Disturbed sleep in children born extremely preterm is associated with behavioural and emotional symptoms

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Abstract

Aim: To determine whether children born extremely preterm are at increased risk for sleep disturbances and to explore relationships between extremely preterm birth, sleep and Attention Deficit and Hyperactivity Disorder (ADHD) and emotional symptoms.

Method: EPICure2 cohort study. Parents of 165 children born ≤26 weeks' gestation (53% male) and 121 children born at term (43% male) completed the Children's Sleep Habits Questionnaire, sleep disordered breathing subscale of the Pediatric Sleep Questionnaire, the emotional problems scale of the Strengths and Difficulties Questionnaire and the ADHD Rating Scale-5 at 11 years of age.

Results: Extremely preterm children had greater habitual snoring (adjusted odd ratio 6.8; 95% confidence interval 2.3, 20.3), longer sleep onset latency (Cohen's *d* 0.33), more severe night waking (*d* 0.44) and more daytime sleepiness (*d* 0.40) than term-born children; there was no between-group difference in sleep duration. Among children without severe disability, night waking partially mediated the relationship between preterm birth and inattention (additional 5% of variance explained), hyperactivity/impulsivity (13%) and emotional problems (9%). Snoring partially mediated the relationship between preterm birth, hyperactivity/impulsivity and inattention (additional 1-5% of variance).

Conclusion: Children born extremely preterm are at increased risk of disturbed sleep compared to term-born children. As night waking partially mediated the relationship between preterm birth and ADHD symptoms and emotional problems, reducing sleep disturbance may improve sleep and reduce attention and emotional problems in this population.

(227 words)

Keywords: Sleep, preterm birth, childhood, emotional problems, ADHD

Introduction

Compared with children born at term, children born extremely preterm (<28 weeks' gestation) are at increased risk of emotional problems and attention-deficit/hyperactivity disorder (ADHD) [1]. These problems may be exacerbated by sleep disturbances given the association between disturbed sleep and psychiatric disorders in the general population [2]. Indeed, sleep disturbances may be increased following extremely preterm birth. Immaturity of breathing control and severity of respiratory disease during the neonatal period may contribute to the risk of sleep disordered breathing (SDB) later in childhood [3]. Moreover, the neonatal unit environment does not optimise sleep; very preterm (<32 weeks' gestation) infants are sensitive to small variations in light levels which can result in fragmented sleep [4]. Beyond the neonatal period, very preterm children have been shown to sleep for shorter periods at night at 12 months of age, and actigraphy data at 20 months of age indicate poorer sleep quality in children born <34 weeks' gestation compared with term-born controls [5,6].

The few studies that have assessed sleep in preterm populations later in childhood have revealed mixed findings. Using parent reports, some have reported no difference in sleep problems in children born very preterm compared with term-born controls at 10 years of age [7], whilst others have found significant differences in specific components of parent reported sleep problems. For example, at 5-9 years of age, very preterm children had greater difficulty initiating and maintaining sleep, more frequent symptoms of sleep disordered breathing (SDB) and sleep-wake transition disorders, including rhythmic movement disorders, involuntary movements, sleep-talking and teeth-grinding than term-born peers [8]; however there was no between-group difference in daytime somnolence [8]. School-aged children born extremely preterm or with extremely low birthweight (ELBW; <1000g), were reported to have longer sleep duration, earlier bedtimes and longer sleep onset latency, and to be more likely to wake frequently during the night, have difficulty falling asleep and wake unusually early in the morning compared with term-born children [9].

Studies using more objective measures of sleep have also reported mixed findings. Using polysomnography, an excess of night waking was observed among very preterm children without severe developmental delay compared with term-born children at 8 years of age, however no difference in sleep duration or sleep efficiency was observed [10]. At 9 years of age, polysomnography revealed shorter sleep duration, a higher percentage of the sleep period spent awake and poorer sleep efficiency in children born at 24-36 weeks of gestation with appropriate weight for gestational age compared with children born at term [11]. In contrast, a study using electroencephalogram (EEG) found no difference in measures of sleep quality and duration between children born very preterm and at term at a mean age of 13 years, although this sample excluded children with below average IQ [12]. In the only study that has used actigraphy, children with birthweight <1250g had shorter sleep duration than population recommendations at 5-12 years of age [13]. A recent systematic review concluded that, when taking into account study quality, there is strong evidence for more night waking and moderate evidence for earlier bedtimes in children born preterm [14], but more research is needed among children born at the most preterm gestations.

Preterm birth is also a recognised risk factor for obstructive SDB [15]. Individuals born extremely preterm have been shown to have a 2.6-fold (95% confidence interval (CI) 2.4, 2.9) increased risk of SDB throughout childhood and mid-adulthood [16]. Chronic snoring (≥1-2 times a week) was also more prevalent among school-aged children born <36 weeks' gestation compared with those born at term (21% vs. 14%)[17] and in young adults born <1500g compared with individuals born at term at appropriate weight for gestational age (odds ratio (OR) 2.2; 95% CI 1.1, 4.5) [18]. Higher slow wave sleep in the second non-Rapid Eye Movement (REM) period of the night has been observed among children born <37 weeks' gestation with snoring/SDB compared with children born at term with snoring/SDB [19]. The authors proposed that this indicates an accumulation, and reduced dissipation, of sleep debt. As such, SDB may confer additional risk for daytime sleepiness and subsequent behaviour problems in children born preterm relative to children born at term [19]. Indeed, very preterm children without severe developmental delay have a pattern of sleep macro-architecture that indicates less restorative sleep than term-born children, represented by the ratio of slow wave sleep to non-REM sleep stages 1 and 2 [20]. This was found to partially mediate the relationship between very preterm birth and a composite measure of emotional, conduct, ADHD and peer problems in children aged 6-10 years [20]. Whilst the causal mechanisms implicating snoring in behavioural problems are unknown, parent-reported snoring two or more times a week was a stronger predictor of hyperactivity, inattention, psychosomatic, internalising and externalising problems than polysomnography-assessed and sleep-expert-scored apnea-hypopnea index severity in a community sample of children aged 6-10 years [21]. The only study in children born extremely preterm/ELBW showed that, at age 11, those children who snored had significantly greater emotional and conduct problems and there were trends towards higher hyperactivity/inattention and peer problems than extremely preterm/ELBW children who did not snore [22].

Regarding the association between sleep disturbance and behaviour, only one study has investigated this relationship in extremely preterm children [22]. Greater difficulties falling asleep or waking frequently were associated with greater emotional, conduct, hyperactivity/inattention and peer problems at age 11 years [22]. Sleep disturbances such as difficulties falling asleep, sleep duration or night wakings may be impacted by daytime behaviour and environmental influences, but snoring, a physiological problem would not be. Using cross-lagged longitudinal data from the ages of 10 to 13 years, externalising problems predicted parent-reported sleep problems but not vice versa, but emotional problems were only predicted by sleep, not vice versa [23]. Moreover, sleep scores were associated with concurrent emotional problems (r=0.64) and externalising problems (r=0.46) at age 10-11 [23]. Conversely, in the general population, there was a concurrent relationship between sleep and ADHD symptoms at age 10, but not at age 12 or 13. Neither sleep nor ADHD symptoms significantly predicted or were predicted by each other between the ages of 10 and 13 years in one cohort, but ADHD symptoms at age 10 did significantly predict sleep disturbance at age 11 in a different cohort [24]. As there is mixed evidence as to whether sleep problems predict or are predicted by behavioural problems in the general population [23,24], models should test bi-directional relationships between sleep and emotional/behavioural problems, where sleep problems can be considered both the outcome and predictor.

In summary, previous research suggests that there may be an excess of sleep disturbances and snoring/SDB in children born extremely preterm and that these may mediate the association with ADHD and emotional symptoms, or vice versa. Understanding these associations is important for identifying potential targets for intervention. The aims of the present study were to (1) determine whether children born extremely preterm are at increased risk for sleep disturbances and snoring/SDB, and (2) explore relationships between extremely preterm birth, sleep, snoring and ADHD and emotional symptoms.

Method

Participants

The EPICure2 Study comprised all births ≤26 weeks' gestation in England during 2006. Cohort descriptors and data on IQ and neurodevelopmental disability have previously been published [25]. Of 1041 survivors to discharge, invitations to take part in an 11-year assessment were sent to the parents of 482 children admitted for care in 17 of the 45 neonatal units and their networked hospitals operating in 2006. A comparison group of children born at term (≥37 weeks' gestation) was recruited from classmates of the same age (±3 months) and sex as extremely preterm children attending mainstream schools. Up to three classmates for each child born extremely preterm were invited. For extremely preterm children who were assessed at home, a term-born friend of the same age and sex was identified by the parents of the preterm child where possible. Data were collected between June 2017 and December 2018.

Measures

Sleep disturbance: Parents completed the Children's Sleep Habits Questionnaire (CSHQ) from which sub-scale scores for sleep duration (3 items), sleep onset latency (1 item), night waking (3 items) and daytime sleepiness (8 items) were derived [26]. Higher scores indicate more severe problems. Sub-scale scores were not computed for children with missing items.

SDB: Parents completed the SDB subscale of the Pediatric Sleep Questionnaire (PSQ) comprising 22 items [27]. For missing items, the score was pro-rated using the mean score on non-missing items. Children with >3 missing items were excluded. Scores ≥0.33 were used to classify children with SDB. This cut-off identified 85% of individuals with an Apnea/Hypopnea Index >5 with 0.81 sensitivity and 0.87 specificity in a previous study [27]. Habitual snoring (snore more than half the time) was used to model the relationship between SDB and ADHD symptoms as this was a strong predictor of hyperactivity in a paediatric sample [28].

ADHD symptoms: Parents completed the Du Paul ADHD Rating Scale-5 (ADHD-RS-5) [29]. This yields sub-scale scores for inattention (9 items) and hyperactivity/impulsivity (9 items). Higher scores indicate greater symptom severity. Items were prorated at the sub-scale level using the mean of the completed items if ≤3 were missing. Children with >3 missing items were excluded.

Emotional problems: Parents completed the Strengths and Difficulties Questionnaire (SDQ) emotional problems sub-scale (5 items) [30]. If ≤2 items were missing, item scores were prorated using the mean of the completed items. These items were: "Often complains of headaches, stomach aches or sickness"; "Many worries, often seems worried"; "Often unhappy, down-hearted or tearful"; "Nervous or clingy in new situations, easily loses confidence"; and "Many fears, easily scared".

See supporting information for further information about these measures.

IQ: IQ was assessed using the Mental Processing Index (MPI) from the Kaufman Assessment Battery for Children 2nd Edition (KABC-II[31]). Where this could not be completed due to severe cognitive impairment, a nominal score one point below the basal score was assigned (MPI=42). Scores were not substituted for children failing to complete the test for other reasons (e.g., lack of time, poor attention/cooperation).

Neurodevelopmental disability: A clinical assessment of vision, hearing and motor function was performed. Severe disability was classified where the child had one or more of: MPI scores more than 3 SD below the control mean (score <67); Gross Motor Function Classification Scale (GMFCS)/Manual Abilities Classification Scale (MACS)[32,33] level ≥3; no useful hearing with aids; sees gross light/movement only or no useful vision.

Body mass index (BMI): Weight and height were measured and children were classified as overweight or obese (vs normal weight or thinness) according to international standards using age- and sex-specific BMI cut-offs [34,35].

Socio-economic status (SES): The Office for National Statistics' Index of Multiple Deprivation (IMD)[36] was obtained using the child's postcode of residence at the time of assessment. IMD ranks were used to derive deciles based on the English population with Decile 1 (most deprived) to Decile 10 (least deprived) as an index of SES.

Statistical analysis

Analyses were conducted using SPSS v25 and STATA 15.1. As both sex and SES are associated with sleep disturbance [37,38], between-group analyses were adjusted for sex and SES using ANCOVA. Effect sizes were quantified using Cohen's d [39]. Adjusted ORs were calculated using binary logistic regression for dichotomous outcomes.

Mediation analyses were conducted using hierarchical and binary logistic regression and evaluated using the causal steps approach as two of the models used a binary mediator [40]. Children with severe disability were excluded from the mediation analyses as severe disability was associated with night waking (beta=.37, p<.001, R^2=.14) and habitual snoring (OR 4.94, 95% CI 1.97, 12.37). Excluding children with severe disabilities avoids the confound of disability explaining variance in the mediator between the extremely preterm and the term-born group. Sex and IMD were added as covariates for all paths. For mediation to be evidenced, a significant association should be observed between the independent variable (X) and mediating variable (M) (path a), the mediating variable (M) and dependent variable (Y) (path b), and between the independent (X) and dependent variable (Y) (path c). To evidence partial mediation, the strength of X to predict Y should be lower when the mediating variable is controlled for (path c') (Figure 1). Night waking was chosen as the primary measure of sleep quality as this subscale is correlated (r=0.47) with both actigraphy-assessed night wakings and actigraphy-assessed sleep duration (r=-0.42), whilst other subscales do not correlate with actigraphy measurements [41].

Six mediation models were conducted: three with inattention, hyperactivity/impulsivity and emotional problems as the mediator between extremely preterm birth status and night waking, and three reverse mediation models with night waking as the mediator between extremely preterm birth and inattention, hyperactivity/impulsivity and emotional problems. Two mediation models for snoring were tested with habitual snoring as the mediator between extremely preterm birth and inattention and hyperactivity/impulsivity. Six items on the SDB subscale relate to ADHD symptoms, therefore meeting the SDB cut-off could not be used as an independent predictor of ADHD symptoms. Extremely preterm children without a severe disability who snored did not have significantly higher scores on the emotional problems subscale compared with extremely preterm children who did not snore (see Table S1), therefore the mediation model for snoring as a mediator between extremely preterm birth and emotional problems was not constructed. As behavioural symptoms would not influence snoring only unidirectional models were tested. The Benjamini-Hochberg procedure was used to correct for multiple comparisons [42].

Results

Sample characteristics

Of 482 extremely preterm-born children invited, 220 participated of which 200 were assessed (41.5% of invited children; 19.2% of survivors to discharge). There was no significant difference in clinical characteristics between children born extremely preterm who were assessed and not assessed at 11 years of age (Table 1). Of those assessed, the parents of 170 (85%) completed study questionnaires. MPI scores were substituted for 5 extremely preterm children. 143 term-born children were recruited and assessed of which the parents of 125 (87%) returned questionnaires. Of participants with returned questionnaires, data for 5 extremely preterm children and 4 term-born children were excluded due to missing IMD scores. Thus, the final sample with returned questionnaires and IMD data comprised 165 extremely preterm and 121 term-born children. Due to missing items on the sleep questionnaires, the total number of participants for each subscale score/item is reported in Tables 3 and S2.

Table 1. Comparison of children in the EPICure-2 cohort assessed and not assessed at age 11 years.

	Assessed at age 11 (n=200)	Not Assessed at age 11 (n=831)[a]	Mean difference (95% CI) Assessed vs Not Assessed	P
Male sex, n (%)	100 (50.0)	399 (48.0)	-	0.61
Gestational age, Mean (SD)	25.6 (1.0)	25.6 (0.9)	<0.1 (-0.1, 0.2)	0.79

Birthweight z score, Mean (SD)	-0.2 (0.8)	-0.3 (0.8)	0.1 (-<0.1, 0.2)	0.16
IMD decile at infancy, Mean (SD)	4.5 (2.7)	4.3 (2.9)	0.2 (-0.2, 0.7)	0.29
IMD decile at 3 years, Mean (SD)	4.8 (2.7)	5.0 (3.0)	-0.3 (-0.8, 0.3)	0.36

[a]Denominator is all children alive at the 3-year assessment. IMD: Index of Multiple Deprivation.[36]

There was no significant difference in age, IMD, sex or BMI category between extremely preterm and term-born children (Table 2). Twenty-nine (18%) extremely preterm children had severe disability. ADHD symptoms and emotional problems were significantly higher among extremely preterm than term-born children (Table 2). These differences remained significant after adjusting for sex and IMD.

Table 2. Characteristics of the final study sample*

		Term-born children (n=121)	**Extremely preterm children (n=165)**	**P value**
Male	n (%)	51 (43)	86 (53)	.08
Age at assessment, years	mean (SD)	11.7 (0.6)	11.8 (0.5)	.20
IMD decile	mean (SD)	5.5 (2.9)	5.45 (2.8)	.79
Gestational age	Mean (SD)	-	25.6 (1.0)	-
	23 weeks, n (%)	-	11 (7)	
	24 weeks, n (%)	-	21 (13)	
	25 weeks, n (%)	-	59 (36)	
	26 weeks, n (%)	-	74 (45)	
Severe neurodevelopmental disability	n (%)	0	29 (18)	-
Body Mass Index Classification[a]	Thinness n (%)	8 (6.7)	26 (15.9)	.08
	Normal weight n (%)	89 (74.2)	105 (64.4)	
	Overweight n (%)	17 (14.2)	27 (16.6)	
	Obese, n (%)	6 (5.0)	5 (3.1)	
Sleep medications (melatonin)		0	6 (<1)	
Inattention[b]	Mean (SD)	3.9 (4.4)	10.6 (7.6)	<.001
Hyperactivity/impulsivity	Mean (SD)	1.8 (2.4)	5.8 (6.1)	<.001
Emotional problems subscale score	Mean (SD)	1.6 (2.0)	2.7 (2.5)	<.001

[*] Final study sample comprises children for whom complete parent questionnaire and IMD data were available; [a] n= 120 controls, n= 163 extremely preterm children. [b] =121 controls, n=164 extremely preterm children. IMD: Index of Multiple Deprivation.[36]

Sleep disturbance and SDB

Children born extremely preterm had significantly worse scores than term-born children for sleep onset latency, night waking and daytime sleepiness, with small effect sizes; however, there was no significant difference in sleep duration (Table 3). A greater proportion of extremely preterm than term-born children were classified with SDB, had habitual snoring (always snored/snored more than half the time), heavy or loud breathing, snored loudly or stopped breathing during the night. There was no significant between-group difference in the proportion of children who had trouble breathing (Table 3). All differences remained significant after applying correction for multiple comparisons. Between-group differences remained significant but were smaller in magnitude when children with severe disabilities were excluded (Table S2). There was no significant difference in the proportion of children who were overweight or obese among children who habitually snored compared to children who did not, for both extremely preterm (X^2 =1.68, p=.195) and term-born children (X^2 =3.05, p=.082) (Table S3). In children without severe disabilities, night waking was correlated with inattention (r=.29), hyperactivity/impulsivity (r=.40) and emotional problems (r=.32) controlling for sex and IMD (Table S4).

Table 3. Sleep disturbance and symptoms of sleep disordered breathing in extremely preterm children and term-born controls at 11 years of age.

	Term-born children		Extremely preterm		Mean difference (95% CI)	p value	Adjusted Mean difference (95% CI) [a]	Adjusted p value	Benjamini-Hochberg critical value [b]	Unadjusted Cohen's d
	n	**Mean (SD)**	**n**	**Mean (SD)**						
Sleep duration	121	3.83 (1.33)	162	4.10 (1.62)	0.26 (-0.08, 0.61)	.133	0.26 (-0.10, 0.62)	.155	.045	0.18
Sleep onset latency	121	1.55 (0.74)	164	1.81 (0.83)	0.26 (0.07, 0.44)	**.007**	0.26 (0.07, 0.45)	**.007***	.025	0.33
Night waking	116	3.38 (0.85)	161	3.90 (1.42)	0.52 (0.25, 0.79)	**<.001**	0.52 (0.23, 0.82)	**<.001***	.005	0.44
Daytime sleepiness	117	10.64 (2.58)	163	11.81 (3.28)	1.17 (0.48, 1.86)	**.001**	1.15 (0.44, 1.86)	**.002***	.020	0.40
	n	**n (%)**	**n**	**n (%)**	**OR (95% CI)**		**Adjusted OR (95% CI)**			
Sleep disordered breathing	112	2 (1.8)	156	50 (32.1)	25.94 (6.16, 109.31)	**<.001**	25.83 (6.08, 109.79)	**<.001***	.010	-
Always snores	113	1 (0.9)	156	18 (11.5)	14.61 (1.92, 111.13)	**.010**	14.51 (1.90, 110.88)	**.010***	.030	-
Snores more than half the time	104	4 (3.8)	152	32 (21.1)	6.67 (2.28, 19.49)	**<.001**	6.81 (2.29, 20.27)	**.001***	.015	-
Snores loudly	114	3 (2.6)	157	19 (12.1)	5.09 (1.47, 17.66)	**.005**	5.08 (1.46, 17.74)	**.011***	.035	-
Heavy/loud breathing	115	13 (11.3)	160	36 (22.5)	2.28 (1.15, 4.52)	**.017**	2.27 (1.14, 4.52)	**.020***	.040	-
Trouble breathing /struggle to breathe	119	1 (0.8)	158	6 (3.8)	4.66 (0.55, 39.22)	.121	4.60 (0.54, 38.99)	.162	.050	-
Stops breathing during the night	119	0	159	10 (6.3)	-	**.005**	-	-		-

[a] Adjusted for sex and Index of Multiple Deprivation[36];p values <.05 in bold. *p values remained significant after Benjamini-Hochberg correction, i.e. p value lower than Benjamini-Hochberg critical value. [b] Adjusted p value ranked from smallest to largest. Ten tests. False discovery rate selected was 5% Critical value calculated using (rank/total number of tests) x 0.05. See [42]

Mediation analysis: Extremely preterm birth, night waking and ADHD symptoms in children without severe disability

There were significant associations between extremely preterm birth and inattention, extremely preterm birth and night waking, and night waking and inattention (Table 4, Model a, Figure 1a). The unique contribution of extremely preterm birth was reduced when night waking was controlled for (β reduced .41 to .38); R^2 for path c' was higher than for path c, explaining an additional 5% of the variance in inattention. Overall, 27% of the variance in inattention was explained by the mediated model.

The relationship between extremely preterm birth and hyperactivity/impulsivity was partially mediated by night waking, which explained an additional 13% of variance in hyperactivity/impulsivity (Table 4, Model c, Figure 1c). Overall, 27% of the variance in hyperactivity/impulsivity was explained by the mediated model.

In the reverse mediation models (i.e., inattention or hyperactivity/impulsivity as the mediator; Table 4, Models b and d, Figures 1b and 1d), an additional 7% and 15% of the variance in night waking was explained by the mediated models for inattention and hyperactivity/impulsivity respectively. Both models fully mediated the relationship between extremely preterm birth and night waking. However, these reverse mediation models explained less overall variance in the outcomes 9%-17% (Models b and d) compared to the models with night waking as the mediator (27%, both Models a and c).

Mediation analysis: Extremely preterm birth, night waking and emotional problems in children without severe disability

Night waking partially mediated the relationship between extremely preterm birth and emotional problems. The mediation model explained an additional 9% of variance in emotional problems (Table 4, Model e, Figure 1e).

In the reverse mediation model (i.e. emotional problems as the mediator between extremely preterm birth and night waking; Table 4, Model f, Figure 1f), emotional problems fully mediated the relationship between extremely preterm birth and night waking. Emotional problems as the mediator between extremely preterm birth and night waking explained less variance in night waking (11%, Model f] compared with the variance in emotional problems explained by night waking as the mediator between extremely preterm birth and emotional problems [15%, Model e].

Table 4. Mediation models for children without severe neurodevelopmental disability

Path	Outcome	Predictor	R^2 of each model	β	t	P value
Mediation model (a) between extremely preterm (EP) birth→ night waking→ inattention symptoms (N=249)						
a (X to M)	Night waking	EP birth	.02	.13	2.10	.037
b (M to Y)	Inattention	Night waking	.13	.29	4.81	<.001
c (X to Y)	Inattention	EP birth	.22	.41	7.31	<.001
c' (X to Y controlling for M)	Inattention	EP birth	.27	.38	6.93	<.001
Mediation model (b) between extremely preterm (EP) birth → inattention symptoms→ night waking (N=249)						
a (X to M)	Inattention	EP birth	.22	.41	7.31	<.001
b (M to Y)	Night waking	Inattention	.09	.30	4.81	<.001
c (X to Y)	Night waking	EP birth	.02	.13	2.10	.037
c' (X to Y controlling for M)	Night waking	EP birth	.09	.01	0.16	.874
Mediation model (c) between extremely preterm (EP) birth → night waking → hyperactivity/impulsivity symptoms (N=249)						
a (X to M)	Night waking	EP birth	.02	.13	2.10	.037
b (M to Y)	Hyperactivity/Impulsivity	Night waking	19	.40	6.90	<.001
c (X to Y)	Hyperactivity/Impulsivity	EP birth	.14	.32	5.43	<.001
c' (X to Y controlling for M)	Hyperactivity/Impulsivity	EP birth	.27	.28	4.96	<.001
Mediation model (d) between extremely preterm (EP) birth → hyperactivity/impulsivity symptoms → night waking (N=249)						
a (X to M)	Hyperactivity/Impulsivity	EP birth	.14	.32	5.43	<.001
b (M to Y)	Night waking	Hyperactivity	.17	.41	6.90	<.001
c (X to Y)	Night waking	EP birth	.02	.13	2.10	.037
c' (X to Y controlling for M)	Night waking	EP birth	.17	<.01	0.02	.987
Mediation model (e) between extremely preterm (EP) birth → night waking→ emotional problems (N=249)						
a (X to M)	Night waking	EP birth	.02	.13	2.10	.037
b (M to Y)	Emotional problems	Night waking	.12	.32	5.32	<.001
c (X to Y)	Emotional problems	EP birth	.06	.21	3.37	.001
c' (X to Y controlling for M)	Emotional problems	EP birth	.15	.17	2.84	.005
Mediation model (f) between extremely preterm (EP) birth → emotional problems→ night waking (N=249)						

a (X to M)	Emotional problems	EP birth	.06	.21	3.37	.001
b (M to Y)	Night waking	Emotional problems	.11	.32	5.32	<.001
c (X to Y)	Night waking	EP birth	.02	.13	2.10	.037
c’ (X to Y controlling for M)	Night waking	EP birth	.11	.07	1.11	.270
Mediation model (g) between extremely preterm (EP) birth → habitual snoring → inattention symptoms (N=231)						
a (X to M)	Habitual snoring	EP birth	.08 [a]	.20 [b]	-	.006
b (M to Y)	Inattention	Habitual snoring	.10	.20	3.17	.002
c (X to Y)	Inattention	EP birth	.23	.41	7.04	<.001
c’ (X to Y controlling for M)	Inattention	EP birth	.24	.39	6.56	<.001
Mediation model (h) between extremely preterm (EP) birth → habitual snoring → hyperactivity/impulsivity (N=231)						
a (X to M)	Habitual snoring	EP birth	.08 [a]	.20 [b]	-	.006
b (M to Y)	Hyperactivity/Impulsivity	Habitual snoring	.12	.29	4.52	<.001
c (X to Y)	Hyperactivity/Impulsivity	EP birth	.15	.33	5.33	<.001
c’ (X to Y controlling for M)	Hyperactivity/Impulsivity	EP birth	.20	.28	4.67	<.001

Note model also includes sex, Index of Multiple Deprivation [36] (predictors not reported)

[a] R^2 value is Cox and Snell R Square

[b] Standardised beta calculated using the following formula: $\beta = b(s_x)R/s_{logit(\hat{Y})}$

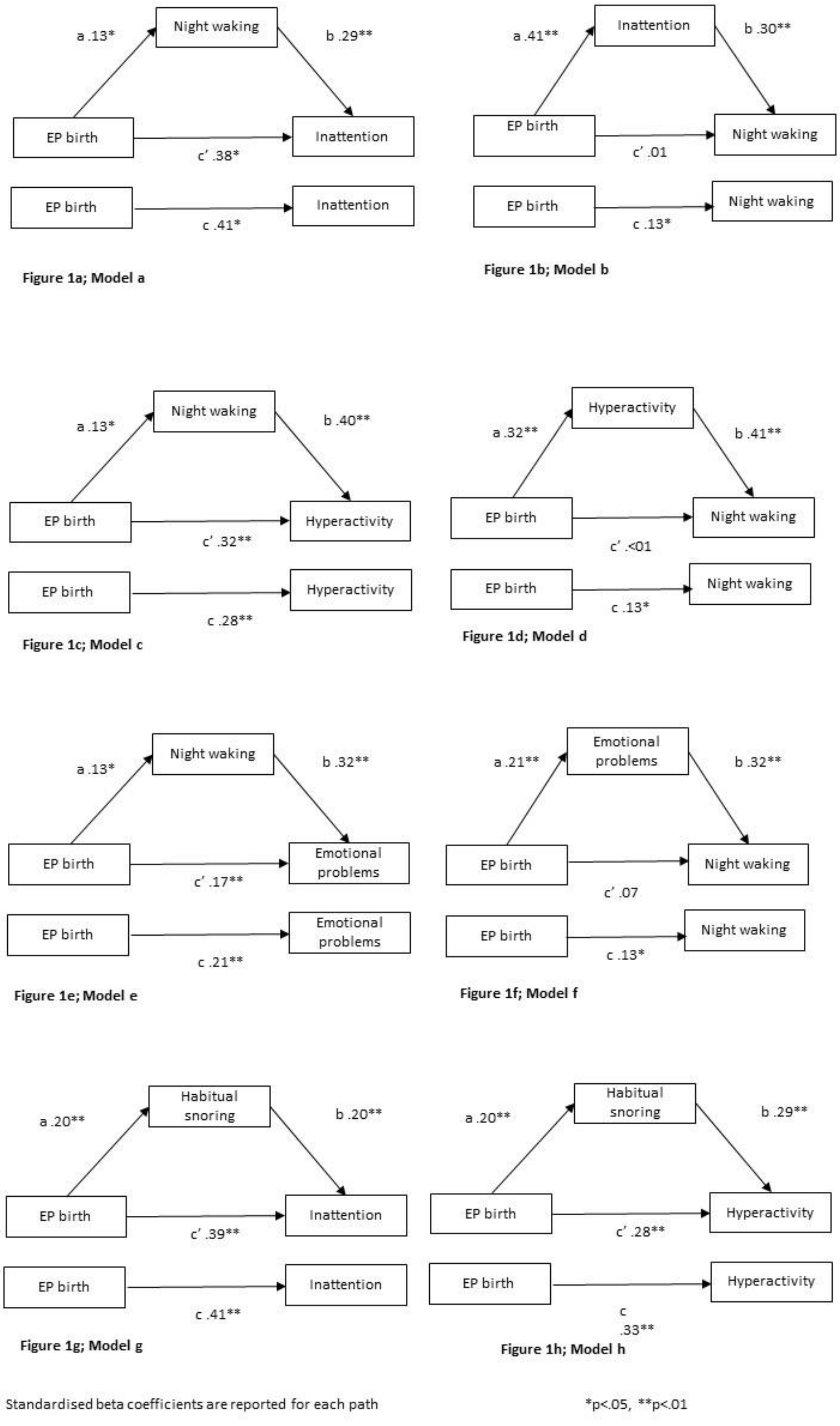

Figure 1 Mediation models. Figures 1a & 1c: mediator: night waking; outcome: behavioural symptoms; Figure 1e: mediator: night waking; outcome: emotional problems. Figures 1b, 1d & 1f: mediators: behavioural/emotional symptoms; outcome: night waking; Figures 1g & 1h: mediator: snoring; outcome: behavioural symptoms

Mediation analysis: Extremely preterm birth, habitual snoring and ADHD symptoms in children without severe disability

Children who habitually snored had significantly higher inattention and hyperactivity/impulsivity scores (Table S1). Habitual snoring partially mediated the relationship between extremely preterm birth and inattention and hyperactivity/impulsivity, explaining an additional 1% (Model g; Table 4, Figure 1g) and 5% (Model h; Table 4, Figure 1h) of the variance, respectively.

Discussion

In this study, extremely preterm children had more parent-reported sleep problems than their term-born peers. Specifically, they had longer sleep onset latency, more night waking and more daytime sleepiness, along with a seven-fold increased risk of habitual snoring and increased risk of SDB. We did not find evidence of a group difference in sleep duration in the present study. We also showed that night waking partially mediated the relationship between extremely preterm birth status and ADHD symptoms and emotional problems in children without severe disability. Specifically, the mediating role of night waking explained an additional 5% of the variance between extremely preterm birth and inattention symptoms, 13% in hyperactivity/impulsivity symptoms and 9% in emotional problems. Snoring explained only a small proportion of variance between extremely preterm birth and inattention (1%) and hyperactivity-impulsivity (5%) symptoms.

With reference to previous studies, our findings regarding night waking and sleep onset latency are commensurate with the excess of parent-reported night waking and longer sleep onset latency in extremely preterm children described previously [9]. There remains inconclusive evidence regarding the association of preterm birth with altered sleep duration given the increase in sleep duration described using parent report [9], no significant difference in sleep duration in some polysomnography/EEG studies [10,12], and one polysomnography and one actigraphy study indicating a shorter sleep duration in preterm versus term-born children [11,13]. Future studies should evaluate daytime sleepiness, ideally using self-report, given the excess of daytime sleepiness among children born extremely preterm in the present study, but not evidenced in children born very preterm compared with term-born children [8]. The present study provides further evidence of an increased risk of snoring and SDB in school-aged children born preterm, adding to the extant literature [see 16–18].

That night waking partially mediates the relationship between extremely preterm birth and ADHD symptoms and emotional problems corroborates the finding that less restorative sleep mediates the relationship between very preterm birth and behavioural and emotional problems [20]. Although night waking explained only a small proportion of variance in behavioural/emotional problems in the present study, this might suggest that interventions to improve sleep quality may be beneficial for reducing both sleep problems and behavioural/emotional problems in this population. However, there was also some evidence for a reciprocal relationship, as emotional and behavioural problems fully mediated the relationship between extremely preterm birth status and night waking. This reciprocal relationship may be explained by shared brain structures implicated in both sleep disturbance and ADHD symptoms. In the general population, ADHD symptoms mediate the relationship between lower average grey matter volume in the right middle frontal gyrus and inferior frontal gyrus, the bilateral insula, left caudate, and putamen and the right parahippocampus, hippocampus and amygdala and sleep disturbance in middle childhood [24]. Given that for adolescents and adults born <33 weeks' gestation, lower grey matter volume is found in the putamen, insula, caudate nucleus, hippocampus and amygdala compared with individuals born at term [43], the brain morphology following very preterm birth may be implicated in the additional risk of sleep and ADHD symptoms. Evidence from research with the general population on sleep and ADHD suggests that strategies to address both sleep and ADHD are needed [24]. From our findings we suggest that interventions that target both sleep and emotional/behavioural problems concurrently may be most effective.

Both cognitive behavioural therapy for anxiety and behavioural therapy targeting anxiety and sleep problems in children with generalised anxiety disorder show moderate to large effect sizes for reductions in parent- and child-reported sleep problems and parent-reported anxiety [44]. A two-session sleep hygiene and behavioural sleep intervention in children with ADHD and a co-occurring sleep disorder has also been shown to reduce ADHD symptoms and sleep problems after 3 months, with moderate and large effect sizes respectively [45]. Of note, sleep mediated 50% of the effect size of the intervention on reduced ADHD symptoms three months post-intervention [45]. Interventions to improve sleep may therefore prove a useful target for reducing sleep problems, anxiety and ADHD symptoms in extremely preterm populations.

Given the high prevalence of SDB in the present study, professionals should be aware of the elevated risk of SDB following extremely preterm birth. The National Institute for Health and Care Excellence in the UK recommends that sleep problems, including sleep apnea symptoms, be monitored among children born <30 weeks' gestation or preterm with additional risk factors for developmental disorders [46]. The findings from the present study support this recommendation.

Strengths and limitations

The strengths of this study include a nationally representative population-based cohort of children born before 27 weeks of gestation, the inclusion of a contemporaneous term-born comparison group and the use of validated questionnaires to assess sleep disturbance and SDB. It is possible that the comparison group may represent a selected sample with fewer sleep problems and ADHD symptoms than in the general population. For example, 3.8% of controls had habitual snoring compared with 9% of 10-year-old children recruited through general practice clinics [28]. It is thus possible that the higher OR for habitual snoring found in this study compared to other studies of children and young adults born preterm [16–18] may be attributed to underrepresentation of habitual snoring amongst our term-born group [16–18]. Given the wide confidence interval for SDB, this result should be considered with caution. There are also limitations associated with the use of parent report to assess sleep. For example, parents may overestimate sleep duration compared to objective assessment [13]. Further research using actigraphy is needed to provide a more objective measure of sleep duration and quality and to confirm the findings of the present study [13]. Future studies could also use features of ballistocardiography, such as heart and breathing rate variability to assess sleep architecture [47] and assess children's daytime physical activity and light exposure. This was not possible in the context of the present study. This study was also limited by the lack of clinical assessment of SDB, which is required to confirm a diagnosis of obstructive sleep apnea, and the lack of multi-informant data for assessing behavioural and emotional problems. Finally, given the cross-sectional nature of the study, the direction of causality between sleep disturbance and ADHD symptom and emotional problems cannot be inferred. Future longitudinal studies should consider collecting data on sleep disturbance and ADHD symptoms to identify whether sleep disturbance precedes the onset of behavioural and emotional symptoms.

Conclusions

Children born extremely preterm were at higher risk of sleep problems than children born at term, including more night waking, taking longer to fall asleep, daytime sleepiness and symptoms of SDB. Night waking partially mediated the relationship between extremely preterm birth and ADHD symptoms and emotional problems. These findings suggest that targeting sleep disturbance and emotional problems concurrently may improve sleep and reduce ADHD and emotional symptoms in children born extremely preterm.

Declarations:

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Conflicts of interest/Competing interests: Neil Marlow declares financial relationships with Shire/Takeda and Novartis outside the submitted work. No other relevant conflicts of interest are present.

Availability of data and material: Data are available subject to the EPICure Data Sharing Policy (www.epicure.ac.uk) and will be available as part of the RECAP preterm Cohort Platform (https://recap-preterm.eu).

Code availability: Not Applicable

Ethics approval: Ethics approval was obtained from University College London (Ref: 10175/001) and University of Leicester (Ref: 10225).

Consent to participate: Parental consent and child assent were obtained.

Consent for publication: Not Applicable.

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Supporting information: Description of measures, comparison of inattention, hyperactivity and emotional problems scores for whole sample for children who do and do not habitually snore (Table S1) comparison of sleep disturbance between children born extremely preterm without a severe disability compared to term-born children (Table S2), proportion of children overweight/obese according to habitual snoring status (Table S3) and partial correlations between sleep disturbance and emotional/behavioural problems (Table S4)

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