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PSYCHOSOCIAL AND SUPPORTIVE CARE:  
RESEARCH ARTICLE

# High prevalence of parent-reported sleep problems in pediatric patients with acute lymphoblastic leukemia after induction therapy

Lindsay M. H. Steur<sup>1</sup>  | Martha A. Grootenhuis<sup>2</sup> | Eus J. W. Van Someren<sup>3,4,5</sup>  |  
Natasha K. A. Van Eijkelenburg<sup>2</sup>  | Inge M. Van der Sluis<sup>2,6</sup>  | Natasja Dors<sup>2,7</sup> |  
Cor Van den Bos<sup>2,8</sup>  | Wim J. E. Tissing<sup>2,9</sup>  | Gertjan J. L. Kaspers<sup>1,2,10</sup>  |  
Raphaële R. L. Van Litsenburg<sup>1,2</sup> 

<sup>1</sup>Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Pediatric Oncology, Cancer Center Amsterdam, Amsterdam, The Netherlands

<sup>2</sup>Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

<sup>3</sup>Department of Sleep and Cognition, Netherlands Institute for Neuroscience (An institute of the Royal Netherlands Academy of Arts and Sciences), Amsterdam, The Netherlands

<sup>4</sup>Department of Integrative Neurophysiology, Amsterdam Neuroscience, Center for Neurogenomics and Cognitive Research (CNCR), Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

<sup>5</sup>Amsterdam UMC, Vrije Universiteit Amsterdam, Psychiatry, Amsterdam Neuroscience, Amsterdam, The Netherlands

<sup>6</sup>Department of Pediatric Oncology, Sophia Children's Hospital, Erasmus Medical Center, Rotterdam, The Netherlands

<sup>7</sup>Department of Pediatric Oncology, Amalia Children's Hospital, Radboud University Medical Center, Nijmegen, The Netherlands

<sup>8</sup>Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam UMC, Academic Medical Center, Amsterdam, The Netherlands

<sup>9</sup>Department of Pediatric Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

<sup>10</sup>Dutch Childhood Oncology Group, Utrecht, The Netherlands

## Correspondence

Raphaële R.L. Van Litsenburg, Princess Máxima Center for Pediatric Oncology, PO box 113, 3720 AC Bilthoven, The Netherlands.

Email: r.r.l.vanlitsenburg@prinsesmaximacentrum.nl

## Abstract

**Objective:** To assess sleep problems (prevalence and predictors) in pediatric patients with acute lymphoblastic leukemia (ALL) after the most intensive phase of therapy (induction).

**Methods:** Patients ( $\geq 2$  years) treated according to the Dutch ALL-11 protocol were included. Sleep was measured using parent-reports and self-reports (Children's Sleep Habits Questionnaire; CSHQ) and actigraphy. Parental sleep (Medical Outcome Study Sleep Scale) and distress and parenting problems (Distress Thermometer for Parents) were assessed with questionnaires. Z-scores were calculated for total CSHQ scores using age-appropriate scores of healthy Dutch children. The prevalence of sleep problems (defined as a Z-score  $> 1$ ) in patients with ALL was compared to healthy children (chi-square tests). Actigraphic sleep estimates were collected in healthy Dutch children ( $n = 86$ , 2-18 years) for comparison with patients (linear regression). Determinants of parent-reported child sleep (total CSHQ Z-score) were identified with regression models.

Abbreviations: ALL, acute lymphoblastic leukemia; ASHQ, Adolescent Sleep Habits Questionnaire; CSHQ, Children Sleep Habits Questionnaire; DCOG, Dutch Childhood Oncology Group; DT-P, Distress Thermometer for Parents; IQR, interquartile range; MOS, Medical Outcome Study Sleep Scale; PRO, patient-reported outcome; SLP-9, 9-item sleep problem index; SSR, Sleep Self Report; TIB, total time in bed; TST, total sleep time.

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**Results:** Responses were collected for 124 patients (response rate 67%), comprising 123 parent-reports, 34 self-reports, and 69 actigraphy assessments. Parents reported sleep problems in 38.0% of the patients compared to 15.2% in healthy children ( $P < .001$ ). Patients reported fewer sleep problems themselves: 12.1% compared to 15.8% in healthy children ( $P = .33$ ). Total time in bed (B (95% CI): 22.89 (9.55-36.22)) and total sleep time (B (95% CI):16.30 (1.40-31.19)), as derived from actigraphy, were significantly longer in patients. More parent-reported child sleep problems were predicted by parenting problems, more parental sleep problems, bedroom sharing, and child's sleep medication use (explained variance: 27.4%).

**Conclusions:** Systematic monitoring of child and parental sleep and implementation of effective interventions may be a gateway to improve quality of survival in pediatric ALL.

#### KEYWORDS

actigraphy, acute lymphoblastic leukemia, parenting, pediatric, questionnaires, sleep

## 1 | BACKGROUND

Impaired sleep quality and quantity are associated with many adverse psychosocial and physical health outcomes. Self- or proxy-reported sleep disturbances are, for example, associated with impaired quality of life, altered pain perception, and fatigue,<sup>1-4</sup> whereas insufficient sleep is associated with depressive symptoms, impaired cognitive functioning, and an increased risk of metabolic syndrome.<sup>5-7</sup> Moreover, in adults a longer sleep duration (>7.5 h) has also been related to an increased risk of cardiovascular diseases, diabetes mellitus, and obesity.<sup>8</sup> The development of sleep problems during early childhood is a risk factor for chronic sleep problems.<sup>9</sup> Children with a chronic illness have an increased risk of acute as well as chronic sleep problems compared to their healthy peers.<sup>10</sup> Therefore, attention to and treatment of sleep problems in these vulnerable children is important.

Pediatric patients with cancer are prone to sleep problems due to physical (i.e., tumor location, treatment, and toxicity) as well as psychosocial factors (i.e., anxiety and fatigue).<sup>11-13</sup> Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer and it requires an intensive treatment regimen of frequent chemotherapy administrations over the course of 2-3 years.<sup>14</sup> During maintenance treatment, a relatively stable phase in which most children resume their daily activities, sleep problems are common and often include a behavioral component.<sup>4,15,16</sup> Sleep duration is often adequate, but nighttime awakenings are frequent and sleep onset latency (defined as the minutes between bedtime and the first minute of sleep) is longer.<sup>17,18</sup> This indicates that the total minutes of sleep is sufficient but sleep is fragmented. The fragmentation of sleep could still affect patient and parental perceptions of sleep quality.

Some risk factors for sleep problems in childhood cancer patients have previously been identified, such as glucocorticoid treatment, younger age, sex, and co-sleeping.<sup>4,13,15,16,18</sup> In young and severely ill children, patient-reported outcomes (PROs) often depend on parental reports. The potential influence of parental functioning and parenting behaviors on these outcomes is often not taken into account.<sup>15,19</sup> However, sleep problems are common in parents of pediatric cancer patients, with prevalence rates up to 71% in the hospital

setting.<sup>17,19-25</sup> Many parents report elevated levels of distress shortly after diagnosis and during treatment.<sup>26</sup> Furthermore, altered parenting strategies have been described.<sup>15,27</sup>

Therefore, it is important to capture all of the potential risk factors (patient, medical, and parental factors) in one model, since such a profile will help to identify families most in need of support. Sleep disturbances are an additional stressor to families facing childhood cancer. Early identification of patients at risk for sleep problems in order to begin intervening in a timely manner is therefore of the utmost importance. However, studies during the earlier, more intensive treatment phases are scarce.<sup>28</sup>

Additionally, most previous studies employed only a single mode of sleep assessment, while PROs and objective sleep outcomes (such as polysomnography and actigraphy) provide complementary information.<sup>29,30</sup> Although polysomnography is considered the gold standard, in an ambulant setting objective sleep outcomes are best measured with actigraphy.<sup>31</sup> Actigraphy provides quantitative sleep parameters such as sleep duration, wake after sleep onset, and sleep efficiency. The sleep estimates obtained with actigraphy can contribute to our understanding of clinical sleep disorders.<sup>31,32</sup> PROs provide valuable qualitative and subjective information on sleep behaviors and consequences of impaired sleep (such as bedtime routines, sleep anxiety, and daytime sleepiness) that cannot be assessed with actigraphy. Moreover, PROs can explore environmental and behavioral dimensions that could have implications for sleep.

In accordance with the literature during maintenance therapy for ALL, we hypothesized that behavioral sleep problems (based on PROs) would be even more common after induction therapy. Regarding actigraphic outcomes, we expected longer sleep times and more fragmented sleep, since patients are still recovering from the intensive induction phase and normal daily routines are not yet resumed. To provide a comprehensive overview on sleep, the current study combined PROs and actigraphy assessments and aimed to (1) assess the prevalence and types of parent- and self-reported sleep problems in pediatric patients with ALL after the first, most intensive phase of therapy (induction); (2) describe actigraphic sleep estimates; and (3) identify determinants of parent-reported sleep problems.



## 2.2.2 | Child sleep: Parent- and patient-reported outcomes

The Dutch Children Sleep Habits Questionnaire (CSHQ), Adolescent Sleep Habits Questionnaire (ASHQ), and the Sleep Self-Report (SSR) were used to assess child sleep.<sup>34–37</sup> Scores of healthy Dutch children are available.<sup>34–36,38</sup> Only (sub)scales with an acceptable internal consistency (Cronbach's alpha  $\geq 0.60$ ) in both the study population and in healthy children are reported here. Recall period was the last week for all child sleep questionnaires and higher scores were indicative of more sleep problems. Missing items were imputed as item means of the population if less than half of the items on a scale were missing.<sup>36</sup>

The 33-item CSHQ was used to assess parent-reported sleep in patients aged 2–12 years.<sup>36,37</sup> A 33-item total score as well as subscale scores were calculated. The internal consistency of the total score and the following subscales was acceptable: bedtime resistance, sleep-onset delay, night waking (2- to 3-year old children), sleep duration (2- to 3-year old children), sleep anxiety (2- to 3-year old children), and daytime sleepiness (4- to 12-year old children).

The 26-item SSR was used to assess patient-reported sleep in patients 8–12 years of age.<sup>35–37</sup> It consists of 23-items that allow for a total score and three additional questions providing information on bedtime routines. The 23-item total score is reported here.

The ASHQ was developed parallel to the CSHQ and was used for patient- and parent-reported sleep in adolescents aged 13–18 years.<sup>34</sup> The ASHQ patient- and parent-reported versions comprise 50-items and 54-items, respectively. The items allow for total and subscale scores. The internal consistency of the total scores and the subscales morning waking (parent-report) and daytime sleepiness was acceptable.

## 2.2.3 | Child sleep: Actigraphic sleep estimates

Objective sleep was estimated from an actigraphy (ActiGraph wGT3X-BT, Pensacola, FL) assessment. An actigraph is a noninvasive device that quantifies sleep-wake rhythm by the occurrence and intensity of limb movements. Patients were instructed to wear the actigraph on their wrist for 24-h for 7 days. Actigraphy has been validated against polysomnography. It has been proven adequate for the assessment of sleep-wake patterns in infants, children, and adolescents.<sup>39,40</sup> Participants kept a sleep log to facilitate correct interpretation of the actigraphy data. Based on sleep logs and visual inspection of the data, invalid data were identified and removed from further analyses.

Actigraphy data were processed with ActiLife version 6.13.3. Sleep outcomes were calculated using sleep log bedtime and wake time. The following variables were obtained based on the Sadeh algorithm (definitions are provided in Table 1): sleep onset latency, total sleep time (TST), sleep efficiency, wake after sleep onset, and number of nighttime awakenings.<sup>40</sup> Total time in bed (TIB), defined as the number of minutes spent in bed based on sleep log bedtime and wake time. To reflect daytime napping, 24-h TST and TIB were calculated. Variables were calculated if valid data was available for at least five nights in order to correct for individual differences and acquire stable sleep outcomes

**TABLE 1** Definitions of actigraphic sleep estimates

Variable	Definition
Sleep onset latency	The number of minutes between bedtime and the first minute scored as sleep
Total sleep time	The number of minutes scored as sleep during the time spent in bed
Sleep efficiency	The ratio between total sleep time and time spent in bed
Wake after sleep onset	The number of minutes awake after sleep onset
Number of nighttime awakenings	The total number of awakenings after sleep onset

in children and adolescents.<sup>41</sup> Actigraphic sleep estimates were also obtained in healthy children (without sleep problems or sleep medications use) aged 2–18 years, with the same type of actigraph (ActiGraph wGT3X-BT). Valid actigraphy data were available for 86 healthy children (median age: 8.7 years [interquartile range, IQR]: [5.6–15.4], 52.3% males). Additional information on the recruitment, inclusion and exclusion criteria, and sociodemographics of these healthy children is provided in the Supporting Information Appendix.

## 2.2.4 | Parental sleep

Parental sleep was assessed with the Medical Outcome Study Sleep Scale (MOS-Sleep).<sup>42</sup> This 12-item questionnaire allows for six subscales and a 9-item sleep problem index (SLP-9). The SLP-9 was used to reflect parental sleep problems and represents symptoms consistent with insomnia. The SLP-9 score ranges from 0 to 100 (higher scores indicate more disturbed sleep) and was generated based on the MOS manual's guidelines.<sup>43</sup>

## 2.2.5 | Parental distress and parenting problems

The Distress Thermometer for Parents (DT-P) consists of a thermometer (0–10 scale) on which parents indicate their overall distress, with a score of  $\geq 4$  indicative of clinical distress.<sup>44</sup> Additionally, it evaluates problem domains: practical, social, emotional, physical, cognitive and parenting. The parenting problem domain evaluates whether the parent-perceived problems were derived from contact with their child, dealing with their child's feelings, communication about (consequences of) the illness, child independence, or issues with compliance to advice/treatment and medication administration. The thermometer score and parenting problem domain (dichotomized as no parenting problems versus at least one) were included as potential predictors of parent-rated child sleep.

## 2.3 | Statistical Analysis

### 2.3.1 | Sociodemographics

Differences in age and sex between participants, nonparticipants, and patients who were not invited to participate in the study were evaluated with Mann-Whitney *U* tests and chi-square tests, respectively.

### 2.3.2 | Prevalence and types of parent- and patient-reported sleep problems

CSHQ scores (parent-reported) were presented for toddlers (2-3 years) and school-aged children (4-12 years) separately. Age groups were defined based on the normal development of sleep behaviors during childhood and the availability of sleep scores of healthy children. Patient scores were compared to age appropriate scores of healthy children. Original databases of previously collected scores of healthy children were used for analyses.<sup>34-36,38</sup> Independent samples *T*-tests or Mann-Whitney *U* tests were used for comparison with healthy children. A two-sided *P*-value of  $<.05$  was considered statistically significant.

To reflect the prevalence of sleep problems, *Z*-scores were calculated for all sleep questionnaire total scores. For this purpose, the questionnaire score (CSHQ/ASHQ/SSR) of each individual patient was standardized to the distribution of scores of similarly aged healthy Dutch children ( $Z\text{-score} = (\text{Patient's score} - \text{mean score of similarly aged healthy children}) / \text{standard deviation [SD] of similarly aged healthy children}$ ). Patients with a *Z*-score  $> 1$  were considered to have clinically relevant sleep problems, and of those, patients with a *Z*-score  $> 2$  were considered to have severe sleep problems. The percentages of patients with *Z*-scores exceeding 1 and 2 were calculated and compared to the population of healthy children with chi-square tests.

### 2.3.3 | Actigraphic sleep estimates

Actigraphic sleep estimates were compared to healthy children using linear regression models. Regression models were adjusted for age, sex, and use of sleep medication.

### 2.3.4 | Determinants of parent-reported child sleep

Linear regression models were built to identify predictors of child sleep (CSHQ/ASHQ total *Z*-score). As there were few self-reports, only parent-reported scores were used. All child, medical, and parental variables mentioned above were tested, except for parental age and sex (used for sample description only), and time since diagnosis (correlated with phase of treatment).

A backward selection procedure was performed. First, univariate regressions were performed for all variables. Second, variables with a *P*-value  $< 0.15$  were added to the multivariable model. Third, in a stepwise approach, variables with the highest *P*-value were deleted from the multivariable model until only variables with a *P*-value  $< 0.10$  remained. The proportion of explained variance of the final model was determined.

IBM SPSS statistics version 22.0 was used for all analyses.

## 3 | RESULTS

### 3.1 | Study population

Of 276 eligible patients, 225 were invited to participate. Fifty-one patients were not invited to participate mainly due to logistical issues

or severity of disease. Informed consent was provided for 151 patients (response rate 67%). The main reason for nonparticipation was the burden of the study. Twenty-seven patients did not complete any of the study assessments because of withdrawal of informed consent before the first measurement, invalid data, or willingness to participate only from the second measurement onwards. Finally, 124 patients completed at least one of the study measurements: parent-reports ( $n = 123$ ), self-reports ( $n = 34$ ), and actigraphy assessment ( $n = 69$ ) (Figure 2). In accordance with the study design, the majority of measurements took place during central nervous system directed therapy (Table 2). Nevertheless, some measurements were planned during induction or maintenance treatment because of parent/patient preference. For patients during maintenance treatment, receiving cyclic dexamethasone ( $n = 14$ ), measurements were planned during a week without dexamethasone treatment in order to limit the potential effect of dexamethasone on sleep outcomes. Additional analyses showed that the variability in timing of the study assessment did not significantly influence total sleep *Z*-score or actigraphic sleep estimates (Table S1).

### 3.2 | Sociodemographics

There were no significant differences in age and sex between participants (median age at diagnosis: 5.1 years, IQR: 3.1-9.2, 39.5% females) and nonparticipants (median age at diagnosis: 5.5 years, IQR: 3.5-11.5, 43.6% females) and patients who were not invited to participate (median age at diagnosis: 5.8 years, IQR: 3.8-11.5, 45.1% females). Median age at diagnosis of the patients who participated in the self-reports and actigraphy was 12.2 years (IQR: 9.4-16.0) and 5.8 years (IQR: 3.8-9.8), respectively. Sex distribution and time since diagnosis were similar to the total study population.

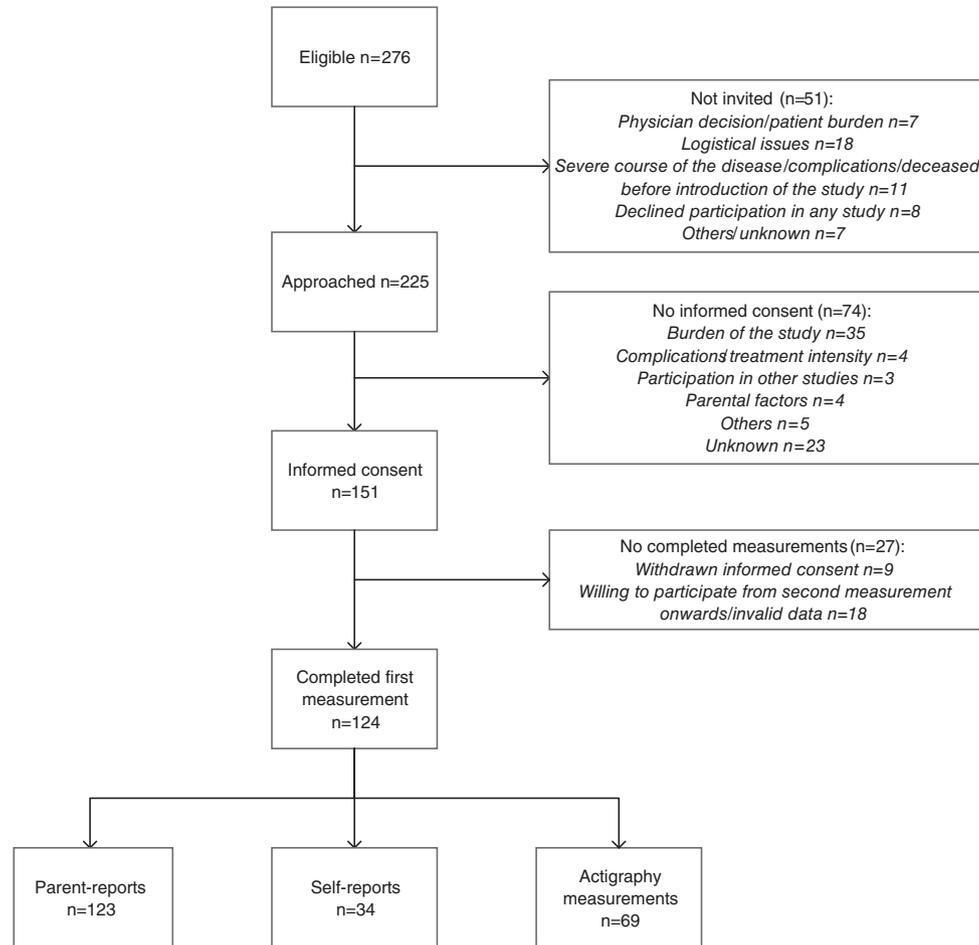
Eight patients used sleep medication at time of the study (melatonin ( $n = 5$ ), lorazepam ( $n = 1$ ), unknown ( $n = 2$ )). Pre-existent sleep problems were reported by parents of 19 patients and consisted of problems with initiating and maintaining sleep ( $n = 15$ ), somnambulism ( $n = 1$ ), need of sibling in the room ( $n = 1$ ), and two parents reported less need of sleep for their child compared to other children.

### 3.3 | Parental outcomes

The mean SLP-9 score of parents of patients with ALL was  $36.4 \pm 16.7$  compared to  $21.7 \pm 13.8$  in the general population. Almost half of the parents reported at least one parenting problem. Furthermore, the median distress thermometer score was 6.0 (IQR: 3.0-8.0).

### 3.4 | Prevalence and types of parent- and patient-reported sleep problems

In toddlers (aged 2-3 years), CSHQ (sub)scale scores were higher (i.e., more sleep problems) compared to scores of healthy children (Table 3). In school-aged patients (aged 4-12 years), parents reported more overall sleep problems and more bedtime resistance compared to healthy children. Parents reported more overall sleep problems and more daytime sleepiness in adolescents (aged 13-18 years) with ALL compared



**FIGURE 2** Patient enrollment

to healthy adolescents. Self-reports (SSR and ASHQ scores) were not different from scores of healthy children.

In patients (2-18 years), the prevalence of parent-reported clinically relevant sleep problems was 38.0% ( $Z$ -score > 1) and severe sleep problems were reported in 16.7% ( $Z$ -score > 2), compared to 15.2% and 4.3%, respectively, in healthy children ( $P < .001$ ). The self-reported prevalence of clinically relevant sleep problems was 12.1% compared to 15.8% in healthy children ( $P = .33$ ). None of the patients self-reported severe sleep problems, compared to 4.3% in healthy children.

### 3.5 | Actigraphic sleep estimates

Patients spent significantly more minutes in bed and slept significantly more minutes during the night (nighttime TST:  $B:15.27$ ,  $P = 0.001$ , nighttime TIB:  $B:22.89$ ,  $P = 0.046$ ) as well as during 24-h (24-h TST:  $B:26.10$ ,  $P < 0.001$ , 24-h TIB:  $B:39.04$ ,  $P < 0.001$ ) compared to healthy children (Table 4). There were no differences in other actigraphic sleep estimates.

### 3.6 | Determinants of parent-reported child sleep

Results of the univariate analyses are shown in Table 5. Bedroom sharing, parental sleep problems, parenting problems, and current child

sleep medication use predicted parent-reported child sleep problems in the final multivariable model (explained variance: 27.4%) (Table 5).

## 4 | DISCUSSION

This study assessed sleep in pediatric patients with ALL in the first period after diagnosis combining both PROs and actigraphy assessments. There was a high parent-perceived burden of sleep problems and these were predicted by parental sleep, parenting problems, bedroom sharing, and child's sleep medication use. Patients did not report an increased prevalence of sleep problems themselves. Furthermore, except for longer sleep times, actigraphic sleep estimates were not different from sleep estimates in healthy children.

Parents reported a wide range of sleep difficulties in patients with ALL instead of problems indicative of a specific sleep disorder. Parents may perceive general sleep problems that do not meet all criteria for a specific clinical sleep disorder (such as insomnia, sleep-related breathing disorders, or hypersomnolence) according to the International Classification of Sleep Disorders.<sup>45</sup> However, the high prevalence of clinically relevant sleep problems is still a reflection of the overall burden of sleep difficulties during this treatment phase.

**TABLE 2** Baseline characteristics

	Study participants (n = 124)
<b>Child and medical factors</b>	
Child age at diagnosis in years, median [IQR]	5.1 [3.1-9.2]
Female child sex, N (%)	49 (39.5)
Time since diagnosis in months, median [IQR]	4.5 [4.1-5.1]
Phase of treatment, N (%)	
- Induction	10 (8.1)
- Central nervous system directed therapy <sup>a</sup> /high risk courses (n = 1)	100 (80.6)
- Maintenance	14 (11.3)
Preexisting sleep problems, N (%)	19 (15.3)
Use of sleep medication, N (%)	8 (6.5)
Comorbidity, N (%) <sup>b</sup>	8 (6.5)
Bedroom sharing, N (%)	26 (21.0)
Pain VAS score, median [IQR]	3.0 [0.0-6.0]
<b>Parental factors (n = 123)</b>	
Parental age, median [IQR]	37.0 [34.0-43.0]
Female parental sex, N (%)	97 (78.9)
Educational level, N (%) <sup>c</sup>	
- Low	5 (4.1)
- Middle	36 (29.3)
- High	82 (66.7)
Parental sleep score (SLP-9) <sup>d</sup> (n = 120), mean (SD)	36.4 (16.7)
Parental distress thermometer score <sup>e</sup> (n = 107), median [IQR]	6.0 [3.0-8.0]
≥1 Parenting problem (n = 119), N (%)	56 (47.1)

Abbreviations: IQR, interquartile range; SLP-9, 9-item sleep problem index.

<sup>a</sup>Also referred to as Protocol M.

<sup>b</sup>Down syndrome (n = 3), autism (n = 1), hypermobility (n = 1), coeliac disease (n = 1), anorectal malformation (n = 1), and cavernomas in the brain (n = 1).

<sup>c</sup>Low = no education, primary school, lower secondary education; middle = upper secondary education, preuniversity education, intermediate vocational education; high = higher vocational education, university.

<sup>d</sup>Higher score indicates more sleep problems.

<sup>e</sup>Higher score indicates more distress.

The disagreement between parent- and self-reports is consistent with literature.<sup>34,46</sup> A "repressive adaptive style" (a coping style including defensiveness and minimization) has previously been described as a possible factor of bias in self-reports of pediatric cancer patients.<sup>47</sup> Furthermore, patients may change their judgment of symptoms during cancer treatment (also referred to as "response shift").<sup>34,48</sup> Parental coping can also contribute to this disagreement. Parents of pediatric cancer patients are known to be more concerned about their child's health and social adjustment.<sup>27</sup> This could lead to an overreporting of problems.

The longer actigraphic sleep times are probably favorable for physical recovery in this treatment phase and may result from cancer-related fatigue, a common side-effect of cancer treatment.<sup>49</sup>

However, more sedentary behavior has been associated with adverse health outcomes, such as a higher cardiovascular risk and an unfavorable body composition.<sup>50</sup> In adult cancer patients, sedentary behavior has also been associated with an increased risk of cancer-specific mortality.<sup>51</sup> Therefore, monitoring time in bed and encouraging appropriate degrees of physical activity as early as possible is important and has shown to be feasible in pediatric patients with ALL.<sup>52</sup>

The parent-reported problems with initiating and maintaining sleep in toddlers were not detected with actigraphy. This may have several explanations. First, actigraphy may be less accurate in patients with sleep problems than in good sleepers.<sup>40</sup> Moreover, subjective and objective sleep quality can strongly differ. Second, parents of patients with ALL employ more sleep managing strategies (such as co-sleeping, providing food in the bedroom, and comforting activities).<sup>15</sup> Our results may indicate that these strategies are successful, but require substantial efforts from parents. Third, the high prevalence of parent-reported sleep problems may reflect impaired parental psychosocial functioning. Parental distress levels were high and significantly associated with parent-reported child sleep in the univariate analysis. Parental distress was not retained in the multivariable model, but this is most likely the result of the high correlation between parental sleep and distress, which has been previously described.<sup>21</sup>

Parent-reported sleep problems were mainly predicted by parental sleep and parenting factors in our model. The correlation between parental and child sleep has previously been described during ALL maintenance treatment.<sup>19</sup> This relationship is probably bidirectional. Child sleep can interfere with parental sleep, which may in turn impact both parenting strategies as well as parents' perception of their child's sleep. Child sleep improves with consistent bedtime routines.<sup>53</sup> To achieve this, parents need to be consistent, engage in limit setting, and teach their children healthy sleep behaviors. This is a challenge for parents with poor sleep as they might, for example, feel more fatigued. It is therefore important to address both child and parental sleep. Also, it can be challenging for parents of pediatric cancer patients to reinforce rules, since they tend to be more lenient toward their children.<sup>15,27</sup>

Parents' knowledge on healthy child sleep is generally poor and may contribute to parenting problems regarding sleep.<sup>54</sup> An educational intervention to improve sleep knowledge in parents of healthy children has proven to be effective.<sup>55</sup> Implementing interventions incorporating psycho-education and parenting support may prevent development of chronic sleep problems in pediatric patients with ALL.

Since the determinants in our model explained 27.4% of the variance, future research is needed to identify additional predictors of parent-reported sleep problems in pediatric ALL.

This study has some limitations. First, not all patients participated in all study elements (parent-reports, self-reports, and actigraphy). Participation bias, for example, based on treatment toxicity, cannot be excluded. Second, because of the small sample of self-reports, these results should be interpreted with caution. Third, parenting strategies and preexisting parenting problems were not evaluated in this study, although this would have provided information on the psychosocial

**TABLE 3** Descriptive statistics of parent- and patient-reported sleep outcomes and comparison between patients with ALL and healthy children

	Patients with ALL Mean (SD)/median [IQR]	Healthy children Mean (SD)/median [IQR]	P-value
<b>Parent-reports</b>			
<b>CSHQ 2–3 years (n = 42)<sup>a</sup></b>			
Total score	48.91 (7.75)	41.89 (5.56)	<b>&lt;.001</b>
Bedtime resistance	7.09 [6.31-11.00]	6.00 [6.00-7.50]	<b>&lt;.001</b>
Sleep duration	3.00 [3.00-5.00]	3.00 [3.00-4.00]	<b>.006</b>
Sleep Anxiety	5.63 [4.00-7.00]	5.00 [4.00-6.00]	<b>.001</b>
Night waking	6.00 [4.00-7.00]	4.00 [3.00-5.00]	<b>&lt;.001</b>
Sleep onset delay	1.00 [1.00-2.00]	1.00 [1.00-1.00]	<b>.010</b>
<b>CSHQ 4–12 years (n = 61)<sup>a</sup></b>			
Total score	44.02 (5.99)	40.44 (5.40)	<b>&lt;.001</b>
Bedtime resistance	7.00 [6.00-8.00]	6.00 [6.00-7.00]	<b>&lt;.001</b>
Daytime sleepiness	11.00 [9.06-13.00]	11.00 [9.00-13.00]	.234
Sleep onset delay	1.00 [1.00-1.00]	1.00 [1.00-1.00]	.984
<b>ASHQ 13–18 (n = 20)<sup>a</sup></b>			
Total score	34.58 (9.23)	29.23 (9.72)	<b>.022</b>
Morning waking	7.08 [6.00-11.75]	8.00 [5.49-10.00]	.897
Daytime sleepiness	3.00 [2.00-5.00]	2.00 [1.00-3.71]	<b>.024</b>
<b>Self-reports</b>			
<b>SSR 8–12 years (n = 17)<sup>a</sup></b>			
Total score	32.59 (4.82)	31.61 (5.31)	.455
<b>ASHQ 13–18 years (n = 16)<sup>a</sup></b>			
Total score	39.43 (10.18)	41.87 (10.52)	.361
Daytime sleepiness	12.00 [9.50-14.75]	12.00 [10.00-14.00]	.832

Abbreviations: ALL, acute lymphoblastic leukemia; ASHQ, Adolescent Sleep Habits Questionnaire; CSHQ, Children Sleep Habits Questionnaire; IQR, interquartile range; SSR, sleep self-report.

Significant P-values are bold.

<sup>a</sup>Higher scores indicate more sleep problems.

**TABLE 4** Descriptive statistics of actigraphic sleep estimates and linear regression models for comparison between patients with ALL and healthy children

	Patients with ALL (n = 69) Mean (SD)/median [IQR]	Healthy children (n = 86) Mean (SD)/median [IQR]	B (95% CI) <sup>a</sup>	P-value
<b>Nighttime sleep</b>				
Sleep onset latency (minutes)	22.86 [16.43-38.04]	20.29 [12.25-30.79]	1.68 (-3.73; 7.09)	.541
Sleep efficiency (%)	76.56 (7.71)	78.30 (6.86)	-0.55 (-2.83; 1.73)	.633
Total time in bed (minutes)	663.64 (46.60)	646.07 [569.00-667.59]	22.89 (9.55; 36.22)	<b>.001</b>
Total sleep time (minutes)	506.76 (52.84)	482.24 (51.39)	15.27 (0.31; 30.22)	<b>.046</b>
Wake after sleep onset (minutes)	128.96 (46.98)	113.31 (42.64)	6.37 (-7.14; 19.88)	.353
Number of nighttime awakenings (N)	29.19 (6.70)	28.35 (6.63)	0.14 (-2.03; 2.30)	.902
<b>24-Hour sleep</b>				
Total time in bed (minutes)	687.85 (64.67)	623.88 (78.36)	39.04 (23.53; 54.54)	<b>&lt;.001</b>
Total sleep time (minutes)	523.83 (55.88)	486.71 (53.96)	26.10 (11.72; 40.48)	<b>&lt;.001</b>

Abbreviation: IQR, interquartile range.

Significant P-values are bold.

<sup>a</sup>Models adjusted for age, sex, and current sleep medication use.

**TABLE 5** Univariate regression models for associations with overall parent reported child sleep (total sleep questionnaire scores) and final multivariable model

Univariate analyses			Final multivariable model		
	Total sleep score B (95% CI)	P-value	Total sleep score B (95% CI)	Standardized beta	P-value
<b>Child and medical factors</b>					
Child age at assessment	-0.06 (-0.10; -0.01)	<b>.025</b>	-	-	-
Female child sex	0.13 (-0.34; 0.60)	.584	-	-	-
Phase of treatment <sup>a</sup> :			-	-	-
- Induction	0.51 (-0.43; 1.45)	.287			
- Maintenance	0.17 (-0.60; 0.93)	.670			
Pre-existent sleep problems	0.64 (0.01; 1.26)	<b>.047</b>	-	-	-
Sleep medication use	0.84 (-0.25; 1.94)	<b>.131</b>	0.97 (0.11; 1.82)	0.19	<b>.027</b>
Comorbidity	1.22 (0.31; 2.13)	<b>.009</b>	-	-	-
Pain VAS score	0.09 (0.02; 0.17)	<b>.011</b>	-	-	-
<b>Parental and parenting factors</b>					
Higher educational level	-0.06 (-0.56; 0.45)	.831	-	-	-
Bedroom sharing	0.90 (0.38; 1.42)	<b>.001</b>	0.90 (0.46; 1.34)	0.35	<.001
Parental distress	0.10 (0.02; 0.19)	<b>.013</b>	-	-	-
Parenting problems	0.69 (0.28; 1.10)	<b>.001</b>	0.02 (0.01; 0.03)	0.26	<b>.004</b>
Parental sleep problems	0.02 (0.01; 0.04)	< <b>.001</b>	0.51 (0.13; 0.89)	0.23	<b>.009</b>

<sup>a</sup>Central nervous system directed therapy (protocol M) was used as a reference category.

CI: confidence interval P-values < 0.15 (cut-off value for multivariable regression model) are bold.

risk of families. Finally, a lower socioeconomic status has been associated with less healthy sleep behaviors; the overrepresentation of highly educated families in our study may therefore have underestimated sleep disturbances.<sup>33,56</sup>

In conclusion, parent-reported sleep problems are common after induction therapy and parental sleep and parenting factors are the most important predictors in our model. Parents should therefore be supported in parenting and coping with their child's sleep behaviors. Furthermore, systematic attention to both child and parental sleep by clinicians is of major importance. Given the adverse outcomes associated with impaired sleep, systematic sleep monitoring and developing effective interventions may be a gateway to improve quality of survival.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

Lindsay M. H. Steur  <https://orcid.org/0000-0002-5177-030X>

Eus J. W. Van Someren  <https://orcid.org/0000-0002-9970-8791>

Natasha K. A. Van Eijkelenburg 

<https://orcid.org/0000-0002-0526-3737>

Inge M. Van der Sluis  <https://orcid.org/0000-0002-5822-7668>

Cor Van den Bos  <https://orcid.org/0000-0002-6175-6077>

Wim J. E. Tissing  <https://orcid.org/0000-0001-9101-507X>

Gertjan J. L. Kaspers  <https://orcid.org/0000-0001-7716-8475>

Raphaële R. L. Van Litsenburg 

<https://orcid.org/0000-0003-1779-6159>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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