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CLINICAL REVIEW

The relationship between preterm birth and sleep in children at school age: A systematic review

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SUMMARY

Premature birth (before 37 weeks of gestation) has been linked to a variety of adverse neurological outcomes. Sleep problems are associated with decreased neurocognitive functioning, which is especially common in children born preterm. The exact relationship between prematurity and sleep at school age is unknown. A systematic review is performed with the aim to assess the relationship between prematurity and sleep at school age (5th to 18th year of life), in comparison to sleep of their peers born full-term. Of 347 possibly eligible studies, nine were included. The overall conclusion is that prematurity is associated with earlier bedtimes and a lower sleep quality, in particular more nocturnal awakenings and more non-rapid eye movement stage 2 sleep. Interpretations and limitations of the review are discussed. Moreover, suggestions for future research are brought forward, including the need for a systematic approach with consistent outcome measures in this field of research. A better understanding of the mechanisms that influence sleep in the vulnerable group of children born preterm could help optimize these children's behavioral and intellectual development.

Introduction

Every year, nearly 15 million infants worldwide are born preterm (i.e., before 37 weeks of gestation), which equates to about 11% of all live births [1–3]. Although mortality rates have decreased with increasing advances in perinatal and neonatal care, the surviving children still face an increased risk of severe neurodevelopmental disorders (NDD) [4]. Studies have found a positive association between the degree of prematurity and the likelihood of adverse neurological outcomes: infants born at the earliest gestational ages have the greatest risk of adverse outcomes [5,6]. At school age, up to 50% of infants born before 28 weeks of gestation require some degree of educational support [7]. Several factors linked to preterm birth may influence school performance: adverse events in the perinatal period (e.g., sepsis, hypoglycemia, intraventricular hemorrhage, etc.), white matter injury (axonal disease), as well as sociodemographic and genetic factors [8]. Another determinant of school performance is sleep. Though this is less well studied in ex-preterm infants, healthy sleep, with respect to both quality and duration, is important for optimal school performance, as shown in a comprehensive meta-analysis [9–13].

Although the specific roles of sleep in humans are still considered unclear, a variety of functions and functional outcomes have been associated with both sleep quality and quantity, such as neurodevelopment, memory consolidation, reparation of neural damage, emotional coping, and executive functioning [14–17]. Several studies have shown an association between sleep duration and school functioning as well as behavioral functioning [5,18]. To promote optimal health outcomes in school-aged children, the Sleep Research Society, together with the American Association of Sleep Technologists and the American Academy of Pediatrics

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Abbreviations

AGA	appropriate for gestational age
EEG	electroencephalography
FGR	fetal growth restriction
GA	gestational age
NDD	neurodevelopmental disabilities
OSA	obstructive sleep apnea
PSG	polysomnography
REM	rapid eye movement
SDB	sleep disordered breathing
SWS	slow wave sleep
NREM	non-rapid eye movement

endorsed the pediatric sleep recommendations by Paruthi et al. [19]. Children aged 3–5 years should sleep 10–13 h per 24 h on a regular basis; children aged 6–12 years 9–12 h; and teenagers, aged 13–18 years, 8–10 h [19].

Sleep problems, however, are relatively common in children, with estimations up to 12% for children that experience sleep problems every night [20]. Difficulties initiating sleep (4%–10%) are reported more frequently than difficulties maintaining sleep (5%) [21]. Sleep problems are thought to be even more prevalent in ex-preterm children [22]. The exact relationship between preterm birth and sleep problems at school age is not yet clear. It has been suggested, however, that adverse events related to preterm birth, such as brain injury, altered brain maturation, and respiratory problems, play a role herein [4,22]. Sleep problems in ex-preterm children might affect cognitive performance at school age, such as IQ, arithmetic, selective attention, and visuospatial memory [23]. The potentially reversible nature of sleep abnormalities offers the opportunity for the introduction of early and effective treatment for sleep disturbances that might enhance a child's neurodevelopment. We need to gain a better understanding of the specific factors that render this population more at risk for sleep problems.

Considering the limited amount of research into the relationship between preterm birth and sleep at school age, we undertook a systematic review to assess sleep of school-aged children and the link with preterm or full-term birth.

Methods

Search

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24] and was submitted to PROSPERO on the fourth of January, 2020 (registration number: CRD42020164251). An electronic database search was conducted in PubMed, Medline, and Embase on October 11, 2019. An updated search was performed on June 6, 2020, which yielded 13 new citations that all did not meet the inclusion criteria. The search strategy was as follows:

((("Child" [Mesh:NoExp])OR"Adolescent" [Mesh])OR ((Adolescent*[Title/Abstract])OR (Teens [Title/Abstract]ORteen [Title/Abstract]ORTeenager [Title/Abstract]ORYouth*[Title/Abstract]))) AND ("Sleep" [Mesh]OR"Sleep Wake Disorders" [Mesh]ORsleep* [Title/Abstract])AND ("Infant, Premature" [Mesh]OR"Infant, Very Low Birth Weight" [Mesh]OR"Premature Birth" [Mesh]ORprematur* [tiab]ORvlbw [tiab]ORelbw [tiab]OR"low birth weight" [tiab] ORpreterm*[tiab]ORprematur*[tiab]ORpreterm*[tiab]ORpreterm* [tiab])AND ((("Actigraphy" [Mesh])ORActigraph*[Title/Abstract])OR (("Polysomnography" [Mesh])OR (Polysomnograph*[Title/Abstract] OR Sleep Monitor*[Title/Abstract]))OR (("Electroencephalography" [Mesh])OR (Electroencephalogram*[Title/Abstract]OREEG [Title/Abstract]))OR ("Surveys and Questionnaires" [Mesh]ORSurvey*OR survey method O Rquestionnair*))Filters:Humans;English;Dutch.

Selection criteria

To be eligible, studies needed to address the relationship between preterm birth and sleep of school-aged children (5th to 18th year of life) compared to sleep of peers born full-term (born at a gestational age (GA) between 37 and 42 weeks) was studied. Preterm birth is defined as the birth of an infant less than 37 weeks of gestation. Both subjective and objective sleep measurements were included that assessed either sleep quality or quantity, that is sleep duration, nocturnal awakenings, sleep architecture, etc. Articles written in a language other than English and Dutch were excluded, as well as animal studies.

Study selection

Two of the researchers (WD and SV) independently screened on relevance the titles and abstracts of the citations retrieved from the two searches, using Rayyan QCRI (Qatar Computing Research Institute (Data Analytics)). If their opinions on inclusion or exclusion differed, a third researcher (JD) resolved the issue. Full-text screening of the articles that had remained after the title and abstract screening procedure was performed by two researchers (WD and SV). The reference lists of the selected articles were hand-searched for eligible articles that had been missed in the electronic searches.

Data extraction

The included study characteristics are the degree of prematurity, number of children born preterm and full-term, age range in years, sleep assessment tools, objective and subjective sleep characteristics, and the relevant findings. The characteristics were extracted and stored in a data extraction form by one researcher (WD) and subsequently confirmed by a second researcher (SV). Effect sizes and exact p-values were extracted and are reported whenever they were provided in the original articles, otherwise the reported cut-off for significance is presented.

Methodological quality

To assess the methodological quality of the studies included in the full-text qualitative synthesis, two of the authors (WD and SV) independently performed a critical appraisal according to the Critical Appraisal Checklist for Cohort Studies of the Joanna Briggs Institute [25]. This checklist consists of 11 questions to assess the methodological quality of studies and the risk of bias. The question "Were the two groups similar and recruited from the same population?" was not applicable and therefore excluded for the purpose of this systematic review. The response categories are Yes (+), No (−), or Unclear (?), counted as follows: + = 1 point, - = 0 point, and ? = 0 point. The total score is divided by the number of questions addressed and multiplied by 100%. A resulting percentage of 80% or more is considered high quality, between 50 and 80% is considered moderate quality, and below 50% is considered low quality. The critical appraisals of methodological quality were performed by two researchers (WD and SV); if no consensus was reached, a third researcher (JD or AH) was consulted to resolve the issue.

Synthesis of results

Data about the relationship between prematurity and sleep of school-aged were obtained from the included articles. We performed a best-evidence synthesis to assess the quality and consistency of the results from the included studies and to draw conclusions. Results were considered to be consistent when at least 75% of the studies showed results in the same direction, which was defined according to significance ($p < 0.05$) [26].

Results

Results of search

The first search yielded 334 articles, excluding duplicates and the second search yielded an additional 13 articles. Eventually, nine full-text articles were assessed for eligibility and included in the qualitative synthesis (Fig. 1). As the sleep characteristics and sleep measurements in the included studies highly varied, we concluded that a meta-analysis was not possible.

Study characteristics

The nine included studies were all cohort studies. Six made use of one sleep measurement instrument [23,27–31]; the other three studies used more than one instrument [32–34]. In five studies, sleep was assessed with the use of overnight polysomnography (PSG) [23,28,32–34]; two studies collected sleep data during one night in–home sleep electroencephalography (EEG) [30,31]; two studies made use of sleep logs [33,34]; one study used questionnaires [27]; another one used structured interviews [29]; and one study used wrist actigraphy [34]. Two studies, which measured sleep with PSG, were conducted at a research center [28,34]; the other studies collected sleep data in the participants' homes [23,27,29–33]. Of note, three studies collected data from the same study sample [23,31,33], and another study measured a second wave of this study sample, making it only partially overlapping [32]. The nine studies included a total of 743 preterm-born children and 1081 controls, with the children of the same study sample counted only once. The age range of the included children varied between 5 and 19 years of age. While the majority of the study samples admitted children ranging up to the age of 12

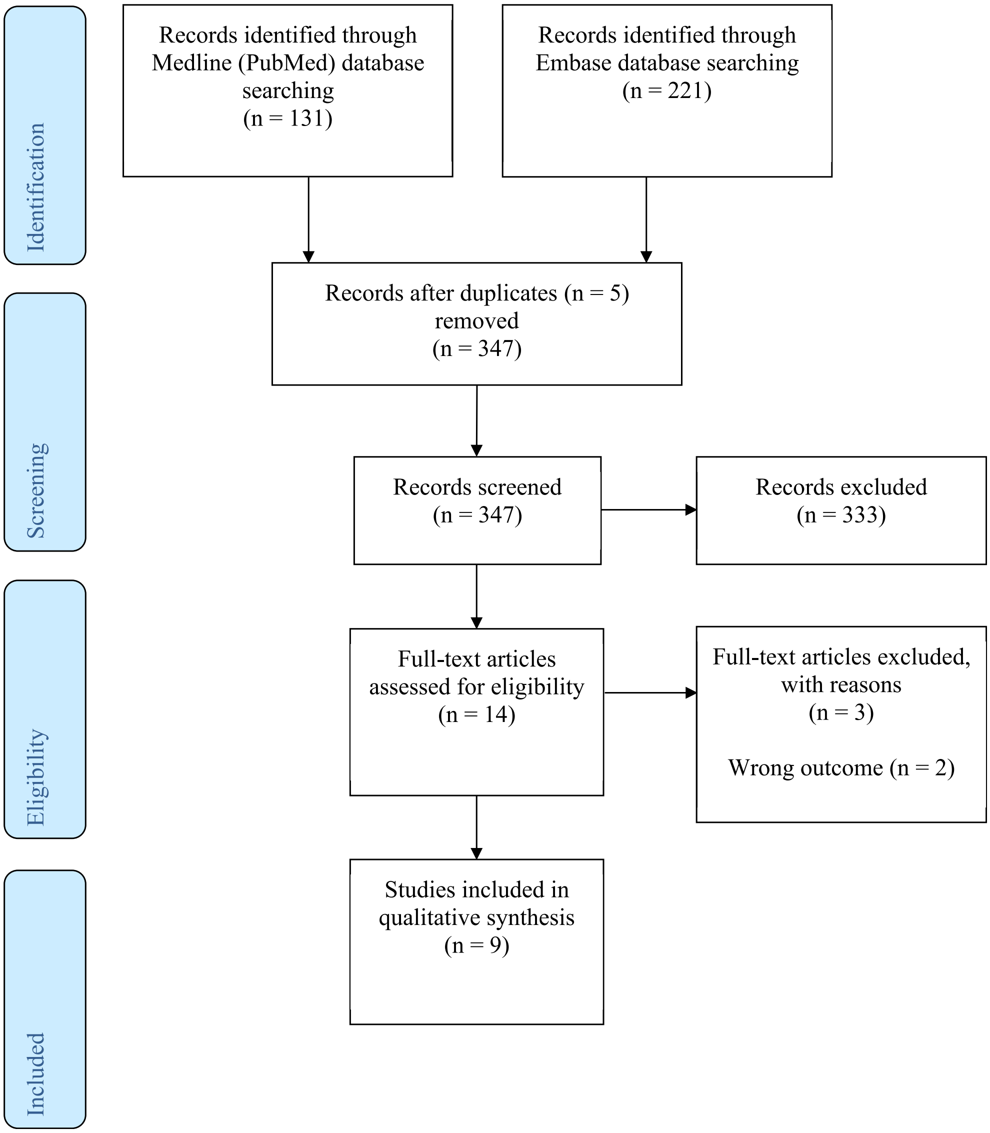

Fig. 1. Prisma flowchart of study selection.

[23,27–29,31–33], two studies included adolescents up to 16 [30] and 19 years of age [34]. The study characteristics and main findings are shown in Table 1.

Risk of bias within studies

Critical appraisal with the Critical Appraisal Checklist for Cohort Studies found three studies to be of high quality [23,28,32]; four of moderate quality [30,31,33,34]; and two of low quality [27,29] (Table 2).

Results of individual studies

Results of the individual studies are described by the sub categories sleep duration, sleep-waking times, nocturnal awakenings, sleep architecture, sleep efficiency and others, classified by the sleep characteristics (Table 3).

Sleep duration

All included studies had measured sleep duration. Three studies used subjective sleep-measures to this aim [27,29,34], of which only Stangenes et al. [27] found a significant result. Stangenes et al. [27] collected information with the use of questionnaires completed by the children's parents, but did not provide information about how these questionnaires were created and whether they had been validated or not. They reported longer sleep durations in children born preterm ($n = 231$) compared to children born full-term ($n = 556$) at 11 years of age (mean difference [MD] = 0.3, 95% CI = 0.2–0.4, $p < 0.05$ in both crude and adjusted analyses) [27]. Moreover, they found that children born preterm without

Table 1

Characteristics of studies included in the systematic review.

First Author (year)	Degree of prematurity (in weeks of GA or BW in grams)	Preterm children Number (N)	Control group Number (N)	Age range in years (mean)	Sleep measure instruments	Relevant Findings
Hagmann-von Arx et al. (2014) [23][a]	<32	N = 58	N = 55	6-10 (8.3)	Overnight in —home polysomnography	Preterm children showed significant more nocturnal awakenings ($p = 0.030$), and no significance differences were found for sleep duration ($p = 0.226$) or sleep efficiency ($p = 0.292$).
Hibbs et al. (2014) [34]	<37	N = 217	N = 284	16-19 (17.8)	Overnight polysomnography at Research Centre; Wrist actigraphy and daily sleep log (7 days)	Earlier bedtimes and wake times were observed in children born preterm ($p < 0.05$), as well as fewer EEG arousals ($p = 0.006$). However, no significant differences in sleep duration, -efficiency, -architecture and sleep onset latency were found between children born preterm and full-term.
Iglowstein et al. (2006) [29]	<37	N = 130	N = 75	From birth till 10 years of age	Structured interviews (not validated)	No differences were found on sleep duration, bedsharing, nocturnal awakenings, bedtime resistance and sleep-onset difficulties between full-term and preterm born children.
Lemola et al. (2015) [31][a]	<32	N = 58	N = 55	6-10 (8.3)	Overnight in —home polysomnography	Children born preterm showed significant more nocturnal awakenings compared to the children born full-term ($p < 0.01$). No significant differences were found in sleep duration, wake times, sleep efficiency and sleep architecture.
Maurer et al. (2016) [32][b]	<32	N = 85	N = 91	7-12 (9.6)	Overnight in —home polysomnography	Very preterm children had significantly earlier sleep onset time ($p = 0.013$). No significance difference in wake times ($p = 0.872$), sleep duration ($p = 0.066$), sleep efficiency ($p = 0.849$) and sleep architecture (all p-values > 0.10).
Perkinson-Gloor et al. (2015) [33][a]	<32	N = 58	N = 55	6-10 (8.3)	Overnight in —home polysomnography; Short sleep log	Children born preterm showed significantly more nocturnal awakenings ($p = 0.03$), and stage 2 sleep ($p = 0.03$) and significantly less N3 ($p = 0.02$). No difference was found in sleep duration and sleep efficiency.
Stangenes et al. (2017) [27]	<28 or BW less than 1000 g	At 5 years: N = 306 At 11 years: N = 231	At 5 years: N = 1119 At 11 years: N = 556	5 and 11	Questionnaire (different for both groups; not validated)	Children born EPT had longer sleep durations, earlier bedtimes and wake times, longer sleep onset latencies, spend more time in bed, and had more nocturnal awakenings than children born full-term (all $p < 0.05$).
Wehrle et al. (2017) [30]	<32	N = 38	N = 43	10-16 (13.1)	All-night EEG	No significant differences between term and preterm-born participants were found in sleep duration, sleep onset latency, time in bed, sleep awakenings and sleep architecture.
Yiallourou et al. (2018) [28]	24–36	Preterm FGR: N = 17 Preterm AGA: N = 13	N = 20	5-12 (9.0)	Overnight polysomnography at Sleep Centre	Shorter sleep durations ($p < 0.05$), more nocturnal awakenings ($p = 0.029$) and lower sleep efficiency ($p = 0.022$) was found in preterm AGA children compared to preterm FGR and/or term AGA. No difference in sleep onset latency was found. Moreover, more N2 and N3 sleep is in preterm FGR children is found compared to both other groups, as well as less NREM and more N3 sleep. Also, differences in microarchitecture have been identified.

Abbreviations: AGA, appropriate weight for gestational age; BW, body weight; EEG, electroencephalography; EPT, extremely preterm (<28 weeks GA); FGR, fetal growth restriction; GA, gestational age; NDD, neurodevelopmental disorder; REM, rapid eye movement.

[a] Studies with the same study sample.

[b] Study with the second wave of the same study sample.

Table 2
Methodological Quality Analysis of the included studies.

	Hagmann- von Arx et al. (2014) [23]	Hibbs et al. (2014) [34]	Iglowstein et al. (2006) [29]	Lemola et al. (2015) [31]	Maurer et al. (2016) [32]	Perkinson-Gloor et al. (2015) [33]	Stangenes et al. (2017) [27]	Wehrle et al. (2017) [30]	Yiallourou et al. (2018) [28]
Exposures measured similarly?	+	+	+	+	+	+	−	+	+
Exposure measured in a valid and reliable way?	+	+	?	+	+	+	?	+	+
Confounding factors identified?	+	+	−	?	+	−	+	?	+
Strategies for confounding factors stated?	+	+	−	?	+	−	+	?	+
Free of outcome at start?	+	?	+	+	?	+	?	+	?
Outcomes measured in a valid and reliable way?	+	+	?	+	+	+	?	+	+
Follow up time reported and sufficient to be long enough?	?	?	?	?	?	?	?	?	?
Follow up complete, if not, described and explored?	+	+	?	−	+	?	+	+	+
Strategies to address incomplete follow up utilized?	+	?	?	−	+	−	?	−	+
Appropriate statistical analysis?	+	+	−	+	+	+	+	+	+
Quality	High	Moderate	Low	Moderate	High	Moderate	Low	Moderate	High

NDD ($n = 93$) had longer sleep durations than children born full-term ($n = 556$; MD = 0.03, 95% CI = 0.2–0.4, $p < 0.05$). Nevertheless, using structured interviews, Iglowstein et al. [29] did not find a significant difference in sleep duration between preterm and term born children ($p > 0.05$). Likewise, Hibbs et al. [34] found no significant difference in sleep log-derived sleep duration between preterm and term born children both during weekdays ($d = 0.17$, $p = 0.06$) and weekends ($d = 0.16$, $p = 0.08$).

Seven studies assessed sleep duration with objective sleep-measures [23,28,30–34]. Hibbs et al. [34], apart from sleep logs, also used actigraphy. This revealed no significant differences in sleep duration during both weekdays ($d = 0.04$, $p = 0.74$) and weekends ($d = 0.19$, $p = 0.09$) between adolescents born preterm ($n = 217$) and those born full-term ($n = 284$), with adolescence defined as a person aged between 10 and 19 years [35]. Five other studies using objective measures likewise found no difference in sleep duration between children born preterm and children born full-term [23,30–33]. Nonetheless, using PSG, Yiallourou et al. [28] did find an effect of preterm birth on micro- and macro-sleep architecture. They reported 45 min shorter sleep durations in children born preterm with an appropriate birthweight for gestational age (AGA) ($n = 13$) than in children born preterm with fetal growth restriction (FGR) ($n = 17$; $p = 0.05$) and 64 min shorter sleep durations than in children born full-term with AGA ($n = 20$; $p = 0.008$).

Seven of the included studies [23,27,29,31–34] found sleep durations that are in accordance with the sleep recommendations introduced by Paruthi et al. [19]; the other two studies demonstrated a small, though still acceptable, reduction of the recommended sleep duration [28,30].

Sleep-wake times

Several factors are associated with sleep-wake times. Firstly, bedtimes and/or wake times were assessed in four studies. Hibbs et al. [34] found earlier bedtimes and wake times in adolescents born preterm than in term born adolescents, during weekdays and weekends, measured both subjectively, via sleep logs (all $p \leq 0.01$, except wake times during weekends; $p = 0.14$), and objectively, with actigraphy (for weekdays: bedtimes $d = 0.23$, $p = 0.05$ and wake-times $d = 0.22$, $p = 0.04$; for weekends: bedtimes $d = 0.22$, $p = 0.004$ and wake-times $d = 0.16$, $p = 0.14$). Maurer et al. [32], by using PSG, also found earlier sleep onset times in children born preterm ($n = 85$; $d = 0.44$, $p = 0.013$), but found no difference in wake times ($d = 0.03$, $p = 0.87$). Sleep onset time is defined as the sleep onset latency added to the bedtime. Stangenes et al. [27] found 24 min earlier bedtimes in children born preterm compared to term born children in both crude and adjusted analyses (MD = 0.4, 95% CI = 0.3 to 0.5, $p < 0.05$), even when accounting for NDD (MD = 0.4, 95% CI = 0.07–0.9, $p < 0.05$), whereas no difference in wake times was found ($p > 0.05$). They reported significantly more problems with falling asleep in children born preterm (odds ratio [OR] = 2.0, 95% CI = 0.5–1.1, $p < 0.05$), as well as more problems with waking up early (OR = 8.7, 95% CI = 3.1–24.0, $p < 0.05$) [27]. Yet, with the use of PSG, Lemola et al. [31] did not find differences in wake times between children born preterm ($n = 58$) and the term born controls ($n = 55$; $p > 0.10$); they did not assess bedtimes.

Secondly, longer sleep onset latencies in preterm born children compared to term controls have been described, but the difference often failed to reach statistical significance [28–30,34]. Only Stangenes et al. [27] showed increased sleep onset latencies in children born preterm compared to children born full-term (MD = 6.2, 95% CI = 2.0–10.5, $p < 0.05$).

Thirdly, time in bed was found to be longer in children born preterm compared to children born full-term in both crude and adjusted analyses (MD = 0.4, 95% CI = 0.3–0.5, $p < 0.05$), also when accounting for NDD (MD = 0.4, 95% CI = 0.2–0.5, $p < 0.05$) [27]. In contrast, Yiallourou et al. [28] found no statistically significant difference in time spent in bed between the preterm AGA, preterm FGR and full-term AGA children ($p = 0.250$). Likewise, Wehrle et al.

Table 3
Summarized results of the sleep behavior of preterm born children, when comparing this to full-term born children.

	Hagmann-von Arx et al. (2014) [23][a]	Hibbs et al. (2014) [34]	Iglowstein et al. (2006) [29]	Lemola et al. (2015) [31][a]	Maurer et al. (2016) [32][b]	Perkinson-Gloor et al. (2015) [33][a]	Stangenes et al. (2017) [27]	Wehrle et al. (2017) [30]	Yiallourou et al. (2018) [28]
Sleep duration	-[c]	–	-	-	-	-	Longer	-	Shorter
Bedtimes and wake times	NA	Earlier bedtimes and wake times	NA	- *(wake times)*	Earlier bedtimes	NA	Earlier bedtimes and wake times	NA	NA
Sleep onset latency	NA	-	-	NA	NA	NA	Longer	-	–
Time in bed	NA	NA	NA	NA	NA	NA	Longer	-	–
Nocturnal awakenings	More	NA	-	More	- *(more in girls)*	More	More	NA	More (vs. full-term)
Sleep efficiency	-	-	NA	-	-	-	NA	-	Lower (vs. full-term)
Sleep architecture	NA	-	NA	-	-	More stage 2 and less stage 3 - *(stage 1, REM sleep, -latency)*	NA	-	Preterm FGR: more stage 2 and less stage 3 (vs. both groups) Preterm AGA: less NREM (vs. both groups), more stage 3 (vs. FGR) - *(stage 1, REM)*
Other	NA	Lower arousal index Wake up easy, function best and fast in morning, less daytime sleepiness and fatigue, more vigor	- *(bed sharing and bedtime resistance)*	NA	NA	NA	NA	NA	Preterm FGR: more total- and delta power (vs. both groups), higher theta (vs. preterm AGA), higher alpha in stage 2 and 3 (vs. both groups) - *(arousal index)*

Abbreviations: AGA, appropriate weight for gestational age; FGR, fetal growth restriction; NA, not applicable (has not been studied); NREM, non-rapid eye movement; REM, rapid eye movement.

[a] Studies with the same study sample.

[b] Study with the second wave of the same study sample.

[c] No difference is found between children born preterm compared to children born full-term.

[30] also found no difference in time spent in bed between adolescents born preterm (n = 38) and those born full-term (n = 43) in their EEG study ($p = 0.82$).

Hagmann-von Arx et al. [23] and Perkinson-Gloor et al. [33] did not address the above-mentioned sleep-wake factors.

Nocturnal awakenings

All studies but Hibbs et al. [34] and Wehrle et al. [30] looked at the association between preterm birth and nocturnal awakenings in school-aged children. A significantly higher number or percentage of nocturnal awakenings was found in preterm born children compared to children born full-term in several studies that measured sleep with PSG, namely Hagmann-von Arx et al. [23] ($d = 0.40$, $p = 0.03$), Lemola et al. [31] ($p < 0.01$), Perkinson-Gloor et al. [33] ($d = 0.40$, $p = 0.03$), and Yiallourou et al. [28] ($p = 0.029$). Moreover, Stangenes et al. [27] found that the parents of children born preterm reported more frequent awakenings during the night compared to the parents of children born term (OR = 4.1, 95% CI = 2.3–7.3, $p < 0.05$), even when controlling for NDD (OR = 2.6, 95% CI = 1.1–6.1, $p < 0.05$). They further showed that increasing degrees of NDD in children born preterm is associated with an increase in the number of nocturnal awakenings ($p = 0.024$).

Still, Iglowstein et al. [29] with the use of structured interviews found no difference in the number of nocturnal awakenings between children born preterm (n = 130) and children born full-term (n = 75) ($p > 0.05$). The PSG-study of Maurer et al. [32] neither showed a difference ($d = 0.23$, $p = 0.194$), however, looking at the sexes, the authors found a significantly higher number of nocturnal awakenings in very preterm girls (i.e., born before 32 weeks GA) compared to full-term girls ($d = 0.56$, $p = 0.048$), whereas this was not seen in the boys ($d = 0.06$, $p = 0.801$).

Sleep efficiency

Seven studies assessed sleep efficiency [23,28,30–34], defined as the percentage of time asleep during the total time in bed or during the period between sleep onset and offset. Six of these, all measuring sleep with PSG or EEG, found no difference in sleep efficiency between children born preterm and children born full-term [23,30–34]. Yiallourou et al. [28] found a statistically significant difference in their PSG study, however, demonstrating a lower sleep efficiency in preterm AGA children compared to term AGA children ($p = 0.022$).

Sleep architecture

Sleep architecture is defined as the different sleep phases that compose a sleep cycle [36]. For adults this includes non-rapid eye movement (NREM) stage 1 sleep (N1), stage 2 sleep (N2) and stage 3 (N3) or slow wave sleep (SWS), and rapid eye movement (REM) sleep. Six of the nine studies assessed sleep architecture [28,30–34], with the use of either PSG or EEG.

Four studies found no difference in sleep architecture between children born preterm and children born full-term [30–32,34]. Perkinson-Gloor et al. [33], however, did find differences in sleep state distributions, namely a higher amount of N2 sleep ($d = 0.41$, $p = 0.03$) and a lower amount of N3 sleep ($d = 0.42$, $p = 0.02$) in children born very preterm (n = 58) compared to children born full-term (n = 55). Differences regarding the other sleep phases were not statistically significant: N1 sleep ($d = 0.14$, $p = 0.26$), REM sleep ($d = 0.31$, $p = 0.14$), and REM latency ($d = 0.10$, $p = 0.65$). Yiallourou et al. [28] demonstrated several differences in sleep architecture. The sleep stage distribution in preterm born FGR children was largely similar to that in the other groups. The exceptions comprised the percentage of N2 sleep, which in the preterm born FGR children was significantly higher than in the preterm born AGA ($p < 0.001$) and the term born AGA ($p = 0.014$) children, as well as the percentage of N3 sleep, which in the preterm born FGR children was significantly lower than in the preterm born AGA children ($p = 0.006$). Moreover, both the amount of NREM sleep and the amount of N2 sleep in the preterm born AGA children were lower than that in the term born AGA ($p = 0.003$) and the preterm born FGR children ($p = 0.013$). There were no statistically significant differences in the amounts of N1 sleep ($p = 0.354$), N3 sleep ($p = 0.223$) and REM sleep ($p = 0.069$), as well as the percentages of N1 sleep ($p = 0.287$), NREM sleep ($p = 0.153$) and REM sleep ($p = 0.133$).

Other

Both Hibbs et al. [34] and Yiallourou et al. [28] assessed the presence of EEG arousals, which reflects poorer sleep quality. Hibbs et al. [34] found a significantly lower arousal index found by in adolescents born preterm compared to adolescents born term ($d = 0.12$, $p = 0.006$). Yiallourou et al. [28] showed no difference in this regard ($p = 0.97$). These authors, however, also studies the sleep microarchitecture with the use of power spectral analysis, which refers to analysis of the individual EEG waveforms. This is thought to be a more sensitive measure of sleep quality compared to EEG arousals. The analysis revealed a higher amount of total and delta power in the preterm born FGR children compared to both the preterm born AGA children (total $p = 0.008$, delta $p = 0.01$) and the term born AGA children (total power $p = 0.028$, delta power $p = 0.019$), and a higher theta power compared to only the preterm born AGA children ($p = 0.04$). The alpha power in the preterm born FGR children was significantly higher than that in both other groups during N2 (preterm AGA $p < 0.001$, term AGA $p = 0.043$) and the preterm born AGA children during N3 sleep ($p = 0.006$). Increased delta power is linked to restorative functions and deepness of sleep; alpha power is thought to reflect sleep fragility. The implication of theta power remains uncertain [28].

Hibbs et al. [34] also assessed subjective factors related to sleep and illustrated that adolescents born preterm needed less time to become fully alert and functional in the morning ($d = 0.29$, $p = 0.002$), and reported less daytime sleepiness ($d = 0.39$, $p < 0.001$), higher levels of vigor ($d = 0.29$, $p = 0.002$), and lower levels of fatigue ($d = 0.31$, $p < 0.001$). Iglowstein et al. [29] looked into bedtime resistance and the amount of bed sharing, but found no statistically significant difference between children born preterm and children born full-term ($p > 0.05$). Only two of the included studies in this review addressed respiratory disorders related to sleep. Perkinson-Gloor et al. [33] looked into the prevalence of sleep disordered breathing (SDB) and Yiallourou et al. [28] studied the prevalence of obstructive sleep apnea (OSA) and none found a difference in the prevalence between children born preterm and children born full-term. Of note, Hibbs et al. [34] excluded children with OSA from their study sample.

Summary of the results

Overall, the studies included in this review indicate that prematurity is associated with earlier bedtimes and a lower sleep quality at school age. The lower sleep quality is in particular caused by more nocturnal awakenings and more N2 sleep (Table 3).

Synthesis of results

Taking quality into consideration, we need to cautiously interpret the results (Table 2). Strong evidence for an association with preterm birth is present for nocturnal awakenings, as two studies of high quality showed more nocturnal awakenings in children born preterm than in children born full-term [23,28]. Moderate evidence is present for bedtimes, as one study of high quality found earlier sleep onset times in children born preterm than in children born full-term [32], as well as for sleep architecture, as one study of high quality found a difference between groups [28].

Discussion

To our knowledge, this is the first systematic review on the relationship between preterm birth and sleep of children at school-age. The synthesis of results suggests that prematurity is related to earlier bedtimes and decreased sleep quality at school age, including more nocturnal awakenings and different sleep architecture. However, the study designs are considerably heterogeneous with regard to inclusion criteria, sleep measurement tools, and outcomes. Furthermore, the methodological quality of most of the studies was qualified as moderate or low, reflecting the lack of targeted studies on this topic and resulting in the inability to establish firm conclusions.

Seven of the nine included studies found significant differences in sleep between school-aged children born preterm and their peers born full-term. Several studies characterized children born preterm as ‘early bird’ phenotypes on the grounds of earlier bedtimes and earlier wake times, although the overall sleep duration was not significantly different from that in peers born full-term [27,32,34]. This early bird phenotype of children born preterm compared to term born peers was observed across the age range of the included studies, i.e., during childhood and adolescence. In general, strong changes in later bedtimes and later rise times occur during childhood and adolescence. This change is – at least partly – due to a delay in a teen's circadian rhythm as well as a decrease in the homeostatic sleep drive [37–39]. The earlier bedtimes and wake times in children and adolescents born preterm compared to their term born peers may suggest that these biological processes are delayed or altered. Extrinsic and behavioral aspects might be worth investigating to explain this. Increased social interactions, jobs and academic demands, and less parental involvement with bedtimes are factors known to influence sleep duration and bedtimes [40,41]. Differences in these factors between adolescents born preterm and full-term might explain the differences in sleep timing between these two groups. For example, less risk taking behavior and more social segregation have been observed in children born preterm compared to children born full-term, protecting them from the possible influences of social factors that could cause the delay in sleep onset times [42]. This interpretation corresponds to studies in the current review which link increased internalizing behaviors to children born preterm [33,34].

Moreover, increased parental concern with preterm born children could result in earlier bedtimes [41]. Interestingly, one of the three studies included in the current review that assessed time spent in bed, found increased time spent in bed, irrespective of sleep duration, in children born preterm compared to children born full-term [27]. This finding could suggest that parental concern does not automatically lead to longer sleep durations, however this result is not consistently demonstrated and needs further research. Future studies are recommended to incorporate level measurements melatonin, a hormone involved in the regulation of the sleep-wake cycle [43]. Knowledge of the chronobiology of children born preterm, based on melatonin levels and day—night rhythms, might help to optimize their sleep.

Related to the pubertal changes is the sex difference described by Maurer et al. [32], implying that only the sleep quality of girls differs between preterm born and full-term born children. A possible explanation could be the timing of onset of puberty, which occurs earlier in girls than in boys, and is related to the changes in the circadian regulation of sleep described above [43,44]. Because other studies have not found a sex difference [31,33], the finding by Maurer et al. [32] needs to be supported by further research.

Five of the nine studies reviewed reported a higher number of nocturnal awakenings in children born preterm than in their peers born full-term [23,27,28,31,33]. Nocturnal awakenings have been associated with SDB [45], for which former preterm infants may be at increased risk, in particular sleep apnea [45,46]. A possible underlying mechanism has been proposed by Yiallourou et al. [28], that link the higher amount of nocturnal awakenings in children born preterm to increased alpha power during NREM sleep, as observed in their EEG data. They relate elevated alpha power to more sleep fragility and disturbances, possibly resulting in the higher number of nocturnal awakenings found in preterm born children [28]. At the same time, epilepsy and psychiatric disorders, both prevalent in preterm born children, have been associated with increased EEG arousals that could lead to night fragmentations [47,48]. In addition to sleep microstructure, sleep architecture also seems to relate to preterm birth. For example, some results in the current review suggest a percentual [28] and quantitative [33] decrease in N3 in children born preterm compared to their peers born full-term, however further research is necessary to strengthen this association. More profound evidence has been found for increased N2 sleep [28,33]. More N2 sleep has been linked to increased behavioral and emotional problems, which are often seen in children born preterm [49], as well as to SDB severity in children born preterm – but not in children born full-term born children [50]. Moreover, research has linked SDB to poor emotion regulation, possibly due to blood gas abnormalities [49]. These abnormalities prevent sleep-related restorative processes and thereby affect the central nervous system. There is, however, still very limited data about sleep microarchitecture and its behavioral consequences, leaving questions regarding this unanswered. Unravelling the underlying mechanisms of nocturnal awakening and its relationship with sleep architecture and microstructures should be considered in future research aimed to optimize sleep quality and quantity in children born preterm.

Besides studying sleep differences between preterm born and full-term born school-aged children, Stangenes et al. [27] interviewed parents about the relationship between NDD and the child's sleep. The parents of the children born preterm with and without NDD indicated more sleep problems in their children than did the parents of the children born full-term, suggesting that preterm birth, rather than NDD, was associated with more sleep problems in this cohort. Others, however, have found a clear relationship between the presence of NDD (e.g., cerebral palsy) and sleep problems, and suggested that sleep intervention should be part of rehabilitation programs [51]. Noteworthily, various comorbidities besides NDD have been related to the development of sleep problems in school-aged children, including autism spectrum disorders, attention deficit hyperactivity disorder, and intellectual disabilities [52]. At the same time, many of these developmental disorders themselves are related to preterm birth [53]. This raises questions about cause and effect, illustrating the difficulty as well as the necessity of grasping the nature of sleeping problems. Future studies should, therefore, focus on the precursors of sleep problems and the relations with comorbidities.

We noted quite some heterogeneity among the included studies. Besides PSG, often considered the golden standard for sleep research, the various investigators assessed sleep with the use of actigraphy, questionnaires, sleep logs and interviews. The results of the studies are, therefore, not directly comparable. At the same time, since PSG can have undesirable effects as well (e.g., changed sleep patterns in children admitted to a hospital or research center), the variety of methods contributes to the translatability of the results more translational. Additionally, the children's age and degrees of prematurity widely varied, which are factors that both influence differential outcomes later in life [5]. To assure clear inferences, these factors should be more closely defined. Lastly, the inclusion and exclusion varied. For example, some studies excluded children with obstructive apnea-hypopnea [34], brain damage [23,30], or neurodevelopmental disabilities [23,30,32,33], whereas others did not.

Some limitations of this review need to be addressed. Firstly, only articles written in English and Dutch were included. Secondly, due to the heterogeneity of the included studies, a meta-analysis was not possible. In addition, Moreover, no inferences about causality can be made based on the current systematic review. Lastly, the study population overlapped in whole or in part in four of the nine studies, thereby limiting the generalizability of the results.

In conclusion, prematurity seems to be related to worsened sleep quality and altered bedtimes in school-aged children compared to children born full-term. However, due to the correlational nature of the current study, no causal relationships can be determined. Regarding the possibility for reversing the sleep disturbances, future research should focus on the mechanisms by which bedtimes and nocturnal awakenings effect sleep in the vulnerable group of children born preterm, to optimize the possibilities for behavioral and intellectual development by improving sleep in these children. Studying large prospective cohorts with the use of validated sleep measurement methods, well-defined inclusion and exclusion criteria, and both age range and GA tightly defined, could help further determine the effect of prematurity on sleep at school age.

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Practice points

Children born preterm show several sleep-related behaviors at school age that are different from their peers born full-term, including:

- Earlier bedtimes
- More nocturnal awakenings
- More stage 2 non-rapid eye movement sleep

Research agenda

To optimize behavioral and cognitive functioning in children born preterm, future research should focus on understanding the mechanisms underlying the factors that influence sleep in these children by looking at:

- Melatonin levels, to identify the sleep-wake cycle and better understand the earlier bedtimes found in children born preterm
- Behavioral and socioemotional factors, in order to unravel their presence and influence on sleep behavior in children born preterm compared to their peers born full-term
- The link between sleep microarchitecture and behavior, to get a better understanding of the relationship with nocturnal awakenings
- The relationship between sleep-related disorders and neurodevelopmental disorders in children born preterm to assess possible interactions
- Differences in sleep related to the children's sex
- Differences in respiratory difficulties related to sleep between children born preterm and children born full-term

Conflicts of interest

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