

# Sleep problems, behavioural problems and respiratory health in children born extremely preterm: a parental questionnaire study

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## ABSTRACT

**Objective** To explore whether children born extremely preterm (EPT) with different types of sleep problems had more behavioural and respiratory health problems than EPT children without sleep problems.

**Design** Prospective, nationwide, questionnaire-based study. At 11 years of age, parents reported on four current sleep problems: difficulty falling asleep or frequent awakenings, snoring, daytime sleepiness and not recommended sleep duration (<9 hours). Behavioural problems were assessed by parents and teachers with the Strengths and Difficulties Questionnaire (SDQ). Parents assessed respiratory symptoms with the International Study of Asthma and Allergies in Childhood questionnaire and described use of asthma medication.

**Setting** Norway.

**Patients** EPT children.

**Main outcome measures** Specified sleep problems, behavioural problems and respiratory health.

**Results** Data were obtained from 216 of 372 (58 %) of eligible children. All four specified sleep problems were associated with significantly higher parent-reported SDQ total-score (OR 1.1 for all), and except for not recommended sleep duration, also with higher teacher-reported SDQ total-score (OR 1.1 for all). Daytime sleepiness was strongly associated with wheezing last 12 months (OR 3.4), disturbed sleep due to wheezing (OR 3.9), wheeze during or after exercise (OR 2.9), use of inhaled corticosteroids or oral leukotriene modifiers (OR 3.4) and use of bronchodilators (OR 3.9). Snoring was associated with wheezing during or after exercise (OR 2.8) and current asthma (OR 4.2).

**Conclusion** EPT children with different types of sleep problems had more behavioural and respiratory health problems than EPT children without sleep problems.

## INTRODUCTION

Sleep is critical for development, maturation and health on the journey from infancy to adulthood.<sup>1</sup> Sleep problems in children have been associated with asthma and other respiratory symptoms,<sup>2</sup> and with mental health problems, such as conduct problems, hyperactivity and emotional problems.<sup>3–5</sup> Children with neurological disabilities often have sleep problems,<sup>6</sup> but somatic and mental

## What is known about the subject?

- ▶ School-aged extremely preterm (EPT) children are at increased risk of sleep problems, behavioural problems and respiratory symptoms.
- ▶ Whether sleep problems are associated with behavioural problems and respiratory symptoms in school-aged EPT children, have not been explored previously.

## What this study adds?

- ▶ Sleep disturbances in EPT children were strongly linked to behavioural problems and to respiratory symptoms.
- ▶ The study suggests that sleep disturbances may be an overlooked area of concern in EPT children.

comorbidities may contribute to these problems.<sup>7–9</sup>

We have previously shown that children born extremely preterm (EPT) have more sleep problems throughout childhood than children born at term, and that the prevalence increases with the degree of neurodevelopmental disability.<sup>10</sup> Children born EPT are also at increased risk of behavioural problems and respiratory morbidities,<sup>11 12</sup> but we do not know how such difficulties affect their sleep.

We hypothesised that sleep problems at 11 years in children born EPT are associated with behavioural problems and respiratory symptoms and aimed to explore the significance of these relationships by addressing four specified sleep problems: difficulty falling asleep or frequent awakenings, snoring, daytime sleepiness and insufficient sleep duration.



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## METHODS

### Population

The study population was a national cohort of all children born EPT ( $n=372$ ) in Norway during 1999–2000. EPT was defined as gestational age (GA) <28 completed weeks or birth weight (BW) <1000 g. The children were prospectively followed from birth and assessed at 2, 5 and 11 years of age. Method for determination of GA and overall outcome in terms of mortality and morbidities until 11 years have been published previously.<sup>9 13–16</sup> At 11 years, we obtained information on the families' sociodemographic characteristics and lifestyles, and the children's health, including sleep characteristics, behavioural issues and respiratory health, from postal questionnaires completed by the parents (for behaviour also the children's teacher). EPT children with severe disability were included. (The degree of neurodevelopmental disability was assessed by clinical examination when the children were 5 years old.<sup>10</sup>)

### Sleep problems

The parents assessed the sleep problems in terms of whether their child had difficulty falling asleep or had frequent awakenings, snored or had daytime sleepiness. The response options to these questions were 'Not true', 'Partly true' and 'Absolutely true'. In our analyses, the responses 'Partly true' and 'Absolutely true' were merged and defined as a sleep problem. Sleep duration was assessed by the following items: at what time their child went to bed and got up on weekdays, how long time it took from going to bed until falling asleep (sleep onset latency) and how long the child was awake during the night after sleep onset. We calculated total sleep duration as the time in bed minus sleep onset latency and time awake after sleep onset. In accordance with recently published guidelines, recommended sleep duration at 11 years was defined as 9–11 hours.<sup>17</sup> The same sleep variables have been used in a previous paper.<sup>18</sup>

### Behavioural problems

Parents and teachers completed the Strengths and Difficulties Questionnaire (SDQ). SDQ is a general behavioural screening questionnaire for 4–17-year-old children and has good psychometric properties also for children born preterm.<sup>19 20</sup> It contains five items in each of four subscales: emotional problems, hyperactivity/inattention, conduct problems and peer problems. Each item is scored on a three-point scale; 'Not true' (0), 'Somewhat true'<sup>1</sup> and 'Certainly true'.<sup>2</sup> The total subscale score ranges from 0 to 10 and the total score from 0 to 40.

### Respiratory health

The parents completed the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire<sup>21</sup> which contains the following questions on respiratory symptoms during the last 12 months: did your child experience wheezing or whistling in the chest and, if so, how many attacks; how often was the child's sleep disturbed

due to wheezing; was wheezing ever so severe that the child had trouble saying more than one or two words at a time between breaths; did the child's chest sounded wheezy during or after exercise; and did the child have a dry cough at night, apart from cough associated with a cold or chest infection.

We also asked for current use of asthma medications, including inhaled corticosteroids, short or long acting  $\beta_2$ -agonists and oral leukotriene modifiers, and whether the child had ever been diagnosed with asthma. Current asthma was defined as yes to 'ever asthma' combined with either respiratory symptoms or use of asthma medication during the previous 12 months, or asthma medication and symptoms during the past 12 months regardless of reporting asthma.

### Statistical analyses

For each specific dichotomised sleep outcome variable, the groups were compared according to the results on the SDQ, ISAAC, current asthma versus no asthma, use versus no use of inhaled corticosteroids or oral leukotriene modifiers, and use versus no use of inhaled bronchodilators.

Group comparisons were performed using Student's  $t$ -tests,  $\chi^2$  tests or Fisher's exact tests. ORs and 95% CIs were calculated after adjusting for sex, single parenthood and maternal education (dichotomised as a 3-year college education or not) in logistic regression analyses. Significance level was set at  $\alpha$ -level 0.05. We also performed subanalyses where we included small for gestational age (SGA) as a covariate. This was done for the SDQ and for the questions about respiratory health. SGA was defined as a BW below the 10th percentile.<sup>22</sup> For the questions about respiratory health, subanalyses were also made in which information about current smoking among parents (mother or father) was included as a covariate

### Patient and public involvement

Patient representatives were involved in this national follow-up study.

## RESULTS

Sleep and ISAAC data were obtained for 216/372 (58%) children. SDQ was completed by the parents for 215 and by the teachers for 184 of them. Difficulty falling asleep or frequent awakenings was reported for 27.3%, snoring for 28.0%, daytime sleepiness for 17.1% and sleep duration less than the recommended 9 hours for 24.1% of the children. None of the children slept more than recommended. There were no significant sex differences regarding the prevalence of the specified sleep problems. The average total SDQ score was 8.8 and the prevalence of current asthma was 18%. Of the 216 participating children, six had severe disability at age 5 years. Parent and child characteristics are described in [table 1](#). Participants and non-participants did not differ regarding GA or the ratio of SGA, bronchopulmonary dysplasia or

**Table 1** Characteristics of the 216 of 372 eligible children who were born extremely preterm\* in Norway in 1999–2000 and participated in the follow-up at 11 years of age

Family background	% (n)
Single parent	8.8 (19)
Higher education mother†	68.8 (148)
Higher education father‡	45.1 (96)
Demographic characteristics	Mean (range)
Gestational age, weeks	26.6 (23.0–32.0)
Birth weight, grams	869 (450–1370)
	% (n)
Small for gestational age‡	18.1 (39)
Boy	51.4 (111)
Severe disability§ (based on clinical examination at 5 years)	3.3 (6)
Current smoking, mother or father	35.2 (76)

\*Gestational age <28 weeks or birth weight <1000 g.

†College or university education when the child was 11 years old.

‡Small for gestational age: birth weights <10th percentile.<sup>22</sup>

§Severe disability defined as one or more of the following: cerebral palsy class 4–5 on the Gross Motor Function Classification System for Cerebral Palsy, Full intelligence quotient (IQ) score more than 3SDs below the reference mean value of 100, legal blindness, or complete deafness.<sup>10</sup>

retinopathy of prematurity, but there was a tendency for less severe disability among the participants (3.3% (n=6) vs 9.8% (n=12)).

### Sleep problems and behavioural problems

The children who had difficulty falling asleep or frequent awakenings had a higher parent-reported SDQ total-score, and they had higher scores on all four subscales compared with the children who did not have this sleep problem. They also had a higher teacher-reported SDQ total-score and a higher teacher-reported emotional problems score (table 2). The children who snored had a higher parent-reported and teacher-reported SDQ total-score and a higher score on conduct problems than the children who did not snore. The children who snored had also more emotional problems (see table 2 for details).

The children with daytime sleepiness had a higher parent-reported and teacher-reported SDQ total-score and a higher score on emotional problems than children without daytime sleepiness. The parents also reported that these children also had more hyperactivity/inattention problems and peer problems. The children who had a sleep duration of less than the recommended 9 hours, had a higher parent-reported SDQ total-score than the children who slept longer (table 2). The association between the specified sleep problems and the respective SDQ scores remained unchanged after including SGA (n=60) as a covariate in the adjusted analysis, except for the association between snoring and teacher-reported conduct problems which became non-significant (data not shown).

### Sleep problems and respiratory health

The children who had difficulty falling asleep or frequent awakenings more often had wheezing during the last 12 months, but the association did not remain significant after adjustment (table 3). Only two children had problems with speaking due to wheezing. This question was therefore not included in the further analyses.

Snoring was associated with wheezing during or after exercise, current asthma and use of bronchodilators (table 3). Daytime sleepiness was associated with wheezing during the last 12 months, disturbed sleep due to wheezing, wheeze during or after exercise, use of inhaled corticosteroids or oral leukotriene modifiers and use of bronchodilators (table 3). Sleep duration less than recommended was associated with disturbed sleep due to wheezing and use of inhaled corticosteroids or oral leukotriene modifiers (table 3). The association between these specified sleep problems and the respiratory health problems remained unchanged after including SGA and the parents' current smoking habits (mother or father smoking) as covariates in the adjusted analysis (data not shown).

### DISCUSSION

In this nationwide cohort of EPT children, sleep problems were significantly associated with behavioural and respiratory health problems. Difficulty falling asleep or frequent awakenings, snoring and daytime sleepiness were associated with more parent-reported and teacher-reported behavioural problems, whereas sleeping less than recommended was associated with more parent-reported behavioural problems. The sleep problems, and especially daytime sleepiness, were strongly associated with respiratory symptoms, asthma and use of asthma medication.

The average total SDQ scores in our study were higher (total score 8.8) than previously found in unselected Norwegian children (total score 5.4).<sup>11</sup> The prevalence of current asthma (18%) was higher than the prevalence of 11% in an unselected Norwegian cohort of 10-year-old children.<sup>23</sup> Thus, this EPT cohort had more respiratory,<sup>24</sup> behavioural<sup>11</sup> and sleep problems<sup>10</sup> in mid-childhood than Norwegian children who were not prematurely born, underscoring the overall vulnerability in these children. To what extent such difficulties are interrelated in children born preterm have not been extensively explored.

In a small study of children born at GA less than 32 weeks, Perkinson-Gloor *et al* found that less restorative sleep was associated with more behavioural problems as reflected in higher SDQ-scores.<sup>25</sup> However, they did not find more nocturnal awakenings or shorter sleep duration compared with their control group, nor did they find that total sleep time or nocturnal awakenings were associated with SDQ total-scores. Caravale *et al* studied 2-year-old preterm children (mean GA 31 weeks), and found that they had more frequent sleep difficulties

**Table 2** Parent-reported sleep problems in relation to behavioural problems in 11-year-old children born extremely preterm† in Norway during 1999 and 2000

SDQ scores	Difficulty falling asleep or frequent awakenings				Snoring		Daytime sleepiness			Not recommended sleep duration‡		
	No (n=143) mean	Yes (n=54) mean	Adjusted\$ (n=195) OR (95% CI)	No (n=144) mean	Yes (n=55) mean	Adjusted\$ (n=197) OR (95% CI)	No (n=165) mean	Yes (n=33) mean	Adjusted\$ (n=196) OR (95% CI)	No (n=104) mean	Yes (n=32) mean	Adjusted\$ (n=135) OR (95% CI)
<b>Parent-reported</b>												
Emotional problems	2.2	3.8***	1.4 (1.2 to 1.6)	2.4	3.2*	1.2 (1.0 to 1.3)	2.3	3.9***	1.4 (1.1 to 1.6)	2.4	3.3	1.2 (0.9 to 1.4)
Conduct problems	0.9	1.5*	1.3 (1.1 to 1.7)	1.0	1.4*	1.3 (1.0 to 1.6)	1.0	1.5	1.3 (0.9 to 1.7)	1.0	1.4	1.2 (0.9 to 1.6)
Hyperactivity/inattention problems	3.2	4.6**	1.2 (1.1 to 1.4)	3.4	4.0	1.1 (0.9 to 1.2)	3.4	4.6*	1.2 (1.0 to 1.4)	3.3	4.4	1.2 (0.9 to 1.3)
Peer problems	1.2	2.1**	1.3 (1.1 to 1.5)	1.3	1.8	1.2 (0.9 to 1.4)	1.3	2.1*	1.2 (1.0 to 1.5)	1.4	1.6	1.1 (0.9 to 1.4)
Total difficulties	7.6	11.9***	1.1 (1.1 to 1.2)	8.0	10.4*	1.1 (1.0 to 1.1)	8.0	12.1***	1.1 (1.1, 1.2)	7.9	10.6*	1.1 (1.0 to 1.1)
<b>Teacher-reported</b>												
Emotional problems	1.5	2.7**	1.2 (1.1 to 1.4)	1.7	2.3	1.1 (0.9 to 1.3)	2.0	2.7**	1.3 (1.1 to 1.5)	1.7	1.9	1.1 (0.9 to 1.3)
Conduct problems	1.0	1.5	1.3 (0.9 to 1.7)	0.5	0.9*	1.4 (1.0 to 1.8)	1.1	1.6	1.2 (0.9 to 1.6)	0.5	0.7	1.3 (0.8 to 2.1)
Hyperactivity/inattention problems	2.9	3.8	1.1 (1.0 to 1.3)	2.9	3.8*	1.1 (1.0 to 1.3)	2.9	3.9	1.2 (0.9 to 1.3)	3.2	3.4	1.0 (0.9 to 1.2)
Peer problems	1.3	1.8	1.1 (0.9 to 1.3)	1.2	2.0*	1.2 (1.0 to 1.4)	1.4	1.9	1.1 (0.9 to 1.4)	1.7	2.1	1.1 (0.9 to 1.4)
Total difficulties	6.3	9.1**	1.1 (1.0 to 1.1)	6.2	9.0**	1.1 (1.0 to 1.1)	6.5	9.6*	1.1 (1.0 to 1.2)	6.6	7.7	1.0 (0.9 to 1.1)

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001 (t-test). Boldface denotes significant group differences.

†Gestational age <28 weeks or birth weight <1000g.

‡Not recommended sleep duration at 11 years was defined as <9 hours.

\$Logistic regression: adjusted for sex, single parenthood and maternal education (dichotomised as less than a 3-year college education or not). SDQ, Strengths and Difficulties Questionnaire.



**Table 3** Parent-reported sleep problems in relation to respiratory health in 11-year-old children born extremely preterm† in Norway during 1999 and 2000

	Difficulty falling asleep or frequent awakenings		Snoring		Daytime sleepiness		Not recommended sleep duration‡					
	No (n=144) % (n)	Yes (n=54) % (n)	Adjusted§ (n=146–197) OR (95% CI)	No (n=144) % (n)	Yes (n=56) % (n)	Adjusted§ (n=148–199) OR (95% CI)	No (n=165) % (n)	Yes (n=34) % (n)	Adjusted§ (n=147–198) OR (95% CI)	No (n=104) % (n)	Yes (n=33) % (n)	Adjusted§ (n=95–136) OR (95% CI)
<b>Last 12 months at 11 years age¶</b>												
Wheezing (yes)	17.3 (18)	32.6 (14)*	2.1 (0.9 to 4.9)	20.8 (22)	27.9 (12)	1.4 (0.6 to 3.3)	17.8 (21)	40.0 (12)**	3.4 (1.4 to 8.3)	13.9 (10)	29.2 (7)	2.5 (0.8 to 8.1)
Number of attacks last 12 months**												
None	0 (0)	21.4 (3)		13.6 (3)	9.1 (1)		4.8 (1)	27.3 (3)		10.0 (1)	33.3 (2)	
1–3	52.9 (9)	57.1 (8)		59.1 (13)	45.5 (5)		61.9 (13)	36.4 (4)		50.0 (5)	50.0 (3)	
>4	47.1 (8)	21.4 (3)		27.3 (6)	45.5 (5)		33.3 (7)	36.4 (4)		40.0 (4)	16.7 (1)	
Disturbed sleep due to wheezing (yes)††	6.8 (7)	16.3 (7)	2.6 (0.8 to 8.1)	7.6 (8)	14.0 (6)	1.8 (0.6 to 5.8)	6.0 (7)	20.0 (6)*	3.9 (1.2 to 13.0)	1.4 (1)	16.7 (4)	§§
Wheeze during or after exercise (yes)	15.5 (22)	22.2 (12)	1.4 (0.6 to 3.2)	12.6 (18)	29.1 (16)**	2.8 (1.3 to 6.1)	14.1 (23)	32.4 (11)*	2.9 (1.2 to 6.8)	12.9 (13)	15.2 (5)	1.0 (0.3 to 3.3)
Dry cough at night (yes)	15.4 (22)	20.4 (11)	1.4 (0.6 to 3.2)	13.9 (20)	25.5 (14)	2.1 (0.9 to 4.6)	15.9 (26)	23.5 (8)	1.6 (0.7 to 4.0)	10.7 (11)	12.5 (4)	1.2 (0.4 to 4.2)
<b>Currently at 11 years age</b>												
Current asthma (criteria-based)‡‡	18.2 (26)	20.8 (11)	1.1 (0.5 to 2.5)	11.9 (17)	36.4 (20)***	4.2 (1.9 to 8.9)	17.2 (28)	29.4 (10)	1.9 (0.9 to 4.7)	9.8 (10)	21.2 (7)	2.6 (0.9 to 7.6)
Asthma medication use												
Inhaled corticosteroids or oral leukotriene modifiers	8.3 (12)	16.7 (9)	2.3 (0.9 to 5.9)	8.3 (12)	17.9 (10)	2.4 (0.9 to 5.9)	8.5 (14)	23.5 (8)*	3.4 (1.3 to 9.0)	3.8 (4)	18.2 (6)*	5.6 (1.5 to 21.9)
Inhaled bronchodilators	9.0 (13)	14.8 (8)	1.9 (0.7 to 5.1)	7.6 (11)	19.6 (11)*	3.2 (1.3 to 8.2)	8.5 (14)	23.5 (8)*	3.9 (1.4 to 10.9)	5.8 (6)	15.2 (5)	3.4 (0.9 to 12.6)

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001 (χ<sup>2</sup> test or Fisher's exact test). Boldface denotes significant group differences.

†Gestational age <28 weeks or birth weight <1000g.

‡Not recommended sleep duration at 11 years was defined as <9 hours.

§Logistic regression: adjusted for sex, single parenthood and maternal education (dichotomised as less than a 3-year college education or not).

¶The International Study of Asthma and Allergies in Childhood questionnaire.

\*\*The response options to the number of attacks were 'none', '1–3', '4–12' and 'more than 12'. We merged the answer '4–12' attacks and 'more than 12' attacks to '>4' attacks.

††The response option was: 'never woken', 'less than one night per week' and 'one or more nights per week'. In our analyses, the answers 'less than one night per week' and 'one or more nights per week' were merged into a yes.

‡‡Current asthma was defined as yes to 'ever asthma' combined with either respiratory symptoms or use of asthma medication in the previous 12 months, or asthma medication and symptoms in the past 12 months regardless of reporting asthma.

§§Adjusted analyses not performed due to low number.

¶¶



during the night, and that these difficulties were related to problems with emotions and attention,<sup>26</sup> which is in agreement with our findings. It is worth noting that Perkinson-Gloor *et al* excluded children with severe developmental delay<sup>25</sup> and that Caravale *et al* included only children with normal cognitive, language, and motor development<sup>26</sup> as opposed to no selections in our study.

Our finding that sleep problems and behavioural problems were associated is in agreement with what has been reported for young children who were not born preterm,<sup>27</sup> suggesting that studies on sleep and behavioural problems among children in general may be applicable also for children born EPT. Insomnia and restless sleep have been linked to emotional problems, hyperactivity/inattention problems, conduct problems and peer problems as assessed by SDQ.<sup>28</sup> Moreover, daytime sleepiness was associated with emotional problems, conduct problems and hyperactivity/inattention problems in term born children measured by SDQ of Hestetun *et al*.<sup>29</sup> These are findings that are in line with our observations in EPT-born children, strengthening the notion that sleep problems are likely to be similarly involved in mental health issues in preterm as well as term-born children.

Snoring in term-born children has also been associated with emotional problems, conduct problems and hyperactivity/inattention problems as assessed by SDQ.<sup>30</sup> Correspondingly, we found more emotional and conduct problems, but not more hyperactivity/inattention problems among our snoring EPT children. Snoring is a common symptom of sleep disordered breathing (SDB), and previous studies have shown that children born prematurely have an increased risk of SDB.<sup>31–35</sup> The prevalence SDB during childhood in children born EPT is unknown. In general, SDB in childhood is a risk factor for behavioural problems, externalising symptoms and inattention. More studies are needed to map the association between SDB and behavioural problems in children born EPT.

Our finding that insufficient sleep duration was associated with higher SDQ total-scores is in agreement with findings of an association between short sleep duration and emotional problems, conduct problems and hyperactivity/inattention problems in an unselected cohort of Norwegian children of similar age.<sup>36</sup>

We are unaware of other studies that have addressed relationships between respiratory symptoms and sleep in children born EPT, but our finding that several sleep problems were associated with wheezing and asthma is in agreement with similar findings in children born at term.<sup>37–39</sup> Although respiratory symptoms in EPT-born children resemble asthma, the pathophysiology of lung disease after preterm birth is different which, for instance, is reflected in that the disease is unresponsive to inhaled corticosteroids.<sup>12 40–42</sup> Their burden of respiratory symptoms may therefore be substantially higher, and more chronic<sup>16</sup> and therefore more easily overlooked. For example, it is conceivable that poor sleep due to respiratory problems may cause daytime sleepiness and

contribute to inattention and learning difficulties which are major challenges for children born EPT.<sup>43 44</sup> Previous studies on term-born children have shown that nocturnal awakening due to asthma is a risk factor for poor school functioning.<sup>45</sup>

The strengths of the present study were the national population-based sample of EPT children, the prospective design, the assessment of behavioural problems by both parents and teachers, and the use of validated instruments for assessing both behavioural problems and respiratory symptoms. The limited response rate at follow-up was a weakness. However, we found that for most variables the assessed children were representative of all survivors at the age of 11 years. We adjusted for single parenthood, maternal education and sex in our analyses, and in subanalyses we also adjusted for SGA and current smoking among parents. We cannot, however, exclude residual confounding. We did not correct for multiple testing, and therefore, the results must be interpreted with caution. Other limitations were lack of detailed information about socioeconomic status, the child's sleep environment, what season the parents answered the questionnaires, and whether the children had been treated for snoring or for sleep problems.

## CONCLUSIONS

In the present study, behavioural problems and respiratory symptoms were strongly associated with sleep disturbances in 11-year-old children born EPT. The associations were similar to what has been found in unselected groups of children. Given the high prevalence of behavioural problems and respiratory symptoms after preterm birth, the study suggests that sleep disturbances may be an overlooked area of concern in preterm born children, and that questions mapping sleep should be included when seeing these children in clinics.

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**Contributors** KMS has conceptualised and designed the study, analysed and interpreted the data, drafted and revised the manuscript critically for important intellectual content and has approved that this version of the manuscript was published. MH, IBE, TH and BB have participated in the concept and design, interpretation of the data and have revised the manuscript and have approved that this version of the manuscript was published. TM has acquired the data, participated in the concept and design, interpretation of the data and has revised the manuscript and has approved that this version of the manuscript was published.

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