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Maternal Childhood Adversity and Infant Epigenetic Aging: Moderation by Restless Sleep During Pregnancy

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Abstract

Maternal exposure to childhood adversity is associated with detrimental health outcomes throughout the lifespan and may have implications for offspring. Evidence links maternal adverse childhood experiences (ACEs) to detrimental birth outcomes, yet the impact on the infant's epigenome is unclear. Moreover, maternal sleep habits during pregnancy may influence this association. Here, we explore whether restless sleep during pregnancy moderates the association between exposure to maternal childhood adversity and infant epigenetic age acceleration in 332 mother-infant dyads (56% female; 39% Black; 25% Hispanic). During the 2nd trimester, mothers self-reported childhood adversity and past-week restless sleep; DNA methylation from umbilical vein endothelial cells was used to estimate five epigenetic clocks. Multivariable linear regression was used to test study hypotheses. Despite no evidence of main effects, there was evidence of an interaction between maternal ACEs and restless sleep in predicting infant epigenetic age acceleration using the EPIC Gestational Age clock. Only infants whose mothers reported exposure to both ACEs and restless sleep demonstrated accelerated epigenetic aging. Results

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The authors declare that they have no competing interests.

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provide preliminary evidence that maternal childhood adversity and sleep may influence the infant epigenome.

Keywords

Adverse Childhood Experience; Sleep; Pregnancy; Epigenomics

Introduction

Extant evidence supports the notion that children are affected by parental exposure to environmental cues, including adversity and trauma occurring before birth, and possibly even prior to conception (Yehuda & Lehrner, 2018). Specifically, maternal exposure to adverse childhood experiences (ACEs) is linked to pregnancy complications and poorer infant health (Ciciolla et al., 2021; Racine et al., 2018; Smith et al., 2016). Epigenetic alterations are a potential mechanism through which maternal exposure to adversity may influence phenotypic variation in health and developmental outcomes in infants (Moore et al., 2022). Gene-specific changes in DNA methylation (DNAm), the most studied epigenetic mechanism, are hypothesized to mediate the association between parental adversity and infant health (Yehuda & Lehrner, 2018). Prior research demonstrates a modest link between adversity experienced during pregnancy (e.g., perceived stress, war-time trauma) and infant DNAm within specific genomic regions, often those linked to the human stress response (e.g., *NR3C1*; (Sosnowski et al., 2018). Less research has extended this window to include parental exposure to adversity prior to conception, though there is emerging evidence to suggest that maternal and paternal exposure to childhood adversity is linked to variable methylation in infants (Folger et al., 2022; Merrill et al., 2021).

Epigenetic clocks have emerged as an overarching summary indicator of biological aging that captures broad effects of stress exposure on the epigenome and can serve as biomarkers of risk for later health and developmental outcomes (Wang & Zhou, 2021). Briefly, adult epigenetic clocks are derived by identifying a subset of CG dinucleotides (i.e., CpG sites) whose methylation patterns are highly correlated with chronological age; the resulting “clock” reflects a person’s biological age and is highly correlated with their chronological age (Fransquet et al., 2019). Deviations in biological age compared to chronological age (i.e., epigenetic age acceleration) are linked to a host of detrimental aging-related outcomes such as frailty, cancer, and all-cause mortality (Fransquet et al., 2019). More recently, efforts have been made to develop pediatric epigenetic clocks, as evidence demonstrates poor accuracy of adult-based clocks in pediatric samples (Simpkin et al., 2016).

Several epigenetic clocks have been developed in pediatric samples, including the PedBE clock (McEwen et al., 2020), Knight’s clock (Knight et al., 2016), Bohlin’s clock (Bohlin et al., 2016), and the EPIC gestational age (GA) clock (Haftorn et al., 2021). Aside from the PedBE clock, which used buccal cell DNAm data from persons from ages 0–20 years, existing pediatric clocks were generated using umbilical cord blood from newborns. The number of CpG sites used in each clock varies, with minimal to moderate overlap in the CpGs included in each clock. Notably, the samples used to generate these clocks are comprised mainly from persons of European ancestry, potentially limiting their generalizability across racial and ethnic groups. Nonetheless, evidence suggests these clocks perform well in correlating with chronological age, and epigenetic age acceleration is associated with obstetric and infant outcomes such as gestational age at birth (McEwen et al., 2020), birthweight (Knight et al., 2016), and infant weight at nine months (Bright et al., 2019). Although these clocks add value and accuracy to estimating biological aging in pediatric samples, it remains unclear how these clocks perform in racially and ethnically diverse samples, and which factors exacerbate the association between maternal stress and infant biological aging (McEwen et al., 2020).

Maternal sleep disturbance is one factor that is associated with both maternal exposure to ACEs and untoward fetal outcomes (Kajeepeta et al., 2015; Nevarez-Brewster et al., 2022; Warland et al., 2018). A possible shared mechanism for this link is that exposure to ACEs may influence sleep through development of mental health disorders such as depression and posttraumatic stress disorder; however, this association persists in the absence of these disorders (Kajeepeta et al., 2015). Similarly, there is evidence for an association between maternal sleep disturbances (e.g., sleep apnea, short sleep duration) during pregnancy and poor fetal outcomes (e.g., altered growth, early gestational age), but these associations are less robust and vary depending on the aspect of sleep (e.g., sleep duration versus sleep-disordered breathing) and fetal outcome under investigation. To date, there are no studies examining associations between maternal sleep during pregnancy and infant epigenetic age.

The goal of this study was to explore whether maternal self-reported restless sleep during pregnancy moderates the association between exposure to childhood adversity and infant epigenetic age acceleration. To date, only one peer-reviewed study has explicitly tested the association between maternal exposure to ACEs and child epigenetic age acceleration – the authors found that a higher maternal ACE score was associated with epigenetic age acceleration in children (at ages 7, 9, and 14 years), measured by the adult Horvath epigenetic clock (Nwanaji-Enwerem et al., 2021). No studies have examined either (a) the association between maternal ACEs and infant epigenetic aging using pediatric epigenetic clocks or (b) the association between maternal sleep and infant epigenetic aging. Moreover, there is limited evidence around pediatric epigenetic clocks in racially and ethnically diverse samples. By assessing these associations (and their interaction) using pediatric clocks in a diverse sample, we aimed to clarify the influence of maternal adversity and sleep on the infant epigenome, and subsequently on infant development.

Method

Participants and Procedure

Pregnant women (n = 577) were enrolled between April 2018 and March 2020 in two cohorts—the Stress and Health in Pregnancy (SHIP) cohort in North Carolina and the Prospective Research on Early Determinants of Illness and Children's Health Trajectories (PREDICT) cohort in Florida. Both cohorts enrolled from university-affiliated obstetric clinics. Women were eligible if the mother was >18 years old, spoke and read English (SHIP), or English or Spanish (PREDICT), and planned to deliver at the respective study-affiliated hospital. Women were ineligible if the fetus had a known congenital anomaly or chromosomal abnormality, or if the mother had HIV, Hepatitis C, or Hepatitis B. Average gestational age at enrollment was 20.8 weeks (SD = 6.9) for SHIP and 24.6 weeks (SD = 6.3) for PREDICT. After enrollment, women completed questionnaires about demographic characteristics and health behaviors and provided obstetric, medical, and social histories. As soon as clinically practical after delivery, parturition data and specimens were collected from participants by providers or study staff who attended deliveries. These included umbilical cord (to obtain human umbilical vein endothelial cells). Additional maternal obstetric and infant delivery records were abstracted following delivery. This study was approved by the two sites' respective institutional review boards. Mothers provided written informed consent for themselves and their children.

DNA Methylation Measurement and Preprocessing

DNA methylation data was available for 411 of the 577 children using the Illumina MethylationEPIC array (Pidsley et al., 2016). Raw data were preprocessed, and quantile normalized using the R package *minfi* (Aryee et al., 2014; Fortin et al., 2017). At the probe level, the following probes were removed: probes with detection p-value larger than 0.01 in more than 5% of total samples; probes with SNPs at CpG sites; probes on sex chromosomes; and cross-reactive probes (Chen et al., 2013). A total of 64,254 probes were removed. Functional normalization with control probes also was adopted for batch effect correction of the data (Fortin et al., 2014). We filtered samples according to the following criteria: samples with more than 1% low-quality probes (i.e., probes with a detection *p*-value larger than 0.01); samples with mismatched sex between our record and prediction from methylation data; and samples with DNA contamination (i.e., log2 odds ratio of contamination larger than −2). In total, 71 samples were removed through quality control. We also excluded a pair of twins, two infants missing data on gestational age, and four infants who were not White, Hispanic, or Black. In total, 332 samples remained and were included in subsequent analyses.

Epigenetic Gestational Age

We estimated epigenetic gestational age using five different methods. The first four include the PedBE clock (McEwen et al., 2020), Knight's clock (Knight et al., 2016), Bohlin's clock (Bohlin et al., 2016), and EPIC GA clock (Haftorn et al., 2021). We also used elastic net regression with the R package *glmnet* (Friedman et al., 2010) to create an epigenetic gestational age clock based on our data, herein referred to as the SHIP-PREDICT clock. For the elastic net regression parameters, we set alpha (i.e., mixing parameter) to 0.5 and lambda was selected using the cv.glmnet function with 10-fold cross-validation that minimizes the mean absolute error of the model. To obtain epigenetic age acceleration estimates, we regressed each clock on estimated clinical gestational age and used the residuals as continuous dependent variables in downstream analyses.

Phenotypic Measures

Adverse Childhood Experiences—Mothers reported on their exposure to ACEs during the first study visit (i.e., 2nd trimester) using the 10-item ACE questionnaire developed by Felitti et al (Felitti et al., 1998). Scores are summed to create a total ACE score. Given the substantial portion of mothers reporting no exposure to ACEs (55%) and low number of participants with higher ACE counts, scores were then recoded to 0 (*no ACEs*) and 1 (*any ACE*).

Restless Sleep—Mothers' restless sleep during pregnancy was assessed using a single item from the Center for Epidemiological Studies Depression (CES-D) Scale (Radloff, 1977), "During the past week my sleep was restless." Response options range from 0 (*Rarely or none of the time [less than 1 day]*) to 3 (*Most or all of the time [5–7 days]*). Evidence suggests this particular restless sleep item is moderately-to-highly correlated with the Pittsburgh Sleep Quality Index (PSQI), which is a more comprehensive, well-validated measure of overall sleep quality (Carpenter & Andrykowski, 1998; Dai et al., 2020; Nicassio et al., 2014). We created a binary variable to capture clinically significant restless sleep during the week. Responses were recoded to 0 (*Rarely or none of the time [less than 1 day]/Some or a little of the time [1–2 days]*) and 1 (*Occasionally or a moderate amount of time [3–4 days]/Most or all the time [5–7 days]*) based on diagnostic criteria for insomnia, which requires patients to experience trouble falling asleep, staying asleep, or waking up too early 3 or more days per week (American Psychiatric Association, 2013).

Control Variables—Variables adjusted for in all models included: racial identity (White versus Black [including those who identified as Black and another racial group]), Hispanic ethnicity, any pregnancy complication (i.e., gestational hypertension, gestational diabetes, and pre-eclampsia), smoking (lifetime, pregnancy-limited, or never), maternal body mass index (BMI), and summary scores reflecting lifetime experiences of discrimination (Everyday Discrimination Scale) (Williams et al., 1997), past-month perceived stress (Perceived Stress Scale) (Cohen et al., 1983), financial stress during pregnancy (Financial Stress Index) (Riis et al., 2016), and prenatal distress (Prenatal Distress Scale) (Yali & Lobel, 1999). Study cohort was not included as a covariate since the two cohorts in this study reflected largely separate racial and ethnic groups; cohort was moderately correlated with the race and ethnicity variables (i.e., $r > 0.30$), and we did not want to adjust for additional proxy variables of race or ethnicity. Lastly, we adjusted for gestational age at birth in each model, following best practices when predicting epigenetic age deviation (Krieger et al., 2023).

Statistical Analyses

All analyses were conducted using R statistical software. Prior to analysis, data were inspected for missingness, normality, and outliers. Data were approximately normally distributed, and no outliers were detected. Data were missing across numerous variables, including the ACE item (6% of total cases) and restless sleep item (5% of total cases). No data were missing for gestational age or the subsequent epigenetic age estimates. Little's Missing Completely at Random (MCAR) Test suggested that data were not MCAR (p = 0.005), and evidence from bivariate correlations revealed that study cohort was associated with missingness on the primary study predictors. Thus, data were assumed to be missing at random (MAR) and we used multiple imputation by chained equations (van Buuren & Groothuis-Oudshoorn, 2011) with auxiliary variables, including study cohort and averages of non-missing ACE and CES-D items to impute missing data. Using the R package *mice* (van Buuren & Groothuis-Oudshoorn, 2011), we generated 50 multiply-imputed datasets; diagnostic checks (e.g., strip plots, density plots) revealed adequate imputations (data not shown). Results were presented using pooled estimates from linear regression models on each imputed data set using Rubin's rules (Little & Rubin, 2019). For each of the five epigenetic age deviation outcomes, we first tested an unadjusted model, followed by a model adjusting for potential confounders (10 total models). If a significant interaction was detected in the adjusted model, we plotted the model-derived estimates from the multiply imputed data. An alpha level of 0.05 was used for all statistical tests, and all interaction terms (n = 10) were corrected for multiple testing using the false discovery rate procedure (Benjamini & Hochberg, 1995). This method controls for the expected proportion of false positives among all statistical tests. It is less conservative than the commonly used Bonferroni correction, which controls for any expected false positive, but benefits from increased statistical power. However, because this study was likely underpowered to detect interaction effects and largely exploratory, we did not solely rely on the corrected p-values. To attempt to reach a balance between reducing potential for both type I *and* type II error, we presented unadjusted and adjusted p-values, and considered effect sizes of the estimates when interpreting our findings.

Results

Descriptive statistics of the non-imputed (i.e., complete-case) data are presented in Table 1. Mothers were, on average, 29 years old (SD = 5.7 years) at the time of delivery; 36% of mothers identified as non-Hispanic Black and 25% of mothers identified as Hispanic. Mothers reported anywhere from zero to eight ACEs (Median = 0, Interquartile Range [IQR] = 2) and 38% reported restless sleep a moderate amount of the time or most/all of the time. The majority (56%) of infants were female and were born at approximately 38 weeks of gestation (SD = 1.6 weeks). Using chi-square tests for categorical variables and independent samples t-tests for continuous variables, we detected differences in demographic and study variables by study cohort (see Table 1); As expected, the SHIP cohort had a larger proportion of Black and Hispanic mothers; the SHIP cohort had more pregnancy complications, self-reported smoking during pregnancy, and higher average pre-pregnancy BMI compared to mothers in the PREDICT cohort. Mothers in the SHIP cohort also reported higher levels of financial stress, but lower levels of restless sleep and prenatal distress compared to mothers in the PREDICT cohort. Lastly, infants in the SHIP cohort demonstrated slower PedBE, EPIC, and SHIP-PREDICT acceleration compared to infants in the PREDICT cohort. No other differences were detected between cohorts.

ACEs, Sleep, and Epigenetic Age Acceleration

In the unadjusted and adjusted models, there was no evidence of an association for ACEs, restless sleep, or their interaction in predicting PedBE, Knight, Bohlin, or SHIP-PREDICT age acceleration. Results for these models can be found in Table 2, and complete results including covariates can be found in File S1. In contrast, there was evidence of an interaction between ACEs and restless sleep for predicting EPIC GA acceleration ($b = 1.02$, $se = 0.51$, $p = 0.04$). This interaction persisted after adjusting for potential confounders ($b = 1.04$, $se = 0.51$, $p = 0.04$). Neither interaction term survived correction for multiple testing (adjusted *p*-values = 0.20). Nonetheless, we further probed this interaction by plotting the model-derived estimates from the adjusted model.

As can be seen in Figure 1, the association between maternal ACEs and infant EPIC GA acceleration was dependent upon mothers' restless sleep. Infants of mothers who reported exposure to ACEs demonstrated faster EPIC GA acceleration when the mother reported moderate-to-severe restless sleep. On the other hand, infants of mothers who reported no exposure to ACEs demonstrated faster EPIC GA acceleration when the mother reported little-to-no restless sleep during pregnancy. Notably, as shown in Figure 1, all of the infants in the group with maternal ACE exposure and restless sleep during pregnancy demonstrated epigenetic age acceleration exposure (Mean EPIC GA acceleration = 1.04, 95% CI = 0.25, 1.83 [Supplemental Table 6]), as did most of those with neither exposure. Among those with either exposure, there was variability in epigenetic age such that some were decelerators while others were accelerators (see Figure 1 and Supplemental Table 6). Lastly, we re-ran this model using "raw" epigenetic age deviation estimates (i.e., subtracting chronological age from epigenetic age) to obtain interpretable values of age deviation. In weeks, infants whose mothers experienced both ACEs and restless sleep during pregnancy exhibited a faster mean EPIC GA acceleration of approximately ¾ of a week compared to infants whose mothers only experienced one of the exposures, and by approximately ½ of a week compared to infants whose mother had neither exposure.

Discussion

The goal of this study was to explore whether maternal reports of restless sleep during pregnancy moderate the association between maternal exposure to ACEs and infant epigenetic age deviation at birth. Results suggest that the association between maternal exposure to ACEs and infant epigenetic age acceleration (measured using the EPIC GA clock) may be dependent upon maternal restless sleep during pregnancy. Infants of mothers who reported both exposure to ACEs and restless sleep (or neither) evidenced epigenetic age acceleration relative to infants whose mothers reported only ACEs or only restless sleep. This interaction was only detected using one of five pediatric epigenetic clocks and did not survive correction for multiple testing. On the other hand, there is a high likelihood that we were underpowered to detect interaction effects, and these analyses were largely exploratory. As a result, findings should be considered hypothesis-generating, and holistically interpreted, including both adjusted and unadjusted p-values, and effect sizes.

We did not find evidence for independent associations between maternal exposure to ACEs and newborn epigenetic aging or between maternal restless sleep and newborn epigenetic aging. This could partially be attributed to low variability in ACE scores in our sample, and a large proportion of participants with 0 ACEs. The proportion of participants in our study who reported experiencing one or more ACE was 44%, which is similar to estimates of 32–46% among women attending private healthcare clinics in the US (Flanagan et al., 2018; Racine et al., 2022), but is substantially lower compared to estimates of 70–80% among women in the US attending public healthcare clinics (Bowers et al., 2018; Howell et al., 2020; Johnson et al., 2017; McDonnell & Valentino, 2016; Miller-Graff & Cheng, 2017). Other investigations have detected associations between maternal *lifetime* stress and newborn epigenetic aging. Notably, Katrinli et al. (2023) found that, among Hispanic mothers, lifetime PTSD symptoms (including insomnia symptoms) were associated with EPIC GA deceleration in infants. Another study by Koen et al., 2021 found that maternal PTSD was associated with Bohlin age deceleration in South African infants.

In a recent pre-print, Dye et al. (2023) found that mothers' total ACE score (and parental substance use, specifically) was positively associated with Bohlin clock acceleration in male newborns. Male newborns whose mothers reported exposure to neglect during childhood also demonstrated epigenetic age acceleration using the Knight clock. Conversely, maternal exposure to domestic violence in childhood was associated with female newborns' epigenetic age acceleration using the Knight clock. It is important to note that the latter two studies did not test associations with the EPIC GA or PedBE clocks, and, similar to other prior investigations, they used cord blood samples to estimate the epigenetic clocks. It is possible that differences in cell population contributed to differential findings between our studies. Moreover, methylation data in our study were run on the Illumina EPIC array, and the EPIC GA clock was developed to use CpG sites unique to this array. The EPIC GA clock demonstrates improved precision and accuracy in predicting gestational age compared to previous clocks (Haftorn et al., 2021). Thus, it is possible that our use of the EPIC array contributes to more accurate estimates with methylation data derived from this clock. Nonetheless, existing results suggest that the association between maternal exposure to ACEs and newborn epigenetic aging is detectable using multiple clocks (including the EPIC GA clock), and dependent upon certain characteristics (e.g., sex).

This study presents the first test of whether maternal sleep quality during pregnancy is associated with newborn epigenetic aging. Experiences of maltreatment during childhood are associated with poor sleep outcomes both in childhood and adulthood (Brown et al., 2022). Further, sleep disturbances related to early life adversity have been proposed to be a central mechanism linking early life adversity to subsequent poor health outcomes across the lifespan via alterations to various neurobiological systems (e.g., HPA-axis; Fuligni et al., 2021). During developmental transitions marked by increases in sleep disturbances (e.g., pregnancy), these sleep disturbances may act as a "second hit" among people with early life adversity, putting them (and their offspring) past the threshold for health risk (Fuligni et al., 2021; Gallaher et al., 2018). This may then contribute to variable methylation (and subsequent epigenetic aging) among newborns.

Despite evidence suggesting that both maternal exposure to childhood adversity and restless sleep have implications for infant health and wellbeing, the exact role of pediatric epigenetic age deviation remains unclear. That is, it is unclear whether infant epigenetic age acceleration, specifically, is predictive of infant health outcomes. Recent evidence demonstrates a positive association between maternal exposure to adversity and infant and child epigenetic age acceleration (Dye et al., 2023; Nwanaji-Enwerem et al., 2021), though others find different maternal stressors (e.g., antenatal depression) are associated with epigenetic age deceleration (Wang & Zhou, 2021), and none of these studies look at subsequent health outcomes. The lack of postnatal data on infants and children makes it difficult to determine whether epigenetic age deviation is indeed a mechanism linking maternal exposure to ACEs to infant health.

It is possible that infant epigenetic age deviation in the context of adversity reflects an adaptive, rather than solely harmful, response to the environment. For example, epigenetic age acceleration in infants is linked to later gestational age at birth (McEwen et al., 2020) and higher birth weight (Knight et al., 2016), which could be viewed positively in newborns, reflecting advanced maturation. In the context of the current findings, it is possible that infants whose mothers had a "double hit" of ACEs and restless sleep demonstrate accelerated epigenetic aging as a preemptive response to a potentially stressful environment during childhood. Conversely, infants of mothers reporting neither ACEs nor restless sleep, could be demonstrating epigenetic age acceleration that reflects maturation in the context of an enriching environment. This is speculative, though, as longitudinal postnatal data on offspring outcomes is needed to clarify the meaning and mechanisms behind infant epigenetic age deviation.

The current study has several strengths, namely the use of a racially and ethnically diverse sample and unique cell population (HUVEC). This also allowed us to generate our own epigenetic clock. These data can and should be used to develop a pan-tissue clock that can improve predictive accuracy of pediatric epigenetic clocks for various behavioral and health outcomes for a wide range of individuals during childhood. The current study also was strengthened by the temporal ordering of the constructs and inclusion of numerous potential confounders. Despite these strengths, the current findings should be interpreted in light of several limitations. First, restless sleep was only assessed using a single item from the CES-D measure. There is evidence, however, indicating that this particular restless sleep item is moderately-to-highly correlated with the Pittsburgh Sleep Quality Index (Carpenter & Andrykowski, 1998; Dai et al., 2020; Nicassio et al., 2014), and that this same item is moderately predictive of probable insomnia disorder based on DSM5 diagnostic criteria (Hughes et al., 2018). Second, this study was limited in that mothers self-reported on all measures, from ACEs to sleep and potential confounders (e.g., tobacco use). Thus, the data are subject to single informant bias. Also, due to concerns about statistical power, we did not stratify by sex, though existing evidence demonstrates sex-specific differences in prenatal programming (Hicks et al., 2019). Lastly, we did not have data on infant outcomes, which limits our understanding of whether epigenetic age acceleration at birth is predictive of positive or negative behavioral or health outcomes.

Conclusion

Our results provide preliminary evidence that maternal restless sleep during pregnancy may exacerbate the association between maternal exposure to ACEs and newborn epigenetic age acceleration. Future studies with larger samples across diverse healthcare settings with more variability in ACEs, more comprehensive sleep measurement, measurement of methylation across multiple tissue and cell populations, and assessment of infant outcomes will help elucidate the current findings more definitively and clarify whether there are clinically meaningful implications of infant epigenetic age deviation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

The datasets generated and analyzed during this study are not publicly available due to reasons of sensitivity but are available from the corresponding author on reasonable request.

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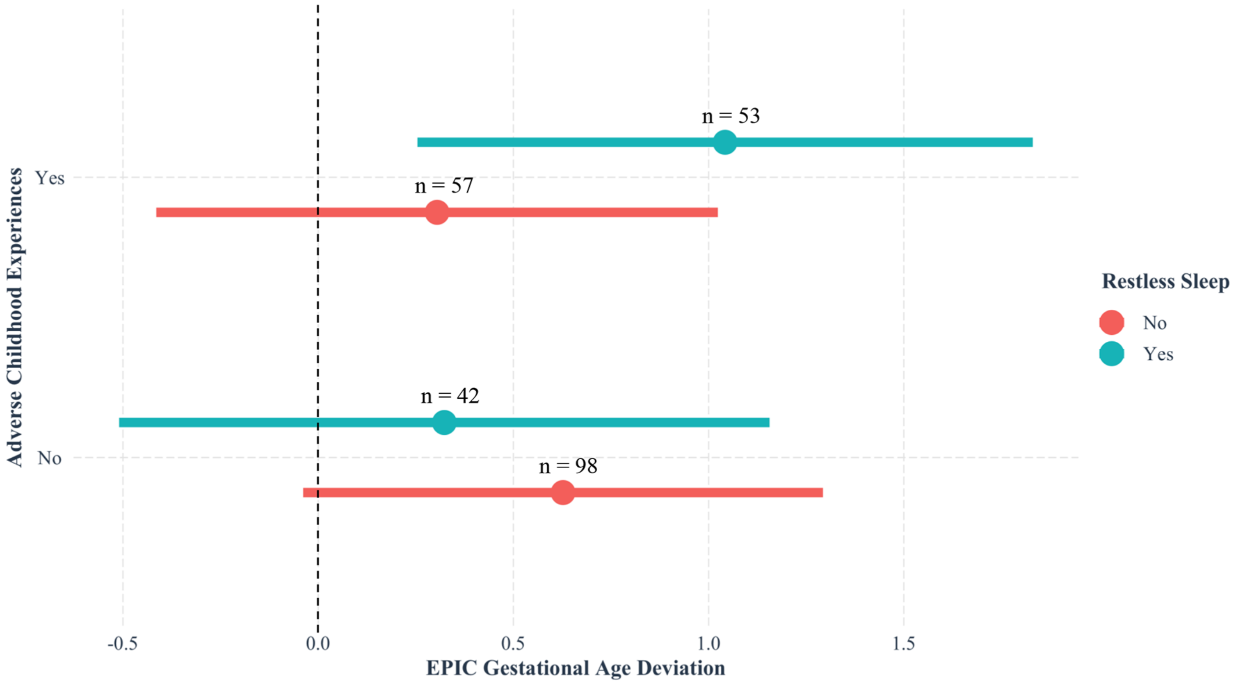

Figure 1.

Interaction Between Maternal Adverse Childhood Experiences and Restless Sleep Predicting Newborn Epigenetic Age Deviation

Note. Group sizes reflect complete-case data since group sizes may vary across imputed data sets.

Table 1

Demographic and Study Characteristics of Complete-Case Data

Variables	Combined Sample (n = 250)	SHIP (n = 152)	PREDICT (n = 98)	*p*-value for difference
Ethnicity, N (% Hispanic)	59 (24)	53 (35)	6 (6)	**< 0.001**
Race, N (% Black multiracial)	91 (36)	79 (52)	11 (11)	**< 0.001**
Smoking, N (% Yes)	14 (6)	14 (9)	0 (0)	**< 0.001**
Complication, N (% Yes)	76 (30)	54 (37)	22 (22)	**0.02**
BMI, Median (IQR)	27.2 (12.2)	29.5 (12.9)	25.4 (8.6)	**< 0.001**
Discrimination, Median (IQR)	0 (3)	0 (3)	1 (3)	0.75
Perceived Stress, Median (IQR)	13 (7)	14 (8)	12 (6)	0.30
Prenatal Distress, Median (IQR)	9 (8)	7.5 (9)	9 (7.8)	**0.03**
Financial Stress, Median (IQR)	4 (8)	7 (9)	2 (6)	**< 0.001**
ACEs, N (% Yes)	110 (44)	67 (44)	43 (44)	1.00
Restless Sleep, N (% Yes)	95 (38)	47 (31)	48 (49)	**0.01**
PedBE Acceleration, Median (IQR)	−0.1 (0.7)	−0.1 (0.6)	0.0 (0.6)	**0.001**
Knight Acceleration, Median (IQR)	−0.98 (4.0)	−0.7 (4.1)	−1.4 (3.9)	0.38
Bohlin Acceleration, Median (IQR)	−0.5 (2.2)	−0.5 (2.3)	−0.5 (2.3)	0.25
EPIC Acceleration, Median (IQR)	−0.5 (2.6)	−0.2 (2.5)	−1.2 (2.6)	**0.03**
SP Acceleration, Median (IQR)	0.01 (0.5)	−0.1 (0.5)	0.2 (0.6)	**< 0.001**

Note. Smoking reflects self-reported smoking during pregnancy. BMI = body mass index. IQR = Interquartile Range. SP = SHIP-PREDICT. Bolded values reflect significant differences between cohorts.

Table 2

Results for Multivariable Linear Regression Models

	PedBE Acceleration *b* (*SE*)	Knight Acceleration *b* (*SE*)	Bohlin Acceleration *b* (*SE*)	EPIC Acceleration *b* (*SE*)	SP Acceleration *b* (*SE*)
Unadjusted					
ACEs	−0.01 (*0.08*)	−0.14 (*0.50*)	−0.09 (*0.27*)	−0.26 (*0.30*)	0.08 (*0.06*)
Restless Sleep	0.10 (*0.09*)	−0.20 (*0.56*)	−0.04 (*0.31*)	−0.48 (*0.34*)	0.10 (*0.07*)
ACE × Restless Sleep	−0.01 (*0.14*)	0.93 (*0.83*)	0.44 (*0.45*)	1.02 (*0.51*) *	−0.09 (*0.10*)
Adjusted					
ACEs	−0.02 (*0.09*)	−0.14 (*0.50*)	−0.13 (*0.28*)	−0.32 (*0.31*)	0.07 (*0.06*)
Restless Sleep	0.10 (*0.10*)	0.10 (*0.58*)	0.01 (*0.32*)	−0.30 (*0.35*)	0.07 (*0.07*)
ACE × Restless Sleep	−0.01 (*0.14*)	0.85 (*0.84*)	0.45 (*0.46*)	1.04 (*0.51*) *	−0.06 (*0.10*)

Note. SP = SHIP-PREDICT.

* $p < 0.05$