary pediatric brain tumor diagnosis. Our primary goal was to describe patient and parent reported sleep problems and daytime consequences, and sleep estimates within three months after diagnosis. Secondly, we defined biological and psychological risk factors of poor sleep. This study is part of a larger longitudinal study into sleep, post-traumatic stress, and neurocognitive functioning (SuSPeCT-study).

Materials and Methods

Participants and procedures

The Princess Máxima Center for Pediatric Oncology opened in 2018 and is a Dutch nationwide center where specialized pediatric oncology care is centralized. A small number of patients with a low grade brain tumor, requiring neurosurgery only, are treated in former pediatric oncology centers. All new patients with a primary brain tumor diagnosis between January 2019 and October 2021 and treated at the Princess Máxima Center were eligible if they were between the age of 6 and 16 years, had sufficient understanding of the Dutch language, had no evident pre-existing developmental delay and did not receive end-of-life care. All participants and their parents/caregivers provided written informed consent. Sleep assessments took place around four weeks after the child entered the hospital, with a maximum of three months. This study was reviewed and approved by the Clinical Research Committee of the Princess Maxima Center and confirmed subsequently by the Medical Research Ethics Committee of the University Medical Center Utrecht.

Demographic and medical information

Children's demographic and medical information was abstracted from their medical records. This included sex, age, body mass index (BMI), date of diagnosis, tumor type and tumor location. Any treatment that had taken place before the time of assessment was collected, including neurosurgery, start of radiotherapy, and start of chemotherapy, as well as complications of hydrocephalus and epilepsy. Patients and their parents provided information on pre-existing sleep problems, use of sleep medication during the seven day sleep assessment, daytime naps and whether they slept at home or in the hospital during the assessment. Lastly, through a general survey, parents provided sociodemographic information.

Sleep questionnaires

Subjective sleep was assessed with two questionnaires (both self-report and proxy-report) from the Patient-Reported Outcomes Measurement Information System (PROMIS)[23].

The PROMIS Pediatric Sleep Disturbance short form 8a consists of eight questions and assesses satisfaction

with sleep, including difficulties and concerns with falling asleep and staying asleep. The PROMIS Pediatric Sleep Related Impairment short form 8a is another eight-item questionnaire, focusing on perceptions associated with sleep problems. It measures impaired alertness, tiredness and sleepiness during usual waking hours and impaired functioning. Parents complete similar proxy-versions. The questionnaires assess sleep over the past seven days, are generic rather than disease-specific and do not focus on symptoms of specific sleep disorders. Both questionnaires demonstrated strong internal consistency reliability and clinical validiy[24]. Raw scores are rescaled into T-scores with a mean of 50 and a standard deviation (SD) of 10. Questionnaire-specific cut-off points for moderate (75–94th percentile) and severe ([?] 95th percentile) sleep problems were used[25].

Actigraphic measures

Sleep estimates were assessed using a wrist-worn actigraph (type wGT3XBT, Pensacola, FL). This device registers the occurrence and the intensity of arm movements and distinguishes the wake state from sleep. This low-cost measurement has been validated against polysomnography, and is well-tolerated during this intense stage of cancer therapy[26]. Participants were instructed to wear the actigraph for seven days and seven nights. Also, they were asked to keep a sleep log, to facilitate correct interpretation of the data.

The actigraphy software ActiLife (version 6.13.4, Sadeh algorithm) and the sleep- and wake times from the sleep log were used to process the actigraph data and calculate sleep outcomes. Sleep outcomes were only calculated if there were available recordings of at least five nights, as this is advised to obtain reliable actigraphic measures[27]. The following outcomes were obtained: sleep efficiency (SE; ratio between the time spent in bed and the total sleep time), sleep onset latency (SOL; number of minutes between bedtime and onset of sleep), wake after sleep onset (WASO; number of minutes awake after the onset of sleep), total sleep time (TST), total time spent in bed (TIB) and number of awakenings (NA). Norm data of 47 healthy Dutch children within the same age range were used to compare actigraphic sleep outcomes[28].

Statistical analysis

Baseline characteristics were descriptively reported. T-tests and chi-square tests were used to examine potential differences in age, sex and tumor location between participants and non-participants (active or passive refusal), and between participants and patients who were not approached (due to severe illness/palliative care or logistical issues).

To examine differences in reported sleep between participants and healthy children, scores of the PROMIS questionnaires were compared to a mean score of 50, using one-sided t-tests. Statistical significance was considered as a P -value of $<.05$. The percentage of moderate and severe sleep problems was described by using the questionnaire-specific cut-offs[25] and compared to the normal population by using non-parametric chi-square tests.

Linear regression models were used for comparing actigraphic sleep estimates between the participants and healthy children. As sleep estimates are age-dependent, regression models were adjusted for age[28].

Risk factors for impaired sleep were explored by building linear regression models. Demographic and medical variables relevant for sleep outcomes were examined with univariate analyses. Variables with aP -value of $<.10$ were subsequently added to a multivariable model. A P -value of $<.05$ was considered significant. All analyses were carried out with IBM SPSS Statistics version 26.0.0.1.

Results

Demographic and medical information

In total, 69 (75%) children consented to the study; details of participant enrollment are described in Figure 1. There were no differences in age and sex between participants and nonparticipants, however, nonparticipants more often had cerebral tumors compared to participants (Table 1). There were no differences in age, sex, and tumor location between participants and patients who were not approached.

The baseline characteristics of the participants are described in Table 1. Of the children with supratentorial midline tumors (N=26, 38%), fifteen children (22%) had a tumor in the pituitary region, and no child had a tumor in the hypothalamus. In the whole participant group, pre-existing sleep problems were reported by the parents of seven (10%) participants, six (9%) participants took daytime naps and two (3%) participants used melatonin during the assessment. No nights were spent in the hospital during sleep examination.

Sleep questionnaires

Results of the PROMIS Sleep Disturbance (N=53 self-report, N=65 proxy-report) and Sleep Related Impairment (N=53 self-report, N=65 proxy-report) questionnaires are presented in Table 2. Compared to norm data, parents reported significantly more sleep problems on the Sleep Disturbance questionnaire (mean T=53.7, $P<$ .01). This was not reported by the children themselves (mean T=50.6, P =.64).

Severe sleep disturbance was experienced by 11% of the children compared to 5% in the general population, according to both parent and self-reports ($P=$ 0.03 and P =.04, respectively). Moderate sleep disturbance was also frequently reported by parents: 31% compared to 20% in the general population (P =.03). Rates of severe sleep related impairment were not significantly elevated according to both parents and children themselves. However, moderate sleep related impairment was more prevalent according to parents (42% vs 20%$P<$ .01).

Actigraphic sleep estimates

Actigraphic sleep outcomes were avialble from 53 participants. There were no statistical differences between participants and controls (Table 3). Based on the sleeplog, participants' bedtime (mean 21:36) was 30 minutes later, compared to controls (P =0.04). Also, participants' wake time (mean 07:57) was 32 minutes later, compared to controls (P <0.001).

Risk factors

Univariable risk factors for patient- and parent reported sleep outcomes are presented in Supplementary Table 1. Higher sleep disturbances were reported by children more shortly after diagnosis (B=-.12, 95%CI -.20;-.04, P <.01), and by those with cerebral or posterior fossa tumors, compared to children with supratentorial midline tumors (B=-4.56, 95%CI 10.01;-.88, $P=$ .10). Parents reported higher child sleep disturbances more shortly after diagnosis (B=-.10, 95%CI -.18;-.01, $P=$ .03*)* and before radiotherapy (B=-6.41, 95%CI -12.46;-.35, $P=$ .04). However, in the multivariable models (Table 4) shorter time after diagnosis (B=-.11, 95%CI -.19;-.03,P =<.01) remained the only independent significant determinant for self-reported sleep disturbance. For sleep related impairment, no significant risk factors were identified on both the self- and proxy-reports.

For actigraphic outcomes, univariable analyses (Supplementary Table 2) showed females had higher sleep efficiency (B=3.60, 95%CI -.60;-7.78,P =.09). The history of an obstructive hydrocephalus was associated with shorter sleep onset latency (B=-8.92, 95%CI -16.83;-1.01, $P=$ .03) and longer total sleeping time (B=32.86, 95CI 1.10;64.62, P =.04). More nighttime awakenings were related to neurosurgery (B=5.37, 95% CI -.54;11.29, $P=$ .07) and radiotherapy (proton or photon, B=4.27, 95%CI -.74;9.28, $P=$ .09). Younger children had higher sleep onset latency (B=-1.96, 95%CI -3.36;-.56, P <.01), more total sleep time (B=-7.35, 95%CI -12.98;-1.73, $P=$ .01) and spent more time in bed (B=-10.59, 95%CI 15.33;-5.85, P <.01). Multivariable analyses (Table 5) showed the history of an obstructive hydrocephalus independently predicted longer sleeping times (B=41.04, 95%CI 11.41;70.68, $P<$ .01). Finally, younger age remained associated with longer sleep onset latency (B=-1.73, 95%CI -3.12;-.35,$P=$ .02) and more total sleeping time (B=-8.63, 95%CI -14.00;-3.26, P <.01).

Body mass index, parental education level, start of chemotherapy, hormone deficiency and epilepsy were not significantly associated with any of the sleep outcomes.

Discussion

The results of this unique prospective nationwide cohort study of children with a newly diagnosed brain tumor demonstrate a high prevalence of sleep problems at brain tumor diagnosis, mostly reported by parents of

patients. Actigraphic sleep outcomes were not different from those of healthy controls.

We found a high rate of parent reported child sleep disturbance and sleep related impairment, with up to half of the parents reporting moderate or severe problems. Children themselves frequently reported severe sleep disturbances, especially more shortly after brain tumor diagnosis. These findings are consistent with our expectations, indicating sleep problems are experienced regularly and already at the earliest phase of cancer treatment, possibly arising as a result of factors such as distress and neurological damage. Interestingly, alhough parents reported high rates of sleep related impairments, children did not report this and on average these scores did not differ from the general population.

Differences in self- and proxy-report are common in pediatric research and may be explained by several factors[29-31]. Firstly, children may underreport symptoms. This can be the result of "response shift", meaning symptoms are judged differently during cancer treatment than how they would be judged before diagnosis[32]. It could also be that neurocognitive-, stress- and sleep disturbances impact children's' capability of adequately recalling sleep experiences[33]. Second, parents may overreport symptoms due to feelings of stress and concern. Earlier research suggests that parental distress, parental sleep problems and parenting problems are related to parent reported child sleep[30]. Hence, differences in self- and proxy-reports emphasize the importance of using both types when measuring sleep, as they are both informative and may provide complementary information in this phase of treatment.

We hypothesized that actigraphic outcomes would show lower sleep estimates compared to age-matched, healthy controls, due to the physical and psychosocial stressors associated with the period following pediatric brain tumor diagnosis. The absence of these findings is largely consistent with earlier, similar research in patients with acute lymphoblastic leukemia (ALL)[30]. However, children with ALL did show longer sleeping times than healthy peers, possibly because these children require more sleep, as they are ill and physically recovering. It could therefore be argued that although the number of minutes children with recently diagnosed brain tumors sleep is similar to healthy children, they might have a higher need for sleep to support optimal recovery[34,35]. Furthermore, this study sample was almost entirely assessed during the Covid-19 pandemic, while data of the control group was collected before. It is plausible that children sleep better during the pandemic, as they were able to sleep longer due to home schooling and were less exposed to stimuli during the day[36]. In the healthy population, it was found that people with insomnia complaints experienced clinically meaningful alleviations of symptoms during the pandemic[37]. Another factor that may influence sleep during the diagnostic period are substantial efforts and strategies of parents, such as co-sleeping and comforting activities, as illustrated in parents of children with ALL[38]. Possibly, as parents put in a great deal of energy, they do report sleep problems, and yet these efforts seem relatively effective in terms of sleep duration.

Generally, little research has been done with actigraphy and children with cancer during treatment. However, sleep problems are well described and measured amongst brain tumor survivors[11,39]. Toxic treatmens effects such as radiation therapy or endocrine disturbances may lead to those sleep problems at a later stage. Longitudinal data from this current study should provide more insight into this matter[11,40].

This study has several limitations. Although the participant group is relatively large for pediatric brain tumor research, there may not have been enough power to demonstrate specific predictors for sleep problems. In addition, not all parents and children participated in all sleep measurements, due to for example treatment toxicity or study burden, increasing the risk of participation bias. Subsequently, even though participants were recruited from a national pediatric oncology hospital, specific tumor groups were underrepresented which may have lead to selection bias. Twenty-four children with low grade brain tumors who required neurosurgery only and had a favorable prognosis were primarily treated in affiliated hospitals and therefore not participating in this study. Twelve children with high grade tumors were not invited, as they were receiving palliative care with high morbidity, and the treating physician requested not to burden the family.

Actigraphy measures movement and is well validated, but does not measure sleep phases (light, deep and REM sleep). Also, children may have shifted circadian rhythms or inconsistent bedtimes, which is not reflected in the actual number of minutes asleep, but may still contribe to fatigue[3,7,41]. Future research

should explore sleep phases and rhythms to gain more insight into sleep quality. Lastly, previous research suggests more knowledge of parents on sleep hygiene benefits child sleep, suggesting education and support for parents may be an efficient intervention[42,43]. Future research should therefore consider collecting more comprehensive data on parents and parenting strategies as well.

In conclusion, sleep problems in children with a brain tumor are frequently reported in the first three months after brain tumor diagnosis. Clinicians should be attentive to sleep problems, as it may induce serious, negative consequences in this already vulnerable group. Increasing our understanding of sleep is of major importance because sleep is vital for recovery and health-related quality of life.

Conflict of Interest. The authors have no conflict of interest to declare.

Acknowledgements. The authors would like to thank the psycho-oncology and neuro-oncology teams for their contribution and support.

Funding. This study was funded by The Princess Maxima Center for Pediatric Oncology.

References

1. Kaleyias J, Manley P, Kothare SV. Sleep disorders in children with cancer. *Semin Pediatr Neurol.* 2012;19(1):25-34.

2. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. *Nat Sci Sleep.* 2017;9:151-161.

3. Daniel LC, Wang M, Mulrooney DA, et al. Sleep, emotional distress, and physical health in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Psychooncology.*2019;28(4):903-912.

4. van Litsenburg RR, Huisman J, Hoogerbrugge PM, Egeler RM, Kaspers GJ, Gemke RJ. Impaired sleep affects quality of life in children during maintenance treatment for acute lymphoblastic leukemia: an exploratory study. *Health Qual Life Outcomes.* 2011;9:25.

5. Gordijn MS, van Litsenburg RR, Gemke RJ, et al. Sleep, fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2013;60(3):479-485.

6. Pickering L, Main KM, Sehested A, et al. Brain tumours result in sleep disorders in children and adolescents. *Sleep Med.*2021;88:13-21.

7. Daniel LC, van Litsenburg RRL, Rogers VE, et al. A call to action for expanded sleep research in pediatric oncology: A position paper on behalf of the International Psycho-Oncology Society Pediatrics Special Interest Group. *Psychooncology.* 2020;29(3):465-474.

8. Eismann EA, Lush E, Sephton SE. Circadian effects in cancer-relevant psychoneuroendocrine and immune pathways.*Psychoneuroendocrinology.* 2010;35(7):963-976.

9. Hakim F, Wang Y, Zhang SX, et al. Fragmented sleep accelerates tumor growth and progression through recruitment of tumor-associated macrophages and TLR4 signaling. *Cancer Res.* 2014;74(5):1329-1337.

10. Rosen G, Brand SR. Sleep in children with cancer: case review of 70 children evaluated in a comprehensive pediatric sleep center.*Support Care Cancer.* 2011;19(7):985-994.

11. Gapstur R, Gross CR, Ness K. Factors associated with sleep-wake disturbances in child and adult survivors of pediatric brain tumors: a review. *Oncol Nurs Forum.* 2009;36(6):723-731.

12. Reedijk AMJ, van der Heiden-van der Loo M, Visser O, et al. Site of childhood cancer care in the Netherlands. *Eur J Cancer.*2017;87:38-46.

13. Graef DM, Crabtree VM, Srivastava DK, et al. Sleep and mood during hospitalization for high-dose chemotherapy and hematopoietic rescue in pediatric medulloblastoma. *Psychooncology.* 2018;27(7):1847-1853.

14. Marusak HA, Harper FW, Taub JW, Rabinak CA. Pediatric cancer, posttraumatic stress and fear-related neural circuitry. *Int J Hematol Oncol.* 2019;8(2):IJH17.

15. Markovich AN, Gendron MA, Corkum PV. Validating the Children's Sleep Habits Questionnaire Against Polysomnography and Actigraphy in School-Aged Children. *Front Psychiatry.* 2014;5:188.

16. Ince D, Demirag B, Karapinar TH, et al. Assessment of sleep in pediatric cancer patients. *Turk J Pediatr.* 2017;59(4):379-386.

17. Holley S, Hill CM, Stevenson J. A comparison of actigraphy and parental report of sleep habits in typically developing children aged 6 to 11 years. *Behav Sleep Med.* 2010;8(1):16-27.

18. Smith MT, McCrae CS, Cheung J, et al. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Clinical Practice Guideline.*J Clin Sleep Med.* 2018;14(7):1231-1237.

19. Helligsoe ASL, Weile KS, Kenborg L, et al. Systematic Review: Sleep Disorders Based on Objective Data in Children and Adolescents Treated for a Brain Tumor. *Front Neurosci.* 2022;16:808398.

20. Langford DJ, Lee K, Miaskowski C. Sleep disturbance interventions in oncology patients and family caregivers: a comprehensive review and meta-analysis. *Sleep Med Rev.* 2012;16(5):397-414.

21. McKay, C., Nugent, K. L., Johnsen, M., Eaton, W. W., & Lidz, C. W. (2018). A systematic review of evidence for the clubhouse model of psychosocial rehabilitation. Administration and Policy in Mental Health and Mental Health Services Research, 45(1), 28-47.

22. Rogers VE, Zhu S, Ancoli-Israel S, Liu L, Mandrell BN, Hinds PS. A pilot randomized controlled trial to improve sleep and fatigue in children with central nervous system tumors hospitalized for high-dose chemotherapy. *Pediatr Blood Cancer.* 2019;66(8):e27814.

23. Forrest CB, Meltzer LJ, Marcus CL, et al. Development and validation of the PROMIS Pediatric Sleep Disturbance and Sleep-Related Impairment item banks. *Sleep.* 2018;41(6).

24. Daniel LC, Gross JY, Meltzer LJ, Flannery JL, Forrest CB, Barakat LP. Clinical validity of the PROMIS pediatric sleep short forms in children receiving treatment for cancer. *Pediatr Blood Cancer.*2020;67(9):e28535.

25. Carle AC, Bevans KB, Tucker CA, Forrest CB. Using nationally representative percentiles to interpret PROMIS pediatric measures.*Qual Life Res.* 2021;30(4):997-1004.

26. Niel K, LaRosa KN, Klages KL, et al. Actigraphy versus Polysomnography to Measure Sleep in Youth Treated for Craniopharyngioma.*Behav Sleep Med.* 2020;18(5):589-597.

27. Acebo C, Sadeh A, Seifer R, et al. Estimating sleep patterns with activity monitoring in children and adolescents: how many nights are necessary for reliable measures? *Sleep.* 1999;22(1):95-103.

28. Rensen N, Steur LMH, Wijnen N, van Someren EJW, Kaspers GJL, van Litsenburg RRL. Actigraphic estimates of sleep and the sleep-wake rhythm, and 6-sulfatoxymelatonin levels in healthy Dutch children.*Chronobiol Int.* 2020;37(5):660-672.

29. Mack JW, McFatrich M, Withycombe JS, et al. Agreement Between Child Self-report and Caregiver-Proxy Report for Symptoms and Functioning of Children Undergoing Cancer Treatment. *JAMA Pediatr.* 2020:e202861.

30. Steur LMH, Grootenhuis MA, Van Someren EJW, et al. High prevalence of parent-reported sleep problems in pediatric patients with acute lymphoblastic leukemia after induction therapy. *Pediatr Blood Cancer.* 2020;67(4):e28165.

31. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature.*Qual Life Res.* 2008;17(6):895-913.

32. Visser MR, Smets EM, Sprangers MA, de Haes HJ. How response shift may affect the measurement of change in fatigue. *J Pain Symptom Manage.* 2000;20(1):12-18.

33. Lubas MM, Szklo-Coxe M, Mandrell BN, et al. Concordance between self-reported sleep and actigraphy-assessed sleep in adult survivors of childhood cancer: the impact of psychological and neurocognitive late effects. *Support Care Cancer.* 2021.

34. Hinds PS, Hockenberry M, Rai SN, et al. Nocturnal awakenings, sleep environment interruptions, and fatigue in hospitalized children with cancer. *Oncol Nurs Forum.* 2007;34(2):393-402.

35. Hillman DR. Sleep Loss in the Hospitalized Patient and Its Influence on Recovery From Illness and Operation. *Anesth Analg.*2021;132(5):1314-1320.

36. van Gorp M, Maurice-Stam H, Teunissen LC, et al. Psychosocial function of Dutch children with cancer and their caregivers during different phases of the COVID-19 pandemic. *Pediatr Blood Cancer.*2022;69(4):e29535.

37. Kocevska D, Blanken TF, Van Someren EJW, Rosler L. Sleep quality during the COVID-19 pandemic: not one size fits all. *Sleep Med.*2020;76:86-88.

38. McCarthy MC, Bastiani J, Williams LK. Are parenting behaviors associated with child sleep problems during treatment for acute lymphoblastic leukemia? *Cancer Med.* 2016;5(7):1473-1480.

39. Verberne LM, Maurice-Stam H, Grootenhuis MA, Van Santen HM, Schouten-Van Meeteren AY. Sleep disorders in children after treatment for a CNS tumour. *J Sleep Res.* 2012;21(4):461-469.

40. Sato I, Higuchi A, Yanagisawa T, et al. Impact of late effects on health-related quality of life in survivors of pediatric brain tumors: motility disturbance of limb(s), seizure, ocular/visual impairment, endocrine abnormality, and higher brain dysfunction. *Cancer Nurs.*2014;37(6):E1-E14.

41. Rogers VE, Zhu S, Mandrell BN, Ancoli-Israel S, Liu L, Hinds PS. Relationship between circadian activity rhythms and fatigue in hospitalized children with CNS cancers receiving high-dose chemotherapy.*Support Care Cancer.* 2020;28(3):1459-1467.

42. Kim H, Zhou ES, Chevalier L, et al. Parental Behaviors, Emotions at Bedtime, and Sleep Disturbances in Children with Cancer. *J Pediatr Psychol.* 2020;45(5):550-560.

43. McDowall PS, Elder DE, Campbell AJ. Relationship between parent knowledge of child sleep, and child sleep practices and problems: A pilot study in a children's hospital cohort. *J Paediatr Child Health.* 2017;53(8):788-793.

Figure 1. Flowchart of participant enrollment

TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants			
				Study participants (N=69)	Study participants (N=69)	Non-participants (N=23), *P*-value[3]	Not approached (N=14), *P*-value[3]
Child variables	Child variables	Child variables	Child variables				
	Male sex, N (%)	Male sex, N (%)	Male sex, N (%)	47 (68%)	47 (68%)	14 (61%), *P*=.52	8 (57%), *P*=.44

TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants			
	Age at assessment, mean years (SD)	Age at assessment, mean years (SD)	Age at assessment, mean years (SD)	11.6 (2.8)	11.6 (2.8)	11.1 (4.3), P=.76	9.9 (2.3), P=.08
	Time since diagnosis, mean days (SD)	Time since diagnosis, mean days (SD)	Time since diagnosis, mean days (SD)	53 (28)	53 (28)		
	Body Mass Index, mean (SD)	Body Mass Index, mean (SD)	Body Mass Index, mean (SD)	18.7 (3.7)	18.7 (3.7)		
	Parental education level[1]	Parental education level[1]	Parental education level[1]				
		Low-Middle N (%)	Low-Middle N (%)	33 (51%)	33 (51%)		
		High, N (%)	High, N (%)	32 (49%)	32 (49%)		
Medical variables	Medical variables	Medical variables	Medical variables				
	Tumor type	Tumor type	Tumor type				
		Low grade glioma, N (%)	Low grade glioma, N (%)	33 (48%)	33 (48%)		
		Germ cell tumor, N (%)	Germ cell tumor, N (%)	10 (15%)	10 (15%)		
		Craniopharyngioma, N (%)	Craniopharyngioma, N (%)	9 (13%)	9 (13%)		
		High grade glioma, N (%)	High grade glioma, N (%)	6 (8%)	6 (8%)		
		Medulloblastoma, N (%)	Medulloblastoma, N (%)	6 (8%)	6 (8%)		
		Ependymoma, N (%)	Ependymoma, N (%)	2 (3%)	2 (3%)		
		Other, N (%)[2]	Other, N (%)[2]	3 (4%)	3 (4%)		
	Tumor location	Tumor location	Tumor location				

TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants	TABLE 1 Baseline characteristics of participants			
		Posterior fossa, N (%)	Posterior fossa, N (%)	29 (42%)	29 (42%)	8 (35%), P=.54	6 (43%), P=.95
		Supratentorial medial structures, N (%)	Supratentorial medial structures, N (%)	26 (38%)	26 (38%)	5 (22%), P=.16	5 (36%), P=.89
		Cerebral lobes, N (%)	Cerebral lobes, N (%)	14 (20%)	14 (20%)	10 (44%), P=.03*	3 (21%), P=.92
	Started treatment	Started treatment	Started treatment				
		Neurosurgery, N (%)	Neurosurgery, N (%)	63 (91%)	63 (91%)		
		Started chemotherapy, N (%)	Started chemotherapy, N (%)	12 (17%)	12 (17%)		
		Started radiotherapy, N (%)	Started radiotherapy, N (%)	13 (19%)	13 (19%)		
			Proton therapy, N (%)	5 (7%)	5 (7%)		
			Photon therapy, N (%)	8 (12%)	8 (12%)		
		Obstructive hydrocephalus, N (%)	Obstructive hydrocephalus, N (%)	33 (48%)	33 (48%)		
		Hormone deficiency, N (%)	Hormone deficiency, N (%)	18 (26%)	18 (26%)		
		Epilepsy, N (%)	Epilepsy, N (%)	9 (13%)	9 (13%)		

[1] Low = no education, primary school, lower secondary education; middle = upper secondary education, preuniversity education, intermediate vocational education; high = higher vocational education, university.

[2] ATRT (N=1), plexus tumor (N=1), meningioma (N=1).

[3] Compared to participant group.

* Statistically significant

TABLE 2 Patient- and parent-reported child sleep and prevalence of sleep problems

	T-score[1] Mean (SD) or median [IQR]	T-score[1] *P*-value[2]	T-score[1] *P*-value[2]	T-score[1] *P*-value[2]	T-score[1] N (%)	Moderate sleep problems N (%)	Moderate sleep problems *P*-value[3]	Moderate sleep problems *P*-value[3]	Severe sleep problems N (%)	Severe sleep problems N (%)	Severe sleep problems *P*-value[4]	Severe sleep problems *P*-value[4]	Severe sleep problems *P*-value[4]	Severe sleep problems N (%)	An sle pr N (%
Self-report (n=53)															
Sleep Disturbance	50.6 (9.5)	50.6 (9.5)	.64	8 (15%)	8 (15%)	8 (15%)	8 (15%)	.37	.37	6 (11%)	6 (11%)	**.04**	**.04**	14 (26%)	14 (2
Sleep Related Impairment	49.7 [40.1 – 54.2]	49.7 [40.1 – 54.2]	-	7 (13%)	7 (13%)	7 (13%)	7 (13%)	.22	.22	3 (6%)	3 (6%)	.83	.83	10 (19%)	10 (1
Proxy-report (n=65)															
Sleep Disturbance	53.7 (10.0)	53.7 (10.0)	**<.01**	20 (31%)	20 (31%)	20 (31%)	20 (31%)	**.03**	**.03**	7 (11%)	7 (11%)	**.03**	**.03**	27 (42%)	27 (4
Sleep Related Impairment	57.1 [37.9 – 61.8]	57.1 [37.9 – 61.8]	-	27 (42%)	27 (42%)	27 (42%)	27 (42%)	**<.01**	**<.01**	5 (8%)	5 (8%)	.32	.32	32 (49%)	32 (4

Abbreviations: SD = standard deviation, IQR = interquartile range.

Significant *P* -values are bold.

[1] Higher scores indicate more sleep problems

[2] Compared to norm population (mean=50, SD=10)

[3] Compared to percentage of moderate sleep problems in the norm population (20%)

[4] Compared to percentage of severe sleep problems in the norm population (5%)

[5] Compared to percentage of sleep problems (moderate or severe) in the norm population (25%)

TABLE 3 Differences in actigraphic sleep estimates between participants and healthy controls

	Participants (n=53) Mean (SD)	Control group (n=47) Mean (SD)	B (95% CI)	*P*-value
SE (%)	79.0 (7.1)	77.8 (7.3)	-1.1 (-3.9 – 1.8)	.47
SOL (min)	20.7 (14.8)	25.9 (15.4)	4.2 (-1.6 – 10.1)	.15
WASO (min)	107.3 (39.7)	113.9 (45.5)	4.5 (-12.2 – 21.2)	.60
TST (min)	480.9 (58.9)	479.1 (48.0)	-7.8 (-26.9 – 11.3)	.42
TIB (min)	608.9 (55.0)	618.6 (56.7)	.8 (-15.3 – 16.9)	.92
NA (N)	28.6 (6.9)	28.6 (6.2)	-.3 (-3.0 – 2.3)	.80

Abbreviations: SE = sleep efficiency, SOL = sleep onset latency, WASO = wake after sleep onset, TST = total sleep time, TIB = total time spent in bed, NA = number of awakenings, min = minutes. Models were adjusted for age.

TABLE 4 Multivariable regression models of risk factors for patient- and parent reported sleep outcomes

Questionnaires, B (95% CI)

	PROMIS Sleep Disturbance Self-report	PROMIS Sleep Related Impairment Self-report	PROMIS Sleep Disturbance Proxy-report	PROMIS Sleep Related Impairment Proxy-report
Time since diagnosis *Continuous*	**-.11* (-.19 – -.03)**	-	-.07 (-.16 – .02)	-
Tumor location *Suprat. midline vs. others*	-3.56 (-8.74 – 1.62)	-	-	-
Started radiotherapy[1] *Yes vs. no*	-	-	-4.60 (-10.96 – 1.76)	-

[1] Proton and photon radiation therapy grouped together

* Statistically significant (P <0.01)

TABLE 5 Multivariable regression models of risk factors for actigraphic sleep outcomes

Actigraphic outcomes, B (95% CI)

	SE	SOL	WASO	TST	TIB	NA
Age *Continuous*	-	**-1.73* (-3.12 – -.35)**	-	**-8.63** (-14.00 – -3.26)**	**-10.59** (-15.33 – -5.85)**	-
Neurosurgery *Yes vs. no*	-	-	-	-	-	4.68 (-1.26 – 10.61)

Started radiotherapy[1] *Yes vs. no*	-	-	-	-	-	3.63 (-1.37 – 8.64)
Obstr. hydrocephalus *Yes vs. no*	-	-7.28 (-14.93 - .37)	-	**41.04** (11.41 – 70.68)**	-	-

Abbreviations: SE = sleep efficiency, SOL = sleep onset latency, TST = total sleep time, TIB = total time in bed, NA = number of awakenings, suprat. = supratentorial, obstr. = obstructive.

[1] Proton and photon radiation therapy grouped together

* Statistically significant (P <0.05)

** Statistically significant (P <0.01)