

Development of sleep-wake rhythms during the first year of age

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ABSTRACT

Circadian rhythms refer to biological rhythms that have an endogenous period length of approximately 24 hours. However, not much is known about the variance in the development of the sleep-wake rhythm. The study objectives were 1) to describe the normative variation in the development of sleep-wake rhythm in infancy 2) to assess whether slower development is related to sleep quality and 3) to evaluate factors that are related to the slower development of sleep-wake rhythm. The study is based on a representative birth cohort. Questionnaires at the ages of three (N=1427) and eight months (N=1302) and actigraph measurement at eight months (N=372) were available. Infants with significant developmental delays (N=11) were excluded. The results are based on statistical testing and multivariate modelling. We found that the average percentage of daytime sleep was 36.3% (SD 8.5%) at three and 25.6% (SD 6.6%) at eight months. At both time points, infants with slower sleep-wake rhythm development slept more hours per day, had a later sleep-wake rhythm, more difficulties to settle to sleep and longer sleep-onset latency; they also spent a longer time awake during the night. According to actigraph registrations, we found that the infants with slow development of sleep-wake rhythm slept less and had a later start and ending in night-time sleep than the other infants. Infants' sleep-wake rhythm development is highly variable and is related to parent-reported and objectively measured sleep quality/quantity. Interventions to improve sleep-wake rhythm might improve sleep quality in these infants.

Keywords: Sleep-wake rhythms, sleep, infant.

Introduction

Humans display various types of rhythms with an endogenous period length of approximately 24 hours among which the rest–activity rhythm is of major importance (Turek et al., 2001). The human circadian system is driven by the circadian clock in the suprachiasmatic nucleus and is sensitive to environmental factors in mid-pregnancy, although it takes much longer before the infants start to display mature sleep–wake rhythms (Rivkees, 2007). This gradual development starts after birth and by the age of two months, there are clear signs of circadian rhythmicity regarding both the sleep–wake cycle and hormone secretion. After the first months of life, the longest sleep periods start to accumulate into the night-time, while daytime sleep begins to diminish. Consequently, by the age of three to four months infants are usually more awake during the daytime than at night (Rivkees, 2003). The development in diurnal rhythm parallels the consolidation of night-time sleep, in other words, improvement in the quality of night-time sleep (Hendersson et al., 2011).

The developing diurnal sleep–wake rhythm has been described previously in a questionnaire-based study by reporting the night-day ratio (Sadeh et al., 2009). This study showed that the proportion of night-time sleep increases from 60% at 0–2 months old, to 70% at 3–5 months old and 75% at 9–11 months old up to 78% at two years old. Slightly higher percentages of nocturnal sleep have been observed using polysomnography: infants were reported to sleep on average 78% at night at the age of three months, 81% at nine months, and 84% at two years (Louis et al., 1997). There is, however, large variability in the development of diurnal sleep–wake rhythm. Some infants may already have clear day–night differences soon after birth, while others exhibit such rhythms much later (Rivkees, 2003). Yet not much is known about the variance in the development the sleep–wake rhythm and its clinical significance.

Animal studies provide evidence that the postnatal light environment affects the development of circadian rhythms (Brooks and Canal, 2013). Alternations in natural and artificial photoperiods have also been related to infants' night-time sleep duration (Iwata et al., 2016). Moreover, the development of sleep-wake rhythm might be related to feeding and social cues (McGraw et al., 1999; Mirmiran et al., 2003). Finally, although it is clear that environmental factors may affect activity patterns, it has been argued that inter-individual differences in developing circadian rhythms can also be driven by endogenous rhythmicity more than by the caregivers' influences (Rivkees, 2003). Along these lines, gestational age, birth weight, birth order, or breastfeeding duration were not associated with sleep-wake rhythm development (Jenni et al., 2006).

The main aim of the present study was to describe the normative variation in the development of the diurnal sleep–wake rhythm at the ages of three and eight months, as well as to assess whether the slower development of the diurnal sleep–wake rhythm is related to sleep quality, either based on parents’ reports or on actigraphy recordings of sleep. Finally, we also evaluated whether the slow development of the diurnal sleep–wake rhythm is related to age, gender, and season of birth.

Methods

Sample

This study is based on the CHILD-SLEEP birth cohort. The sample was recruited during pregnancy in well-baby clinics approximately at the 32nd pregnancy week. In total, 1673 families agreed to participate in the study. Specifically for this study, the follow up time points were at the age of three and eight months. Details of the recruitment procedure have been reported elsewhere (Paavonen et al., 2017). The study protocol of the cohort was approved by the local ethical committee (ethical research permission code R11032). The parents gave written informed consent at the beginning of the study.

At three months, the response rate was 85.3% (N = 1427). We excluded infants with severe developmental conditions (such as Down syndrome, blindness) (N = 11), as reported by the parents by the age of two years. A small proportion of the parents (7.1%, N = 101) returned the questionnaires late (age >4 months) and in four cases it was not possible to define the infants’ age due to missing data. Therefore, the final sample consisted of 1311 infants aged 72–120 days (Table 1). As many as 97.0% (N = 1272) had responded to the Brief Infant Sleep Questionnaire (BISQ); however, 2.4% of them (N = 30) did not have both daytime and night-time sleep durations reported and were thus excluded from further analyses leaving 1242 infants aged 3-4 months for the analyses.

At eight months, the response rate was 77.8% (N = 1302). A few parents (0.5%, N = 6) returned the questionnaire late (age >10 months) and in one case it was not possible to define the age of the infant due to missing data. These infants and those with a developmental condition (the same as at the age of 3 months) (N = 11) were excluded from the study leaving 1284 infants (Table 1). Of these, 99.1% (N = 1272) had responded to the BISQ. Finally, we excluded cases who had missing information either in the daytime or night-time sleep variables (1.1%, N = 14) leaving 1258 infants aged 7–10 months for the analyses.

In addition, a subsample of 372 infants also participated in the actigraph study. Of these 329 had valid data and were aged 8-10 months at the time of measurement. The cases with severe illnesses

(the same as reported above) were excluded from the data leaving 324 infants for the analyses (155 girls and 174 boys, mean age: 8.1 months, SD: 0.5 months). These infants were randomly selected at birth by contacting the parents in the birth hospital to invite them to the actigraph study. The only exclusion criterion was gestational age <37 weeks. The subsample with actigraph registration did not differ from the main cohort in any of the demographic parameters (all p-values >0.075)

Measures

Questionnaires

There were separate questionnaires for both parents and their children, filled out by either one or both parents together. All three questionnaires comprised several standardized questionnaires and other questions regarding health, welfare, and family socio-economic status. In addition, hospital register data was available for 97.4% (N = 1278) and 97.7% (N = 1217) of those eligible at 3 and 8 months, respectively.

To assess infants' sleep duration and sleep quality, we used both the BISQ and the Infant Sleep Questionnaire (ISQ) at 3 and 8 months.

The BISQ is a brief parental questionnaire for screening infant and toddler sleeping problems (Sadeh, 2004). It consists of 13 items of which we used the following six items: sleep duration during the day (07.00–19.00) and night (19.00–07.00), the number of night wakings, bedtime, sleep latency, and time spent awake at night (22.00–06.00), which are measured as open questions.

The ISQ is a parental questionnaire of sleep quality among infants and toddlers (Morrell, 1999). There are 10 items to study the frequency and severity of difficulties. In this study, we used the following three items: difficulties in setting to sleep (times per week, eight response alternatives), sleep-onset problems in the evening (minutes in the evening, seven response alternatives) and at night (minutes at night, seven response alternatives). These variables were dichotomized to divide the infants into two groups: those who represent quite typical behaviours for the age; and those with sleep difficulties. The cut-off values are reported in Tables 3a and 3b.

The development of the diurnal sleep–wake rhythm was evaluated by calculating the percentage of daytime and night-time sleep relative to total sleep duration. Cut-off points for the slow development of sleep-wake rhythm at three and eight months in this study were set at a proportion of daytime sleep of more than 41.4% and 29.6% respectively (≥ 75 th percentile), based on our own sample.

Actigraphy

Actiwatch AW7s (manufactured by Cambridge Neurotechnology Ltd, Cambridge, UK) were used in this study. This device uses a validated algorithm (Oakley, 1997) in which activity counts recorded during the measured epoch are modified by the level of activity in the surrounding two-minute time period (i.e., ± 2 min) to yield the final activity count for each epoch (Kushida et al., 2001). The parents were asked to place the actigraph around the ankle of their infant for three consecutive days and to carefully keep a sleep log of their infant. Night-time activity data was scored using the Sleep Analysis program provided by the manufacturer and the sleep variables used in this study represent the average values of the measured nights. Bedtimes and wake-up times were defined according to parental reports in the sleep log. The data was thoroughly inspected for any deviances and indicators of mechanical measurement errors. Five registrations were excluded.

Statistical analysis

We first studied the distributions of the main variables of interest. Next, using t-test or X^2 -test we compared the two groups of infants (those with slower development of sleep-wake rhythm vs. others) relative to background and sleep variables. In order to control for confounding factors (age, gender, breastfeeding and season of birth), we computed multivariate models (analysis of covariance, ANCOVA or logistic regression) to confirm the potential differences in sleep quality between these two groups. In these models, the sleep measures from questionnaires or from actigraphs served as dependent variables, while using the slow development of sleep-wake rhythm and age, sex, breastfeeding, season of birth, and season of actigraph recording as independent variables. The prevalence of sleep-wake rhythm problems was studied using the McNemar test. The infants with persistent problems were defined as those who belonged to the slow development group at both time points. Finally, we constructed logistic regression models to study factors that are related to slow development. In these models we used age, sex, breastfeeding, and season of birth as explanatory factors. The seasons were defined as summer solstice season, autumnal equinox season, winter solstice season, and spring equinox season, all corresponding to the years of birth and actigraph recordings, respectively.

Results

Differences within sociodemographic variables between infants with and without slow development of their diurnal sleep-wake rhythm at three and eight months are described in Table 1.

As reported in Table 2, at three months, the majority of the infants slept less during the day than during the night with the average percentage of daytime sleep being 36.3%. In addition, this

percentage of daytime sleep continued to decrease over the following months so that at eight months of age it was 25.6%.

Slow sleep-wake rhythm development was considered to occur in 25.0% (N = 310) of the infants at the age of three months and in 25.8% (N = 324) at the age of eight months.

Overall, 60.1% (N = 654) of the infants did not have developmental sleep-wake rhythm problems at either time point, while 9.7% (N = 105) had them both at three and eight months of age. The distribution was similar at both time points ($p = 0.826$), but there was a tendency for persistent problems (risk ratio 2.5, 95% CI 1.9-3.4; negative predictive value 79.7%; positive predictive value 39.3%).

As expected, we found that at the age of three months, infants with a slow development of the diurnal sleep-wake rhythm were reported to sleep less during the night and more during the daytime. More importantly, they also slept more hours per day, had a later bedtime, longer sleep-onset latency and more often difficulties to settle to sleep; they also spent a longer time awake during the night (see Table 3a, Figure 1).

Similarly, at eight months of age, slow development of sleep-wake rhythm was related to less sleep during the night and more sleep during the daytime. It was also related to longer total sleep per 24 hours, a later bedtime, longer sleep-onset latency, more difficulties to settle to sleep and longer time awake during the night (see Table 3b, Figure 2).

Concerning actigraphy variables, consistent with the questionnaire findings, we found that the infants with slow development of sleep-wake rhythm spent less time in bed, slept less at night and had later sleep starting and ending times, than the infants in the comparison group (see Table 4). No significant differences were found in sleep latency, actual time awake at night, sleep efficiency, fragmentation index or number of night waking bouts using actigraphy. However, these sleep variables were different between groups using parent-reported sleep questionnaire.

Using multivariate modelling, we aimed to confirm these results while statistically controlling for potential confounding factors (age, sex, breastfeeding and season of birth). Both at three and eight months, slow development of sleep-wake rhythm remained significant in all models. Moreover, the sleep parameters were variably related to age, sex, breastfeeding and season of birth. For example, at three months sleep during the daytime was also explained by younger age ($p = 0.014$), and season of birth ($p = 0.028$); total sleep by sex ($p = 0.047$); and bedtime by sex ($p = 0.049$), breastfeeding ($p = 0.001$) and season of birth ($p = 0.015$). Similarly, at eight months, daytime sleep was also related to

season of birth ($p = 0.008$); night-time sleep to age ($p = 0.006$) and breastfeeding ($p=0.047$); total sleep to age ($p = 0.001$) and season of birth ($p = 0.001$); and bedtime to season of birth ($p < 0.001$), breastfeeding ($p = 0.017$) and sex ($p = 0.036$).

Concerning actigraphy variables, in multivariate models, all the significant results remained and in addition to slow sleep-wake rhythm development assumed night time sleep was related to season of acg ($p=0.043$), bedtime and sleep ending times were related to season of birth (p -values 0.035 and 0.012, respectively), and sleep efficiency was related to sex ($p=0.023$, respectively).

Finally, we conducted logistic regression modelling to study the risk factors for the slow development of sleep-wake rhythms at three or eight months. At three months, season of birth and sex were related to sleep-wake rhythm development. Girls had a higher risk for problems compared to boys (OR 1.33, 95% CI 1.02-1.73, $p = 0.035$) and infants born in the summer and autumn had a higher risk for the slow development of sleep-wake rhythm compared to those born in spring (OR 1.56, 95% CI 1.08-2.27, $p = 0.018$; OR 2.48, 95% CI 1.69-3.65, respectively). The prevalence rate of slow sleep-wake development was 17.2% in those born in the spring, 25.2% in those born during the summer, 35.1% in those born in the autumn and 21.4% in those born in the winter. At eight months, no significant risk factors were identified.

Discussion

In this study, we investigated the development of sleep-wake rhythm in infants of the CHILD-SLEEP birth cohort at three and eight months of age. We were especially interested in the normative range in the development of sleep-wake rhythms and its clinical significance (i.e. whether slower development is related to sleep quality while other confounding factors are controlled).

Previously, only a few longitudinal studies have provided normative reference information of circadian rhythm development and little is known about the individual changes and the stability of the infant sleep-wake behaviour during the first months of life. In this study, at 3-month olds were found to sleep an average of 5.1 hours during the daytime, 9.1 hours during the night-time, and 14.1 hours during the whole day, which is in line with previous studies (Bruni et al., 2014; Figueiredo et al., 2016). After three months of age, the consolidation of sleep towards night-centred sleep occurs, and daytime sleep decreases (Bruni et al., 2014; Figueiredo et al., 2016). Consistently, our results showed that eight-month-old infants slept an average of 3.4 hours during the daytime, 9.9 hours during the night-time, and 13.3 hours during the whole day.

Interestingly, both at three and eight months of age the infants with slower development of sleep-wake rhythm not only slept less during the night and more during the daytime, but they also slept more, had a later sleep-wake rhythm, were more awake during the night, and it took longer for them to fall asleep. These differences remained significant when we controlled for background factors, suggesting that slower diurnal sleep-wake rhythm development is a clinically relevant developmental issue.

Concerning the objective sleep quality measured with the actigraph at eight months, our questionnaire results were partially supported. The results showed that the infants with slow development of sleep-wake rhythm spent less time in bed, had less hours of assumed and actual sleep during the night, and later sleep onset and waking. However, sleep latency, actual time awake at night, and number of night waking bouts, which significantly differed between groups using parent-reported sleep questionnaire, did not show any significant differences between the two groups. These findings are consistent with previous research reporting that objective and subjective sleep measures may be interchangeably used for the assessment of sleep start, sleep end, and assumed sleep in children, but not for nocturnal wake times (Werner et al., 2008).

Previous studies conducted among toddlers have shown that daytime sleep is relevant in terms of circadian phase and night-time sleep quality. For instance, one study showed that habitually napping toddlers have later melatonin onset time, later bedtime, longer sleep-onset latency, and shorter night-time sleep (Akacem et al., 2015). Another study showed that there was a negative correlation between nap duration, sleep onset time and night-time sleep duration (Nakagawa et al., 2016). These results are in accordance with our findings and suggest that inappropriate amounts of daytime sleep can have a negative effect on subsequent night-time sleep.

We also studied factors that are related to slow diurnal sleep-wake rhythm development. While no significant risk factors were found in eight-month-olds, photoperiod during the first three months was related to slower development of sleep-wake rhythm at the age of three months. This corresponds with findings in animal and infant studies (Brooks and Canal, 2013; Iwata et al., 2016). Exposure to a long photoperiod leads to a phase delay in circadian rhythms and thus also affects the sleep-wake cycle. It should be noted that although the effect of season of birth on sleep-wake cycles might be statistically significant, in young adults and adolescents it affects the preferred sleep onset time rather than the preferred sleep offset times, and remains quantitatively small (Natale et al. 2009, Tonetti et al. 2011). Furthermore, such an effect was not found in preschool children (Doi et al. 2014), suggesting a major influence by the schedules of society and the circadian preference of the family.

However, the development of sleep-wake rhythm in infants might be more vulnerable to environmental effects of light particularly in the northern latitudes where the alternations in photoperiod are very large (ranging from 19 h 35 min in the summertime to 5 h 25 min in the wintertime in Tampere area) as suggested by our findings.

Moreover, other factors, such as circadian preference, might also have contributed to these individual differences in sleep functioning. Sleep problems have been found to be greater in evening-types compared to morning-types, both in toddlers (Simpkin et al., 2014) and preschool children (Jafar et al., 2017), and a change towards the circadian preference to evening hours appears to occur already during the toddler age (Randler et al., 2017). In addition, recent findings from our group suggest that maternal circadian preference is related to several sleep difficulties of infants in early childhood, and especially to increased risk for slower sleep-wake rhythm development (Morales-Muñoz et al., 2019).

Although slow development of diurnal rhythm can also represent normative variation, previous research (McGraw et al., 1999; Mirmiran et al., 2003; Rivkees, 2007) suggests that the capability for consistent sleep-wake rhythms develops quite rapidly during the first weeks of life, and thus it could be moderated by environmental factors (such as differences in parenting or daily activities in these families). If this is confirmed in further studies, these infants might benefit from interventions to support more “age-appropriate” sleep-wake rhythms, which in turn might help them in enhancing the quality of their night-time sleep (e.g., less night wakening, faster sleep onset). In fact, many behavioural interventions include aspects regarding sleep hygiene (i.e., constant bedtime routines) and stable and age-appropriate day-to-night rhythm (Allen et al., 2016). However, intervention studies are needed to gather data on the benefits of sleep-wake rhythm modifications in infants with slower sleep-wake rhythm development.

Taken together, our findings showed that both subjective and objective sleep quality were worse in the infants with slow development of sleep-wake rhythm, with age, sex, breastfeeding, and season of birth as confounding factors. In adulthood and later childhood, circadian rhythm sleep disorders are considered a group of sleep disorders, which affect the timing of sleep, among other aspects of sleep (Dagan, 2002). Our results suggest that already in the early stages of life some common sleeping problems (such as sleep onset problems and night waking) could be connected to delays in diurnal sleep-wake rhythm development.

To date, there is little previous clinical research on the topic regarding sleep-wake rhythm development and circadian sleeping problems in infancy. The diagnostic classification systems of

sleep disorders do not define specific developmental circadian rhythm problems. According to our findings, slow sleep-wake rhythm development seems to explain some sleeping problems in early childhood (such as sleep onset difficulties and short night-time sleep), and therefore it might be a clinically significant problem, warranting specific attention in clinical settings. It might be possible to improve infant sleep quality by supporting age appropriate sleep-wake rhythms (by maintaining consistent sleep-wake rhythms and avoiding inappropriately long naps during the daytime). Clinical studies, however, are needed to study the effectiveness of such behavioural interventions.

These findings must be interpreted within the context of potential limitations. First, the criteria for sleep-wake rhythm problems were subjectively determined by parents' report, and no objective criteria were used in this case. Second, it is important to notice that in this study, we used cut-off values based on our own data, whereas the other study comprising US-Canadian children during the first year of life reported quite different distributions (41% vs. ~35% at the age of 3 months and 30% vs. ~28% at the age of 8 months) (Sadeh et al., 2009). While there may be cross-cultural differences in sleep-wake development, it is also worth noticing that the US-Canadian data was collected via advertising in the internet and therefore might not represent a random sample of infants. More studies on the topic are needed to clarify the normative developmental trajectories in infants. Third, sleep quality was only examined with actigraphy at the age of eight months but not at three months. Therefore, at three months we only reported subjective sleep difficulties and thus further studies should aim to include objective data at this age. Fourth, the number of eight-month-old infants who participated in the actigraph study was relatively small compared to the total number of infants in the whole study. In addition, daytime sleep duration was not analysed with actigraphy, and thus information about objective total sleep is missing.

To summarize these findings, we found that infant sleep-wake development is highly variable, and this variability is related to poorer sleep quality. Thus, some infants may display clinically significant delays in sleep-wake development that may warrant treatment.

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Author Contributions

EJP, OSH, AK, PP, TPH and TP designed the study and wrote the protocol. EJP and IMM conducted the statistical analyses and literature reviews. EJP wrote the manuscript. All authors contributed to and approved the final manuscript.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Fig 1. Significant differences within sleep quality measured with questionnaires between infants with and without sleep-wake rhythm problems, at 3 months of age. These graphs show that infants with sleep-wake rhythm problems at 3 months sleep less at night (A), sleep more during daytime (B), have more hours of total sleep per 24 hours (C), spend more time awake during the night (D), and have more frequency of late sleep onset (> 30 mins) (E), when compared to infants without sleep-wake rhythm problems. Error bars represent the 95% confidence interval (CI).

Fig 2. Significant differences within sleep quality measured with questionnaires between infants with and without sleep-wake rhythm problems, at 8 months of age. These graphs show that infants with sleep-wake rhythm problems at 8 months sleep less at night (A), sleep more during daytime (B), have more hours of total sleep per 24 hours (C), have later bedtime (D), spend more time awake during the night (E), and have more frequency of late sleep onset (> 30 mins) (F), when compared to infants without sleep-wake rhythm problems. Error bars represent the 95% confidence interval (CI).

Table 1. Description of the background variables in infants at 3 and 8 months ($N = 1242$ at 3 months, and $N = 1258$ at 8 months).

3 months	Comparison group (N=932)	Slow development group (N=310)	<i>p value</i> ^{a,b}
Gender			
Girls, N (%)	423 (45.4%)	164 (52.9%)	0.022 ^a
Boys, N (%)	509 (54.6%)	146 (47.1%)	
Age, in days (mean, SD)	96.0 (8.4)	95.6 (8.8)	0.484 ^b
Feeding			
breastfeeding, N (%)	799 (85.9%)	277 (89.6%)	0.093 ^a
supplemental milk only, N (%)	131 (14.1%)	32 (10.4%)	
Season of birth, N (%)			
winter (21.12-19.3.)	162 (17.4%)	44 (14.2%)	<0.001 ^a
spring (20.3.-20.6.)	255 (27.4%)	53 (17.1%)	
summer (21.6.-21.9.)	323 (34.7%)	109 (35.2%)	
autumn (22.9.-20.12)	192 (20.6%)	104 (33.5%)	
8 months	Comparison group (N=934)	Slow development group (N=324)	<i>p value</i> ^{a,b}
Gender			
Girls, N (%)	446 (47.8%)	151 (46.6%)	0.722 ^a
Boys, N (%)	488 (52.2%)	173 (53.4%)	
Age, in months (mean, SD)	8.2 (0.3)	8.2 (0.3)	0.931 ^b
Feeding			
breastfeeding, N (%)	591 (64.1%)	216 (67.9%)	0.217 ^a
supplemental milk only, N (%)	331 (35.9%)	102 (32.1%)	
Season of birth, N (%)			
winter (21.12-19.3.)	164 (17.6%)	51 (15.7%)	0.149 ^a
spring (20.3.-20.6.)	217 (23.2%)	89 (27.5%)	
summer (21.6.-21.9.)	309 (33.1%)	116 (35.8%)	
autumn (22.9.-20.12)	244 (26.1%)	68 (21.0%)	
Season of actigraph, N (%)			
winter (21.12-19.3.)	46 (20.2%)	11 (15.1%)	0.682 ^a
spring (20.3.-20.6.)	77 (33.8%)	25 (34.24%)	
summer (21.6.-21.9.)	69 (30.3%)	18 (24.7%)	
autumn (22.9.-20.12)	46 (20.2%)	19 (26.0%)	

^aChi-Square tests were used in the analysis.

^bT-test was used in the analysis.

Table 2. Sleep duration and sleep-wake rhythm development at the ages of 3 and 8 months, reported by parents.

	Mean	SD	10th	25th	50th	75th	90th
			percentile	percentile	percentile	percentile	percentile
3 months							
Daytime sleep (min)	314	88	210	240	300	360	420
Night-time sleep (min)	546	85	450	498	540	600	630
Total sleep (min)	859	114	720	780	870	930	990
Proportion of daytime sleep (%)	36.3	8.5	25.4	31.0	36.4	41.4	46.2
Proportion of night-time sleep (%)	63.7	8.5	53.8	58.6	63.6	69.0	74.6
8 months							
Daytime sleep (min)	207	62	135	160	205	240	300
Night-time sleep (min)	593	60	510	555	600	630	660
Total sleep (min)	799	71	720	750	810	840	885
Proportion of daytime sleep (%)	25.6	6.6	17.9	21.2	25.0	29.6	33.7
Proportion of night-time sleep (%)	74.4	6.6	66.3	70.4	75.0	78.8	82.1

Table 3a. Differences between infants with slow sleep-wake rhythm development vs. others at three months in questionnaire data.

QUESTIONNAIRE DATA AT 3 MONTHS	Comparison group, mean (SD) or N (%)	Slow sleep-wake rhythm development, mean (SD) or % N (%)	<i>p</i> values ^{a, b}	<i>p</i> values ^{c, d}
Daytime total sleep, in minutes	282 (69)	409 (65)	<0.001 ^a	<0.001 ^c
Night-time total sleep, in minutes	569 (65)	475 (100)	<0.001 ^a	<0.001 ^c
Total sleep per 24 hours, in minutes	851 (99)	883 (147)	<0.001 ^a	<0.001 ^c
Bedtime (hh:mm)	21:31 (1:03)	22:34 (1:13)	<0.001 ^a	0.001 ^c
Mean sleep-onset latency, in minutes	35.6 (30.9)	44.0 (39.8)	0.001 ^a	0.001 ^c
Difficulties to settle to sleep (N, %)	53 (5.7%)	42 (13.7%)	<0.001 ^b	<0.001 ^d
Average number of night wakings per night	2.2 (1.3)	2.1 (1.2)	0.363 ^a	0.118 ^c
Time spent awake during the night, in minutes	44 (42)	76 (59)	<0.001 ^a	<0.001 ^c
Long sleep-onset (≥30 min) in the evening (N, %)	221 (24.6%)	86 (29.2%)	0.122 ^b	0.298 ^d
Long sleep-onset (≥20 min) at night (N, %)	144 (16.5%)	62 (22.2%)	0.029 ^b	0.031 ^d

^at-test, ^bX2-test, ^cANCOVA, ^dLogistic regression. Both model types controlled for age, gender, breastfeeding, group, and season of birth.

Table 3b. Differences between infants with sleep-wake rhythm problems vs. others at eight months in questionnaire data.

QUESTIONNAIRE DATA AT 8 MONTHS	Comparison group, mean (SD) or % (N)	Slow sleep-wake rhythm development, mean (SD) or N (%)	<i>p</i> -values ^{a,b}	<i>p</i> values ^{c,d}
Daytime total sleep, in minutes	180 (40)	285 (48)	<0.001 ^a	<0.001 ^c
Night-time total sleep, in minutes	609 (51)	547 (55)	<0.001 ^a	<0.001 ^c
Total sleep per 24 hours, in minutes	788 (66)	832 (75)	<0.001 ^a	<0.001 ^c
Bedtime, hh:mm	20:39 (0:47)	21:32 (0:55)	<0.001 ^a	<0.001 ^c
Mean sleep-onset latency, in minutes	21.1 (17.3)	25.9 (18.2)	<0.001 ^a	<0.001 ^c
Difficulties to settle to sleep \geq 3 times/week <i>Yes/No</i>	92 (10.0%)	54 (17.2%)	0.001 ^b	0.001 ^d
Average number of night wakings per night	2.4 (1.7)	2.2 (1.5)	0.039	0.021 ^c
Time spent awake during the night, in minutes	23 (31)	30 (32)	0.001 ^a	0.001 ^c
Sleep onset in the evening \geq 30 min <i>Yes/No</i>	76 (8.4%)	38 (12.3%)	0.041 ^b	0.057 ^d
Sleep onset at night \geq 20 min <i>Yes/No</i>	54 (6.2%)	27 (9.3%)	0.079 ^b	0.194 ^d

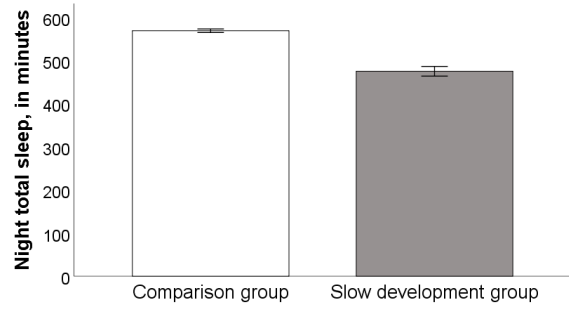
^at-test, ^bX2-test, ^cANCOVA, ^dLogistic regression. Both model types controlled for age, gender, breastfeeding, group, and season of birth.

Table 4. Differences between infants with slow sleep-wake rhythm development vs. others according to actigraphy data at 8 months (N=324).

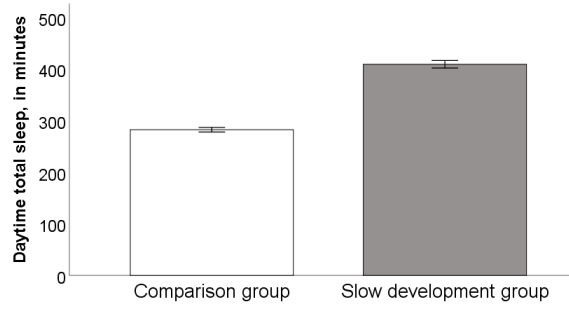
ACTIGRAPH DATA AT 8 MONTHS	Comparison group (N = 249), mean (SD)	Slow development group, (N = 75), mean (SD)	<i>p-values</i> ^a	<i>p values</i> ^b
Time in bed, in minutes	650 (59)	631 (66)	0.015	0.021
Assumed night sleep time, in minutes	622 (56)	596 (64)	0.001	0.001
Actual night sleep time, in minutes	520 (56)	498 (60)	0.004	0.003
Night sleep starts, hh:mm	20:37 (0:49)	21:38 (1:07)	<0.001	<0.001
Night sleep ends, hh:mm	7:29 (0:48)	8:09 (1:10)	<0.001	<0.001
Night sleep latency, min	17.2 (16.5)	21.4 (17.8)	0.068	0.121
Actual time awake at night, hh:mm	1:41 (0:39)	1:37 (0:40)	0.490	0.647
Night sleep efficiency	79.9 (6.6)	78.6 (6.5)	0.174	0.126
Fragmentation index	44.8 (10.1)	44.9 (10.5)	0.981	0.958
Number of night waking bouts	34.7 (9.8)	33.8 (8.3)	0.472	0.634

^at-test. ^bANCOVA. All models included age, gender, group, season of birth and season of actigraph registration as covariates.

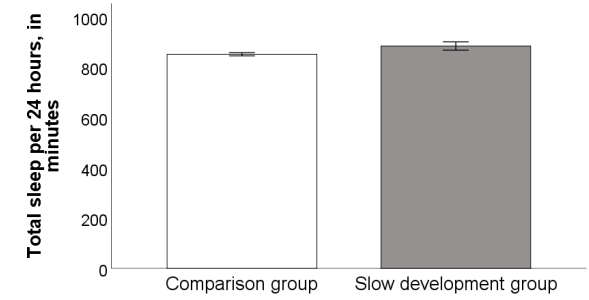
Fig. 1



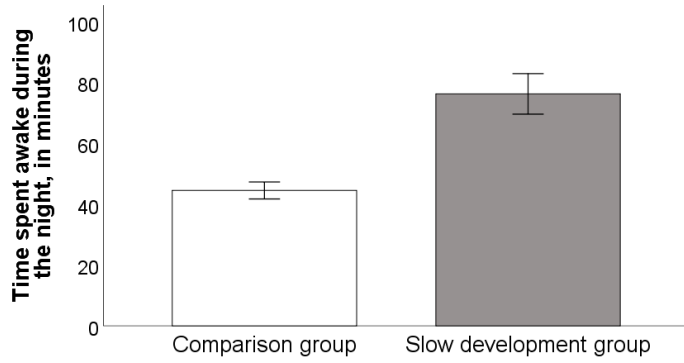
A $p < 0.001$



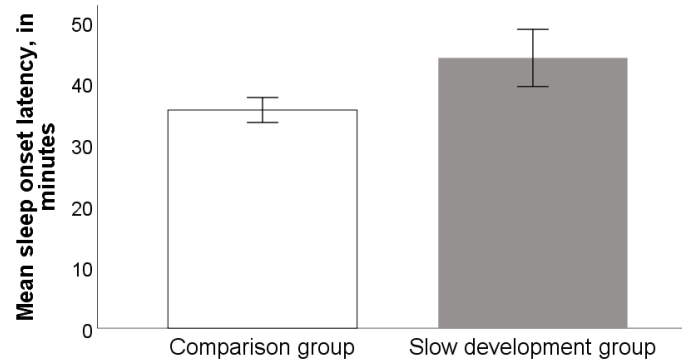
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C $p < 0.001$

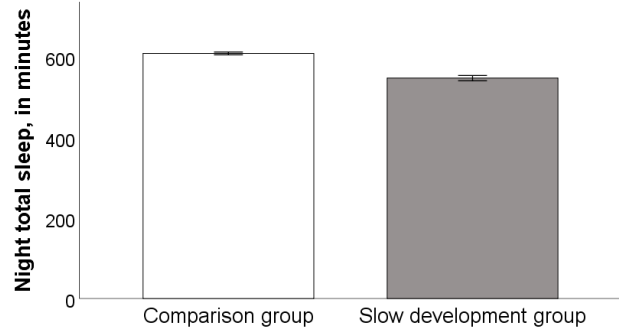


D $p < 0.001$

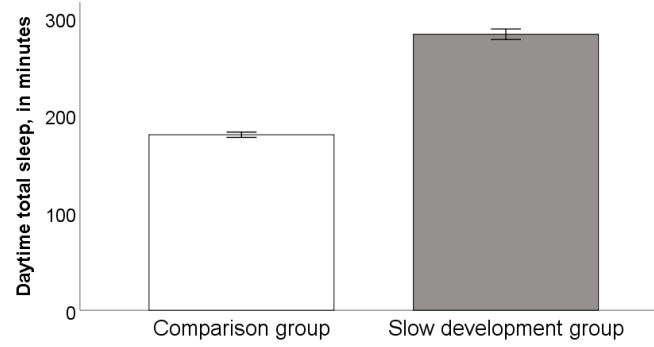


E $p = 0.001$

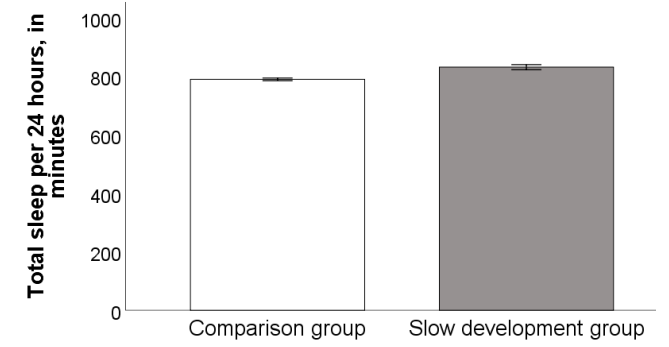
Fig 2.



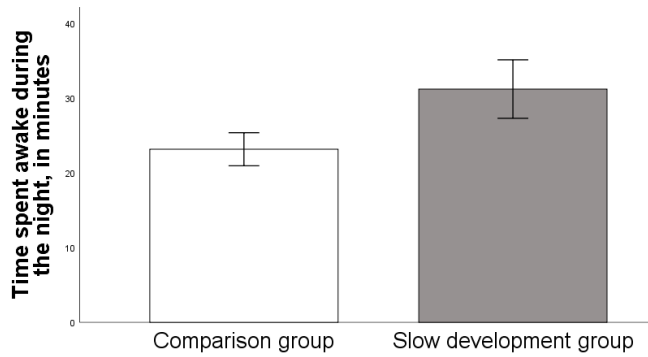
A $p < 0.001$



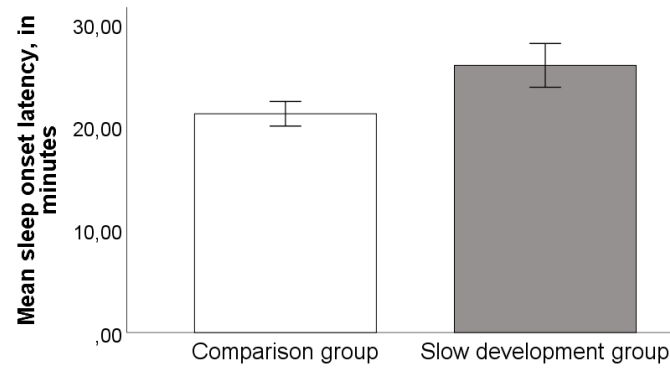
B $p < 0.001$



C $p < 0.001$



D $p < 0.001$



F $p = 0.017$