Does preterm period sleep development predict early childhood growth trajectories?

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Abstract

\textbf{Objective}—The current study examined the relationship between sleep state development across the preterm and early post-term periods and subsequent growth trajectories from 1 to 27 months corrected age.

\textbf{Study Design}—Retrospective analysis of data collected prospectively from 111 preterm infants (≤34 weeks gestation) who participated in a multi-site longitudinal study. Separate longitudinal parallel process models were calculated for each sleep state (active and quiet sleep) and growth (weight, length, and BMI z scores) variable to estimate the associations between their developmental trajectories.

\textbf{Results}—Significant associations were identified between the trajectories of quiet sleep and weight, active sleep and weight, quiet sleep and BMI, and active sleep and BMI. No statistically meaningful associations were identified between the trajectories of early childhood length and the preterm sleep states.

\textbf{Conclusions}—Faster preterm period sleep development appears to predict more favorable early childhood growth trajectories, particularly for weight, indicating preterm sleep may be an important biomarker for subsequent growth outcomes.

Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)
Introduction

Premature infants are vulnerable to numerous acute and lifelong health complications. Among these, wide variations in growth patterns and metabolic conditions have been observed. Prematurity is associated with poor growth, accelerated growth velocity, increased central fat distribution, insulin resistance, increased blood pressure, and obesity. Some of these growth patterns in infancy and early childhood (i.e., catch-up and delayed growth) increase the risk for later health problems, such as adult obesity and impaired childhood neurodevelopment. Thus, examining factors in the preterm period—a time when infants are readily available for monitoring—that potentially contribute to early childhood growth is valuable.

Sleep, which plays an important role in endocrine function and metabolism, is one critical factor to examine because its relationship with growth, particularly obesity, has been identified across child, adolescent, and adult populations. Yet the relationship between sleep and growth in infants and young children remains less clear. Moreover, the majority of infant and early childhood literature exploring associations between sleep and growth have focused on sleep duration and overlooked other sleep features, including sleep state development. Sleep state development reflects brain maturation and has been consistently shown to predict neurodevelopmental outcomes. Understanding what, if any, relationship that sleep development has with early childhood growth outcomes may help to provide further support for using sleep state development as an early indicator to identify infants at risk for negative neurodevelopmental and other health outcomes. The current study tested the hypothesis that a relationship exists between sleep state development during the preterm and early post-term period and later growth trajectories from 1 to 27 months corrected age.

Methods

Participants

The sample of 111 preterm infants (≤34 weeks gestational age at birth) was drawn from a larger, longitudinal study that evaluated the extent that biological and social risk predicted developmental and health outcomes. In the original study, infants considered at high risk for developmental problems (i.e., required mechanical ventilation or weighed less than 1500 grams at birth) were recruited from the neonatal intensive care units (NICU) of three tertiary hospitals in the southeastern, northeastern, and midwestern U.S. The NICU setting across hospitals was similar, as lights were kept low and incubators covered if desired by care providers. None systematically provided cycled light or placed infants in darkness, and noise levels were variable. Infants included in this analysis had at least one sleep observation before hospital discharge and at least one weight and length measure following hospital discharge. The demographic characteristics for the sample are provided in Table 1.

Procedures and Measures

Institutional human subjects review boards for all sites approved the original study, and the oversight IRB approved this analysis. In the original study, mothers of premature infants...
were contacted for enrollment when infants were no longer critically ill. The study purpose was explained and written informed consent was obtained. Data used in this current analysis were collected from 1996–2003 and are available upon request.

Sleep States—The two sleep state variables of interest in this study were active sleep and quiet sleep. Sleep states were collected weekly from enrollment until hospital discharge by observing a 2-hour inter-feeding period when NICUs were well lit (8 a.m. to 5 p.m.) and when infants were not receiving hands-on care. Behavioral observation is a standard and practical approach to measure sleep in the preterm population, demonstrating concordance with other objective measures, such as actigraphy and EEG scoring.24,25

During observations, sleep and wake states and the presence of other infant behaviors were recorded every 10 seconds.19 Each observation was conducted by one of nine observers trained to at least 85% agreement with the last author on all variables. Active sleep was recorded by observers when infants exhibited closed eyes, irregular respirations, intermittent rapid eye movements, and sporadic motor movements with low muscle tone between movements. Quiet sleep was recorded when the infant displayed closed eyes, relatively regular and abdominal respirations, a tonic level of muscle tone, and motor activity was restricted to occasional sighs and startles.19 Inter-rater reliability averaged 97% (κ = 0.89) for active sleep and 95% (κ = 0.93) for quiet sleep, and both sleep states were measured as percentages of the total observation period.

Growth—The growth outcomes were weight, length, and body mass index (BMI). Weight and length were collected at 1, 6, 9, 18, and 27 months corrected age during a scheduled post-term contact. Infants were weighed on an electronic scale (accuracy within 10 grams) and measured for length on the Shorr Infant/Child Height Measuring Board measuring to the nearest 0.1 centimeter. BMI (weight [g]/length^2 [cm] × 10) was calculated with the weight and length data and examined proportional growth. Z scores (number of standard deviations above or below the population mean) were calculated for each growth outcome for infant’s corrected age and sex according to The World Health Organization (WHO) Multicenter Growth Reference Study growth charts26 using the WHO Anthro software (version 3.2.2, 2011). These allow for each infant’s growth trajectory to be compared to a population reflecting normal growth under ideal conditions.27

Infant and Mother Characteristics—Seven infant and mother characteristics were also studied for their possible confounding effects on each growth outcome: birth size (small-for-gestational-age versus appropriate- and large-for-gestational-age), ranitidine treatment, chronic lung disease, necrotizing enterocolitis, intraventricular hemorrhage, maternal race (White versus Black and Asian), and mother’s education at baseline. Ranitidine was a proxy for gastro-esophageal reflux. Mother’s education was used as socioeconomic status indicator. These characteristics were obtained from the demographic questionnaire that mothers completed at enrollment or from the medical record. Infant’s hospital site and the presence of Methylxanthine treatment during a sleep observation were not examined as covariates, as these did not demonstrate significant effects on the quiet and active sleep state trajectories in prior analyses.19
Statistical Analysis

Descriptive statistics were computed for sample characteristics (Table 1). There were no missing values in covariates. Although some missing values in the sleep state and growth variables occurred, the multilevel modeling approach described below handled the missing data.

To test the hypothesis, longitudinal parallel process (LPP), a process of two-step multilevel modeling, was conducted using SAS 9.4 (SAS Institute, Cary, NC, USA, 2012; code available upon request). In the first step, univariate growth curves were created for each sleep (active sleep and quiet sleep) and growth (weight, length, and BMI Z scores) variable. To manage unbalanced weekly sleep observations, sleep variables were modeled over five post-menstrual age (PMA) intervals (29–31, 32–34, 35–37, 38–40, and 41–43 weeks PMA). Nonlinear effects were also tested in all models, and model fit criteria, such as Akaike information criterion and Bayesian information criterion, were used to inform model selection.

In the second step, a conditional multilevel model for each growth outcome was calculated using each infant’s estimated sleep state intercept and slope (from the first step) as predictors (both centered at the median). Thus, associations between the intercept (initial status) and slope (rate of change) for each sleep variable and the intercept, slope, and (as applicable) quadratic slope (acceleration/ deceleration) for each growth outcome were explored in separate parallel process growth models. These models were adjusted for significant covariates (infant and mother characteristics) selected by backward elimination.

In both steps, we used unstructured covariance structure with maximum likelihood estimation. The multilevel modeling approach was selected as it accounts for the within-subject covariance (i.e., individuals measured at multiple times) and the unbalanced nature of the data, such as varying numbers of observations per infant. Further, LPP was utilized to manage the different time intervals for the sleep state variables from those for the growth outcomes. Statistical significance was set at $\alpha = .05$; however, given the exploratory nature of this study and the relatively small sample, relationships with $p$ values less than .10 were also identified.

Results

Univariate Growth Curves

Among the univariate growth curves, model fit criteria supported the use of a nonlinear model only for weight Z scores (Supplementary Appendix 1; Z scores are the number of standard deviations above or below the WHO population mean). The parameter estimates for the intercept, slope, and (as applicable) quadratic slope parameters are provided in Supplementary Appendix 2. Slope results indicated that quiet sleep, weight Z scores, and length Z scores increased linearly over their respective time periods, while active sleep linearly decreased. Quadratic slope results indicated that weight Z scores decelerated over time. Model fit criteria supported a univariate linear growth curve model for BMI Z scores, despite the slope not meeting conventional levels of significance.
**Associations between Sleep State and Growth Trajectories**

Figure 1 presents the results of the LPP model exploring associations between quiet sleep development and the weight Z score trajectory while controlling for significant covariates. No significant associations were present between the intercept of quiet sleep state and the intercept, slope, or quadratic slope of weight Z score. Statistically meaningful associations were observed between the slope of quiet sleep and both the slope and quadratic slope of weight Z score. More rapid increases in quiet sleep development (percent of time spent in quiet sleep state) during the preterm period predicted more rapid linear increases in weight Z scores ($\beta = 0.0635$, SE= 0.0349, $p =0.07$) along with weight Z scores that decelerate ($\beta = -0.0033$, SE= 0.0012, $p =0.008$) across early childhood.

Results of the adjusted model exploring associations between active sleep and weight Z scores demonstrated no significant associations between the intercept of active sleep and the intercept, slope, or quadratic slope of weight Z score (Figure 1). There was a statistically meaningful association between the slope for active sleep and the quadratic slope of weight Z scores ($\beta = 0.0019$, SE= 0.001, $p =0.06$), such that slower active sleep development (less steep linear decreases in the percent of time spent in active sleep state) during the preterm period predicted weight Z scores that accelerated in early childhood. For adjusted models examining length, the intercepts and slopes of both quiet and active sleep were not significantly associated with the intercept or slope of length Z scores (Supplementary Appendix 3).

Figure 2 presents the results of the model exploring associations between quiet sleep and BMI Z score while controlling for significant covariates. The intercept of quiet sleep was not related to the intercept or slope of BMI Z score. The slope of quiet sleep and the intercept of BMI Z score were positively associated ($\beta = 0.714$, SE= 0.2901, $p =0.02$); more rapid increases in preterm period quiet sleep development (percent of time spent in quiet sleep state) predicted a higher initial BMI Z score at 1-month corrected age.

Figure 2 also displays the results of the adjusted model exploring associations between active sleep state and BMI Z scores. The intercept of active sleep state was associated with the intercept of BMI Z score ($\beta = -0.1658$, SE= 0.0979, $p =0.09$), such that a lower percent of time in active sleep at 29–31 weeks PMA predicted a higher initial BMI Z score at 1-month corrected age. The slope of active sleep state was also associated with the intercept of BMI Z score ($\beta = -0.4859$, SE= 0.2545, $p =0.06$); more rapid decreases in the percent of time in active sleep over the preterm period predicted a higher initial BMI Z score at 1-month corrected age.

Figure 3 depicts the estimated early childhood growth curves for faster and slower preterm sleep development for the LPP models with significant associations between the slopes of the preterm sleep variables and the intercepts, slopes, and/or quadratic slopes of the early childhood growth outcomes. Faster preterm period sleep development is represented as the median or above (more rapid increases) for individual slope estimates of the percent of time spent in a quiet sleep state over the preterm period and the median or below (more rapid decreases) for individual slope estimates of the percent of time spent in an active sleep over the preterm period.
Discussion

This study preliminarily explored whether sleep state development during the preterm period predicted the developmental trajectories of growth across early childhood. Multiple statistically meaningful relationships were found between the sleep and growth trajectories. Preterm infants with more rapid development of active and quiet sleep had early childhood weight Z score (number of standard deviations above or below the WHO population mean) trajectories that decelerated over time. Thus, as Figure 3 shows, once these infants were near the WHO 50th percentile (Z score= 0) their increasing weight Z score trajectories tended to flatten. This is in contrast to infants with slower development of quiet and active sleep, as these preterm infants had weight trajectories that accelerated across early childhood. Gains in infant and early childhood weight among prematurely born infants are positively associated with child and adult obesity, adiposity, and metabolic outcomes. Moreover, rapid early childhood growth, defined as +0.67 weight Z score change between birth and 2 years, has been associated with greater weight, BMI, waist circumference, and body fat in preschool and school-age children and obese/overweight weight status in adolescence. In our study, preterm infants with slower active and quiet sleep development demonstrated a +1.0 to +1.2 change in predicted weight Z scores from 1- to 27-months corrected age, potentially indicating growth trajectories associated with later metabolic risk. However, whether this growth trajectory should be avoided among preterm infants is unclear, as early childhood weight gain also exhibits positive associations with neurodevelopmental outcomes.

Relationships between preterm sleep development and BMI Z scores in early childhood were also identified. More rapid development in both active and quiet sleep states predicted higher initial BMI Z scores, indicating faster preterm sleep development was associated with disproportionate gains in weight compared to length at 1 month corrected-age. No significant relationships between the sleep development slopes and the BMI Z score slopes were identified. However, given the variability in the predicted trajectories observed in Figure 3 and the limited exploration of BMI Z score trajectories in early childhood, this relationship warrants further investigation with samples able to accommodate the more complex trajectories.

The analogous findings demonstrated by both active and quiet sleep state development with weight and BMI Z score trajectories was anticipated since during the preterm period the percent of time spent in active sleep decreases as quiet sleep increases. While an inverse relationship exists and both states predicted similar growth trajectories, their relationships across the growth outcomes were not identical. This variation highlights the need for additional work to help identify which developmental sleep state pattern may be most predictive of subsequent early childhood growth outcomes.

We speculate that a number of potential mechanisms, including biological, nutritional, and neurodevelopmental, may help to explain the sleep and growth associations identified in this investigation. For instance, preterm sleep expression may predict varied early childhood growth trajectories as a proxy for altered interconnected brain circuitries that occur in response to prenatal stress and medical conditions. Any implications these alterations may
have on neuroendocrine secretion and the hypothalamic-pituitary adrenocortical axis, in which variations have been previously observed in prematurely born populations.\textsuperscript{17,18} This investigation specifically identified these sleep and growth relationships in preterm infants. Further, we explored sleep characteristics less commonly studied for their association with growth and when studied are more often examined among older children or term infants.\textsuperscript{36,35} While the findings of this study are preliminary, they highlight both the value of using preterm sleep state development to predict subsequent health outcomes and the importance of identifying environmental features (i.e., nursing care routines) that may positively support preterm sleep development.\textsuperscript{20,22,38}

Strengths of this study include controlling the effects of birth size (small-for-gestational age) on growth, which is not always accounted for in the preterm infant literature. Additionally, we explored the relationships between sleep and growth across a variety of physical outcomes, including proportional growth, though relationships with head circumference should be examined in the future. Although we examined a number of relevant growth covariates (including medical conditions), other variables (e.g., early childhood sleep duration) that might be associated with growth during early childhood\textsuperscript{16} could not be controlled, and our findings may be confounded by these factors. Importantly, the study possessed a relatively small and under-powered sample size (a sample size of 199 would have been required to evaluate medium effects of both linear and quadratic change at a power=0.80 and alpha=0.05), and two infants (1.8\%) included in this study had a single preterm sleep observation and a single early childhood growth observation. While our results should thus be interpreted with caution, the extensive longitudinal data on sleep development across the entire preterm period and detailed growth data at several time points following term are key advantages of this investigation. Finally, future research with larger samples may benefit from conducting subgroup analyses across different infant characteristics (e.g. birth size).

Preterm period sleep appears to serve as a significant biomarker for subsequent growth. We found support for this relationship, as sleep state development in the preterm period was associated with weight and BMI growth trajectories across early childhood. While additional research is required to understand the optimal early childhood growth patterns to reduce metabolic risk while maximizing neurodevelopmental outcomes among premature infants, our findings help illuminate the importance of (1) using developmental changes in preterm period sleep to predict later growth and (2) considering other targeted areas of intervention—beyond nutritional approaches—to promote healthy growth for preterm infants.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Results of longitudinal parallel process models describing associations between preterm/early post-term sleep state development and early childhood weight Z score growth trajectories (N = 111). A, quiet sleep state development, and B, active sleep state development. Significant covariates controlled were A, birth size (β = 1.138, P = <.001) and B, birth size (β = 1.188, P = <.001). 90% confidence intervals are presented in parentheses. † P < .10, * P < .05, 2-tailed.
Figure 2.
Results of longitudinal parallel process models describing associations between preterm/early post-term sleep state development and early childhood BMI Z score growth trajectories (N = 111). A, quiet sleep state development, and B, active sleep state development. Significant covariates controlled were A, birth size (β = 0.759, P = 0.008) and maternal race (β = −0.546, P = 0.006), and B, birth size (β = 0.784, P = 0.009) and maternal race (β = −0.487, P = 0.02). 90% confidence intervals are presented in parentheses. BMI = body mass index, † P < .10, * P < .05, 2-tailed.
Figure 3.
Predicted early childhood growth trajectories of slower and faster rates of sleep development. Faster rates of sleep development are represented by infants with steeper slopes (a slope at the median or above for quiet sleep and the median or below for active sleep). Solid horizontal line indicates the World Health Organization 50th percentile ($z$ score=0). Significant covariates controlled (*=birth size; += maternal race). AS=active sleep; BMI= body mass index; m=Months corrected-age; QS= quiet sleep.
### Table I

Characteristics of the 111 preterm infants and their mothers

| Characteristic                             | Mean (SD) | n (%)* |
|--------------------------------------------|-----------|--------|
| Gestational Age (weeks)                    | 28.7 (2.7)|        |
| Birthweight (grams)                        | 1222 (425)|        |
| Birth length (centimeters)                 | 35.6 (10.6)|        |
| Birth size                                 |           |        |
| Small-for-gestational-age                  | 14 (13)   |        |
| Appropriate-for-gestational-age            | 96 (87)   |        |
| Large-for-gestational-age                  | 1 (1)     |        |
| Sex                                        |           |        |
| Male                                       | 58 (52)   |        |
| Female                                     | 53 (48)   |        |
| Site                                       |           |        |
| Southeastern hospital                      | 61 (55)   |        |
| Midwestern/ northeastern hospitals         | 50 (45)   |        |
| Treatments                                 |           |        |
| Mechanical ventilation (days)              | 10.4 (17.4)|       |
| CPAP (days)                                | 6.1 (8.5) |        |
| Methylxanthine (days)                      | 21.5 (19.9)|       |
| Indomethacin                               | 43 (39)   |        |
| Ranitidine                                 | 26 (23)   |        |
| Diagnoses                                  |           |        |
| Chronic lung disease                       | 45 (41)   |        |
| Necrotizing enterocolitis                  | 17 (16)   |        |
| Patent ductus arteriosus                   | 26 (23)   |        |
| Intraventricular hemorrhage                |           |        |
| None                                       | 86 (77)   |        |
| Grade I                                    | 14 (13)   |        |
| Grade II                                   | 5 (5)     |        |
| Grade III                                  | 3 (3)     |        |
| Grade IV                                   | 3 (3)     |        |
| Neurobehavioral Risk Scaleb                | 2.8 (3.0) |        |
| Postmenstrual age at discharge (weeks)     | 37.2 (3.4) |       |
| Maternal age (years)                       | 28.4 (6.6)|        |
| Maternal education at baseline (years)     | 13.7 (2.3)|        |
| Maternal Race                              |           |        |
| Asian                                      | 1 (1)     |        |
| Black/African American                     | 49 (44)   |        |
| White                                      | 61 (55)   |        |
| Mothers married at baseline                | 64 (58)   |        |

* J Perinatol. Author manuscript; available in PMC 2017 December 15.
Due to rounding error, sub-categories may not sum to 100%.

Scale measures potential insults to brain. Seven potential insults are scored for severity on a 4-point scale; higher scores indicate more severe neurological insults [23].

CPAP, continuous positive airway pressure.