



SHORT REPORT

Sleep and circadian rhythms during pregnancy, social disadvantage, and alterations in brain development in neonates

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Abstract

Pregnant women in poverty may be especially likely to experience sleep and circadian rhythm disturbances, which may have downstream effects on fetal neurodevelopment. However, the associations between sleep and circadian rhythm disturbances, social disadvantage during pregnancy, and neonatal brain structure remains poorly understood. The current study explored the association between maternal sleep and circadian rhythm disturbances during pregnancy and neonatal brain outcomes, examining sleep and circadian rhythm disturbances as a mediator of the effect of social disadvantage during pregnancy on infant structural brain outcomes. The study included 148 mother-infant dyads, recruited during early pregnancy, who had both actigraphy and neuroimaging data. Mothers' sleep was assessed throughout their pregnancy using actigraphy, and neonates underwent brain magnetic resonance imaging in the first weeks of life. Neonatal structural brain outcomes included cortical gray matter, subcortical gray matter, and white matter volumes along with a measure of the total surface area of the cortex. Neonates of mothers who experienced greater inter-daily deviations in sleep duration had smaller total cortical gray and white matter volumes and reduced cortical surface areas. Neonates of mothers who had higher levels of circadian misalignment and later sleep timing during pregnancy showed smaller subcortical gray matter volumes. Inter-daily deviations in sleep duration during pregnancy mediated the association between maternal social disadvantage and neonatal structural brain outcomes. Findings highlight the importance of regularity and rhythmicity in sleep schedules during pregnancy and bring to light the role of chronodisruption as a potential mechanism underlying the deleterious neurodevelopmental effects of prenatal adversity.

KEYWORDS

adversity, circadian rhythms, sleep, MRI, infant



Research Highlights

1. Social disadvantage was associated with sleep and circadian rhythm disturbances during pregnancy, including later sleep schedules, increased variability in sleep duration, circadian misalignment, and a higher proportion of the sleep period spent awake.
2. Maternal sleep and circadian rhythm disturbances during pregnancy were associated with decreased brain volume and reduced cortical surface area in neonates.
3. Maternal inter-daily deviations in sleep duration during pregnancy mediated the association between social disadvantage and neonatal brain volume and cortical surface area.

1 | INTRODUCTION

Early adversity has been shown to profoundly impact fetal and infant development (Barrero-Castillero et al., 2019). Prenatal exposure to adversity, including poverty and exposure to stressors, trauma, abuse, and racism, is implicated in a host of negative biological, emotional, and social consequences for offspring beginning early in life and often lasting into adulthood (Ahmad et al., 2021; Conrath et al., 2020; Monk et al., 2012; Rakers et al., 2017). A recent study demonstrated that exposure to adversity in utero impacts neonatal brain structure at birth (Triplett et al., 2022), with other findings showing effects on brain structure and function in the first months of life (Betancourt et al., 2016; Knickmeyer et al., 2016). Yet, despite decades of human and animal research, the pathways through which prenatal exposure to adversity shapes fetal and infant neurodevelopment remain poorly understood.

Exposure to poverty in utero has been associated with enduring, negative health and neurodevelopmental outcomes in offspring (Betancourt et al., 2016; Knickmeyer et al., 2016; Gilman et al., 2017; Johnson et al., 2016). According to the fetal origins hypothesis (Almond & Currie, 2011; Barker, 1995), factors affecting the intrauterine environment, such as poor maternal nutrition, toxin exposure, and psychosocial stress, can impair fetal neurodevelopment (Antonelli et al., 2017). Such factors are known to be elevated in individuals living in poverty (Evans & Kantrowitz, 2002), leading researchers to explore the potentially robust effects of poverty on fetal development and the pathways through which exposure to poverty in utero affects neurodevelopment. Epigenetic alterations and dysregulation of the hypothalamic-pituitary-adrenal axis (Barrero-Castillero et al., 2019; Scorza et al., 2019) have been explored as potential mechanisms of these effects, but additional research identifying other plausible pathways is needed.

Maternal sleep and circadian rhythm disruption has received less attention as a pathway through which intrauterine exposure to poverty affects offspring neurodevelopment, but a growing literature suggests that this may be an important pathway to consider when exploring the effects of poverty on fetal development. Sleep and circadian rhythms are intertwined but have separable functions and mechanisms: cir-

cadian mechanisms optimally time physiological functions (e.g., sleep, hormone secretion) to the 24-hour day, whereas sleep is a brain state necessary for rest and restoration that can occur at any time but is of best quality when aligned with the circadian clock (Kushida, 2013). Homeostatic mechanisms increase the drive to sleep with time spent awake. In addition, circadian mechanisms time physiological functions to specific times of day. There are well-documented health disparities in sleep and circadian health, with individuals living in poverty more likely to have shorter sleep durations, poorer quality sleep, and to experience disruptions in their daily rhythms (i.e., chronodisruption) often due to work schedules (e.g., shift work) and increased noise and light in lower-resourced environments (Billings et al., 2021; Johnson et al., 2018; Mezick et al., 2008; Patel et al., 2010). Pregnant women in poverty may be especially sensitive to sleep disturbances (Kalmbach et al., 2019; Okun et al., 2014), which may affect fetal neurodevelopment. Evidence across animal models and humans suggests that circadian rhythms synchronize between mother and fetus, likely through hormonal signaling via melatonin, dopamine, and corticosterone, which can cross the placenta and bind to receptors on fetal tissue (see Bates & Herzog, 2020; Mark et al., 2017, for review). Lack of synchronization of maternal and fetal circadian rhythms due to irregular maternal sleep-wake cycles may negatively affect fetal neurodevelopment (Pires et al., 2021).

In rodents, in utero exposure to sleep or circadian disruption can program a range of endocrine, circadian, mood, and metabolic effects that last into adulthood (Mendez et al., 2016; Smarr et al., 2017; Varcoe et al., 2018, 2011). Sleep disruption in pregnant dams, including REM sleep deprivation and sleep restriction, is associated with brain immaturity in pups at birth, including reduced hippocampal neurogenesis (Aswathy, Kumar, & Gulia, 2018a) and higher ratios of active sleep to quiet sleep in the early postnatal period (thought to be an index of delayed brain maturation, particularly in areas governing sleep and wakefulness (Aswathy, Kumar, & Gulia, 2018a, 2018b)). In humans, infants whose mothers had sleep disturbances during pregnancy have altered auditory event-related potentials to emotional pseudo-word stimuli at birth (Lavonius et al., 2020) and show increased irritability at one month of age (Nakahara et al., 2020). To our knowledge, no studies



have examined how sleep or circadian rhythms during pregnancy affect structural brain development of offspring at birth.

In the current study, we used the longitudinal Early Life Adversity and Biological Embedding (eLABE) sample to explore the association between maternal sleep and circadian rhythm disturbances during pregnancy and infant brain outcomes at birth. We examined this as both a direct association and as a possible mediator of the effect of exposure to adversity in utero on infant structural brain outcomes. The current study examined five metrics of sleep and circadian function derived from actigraphy data (a measure of sleep/wake states based on wrist movements): (1) sleep duration, (2) sleep midpoint, (3) inter-daily variability in sleep duration, (4) Composite Phase Deviation (CPD), a metric of circadian misalignment (mismatch between an individual's habitual sleep schedule with their preferred rhythms), and (5) sleep activity density, an indicator of sleep fragmentation that reflects the proportion of minutes spent awake during the sleep period. These sleep and circadian metrics are commonly used in research and enabled us to explore various domains of sleep and circadian rhythm disturbances.

Previous work in this sample reported that exposure to early adversity was associated with structural brain differences in neonates (Triplett et al., 2022), including reduced cortical and subcortical gray and white matter volumes and reduced cortical surface area. In the current study, we focused explicitly on the tissue types and surface area metrics previously identified to be associated with early adversity (Triplett et al., 2022) in an effort to explore whether maternal sleep and circadian rhythm disruptions during pregnancy are mechanisms underlying these effects. Exposure to adversity during pregnancy was quantified by the construct of maternal social disadvantage during pregnancy, a latent factor that combined several indexes of socioeconomic status and related factors, as reported by mothers during pregnancy (Luby et al., 2023). We test the specific hypotheses that: (1) social disadvantage during pregnancy is associated with sleep and circadian rhythms disturbances (i.e., shorter sleep durations, later sleep midpoints, increased inter-daily variability in sleep durations, increased circadian misalignment, and more minutes spent awake during the sleep period); (2) sleep and circadian disturbances are associated with smaller infant brain volumes (cortical and subcortical gray, white matter) at birth and reduced cortical surface area; and (3) sleep and circadian disturbances mediate the association between social disadvantage during pregnancy and infant brain structure at birth.

2 | METHODS

2.1 | Participants

Mother-child dyads were drawn from a larger prospective observational study the Early Life Adversity Biological Embedding and Risk for Developmental Precursors of Mental Disorders Study (eLABE; details provided in Triplett et al. (2022)), with pregnant women ($N = 399$) recruited from the March of Dimes (MOD) Prematurity Research Center at Washington University in St. Louis between 2017–2020 and delivering at Barnes Jewish Hospital in St. Louis (Stout et al., 2022).

Although the study of the original cohort was focused on exploring pathways and predictors of preterm birth, mother-child dyads selected for the follow-up study were those who delivered at term (children born ≥ 37 weeks gestational age). Participants in the eLABE study provided detailed survey and circadian data (actigraphy and daily hormone profiles) throughout pregnancy, birth outcomes, and detailed survey, developmental, and imaging data in the children from birth through age 3 years. Exclusion criteria included: multiple gestations, diagnosed infections known to cause congenital disease (e.g., syphilis), and maternal alcohol or drug use during pregnancy (excluding tobacco and marijuana). Of the 399 mother-child dyads who participated in the eLABE study, 201 provided usable actigraphy data during pregnancy. Of these, 148 full-term infants (born ≥ 37 weeks gestational age) had high-quality magnetic resonance imaging (MRI) data and met our previously defined inclusion criteria (Triplett et al., 2022): birth weight >2000 g, no Neonatal Intensive Care Unit admission >7 days, and no evidence of brain injury on MRI. The racial breakdown of the mothers in the final sample of 148 mother-child dyads was 51% White, 47% Black or African American, 2% Other, and families had an average Income-to-Needs ratio of 3.84 ($SD = 3.09$, range = 0.44–12.04). Mothers ranged in age from 18.77 to 41.80 years ($M = 29.83$ years; $SD = 5.47$ years) at the time of birth, and at the time of MRI scan infants were an average postmenstrual age (PMA) of 41.68 weeks (range 38–45 weeks). The eLABE study was approved by the Washington University Human Research Protection Office. Informed consent was obtained for each participant and subsequent parental informed consent was obtained for each infant prior to participation. Data were collected with consent forms that allow data sharing. De-identified data is being deposited in the NIMH Data Archive and will be available after the conclusion of the eLABE Year 3 wave.

2.2 | Measures

2.2.1 | Social disadvantage

Adversity-related information was obtained from participants either during pregnancy or at delivery. Confirmatory factor analysis (CFA) was used to derive a latent factor reflecting maternal social disadvantage during pregnancy (CFA results detailed in Luby et al. (2023)). The following indexes were used to estimate the Social Disadvantage latent factor: (1) household Income to Needs Ratio (Brooks-Gunn & Duncan, 1997) from each trimester of pregnancy, (2) national Area Deprivation Index percentiles (Kind & Buckingham, 2018), a measure of sociodemographic disadvantage at the census block level calculated based on family addresses at birth, (3) maternal nutrition as measured by the Healthy Eating Index (Krebs-Smith et al., 2018) reported by mothers during the third trimester or at delivery, (4) highest level of maternal educational attainment at the time of study enrollment, and (5) health insurance status at the time of study enrollment (verified by mothers in the third trimester or at delivery). This latent factor was used in subsequent analysis. Race was highly correlated with the social disadvantage factor and offered no additional improvement to the model after other



variables were accounted for, thus it was not included in the latent social disadvantage factor (Luby et al., 2023).

2.2.2 | Maternal sleep and circadian rhythms

A minimum of 2 weeks of actigraphy data were collected from mothers during their first, second, and third trimesters of pregnancy. Actigraphy watches (MotionWatch 8, CamNtech Ltd., Cambridge, UK), worn by mothers on their non-dominant wrist, collected activity per minute based on a piezoelectric accelerometer (sensitivity greater than 0.05 g, 32 Hz sampling, and 3–11 Hz bandpass filtered). For inclusion in data analysis, mothers were required to provide at least 11 days of consecutive actigraph wear. Included actigraphy data were processed (MotionWare software 2.5, CamNtech Ltd.) and analyzed using a high-throughput, automated method to derive the sleeping time indexes (Zhao, 2021). In analysis, we focused on five sleep and circadian metrics derived from actigraphy data collected at each time point: (1) sleep duration – the length of time between sleep onset and offset, (2) sleep midpoint – the time equidistant between sleep onset time and offset times, (3) inter-daily deviation in sleep duration, (4) Composite Phase Deviation (CPD), and (5) a measure of the proportion of minutes spent awake during the sleep period, a form of wake after sleep onset (WASO), that we are referring to as sleep activity density. Inter-daily deviation in sleep duration, the median value of day-to-day sleep duration change (absolute value) during the recording period, is a consecutive metric that quantifies changes in sleep durations across consecutive days. This metric showed high correspondence with the standard deviation of sleep duration ($r = 0.67$), but had the added benefit of reflecting deviation across consecutive days, rather than across the entire recording period (an advantage over standard deviation metrics). CPD is a metric of mistiming of sleep that quantifies the difference between sleep midpoint from the prior day and habitual sleep midpoints (i.e., the individual's chronotype) (Fischer et al., 2016, 2021), where higher CPD scores indicate greater circadian misalignment.

Although mothers were asked to provide actigraphy data during each trimester, the number of data points collected from the sample varied, with 73 mothers providing usable data during the first trimester, 105 mothers providing usable data during the second trimester, and 99 mothers providing usable data during the third trimester. Correlations between the sleep indexes at each trimester are included in Tables S1–S5. Across trimesters, the sleep variables were largely correlated with each other, with three exceptions: sleep duration was not correlated with other sleep metrics in trimesters 1 and 2 and sleep duration deviation was not correlated between trimester 1 and either trimester 2 or 3 (but was correlated across trimesters 2 and 3). The significant cross-time correlations were fairly large in magnitude ($0.29 \leq r \leq 0.82$). Given this—and to retain the largest sample for our neuroimaging analysis—we examined the mean values of sleep indexes, averaged across available data from each trimester of pregnancy.

2.2.3 | Infant brain volumes at birth: MRI acquisition, processing, and measures

All infants underwent non-sedated MRI scans within the first weeks of life using a Siemens Prisma 3T scanner and a 64-channel head coil. MRI sequence parameters and our standardized preprocessing pipeline have been previously published (Triplett et al., 2022). Briefly, in this analysis, brain volumetric measures of interest included the total white matter, cortical and subcortical gray matter, and cortical surface area. To generate these measures, the age-specific, automated, Melbourne Children's Regional Infant Brain atlas Surface (M-CRIB-S) segmentation and surface extraction toolkit was applied to high-quality (low-motion), preprocessed T2-weighted images (Adamson et al., 2020; Alexander et al., 2017). The M-CRIB-S toolkit output included spatially normalized (within group and to the M-CRIB atlas) segmentations and surface-based cortical parcellations of the white and gray matter, cerebellum, brainstem, and subcortical gray matter subdivisions with FreeSurfer-like labeling. All segmentations and surfaces were qualitatively inspected for accuracy, manually edited as necessary, and designated as complete by a highly experienced team of two imaging scientists and a pediatric neurologist.

2.3 | Data analytic plan

All analyses were conducted in SAS v9.4. Covariates in all analyses included: PMA, infant sex, maternal age at birth, pre-pregnancy maternal obesity (calculated using standard procedures, Body Mass Index ≥ 30), and parity. Linear regressions were conducted in order to determine whether social disadvantage and/or infant brain volume at birth were associated with maternal sleep and circadian metrics during pregnancy. Models were run separately for the four sleep and circadian metrics of interest (sleep duration, inter-daily variability in sleep duration, sleep midpoint, and CPD). In line with our past work (Triplett et al., 2022), the following infant brain volume regions were examined: total cortical gray matter, subcortical gray matter, and total white matter. Cortical surface area was measured across both hemispheres. False discovery rate (FDR) correction was used to account for multiple comparisons in the regression analyses. To explore the possibility that the effects of sleep and circadian disturbances during pregnancy on infant brain outcomes varied by trimester, we ran linear regressions examining the association between the sleep and circadian metrics and infant brain variables across each trimester separately, comparing effect sizes of each trimester.

Finally, mediation analyses using ordinary least squares path analyses (Hayes, 2013) were conducted to determine whether the sleep and circadian metrics mediated the association between social disadvantage and infant brain volumes and cortical surface area. In all models, social disadvantage across pregnancy was the predictor. The four maternal sleep and circadian metrics of interest were independently tested as mediators using the SPSS PROCESS macro (Hayes, 2012). Covariates were applied to both mediators and outcome variables.

3 | RESULTS

Descriptive statistics and bivariate correlations for all study variables are included in Table 1. Maternal race and the social disadvantage factor were highly related in this sample ($M_{\text{black}} = 1.06$; $SD = 0.68$; $M_{\text{white}} = -0.48$; $SD = 0.56$; $t_{140} = 14.60$; $p < 0.001$). Race, a socially-defined construct that is likely a proxy variable for constructs related to social disadvantage and discrimination experiences, did not offer any additional improvement to the model after the other variables were accounted for. Thus, all analyses focused on the factor of social disadvantage.

3.1 | Is social disadvantage associated with maternal sleep and circadian metrics?

Linear regressions between social disadvantage and maternal sleep and circadian metrics during pregnancy are presented in Table 2. Social disadvantage was associated with later sleep midpoints, increased inter-daily variability in sleep durations, increased CPD values, and higher sleep activity density. Individuals facing higher levels of social disadvantage had later sleep schedules (i.e., went to bed and woke up later), had more inter-daily deviation in their sleep durations, showed increased circadian misalignment, and spent a larger portion of the sleep period awake.

3.2 | Are maternal sleep and circadian metrics associated with infant brain volumes and cortical surface areas at birth?

Linear regressions between the sleep and circadian metrics and the neonatal brain outcomes are presented in Table 3. At birth, infants of mothers who experienced more inter-daily deviation in their sleep durations had smaller total cortical gray matter, smaller white matter volumes, and reduced cortical surface area. At birth, infants of mothers who had higher levels of circadian misalignment during pregnancy had smaller subcortical gray matter volumes. Additionally, at birth, infants of mothers who had later sleep midpoints also had smaller subcortical gray matter volumes. There were no other significant associations between the other sleep and circadian metrics and infant brain outcomes.

To account for the possibility that the effects of sleep and circadian disturbances during pregnancy on infant brain outcomes varied by trimester, we also examined the associations between the sleep and circadian metrics and infant brain variables across each trimester separately (see Table S6). Although there was a tendency for sleep and circadian disturbances in the third trimester to show effects on neonatal brain metrics, this was not consistent across sleep and circadian metrics or brain outcomes examined. As such, subsequent analysis focused on the variable average across trimesters.

3.3 | Do maternal sleep and circadian metrics during pregnancy mediate associations between social disadvantage and infant brain outcomes at birth?

Mediation models were examined to determine whether maternal social disadvantage predicted each index of infant brain volume (i.e., cortical gray matter, subcortical gray matter, white matter volumes, and cortical surface area, separately) through its effect on sleep and metrics of circadian rhythms during pregnancy. Of the models examined, two models (described below) provided evidence of significant mediation. All models controlled for PMA at the time of the scan, infant sex, maternal age at birth, maternal obesity, and parity.

Maternal social disadvantage indirectly predicted both cortical gray matter volumes through its effect on inter-daily deviation in sleep duration during pregnancy. Mothers with greater social disadvantage showed more deviation in their sleep durations when compared to mothers with less social disadvantage. Furthermore, infants whose mothers experienced increased deviation in their sleep durations during pregnancy had smaller cortical gray matter volumes (see Figure 1a). A bootstrap confidence interval for the indirect effects for each model based on 5,000 bootstrap samples was entirely below zero, indicating significant mediation.

Maternal social disadvantage also indirectly predicted child cortical surface area through its effect on inter-daily deviation in sleep duration during pregnancy. As shown in Figure 1b, mothers with greater social disadvantage showed more deviation in their sleep durations during pregnancy when compared to mothers with less social disadvantage, and infants whose mothers had increased deviation in sleep durations during pregnancy had reductions in cortical surface area. The bootstrap confidence interval for the indirect effect was again entirely below zero, indicating significant mediation.

There was no evidence for significant mediation of the association between social disadvantage and neonatal brain outcomes by any of the other examined sleep and circadian metrics (see Table S7).

4 | DISCUSSION

The current study examined the effect of maternal sleep and circadian disturbances during pregnancy on infant brain outcomes at birth, further exploring whether maternal sleep and circadian disturbances mediated the association between social disadvantage during pregnancy and structural brain alterations at birth. First, our findings suggest a robust association between social disadvantage and various domains of sleep and circadian functioning during pregnancy. Next, of the sleep and circadian metrics examined, inter-daily deviation in sleep duration, sleep midpoints, and circadian misalignment were associated with decreased brain volumes and reduced cortical surface areas in neonates. Inter-daily deviation in sleep duration during pregnancy was also found to mediate the association between greater social disadvantage and reduced infant cortical gray matter volumes and

**TABLE 1** Descriptive statistics and correlations for major study variables (averaged across trimesters) and co-variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Social disadvantage factor score	1.00														
2. Sleep Duration (minutes)	-0.15	1.00													
3. Sleep Midpoint (minutes since noon)	0.54**	-0.05	1.00												
4. Deviation in Sleep Duration (minutes)	0.39**	-0.07	0.28**	1.00											
5. Composite phase deviation	0.56**	-0.26**	0.45**	0.41**	1.00										
6. Sleep activity density	0.43**	0.004	0.16*	0.15	0.16	1.00									
7. Infant cortical gray matter volume (mm ³)	-0.36**	-0.07	-0.25**	-0.35**	-0.18*	-0.19**	1.00								
8. Infant subcortical gray matter volume (mm ³)	-0.42**	0.01	-0.30**	-0.31**	-0.25**	-0.25**	0.89**	1.00							
9. Infant white matter volume (mm ³)	-0.48**	-0.02	-0.26**	-0.31**	-0.21*	-0.21**	0.83**	0.79**	1.00						
10. Cortical surface area (mm ²)	-0.44**	-0.02	-0.25**	-0.34**	-0.20*	-0.27**	0.92**	0.86**	0.87**	1.00					
11. Post-menstrual age (weeks)	-0.20*	-0.04	-0.13	-0.23**	-0.07	-0.11	0.64**	0.64**	0.34**	0.60**	1.00				
12. Infant Sex (n, % female)	0.07	0.09	0.07	0.04	-0.02	0.12	-0.35**	-0.35**	-0.37**	-0.34**	-0.08	1.00			
13. Maternal age (years)	-0.52**	0.09	-0.46**	-0.20*	-0.40**	-0.20*	0.10	0.11	0.20*	.16	-0.04	0.12	1.00		
14. Maternal obesity (BMI)	0.20*	-0.14	0.03	0.03	0.21*	0.14	0.06	0.03	0.01	0.04	0.05	-0.03	0.12	1.00	
15. Parity (n, % first born)	0.32**	-0.15	-0.10	.01	-0.00	0.17*	-0.17*	-0.21*	-0.23**	-0.18*	-0.12	0.03	0.15	0.14	1.00
Mean/%	-0.33	537.1	903.4	90.58	3.77	0.18	121676	28068	185862	88798	41.68	44.6%	29.83	28.06	52.7%
SD/n	1.00	65.1	73.5	44.12	2.63	0.05	15071	2895	20268	11103	1.33	n = 66	5.47	7.13	n = 78

** $p < 0.01$; * $p < 0.05$.



TABLE 2 Linear regressions between social disadvantage and mean maternal sleep and circadian metrics controlling for gestational age, infant sex, maternal age at birth, maternal obesity, and parity.

Dependent variable	Predictor	B	95% CI	β	t	p	FDR p
Sleep duration	Social disadvantage	-4.16	-19.48-11.17	-0.06	-0.54	0.59	0.59
Sleep midpoint	Social disadvantage	38.58	24.64-52.53	0.53	5.47	<0.001	<0.001
Inter-daily deviation in sleep duration	Social disadvantage	19.21	9.56-28.86	0.44	3.93	<0.001	<0.001
Composite phase deviation	Social disadvantage	1.33	0.81-1.85	0.50	5.07	<0.001	<0.001
Sleep activity density	Social disadvantage	0.02	0.01-0.03	0.37	3.32	0.001	0.001

Abbreviation: FDR, false discovery rate.

TABLE 3 Linear regressions between mean maternal sleep and circadian metrics and infant brain structure at birth controlling for postmenstrual age, infant sex, maternal age at birth, maternal obesity, and parity.

Dependent variable	Predictor	n	β	t	p	FDR p
Infant total cortical gray matter volume	Mean sleep duration	148	-0.05	-0.88	0.38	0.50
	Mean sleep midpoint	148	-0.10	-1.57	0.12	0.29
	Inter-daily deviation in sleep duration	148	-0.18	-3.17	0.002	0.04
	Mean composite phase deviation	140	-0.10	-1.42	0.16	0.29
	Sleep activity density	148	-0.03	-0.50	0.61	0.68
Infant subcortical gray matter volume	Mean sleep duration	148	0.02	0.33	0.74	0.78
	Mean sleep midpoint	148	-0.16	-2.56	0.01	0.04
	Inter-daily deviation in sleep duration	148	-0.13	-2.22	0.028	0.09
	Mean composite phase deviation	140	-0.18	-2.69	0.008	0.04
	Sleep activity density	148	-0.09	-1.49	0.14	0.29
Infant white matter volume	Mean sleep duration	148	-0.04	-0.51	0.61	0.68
	Mean sleep midpoint	148	-0.11	-1.43	0.15	0.29
	Inter-daily deviation in sleep duration	148	-0.19	-2.70	0.008	0.04
	Mean composite phase deviation	140	-0.08	-1.03	0.30	0.43
	Sleep activity density	148	-0.04	-0.57	0.57	0.68
Infant cortical surface area	Mean sleep duration	148	-0.01	-0.19	0.85	0.85
	Mean sleep midpoint	148	-0.08	-1.16	0.25	0.40
	Inter-daily deviation in sleep duration	148	-0.17	-2.76	0.007	0.04
	Mean composite phase deviation	140	-0.08	-1.14	0.26	0.40
	Sleep activity density	148	-0.11	-1.68	0.10	0.29

Abbreviation: FDR, false discovery rate.

cortical surface areas, suggesting that inter-daily variability in sleep duration is one pathway through which social disadvantage leads to disrupted brain development at birth. We did not find an association between sleep duration or sleep activity density and infant brain outcomes, potentially suggesting a unique role for variable sleep patterns and circadian disruption in affecting offspring neurodevelopmental outcomes.

Our results add to an emerging literature on the association between social disadvantage and sleep and circadian disturbances during pregnancy. Prior research indicates an association between lower socioeconomic status and poorer perceived sleep quality in

pregnant women (Okun et al., 2014), and between poverty and heightened insomnia symptoms during pregnancy (Kalmbach et al., 2019). Increased exposure to stressors, pre-sleep worries, and environmental conditions that are non-conducive to sleep (e.g., noise, light, parent-child bedsharing) may also underlie these associations. Our work extends these previous studies, by showing that higher levels of social disadvantage were associated with later sleep schedules, increased variability in sleep durations, increased circadian misalignment during pregnancy, and a spent larger portion of the sleep period awake.

Additionally, we found that inter-daily deviation in maternal sleep duration during pregnancy was associated with smaller total cortical

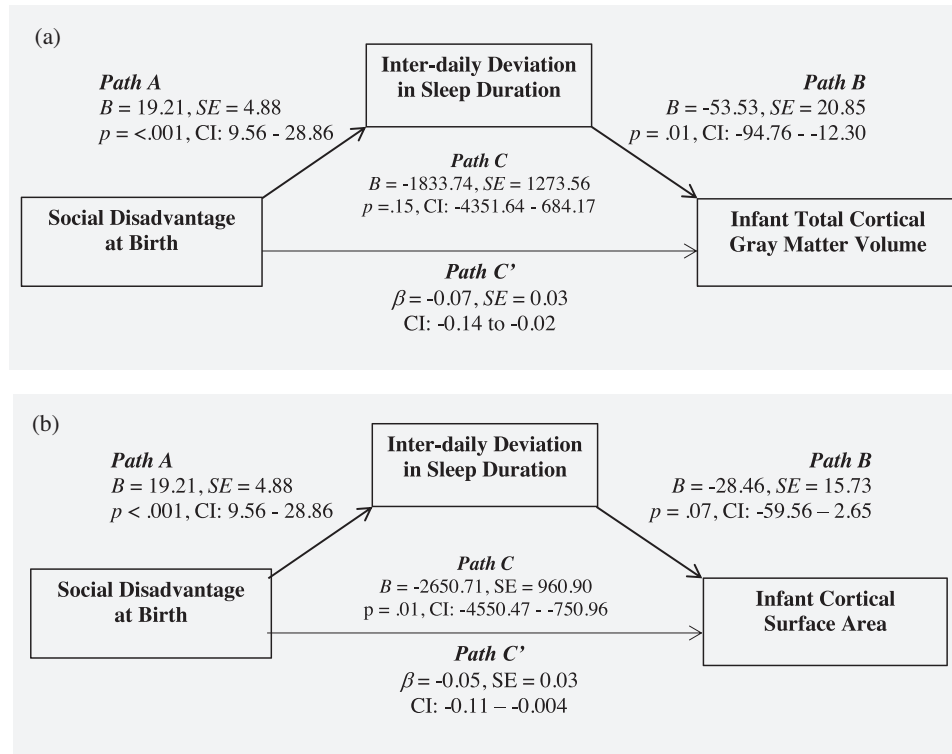


FIGURE 1 Maternal inter-daily deviation in sleep duration (mean across trimesters) mediates the relationship between social disadvantage and (a) infant total cortical gray matter volume and (b) infant cortical surface area. All standardized indirect effects of social disadvantage on infant imaging outcomes in (a) and (b) were significant.

gray and white matter volumes and reduced cortical surface area at birth, and that the infants of mothers who had later sleep midpoints and evidenced more circadian misalignment (i.e., higher CPD values) showed smaller subcortical gray matter volumes. An emerging literature has shown that sleep/wake disruptions during pregnancy affect birth outcomes (Facco et al., 2019; Reschke et al., 2018; Warland et al., 2018), but to our knowledge, our study is the first that has found an association between maternal daily rest-activity rhythms during pregnancy and neonatal brain development. These findings highlight that maternal sleep interventions may be a novel potential therapeutic target for enhancing neonatal brain development.

There are a number of plausible mechanisms through which sleep and circadian disturbances contribute to an adverse intrauterine environment and affect neurodevelopmental outcomes in offspring. A growing literature exploring these mechanisms highlights a key role for circadian-controlled hormones, melatonin and cortisol, in fetal neurodevelopment (Bates & Herzog, 2020; Sgrillo-Fagundes et al., 2016). Melatonin and cortisol levels increase during pregnancy, can cross the placenta, and bind to their cognate receptors in fetal tissue (Mark et al., 2017; Reppert et al., 1988). In rodents, melatonin or glucocorticoid administration can shift fetal daily rhythms and influence subsequent development of organ systems and sleep-wake rhythms (Čečmanová et al., 2019; Davis & Mannon, 1988). Disruptions in the daily patterning of these hormones during pregnancy could potentially have long-term consequences on offspring development (Sgrillo-Fagundes et al., 2016). Additionally, variability in sleep schedules and circadian

misalignment can lead to the disruption of sleep and its restorative mechanisms, which may have downstream effects on offspring neurodevelopment (Selvi et al., 2012). However, we did not find a significant association between sleep duration or sleep activity density and brain outcomes – perhaps reflecting a unique role for inter-daily variability in sleep durations in affecting offspring neurodevelopment. The mechanisms by which variable maternal sleep impacts offspring neurodevelopment are understudied. Sleep variability can misalign daily rhythms including neural, humoral, and cardiovascular functions (Allada & Bass, 2021). Whereas circadian rhythms can remain aligned to each other and local time in the context of shortened sleep, circadian misalignment that occurs due to genetic or environmental disruption (e.g., shift work) during pregnancy may underlie specific associations with disrupted offspring neurodevelopment (Ashbrook et al., 2020).

We also found that inter-daily deviation in sleep durations during pregnancy, in part, explained why some neonates whose mothers experience greater social disadvantage evidence smaller cortical gray matter volumes and reduced cortical surface area. These findings suggest the importance of regular maternal sleep during pregnancy in promoting optimal brain development in offspring. However, it is not entirely clear why variability in sleep durations mediated the relationship of social disadvantage to cortical gray matter volumes and cortical surface area, but not subcortical gray matter or total white matter. One possibility is that the relationship of social disadvantage to subcortical gray or white matter volume is more strongly influenced by other factors associated with social disadvantage, such as



exposure to environmental toxins. Future research should examine whether the significant mediations between maternal sleep and infant brain volumes are associated with neural and behavioral outcomes later in childhood.

This study had a number of strengths and contributes meaningfully to a sparse literature on the effects of prenatal sleep and circadian disturbances in humans. We included in-depth, objective measures of sleep collected during each trimester of pregnancy, enabling us to avoid subjective errors associated with self-report sleep questionnaires, a thorough assessment of social disadvantage, and a large sample for neonatal neuroimaging ($n = 148$). This study should also be viewed in light of its limitations. The sample size, while large for neonatal neuroimaging, limits our power to detect small effects. There was variability in the amount of data we were able to collect during each trimester of pregnancy, thus the current study was under-powered to explore trimester-specific effects or to explore trajectories of sleep across trimesters. Taking the mean of the sleep assessments during pregnancy allowed us to retain the largest sample size possible and was justified by the relatively high correlations between the sleep and circadian indexes across time. However, this analytic choice did not enable us to fully explore known changes in sleep throughout pregnancy (Christian et al., 2019; Sweet et al., 2020). Additionally, there are a number of metrics that can be used to quantify variability of sleep and circadian rhythms (Fischer et al., 2021). The variables we opted to examine in the current study (i.e., inter-daily deviation in sleep duration and CPD) fit our data structure and questions of interest, providing metrics of variability that rely on comparisons across separate days and vary across the recording period allowing the use of non-parametric data. However, other metrics (i.e., intra-daily variability and inter-daily stability), could potentially shed important light on the association between maternal sleep and circadian rhythms and neonatal brain outcomes, and should be considered in future research. Finally, sleep was monitored using actigraphy, which increased the feasibility of data collection, but did not allow us to examine variations in sleep architecture in the mothers. Given evidence of alterations in sleep architecture during pregnancy in animal models (Sivadas et al., 2017), and the potential for these alterations, particularly decreases in delta power and alterations in homeostatic mechanisms, to contribute to offspring neurodevelopmental changes (Aswathy et al., 2018; Sivadas et al., 2017), this is an important area for future investigation.

From a public health perspective, minimizing variable work schedules for pregnant individuals working swing or night shifts may be beneficial for both improving pregnancy outcomes and enhancing neonatal neurodevelopment. Clinically, results from this study suggest the importance of intervening during pregnancy to improve the sleep and circadian health of mothers. Such interventions may not only enhance neonatal brain development but may also reduce health disparities related to social disadvantage. Additional critical questions remain about the continued influence of prenatal social disadvantage and sleep and circadian disturbances on brain development throughout infancy and early childhood. Many of these prenatal effects may be exacerbated, or possibly ameliorated, by the parent-child relationship, social support, or exposure to ongoing adversity and trauma. Future

research will be critical for understanding how maternal sleep and circadian disturbances during pregnancy continue to influence child development across the first years of life and beyond.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

Data were collected with consent forms that allow data sharing. De-identified data is being deposited in the NIMH Data Archive and will be available after the conclusion of the eLABE Year 3 wave.

ETHICS STATEMENT

The study was approved by the Washington University Human Research Protection Office. Informed consent was obtained for each participant and subsequent parental informed consent was obtained for each infant prior to participation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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