Sleep habits and sleep problems among children born extremely preterm: A Norwegian population-based cohort study

Kristine Marie Stangenes

Thesis for the degree of Philosophiae Doctor (PhD)
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Name: Kristine Marie Stangenes

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Scientific environment

This thesis materialised through the PhD program at the Department of Clinical Science, Faculty of Medicine, University of Bergen. The main research environment was the Children and Youth Clinic, Haukeland University Hospital, Bergen, Norway. This thesis is based on the national cohort of extremely preterm children, called 'Project Extreme Prematurity'.

My main supervisor has been the specialist in general medicine and sleep-specialist Prof. Bjørn Bjorvatn, and the study was co-supervised by paediatrician Prof. Emeritus Trond Markestad, paediatrician and child psychiatrist Prof. Irene Elgen and psychologist Prof. Mari Hysing. The Department of Paediatrics, Innlandet Hospital Trust, Lillehammer, Norway, collaborated for the control group in this study.

Acknowledgements

I was fascinated by sleep early and in my work as a paediatrician I discovered that there was a need for increased expertise in the field of children and sleep. I was thus very happy when I was offered the opportunity to take a PhD on sleep in children born extremely preterm. During my PhD period, my fascination for sleep has by no means abated. Completing a PhD has been labour-intensive but also very meaningful and satisfying.

I am grateful to my supervisors – Bjørn Bjorvatn, Mari Hysing, Irene Elgen and Trond Markestad. Thank you very much for giving me the opportunity to take a PhD. Thank you for your good guidance and support. Thanks also to my co-authors Silje Fevang, Thomas Halvorsen, Hilde Mjell Donkor and Jackob Grundt. Special thanks to Thomas for good support and many great tips along the way.

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Kristine Marie Stangenes Bergen, May 2020

Abstract

Objective: The objective of this thesis was to investigate the prevalence of general and specified sleep problems during childhood and the sleep habits of children aged 11 years who had been born extremely preterm (EPT). Furthermore, the study aimed to explore possible associations between sleep characteristics and neurodevelopmental disabilities (NDD), prenatal and neonatal factors, behaviour and respiratory health.

Methods: A national cohort of all EPT children (gestational age [GA] < 28 weeks or birth weight< 1,000 g) born in Norway in 1999–2000 was investigated. In Paper 1, parental questionnaires mapped the children's current sleep habits at 11 years of age and the prevalence of general and specified sleep problems throughout childhood up to this age. The prevalence of sleep problems throughout childhood and sleep habits at 11 years of age were compared with those of a control group. The EPT children were clinically assessed and given an NDD score at five years of age. In Papers 2 and 3, four current specified sleep problems, namely, difficulty falling asleep or frequent awakenings, snoring, daytime sleepiness and non-recommended sleep duration (<9 hours), were mapped at 11 years of age. These problems were further explored for possible associations with prenatal and neonatal factors, behaviour and respiratory health. Prenatal and neonatal data were collected by all Norway's obstetric and paediatric departments. Behavioural problems were assessed by parents and teachers using the Strengths and Difficulties Questionnaire (SDQ). Parents assessed their children's respiratory symptoms with the International Study of Asthma and Allergies in Childhood questionnaire and described the use of asthma medications.

Results: In Paper 1, the study found that the EPT children had different sleep habits than the controls. They also had a higher prevalence of sleep problems than the controls throughout childhood (26% vs. 14%, odds ratio [OR] 2.1). This value was also higher for the EPT children with no NDD (20%) than for the controls (14%) and increased with increasing NDD. In Paper 2, the study found that smoking in pregnancy predicted snoring (OR 4.3), and neonatal cerebral haemorrhage and being born small for gestational age (SGA) predicted difficulty falling asleep or frequent

awakenings (OR 2.2 and 2.3). Other morbidities during pregnancy or the newborn period or the burden of treatment in the neonatal intensive care unit did not predict specified sleep problems. In Paper 3, the study found that all four specified sleep problems, except for non-recommended sleep duration, were associated with higher parent-reported and teacher-reported SDQ total score (OR 1.1 for all). Daytime sleepiness was strongly associated with wheezing for the last 12 months, disturbed sleep due to wheezing, wheezing during or after exercise and use of asthma medications (OR 2.9 to 3.9). Snoring was associated with wheezing during or after exercise and current asthma (OR 2.8 and 4.2).

Conclusion: EPT children are at increased risk of sleep problems in childhood. The prevalence of sleep problems increased with increasing NDD, but the EPT children with no NDD were also at increased risk compared with the controls. Of numerous prenatal and neonatal factors, only smoking during pregnancy, being born SGA and cerebral haemorrhage predicted specified sleep problems at 11 years of age. The EPT children with sleep problems had more behavioural and respiratory health problems compared with the EPT children without sleep problems.

List of papers

I. Stangenes KM, Fevang SK, Grundt J, Donkor HM, Markestad T, Hysing M, Elgen IB, Bjorvatn B.

Children born extremely preterm had different sleeping habits at 11 years of age and more childhood sleep problems than term-born children.
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II. Stangenes KM, Hysing M, Fevang SK, Elgen IB, Halvorsen T, Markestad T, Bjorvatn B.

Prenatal and neonatal factors predicting sleep problems in children born extremely preterm or with extremely low birthweight.
Frontiers in Pediatrics. 2018 Jun 20;6:178.
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III. Stangenes KM, Hysing M, Elgen IB, Halvorsen T, Markestad T, Bjorvatn B.

Sleep problems, behavioural problems and respiratory health in children born extremely preterm: a parental questionnaire study
BMJ Paediatrics Open. 2019 Sep 5;3(1):e000534.
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List of abbreviations

M-ABC test – Movement Assessment Battery for Children

BIC – Behavioural insomnia of childhood

BPD – bronchopulmonary dysplasia

CP – cerebral palsy

EEG – electroencephalography

EMG – electromyography

EPT – extremely preterm

FIQ – full-scale intelligence quotient

GA – gestational age

GMFCS – Gross Motor Function Classification System

IQ – intelligence quotient

ISAAC – International Study of Asthma and Allergies in Childhood

MBRN – Medical Birth Registry of Norway

MNPO – median preoptic nucleus

NDD – neurodevelopmental disabilities

NEC – necrotising enterocolitis

NICU – neonatal intensive care unit

NREM sleep – non-rapid eye movement sleep

PEP – Project Extreme Prematurity

PVL – periventricular leukomalacia

REM sleep – rapid eye movement sleep

ROP – retinopathy of prematurity

SCN – suprachiasmatic nucleus

SDB – sleep-disordered breathing

SDQ – Strengths and Difficulties Questionnaire

SGA – small for gestational age

VLPO – ventrolateral preoptic nucleus

WPPSI-R – Wechsler Preschool and Primary Scale of Intelligence-Revised

1 Introduction

1.1 Prematurity

1.1.1 Definitions of prematurity and low birth weight

The World Health Organization defines preterm birth as any birth before 37 completed weeks of gestation. Preterm birth is further subdivided on the basis of gestational age (GA) (1):

- Extremely preterm (EPT) (<28 weeks)
- Very preterm (28 to 32 weeks)
- Moderate to late preterm (32 to 37 weeks)

The GA is sometimes uncertain, so birth weight data can be used instead. Although some concordance exists between the categories of birth weight and GA, they are not interchangeable. The categories for birth weight are as follow (2):

- Extremely low birth weight (<1,000 g)
- Very low birth weight (<1,500 g)
- Low birth weight (<2,500 g)

1.1.2 Epidemiology of preterm birth

Globally, 15 million babies are born preterm every year; this is estimated to represent approximately 11% of all birth deliveries and ranges from 5% in several European countries to 18% in some African countries (3). In 2016, preterm birth complications were the main reasons for death before the age of five years (4). Low- and middle-income countries have the majority of the world's preterm births; 80% of preterm births occur in sub-Saharan Africa or South Asia (5). The incidence of preterm birth has been 5%–7% of live births in most high-income countries over the last 20–30 years (2). According to the Medical Birth Registry of Norway (MBRN), the incidence of EPT birth in Norway has been 0.3%–0.5% in the last 20 years (6). Most preterm births (84%) occur after 32 completed weeks of gestation. The vast majority of such newborns will survive with supportive care and without neonatal intensive care (7). This is in contrast to EPT children, who, in most cases, rely on neonatal intensive care

to survive. In low-income countries, over 90% of EPT babies die within the first few days of life (7, 8).

The chance of survival without any neurodevelopmental impairment for EPT children born alive in high-income countries increases with increasing GA at birth from 1.2 % for 22 weeks' GA to 64.2 % for 27 weeks' GA (9).

Limitations in terms of offering active life-saving treatments vary within high-income countries. Norway is on a par with several countries in Europe and North America. Countries, such as France and the Netherlands, have a more restrictive attitude than Norway (10). In Norway, a consensus report in 1998 addressed thresholds for the treatment of EPT children (11). It was recommended that the threshold of viability should be between 23 and 25 gestational weeks. A Norwegian study has since found that the average threshold for the resuscitation of newborns at EPT birth decreased from 23.3 weeks in 1998 to 23.0 in 2005 (12). In 2015, it was shown that the practice varied somewhat between different units in Norway (13) but today, in most Norwegian newborn wards treating EPT children, week 23+0 is considered to be a guiding 'lower limit' (14).

In the Norwegian follow-up study in 1999 and 2000 ('Project Extreme Prematurity'), the survival rate until discharge was 58% for all EPT births (GA 23 -16%, GA 24 -44%, GA 25 -66%, GA 26 -72%, GA 27 -82%) (15). Moreover, recent Norwegian research on a national cohort of EPT children born in 2013–2014 shows an unchanged survival rate (16).

1.1.3 Pathophysiology and risk factors of preterm birth

Infants are born preterm at less than 37 weeks GA after: 1) spontaneous labour with intact membranes (approximately 45%); 2) preterm rupture of the membranes (approximately 25%); and 3) labour induction or caesarean delivery for maternal or foetal indications (approximately 30%) (17). Common causes for indicated preterm births include pre-eclampsia or eclampsia and intrauterine growth restriction (17). In

many cases of indicated EPT births, choosing the right time for delivery is a difficult decision. Finding the latest possible time for delivery that still yields maturation and growth but does not diminish foetal resources for survival, does not increase immediate stress in postnatal life or endanger maternal life is a difficult titration.

The cause of most spontaneous preterm births (including spontaneous labour and preterm rupture of the membranes) is unknown, but there are several known risk factors, such as black ethnicity, adolescent pregnancies, advanced maternal age, low level of maternal education, short inter-pregnancy interval, in vitro fertilisation, smoking, use of intoxicants, infections during pregnancy, pre-eclampsia, pre-gestational and gestational diabetes, obesity, cervical incompetence, placental abruption, placenta praevia, polyhydramnios, uterine anomalies and foetal birth defects . Of note, despite the plethora of reported risk factors, the majority of preterm births have no clear risk factor (17, 18).

1.1.4 Neonatal morbidity

The most common neonatal morbidities are respiratory problems, cerebral complications, problems caused by the immaturity of the gastrointestinal tract, retinopathy of prematurity and infections (19-23). Illnesses and complications related to prematurity can be explained by the immaturity of the organs and disrupted normal development, and the risk increases with the degree of immaturity at birth. For many EPT children, it is not only the immaturity of organs that can explain their morbidity; many of them will also have an unfavourable intrauterine environment, which also increases the risk of short- and long-term morbidity (24, 25).

Lung disorders: Lung disorders are one of the major problems in neonatal intensive care units (NICUs). Birth during the early developmental stages of the lungs means that the gas exchange needed by the body is dependent on one anatomically and functionally unfinished organ. The lungs lack surfactant, the surface tension is high and the lung is stiff, so ventilation becomes energy intensive. Alveolarisation has not once started yet, the available area for gas exchange is low and gas diffusion is

inhibited by thick membranes (26). Therefore, mechanical ventilation support and extra oxygen supplementation are often needed. These measures are life-saving in the acute phase but destructive in the long term. Mechanical ventilation can profoundly disrupt the development of the respiratory tract and vasculature, probably due to the stretch and overdistension in the fragile and poorly compatible respiratory tract. The result can be the development of fewer and larger alveoli and a decrease in the total surface area available for gas exchanges (19, 26).

Preterm children who need oxygen supplementation beyond 28 days are diagnosed with bronchopulmonary dysplasia (BPD). The diagnosis is further reclassified at the 36th gestation week. Those breathing room air at this time are diagnosed with mild BPD, those who need less than 30% oxygen have moderate BPD and those who need 30% or more oxygen have severe BPD (27). BPD is a developmental disorder and a multisystem disorder that may be associated with a variety of other conditions, including growth retardation, lung hypertension, neurodevelopmental delay and ROP (28, 29). In Project Extreme Prematurity, a Norwegian follow-up study based on all EPT births in 1999 and 2000, BPD was diagnosed in 85.9% of surviving infants. The prevalence of BPD was inversely proportional to the GA (19).

Cerebral complications: Brain development is a complex process of micro- and macrostructural events that include neuronal migration, formation of neural networks, myelination and development of cortical layers. The brain develops throughout the life of the foetus, and this development is far from complete even in children born full term. A number of important maturation processes occur during the last trimester of pregnancy, and these processes may be affected by preterm birth (30).

In a child born at weeks 27–28 or earlier, the migration of nerve cells and the formation of the cerebral cortex are not complete. In addition, the process in which the various nerve cells form connections and networks to communicate with one another is ongoing (31). Myelination, which is fundamental for good signal transmissions between nerve cells, begins at approximately 20 weeks and continues through

childhood into adulthood (32). At the 26th weeks of gestation, the brain surface is almost completely smooth, with no sulci and gyri, both of which help dramatically to increase the brain surface during the latter part of pregnancy. The total brain volume will normally triple between the 29th and 41st weeks of gestation (31).

EPT children are at risk of neonatal cerebral haemorrhage and ischemic infarcts, and subsequent tissue damage has serious and diverse effects on ongoing brain development (20). Cerebral haemorrhage is found in ca. 15%–25% of preterm children with a birth weight below 1,000 g (33). The haemorrhages originate from a vascular area – the germinal matrix – that lies in the lateral ventricles deep in the brain. With asphyxia and other problems, bleeding can easily occur just under the epithelial lining (ependyma) of the ventricles. Bleeding limited to this area is called subependymal bleeding. The ependyma may rupture, allowing blood to enter the ventricles (intraventricular haemorrhage), and the bleeding can penetrate the brain (intracerebral haemorrhage). Blood in the ventricles can block drainage and thus cause hydrocephaly (34, 35).

Preterm infants have a propensity for developing cerebral ischaemia, especially in white matter. This propensity is probably because of the arterial border and end zones within white matter and the impaired regulation of the cerebral blood flow (36).

Periventricular leukomalacia (PVL) refers to ischemic infarcts in cerebral white matter and has focal and diffuse components.

1.) The focal component of PVL consists of localised necrosis deep in periventricular white matter, with a loss of all cellular elements. These necroses can be macroscopic in size and evolve to multiple cystic lesions, readily visualised by cranial ultrasonography. This form of PVL is known as ‘cystic PVL’. More commonly, focal necroses are microscopic in size and evolve to glial scars. This form of PVL is termed ‘non-cystic PVL’.
2.) The diffuse component of PVL is more diffusely apparent in cerebral white matter and is characterised by a selective degeneration of pre-oligodendrocytes, which are

precursors to the glial cell oligodendrocyte (37). This degeneration leads to hypomyelination, volumetric deficit and ventriculomegaly (20). It can also cause scarring through the diffuse accumulation of glial cells, called gliosis (38).

PVL is frequently accompanied by neuronal/axonal diseases, affecting the cerebral white matter, thalamus, basal ganglia, cerebral cortex, brain stem and cerebellum (31, 39, 40). Neuroimaging studies indicate that PVL, in its various forms, occurs in 40% of EPT children (41).

Volumetric magnetic resonance imaging analyses of very-low-birth-weight infants show a decreased volume of neuronal structures, such as the thalamus, basal ganglia, cerebral cortex and cerebellum, as early as the term-equivalent age and later in childhood, adolescence and adulthood (31, 42, 43).

Cerebral ischemia is the major cause of PVL in preterm children, but it is potentially augmented by foetal infection/inflammation (36).

The constellation of PVL and neuronal/axonal diseases is termed the 'encephalopathy of prematurity'. 'Encephalopathy of prematurity' is described as a complex amalgam of primary destructive disease and secondary maturational and trophic disturbances and appears to account for most of the subsequent neurological sequelae (31).

Necrotising enterocolitis (NEC): NEC is a feared complication of immature bowel in preterm infants. NEC is characterised by bowel wall necrosis and optional perforation of the gut. Despite advances in neonatal care, NEC remains a leading cause of morbidity and mortality among preterm infants (21).

Retinopathy of prematurity (ROP): ROP is a disease related to vascular abnormalities of the retina and may lead to impaired vision and, in the worst-case scenario, blindness.

Too high oxygen pressure (pO2) in the blood is an important risk factor for ROP, but in the smallest EPT infants, immaturity itself can be a sufficient cause (22, 44).

Neonatal sepsis: Sepsis is a major risk factor for death and neonatal morbidity. The Norwegian 'Project Extreme Prematurity' reported a prevalence of approximately 3.3% for very early onset sepsis (diagnosed on the day of delivery), 3.6% for early onset sepsis (45) and 19.7% for late onset sepsis (46).

1.1.5 Long-term outcome

Preterm birth is associated with an increased risk of challenges, such as impaired neurodevelopmental outcomes, chronic lung disease and behavioural problems (47-52).

Neurodevelopmental outcome: The term 'neurodevelopmental outcome' is a composite term that typically refers to neurologic, intellectual and/or sensory outcomes. The most important acknowledged early morbidities that may influence later neurodevelopmental outcomes are brain injuries, ROP, chronic lung diseases, NEC and neonatal sepsis (53, 54).

Neuromotor problems

Neuromotor problems can be classified as cerebral palsy (CP) and minor neuromotor problems without CP. EPT children without CP are at increased risk of minor neuromotor problems, such as clumsiness and reduced coordination and ball skills. The prevalence of such problems in the Norwegian follow-up study 'Project Extreme Prematurity' was 17% (48).

CP is a clinical diagnosis and is classified using the Gross Motor Function Classification System (GMFCS) (55). CP refers to a group of disorders in the development of posture and motor control, occurring as a result of a non-progressive lesion in the developing central nervous system (56). The prevalence of CP in children in the general population in Norway has decreased from 2.6 per 1,000 live births in

1999 to 1.9 per 1,000 live births in 2010 (57). Extreme prematurity is a major risk factor for CP (58).

There are three predominant CP syndromes: spastic, dyskinetic and ataxic (58). Spastic CP is the most common form of CP among preterm children. Injury to the brain at GA 24 to 32 weeks typically occurs in the periventricular area (white matter). At this age, this area has the most exposed blood supply and therefore may be compromised by hypoxia, infections or hypotension. In preterm infants, this area is also prone to damage following intraventricular haemorrhage and haemorrhagic parenchymal infarction in the surrounding cortical tissues. Due to the anatomy of the periventricular white matter, with motoric fibres to the legs passing closest to the ventricle edge, injuries in this area usually result in a leg-dominant spastic motor pattern (spastic diplegia) (59).

The neurodevelopmental outcome for EPT children has improved over the last decades, and the prevalence of CP has been reduced (60). Studies show a 5%–14% prevalence of CP among EPT children born from 2000–2007 (61-63). The prevalence of CP in the Norwegian follow-up study 'Project Extreme Prematurity' was 11% (64).

Intellectual deficits

Cognitive difficulties are now considered the most common neurological sequelae after preterm birth (20). Cognitive difficulties include difficulties with reasoning, problem solving, planning, abstract thinking, assessment, academic learning and learning from experience (65). The general cognitive or ability level can be assessed with tests that provide a measure of general abilities called intelligence quotient (IQ). Gu et al. found, in a meta-analysis, that the mean IQ for children with birth weight <1,000 g was 91 compared with 104 in children with a normal birth weight (66). Previous studies have found that the mean full-scale IQ (FIQ) linearly decreases with GA below 33 weeks and at an average of 1.5–2.5 points for each week (67). For the most immature, there is an increased proportion of IQ scores below 70, i.e. in the area of intellectual disability (68).

Previous studies have also found an association between brain volume deviations and cognitive outcomes in children, adolescents and adults born very preterm or with very low birthweight (43, 69, 70).

Visual and hearing impairments

EPT children are at increased risk of visual impairment caused by ROP or brain damage or a combination of these (71). The prevalence of visual impairment among EPT children is 3%–4% (72, 73), and the prevalence of blindness is 1%–2% (61, 64, 72, 74-76).

EPT children (or children with extremely low birth weight) also have an increased risk of hearing impairment. Neurodegenerative hearing loss leading to deafness has been reported in approximately 1% of children with extremely low birth weight (61, 64, 73, 76), and a hearing aid is needed by approximately 1% of EPT children (64, 73).

Behaviour: Behavioural problems in children are categorised into externalising and internalising problems. Externalising behavioural problems manifest outwardly as aggression, impulsivity, coercion and noncompliance. Internalising behavioural problems are inward occurrences and displayed as inhibited styles, such as being withdrawn, lonely, depressed and anxious. Comorbidity occurs both within and across these problems; for example, a child with aggression may also suffer from anxiety or depression (77).

School-aged EPT children have a higher prevalence of parent- and/or teacher-reported behavioural problems, particularly emotional symptoms, inattention and peer relationship problems, as compared with term-born children (78-80). Longitudinal studies have shown that the increased prevalence of behavioural problems in children and adolescents born preterm persists over time (81, 82) and may have greater stability in these individuals compared with those born at full term (82, 83). Moreover, behavioural problems in EPT children often have more impacts on their home life,

friendships and school and leisure activities compared with those of term-born controls (81).

The altered brain development associated with preterm birth may explain the increased prevalence of behavioural problems but, currently, the mechanism is largely unknown (84). Previous studies have found that the prevalence of behavioural problems in EPT children increases with the degree of neurodevelopmental disabilities (NDDs) (49, 85). EPT children without NDDs also have a higher prevalence of behavioural problems compared with children in a normal population (49).

Studies that have used diagnostic evaluations have also found an increased prevalence of attention deficit/hyperactivity disorders, autism spectrum disorders, and psychiatric disorders in general in children born preterm compared with term-born controls (86, 87).

Chronic lung disease: After EPT birth, impaired lung function and increased respiratory morbidity persist into childhood (52, 88-91). Asthma-like illness has been reported to be three times more prevalent in school-aged EPT children than in school-aged term-born children (88, 90). 'Project Extreme Prematurity' has previously found that the burden of respiratory symptoms declines from ages five to 11 years (88).

Spirometry examinations in preterm children with chronic lung diseases can show an airflow limitation similar to that in children with asthma (decreased forced expiratory volume in one second [FEV1], decreased forced expiratory volume in one second (FEV1)/ forced vital capacity (FVC) or decreased forced expiratory flow between 25% and 75% of forced vital capacity (FEF 25–75) (92)) (52, 93, 94).
Although respiratory symptoms and spirometry findings in EPT children resemble asthma, the pathophysiology of lung diseases after preterm birth is different; for instance, it is reflected in the fact that the disease is unresponsive to inhaled corticosteroids (52, 95-97). The extent to which respiratory symptoms after preterm birth are expressions of an active inflammatory disorder or represent structural

consequences remains unclear (98-100). Skromme et al., in 'Project Extreme Prematurity', have previously found few convincing associations between perinatal variables and respiratory symptoms at 11 years of age and, surprisingly, they also found no association between GA and respiratory symptoms at 11 years (88).

1.2 Sleep

1.2.1 Sleep and sleep stages

Sleep is defined as a 'reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment' (101). Sleep is characterised by synchronised events in billions of synaptically coupled neurons in thalamocortical systems. During sleep, most of the sensory input to the cerebral cortex is actively inhibited (102).

The classic objective method for measuring sleep is polysomnography, which records electroencephalography (EEG), electromyography (EMG) and electrooculography. During the registration, information on both the quantity and quality of sleep is recorded. Sleep can be divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep (101). NREM sleep is further divided into three sleep stages (103):

Stage N1: Stage N1 sleep is the typical transition from wakefulness to sleep. It is characterised by low-amplitude mixed EEG frequencies in the theta range (4 to 7 Hz) for at least 50% of the epoch. Eye movements are typically slow and rolling.

Stage N2: Stage 2 is often called light sleep. The brain waves are slower in frequency and higher in amplitude than during waking and occasionally we see characteristic sleep spindles and K-complexes.

Stage N3: This stage is frequently referred to as 'deep sleep' or 'slow-wave sleep'. The EEG shows a predominance of slow high-amplitude brain waves during this stage (101).

REM sleep: Rapid Eye Movements (REM) are one of the defining features of this stage. The EEG shows relatively fast, low-amplitude brain waves, which are similar to the brain waves during Stage 1 or wakefulness. Muscle tension (EMG) is lower in REM sleep than in any of the other sleep stages (101).

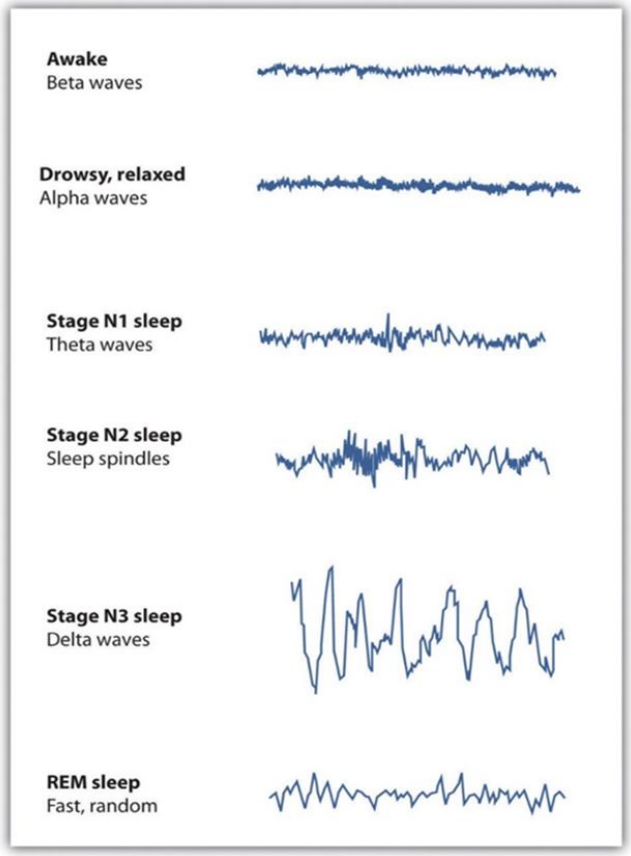

Figure 1 EEG recordings of brain patterns during sleep. Each stage of sleep has its own distinct pattern of brain activity.

(Reprinted from the book *Introduction to Psychology*, Cummings (2014) (CC BY-NC-SA 4.0)(103)).

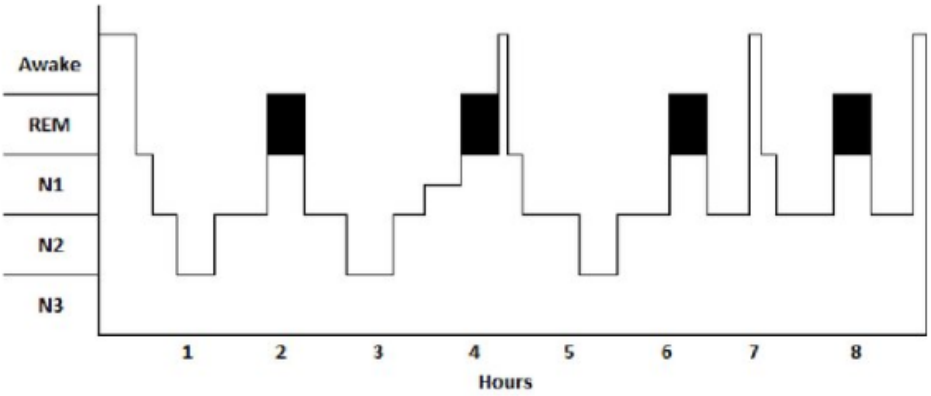

Figure 2 Hypnogram of scored human sleep staging.

(Reprinted, with permission, from the book *Sleep and affect: Assessment, Theory, and Clinical Implications*, Babson et al. (2015) (104)).

Sleep is not a homogenous process and appears to go through multiple cycles during the night. These cycles occur in fairly typical patterns of NREM and REM sleep, with a single cycle lasting approximately 90 to 120 minutes. Four to five cycles occur during a typical eight-hour night of sleep. The first cycle of the night starts with a transition from wake to Stage N1, then into Stage N2, Stage N3, and then REM. This pattern repeats itself with blocks of NREM and REM sleep. As the cycles continue during the night, the percentage of REM sleep in each cycle generally increases. The percentage of Stage N3 tends to decrease over the course of the night, with the largest amount of N3 in the first half of the night (101).

1.2.2 Biological clock and sleep regulation

Many of the body's functions follow a circadian rhythm, that is, a rhythm that varies with the clock. Body temperature; level of activation; secretion of certain hormones, such as cortisol and melatonin; and urine production are examples of such functions (105). The core of the brain that mainly generates this circadian rhythm is located in the hypothalamus and is called the suprachiasmatic nucleus (SCN) or our biological clock. SCN entrains the phase of clocks in numerous peripheral tissues and controls the rhythmicity in various body functions. Our biological clock (SCN) can be

influenced by external environmental factors (zeitgebers). Light is the most important factor (105).

Sleep is biologically regulated through the interplay between this circadian process (process C) and the homeostatic process (process S). The homeostatic process (process S) represents the sleep need or sleep pressure, which is built up during wakefulness (106, 107). Process S regulates the amount of deep sleep. The circadian factor regulates the timing of sleep and its length. Sleep length is dependent on the time one goes to sleep and one's own circadian rhythm. One can, however, override these biological factors by behaviour, for example, by staying awake at night even when tired and usually asleep at that time (108).

Melatonin: Melatonin is a neurohormone principally secreted by the pineal gland at night under normal light/dark conditions. The endogenous rhythm of secretion is generated by the SCN and entrained to the light/dark cycle. Light is able to either suppress or synchronise melatonin production according to the light schedule (109).

Melatonin has two probable interacting effects on the sleep–wake cycle. First, it entrains and shifts the circadian rhythm (process C) into a 'chronobiotic' function. Second, it may promote sleep onset and continuity in a 'hypnotic' function by increasing the homeostatic drive to sleep (process S) (110). Melatonin and body temperature are both recognised as biological markers of the circadian phase (111).

Cerebral brain regions involved in sleep: Staying awake and alert or sleeping restfully largely depend on the function of a few small areas of the brain. The brain's control of sleep and wakefulness is complex and not entirely understood, but scientists have revealed areas of the brain involved in regulating these processes. Arousal or wakefulness is mediated by a system of neurons ascending from the brainstem to the cerebral cortex (112).
There are two anatomic branches of the ascending arousal system: the first branch travels through the thalamus and the second through the hypothalamus and basal

forebrain (113). When neurons in the arousal areas in the brainstem are active, the cortex remains activated, and we stay awake. When the arousal areas of the brain are active, they also inhibit activities in other areas of the brain responsible for promoting sleep. This inhibition of sleep results in stable wakefulness (114).

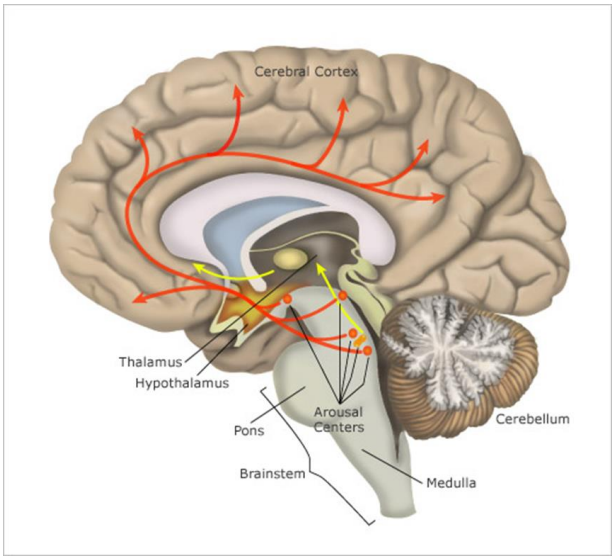

Figure 3 Arousal centres in the brain help maintain wakefulness.
(Reprinted, with permission, from the webpage *Under the Brain's Control* created by Harvard Medical School Division of Sleep Medicine (112)).

An area in the hypothalamus is responsible for shutting down the brain's arousal signals and causing the transition to sleep. These neurons are part of the hypothalamus called the ventrolateral preoptic nucleus (VLPO) and median preoptic nucleus (MNPO). The VLPO and MNPO innervate the nuclei of the ascending arousal system and secrete inhibitory neurotransmitters/neuropeptides, thus inhibiting arousal (113, 115). By shutting down the arousal centres, the VLPO and MNPO promote sleep.

The timing of transitions between sleep and wakefulness is also closely tied to the SCN. The SCN promotes wakefulness by producing a powerful alerting signal that offsets sleep drive, and the SCN promotes sleep by turning off the alerting signal (112).

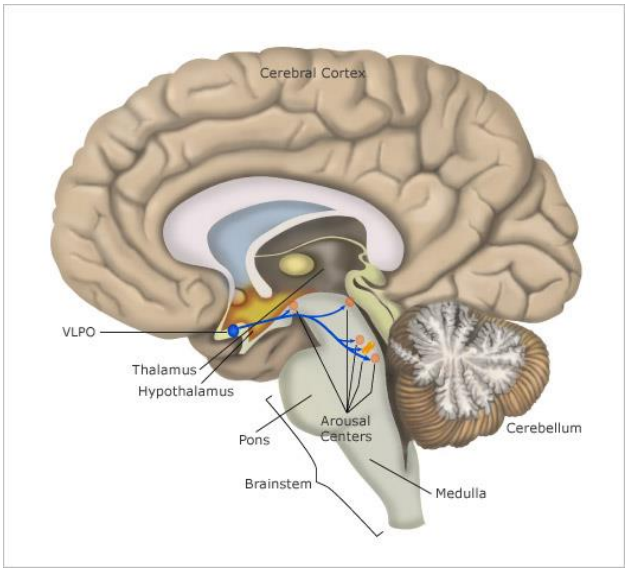

Figure 4 VLPO promotes sleep by inhibiting activities in the brain's arousal centres.
(Reprinted, with permission, from the webpage *Under the Brain's Control*
created by Harvard Medical School Division of Sleep Medicine (112)).

1.2.3 Foetal sleep and development of circadian rhythms

The emergence of different behavioural states, i.e. quiet sleep (NREM), active sleep (REM) and wakefulness, is one of the most significant aspects of early brain maturation. A certain degree of brain maturation is required before the behavioural states can be classified. Early in the development in uterus, a large amount of time is spent in indeterminate sleep. During the last 10 weeks of gestation, quiet (NREM) and active (REM) sleep are distinguishable (116), and active (REM) sleep predominates. Newborns spends 16-18 hours a day asleep, more than half of this sleep is REM sleep. It is believed that sleep, particularly REM sleep, plays a crucial role in optimal brain development (116). During prenatal life, the endogenous rhythmic activity in the biological clock develops. As it matures, the sensitivity to external signals is changed through a gradual and programmed process (117). The development of circadian rhythms is mediated by maternal melatonin (118). The circadian rhythms of body temperature are evident by GA 29 weeks in neonates born preterm (119).

1.2.4 Sleep in childhood

In newborn babies, the amount of sleep is spread out fairly equally between day and night, and the sleep bouts are short and broken. Gradually night-time sleep becomes dominant and becomes continuous and uninterrupted. At the same time, sleep during the day decreases during the first three years (121) (see Figure 5).

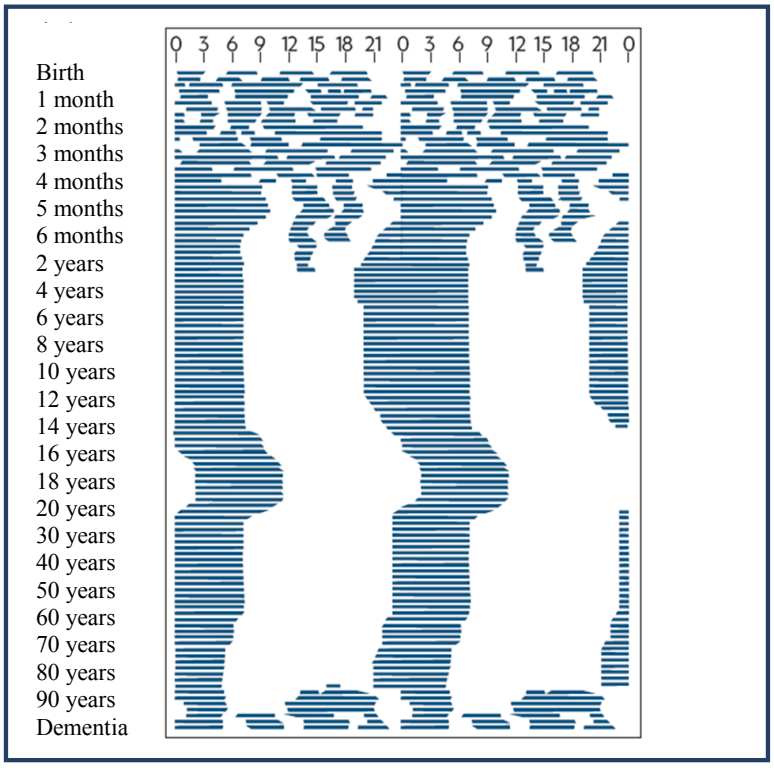

Figure 5 Schematic figure showing how sleep changes during life. Sleep periods are marked as lines. (Reprinted, with permission, from the book *Søvnsykdommer. Moderne utredning og behandling*. Bjorvatn B. 2012 (120)).

Different children will become able to sleep through the night at different ages.

With increasing age, the need for sleep will also decrease. A newborn baby can sleep for up to 18 hours a day, whereas the normal sleep length for a one-year-old child is 11–14 hours. Children and adolescents will have a greater need for sleep than adults until they are 18 years old (123, 124).

1.2.5 Why do we sleep?

Despite decades of effort, among the greatest mysteries in biology is why sleep is restorative and, conversely, why lack of sleep impairs brain function (114, 125). The true purpose of sleep is poorly understood. However, sleep is vital for both brain and body (111, 116, 126-130).

There is compelling evidence that sleep facilitates the encoding and consolidation of information (memory retention and forgetting) (126) and emotional processing and reorganisation of emotion-specific brain activities (127). In addition, sleep appears essential for the maintenance of the neural network, facilitating neuronal and glial connectivity and synaptic plasticity (128, 129).

Up until recently, it remained a mystery how the brain rids itself of waste materials. Recent research has now shown that waste products and potentially neurotoxic substances are transported from the cerebral interstitial fluid space and out of the brain via the glymphatic system (130, 131). In addition to this it has been found that the cerebral sinuses and meningeal arteries are lined with lymphatic vessels, and that these vessels forms a connecting pathway to the glymphatic system (132). Experiments on mice have shown that sleep drives metabolic clearance via the glymphatic system (133) and on the basis of these findings, it is hypothesised that the restorative properties of sleep may be linked to increased clearance of waste products produced in the awake brain. The glial cells, astrocytes, with their water channels, aquaporins, are considered to be central in clearing the brain's interstitial space (131, 134).

1.2.6 Children and sleep

Sleep problems: Sleep problems are relatively frequent in children (135, 136). In many types of illnesses, the prevalence of sleep problems increases, and 75%–80% of children with moderate to severe neurological developmental disorders have sleep problems (137).

What is a sleep problem? In order to define something as abnormal or problematic, one must have knowledge of what is normal. Defining normal sleep patterns and sleep requirements at different ages in childhood is difficult. Any definition must include the broad spectrum of normal development and physical maturation changes that occur in childhood and, at the same time, cultural, environmental and social conditions that may affect children's sleep (138).

In some studies, parents are asked if their children have a sleep problem. However, an understanding of what parents mean when they answer in the affirmative is hard to pinpoint. One might assume that the child's sleeping preferences do not meet parents' expectations of what is normal. This case may also be a matter of whether or not parents' sleep is disturbed. Previous studies on Swedish and American schoolchildren, that have examined sleep problems through parental questioning, have found a prevalence of 5.3% and 10.8%, respectively (139, 140).

In this introduction, the following sleep problems are presented in greater depth: insomnia, snoring, daytime sleepiness and non-recommended sleep duration.

Insomnia: Paediatric insomnia has been defined as 'repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family' (141). In a general sense, the working definition of insomnia in children may be construed as similar to that in adults, e.g. significant difficulty initiating or maintaining sleep (142). Insomnia in children, however, is a less understood condition and the widely used classification systems, the International Classification of Sleep Disorders (ICSD-3)(143) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5)(144), have no specific classification for childhood insomnia (145).

The prevalence of insomnia vary with age. In the first two years of life, the rates are high, at around 30%, and after the third year of life, the prevalence remains stable at around 15% (146). It is worth mentioning that the fact that the definition and

diagnosis of insomnia vary widely among the available studies directly influences the data on prevalence (146). In a recent Norwegian study, 12.7% of children aged 11–13 years reported insomnia symptoms, i.e. difficulties with initiating and/or maintaining sleep (135).

Insomnia in children is often multifactorial (147) and can be the end-result of multiple aetiologies, including behavioural, environmental, psychiatric, medical and psychosocial (141).

When approaching a child with insomnia, it can be helpful to explore several categories of causes, which can be overlapping. A recommended approach may be to identify possible: 1.) biological causes; 2.) medical causes; and 3.) behavioural causes (147).

1.) Biological causes may, among other things, cause the child to be hypersensitive to environmental stimulation, or indicate that they have problems with self-regulation. Causes linked to biological contributors can include circadian abnormalities such as delayed sleep–wake phase disorder (108, 147).
2.) There are multiple medical disorders that can cause insomnia. Some key medical causes that contribute to insomnia include gastrointestinal, pain-related, and pulmonary issues, such as asthma or chronic cough, and upper airway problems, particularly snoring and obstructive sleep apnoea (147). Multiple neurological disorders can affect sleep, including headaches, epilepsy, and restless leg syndrome. Psychiatric problems, such as anxiety and depression and others can also affect a child's ability to sleep. It is also important to be aware that some medications can be stimulating and may interfere with sleep onset or maintenance (147).
3.) Behavioural causes of insomnia are wide-ranging (147). The former widely used definition of behavioural insomnia includes some contributory factors. Behavioural insomnia of childhood is a disorder of young children (0–5 years of age), although it can persist into middle childhood and beyond, especially in those

with special needs (142). This type of insomnia is thought to largely result from ineffective sleep training or difficulties with limit setting by parents or caretakers. It can further be divided into sleep-onset association type and limit-setting type (142, 147).

Snoring: Snoring is a noise that occurs during sleep when the child is breathing in and there is a blockage of the air passing through the back of the mouth. The opening and closing of the air passage cause a vibration of the tissues in the throat. Loud and regular night snoring is often abnormal in otherwise healthy children (148). A meta-analysis of parent-reported snoring found a prevalence of 7.5% in unselected children aged 0–18 years (149).

Snoring may be a sign of a respiratory infection, a stuffy nose or allergy; it may also be a sign of sleep apnoea. Sleep apnoea causes partial or complete awakenings and has a negative effect on sleep quality. Snoring is a primary sign of obstructive sleep apnoea, which is the most common form of sleep-disordered breathing (SDB). A diagnosis of SDB is made after an objective registration of respiration during sleep (148).

Daytime sleepiness: Sleepiness is defined as the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness and sleep (143). Conditions causing excessive daytime sleepiness can be categorised into three groups: conditions that lead to insufficient sleep, decreased quality of sleep and increased sleep drive (hypersomnia). The first two groups account for the majority of cases (150). Experimental studies have found that increased daytime sleepiness can be a direct result of sleep deprivation or restriction in children (151-153).

Hypersomnia is a neurological disorder characterised by excessive time spent sleeping or excessive sleepiness. It can have many possible causes but the symptoms are not due to a disturbed night's sleep or disturbances in the circadian rhythm. Narcolepsy is

a rare chronic disease and is the most common cause of hypersomnia. The symptoms of narcolepsy are primarily strong sleepiness, involuntary sleep attacks and often interrupted sleep at night (150, 154).

Daytime sleepiness in children may be characterised by behaviours such as yawning and complaining about fatigue but additionally it can also be associated with a host of more subtle or even 'paradoxical' behavioural manifestations (e.g. increased activity) (138).

Few studies have researched the prevalence of parent-reported daytime sleepiness in the general population of children. Studies of school children have found a prevalence of 7%, 10% and 15% in children aged 6–15, 4–11 and 5–12 years, respectively (155-157).

Sleep habits and non-recommended sleep duration: Regular sleep schedules and age-appropriate sleep amounts are recommended for children. Several studies have shown a relationship between regularity and sleep outcomes (158). Regular sleep schedules positively relate to sleep onset, incidence of sleep problems and adequate sleep duration (158). The National Sleep Foundation has developed age-specific recommended sleep durations based on a rigorous, systematic review of global scientific literature related to the effect of sleep duration on health, performance and safety (124).

Several studies, including Nordic studies, have found that the total sleep duration for children and adolescents has decreased over the past decades (159-163), and this development results in more children sleeping less than recommended (161, 163, 164). This issue is worrying because even just an hour with too little sleep negatively impacts children's emotional, behavioural and cognitive functioning (165, 166).

Child's age	Recommended sleep length (hours)
0-3 months	14-17
4-11 months	12-15
1-2 years	11-14
3-5 years	10-13
6-13 years	9-11
14-17 years	8-10
18-25 years	7-9

Table 1 Age-specific sleep duration recommendations for children.
(This table is based on the National Sleep Foundation's recommendations (123, 124)).

1.2.7 Sleep and prematurity

How does sleep develop in a brain that does not itself develop normally? Extreme prematurity can result in brain injury and impaired brain development (20, 31), but little is known about how this condition affects sleep in the long term.

In 1996, a study was published on the development of melatonin rhythmicity in preterm children (GA 28–34 weeks) compared with term-born children (167). Melatonin rhythms developed more slowly in preterm children after premature ruptures of membranes, preeclampsia and intrauterine growth restriction as compared with full-term children (167). Whether these conditions have any lasting physiological, psychological or health consequences for these children is unknown. For example, the relationship between gestational length and the amplitude of melatonin rhythms as an adult and whether such an association may have an effect on sleep behaviours in later life still warrants further study.

In the NICU, hands-on care, procedures and interventions frequently disturb the sleep of preterm neonates, and disturbed sleep often leads to unwanted respiratory events (168). This condition can potentially affect early brain maturation. In addition, these preterm neonates often have neonatal morbidity that also disturbs sleep (169). Researchers have studied the effect of sleep interventions in the NICU (170-173). Nearly all of these studies focus only on short-term benefits and do not explore the

potential long-term benefits for development. Data on more subtle long-term consequences of EPT birth, e.g. related to sleep, are just beginning to emerge because survival after EPT is a relatively new phenomenon (174).

There are very few studies that have explored sleep architecture in EPT children they are, so far, inconsistent (175-178). Some studies indicate that early abnormal sleep architecture in EPT newborns may predict later neurological dysfunctions (179).

Few studies have examined the prevalence of sleep problems in preterm children. The increased prevalence of SDB in this group of children has received the most attention (180-184). However, it is surprising that so few studies have explored the prevalence of more general sleep problems or habits in this group of children. It is surprising considering that little is known about how preterm birth affects sleep in childhood and that this is a group of children who, due to their comorbid conditions, such as behavioural problems (78-80, 82, 83), respiratory morbidities (52, 88, 90) and NDDs (60-64), have a higher risk of sleep problems (185-189). It is also surprising because these children are born with a cognitive vulnerability and reduced sleep quality has been shown to increase this vulnerability (190, 191). Among preterm children, EPT children are the most vulnerable in relation to affected brain maturation (41, 192) and other types of morbidity (3, 47, 49, 50, 64, 193, 194). However, studies that explore the prevalence of common types of sleep problem or sleep habits in cohorts of EPT children are missing. Studies that have examined the prevalence of sleep problems and habits in preterm children have been conducted on children with relatively large variations in maturity at birth, and studies also include variations in terms of whether children with NDD are included or not (191,195-197,199-208).

Prematurity and general sleep problems: To the best of our knowledge, no previous studies have examined general sleep problems in EPT children. However, some studies have used validated forms for mapping different types of specified sleep problems in preterm children. McCann et al. used the Sleep Disturbance Scale for

Children and found that 19% of preterm children (GA < 33) at age 6-9 years had a parent-reported score indicating that they had a sleep problem (191).

Prematurity and insomnia symptoms: Previous studies have examined the prevalence of difficulty falling asleep or night awakenings in preterm children. The results here are somewhat contradictory and also difficult to compare as the children have different degrees of immaturity at birth, they have been examined at different ages and the children's sleep problems have been investigated in various ways, for example through parental reporting and polysomnography.

Perkinson-Gloor et al., Maurer et al., Mohring et al. and Iglowstein et al. investigated the prevalence of difficulty falling asleep and problems with night awakenings in preterm children at school age (197, 199, 200, 202). Perkinson-Gloor et al. found an increased prevalence of night awakenings via polysomnography in preterm children (GA < 32) at age 6–10 years compared with term-born children (199). Children with severe developmental delay were excluded from this study. Maurer et al. and Mohring et al. found no difference between preterm children (GA < 32) and term-born children with regard to night awakenings at age 7–12 years via polysomnography (200, 202). Iglowstein et al. found no increased prevalence in parent-reported difficulties for falling asleep or night awakenings in preterm children in the first 10 years of life (median GA 34) compared with term-born children (197).

Mohring et al. also examined sleep latency and did not find increased sleep latency in preterm children (GA <32) (202). Both Murer et al. and Mohring et al. excluded children with severe developmental delay, but Iglowstein et al. included them (197, 200, 202).

Romeo et al., Wolke et al., Caravale et al., Hysing et al. and Bilgin et al. investigated the prevalence of difficulty falling asleep or night awakening in preterm children of pre-school age (196, 201, 203, 204, 205). Romeo et al. examined low-risk preterm children (GA ≤ 31) at three to six years of age and found an increased prevalence in

parent-reported difficulties with initiating and maintaining sleep among preterm children compared with term-born children. The exclusion criteria were: being born SGA, significant cerebral lesions observed in ultrasound scans or congenital malformations, severe postnatal infectious diseases, metabolic complications, CP and epilepsy (203). Wolke et al. compared very preterm (GA < 32) and preterm (GA < 36) children with term-born children at ages 5, 20 and 56 months. However, they found no differences in the parent-reported prevalence of difficulties falling asleep or night awakenings among very preterm, preterm and term infants (196). Children with NDD were not excluded. Caravale et al. found no increased prevalence of parent-reported bedtime difficulties or number of night-time awakenings in preterm children (GA 23–35 weeks) among young children (mean age 21 months) (201). Caravale et al. included only children with normal cognitive, language and motor development. Hysing et al. examined preterm toddlers (GA 23–36 weeks) at six and 18 months; toddlers with NDD were not excluded (204). They found that being born preterm reduced the risk for night awakenings at six months compared with the risk for term-born infants and that the risk for night awakenings at this age was especially low for extremely low-birth-weight infants (<1,000 g). Furthermore, they found an increased risk of night awakenings at age 18 months for preterm toddlers compared with term-born toddlers. The children born with extremely low birth weight had the highest risk (204). Bilgin et al. examined toddlers born very preterm or with very low birthweight and term-born toddlers and found also increased risk of nightly awakenings at age 18 months in the preterm group but little difference between groups at age six months (205).

Hibbs et al. explored sleep patterns and quality in adolescents aged 16 to 19 years born preterm (GA < 37 weeks) and found no differences regarding self-reported problems with falling asleep or maintaining sleep in preterm adolescents compared with term-born adolescents (206). The preterm adolescents did not have significantly longer sleep onset latency as identified by polysomnography, but the arousal index, or number of awakenings per hour, was significantly higher in those born preterm. Adolescents with serious conditions, such as mental retardation or severe CP, and

adolescents diagnosed with sleep apnoea, as identified by polysomnography, were excluded (206).

Prematurity and snoring: A few studies have explored snoring in children and young adults born preterm. Rosen et al. examined preterm children (GA < 36) at school age (8–10 years) and found a prevalence of snoring of 21% among preterm children as compared with 4% among term-born controls (181). They also found that snoring was strongly associated with SDB (OR 7.2). Children with serious conditions (e.g. mental retardation or severe CP) were excluded from this study.

Wang et al. examined extreme preterm toddlers (GA 24–28 weeks) at age 18–22 months and also found a prevalence of snoring of 21% (207). There was no term-born control group in this study. All children with a known congenital anomaly, airway anomaly or neuromuscular disorder were excluded in this study.

Pavonen et al. examined young adults aged 18–27 years born preterm (<1,500 g) and a control group and found that the prevalence of chronic snoring was similar in both groups: 15.8% for the very-low-birth-weight group versus 13.6% for the control group (180). However, after controlling for confounding variables in multivariate logistic regression models (age, sex, current smoking, parental education, height, body mass index and depression), chronic snoring became 2.2 times more likely in the very-low-birth-weight group compared with the control group. Individuals with NDD were not excluded from this study.

Prematurity and daytime sleepiness: The prevalence of daytime sleepiness in preterm children is a little explored area. Rosen et al. studied the prevalence of SDB in school-aged children born preterm (GA < 36) compared with term-born controls and explored the prevalence of parent-reported daytime sleepiness in these groups of children. They found no significant difference between the two groups, and the prevalence was 6% for the preterm group and 7% for the control group (181).

Hibbs et al. explored daytime sleepiness in adolescents born preterm (GA < 37) compared with term-born controls. They found less self-reported sleepiness in the preterm group (206). As mentioned earlier, adolescents born preterm and diagnosed with sleep apnoea or serious conditions, such as mental retardation or severe CP, were excluded from this study.

Prematurity and sleep duration and habits: Several studies have explored sleep duration in children and young adults born preterm. Perkinson-Gloor et al. and Maurer et al. investigated sleep duration via polysomnography in preterm children (GA < 32) at school age (199, 200). None of these studies found any difference in sleep duration for preterm and term children. Both studies excluded children with severe developmental delay. Iglowstein et al. followed preterm children (GA < 37) from birth to age 10 years (197). Neither did they find any differences with regard to parent-reported sleep duration between preterm and term-born children. No children were excluded from this study.

Asaka et al., Caravale et al. and Hysing et al. examined sleep duration in preterm toddlers (201, 204, 208). Asaka et al. examined preterm toddlers (birth weight < 1,500 g and GA < 32) at 12 months of age with actigraphy and found a shorter night's sleep duration in the preterm toddlers compared with term-born toddlers (208). However, there was no difference between the groups in terms of the total amount of sleep for 24 hours. Included toddlers had no neurological or developmental problems, and toddlers with severe illness or congenital abnormality were excluded. Caravale et al. examined parent-reported sleep duration in preterm children (GA < 36) at age 13 to 29 months compared with term-born toddlers. They found no difference in night or daytime sleep duration between the groups (201). The study included preterm toddlers with normal cognitive, language and motor development. Hysing et al. examined total sleep time over 24 hours in preterm toddlers (GA 23–36 weeks) compared with term-born toddlers at age six and 18 months. They found that prematurity was associated with long sleep duration. However, they found that children born with extremely low

birthweight (<1,000 g) had 2.5-3-fold increased odds of sleeping for less than 10 hours compared with the controls. Children with NDD were included (204).

Hibbs et al. examined sleep duration in preterm adolescents (age 16 to 19 years) (GA < 37) (206). They found no differences in self-reported sleep duration or sleep duration mapped with actigraphs between preterm and term-born adolescents.

A few studies have compared sleep onset time and rise time in preterm children compared with term-born children. Maurer et al. found an earlier sleep onset time in school-age children born preterm (GA < 32) compared with full-term children via polysomnography (200). They found no differences in awakening times. Caravale et al. found no differences in parent-reported bedtime and rise time in preterm toddlers (GA < 36) compared with term-born toddlers (201). Asaka et al. also found no increased prevalence of parent-reported early morning awakening in preterm toddlers (birth weight < 1,500 g and GA < 32) compared with term-born toddlers (208). Bjorkqvist et al. found an earlier rising time among preterm adults (birth weight < 1,500 g) compared with term-born controls (198) and found no difference in bedtime.

2 Aims of the study

The overall aim of the study was to explore sleep outcomes in EPT children.

More specifically, the aims were as follow:

I. To compare current sleep habits at 11 years of age and the prevalence and nature of sleep problems up to this age in a national cohort of EPT children and an unselected control group of term-born children and to explore the relationships between NDDs and sleep problems in the EPT children.

II. To explore the extent to which prenatal or neonatal factors may predict the four specified sleep problems at 11 years of age in EPT children, namely, difficulty falling asleep or frequent awakenings, snoring, daytime sleepiness and insufficient sleep duration.

III. The study hypothesised that sleep problems at 11 years in EPT children were associated with behavioural problems and respiratory symptoms. Thus, the study aimed to explore the significance of these relationships to the four specified sleep problems.

3 Study design

3.1 Study population

All papers in this thesis are based on a national cohort of EPT children in Norway from 1999 and 2000 (15). EPT was defined as a GA < 28 weeks or birthweight < 1,000 g.

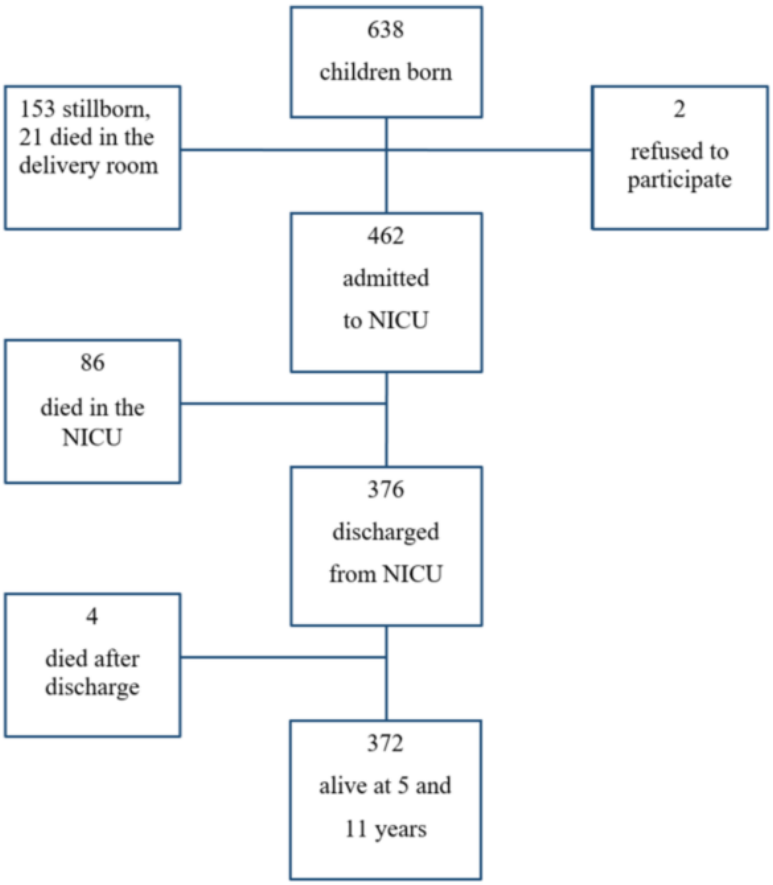

Figure 6 Description of the cohort of EPT children born in Norway in 1999 and 2000, alive at five and 11 years of age.

The children were prospectively followed from birth to ages two, five and 11 years. Of the 638 EPT infants, two chose not to participate, 153 were stillborn and 86 died in

the NICU. Three children died after NICU discharge before two years of age (209), and one died between two and five years (210).

A control group was used in Paper 1: parents of all children born in 2001 in Oppland County, Norway, who attended the school entry health assessment at five years of age were invited to complete a comprehensive questionnaire similar to that for the EPT children at five and 11 years (211). The school entry health assessment at age five years is part of the national health-care programme for children in Norway, and almost 100% of children participate. Of the 1,895 eligible children, data were obtained for 1,119 (59%) of the children at five years of age and for 593 (58% of the respondents at five years) at 11 years of age. Missing data at five years were largely due to low response rates at some of the public health-care clinics (families were recruited at the discretion of the public health-care nurses). The proportion of mothers with higher education was slightly higher (60% vs. 49%, $p < 0.001$) and that of single parents was lower (11% vs. 16%, $p = 0.009$) when comparing participants vs. non-participants at 11 years. Children born preterm (GA < 37, $n = 37$) were excluded from the control group in the statistical analyses. Thus, 556 controls were used in the final analysis.

3.2 Methods

3.2.1 Sources and collection of data from pregnancy and NICU stay

Data from pregnancy and NICU stay for the EPT children were coordinated by the MBRN. Forms for the registration of data were developed for the study and were completed by local obstetricians and paediatricians. Completed forms were returned to the MBRN, and the data were verified and expanded through linkage to the routinely recorded MBRN data. Routines regarding the treatment and examinations of the newborns were left to the discretion of each neonatal unit. Routine cerebral ultrasound evaluations were, with few exceptions, performed at age ≤1 week for all surviving infants and repeated at least once at age ≥3 weeks for all but a few infants. During the hospital stay, the infants were regularly monitored by an ophthalmologist.

3.2.2 Definitions/details of some prenatal and neonatal variables

GA: This is determined by ultrasound at 17–18 postmenstrual weeks. Ultrasound at this stage of pregnancy is a part of the national standardised pregnancy follow-up programme. If ultrasound examinations were unavailable (6%), then the postmenstrual age was based on the date of the last menstrual period (194).

Demographic characteristics
GA, weeks
Birth weight, grams
Sex
In utero exposure
Preeclampsia/eclampsia
SGA
Prenatal steroids
Infection in the amniotic cavity
Smoking – start of pregnancy
Smoking – end of pregnancy
Birth type
Caesarean section
Peripartum resuscitation
Apgar score < 5 after 5 min
Intubated
Illness severity score (4th quartile)
Respiratory morbidity
Mechanical ventilation (yes)
Days on mechanical ventilation
Oscillation
Postnatal steroids for lung diseases
Theophylline/caffeine
Patent ductus arteriosus, surgery treated
Neurologic injury
Subependymal/intraventricular haemorrhage
ROP
Pathological findings by the ophthalmologist at discharge
Other complications/treatment
NEC
Extensive medical treatment
Congenital malformations, syndromes or metabolic diseases

Table 2 Overview of prenatal and neonatal factors examined in the study

SGA: This is defined as birthweight below the 10th percentile (212) according to Norwegian growth references (213).

Preeclampsia (including HELLP syndrome and eclampsia): This corresponds to the maternal systolic blood pressure (BP) ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg in combination with proteinuria.

Chorioamnionitis: Clinical symptoms and findings are combined with biochemical and haematological testing, not histopathology.

Smoking in pregnancy: Information on smoking at the start and end of pregnancy is registered in the MBRN unless the pregnant woman objects to this. In 1999 and 2000, MBRN had information on the smoking habits of 88.2% and 87.2% of pregnant women, respectively (6).

Illness severity score: This is computed from three components of the Clinical Risk Index for Babies, namely, the lowest and highest fractional oxygen requirements and the largest base deficit during the first 12 hours of life (214, 215).

ROP: This variable is graded according to the Committee for the Classification of Retinopathy of Prematurity (216).

NEC: This variable is defined as being treated for either a proven or suspected disease.

Extensive medical treatment: This variable was included to identify children who had received extensive medical treatment at the NICU and was defined as a child having at least one of the three common extensive medical treatments: mechanical ventilation > 40 days, NEC or ≥ four courses of antibiotic treatment.

3.2.3 Follow-up at five years of age

At five years of age, the children were examined at 19 local paediatric departments in accordance with the research protocol. Independent of one another, experienced paediatricians performed a general clinical and neurological examination; a physiotherapist assessed motor functions with the Movement Assessment Battery for Children (M-ABC) test (217) and classified the gross motor function for the children with CP according to the GMFCS for cerebral palsy (55); psychologists tested cognitive abilities (IQ) with the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (218).Visual function and hearing were tested during

the clinical examination or recorded from previous examinations at the public health-care clinics. Each child was given an NDD score according to the definitions used in the Extremely Preterm Infants (surfactant C) cure (EPIcure) study, i.e. no, minor, moderate or severe disability (219).

Movement Assessment Battery for Children (M-ABC) test: The M-ABC test assesses motor function in children and consists of eight tasks in the areas of hand motor skills, ball skills and balance. Each task is scored using a 0–5 point range; higher points indicate poorer motor function. The test gives a total score that is interpreted using norm tables. A total score above the 95th percentile is classified as indicating a motor problem. The M-ABC test has different age bands (217). In our study, age band 1 (4–6 years) was used.

The M-ABC test was conducted by a physiotherapist at each paediatric department. Physiotherapists who were not familiar with the test received formal training before the start of the project. According to the test manual, the inter-rater agreement was 0.75–0.98 % (217).

The Gross Motor Function Classification for Cerebral Palsy (GMFCS): Gross motor function for children with CP was classified according to the GMFCS. The GMFCS is a five-level classification: Class 1, means that the child can move freely around in home, in school with more; Class 2, unable to run or jump; Class 3, dependent on devices for walking; and Classes 4 and 5, non-ambulatory CP (55).

Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R): WPPSI-R is an intelligence test designed for children. The test consists of 12 subtests: six for verbal IQ and six for performance IQ. An FIQ is calculated from the subscales (218). The reference mean value for the IQ scores is 100, and the standard deviation (SD) is 15. The test is designed for children from two years and 11 months to seven years and three months of age. All the psychologists participating in the project were

experienced in using WPPSI-R. The WPPSI-R manual provides information about the inter-rater agreement varying from 0.88 to 0.96 (218).

Sensory impairments: Visual function and hearing were recorded based on the clinical examination or previous examinations. All children in Norway undergo vision screening at four years of age and pure-tone audiometry at five years of age at public health-care clinics using methods and standards in line with national guidelines. Any significant deviation results in a referral to an ophthalmologist or an audiology clinic with ear, nose, and throat specialists.

Neurodevelopmental disability (NDD): The results of the examinations performed by the paediatricians, psychologists and physiotherapists of the EPT children were merged and classified into no, minor, moderate or severe NDD (64):

No NDD: No identified disability was defined as the absence of CP, FIQ of 85 or higher, M-ABC score of less than or equal to the 95th percentile and normal vision and hearing.

NDD 1: Minor disability was defined as CP Class 1, FIQ of 1 to 2 SDs below the mean (i.e. 70–84), a M-ABC score higher than the 95th percentile, squint/refractive error requiring glasses or mild hearing loss.

NDD 2: Moderate disability was defined as CP Classes 2 to 3, FIQ of 2 to 3 SDs below the mean, severe visual impairment or need of hearing aid.

NDD 3: Severe disability was defined as one or more of the following: CP Classes 4 to 5, FIQ of more than 3 SDs below the reference mean value of 100, legal blindness or complete deafness.

3.2.4 Follow-up at 11 years of age

At 11 years, we obtained information on the families' sociodemographic characteristics and lifestyles and the children's health, including sleep characteristics, behavioural and respiratory health, from postal questionnaires completed by the parents (for behaviours, we included each child's teacher).

Sleep variables

Sleep variables (Paper 1)

Sleep habits - The parents answered questions about the child's sleep habits on weekdays on a questionnaire. They were asked what time their child went to bed, when the child stood up and how long the child took to fall asleep (sleep onset latency). Sleep duration was defined as the time in bed minus sleep onset latency.

General sleep problems - The questions relating to general sleep problems differed slightly for the EPT group and the control group. Both groups were asked if their child ever had sleep problems. 'Never had significant sleep problems' was the first alternative for both groups. For sleep problems, the alternatives for the EPT group were 'had sleep problems during the first few years but not anymore', 'has sleep problems now but only in the last years' and 'always had sleep problems including now'. For the control group, the alternatives for sleep problems were 'sleep problems before he/she started school, but not later', 'sleep problems after he/she started school, but not now' or 'still having sleep problems'.

We considered the answer relating to 'sleep problems before he/she started school, but not later' in the controls to be the same as 'sleep problems in the first few years but not anymore' in the EPT group, and the answer 'still having sleep problems' in the control group to be the same as 'always had sleep problems including now' in the EPT group. An EPT child who either 'has sleep problems now but only in the last years' or is 'still having sleep problems' was defined as having current sleep problems. The control children who 'always had sleep problems including now' were defined as

having current sleep problems. If the parents reported sleep problems at any age or always, this answer was transformed into the variable 'has or has had sleep problems' for both groups.

Specified sleep problems - Five categories of sleep problems were addressed. The parents of the EPT children were asked: 'If your child has or has had sleep problems, how would you describe these?' The parents in the control group were asked: 'If your child has had sleep problems since he/she started school, how would you describe these?' The alternatives were the same in both groups: 'difficulty falling asleep', 'frequent awakenings during the night', 'waking up unusually early' and 'waking up unusually late'. The parents were also asked if they thought their child got enough sleep, and the answers were 'not enough', 'a bit too little', 'enough', 'a bit too much' and 'too much'. The answers 'not enough' and 'a bit too little' were combined into 'the child gets too little sleep' in our analyses.

Sleep variables (Papers 2 and 3)

The parents assessed the sleep problems in terms of whether their child had difficulty falling asleep or had frequent awakenings, snored, gasped for air or stopped breathing when asleep and if the child had trouble breathing in the night 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 using the following items: at what time a child go to bed and get up on weekdays, how long did it take from going to bed until falling asleep (sleep onset latency) and how long was the child awake during the night after sleep onset. We calculated the total sleep duration to be the time in bed minus the sleep onset latency and time awake after the sleep onset. In accordance with recently published guidelines, the recommended sleep duration at 11 years was defined as 9–11 hours (123) and we defined non-recommended sleep duration as more or less than this. However, our definition of non-recommended sleep duration differs somewhat from these guidelines. According to the guidelines, the recommended length of sleep at 11 years is 9-11 hours, but 7-8

hours and 12 hours may be appropriate and less than seven hours and more than 12 hours is non-recommended sleep duration (123).

Behaviour: The parents and teachers completed the Strengths and Difficulties Questionnaire (SDQ). SDQ is a general behavioural screening questionnaire for 4–17-year-olds. It contains five items in each of its five subscales: emotional problems, hyperactivity/inattention, conduct problems, peer problems and prosocial behaviour. Each item is scored on a three-point scale: 'Not true' (0), 'Somewhat true' (1) and 'Certainly true' (2). A total score is computed by collapsing the first four subscale scores (excluding the prosocial behaviour scale) and only these first four subscales were included in our study. The total subscale score ranges from 0 to 10 and the total score from 0 to 40. The SDQ has good psychometric properties, including for preterm children (220-224).

Respiratory health: The parents completed the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (225), which contains the following questions on respiratory symptoms during the last 12 months: Has your child experienced wheezing or whistling in the chest and, if so, how many attacks? How often has the child's sleep been disturbed due to wheezing? Has wheezing ever been so severe that the child had trouble saying more than one or two words at a time between breaths? Has the child's chest sounded wheezy during or after exercise? Has the child had a dry cough at night, apart from a cough associated with a cold or chest infection?

We also examined the current use of asthma medications, including inhaled corticosteroids, short- or long-acting β_2 agonists and oral leukotriene modifiers, and whether the child was ever diagnosed with asthma. Current asthma was defined as a 'Yes' response to 'ever asthma' combined with either respiratory symptoms or use of asthma medications during the previous 12 months or asthma medications and symptoms during the past 12 months regardless of reporting asthma.

3.3 Statistical analyses

Forms for registration of data were developed for the study. The completed forms were collected at the MBRN. The forms were read optically and checked for errors. Missing data could be corrected or completed by querying the local paediatrician for the neonatal and perinatal periods and at five years of age.

Group comparisons were performed using Student's t-tests, chi-square tests or Fisher's exact tests. Adjustments for sex, single parenthood and maternal education were performed using a logistic regression analysis for dichotomous variables and a linear regression analysis for continuous variables. In Paper 1, the mean difference, OR and 95% confidence intervals (CIs) were calculated in the unadjusted and adjusted analyses. In Paper 2, the OR and 95% CIs were calculated in the unadjusted and adjusted analyses. In Paper 3, the OR and 95% CIs were calculated in the adjusted analyses. The significance level was set at an α-level of 0.05. SPSS statistical packages were used for all analyses.

3.4 Ethics

The study was approved by the Regional Committee on Medical Research Ethics and Norwegian Data Inspectorate (2009–2271). The cohort of children from Oppland County, which constituted the control group at 11 years of age, was also approved by the Regional Committee on Medical Research Ethics and Norwegian Data Inspectorate (2012–1690). The parents in both cohorts gave written informed consent.

4 Summary of the results from each paper

4.1 Paper 1

The study explored the prevalence of general and specified sleep problems during childhood and current sleep habits for a period of 11 years. Data were available for 231/372 (62%) of the EPT children and for 556 children from the control group. The NDD scores were available for 195 of the 231 EPT children participating at 11 years of age. These findings show that 93 children had no identified disability (no NDD), 83 children had a minor disability (NDD 1), 13 children had a moderate disability (NDD 2) and six children had severe disability (NDD 3).

The sleep habits of the children differed across the two groups. The EPT children went to bed earlier than the term-born children (20.54 vs. 21.18 hours), had longer sleep onset latency (35 vs. 28 minutes), spent more time in bed (10.2 vs. 9.8 hours) and had longer sleep duration (9.6 vs. 9.3 hours).

There were also differences between the EPT children with no NDD and the control children with respect to sleep habits. The EPT children with no NDD went to bed earlier, spent more time in bed and had longer sleep duration than the controls. When we compared the EPT children with no NDD with the controls, there were no longer any differences between the groups with regard to sleep onset latency.

There was also a higher prevalence of general sleep problems in the group of EPT children. In total, 26% of the EPT children and 14% (adjusted OR 2.1) of the controls had experienced sleep problems at some point. EPT children were reported to have more sleep problems in early childhood (11% vs. 3%, adjusted OR 3.9) and have more sleep problems at 11 years of age than the controls (15% vs. 7%, adjusted OR 2.3). The proportion of EPT children who had experienced sleep problems at some point increased with the degree of NDD, from 23% to 67%, but even the EPT children with no NDD had a higher prevalence than the controls (20% vs. 14%).

In the EPT children born before GA of 28 weeks, there were no significant differences in the prevalence of general sleep problems between the 49 EPT children born with GAs of 23–25 weeks and the 120 born with GAs of 26–27 weeks.

When the parents were asked about specified sleep problems, they reported that the EPT children had more problems falling asleep (22% vs. 11%), waking up frequently during the night (13% vs. 4%) and waking up early in the morning (9% vs. 1%) than the controls (226).

4.2 Paper 2

In Paper 2, the parents were asked about the occurrence of specified sleep problems among the EPT children at the 11 years of age. In addition, sleep duration was calculated according to the sleep habits of the EPT children as reported by their parents. Of the 372 eligible children, sleep data were available for 221/372 (59%) at 11 years. Difficulty falling asleep or frequent awakenings were reported for 27.5%, snoring for 28.1%, daytime sleepiness for 17.2% of the children and sleep duration less than the recommended nine hours for 24.7% of the children. None of the children slept more than recommended. Only three children had breathing problems, and two gasped for air when asleep. The predictors of these outcomes were, therefore, not examined, but four of these five children also snored and were thereby included in the group of snorers.

Being born SGA and having neonatal cerebral haemorrhage (subependymal/ intraventricular haemorrhage) were the only prenatal and neonatal factors that significantly predicted difficulty falling asleep or frequent awakenings, i.e. 43% of SGA vs. 25% of non-SGA children (adjusted OR 2.2) and 42% of children with cerebral haemorrhage vs. 24% of those without haemorrhage (adjusted OR 2.3). When restricting analyses to children with GA $\leq$ 27 weeks, SGA still predicted difficulty falling asleep or frequent awakenings. Smoking, both during early and at the end of pregnancy, significantly predicted snoring, i.e. 37% versus 14% for early (adjusted

OR 4.3) and 24% vs. 8% for late pregnancy (adjusted OR 4.3). There were no statistically significant predictors of sleep duration <9 h or daytime sleepiness (227).

4.3 Paper 3

In Paper 3, the study used the same specified sleep problems as in Paper 2. However, because very few children were reported as having breathing problems or gasped for air when asleep, these questions were not included in this paper. The specified sleep data and ISAAC data were obtained for 216/372 (58%) of the children. SDQ was completed by the parents for 215 children and by the teachers for 184 children. Participants and non-participants did not differ regarding GA or the proportion of SGA, bronchopulmonary dysplasia or ROP, but there was a tendency for less severe disability among the participants (3.3% [*n* = 6] vs. 9.8% [*n* = 12]). 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 nine hours for 24.1% of the children. The average total SDQ score was 8.8, and the prevalence of current asthma was 18%. Only two children had problems with speaking due to wheezing. This question was, therefore, not included in further analyses.

Sleep problems and behaviour problems

The children who had difficulty falling asleep or frequent awakenings had a higher parent-reported total score for SDQ (11.9 vs. 7.6, adjusted OR 1.1 for both), 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 total score for SDQ (9.1 vs. 6.3) and a higher teacher-reported emotional problem score.

The children who snored had a higher parent-reported and teacher-reported total score for SDQ (10.4 vs. 8.0 and 9.0 vs. 6.2, adjusted OR 1.1 for both) and a higher score for conduct problems than the children who did not snore. The children who snored also had more parent-reported emotional problems.

The children who had daytime sleepiness had a higher parent-reported and teacher-reported total score for SDQ (12.1 vs. 8.0 and 9.6 vs. 6.5, adjusted OR 1.1 for both) and a higher score for emotional problems than children who did not have daytime sleepiness. The parents further reported that these children also had more hyperactivity/inattention and peer problems.

The children who had a sleep duration of less than the recommended nine hours had a higher parent-reported total score for SDQ (10.6 vs. 7.9, adjusted OR 1.1) than those who slept for longer.

The association between 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 insignificant (228).

Sleep problems and respiratory symptoms

The children who had difficulty falling asleep or frequent awakenings had experienced wheezing more often during the last 12 months (32.6% vs.17.3%), but the association was no longer significant after the adjustment.

Snoring was associated with wheezing during or after exercise (29.1% vs. 12.6%, adjusted OR 2.8), current asthma (36.4% vs. 11.9%, adjusted OR 4.2) and use of bronchodilators (19.6% vs. 7.6%, adjusted OR 3.2).

Daytime sleepiness was associated with wheezing during the last 12 months (40.0% vs. 17.8%, adjusted OR 3.4), disturbed sleep due to wheezing (20.0% vs. 6.0%, adjusted OR 3.9), wheezing during or after exercise (32.4% vs. 14.1%, adjusted OR 2.9), use of inhaled corticosteroids or oral leukotriene modifiers (23.5% vs. 8.5%, adjusted OR 3.4) and use of bronchodilators (23.5% vs. 8.5%, adjusted OR 3.9).

Sleep duration less than the recommended (<9 hours) was associated with disturbed sleep due to wheezing (16.7% vs. 1.4%,*) and use of inhaled corticosteroids or oral leukotriene modifiers (18.2% vs.3.8%, adjusted OR 5.6).

The association between these specified sleep problems and respiratory health problems remained unchanged after including SGA and the parents' current smoking habits (mother or father smoking) as covariates in the adjusted analysis (228).
*Adjusted analyses not performed due to low number.

5 Discussion

5.1 Discussion of the results

The present thesis supports that EPT children have a higher prevalence of sleep-problems through childhood and that the prevalence increases with increasing NDD. It also supports that EPT children have different sleep habits compared to children born at term. Surprisingly, there were few associations between prenatal and neonatal factors and various types of sleep problems at 11 years. However, we found that EPT children with these sleep problems at 11 years had more behavioural problems and more respiratory health problems than EPT children without these sleep problems.

5.1.1 Prevalence of sleep problems in childhood in EPT children

General sleep problems up to 11 years of age

EPT children were reported, about twice as often, to have had sleep problems at some point up to 11 years of age (26% vs. 14%) and they were also twice as likely to have current sleep problems at 11 years of age (15% vs. 7%) compared with the control group. The age when there was the greatest inequality in sleep problems between the two groups was during the first years of life. At that point, the prevalence of sleep problems in the EPT children was 11% versus 3% in the control group (226).

The rates of sleep problems in our control group were comparable to those reported by others, e.g. 7% of our children had current sleep problems compared with 5.4% and 10.8% in unselected schoolchildren (139, 140). The reported rates of sleep problems vary due to differences in methods, e.g. age at assessment, race and culture, but these figures lend support to our assumption that our control group was representative of the eligible cohort.

To the best of our knowledge, no previous studies have examined the prevalence of general sleep problems in EPT children in childhood up to 11 years of age. McCann et al. surveyed different types of sleep problems among preterm children (GA < 33) at school age using the Sleep Disturbance Scale for Children (229) and found that 19.1%

of the preterm children had a total score indicating that they had a sleep problem (191). However, this questionnaire also includes daytime sleepiness, and parents may not necessarily think about sleepiness when asked an open question about whether their child has a sleep problem. This finding may explain why the proportion of children with a sleep problem is somewhat higher in their study.

The greatest difference between the EPT children and controls was found for the first years of life. Hysing et al. examined a large cohort of Norwegian children at ages six and 18 months and found that children born with extremely low birthweight (birthweight < 1,000 g) had a reduced risk of night awakenings at age six months and a significantly increased risk of night awakenings at age 18 months compared with term-born children (204). This observed developmental shift in increased nocturnal awakenings in children born with extremely low birthweight has also been found in a study of very preterm children during the same developmental period (205). The reason for this developmental shift is not certain. This study's questions relating to general sleep problems in the first years of life are, however, not nuanced enough to detect any possible developmental shift in EPT children with regard to night awakenings between six and 18 months.

Wolke et al. and Caravale et al. studied preterm children under three years of age but with a higher degree of maturity at birth (GA<36) (196, 201). They studied the prevalence of difficulties falling asleep or night awakenings but did not find any difference between the children born preterm and the term-born children. The study by Wolke et al. is most comparable to our study as they did not exclude children with NDD. Caravale excluded children with abnormal development. The preterm children in the studies of Wolke et al. and Caravale et al. (196, 201) were more mature at birth compared to the EPT children in our study and it is therefore not surprising that these studies did not find the same increased prevalence of difficulties falling asleep or night awakenings in children born preterm compared to term-born children. We found, in Paper 1, that frequent awakenings during the night in EPT children were related to the degree of NDD and, in Paper 3, that problems involving difficulty

falling asleep or frequent awakenings were related to comorbid conditions (behavioural problems and lung health). Furthermore, it is known that the severity of NDD and the prevalence of comorbidity increase with increasing degree of prematurity (49, 64, 68) and therefore it is unsurprising that the increased problems with difficulty falling asleep or frequent awakenings do not necessarily apply to all children born preterm.

Specified sleep problems up to 11 years of age

In Paper 1, five categories of sleep problems were addressed. The parents of the EPT children were asked to describe any sleep problems experienced by their child at any point, and the control parents were asked to describe any sleep problems experienced by their child after starting school (226). The problems were the same for both groups: difficulty falling asleep, frequently waking up during the night, waking up unusually early and waking up unusually late. Parents were also asked if they thought their child got enough sleep. As the questions were different for the control and EPT groups, comparing the prevalence of these specified sleep problems was somewhat difficult. Having too little sleep was the most frequent sleep problem in both groups, followed by problems with falling asleep.

5.1.2 Sleep habits at 11 years of age in EPT children

The EPT children had different sleep habits at 11 years of age compared to the controls. The EPT children went to bed earlier, spent more time in bed and had longer sleep duration than the controls (226). To the best of our knowledge, no previous studies have explored sleep habits in EPT children, but some studies have explored this issue in preterm children (183, 197-201, 206).

Bedtime and rise time

The fact that the EPT children went to bed earlier provides support for previous studies that have suggested that preterm children may have an earlier sleep phase (198, 206). Hibbs et al. found that adolescents born preterm with a mean GA of 31 weeks demonstrated significantly earlier bed and waking times as reported by both

actigraphy and self-reports (206). Bjorkqvist et al. also found, through actigraphy, that young adults born preterm with a mean GA of 29 weeks woke up earlier than the controls (198). The increased prevalence of early morning awakening in the EPT children in our study (226) may also possibly be explained by an earlier sleep phase.

Time in bed, sleep onset latency and sleep duration

The combination of the earlier bedtime and longer sleep onset latency may indicate that EPT children were put to bed earlier than necessary, e.g. because of the parents' needs since the care of EPT children can be more demanding due to their health problems (49). Other possible explanations for the longer sleep onset time may be biological factors, medical factors or behavioural factors (147) in the EPT children which result in problems falling asleep. However, the data in this thesis do not indicate the reasons for this.

On average, the EPT group also reported longer sleep duration than the controls (226). We have not found previous studies with the same result. The Caffeine for Apnea of Prematurity Study Group examined preterm children with a birth weight < 1250 g (183). They suggested that children born preterm more frequently had shorter sleep duration than other children at age 4–12 years (183). However, they did not include a term-born control group and only included children who were candidates for treatment with methylxanthine in their studies. Other studies on school-age children found no differences when comparing sleep duration in preterm children with term-born children (197, 199, 200). The results from studies exploring sleep duration in preterm children before school age or in adolescence (201, 206, 208) are conflicting.

Whether longer sleep duration in EPT children is a result of an increased need for sleep in this group of children or whether it is a result of different parenting styles in the EPT parents as compared with the parents of the controls is still unknown. The fact that the EPT children also go to bed earlier may indicate that the parents in the two groups give the children different schedules with regard to bedtime and that, as

previously mentioned, this leads to a longer sleep onset latency but perhaps also longer sleep duration.

5.1.3 Sleep problems and habits and NDDs

One of the main contributions of the present thesis is the focus on the associations between NDD and severity of NDD and sleep problems and sleep habits in EPT children (226). The prevalence of general 'sleep problems in the first years', 'sleep problems at one time or another' and 'current sleep problems' tended to increase with the degree of NDD. However, the observed increase was only significant for 'sleep problems at one time or another'. The specified sleep problems, such as frequent awakenings during the night and waking up unusually early, also significantly increased with increasing levels of NDD. EPT children with NDD 0 also had more frequent sleep problems at one time or another, sleep problems in the first years and current sleep problems, but the difference was only significant for sleep problems in the first years (226).

The relationship between the degree of NDD and sleep habits was not investigated. However, we did compare the sleep habits of the EPT children with NDD 0 with the controls and found the same differences that we had found when we examined the entire EPT group in comparison with the controls except that there was no longer any significant difference in sleep onset latency. The EPT children with NDD 0 had earlier bedtimes, longer times in bed and longer sleep duration than the controls compared with the entire EPT group (226).

Underpinning impaired neurodevelopment in preterm children is an altered cerebral architecture (characterised by reduced grey and white matter volumes, diffuse non-cystic white matter loss and reduced cortical folding and gyral complexity) (230, 231). The cerebral architecture is also fundamental for complex neurobehaviours, such as sleep (232). It is therefore not surprising that an increased prevalence of sleep problems was found with an increased degree of NDD in EPT children.

5.1.4 Current specified sleep problems at 11 years of age

There were four current specified sleep problems at 11 years of age that were examined in Papers 2 and 3 (227, 228). The main aim of these papers was to examine the prenatal and neonatal factors that possibly predicted these sleep problems and to investigate whether these sleep problems were associated with behavioural problems and respiratory symptoms in this group of EPT children. Nevertheless, the prevalence of these specified sleep problems in this study compared to earlier findings were briefly discussed.

Difficulty falling asleep or frequent awakenings

The prevalence of difficulty falling asleep or frequent awakenings (insomnia symptoms) in our EPT population was markedly higher than the prevalence in an unselected cohort of 11–13-year-old Norwegian children, 27.5% vs. 12.7% (135, 227). No previous studies have investigated the prevalence of difficulty falling asleep or frequent awakenings in EPT children at school age. The results of the studies that have examined these problems in school-aged preterm children, but with higher GA at birth than our cohort, are contradictory (197, 199, 200, 202). There is no clear trend in these previous studies related to the GA of the included children or related to whether children with NDD are included or not. This is somewhat surprising since we know that children born preterm with an increasing degree of immaturity at birth have an increased risk of several neurological conditions (50, 60, 64, 233, 234) that have been shown to increase the risk of having difficulty falling asleep or frequent awakening (235-238). Examples of such conditions are cerebral palsy (50, 60, 64, 235), epilepsy (233, 236, 239) and ADHD (234, 238). Hysing et al examined a large cohort of preterm toddlers and their findings support our findings (204). Hysing et al. included preterm children with NDD and they found increasing problems with nocturnal awakenings at 18 months of age with decreasing immaturity at birth.

Snoring

The prevalence of snoring (28.1%) in our EPT population (227) was markedly higher than the prevalence of 7.5% in a meta-analysis of parent-reported snoring in

unselected children aged 0–18 years (149). Rosen et al. found that 21% of the children who were born at a mean GA of 31 weeks snored at 8–11 years of age compared with 14% of term-born children (p = 0.0049) (181). Together, these data may suggest that the prevalence of snoring increases with decreasing GA.

Snoring can be a symptom or possibly a precursor of SDB (240). Previous studies have shown that preterm children have an increased risk of SDB in childhood (241) and adulthood (180, 242) and that snoring in preterm children is strongly associated with SDB (OR 7.2) (181). The most frequent movement of the foetus during the second trimester is sucking (243). It is hypothesised that sucking is central for oral-facial growth, and that extreme preterm birth disturbs this process and thereby affects the development of both oral-facial anatomy and muscular tone. This may contribute to paediatric SDB (242).

In general, SDB in childhood is a risk factor for impaired neurocognitive performance, behavioural problems, externalising symptoms and inattention (244-249). Preterm children may be particularly vulnerable to the negative sequelae of SDB in childhood (250). The American Academy of Pediatrics suggests that all children should be screened for snoring and high-risk patients should be referred to a specialist (251).

The prevalence of SDB during childhood in EPT children is unknown, but it may be high as judged from the high prevalence of snoring. The study findings indicate that snoring is a significant problem in EPT children and underline that more studies are required to map the explicit risks and possible consequences of this condition in EPT children.

Daytime sleepiness

According to the findings, 17.2% of the EPT children suffered from daytime sleepiness (227). Rosen et al. found a lower prevalence in children born preterm aged eight to 11 years and no difference between the preterm and a term-born reference group (6% vs. 7%) (181). However, their children were more mature at birth (mean

GA 31 weeks) compared with our cohort, and Rosen et al. defined the children as sleepy if they had fallen asleep during various defined daytime activities. The parents in our cohort were only asked if the child experienced daytime sleepiness. These different ways of defining sleepiness may also explain the variation in the findings.

As mentioned earlier, a few studies have examined daytime sleepiness in children in the normal population. These studies have found a lower prevalence than that found in the EPT children in this study, i.e. 7%, 10% and 15% (155-157) vs. 17.2% in our EPT cohort. This finding shows that EPT children more often have problems with daytime sleepiness than term-born children. Sleepiness can affect a child's learning, behaviour, mood and physical health but it is often an overlooked symptom (150). This study's findings indicate that daytime sleepiness is a significant problem among EPT children and underline that more studies are required to map the possible causes and the explicit risks for this condition in EPT children.

Non-recommended sleep duration

The findings of this study revealed that 24.7% of the EPT children had non-recommended sleep duration (227). Comparing the proportion of EPT children with non-recommended sleep duration with previous studies is difficult as no studies have calculated sleep duration in the same way as this study in Papers 2 and 3 (227, 228).

5.1.5 Sleep problems and prenatal and neonatal factors

The study hypothesis posited that several early life experiences in EPT children would affect sleep at 11 years of age, particularly long-term consequences related to early cerebral and respiratory morbidity. The limited significance of early events and exposures was remarkable; for example, there was a lack of association with the extensive and intrusive treatments that the EPT infants encountered (227). Similarly, studies have suggested that such neonatal exposures do not predict psychiatric disorders in EPT children (87, 252). Sleep and mental health are closely linked, and these studies should, therefore, be seen in context (253).

The high prevalence of snoring in this study was unrelated to most prenatal and neonatal factors (227), suggesting that the general stresses of the extra-uterine life characteristic of EPT birth may explain the excess risk. The finding of this study that smoking in pregnancy is a predictor of snoring (227) is in agreement with a Finnish study that examined young adults who had a birth weight of less than 1,500 g (180). Furthermore, a study on term-born children also found that smoking in pregnancy predicted childhood snoring (254). Together, these studies may suggest that exposure to smoking in pregnancy has a negative effect on respiratory function independent of GA at birth, but the stresses of prematurity may have an additive effect. Possible explanations for an additive effect are speculative, but smoking may reduce foetal growth and the growth of the airways (255). Thus, a smaller size of respiratory tract may contribute to snoring. Moreover, smoking in pregnancy may affect later physiological regulation, including sleep regulation (256, 257).

To our knowledge, our findings that neonatal cerebral haemorrhage and SGA birth predicted difficulty falling asleep or frequent awakenings at 11 years of age (227) are novel. Wang et al. found no association between neonatal risk factors, including grades III–IV intraventricular haemorrhage, and restless sleep in EPT children at age 18–22 months (207). However, our findings were expected because both cerebral haemorrhage and SGA are known risk factors for adverse neurodevelopmental outcomes (64, 258) and because a variety of sleep problems are more prevalent in EPT children with NDDs, as found in Paper 1. Previous studies have shown that being SGA adds risk for several types of morbidity for EPT children (259). The fact that SGA predicts difficulty falling asleep or frequent awakenings at 11 years of age confirms this group's increased vulnerability.

5.1.6 Sleep problems and behavioural problems

Specified sleep problems in the EPT children were associated with behavioural problems. Difficulty falling asleep or frequent awakenings, snoring and daytime sleepiness were associated with more parent- and teacher-reported behavioural

problems, whereas non-recommended sleep duration was associated with more parent-reported behavioural problems (228).

In a small study of school-aged 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 (199). However, they did not find more night awakenings or shorter sleep duration compared with their control group, nor did they find that total sleep time or night awakenings were associated with total scores for SDQ. Caravale et al. studied two-year-old preterm children (mean GA 31 weeks) and found that they had more frequent sleep difficulties during the night and that these difficulties were related to problems with emotions and attention (201), which is in agreement with our findings. Of note, Perkinson-Gloor et al. excluded children with severe developmental delay (199), and Caravale et al. included only children with normal cognitive, language and motor development (201), in contrast to our study.

Our finding that sleep and behavioural problems were associated is in agreement with what has been reported for young children born full term (260-262), suggesting that studies on sleep and behavioural problems among children, in general, may also be applicable for EPT children.

Insomnia and restless sleep have been linked to emotional, conduct, hyperactivity/inattention and peer problems as assessed by SDQ in a normal population (262). Our study found the same results for the EPT children (228).

We found a clear association between behavioural problems and problems with falling asleep or nightly awakenings in the EPT children, and this finding suggests that behavioural problems are also an important factor for insomnia in EPT children. The relationship between sleep and behavioural problems in children may however be bidirectional and the EPT children's sleep problems may thereby also cause the EPT children's behavioural problems (260, 263).

Moreover, daytime sleepiness was associated with emotional, conduct and hyperactivity/inattention problems in term-born children as measured by the SDQ in the study by Hestetun et al. (264). No association was found between daytime sleepiness and conduct problems in the EPT children in this study, but daytime sleepiness was associated with emotional, hyperactivity/inattention and peer problems (228).

Snoring in term-born children has also been associated with emotional, conduct and hyperactivity/inattention problems as assessed by SDQ (265). Correspondingly, our study also found more emotional and conduct problems but not more hyperactivity/inattention problems among snoring EPT children (228). Snoring is a common symptom of SDB, and previous studies have shown that preterm children have an increased risk of SDB (181, 241, 250, 266, 267). The prevalence of SDB during childhood in EPT children 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 EPT children.

Our finding that non-recommended sleep duration was associated with higher total scores for SDQ (228) is in agreement with the findings of an association between short sleep duration and emotional, conduct and hyperactivity/inattention problems in an unselected cohort of Norwegian children of similar age (268).

Sleep and behaviour are closely related, and as earlier mentioned sleep problems can potentially lead to behavioural problems and behavioural problems can also lead to sleep problems. In Paper 2, the study examined whether a wide range of exposures related to pregnancy, birth and the newborn period predicts later sleep problems (227). Other studies have also investigated whether such early exposures are associated with later behavioural difficulties. There are few associations between these early exposures and later sleep and behavioural problems, which may strengthen the association between these types of problems. As discussed earlier, the cerebral

architecture is fundamental to complex neurobehaviours. Sleep and behaviour can be classified as complex neurobehaviours (232) and it is not unreasonable to assume that a cerebral architecture characterised by 'encephalopathy of prematurity' may be a common underlying cause of both the increased prevalence of sleep and behavioural problems in EPT children, and this may also explain the close association between these problems.

5.1.7 Sleep problems and respiratory health

The sleep problems, especially daytime sleepiness, were strongly associated with respiratory symptoms, asthma and the use of asthma medications (228). To the best of our knowledge, no studies have addressed the relationship between respiratory symptoms and sleep in EPT children, but our finding, that several sleep problems were associated with wheezing and asthma, is in agreement with similar findings in term-born children (237, 269, 270). Although respiratory symptoms in EPT children resemble asthma, the pathophysiology of lung diseases after preterm birth is different and respiratory disease in EPT children will not necessarily respond to inhaled corticosteroids (97-100). The burden of respiratory symptoms in EPT children may, therefore, be substantially higher and more chronic (271) 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 EPT children (272, 273). Previous studies on term-born children have shown that night awakenings due to asthma are a risk factor for poor school functioning (274).

However, it is not only respiratory symptoms that can disturb sleep. It has also been shown that too little sleep can adversely affect pulmonary function in chronic lung disease (275). This effect may be important since even a small decrease in pulmonary function can be clinically important in patients with a chronic airflow limitation. The mechanisms here are not known and further studies are needed to explore the associations between lung health and sleep problems in EPT children.

We found a clear association between non-recommended sleep duration and use of inhaled corticosteroids or oral leukotriene modifiers and between daytime sleepiness and use of inhaled corticosteroids or oral leukotriene modifiers and bronchodilators. In this context it is important to be aware that insomnia can be a side effect of both bronchodilators and inhaled corticosteroids (276). The symptom relief these drugs provide positively affect sleep and this effect may outweigh the negative effects of no treatment in, for example, children with asthma. However, these drugs do not have the same effect on EPT children's chronic lung disease, and thus the overall effect may not be positive with regard to EPT children's sleep. Further studies are needed to explore how drug therapy for lung disease in EPT children affects their sleep.

5.1.8 Summary of study outcomes

Despite medical advances and the efforts of child health experts in recent years, EPT children still face a high death risk and at least 20% to 50% are at risk of morbidity if they survive (277). Sleep is, however, a field that has been less explored in these vulnerable children.

EPT children more often have sleep problems in childhood up to 11 years of age as compared with term-born children. Sleep and wakefulness involve interactions between the large and important parts of the brain, such as the brain stem, hypothalamus, thalamus and cerebral cortex. We need well-functioning myelinated networks to orchestrate the well-defined, predictable, organised behavioural states of sleep and wakefulness. The important stages of brain maturation, such as network formation and myelination, are affected by preterm birth. The ‘encephalopathy of prematurity’ is a collective term for the brain damage seen in preterm children. The injuries are primary destructive disease and secondary maturational and trophic disturbances. Quantitatively, this encephalopathy appears to account for most of the subsequent neurological sequelae in children born very preterm, and cognitive deficits without major motor deficits are now the dominant neurodevelopmental sequelae in the survivors of early preterm birth (20). Cognitive impairment increases the risk for behavioural problems in EPT children (49). The brain has a long developmental

period (278), and it is important to be aware that aberrant remodelling may eventually affect the expression of complex neurobehaviours at older ages, such as sleep, cognition, emotional and social skills (232). The fact that the EPT children without any detectable NDD had more sleep problems and different sleep habits compared with the controls may indicate that sleep in EPT children is more vulnerable to the 'encephalopathy of prematurity' than the neurological development classified by NDD. Whether the increased prevalence of sleep problems in EPT children can be explained by the 'encephalopathy of prematurity' needs further research. The fact that, with increasing levels of NDD and with an increasing degree of behavioural problems, this study finds increased prevalence of sleep problems indicates this.

Normally, important parts of the ontogenesis of sleep occur in the uterus during the latter part of pregnancy. For EPT children, these processes take place in an incubator in the NICU, which can interfere with the natural process. A significant proportion of the time in utero for the fetus and for the child the first year of life is spent sleeping. The need for sleep is believed to correlate with the brain's need for growth and maturation, and it is assumed that the amount of REM sleep, in particular, is important for normal brain maturation (116). Interrupted and disturbed sleep may affect the amount of different sleep stages. In rat experiments, neonatal REM sleep deprivation increases the prevalence of anxiety and sleep disorders in adulthood (279-282). However, our study did not find an association between different types of treatment or the extent of treatment among EPT neonates in the NICU and later sleep problems (227). Further studies are, however, necessary to investigate the association between disturbed neonatal sleep in EPT children and possible associations with later problems related to, for example, cognitive abilities, behaviour and sleep.

This study found, however, a strong association between sleep problems and respiratory health in EPT children at 11 years of age (228). This is not unexpected as it is known that conditions with respiratory symptoms often worsen at night and can interfere with sleep (237). However, the challenge with respiratory symptoms in EPT children is that the underlying mechanisms are unclear (91). The extent to which

respiratory symptoms in EPT children contribute to inadequate or disturbed sleep at different ages in childhood is unknown. Childhood sleep is essential for optimal brain development. Research on the permanent adverse effects of chronic sleep loss on neurodevelopment is, however, minimal in humans (283). The extent to which respiratory symptoms in EPT children interfere with their sleep in childhood and thus possibly affect their development is unknown. This field needs further exploration. The main focus must be on clarifying the underlying mechanisms for their respiratory symptoms so that these children can be offered symptomatic relief and hopefully, as a consequence of this, experience better sleep.

5.2 Clinical implications

EPT children are at increased risk of childhood sleep problems. We do not know the cause of the increased risk, but this study has found that children with sleep problems also more often have NDD, behavioural problems and respiratory symptoms.

Too little or disturbed sleep has negative consequences on behaviour and cognitive skills, among other things (152, 166, 284).

Whether sleep problems, behavioural problems and cognitive difficulties have a common underlying aetiology or whether disturbed sleep contributes to the cognitive and behavioural difficulties in EPT children is unknown. This question should be further explored to identify the right interventions and treat children as early as possible. Health professionals should be aware of the risk of sleep problems among EPT children, and their sleep should also be assessed alongside cognitive abilities, behavioural problems and pulmonary health at follow-ups so that these children and their families can be provided with support and guidance.

The best intervention for prevention or treatment of sleep problems in this group of children is unknown. Further research is needed to answer this. On a general basis, health-care professionals should guide parents and children in terms of what supports the natural sleep-inducing processes and what weakens them. Accordingly, parents

should be informed of the increased risk so that they can adjust their expectations of their children and meet the children's need in an appropriate and supportive way.

Special attention should also be given to the high prevalence of snoring in EPT children. Snoring can be an accompanying sign of SDB and both snoring and prematurity are known risk factors for SDB. According to the European Respiratory Society, all children at risk should be investigated (285). More studies are needed to map the explicit risks for SDB and possible consequences of this condition in EPT children.

5.3 Discussion of the methods

Internal validity

Internal validity describes the extent to which the results are valid for the sample and phenomenon studied. The internal validity of an estimate is good if it does not overestimate or underestimate the true value of the target population (286).

Main outcome

The main outcome of the study is the identification of sleep problems and sleep habits. Parent reports have always been the main source of information on children's sleep but are not necessarily the best method. There are methodological challenges associated with research on children's sleep problems and sleep habits. A cost-effective and non-intrusive method for studying sleep in a natural environment is lacking (287).

The most commonly used methods have been questionnaires (usually parent reported), actigraphy and polysomnography. All these methods have weaknesses and strengths, and the information attained from each method is partly overlapping, but each method also offers its own unique and valuable data. An actigraph is worn around the wrist like a clock and it has sensors that detect movement. In this way, sleep (defined as inactivity) and wakefulness can be roughly separated from one another (288).

One of the strengths of questionnaires is that they include subjective experiences, and insomnia, for example, is defined as the subjective experience of problems initiating or maintaining sleep. 'Project Extreme Prematurity' (PEP) is a Norwegian national follow-up study. EPT children live in different places in a country at great distances from one another, and a parental questionnaire was probably the most feasible method for studying sleep at 11 years of age in this national cohort.

Non-standardised questionnaires were used to identify sleep problems, so the validity of the questions provided is unknown. However, several previous studies have used questionnaires that map the same sleep problems and sleep habits explored in this study and compared parent reporting with objective methods, such as actigraphy and polysomnography. The results generally indicate that parental reporting is more accurate for sleep time variables (289) than for sleep problems (287, 290-292). However, parents may overestimate, for example, sleep duration and underestimate the occurrence of sleep problems. Holley et al., however, found a good correlation between parents' estimates of their child's sleep latency and actigraphy findings (290). Several studies found that parents underreport their child's problems with night awakenings as compared with actigraphy (287, 290-292). Moreover, children themselves report more sleep difficulties and problems with night awakenings compared to their parents (293). Parents can only report what they are aware of during the night. If a child is awake at night but is silent and does not require parental attention, then parents may be less aware of the child's problems with night awakenings.

Snoring

Few studies have explored the relationship between parent-reported snoring and objectively measured snoring. Castronovo et al. found a good correlation (294) while Schwartz et al. found a moderate correlation (295 (abstract)). Cane et al. studied parental interpretations of children's respiratory symptoms using video. They found that it was difficult for parents to distinguish between stridor, snoring and stertor (296). Consequently, there is some uncertainty associated with parent-reported

snoring. Furthermore, we have not found studies that have explored the sensitivity of parent-reported snoring. Most EPT children will probably be sleeping in their own rooms and the parents may not necessarily be aware of their child snoring.

Daytime sleepiness

Sleepiness is problematic to measure. Three different approaches to measuring sleepiness have been proposed: subjective, behavioural and physiological. The various established methods are often based on one of these approaches. The methods do not necessarily correlate with each other (297). Thus, referring to objective goals that can validate parent-reported sleepiness may not be natural. One study that assessed sleepiness in children, with validated questionnaires, found a good correlation between children's self-reported daytime sleepiness and parent-reported daytime sleepiness (298). However, in our study, validated questionnaires were not used to assess sleepiness in EPT children; thus, there is some uncertainty associated with this finding.

Sleep habits and non-recommended sleep length

Previous studies found a strong correlation between sleep time variables assessed with parental questionnaires for weeknights and a moderate correlation for weekend nights compared with sleep times assessed by actigraphy (289). The parents of the EPT children were asked about their children's sleep habits on weekdays. Thus, there may be a satisfactory precision in terms of the parent-reported sleep time variables.

However, it is important to note the non-recommended sleep duration variable used in Papers 2 and 3 (227, 228). In these papers, total sleep time was calculated as the time in bed minus sleep onset latency and minus time awake after sleep onset. As mentioned earlier, parents tend to underreport their child's night awakenings. Parent-reported time awake after sleep onset is therefore a measure of uncertainty, and this uncertainty affects the variable non-recommended sleep duration. As a consequence of this, time awake after sleep onset is probably underreported and the proportion of

EPT children with non-recommended sleep duration is thereby probably higher than was found in our study.

Main exposure

The main exposure in the study and the inclusion criterion was either extreme prematurity defined as GA < 28 weeks or birth weight < 1,000 g. This 'composite' definition was used because, in previous studies on children with similar prematurity, some had chosen birth weight < 1,000 g and some had chosen GA < 28 weeks as the inclusion criterion. The current definition was chosen so that the results could be compared both with studies on those with GA < 28 weeks and studies on those with birth weight < 1,000 g as the inclusion criterion. However, children with a GA > 28 weeks at birth and with a birth weight < 1,000 g will often be SGA so the selected definition may thus have resulted in a selection bias.

We performed subanalyses to investigate whether our findings would have been the same if, for example, we had included only EPT children with GA < 28 weeks at birth.

In Paper 2, we found no significant differences in the prevalence of sleep problems, snoring, daytime sleepiness and recommended sleep duration at 11 years of age between the groups of children born with a GA of less than 28 weeks and those born with a GA of 28–32 weeks. We also examined the association between perinatal factors and specified sleep problems, and we limited the analyses to children with GA < 28 weeks. In this context, SGA still predicted difficulties in falling asleep or frequent awakenings. The association between cerebral haemorrhage and difficulty sleeping or frequent awakening was no longer significant when we limited the analyses to children with GA < 28 weeks (227).

In Paper 3, we did not perform subanalyses where we included only EPT children with GA < 28 weeks at birth. However, SGA was included as a covariate in the subanalyses on the association between sleep and behavioural problems and sleep and

respiratory symptoms. The results did not change except that the association between snoring and teacher-reported behavioural problems was no longer significant (228).

Thus far, only a few studies have examined sleep in school-aged preterm children with similar immaturity at birth, but the inclusion criteria used in our follow-up study may present some problems for future studies wishing to compare their results with ours.

It is also worth mentioning that there is some uncertainty associated with the determination of GA by routine ultrasound in the second trimester or by the use of the first day of the last menstruation (299). If our study should have had a higher precision with regard to GA, we must have known the time of fertilisation or the time of insertion of the embryo in cases of in vitro fertilisation. However, this uncertainty with respect to GA at birth will probably be the same today for any comparative study.

Bias

Selection bias

The limited response rate at follow-up was a weakness, as is the case for most population-based follow-up studies. Such a factor includes a risk of selection bias. The number of possible participants at 11 years of age was 372, as described in the *Results* section. In Paper 1, 231 (62%) of these were included; in Paper 2, 221 (59%) were included; and in Paper 3, 216 (58%) (226-228) took part.

In the first paper, the study did not compare the EPT children who participated at age 11 years of age with EPT children who did not participate at this age we but referred to Fevang et al. that had previously examined this in the same cohort (51). Fevang et al. compared participants with non-participants at 11 years of age in terms of sex, maternal education level, perinatal factors and NDD and mental health at five years of age (51). They found no differences between the groups, with the exception of a slightly higher proportion of mothers with higher education among the children who participated. In Paper 1, the following factors were included when adjusting our analyses: mother's education level, single parenthood and sex (226). However, the

differences between the groups were not sufficiently explored, which may have contributed to selection bias.

In the second paper, the study compared the participants with non-participants at 11 years of age in terms of sex, family background and demographic factors. The study found differences between the groups in terms of sex and the proportion of mothers with higher education (227). In Paper 2, sex and mother's level of education were therefore included in the adjusting analyses. This may have reduced the likelihood of selection bias. Information about single parenthood was also included in the adjusting analyses.

In the third paper, the participants and non-participants were compared, and the study found no differences in the GA or prevalence of SGA, bronchopulmonary dysplasia or ROP, but there was a tendency for less severe disability among the participants (3.3% [n = 6] vs. 9.8% [n = 12]) (228). The EPT children who participated at 11 years of age were healthier than those who did not participated. This may have led to underestimation of sleep problems in the EPT population.

Information bias

Information bias refers to any systematic difference from the truth that arises in the collection, recall, recording and handling of information in a study, including how missing data are dealt with. Studies based on subjective reporting and retrospective data are particularly at risk of information bias. A common type of information bias is recall bias (300). Recall bias occurs when participants do not remember previous events or experiences accurately or omit details: the accuracy and volume of memories may be influenced by subsequent events and experiences.

Recall that is only inaccurate and recall that is biased should be distinguished (301). The former can lead to non-differential misclassification and the latter to differential misclassification (300).

In Paper 1, the parents in the PEP study and the control group were asked about their children's previous sleep problems (226). The parents may not necessarily remember this, which could potentially lead to non-differential misclassification. Furthermore, it is conceivable that the parents of the EPT children experienced their child's sleep and the possible challenges associated with this differently to the parents of the term children, thus affecting their recall. Such a condition can then potentially lead to differential misclassification.

Non-differential misclassification of measures will tend to lead to an underestimation of effects. Differential misclassification can lead to either an overestimation or underestimation of the true effects (302).

However, as described earlier, previous research on term-born children shows that parents tend to underreport several specified sleep problems. If this case also applies to the EPT children, then it may have led to the non-misclassification of measures and an underestimation of effect or associations. Possibly, the EPT parents' focus on the child's potential vulnerability leads to a lower threshold for reporting problems related to sleep as a sleep problem. This condition would then lead to an overestimation of effects.

The questions in the two cohorts in Paper 1 were phrased differently because the control cohort was not part of this study but a separate study. Despite some differences in the questionnaires, the study chose to use this group of children as a control cohort because the benefits of using a control group outweighed the disadvantages. The differences in how a few of the questions were phrased may have introduced some bias.

Bias due to confounding

Confounding is the confusion of effects. In other words, the effect of the exposure is mixed with the effect of another variable, and changes create spurious or distorted associations (300).

A low socioeconomic status increases the risk of sleep problems (303-306) and also preterm birth (307). It was therefore important to adjust for socioeconomic status to reduce any confounding factors and the findings in all three papers were therefore adjusted for mother's educational level and being a single parent. Having more information related to the socioeconomic status, such as for example parents' income, would have been advantageous.

Intrauterine growth retardation or information about SGA increases the risk of intervention leading to preterm birth. Intrauterine growth retardation or SGA can thus potentially be a confounder. In Paper 2, the study found that EPT children who were SGA had an increased risk of difficulty falling asleep or frequent awakenings (227). The study, therefore, performed subanalyses in Paper 3 with SGA included as a covariate in the regression of the association between sleep problems and behavioural problems and between sleep problems and lung health (228). Ideally, it should also have been adjusted for SGA in Paper 1.

Smoking in pregnancy is a risk factor for preterm birth (307), and previous studies have also shown that parental smoking is a risk factor for snoring and other general respiratory symptoms in children (308). Parental smoking can thus be a confounder. In Paper 2, the study found an association between maternal smoking in pregnancy and snoring in the EPT children. To avoid confounding factors, parents' current smoking habits (mother or father) were included in the adjusted analysis when exploring the association between maternal smoking in pregnancy and snoring in the EPT children in Paper 2 and when exploring the association between specified sleep problems and lung symptoms in the EPT children in Paper 3.

Sleep problems, such as insomnia and sleep apnoea, have been shown to increase the risk of preterm birth (309). Thus, sleep problems experienced by the mother may increase the risk of sleep problems in the child, which may be a potential confounder. Sleep apnoea and snoring are associated (240), which may imply a genetic predisposition. The study had no information on the mother's possible sleep problems

before or during pregnancy and thus had no opportunity to explore or correct any potential confounding factors.

It is also the case that we cannot exclude any residual confounding factors that could potentially help explain the observed relationships.

Asking if there might be potential mediators of the findings is also natural. Mediation is similar to confounding. The criteria for mediation are as follow: 1) both the predictor of interest and the potential mediator must be associated with the outcome; 2) the predictor of interest and mediator must be associated; and 3) the mediator is an assumed causal consequence of the predictor. The difference between the confounder and mediator criteria is step 3, i.e. the mediator must be an assumed causal consequence of the variable of interest. The mediator thus lies in the middle of the causal chain between the predictor and outcome (310).

Preterm birth is a risk factor for SDB, and SDB in children is, as previously mentioned, associated with snoring and can also cause night awakenings and daytime sleepiness (285, 311). SDB can thus potentially be a mediator and can explain the increased prevalence of several observed sleep problems in the EPT children. The sleep of the EPT children in the current thesis was not examined with polysomnography/ polygraphy, which is necessary in order to diagnose SDB (285). This study was thus unable to explore a possible link between reported sleep problems and possible SDB in our cohort.

As earlier described, there is an association between sleep problems and respiratory symptoms and between sleep problems and behavioural problems in EPT children. Potentially, respiratory symptoms and behavioural problems are also mediators in the association between extreme prematurity and sleep problems (188, 260). There is no adjustment for potential mediators in any of the papers in this study.

5.4 Ethical considerations

The discussion about where the limit for active treatment of EPT neonates should lie is ethically challenging. An important and necessary contribution to this discussion is research on health and quality of life from a life perspective for the persons who receive active treatment at the limit of viability. Sleep is very important for good health and research on the EPT children's sleep is therefore important in this sense.

Furthermore, it is timely to ask whether this study is of benefit to EPT children. The main finding in this thesis is the increased prevalence of sleep problems in EPT children and associated factors. The hope is that this knowledge may help the children to be better looked after and understood both in health-care settings and in within their families but, in order for this research to benefit the EPT children substantially, is it important for further studies to be undertaken which investigate how these sleep problems can possibly be prevented or treated.

In research projects on vulnerable children such as the EPT children, there can easily be a focus on problem areas and dissemination of the research results can potentially contribute to stigmatising EPT children as a group. Therefore, is it important to strive for thoughtful dissemination of the results.

6 Conclusions

- EPT children are at increased risk of sleep problems in childhood and had different sleep habits at 11 years of age compared to the controls. The EPT children went to bed earlier, had longer sleep onset latency, spent more time in bed and had longer sleep duration compared with the controls.
- The prevalence of sleep problems increased with increasing NDD, but the EPT children with no NDD were also at increased risk compared with the controls.
- Of numerous prenatal and neonatal factors, only smoking during pregnancy, being born SGA and cerebral haemorrhage predicted specified sleep problems at 11 years of age.
- The EPT children with specified sleep problems at 11 years of age had more behavioural and respiratory health problems compared with the EPT children without sleep problems.

7 Future research

- Future studies using validated sleep instruments are needed to investigate sleep habits and the prevalence of sleep problems and sleep disorders at different ages through childhood and adulthood in persons born EPT. The studies should combine both subjective and objective measurements.
- This study's findings indicate that both snoring and daytime sleepiness are significant problems among EPT children and more studies are needed to map the explicit risks, possible causes and consequences of these conditions in EPT children.
- 'Encephalopathy of prematurity' may explain some of the increased prevalence of sleep problems in EPT children. Further studies which can confirm or refute this are needed.
- We found that specified sleep problems in EPT children were associated with respiratory symptoms. The mechanisms here are not known and further studies are needed to explore this association. Further studies are also needed to explore how drug therapy for lung disease in EPT children affects the sleep of these children.
- The best intervention for the prevention or treatment of various types of sleep problems in EPT children is unknown. Randomised controlled trial studies are therefore needed.

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REGULAR ARTICLE

Children born extremely preterm had different sleeping habits at 11 years of age and more childhood sleep problems than term-born children

Kristine Marie Stangenes (kristine.stangenes@gmail.com)[1,2], Silje Kathrine Fevang[1], Jacob Grundt[3], Hilde Mjell Donkor[3], Trond Markestad[1,3], Mari Hysing[4], Irene Bircow Elgen[5], Bjørn Bjorvatn[6,7]

1.Department of Clinical Science, University of Bergen, Bergen, Norway
2.Department of Pediatrics, Haukeland University Hospital of Bergen, Bergen, Norway
3.Department of Pediatrics, Innlandet Hospital Trust, Lillehammer, Norway
4.Uni Research Health, Bergen, Norway
5.Department of Clinical Medicine, University of Bergen, Bergen, Norway
6.Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
7.Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway

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Correspondence
Kristine Marie Stangenes, Department of Clinical Science, University of Bergen, Department of Pediatrics, Haukeland University Hospital, Jonas Liesveg 87, 5021 Bergen, Norway.
Tel: 0047 55975000 |
Fax: 0047 55975147 |
Email: kristine.stangenes@gmail.com

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ABSTRACT

Aim: This study explored whether extremely preterm (EPT) children had different sleep characteristics in childhood than children born at term and how neurodevelopmental disabilities (NDD) affected sleep in children born EPT.

Methods: A Norwegian national cohort of 231 children born EPT from 1999 to 2000 and separate study data on 556 children born at term in 2001 were compared. Parental questionnaires mapped the children's current sleep habits at 11 years of age, namely the prevalence of sleep problems throughout childhood until this age and five categories of sleep problems. In addition, the EPT children were clinically assessed at five years of age.

Results: The EPT children had different sleep habits than the controls, for example they went to bed earlier. EPT children had a higher prevalence of sleep problems than the controls throughout childhood (26% versus 14%, $p < 0.001$) and this was also higher for the 93 EPT children with no NDD (20%) than for the controls (14%) and increased with increasing NDD to 67% ($p = 0.015$) for the six children with severe NDD.

Conclusion: EPT children had different sleep habits to term-born controls at 11 years of age, including those with no NDD. The prevalence of sleep problems increased with increasing NDD.

INTRODUCTION

Preterm birth has been associated with an increased prevalence of later physical and mental morbidities and neurodevelopmental disabilities and the risk increases with decreasing gestational age (GA) and birthweight (BW) (1–7). Prematurely born children have also been reported to be at increased risk of sleep problems like nocturnal (8,9) and early morning awakening (10), disturbed sleep due to sleep-related breathing disorders (8,11,12) and maybe the phenomenon known as advanced sleep phase (10,13). Not all previous studies have shown worse sleep outcomes among premature born children. One study actually reported better sleep quality (10). The studies that have explored sleep characteristics have been conducted on children with varying degrees of prematurity and the children have been examined at various ages during childhood.

Abbreviations
BW, Birth weight; EPT, Extremely preterm; GA, Gestational age; NDD, Neurodevelopmental disabilities.

As for other outcomes of prematurity, it is reasonable to assume that the occurrence and severity of sleep problems will increase with decreasing GA. So far, we have only identified one study that included children who were born extremely preterm (EPT), and the mean GA in that study was 27 weeks. The authors suggested that obstructive sleep apnoea, periodic limb movements and shorter sleep

Key notes

- We compared 231 extremely preterm (EPT) born children with 556 term-born controls to identify differences in sleep patterns at 11 years of age.
- EPT children had different sleep habits at this age and more sleep problems throughout childhood compared to the controls.
- The prevalence of sleep problems increased with increasing neurodevelopmental disabilities but even EPT children with no neurodevelopmental disabilities had more sleep problems during childhood than the controls.

duration were more common in children born preterm than in children born at term. However, the study only included children who were candidates for caffeine therapy during the first 10 days of life and it did not include controls born at term (12,14).

To our knowledge, no studies have explicitly explored the sleep habits and prevalence of sleep problems throughout childhood in children born EPT. We do not know if sleep problems in general are more common in children born EPT than in children born at term or whether sleep problems can be predicted by the degree of prematurity. This is remarkable considering that these children, as a group, experience a number of difficulties (3–5,7) that naturally may lead to significant sleep problems (4,15–19).

Therefore, the aim of our study was to compare current sleep habits at 11 years of age and the prevalence and nature of sleep problems until that age in a national cohort of children born EPT and an unselected control group of children born at term. We also wanted to explore the relationships between neurodevelopmental disabilities and sleep problems in the children born EP.

MATERIALS AND METHODS

Populations

This study was part of a national cohort study of all children born EPT, defined here as a GA of less than 28 completed weeks or BW of less than 1000 g, in Norway in 1999 and 2000 (20). The children were prospectively followed from birth and were assessed at two, five and 11 years of age. The methods used to determine gestational age and overall outcome in terms of mortality and morbidities until 11 years have been previously published (3–5,20,21).

When the children were five years old, the parents completed questionnaires on sociodemographic measures and mental health and behavioural characteristics. Experienced paediatricians performed a general clinical and neurological examination, psychologists tested cognitive abilities (IQ) with the Wechsler Preschool and Primary Scale of Intelligence-Revised (22), and physiotherapists assessed motor abilities with the Movement Assessment Battery for children (23). A total Movement Assessment Battery for children score of higher than the 95th percentile, according to the reference values, was classified as a motor problem. The gross motor function for the children with cerebral palsy was classified in five levels of severity according to the Gross Motor Function Classification for Cerebral Palsy (24). Visual function and hearing were determined from the clinical examination or previous examinations at the public healthcare clinics. Each child was given a neurodevelopmental disability (NDD) score according to the definitions used in the Extremely Preterm Infants Surfactant C Cure Study namely no disability or minor, moderate or severe disability (3,25) (Table 3).

At 11 years of age, information was based on a postal questionnaire sent to the parents. Data were obtained on the child's physical and mental health, habits and social conditions, including sleep characteristics.

Of the 372 eligible children, extensive information was available for 370 (99%) until two years of age and for 306 (83%) at five years and 231(62%) at 11 years. We have previously shown that the children assessed at five years were representative of the whole cohort (3).The only significant differences between the participants and non-participants at 11 years of age were a somewhat higher proportion of girls and of mothers with higher education – defined as at least a three-year college education or a university degree – and a lower proportion of children with neonatal retinopathy of prematurity and cerebral palsy among the participants (data not shown). We had NDD scores, determined at the age of five, for 195 of the 231 participants at 11 years of age.

For comparison purposes we included data on a term-born control group from another study (4). The parents of all children born in 2001 in Oppland County, Norway, who attended the school entry health assessment at five years of age were invited to complete a comprehensive questionnaire similar to that completed by the parents of the national cohort of EPT children at five and 11 years of age. Data were obtained for 1119 (59%) of the 1895 eligible children at five years of age and for 593 children at 11 years of age, which was 53% of the respondents who took part when they were five. The missing data at five years of age were largely due to the low response rates at some of the public healthcare clinics, as the families were recruited at the discretion of the public healthcare nurses. When we compared the control cohorts at 11 years of age we found that the proportion of mothers with higher education was slightly higher at five years (60% versus 49%, $p < 0.001$), and there was a lower proportion of single parents (11% versus 16%, $p = 0.009$). We excluded 37 premature children from the control study who were born at below 37 weeks of gestation from the statistical analyses. This meant that there were 556 controls in the final analysis.

The national EPT study on births from 1999 to 2000 and the regional cohort study based on full-term births in 2001 (4) were based on separate questionnaires and these asked different questions. However, despite these differences in methodology, we decided that the benefits of using the data provided by the cohort study outweighed the disadvantages. Both surveys provided data at the age of 11 years, and the birth years were close enough to be comparable. It also provided us with an ideal opportunity to compare EPT and full-term births in comparable Norwegian study populations.

Sleep characteristics

The parents who took part in the national EPT cohort study were asked about their child's sleep habits when they were 11 years old. This included the time on weekdays that their child went to bed, when they got up and how long the child took to fall asleep, namely sleep onset latency. Sleep duration was defined as the time in bed minus sleep onset latency.

The questions on sleep problems differed slightly between the EPT and control group. Both groups were asked if their

child had ever had sleep problems and the first option for both groups was never. The other sleep problem alternatives for the EPT group were that the child had sleep problems during the first few years but not anymore, that they had sleep problems now, but only in the last few years and that they had always had sleep problems, including now. For the control group, the alternatives for sleep problems were sleep problems before they started school, but not later, sleep problems after they started school, but not now or still having sleep problems. In Norway, children routinely start going to school in the calendar year when they have their sixth birthday.

We considered that the control category of sleep problems before school, but not anymore was the same as sleep problems in the first few years but not anymore in the EPT group and that the control group answer still having sleep problems was the same as has always had sleep problems, including now, in the EPT group. The EPT children with current sleep problems included the children who had always had sleep problems and those that had only had them in the last few years and were still experiencing them. The control children who had always had sleep problems, including now, were defined as having current sleep problems. If the parents reported sleep problems at any age or always, this answer was transformed into the variable has or has had sleep problems in both groups.

Five categories of sleep problems were addressed. The parents of children born EPT were asked to describe any sleep problems their child had experienced at any point, and the control parents were asked to describe any sleep problems their child had experienced after starting school. The alternatives were the same in both groups: difficulty falling asleep, frequently waking up during the night, waking up unusually early and waking up unusually late. The parents were also asked if they thought their child got enough sleep and the alternatives were not enough, a bit too little, enough, a bit too much and too much. The answers not enough and a bit too little were combined into the child gets too little sleep in our analyses.

Statistical analyses

The EPT and control groups and the NDD subgroups were compared using *t*-tests, chi-square tests or Fisher's exact tests, as appropriate. Adjustments for sex, single parenthood and maternal education were performed using logistic regression analysis for dichotomous variables and linear regression analysis for continuous variables. The study was approved by the Regional Committee on Medical Research Ethics (2009–2271, 2012–1690, 2013–3276) and the Norwegian Data Inspectorate and the parents gave written, informed consent.

RESULTS

The mean GA of the EPT children who took part in the 11-year follow-up was 27 weeks, and the mean BW was 865 g. A higher proportion of EPT than control children lived with a single parent, but there were no significant differences in the proportions of sex, number of siblings or parental education (Table 1).

NDD scores were available for 195 of the 231 participants at 11 years of age as these had been determined when the children were five. These showed that 93 children had no identified disability (no NDD), 83 children had a minor disability (NDD 1), 13 children had a moderate disability (NDD 2) and six children had a severe disability (NDD 3). The sleep habits of the children in the two groups were different. The EPT children went to bed earlier than the term-born children (at 20.54 versus 21.18 hours), had longer sleep onset latency (35 versus 28 minutes), spent more time in bed (10.2 versus 9.8 hours) and had longer sleep duration (9.6 versus 9.3 hours). There was also a higher prevalence of sleep problems in the group of children born EPT (Table 2). In total, 26% of the EPT children and 14% of the controls had experienced sleep problems at some point ($p < 0.001$). Children born EPT were reported to have more sleep problems in early childhood (11% versus 3%) and to have more sleep problems at 11 years old than the controls (15% versus 7%). When the parents were asked about specific sleep problems they reported that the EPT children had more problems falling asleep (22% versus 11%), waking up frequently during the night (13% versus 4%) and waking up early in the morning (9% versus 1%) than the controls (Table 2). The proportion of EPT children who had parent-reported sleep problems increased significantly with the degree of NDD, from 23% to 67% (Table 3), but even the EPT children with no NDD had more sleep problems than the controls, also after adjusting for potential confounders (20% versus 14%) (Table 4). There were also differences between the EPT children with no NDD and the control children with respect to sleep habits. The EP children with no NDD went to bed earlier, spent more time in bed and had longer sleep duration than the controls, even after adjusting for potential confounders (Table 4). When we compared just the EP children with no NDD with the controls there were no longer any differences between the

Table 1 Background information on the children born extremely preterm (EPT) and the population-based control group born at term

	EPT n = 231	Control n = 556	p-Value
Number of boys, % (n)	50 (116)	50 (278)	0.96
Single parent, % (n)	14 (31)	8 (43)	0.012
Higher education mother[a], % (n)	59 (123)	64 (374)	0.2
Higher education father[a], % (n)	42 (88)	43 230)	0.8
Number of siblings, mean (SD)	1.8 (1.2)	1.8 (1.1)	0.8

Extremely preterm (EPT): gestational age <28 weeks or birthweight <1000 g.
[a]College or university education.

Table 2 Parent-reported current sleep habits on weekdays at 11 years of age and sleep problems during childhood in children born extremely preterm (EPT)[a] and a control group born at term

	EPT n = 231 mean (SD)	Control n = 556 mean (SD)	Unadjusted Mean diff.	Unadjusted 95% CI	Adjusted[d] Mean diff.	Adjusted[d] 95% CI
Current sleep habits						
Bedtime (time of day)	20.54 (24)	21.18 (30)	**−0.4**[e]	**−0.5 to −0.3**	**−0.4**[e]	**−0.5 to −0.3**
Rise time (time of day)	7.06 (24)	7.06 (24)	−0.001[e]	−0.1 to 0.1	−0.02[e]	−0.1 to 0.1
Time in bed (hours)	10.2 (0.5)	9.8 (0.6)	**0.4**	**0.3 to 0.5**	**0.4**	**0.3 to 0.5**
Sleep onset latency (minutes)[b]	35 (30)	28 (25)	**6.2**	**2.0 to 10.4**	**6.2**	**2.0 to 10.5**
Sleep duration (hours)[c]	9.6 (0.7)	9.3 (0.7)	**0.3**	**0.2 to 0.4**	**0.3**	**0.2 to 0.4**
	EPT % (n)	Control % (n)	Unadjusted OR	Unadjusted 95% CI	Adjusted OR	Adjusted 95% CI
Prevalence of sleep problems						
Has, or has had, sleep problems	26 (58)	14 (76)	**2.1**	**1.5 to 3.1**	**2.1**	**1.4 to 3.2**
Sleep problems during the first few years	11 (25)	3 (18)	**3.6**	**1.9 to 6.8**	**3.9**	**1.9 to 7.6**
Current sleep problems	15 (33)	7 (37)	**2.4**	**1.4 to 3.9**	**2.3**	**1.3 to 3.8**
Categories of sleep problems						
Difficulty falling asleep	22 (50)	11 (63)	**2.2**	**1.4 to 3.3**	**2.0**	**0.5 to 1.1**
Frequent awakenings during the night	13 (31)	4 (22)	**3.8**	**2.1 to 6.7**	**4.1**	**2.3 to 7.3**
Wake up unusually early	9 (20)	1 (6)	**8.7**	**3.4 to 22**	**8.7**	**3.1 to 24.0**
Wake up unusually late	1 (2)	0.2 (1)	4.9	0.4 to 54	4.3	0.4 to 50.0
The child gets too little sleep	23 (53)	24 (134)	0.9	0.7 to 1.3	0.9	0.6 to 1.3

[a]Extremely preterm (EPT): gestational age <28 weeks or birthweight <1000 g.
[b]Sleep onset latency = minutes it takes to fall asleep.
[c]Sleep duration= time in bed after falling asleep.
[d]Adjusted for gender, single parent and higher education mother.
[e]in hours.
Bold = p-Values <0.05; n = Number; SD = Standard deviation; OR = Odds ratio; Mean diff. = Mean difference.

Table 3 Parent-reported sleep problems among 11-year-old children born extremely preterm according to degree of neurodevelopmental disabilities (NDD)[a] at age 5

	No NDD n = 93 % (n)	NDD 1 n = 83 % (n)	NDD2 n = 13 % (n)	NDD 3 n = 6 % (n)	p-Value*
Prevalence of sleep problems					
Has, or has had, sleep problems	20 (19)	23 (19)	50 (6)	67 (4)	**0.015**
Sleep problems during the first few years	10 (9)	9 (7)	17 (2)	33 (2)	0.2
Current sleep problems	11 (10)	15 (12)	33 (4)	33 (2)	0.08
Categories of sleep problems					
Difficulty falling asleep	17 (16)	22 (18)	31 (4)	33 (2)	0.4
Frequent awakenings during the night	10 (9)	10 (8)	23 (3)	50 (3)	**0.024**
Wake up unusually early	5 (5)	5 (4)	23 (3)	50 (3)	**0.002**
Wake up unusually late	2 (2)	0 (0)	0 (0)	0 (0)	0.6
The child gets too little sleep	22 (20)	21 (17)	31 (4)	50 (3)	0.3

*Fisher's exact test.
[a]degree of neurodevelopmental disabilities (NDD): No NDD: No identified disability was defined as no cerebral palsy, full IQ (FIQ) 85 or higher, M-ABC score less than or equal to the 95th percentile and normal vision and hearing. NDD 1: Minor disability was defined as cerebral palsy class 1, FIQ 1–2 SDs below mean (i.e. 70–84), an M-ABC score higher than the 95th percentile, squint/refractive error or mild hearing loss. NDD 2: Moderate disability was defined as cerebral palsy class 2–3, FIQ 2–3 SDs below mean, severe visual impairment or need of hearing aid. NDD 3: Severe disability was defined as 1 or more of the following: cerebral palsy class 4–5 on the Gross Motor Function Classification System for Cerebral Palsy, FIQ more than 3SDs below the reference mean value of 100, legal blindness or complete deafness.
Bold = p-Values <0.05.

groups with regard to sleep onset latency and difficulty falling asleep (Table 4). In the EPT children born before week 28, there were no significant differences in the prevalence of sleep problems between the 49 EPT children born with GAs of 23–25 weeks and the 120 born with GAs of 26–27 weeks (data not shown).

Table 4 Parent-reported current sleep habits on weekdays at 11 years of age and sleep problems during childhood in children born extremely preterm with no neurodevelopmental disabilities (no NDD)[a] at age 5 years compared to a control group born at term

	No NDD n = 93 mean (SD)	Control n = 556 mean (SD)	Unadjusted Mean diff.	Unadjusted 95% CI	Adjusted[d] Mean diff.	Adjusted[d] 95% CI
Current sleep habits						
Bedtime (time of day)	20.58 (24)	21.18 (30)	**0.4**[e]	**0.3 to 0.5**	**−0.4**[e]	**−0.07 to 0.9**
Rise time (time of day)	7.03 (24)	7.06 (24)	0.03[e]	−0.1 to 0.1	−0.02[e]	−0.1 to 0.07
Time in bed (hours)	10.1 (0.5)	9.8 (0.6)	**−0.3**	**−0.5 to −0.2**	**0.4**	**0.2 to 0.5**
Sleep onset latency (minutes)[b]	30 (28)	28 (25)	−1.7	−7.4 to 3.9	3.7	−2.1 to 9.5
Sleep duration (hours)[c]	9.6 (0.6)	9.3 (0.7)	**−0.3**	**−0.5 to −0.2**	**0.3**	**0.2 to 0.4**
	No NDD % (n)	Control % (n)	Unadjusted OR	Unadjusted 95% CI	Adjusted OR	Adjusted 95% CI
Prevalence of sleep problems						
Has, or has had, sleep problems	20 (19)	14 (76)	1.6	0.9 to 2.8	1.4	0.8 to 2.5
Sleep problems during the first few years	10 (9)	3 (18)	**3.2**	**1.4 to 7.3**	**2.9**	**1.2 to 7.1**
Current sleep problems	11 (10)	7 (37)	1.7	0.8 to 3.5	1.3	0.6 to 3.0
Categories of sleep problems						
Difficulty falling asleep	17 (16)	11 (63)	1.6	0.9 to 2.9	1.4	0.7 to 2.7
Frequent awakenings during the night	10 (9)	4 (22)	**2.6**	**1.2 to 5.8**	**2.6**	**1.1 to 6.1**
Wake up unusually early	5 (5)	1 (6)	**5.2**	**1.6 to 17.0**	**4.8**	**1.2 to 19.0**
Wake up unusually late	2 (2)	0.2 (1)	**12**	**1.1 to 135.0**	**11.8**	**1.0 to 133.0**
The child gets too little sleep	22 (20)	24 (134)	0.9	0.5 to 1.5	0.9	0.5 to 1.5

[a]No NDD = no neurodevelopmental disability: defined as no cerebral palsy, full IQ (FIQ) 85 or higher, M-ABC score less than or equal to the 95th percentile and normal vision and hearing.
[b]Sleep onset latency = minutes it takes to fall asleep.
[c]Sleep duration = time in bed after falling asleep.
[d]Adjusted for gender, single parent and higher education mother.
[e]in hours.
Bold = p-Values <0.05; n = Number; SD = Standard deviation; OR = Odds ratio; Mean diff. = Mean difference.

DISCUSSION

According to their parents, the children born EPT had a higher prevalence of sleep problems than the unselected control group born at term, throughout childhood until 11 years of age. Sleep problems increased with the severity of NDD when it was assessed at five years of age. Furthermore, even the EPT children with no identified NDD experienced sleep problems more commonly than the controls. At 11 years of age, the sleep habits differed between the two groups, in that the EP children went to bed earlier, had longer sleep onset latency and longer sleep duration than the controls.

The strengths of this study included the national population-based design of the EPT cohort and the size, population-based and unselected inclusion of the control cohort. Our study has some weaknesses. Limited follow-up rates are always a challenge in these kinds of studies, but we have previously reported that the EPT children assessed at 11 years were representative of all the survivors of this birth cohort (7). We also suggest that the control group was representative, as not being invited to take part by the public healthcare nurses was probably the main reason for the limited inclusion rate at five years of age. In addition, the differences in background characteristics of the children lost to follow-up from five to 11 years and participants at 11 years were small. The EPT and term control children who were assessed had similar family backgrounds except for the fact that more EPT children lived with a single parent. However, the differences in outcomes remained after adjustments for differences in background factors.

The children's sleep characteristics were assessed by a questionnaire filled in by the parents. It is a weakness that we did not use a validated questionnaire or objective measurements, for example actigraphy or polysomnography. There were also challenges with recall bias because the parents in both groups were asked about sleep retrospectively and having a child who is exposed to EPT birth can affect how the child's symptoms are interpreted. It is also a limitation that we did not ask the children themselves. It can be difficult for the parents to 11-year-old children to answer some questions, for example, whether there are problems with their child waking up at night.

The questions in the two cohorts were different because the control cohort was not part of this study, but a separate study. Despite some differences in the questionnaires, we chose to use this group of children as a control cohort because we felt that the benefits with this outweighed the disadvantages. The small differences in how a few of the questions were phrased may have introduced some bias. It is a limitation that we only asked for the children's sleep

habits on weekdays. Bed times, rise times and sleep durations on weekdays are probably different from those at the weekends due to school starting times. We would have had more information about the children's sleep habits if we had asked for sleep habits during the weekends as well.

None of our questions were specific enough to detect symptoms of sleep-related breathing disorders. Earlier studies have showed that children born prematurely are at risk of sleep-related breathing disorders (8,11,12) and it would have been beneficial if we had also asked more specifically for symptoms of this. Nocturnal awakenings can be a symptom of a sleep-related breathing disorder (26), but whether or not the increased prevalence of waking up at night in the EPT group were related to sleep-related breathing disorders cannot be further clarified with the present data.

It may also be criticised that the degree of NDD in the EPT subjects was assessed at five years of age, but the parents were asked about sleep when the children were 11 years old. However, another study showed that the prevalence of disability remained stable between six and 11 years of age in the children born EPT and that large individual shifts in classification of disability are unusual (6).

We have previously shown that the prevalence of numerous symptoms related to mental health problems, including those that suggest attention deficit hyperactivity disorders, was higher in this cohort of children born EPT than a reference group (7). Whether sleep habits and sleep problems were more related to such challenges rather than to prematurity *per se* is difficult to ascertain due to the complex interaction between mental health issues and sleep. This warrants further studies.

Rates of sleep problems in our control group were comparable to those reported by others. For example, 7% of our children had current sleep problems compared to 5.4% and 10.8% in other studies (27,28), and 11% had experienced difficulty falling asleep compared to 5.1%–15.9% (29,30) in similar studies. Reported rates of sleep problems vary due to differences in methods, for example the age at assessment, race and culture, but these figures lend support to our assumption that our control group was representative of the eligible cohort.

The EPT children, including those without NDD, went to bed earlier than the controls. This finding may support other studies that have suggested that premature children have an earlier sleep phase (10,13). Hibbs et al. (10) found that adolescents born premature with a mean GA of 31 weeks demonstrated significantly earlier bed and wake times by both actigraphy and self-reports. Bjorkqvist et al. also found, by actigraphy, that young adults born premature with a mean GA of 29 weeks woke up earlier than the controls. The increased prevalence of early morning awakening in the group of EPT children in our study may also be explained by an earlier sleep phase.

The EPT group had longer sleep onset latency. The combination of earlier bedtimes and longer sleep onset latency could also indicate that they were put to bed earlier than necessary, for example because that is what the parents need as the care of EPT children may have been more demanding due to various health problems (4,5).

On average, parents of the EPT group also reported longer sleep duration than the controls at 11 years of age. There are few earlier studies on this issue and the results are conflicting, partly because they are not comparable with respect to background characteristics, the age at assessment and methods, for example to what extent children with NDD were included. Hibbs et al. (10) did not find any differences in sleep duration between adolescents born premature with a mean GA of 31 and controls born at term. On the other hand, Huang et al. (8) found that premature infants with a mean GA of 31.5 weeks had longer nocturnal sleep duration than term controls at six months of age. The Caffeine for Apnea of Prematurity Study Group suggested that children born premature were more likely to have shorter sleep duration than other children at five to 12 years of age (12), but their study did not include a control group born at term.

Children with neurological disabilities and mental health problems are more likely to have sleep problems than other children (15–19). Such disabilities and mental health problems may have explained some of the increased risk of sleep problems in the EPT children in our study, but the rate of sleep problems was also higher among the EP group without NDD compared to the control group. We cannot exclude, however, that the remaining difference was due to unrecognised minor group differences in mental health or somatic health than prematurity *per se*.

CONCLUSION

The 11-year-old EPT born children in our study went to bed earlier, had longer sleep onset latency, slept longer and had more sleep problems throughout childhood than an unselected control group born at term. The earlier bedtime in the group of EPT children may support the growing body of evidence that prematurity may influence circadian phenotypes later in life. Several types of sleep problems increased with the degree of NDD, but even the EP children with no reported NDD differed from the control group in a similar way, although this difference was less pronounced. EPT children are born with an immature and vulnerable brain. It remains to be determined to what extent their sleep problems were related to damage to the brain, as reflected in NDD, or to minor mental health problems due to subtle changes in the development of the brain or to problems with regulation due to prematurity *per se*.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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II

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Prenatal and Neonatal Factors Predicting Sleep Problems in Children Born Extremely Preterm or With Extremely Low Birthweight

Kristine M. Stangenes[1], Mari Hysing[2], Silje K. Fevang[1], Irene B. Elgen[3], Thomas Halvorsen[1], Trond Markestad[1] and Bjørn Bjorvatn[4,5]*

[1] Department of Clinical Science, University of Bergen, Bergen, Norway, [2] Regional Centre for Child and Youth Mental Health and Child Welfare, Uni Research Health, Bergen, Norway, [3] Department of Clinical Medicine, University of Bergen, Bergen, Norway, [4] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, [5] Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway

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Udo Rolle,
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Rolf Lambert Schlößer,
Universitätsklinikum Frankfurt, Germany

****Correspondence:***
Kristine M. Stangenes
kess@helse-bergen.no

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Objective: Prematurely born children have been reported to have more sleep problems throughout childhood than children born at term. The aim of this study was to explore if prenatal or neonatal factors can predict sleep problems at age 11 years in children born extremely preterm (EPT).

Method: A prospective observational study of all infants who were born EPT in Norway in 1999 and 2000. Prenatal and neonatal data were collected by all Norwegian obstetric and pediatric departments. Parental questionnaire mapped sleep problems and sleep habits at the age of 11 years.

Results: Of the 372 eligible children, 221 participated. Of those, 28.1% snored, 27.5% had difficulty falling asleep or frequent awakenings and 17.2% suffered from daytime sleepiness. The mean sleep duration was 9.4 h (range 4.3–11.0 h). Smoking in pregnancy predicted snoring (odds ratio 4.3). Neonatal cerebral hemorrhage and being born small for gestational age predicted difficulty falling asleep or frequent awakenings (odds ratio 2.2 and 2.3). Other morbidities during pregnancy or the newborn period, gestational age or the burden of treatment in the neonatal intensive care unit did not predict sleep problems. None of the studied prenatal or neonatal factors predicted daytime sleepiness or sleep duration <9 h.

Conclusion: Of numerous prenatal and neonatal factors, only smoking during pregnancy, being born small for gestational age and cerebral hemorrhage predicted sleep problems at 11 years of age among these children born EPT.

Keywords: extremely premature, gestational age, prenatal factors, neonatal factors, sleep problems, sleep characteristics, the medical birth registry of Norway

INTRODUCTION

Premature birth in general is associated with an increased risk of experiencing neurodevelopmental impairments, mental health problems, limited respiratory and cardiovascular function and metabolic syndrome. These risks increase with decreasing gestational age (GA) at birth (1–3). Data on more subtle long-term consequences of extremely premature (EPT) birth, e.g., related to sleep, are just starting to emerge since survival after EPT is a relatively new phenomenon (4). Satisfactory sleep is an important part of children's development and quality of life (5), and in general, prematurely born children more commonly experience a variety of sleep problems (6–9, 35). Whether children born EPT are at particular risk is not well studied, but we have recently shown that children born EPT more often have sleep problems throughout childhood until 11 years of age than children born at term (10).

It is important to identify early risk factors for adverse outcomes in order to guide families, health care workers and other professionals who will share responsibilities for these children's development. It has been reported that preeclampsia (11), smoking in pregnancy (12), chorioamnonitis and multiple gestation (13) are associated with later sleep disordered breathing, i.e., conditions that provide unusual breathing patterns during sleep (14), in children born premature. However, whether prenatal or neonatal factors can predict other types of sleep problems, and particularly in children born EPT, have not been explored. Furthermore, it is unknown whether sleep problems in childhood or adolescence can be linked to prematurity *per se* or to specific prenatal and neonatal factors, such as intrauterine growth restriction or treatment and complications during their stay in the neonatal intensive care unit (NICU), e.g., assisted ventilation and cerebral and respiratory morbidities. Since such morbidities as well as EPT *per se* are associated with a number of later neurodevelopmental and respiratory difficulties (15–17), our hypothesis was that early life experiences may also have a significant impact on specific sleep related problems in children born EPT. Our aim was, therefore, to explore to what extent prenatal or neonatal factors may predict specific sleep problems at 11 years of age.

MATERIALS AND METHODS

Population

The study population was a national cohort of all children born EPT ($n = 372$) in Norway in 1999 and 2000. EPT was defined as gestational age (GA) <28 completed weeks or birthweight (BW) < 1,000 g. The children were prospectively followed from birth and were assessed for sleep problems at 11 years of age. The parents gave written informed consent.

Prenatal and Neonatal Factors

All obstetric and pediatric departments in Norway participated, and the study was coordinated by the Medical Birth Registry of Norway (MBRN). Local obstetricians and neonatologists recorded data on maternal health, pregnancy, delivery and diagnoses and treatments in the NICU, and the MBRN provided additional information. Being born small for gestational age (SGA) was defined as birthweight below 10th percentile (18). Details on the definitions of diseases, complications and treatment in the NICU have been published (19, 20). All infants had repeated cerebral ultrasound scans and examinations by ophthalmologists during the hospital stay. An illness severity score which is an index of early disease severity (21) was calculated for each child. It was computed from three components of the Clinical Risk Index for babies namely, the lowest and highest fractional oxygen requirements and the largest base deficit during the first 12 h of life (22). In order to explore whether extensive medical treatment at the NICU would predict sleep problems, we created a variable that identified children who had received at least one of three common extensive medical treatments; mechanical ventilation > 40 days, necrotizing enterocolitis or ≥ four courses of antibiotic treatment.

Sleep Problems and Sleep Habits at 11 Years of Age

Current sleep problems were assessed by parental report, i.e., whether their child had difficulty falling asleep or frequent awakenings, snored, gasped for air or stopped breathing when asleep, and if the child had trouble breathing at night. They were also asked if the child had daytime sleepiness. The response options to these questions were "Not true," "Partly true," and "Absolutely true." In our analyses, the variables "Partly true" and "Absolutely true" were merged. Sleep habits were measured 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 time the child was awake during the night after sleep onset. We calculated total sleep duration as 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 h (23).

Statistical Analyses

For each specific sleep outcome variable (yes or no), the predictors were compared as means and standard deviations (SD) or as proportions using Student's *t*-tests, Chi-square tests or Fisher's exact tests, as appropriate. Odds ratios and 95% confidence intervals (CI) were calculated both unadjusted and after adjusting for sex, single parenthood and maternal education (dichotomized as less than a 3-year college education or not) in logistic regression analyses. Significance level was set at α-level 0.05.

Ethics

The study was approved by the Regional Committee on Medical Research Ethics (2009-2271) and the Norwegian Data Inspectorate. The parents gave written informed consent in accordance with the Declaration of Helsinki.

RESULTS

Sample Characteristics

Of 372 eligible children, sleep data were available for 221 (59%) at 11 years. The mothers answered the questionnaire in 64.7% ($n = 139$) of the cases, the fathers in 3.7% ($n = 8$), both parents in 30.7% ($n = 66$) and the child's foster mother in 0.9% ($n = 2$). The sociodemographic, prenatal and neonatal characteristics are listed in **Table 1**. The significant differences in family background and demographic characteristics between those with and without sleep data were a higher proportion of girls (50 vs. 39%, $p = 0.049$) and of mothers with higher education registered during the pregnancy (48 vs. 34%, $p = 0.009$) among those with sleep data.

Sleep Problems and Sleep Habits in EPT Children

Difficulty falling asleep or frequent awakenings was reported for 27.5%, snoring for 28.1% and daytime sleepiness for 17.2% of the children (**Table 2**). Only three children had breathing problems and two gasped for air when asleep (**Table 2**). Predictors of these outcomes were, therefore, not examined, but four of these five children also snored and were thereby included in the group of snorers. The mean time in bed was 10.2 h ($SD = 0.5$ h; range 9.0–12.0 h) and the mean sleep duration 9.4 h ($SD = 1.0$ h; range 4.3–11.0 h). The sleep duration was within the recommended 9–11 h for 75.3% of the children, within 7–8 h (possibly adequate) for 22.3 % and <7 h (less than recommended) for 2.4% of the children. None of the children slept more than recommended. There were no significant differences in the prevalence of difficulty falling asleep or frequent awakenings (27.2 vs. 28.0%, $p = 0.9$), snoring (26.2 vs. 34.0%, $p = 0.3$), daytime sleepiness (18.8 vs. 12.2%, $p = 0.4$) or sleep duration <9 h (78.2 vs. 66.7%, $p = 0.1$) at the age of 11 years between the groups of children born before GA 28 weeks and those born with GA 28–32 weeks.

Prenatal and Neonatal Predictors of Sleep Problems

Being born SGA and neonatal cerebral hemorrhage (subependymal/ intraventricular hemorrhage) were the only prenatal and neonatal factors that significantly predicted difficulty falling asleep or frequent awakenings, i.e., 43% of SGA vs. 25% ($p = 0.014$) of non-SGA children, and 42% of children with cerebral hemorrhage vs. 24% of those without hemorrhage ($p = 0.012$, **Table 3**). The respective odds ratios (95% CI) were 2.3 (1.2–4.4) and 2.3 (1.2–4.6) and did not differ after adjustments for sex, single parenthood and maternal education (**Table 3**). When restricting analyses to children with GA $\leq$ 27, SGA still predicted difficulty falling asleep or frequent awakenings ($p = 0.001$) (data not shown).

Smoking, both during early and end of pregnancy, significantly predicted snoring, i.e., 37 vs. 14% ($p = 0.001$) for early and 24 vs. 8% ($p = 0.017$) for late pregnancy. The respective odds ratios (95% CI) were 3.5 (1.6–7.7) and 3.4 (1.2–9.6) and did not differ significantly after adjustments (**Table 4**). The predictive value of intrauterine cigarette exposures for later snoring remained unchanged after including the parents' current smoking habits and the child's body mass index at 11 years in the adjusted analysis (data not shown).

There were no statistically significant predictors of sleep duration <9 h or daytime sleepiness (data not shown). None of the factors related to the severity of early lung disease, such as treatment modalities and duration of treatment for lung disease,

TABLE 1 | Characteristics of the 221 children who were born extremely preterm[a] in Norway in 1999–2000 and participated in the follow-up at 11 years of age.

FAMILY BACKGROUND	**%(*n*)**
Single parent	14 (30)
Higher education mother[b]	55 (119)
Higher education father[b]	40 (86)
DEMOGRAPHIC CHARACTERISTICS	**Mean (MIN-MAX)**
Gestational age, weeks	26.6 (23–32)
Birth weight, grams	868 (450–1370)
	% (*n*)
Boy	50 (111)
Girl	50 (110)
***IN UTERO* EXPOSURES**	
Preeclampsia/eclampsia	24 (52)
Small for gestational age[c]	28 (61)
Prenatal steroids	19 (41)
Infection in amnion cavity	10 (23)
Smoking–start of pregnancy	21 (39)
Smoking–end of pregnancy	13 (19)
BIRTH TYPE	
Cesarean section	69 (152)
PERIPARTUM RESUSCITATION	
Apgar <5 after 5 min	6 (12)
Intubated	27 (57)
Illness severity score 4th quartile[d]	22 (45)
RESPIRATORY MORBIDITY	
Mechanical ventilation (yes)	84 (180)
Days on mechanical ventilation Mean (min-max)	11 (1–113)
Oscillation	20 (40)
Postnatal steroids for lung disease	29 (64)
Theophylline/Caffeine	96 (204)
Patent ductus arteriosus, surgery treated	12 (26)
NEUROLOGIC INJURY	
Subependymal/intraventricular hemorrhage	30 (65)
Retinopathy of prematurity	25 (56)
Pathological findings by ophthalmologist at discharge	10 (15)
OTHER COMPLICATIONS/TREATMENT	
Necrotizing enterocolitis	5 (12)
Extensive medical treatment[e]	14 (30)
Congenital malformations, syndromes or metabolic diseases	4 (9)

[a] *Gestational age < 28 weeks or birth weight < 1,000 g.*
[b] *College or university education when the child was 11 year old.*
[c] *Small for gestational age: birthweights < 10th percentile.*
[d] *Illness severity score—computed from 3 components of the Clinical Risk Index for Babies, namely, the lowest and highest fractional oxygen requirements and the largest base deficit during the first 12 h of life.*
[e] *Extensive medical treatment defined as one of the following conditions: respirator more than 40 days, necrotizing enterocolitis or four or more antibiotic-treated infections.*

TABLE 2 | Prevalence of parent reported sleep problems at age 11 years in children born extremely preterm[a] in Norway in 1999–2000.

	Not true % (*n*)	Partly true % (*n*)	Absolutely true % (*n*)
Difficulty falling asleep or frequent awakenings	72.6 (143)	16.8 (33)	10.7 (21)
Snores	71.9 (143)	23.1 (46)	5.0 (10)
Gasps for air or stops breathing when asleep	99.0 (196)	0.5 (1)	0.5 (1)
Difficulty breathing at night	98.5 (194)	1.5 (3)	0 (0)
Daytime sleepiness	82.8 (164)	16.2 (32)	1.0 (2)

[a]*Gestational age < 28 weeks or birth weight < 1,000 g.*

severity of bronchopulmonary dysplasia, or extensive medical treatment in the NICU predicted sleep problems at the age of 11 years (**Tables 3**, **4**).

DISCUSSION

In this national cohort of children born EPT we found that 28.1% snored, 27.5% had difficulty falling asleep or frequent awakenings, 17.2% experienced daytime sleepiness and 24.7% did not get the recommended sleep duration. Smoking was the only predictor of snoring, and SGA birth and neonatal cerebral hemorrhage were the only predictors of difficulty falling asleep and frequent awakenings.

Our hypothesis was that several early life experiences in children born EPT would affect sleep at 11 years of age, in particular long term consequences related to early cerebral and respiratory morbidity. The limited significance of early events and exposures was remarkable, in particular the lack of association with the extensive and intrusive treatments that the EPT infants encounter. Similarly, studies have suggested that such neonatal exposures did not predict psychiatric disorders in EPT children (24, 25). Sleep and mental health are closely linked and these studies should therefore be seen in context (26).

Our finding that smoking in pregnancy was a predictor of snoring is in agreement with a Finnish study that examined young adults who had a birth weight < 1,500 g (12). Furthermore, a study of children born at term also found that smoking in pregnancy predicted childhood snoring (27). Combined, these studies may suggest that exposure to smoking in pregnancy has a negative effect on respiratory function independent of GA at birth, but that the stresses of prematurity may have an additive effect. The most frequent movement of the fetus during the second trimester is sucking (28). It is hypothesized that sucking is central for oral-facial growth and that extreme premature birth disturbs this process and thereby affects the development of both oral facial anatomy and muscular tone. This may contribute to pediatric sleep related breathing disorders, i.e., snoring (29). It is also a possibility that smoking in pregnancy may affect later physiological regulation, including sleep regulation (30, 31).

The prevalence of snoring (28.1%) in our EPT population was markedly higher than the prevalence of 7.5% in a meta-analysis of parent reported snoring in unselected children aged 0–18 years (32). Rosen et al. found that 21% of children who were born at a mean GA of 31 weeks compared to 14% of children born at term snored at the age of 8–11 years ($p = 0.0049$) (6). Together, these data may suggest that the prevalence of snoring increases with decreasing GA. The high prevalence of snoring in our study was unrelated to most pre-and neonatal factors suggesting that the general stresses of extra-uterine life of EPT birth may explain the excess risk. Reversed causality may also be a factor since studies have shown that sleep apnea in pregnant women may increase the risk of spontaneous premature birth (33). Sleep apnea and snoring are associated (34) which may imply a genetic predisposition. We were not able to explore this possibility since we had no information on snoring or other sleep disorders in the parents. Snoring can be a symptom or possibly a precursor of sleep disordered breathing (34).

Previous studies have shown that children born prematurely have an increased risk of sleep disordered breathing in childhood (35) and as an adult (12), and that they may also be particularly vulnerable to the negative sequelae of sleep disordered breathing in childhood (36). In general, sleep disordered breathing in childhood is a risk factor for impaired neurocognitive performance, behavioral problems, externalizing symptoms and inattention (37–42). The American Academy of Pediatrics therefore suggests that all children should be screened for snoring, and that high-risk patients should be referred to a specialist (43). The prevalence of sleep disordered breathing during childhood in children born EPT is unknown, but may be high judged from the high prevalence of snoring. Our findings indicate that snoring is a significant problem in preterm born children, and underline that more studies are needed to map the explicit risks and possible consequences of this condition in children born EPT.

To our knowledge, our findings that neonatal cerebral hemorrhage and SGA birth predicted difficulty falling asleep or frequent awakenings at 11 years of age are novel. Wang et al. found no association between neonatal risk factors, including grade III–IV intraventricular hemorrhage, and restless sleep in children born EPT at the age of 18–22 months (44). However, our findings were not unexpected since both cerebral hemorrhage and SGA are known risk factors for adverse neurodevelopmental outcomes (16, 45), and since we previously reported that a variety of sleep problems are more prevalent in EPT children with neurodevelopmental disabilities (10). Previous studies show that to be SGA add to the risk for several types of morbidity for EPT children (46). The fact that we found that SGA predicts difficulty falling asleep or frequent awakenings at the age of 11 years confirms this group's increased vulnerability. Difficulty falling asleep or frequent awakenings was reported in 27.5% of the EPT children in our cohort as opposed to a prevalence of 12.7% in an unselected cohort of 11–13 year-old Norwegian children (47). A previous study using polysomnography also reported increased number of awakenings in children born prematurely (GA < 32weeks) compared to children born at term (7).

According to the parents, 17.2% of the EPT children suffered from daytime sleepiness. Rosen et al. found a lower prevalence

TABLE 3 | Prenatal and neonatal factors predicting difficulty falling asleep or frequent awakenings at 11 years of age among children born extremely preterm[a].

	Difficulty falling asleep or frequent awakenings				
	No (*n* = 143) % (*n*)	**Yes (*n* = 54) % (*n*)**	***p*-value[1]**	**Unadjusted OR (95% CI) (*n* = 133–197)**	**Adjusted[b] OR (95% CI) (*n* = 132–196)**
DEMOGRAPHIC CHARACTERISTICS					
Gestational age group, weeks			0.6		
23–25	20 (28)	26 (14)		1.3 (0.5–3.1)	1.3 (0.5–3.2)
26–27	55 (79)	48 (26)		0.9 (0.4–1.8)	1.0 (0.4–2.1)
28–32 (reference)	25 (36)	26 (14)			
Single pregnancy (yes)	78 (112)	76 (41)	0.7	0.9 (0.4–1.8)	0.9 (0.4–2.0)
***IN UTERO* EXPOSURES**					
Preeclampsia/eclampsia (yes)	23 (33)	26 (14)	0.7	1.2 (0.6–2.4)	1.2 (0.6–2.4)
Small for gestational age[c] (yes)	**25 (36)**	**43 (23)**	**0.014**	**2.3 (1.2–4.4)**	**2.2 (1.1–4.2)**
Prenatal steroids (yes)	20 (28)	17 (9)	0.7	0.8 (0.4–1.9)	0.9 (0.4–2.0)
Infection in amnion cavity (yes)	11 (15)	9 (5)	0.8	0.9 (0.3–2.5)	1.1 (0.4–3.2)
Smoking – start of pregnancy (yes)	21 (25)	20 (9)	0.9	0.9 (0.4–2.2)	0.8 (0.3–2.1)
Smoking—end of pregnancy (yes)	12 (11)	16 (6)	0.6	1.4 (0.5–4.2)	1.5 (0.5–4.5)
BIRTH TYPE					
Cesarean (yes)	68 (97)	70 (38)	0.7	1.1 (0.6–2.2)	1.1 (0.6–2.3)
PERIPARTUM RESUSCITATION					
Apgar < 5 after 5 min (yes)	4 (6)	6 (3)	0.7	1.3 (0.3–5.6)	1.4 (0.3–6.0)
Intubation (yes)	72 (99)	67 (34)	0.5	0.8 (0.4–1.5)	0.8 (0.4–1.6)
Illness severity score 4th quartile[d] (yes)	20 (27)	28 (14)	0.3	1.5 (0.7–3.2)	1.6 (0.7–3.3)
RESPIRATORY MORBIDITY					
Mechanical ventilation (yes)	82 (115)	84 (43)	0.7	1.2 (0.5–2.8)	1.2 (0.5–2.8)
Days on mechanical ventilation >10	24 (34)	24 (13)	1.0	1.0 (0.5–2.1)	1.2 (0.5–2.8)
Oscillation (yes)	20 (25)	24 (11)	0.5	1.3 (0.6–3.0)	1.2 (0.5–2.8)
Postnatal steroids for lung disease (yes)	28 (39)	30 (16)	0.7	1.1 (0.6–2.3)	1.1 (0.6–2.3)
Theophylline / Caffeine (yes)	95 (130)	98 (50)	0.7	2.7 (0.3–22)	2.5 (0.3–20.6)
Discharged from hospital with oxygen (yes)	9 (13)	9 (5)	1.0	1.0 (0.4–3.0)	1.0 (0.3–3.1)
Patent ductus arteriosus, surgery treated (yes)	11 (15)	15 (8)	0.4	1.5 (0.6–3.7)	0.7 (0.3–1.8)
NEUROLOGIC INJURY					
Subependymal or intraventricular hemorrhage (yes)	**24 (34)**	**42 (22)**	**0.012**	**2.3 (1.2–4.6)**	**2.3 (1.1–4.5)**
Retinopathy of prematurity (yes)	25 (36)	24 (13)	0.9	0.9 (0.5–1.9)	0.9 (0.4–1.9)
Pathological findings by ophthalmologist at discharge (yes)	12 (11)	8 (3)	0.5	0.6 (0.2–2.3)	0.6 (0.2–2.3)
OTHER COMPLICATIONS/TREATMENT					
Necrotizing enterocolitis (yes)	6 (8)	7 (4)	0.7	1.4 (0.4–4.7)	1.1 (0.3–4.1)
Extensive medical treatment[e] (yes)	13 (18)	22 (12)	0.09	1.9 (0.8–4.5)	1.8 (0.8–4.1)
Congenital malformations, syndromes or metabolic diseases	5 (7)	4 (2)	1.0	0.8 (0.2–4.0)	0.7 (0.1–3.5)

[a] *Extremely premature (EP): gestational age < 28 weeks or birth weight < 1,000 g.*
[b] *Adjusted for sex, single parent and higher education mother.* [1] *Chi-square or Fisher-exact test.*
[c] *Small for gestational age: birthweights < 10th percentile.*
[d] *Illness severity score—computed from 3 components of the Clinical Risk Index for Babies, namely, the lowest and highest fractional oxygen requirements and the largest base deficit during the first 12 h of life.*
[e] *Extensive medical treatment defined as one of the following conditions: respirator more than 40 days, necrotizing enterocolitis or four or more antibiotic-treated infections. Bold, p-values < 0.05; n, number; SD, standard deviation; OR, odds ratio; Mean diff.; mean difference.*

in children born premature and no difference between the premature and a reference group born at term (6 vs. 7%) (6). However, their children were more mature at birth (mean gestational age 31 weeks) compared to our cohort. In another population-based unselected study of American children the parent-reported prevalence of daytime sleepiness was 15% (48), which is similar to what we found. Daytime sleepiness may therefore not be a problem related to extreme prematurity. This notion is strengthened by our findings that none of the prenatal or neonatal factors predicted daytime sleepiness.

None of the prenatal and neonatal factors predicted less than recommended sleep duration. Sleeping less than recommended is

TABLE 4 | Prenatal and neonatal factors predicting snoring at 11 years of age among children born extremely preterm[a].

	Snoring				
	No (*n* = 143) % (*n*)	**Yes (*n* = 56) % (*n*)**	***p*-value[1]**	**Unadjusted OR (95% CI) (*n* = 133–199)**	**Adjusted OR[b] (95% CI) (*n* = 133–198)**
DEMOGRAPHIC CHARACTERISTICS					
Gestational age group, weeks			0.3		
23–25	20 (29)	25 (14)		0.9 (0.4–2.2)	1.0 (0.4–2.3)
26–27	57 (81)	45 (25)		0.6 (0.3–1.3)	0.7 (0.3–1.4)
28–32 (reference)	23 (33)	30 (17)			
Single pregnancy (yes)	78 (112)	73 (41)	0.5	0.8 (0.4–1.5)	0.8 (0.4–1.6)
***IN UTERO* EXPOSURES**					
Preeclampsia/eclampsia (yes)	27 (38)	16 (9)	0.1	0.5 (0.2–1.2)	0.5 (0.2–1.2)
Small for gestational age[c] (yes)	31 (44)	27 (15)	0.6	0.8 (0.4–1.6)	0.8 (0.4–1.6)
Prenatal steroids (yes)	18 (26)	19 (10)	0.9	1.0 (0.5–2.3)	1.0 (0.5–2.3)
Infection in amnion cavity (yes)	11 (15)	9 (5)	0.7	0.8 (0.3–2.4)	1.2 (0.4–3.4)
Smoking–start of pregnancy	**14 (17)**	**37 (17)**	**0.001**	**3.5 (1.6–7.7)**	**4.3 (1.8–10)**
Smoking–end of pregnancy	**8 (8)**	**24 (9)**	**0.017**	**3.4 (1.2–9.6)**	**4.3 (1.4–13)**
BIRTH TYPE					
Cesarean (yes)	69 (98)	68 (38)	0.9	0.9 (0.5–1.9)	0.9 (0.5–1.9)
PERIPARTUM RESUSCITATION					
Apgar < 5 after 5 min	3 (4)	7 (4)	0.2	2.7 (0.7–11)	3.1 (0.7–12.9)
Intubation (yes)	30 (40)	28 (15)	0.8	1.0 (0.5–2.1)	1.1 (0.5–2.3)
Illness severity score 4th quartile[d] (yes)	23 (32)	17 (9)	0.4	0.7 (0.3–1.6)	0.7 (0.3–1.6)
RESPIRATORY MORBIDITY					
Mechanical ventilation (yes)	84 (118)	81 (42)	0.6	0.8 (0.4–1.9)	0.8 (0.4–1.9)
Days on mechanical ventilation >10	26 (37)	20 (11)	0.4	0.7 (0.3–1.5)	0.7 (0.3–1.5)
Oscillation (yes)	23 (30)	15 (7)	0.3	0.6 (0.2–1.5)	0.6 (0.2–1.4)
Postnatal steroids for lung disease (yes)	30 (43)	26 (14)	0.6	0.8 (0.4–1.6)	
Theophylline / Caffeine (yes)	96 (131)	94 (51)	0.6	0.7 (0.2–2.8)	0.6 (0.1–2.7)
Discharged from hospital with oxygen (yes)	11 (16)	4 (2)	0.09	0.3 (0.07–1.3)	3.6 (0.8–16.3)
Patent ductus arteriosus, surgery treated (yes)	12 (17)	14 (8)	0.7	1.2 (0.5–3.0)	0.8 (0.3–2.0)
NEUROLOGIC INJURY					
Subependymal or intraventricular hemorrhage (yes)	26 (37)	35 (19)	0.3	1.5 (0.8–2.9)	1.5 (0.7–2.9)
Retinopathy of prematurity (yes)	25 (36)	21 (12)	0.6	0.8 (0.4–1.7)	0.8 (0.4–1.6)
Pathological findings by ophthalmologist at discharge (yes)	7 (7)	17 (6)	0.1	2.6 (0.8–8.3)	2.4 (0.7–7.9)
OTHER COMPLICATIONS / TREATMENT					
Necrotizing enterocolitis (yes)	5 (7)	9 (5)	0.3	1.9 (0.6–6.3)	1.8 (0.5–5.9)
Extensive medical treatment[e] (yes)	15 (21)	16 (9)	0.8	1.1 (0.5–2.6)	1.0 (0.4–2.5)
Congenital malformations, syndromes or metabolic diseases	5 (7)	4 (2)	0.8	0.8 (0.2–3.8)	0.6 (0.1–3.3)

[a] *Gestational age < 28 weeks or birth weight < 1,000 g.*

[b] *Adjusted for sex, single parent and higher education mother.*[1] *Chi-square or Fisher exact test.*

[c] *Small for gestational age: birthweights < 10th percentile.*

[d] *Illness severity score—computed from 3 components of the Clinical Risk Index for Babies, namely, the lowest and highest fractional oxygen requirements and the largest base deficit during the first 12 h of life.*

[e] *Extensive medical treatment defined as one of the following conditions: respirator more than 40 days, necrotizing enterocolitis or four or more antibiotic-treated infections.Bold, p-values < 0.05; n, number; SD, standard deviation; OR, odds ratio; Mean diff.; mean difference.*

shown to have several negative consequences for children (49, 50) and, in adults, long sleep duration is also associated with poor health (51).We previously reported that the EPT children have longer sleep duration than a control group (10). However, in that report we used a slightly different definition of sleep duration, where we did not take into account time awake during nightly awakenings.

Strengths of this study included the national longitudinal population-based design of the EPT cohort. The limited response rate at follow-up was a weakness, as in most population based follow-up studies. This can lead to selection bias, but we have previously shown that the assessed children were probably representative of all the survivors at 11 years of age (52). It would have been desirable to compare the prevalence of sleep

problems in our EPT group with that of children born at term. Unfortunately, we had no control group for comparison. In our previous study, we used a control group to compare the prevalence of sleep problems in childhood (10). Unfortunately, the questions that form the basis of the present article were not included in the questionnaire to this control group. However, the main intention of the study was not to map the prevalence of sleep problems, but to explore which factors may predict sleep problems in children born EPT. The majority of these factors are unique to children born EPT, and not relevant for a control group.

We did not ask the children themselves about their sleep. It may be difficult for parents of 11 year old children to answer some of the questions, for example, nightly awakenings and daytime sleepiness. Another limitation relates to the many prenatal and neonatal factors that were included in the analyses. We did not adjust for multiple testing (type 1 errors), thus the results need to be interpreted with caution. We adjusted for single parenthood, maternal education and sex in all our analyses, and in addition for the parents' smoking habits and the child's BMI at 11 years of age when exploring predictive factors for snoring. We may, however, have overlooked other clinically significant confounders.

CONCLUSIONS

Our main finding was that a multitude of factors related to morbidity and treatment in the prenatal or neonatal period did not predict sleep problems at age 11 years in children born EPT. Smoking in pregnancy predicted snoring, and SGA birth and neonatal cerebral hemorrhage predicted difficulty falling asleep or frequent awakenings.

DATA AVAILABILITY STATEMENTS

According to the approvals granted for this study by The Regional Committee on Medical Research Ethics and The Norwegian Data Inspectorate, the data files are to be stored properly and in line with the Norwegian Law of Privacy Protection. The data file is not made publically available as this might compromise the respondents' privacy, particularly as some of our participating centers are small and the number of extremely preterm births very limited. Moreover, the data file is currently used by other researchers in our group to prepare future research papers. A subset of the data file with anonymized data may be made available to interested researchers upon reasonable request to Thomas Halvorsen (thomas.halvorsen@helse-bergen.no) and providing permission from The Norwegian Data Inspectorate and the other members of our research group.

AUTHOR CONTRIBUTIONS

KS secured the data set, contributed to the design of the study and to the analysis strategy, carried out all the analyses and drafted the initial manuscript. TM coordinated and supervised data collection for the extremely premature children and contributed to the design of the study and to the analysis strategy. MH, SF, IE, TH, and BB contributed to the design of the study and to the analysis strategy. All authors revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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III

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

Kristine Marie Stangenes,[1,2] Mari Hysing,[3] Irene Bircow Elgen,[4,5] Thomas Halvorsen,[2] Trond Markestad,[2] Bjørn Bjorvatn[6,7]

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For numbered affiliations see end of article.

Correspondence to
Dr Kristine Marie Stangenes; kristine.stangenes@gmail.com

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.

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.

INTRODUCTION

Sleep is critical for development, maturation and health on the journey from infancy to adulthood.[1] Sleep problems in children have been associated with asthma and other respiratory symptoms,[2] and with mental health problems, such as conduct problems, hyperactivity and emotional problems.[3–5] Children with neurological disabilities often have sleep problems,[6] but somatic and mental comorbidities may contribute to these problems.[7–9]

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.[10] Children born EPT are also at increased risk of behavioural problems and respiratory morbidities,[11 12] 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.

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.[9 13–16] 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.[10])

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.[17] The same sleep variables have been used in a previous paper.[18]

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.[19 20] 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'[1] and 'Certainly true'.[2] 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[21] 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 β_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, χ^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 α-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.[22] 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.[22]
§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.[10]

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).[11] The prevalence of current asthma (18%) was higher than the prevalence of 11% in an unselected Norwegian cohort of 10-year-old children.[23] Thus, this EPT cohort had more respiratory,[24] behavioural[11] and sleep problems[10] 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.[25] 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

	Difficulty falling asleep or frequent awakenings			Snoring			Daytime sleepiness			Not recommended sleep duration‡		
SDQ scores	**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)**
Parent-reported												
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)**
Teacher-reported			(n=169)			(n=170)			(n=170)			(n=120)
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 <1000 g.
‡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)
Last 12 months at 11 years age¶												
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)
Currently at 11 years age												
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^2 test or Fisher's exact test). Boldface denotes significant group differences.
†Gestational age <28 weeks or birth weight <1000 g.
‡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,[26] which is in agreement with our findings. It is worth noting that Perkinson-Gloor *et al* excluded children with severe developmental delay[25] and that Caravale *et al* included only children with normal cognitive, language, and motor development[26] 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,[27] 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.[28] 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*.[29] 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.[30] 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.[31–35] 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.[36]

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.[37–39] 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.[12 40–42] Their burden of respiratory symptoms may therefore be substantially higher, and more chronic[16] 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.[43 44] Previous studies on term-born children have shown that nocturnal awakening due to asthma is a risk factor for poor school functioning.[45]

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.

Author affiliations
[1]Children and Youth Clinic, Haukeland University Hospital, Bergen, Norway
[2]Department of Clinical Science, University of Bergen, Bergen, Norway
[3]Department of Pcychosocial Science, University of Bergen, Bergen, Norway
[4]Department of Clinical Medicine, University of Bergen, Bergen, Norway
[5]Department of Child and Adolescent Psychiatry, Haukeland University Hospital, Bergen, Norway
[6]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[7]Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway

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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