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Postpartum sleep loss and accelerated epigenetic aging

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ABSTRACT

Background: Insufficient sleep has been linked to accelerated biological aging in adults, providing a possible mechanism through which sleep may influence disease risk. In the current paper, we test the hypothesis that short sleep in postpartum would predict older biological age in women one year post birth, as indicated by accelerated epigenetic aging.

Methods: As part of a larger study of pregnancy and postpartum health (Healthy Babies Before Birth, HB3), 33 mothers provided blood samples for epigenetic aging clock estimates. intrinsic epigenetic age acceleration (IEAA), extrinsic apigenetic age acceleration, phenotypic epigenetic age acceleration (PEAA), GrimAge, DNAmPAI-1, and DNAm telomere length (TL) were calculated using established protocols. Sleep duration was categorized as insufficient sleep (<7 hours per night) or healthy sleep duration (7+ hours per night). Sleep quality was determined using the Pittsburgh Sleep Quality Index (Global score >5).

Results: Maternal postpartum sleep duration at 6 months, but not 12 months, following a birth was predictive of older 12-month IEAA, B (SE) = 3.0 (1.2), P = .02, PEAA, B (SE) = 7.3 (2.0), P = .002, and DNAmTL, B (SE) = −0.18 (0.07), P = .01, but not other indices, all P> .127. Self-reported poor sleep quality at 6 and 12 months was not significantly related to epigenetic age.

Conclusions: These findings suggest that insufficient sleep duration during the early postpartum period is associated with accelerated biological aging. As the sample size is small, additional research is warranted with a larger sample size to replicate these findings.

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Introduction

Parenting of infants and young children is typically accompanied by routine sleep disruptions, often resulting in insufficient sleep for the parents. In the first 6 months of life, in particular, infant sleep patterns are wrought with nighttime awakenings, mostly due to frequent feedings, a responsibility that often falls on mothers.[1] Thus, for many mothers, postpartum is a time of poor sleep quality and shortened sleep duration.[2,3] Although there is evidence that this disjointed and insufficient sleep during postpartum impacts daytime functioning, including increased fatigue, mood disturbances, and sleepiness,[1,2,4] the impact of postpartum sleep disruptions on biological processes related to health and disease is less clear. A considerable body of research has demonstrated that inadequate sleep and chronic poor sleep quality increase vulnerability to age-related disease and early death risk,[5-12] with evidence that inflammatory pathways are likely involved.[13] However, limited research has examined sleep in the context of postpartum biological aging. Addressing whether routine sleep insufficiency may be detrimental for health by accelerating biological aging provides novel insight into this normative challenge during early parenthood and provides evidence for the importance of interventions that might target sleep in this context.[14]

Several molecular mechanisms that drive increased health risk as a result of insufficient sleep have been proposed, including inflammation, declines in physiological system function, and recently, accelerated biological aging.[13,15-17] Rates at which a person ages at the biological level is an important indicator for later risk for morbidity and mortality,[18,19] whereas identifying factors that influence biological aging may prove to prevent or delay the onset of disease.[20,21] For example, a single night of experimental partial sleep deprivation in older adults activated genes consistent with biological aging

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pathways, including increasing inflammation, DNA damage, and cellular senescence.[13,22,23] In mouse models, repeated disruption of sleep altered biological aging processes, including increasing cellular stress, injury, and senescence.[24-26] Short sleep duration, poor sleep quality, and diagnosed insomnia have also been linked to shorter leukocyte telomere length, a marker of biological aging, in varied populations of mid- to late-life adults.[27-33] These findings highlight plausible molecular mechanisms through which insufficient sleep impacts risk for later disease.

In addition to telomere length, the epigenetic clock has been proposed to serve as an estimate of biological age. Several methods of calculating epigenetic clock indicators have been proposed,[34-36] including (1) extrinsic epigenetic age acceleration (EEAA),[16,34,35] (2) intrinsic epigenetic age acceleration (IEAA), (3) phenotypic epigenetic age acceleration (PEAA),[36] (4) GrimAge, and (5) DNAm plasminogen activator inhibitor-1 (PAI-1).[37] Recently, the methylation data have also been used to derive an estimate of telomere length in the sample,[6] called DNA methylation telomere length (DNAmTL). Together these measures were designed to capture cellular aging and age-related disease risk. Several large epidemiological investigations have used estimates of DNA methylation based biological clocks to estimate biological age and predict important outcomes, namely, mortality,[37,38] physical fitness,[39] and disease risk.[40] PEAA in particular has been defined as a predictor of physical (ie, phenotypic signs) of aging and tracks with multiple biological indictors of disease risk,[36] suggesting that these epigenetic clock estimates are useful in tracking the aging process itself and not just lifespan.

Although the existing literature provides initial links between sleep quality and short sleep duration with molecular markers of biological aging, to date the research is limited to adults in mid- to late life. This limits our current knowledge as to whether sleep impacts rates of biological aging in younger adults, such as women of reproductive age. In the current study, we conducted a secondary analysis of pregnant women recruited from a larger study and followed them over 1-year postpartum. We proposed that mothers with significant insufficient sleep during the postpartum period (6 months after pregnancy) would have an accelerated epigenetic age at 1 year after pregnancy.

Methods

Participants

Women were recruited within a larger longitudinal study (Healthy Babies Before Birth; HB3) that was designed to test antenatal maternal mood and disorders on pregnancy and postpartum outcomes, with methods described previously.[41] A subsample of 33 women recruited from one of the 2 western US sites had blood samples available at the 1-year postpartum visit for the assessment of epigenetic age. Inclusion criteria were 18 years of age or older and singleton pregnancies at 12 or fewer weeks gestation at the outset of the study. Exclusion criteria were a current substance abuse diagnosis, HIV-positive status, current smoking habit, and current use of glucocorticoids. All participants provided informed consent, and all protocols and methods were reviewed and approved by appropriate institutional review boards. Sample characteristics are presented in Table 1. Participants were 23-45 years of age at the 6-month postpartum visit, and 43% identified as non-Latina White, 26% Latina, 14% Black, 17% Asian or mixed race. The majority of women were married, and 57% nulliparous.

Protocol

Participants were followed for a total of 6 visits, 3 during pregnancy (8-16 weeks, 20-26 weeks, and 30-36 weeks) and 3 after delivery (6 weeks, 6 months, and 12 months). Here, we focus on the 6-month and 12-month postpartum visits when sleep was assessed.

Table 1
Sample characteristics ($N = 33$)

Variable	Mean ± SD or % (N)
Age (yrs)	33.6 ± 5.29
Marital status (married)	91 (32)
Education (yrs)	16.9 ± 2.90
Race/ethnicity (White)	
White	43 (15)
Black	14 (5)
Latina	26 (9)
Asian	11 (4)
Multirace	6 (2)
BMI at 12 months PP	25.3 ± 5.7
Last assessment (months PP)	11.5 ± .51
6 months PP, sleep duration (<7 hours)	58%(19)
6 months PP, sleep duration (hours)	6.58 ± 1.31
12 months PP, sleep duration (<7 hours)	59%(20)
12 months PP, sleep duration (hours)	6.47 ± 1.30
6 months PP, poor sleep quality (>5 PSQI)	64%(21)
6 months PP, PSQI global score	6.25 ± 3.49
12 months PP, poor sleep quality (>5 PSQI)	65%(22)
12 months PP, PSQI global score	5.58 ± 2.37
12 months PP epigenetic age acceleration	
IEAA (yrs)	−0.043 ± 2.92
EEAA (yrs)	−1.97 ± 4.28
PEAA (yrs)	−3.18 ± 5.41
GrimAge (yrs)	−1.56 ± 3.35
DNAmPAI-1	−387 ± 2580
DNAmTL	0.004 ± 0.186

BMI, body mass index; EEAA, extrinsic epigenetic age acceleration; IEAA, intrinsic epigenetic age acceleration; PEAA, phenotypic epigenetic age acceleration; PP, postpartum; DNAmTL, DNA methylation telomere length; PSQI, Pittsburgh Sleep Quality Index.

Whole blood samples for DNA methylation assay were collected at the 12-month postbirth visit, aliquoted and placed in a −80°C freezer for later processing. Demographics were obtained by interview at study entry, and information about body composition including body mass index (BMI) was collected at each visit.

Sleep assessment

Average self-reported sleep duration and sleep quality over the prior month was determined using the Pittsburgh Sleep Quality Index (PSQI) and scored according to published criterion.[42] Scores >5 were categorized as poor sleep quality in accordance with published recommendations.[42] In addition, as noted by the Center for Disease Control[6] and recommended by the joint commission of the American Academy of Sleep Medicine and the Sleep Research Society,[43] guidelines recommend obtaining 7 or more hours per night to have sufficient sleep amounts. Sleep duration was collected from a single item question asking about typical sleep duration on the PSQI and was categorized as fewer than 7 hours per night as unhealthy sleep duration, while healthy sleep duration as 7 or more hours of sleep per night.

DNA methylation

Genomic DNA was extracted from whole blood samples taken at 12-month postpartum using the DNAEasy Blood and Tissue Kit (Qiagen). SpedVac concentrated DNA suspended in AE buffer was quantified using the Invitrogen Quant-iT dsDNA Assay Kit, high sensitivity (Invitrogen). DNA methylation assays were performed as previously described,[16,35] using the Human Methylation 450k Illumina bead chip (6 months) and the 850K EPIC chip (12 months) (Illumina, San Diego, CA), performed by the UCLA Neuroscience Genomics Core facilities according to the manufacturer's protocols by applying standard settings.

DNA methylation data were preprocessed following standard protocols.[35,44] Raw data were background corrected and normalized using the "Noob" function in the "minfi" package for R statistical software (https://rdrr.io/bioc/minifi/).[44] CpG sites that were not measured by the 450K or EPIC chips but are required for epigenetic clock estimation were added, and processed data were submitted to the epigenetic clock online calculator (https://dnamage.genetics.ucla.edu/). The online calculator includes several quality control checks: all samples were correctly identified as female, with tissue sources of either whole blood or blood PBMCs, and correlations between the sample and the gold standard were greater than 0.80 (mean $r = 0.96$).

Epigenetic age estimates

We examined 5 distinct estimates of epigenetic age acceleration based on established literature,[34,35] recent methods,[36] and as we reported previously.[45] All epigenetic indices were adjusted for chronological age. EEAA is an estimate derived from the Hannum method[34] based on 71 CpGs, with modifications to allow for blood cell counts, described previously,[16,35] and available through the DNAm age calculator (https://dnamage.genetics.ucla.edu/). IEAA is derived from the Horvath method based on 353 CpGs, is independent of blood cell counts, and is highly correlated with chronological age. PEAA is derived from the Levine method[36] based on 513 CpGs, which were selected based on their predictive utility for phenotypic aging characteristics including biomarkers of physical decline, risk for morbidity and mortality, along with chronological age. GrimAge and DNAmPAI-1 are epigenetic age markers enriched for DNA methylation sites that are surrogate biomarkers for blood plasma proteins related to morbidity, mortality, and cigarette smoking (packs per year).[37] An additional estimate derived from the epigenetic clock software provides a measure of DNAmTL. As this estimates telomere length within the sample, lower values indicate shorter telomere length, or evidence of greater cellular aging. All measures of epigenetic and cellular aging are age-adjusted as they are derived from the Horvath DNAm age calculator software which generates variables adjusted by chronological age.

Samples in the present analyses were run in 2 batches such that 19 samples were run on the 450k chip in 2016, and the remaining 16 were run using the EPIC chip in 2017. A test of reliability between these 2 plates confirmed modest concordance in estimates of EEAA, IEAA, PEAA, GrimAge DNAmPAI-1, and DNAmTL $r > 0.46$, and was discussed in a previous publication.[45] To account for potential between-person differences generated by assay, a covariate capturing the chip used for the DNA methylation assays was included in all linear regression models.

Covariates

Covariates considered for inclusion in analyses were selected based on published guidelines[46] by selecting with as a function of historical associations of confounding factors (demographics: race/ethnicity [non-Latina White vs not]),[47] years of education,[48] per capita household income,[49,50] 12-month post-birth BMI (kg/m^2),[45,51] relationship status (married and/or cohabiting or not).[52] In addition, 2 covariates were selected as a function of being reflective of unmeasured possible confounds in the causal model, parity (primiparous or multiparous), and breastfeeding (breastfed through 12 months or less than 12 months), both of which could plausibly impact biological aging through alterative pathways (ie, greater caregiving demands, benefits of breastfeeding for maternal health) but also be related to sleep disturbances.[53] All analyses control for chronological age, as the epigenetic and telomere length estimates are computed by adjusting for chronological age at the time of blood draw. For clarity, we have listed age as a covariate. Assay batch was also included as a covariate in all analyses.

Analytic strategy

Data were entered into REDCap,[54] and all analyses were run using SPSS v.24 (IBM, 2016). Descriptive data were first inspected for outliers and normality. Outliers were defined as values greater than ±3 standard deviations from the respective means, and values were winsorized. Spearman bivariate correlations assessed associations between sleep variables and epigenetic age estimates at each visit. All covariates were included in subsequent linear regression models, in which sleep variables predicted epigenetic age variables, controlling for race/ethnicity, education, per capita household income, marital status, breastfeeding, BMI, and batch.

Results

At both 6- and 12-month postbirth visits, over half of the women had insufficient sleep (<7 hours per night). There were no significant differences in sleep duration ($P = .09$) or prevalence of poor sleep quality ($P = .15$) between the 6-month and 12-month postbirth assessments (Table 1). However, a number of women experienced changes in sleep, with 16% reporting short sleep at 6 months who were no longer short sleepers at 12 months. Another 19% who were not short sleepers at 6 months reported short sleep at 12 months. Similarly, poor sleep quality (as indicated with score of >5 on the PSQI) resolved at 12 months in 16% of women who reported sleep disturbances at 6 months, while 19% developed had poor sleep quality by 12 months that did not report this at 6 months.

Associations of covariates with age-adjusted EEAA, IEAA, PEAA, GrimAge, DNAmPAI-1, and DNAmTL are reported in Supplementary Table 1. Higher 12-month BMI was significantly associated with higher PEAA, GrimAge, DNAmPAI-1, and shorter DNAmTL (all $P < .05$). Being married or cohabiting with a partner was associated with lower PEAA and longer DNAmTL (all $P < .05$).

Table 2
Epigenetic and cellular aging indices as a function of sleep duration at 6-month and 12-month postpartum

Variable	6-month postpartum			12-month postpartum		
	Short sleep <7 hours Mean (SD)	Long sleep 7+ hours Mean (SD)	*t* test, *P* value	Short sleep <7 hours Mean (SD)	Long sleep 7+ hours Mean (SD)	*t* test, *P* value
EEAA	−0.597 (4.29)	−3.50 (3.79)	0.052	−1.17 (3.83)	−3.60 (4.36)	0.094
IEAA	1.01 (2.66)	−1.21 (2.95)	0.031	−0.166 (2.81)	−0.476 (2.22)	0.733
PEAA	−0.555 (5.11)	−6.77 (3.83)	0.001	−3.40 (5.71)	−3.39 (4.97)	0.996
GrimAge	−0.883 (3.52)	−2.39 (3.14)	0.213	−1.99 (3.62)	−1.32 (2.79)	0.561
DNAmPAI-1	173 (3113)	−1178 (1656)	0.151	−666 (2944)	−302 (1770)	0.683
DNAmTL	−0.074 (0.175)	0.107 (0.155)	0.004	−0.015 (0.165)	0.060 (0.183)	0.227

EEAA, Extrinsic Epigenetic Age Acceleration; IEAA, Intrinsic Epigenetic Age Acceleration; PEAA, Phenotypic Epigenetic Age Acceleration; DNAmTL, DNA methylation telomere length; DNAmPAI-1.

In independent sample *t* tests, longer sleep duration at 6-month postbirth was associated with lower IEAA and PEAA, and shorter DNAmTL at 12 months (Table 2). Sleep duration at 12 months was not associated with any indices of epigenetic age acceleration at that time point (Table 2). Global sleep quality scores from the PSQI using either a continuous or dichotomous variable at either time point were not significantly related to EEAA, IEAA, or PEAA (Supplementary Tables 1 & 2).

Linear regression analyses

Linear regression models were run with sleep duration at 6 months predicting age-adjusted epigenetic age at 12-month postbirth, adjusting for race/ethnicity, education, per capita household income, marital status, breastfeeding, BMI, and batch. Short sleep duration at 6-month postpartum was associated with greater epigenetic age acceleration at 12-month postbirth for both IEAA (b = 3.03, SE = 1.17, P = .016, Fig. 1), PEAA (b = 7.26, SE = 2.04, P = .002, Fig. 2), and DNAmTL (b = −0.181, SE = 0.067, P = .012, Fig. 3), but not EEAA, GrimAge, or DNAmPAI-1, all P> .127. Sleep quality scores were unrelated to epigenetic age estimates in linear regression models, and treating the scores as continuous did not change the results. Secondary analyses testing the linear associations of sleep duration as a continuous variable with epigenetic aging outcomes were similar to models with the dichotomous sleep duration variable (IEAA: b = −0.845, SE = 0.458, P = .077; PEAA: b = −1.89, SE = 0.850, P = .036; DNAmTL: b = 0.063, SE = 0.025, P = .020).

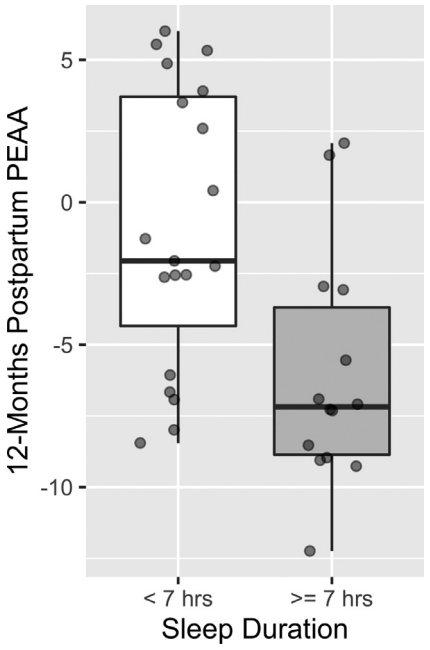

Fig. 2. Postpartum sleep duration at 6 months predicted Phenotypic Epigenetic Age Acceleration (PEAA) at 12-month postpartum, adjusting for batch, race/ethnicity, education, per capita household income, marital status, breastfeeding, and 12-month BMI.

Discussion

In the present study, we found that new mothers' self-reported sleep duration of less than 7 hours at 6-month postpartum was related to older epigenetic age (both IEAA and PEAA) at 12-month postbirth and shortened leukocyte telomere length using the DNAm-based estimate of TL. These findings support the hypothesis that early postpartum sleep loss may accelerate epigenetic and cellular aging and that the early months of postpartum sleep deprivation could have a lasting effect on physical health. Sleep duration measured at 12-month postbirth was not significantly associated with any of the epigenetic age indicators, although findings with EEAA were of modest effect size (r = 0.26), and a larger sample may yield significant results. These initial findings in postpartum mothers need to be replicated before making strong conclusions. One possibility with null effects at 12 months is that insufficient sleep may not have an appreciable impact on estimates of epigenetic aging when assessed concurrently. Rather, the lasting impact of sleep may not be evidenced on biological markers of aging for several months, and a 1-time assessment concurrent to the biological age measure would only be

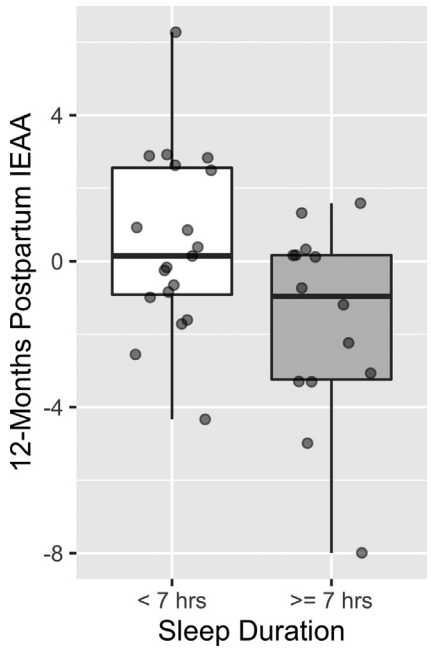

Fig. 1. Postpartum sleep duration at 6 months predicting 12-month postpartum Intrinsic Epigenetic Age Acceleration (IEAA), adjusting for batch, race/ethnicity, education, per capita household income, marital status, breastfeeding, and 12-month BMI.

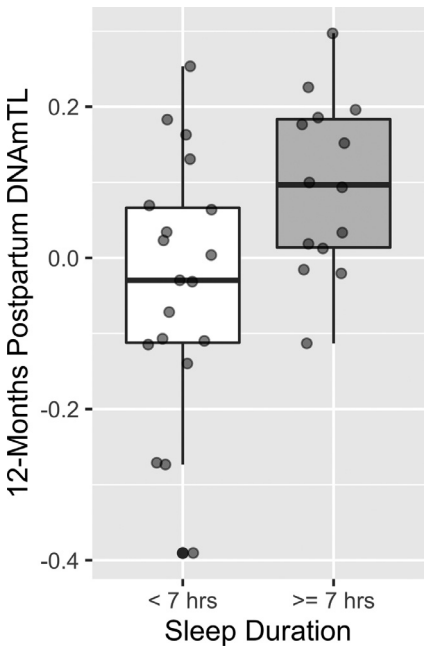

Fig. 3. Postpartum sleep duration at 6 months predicted DNAm telomere length at 12-month postpartum, adjusting for batch, race/ethnicity, education, per capita household income, marital status, breastfeeding, and 12-month BMI.

assessing sleep patterns at that specific time point, and not reflect the sleep duration of months prior to the assessment window.

Our findings linking sleep duration with IEAA are similar to cross-sectional effects observed in postmenopausal women,[16] and the association found here of sleep duration with PEAA is particularly novel. In prior research, PEAA estimates were predictive of aging-related disease and deterioration, suggesting that PEAA may be one of the more predictive indicator of biological age.[36] Likewise, PEAA may also represent an underlying aging signature such as DNA damage, inflammation, and mitochondrial alterations.[36] As sleep duration is vital for maintaining healthy daily functioning, a lack of sufficient sleep may inversely contribute to the accumulation of damage, thus accelerating the aging process. The findings that leukocyte telomere length, a hallmark of damage,[55] was also shorter among those with short sleep duration further supports the idea that damage accumulation is contributing to accelerated cellular aging. As for the other measures of epigenetic aging, EEAA partially reflects immune system aging;[16,56] given the sample in the current study is young, the immune system may not yet show aging in terms of immune cell exhaustion. GrimAge is a measure derived from its prognostic capacity to identify risk for mortality[37] and may not have been significantly related to sleep in the current sample as it might reflect later life aging not yet detectable in our cohort. Effect sizes for several of these indices were modest (see Supplemental Tables), and larger sample size might have yielded significant effects. Future research should replicate these results in a larger cohort of individuals experiencing ongoing restrictions to sleep duration to disentangle the causal models and mechanisms more precisely.

We did not observe any associations between poor sleep quality with any indices of epigenetic age acceleration tested here. These null findings are in contrast to a prior report linking insomnia symptoms with extrinsic epigenetic aging in a large sample of postmenopausal women.[16] Sample differences could also contribute to mixed results because the current sample consists of young adult women of reproductive age with poor sleep quality primarily due to children, while the prior study was with a sample of postmenopausal women with a high prevalence of nocturnal awakenings, likely caused by other factors such as frequent urination or hormonal changes and not necessarily driven by external factors. Poor sleep in the first year following birth of a child are normative, and the high prevalence in this population may reduce our ability to detect effects on biological aging due to the lack of variability. The possibility remains that chronic and severe sleep disturbance not captured with the PSQI may be detrimental to the mother's future health. Future work could consider tracking changes in epigenetic age over time, prior to postpartum changes in sleep quality and after a year of sleep disruption in parallel with similarly aged women with no sleep disruption.

Whether improvements in sleep quality and duration over the postpartum period and beyond might reverse the observed associations with epigenetic aging remains to be tested in a larger cohort with adequate power and additional sampling timeframes. Likewise, whether intervening to extend sleep duration might reverse epigenetic aging has yet to be tested, and future research should consider this important question.

Strengths and limitations

Several notable strengths of the current study design include the focus on postpartum sleep, a particularly understudied topic, within a well-characterized cohort together with the prospective design and novel measures of biological aging. Participants in this prospective cohort of mothers were studied over pregnancy and through 1 year after birth within a large urban southwestern area; however, no claim is made that it would be representative of the larger US population. Insufficient power limits our ability to reach significance with smaller effect sizes, increasing our chances of a type II error. Additional limitations include a lack of basal epigenetic age estimates, something that would need to be assessed prior to pregnancy, lack of objective measures of sleep including exclusion for sleep apnea, no measure of insomnia, and completion of the methylation arrays in 2 separate batches, which was adjusted for in models but may add additional error to the current effects. Further research should consider the plausible role of sleep apnea, ongoing problems with insomnia, or other sleep disorders that might contribute to the observed effects.

Summary

The current sample of young women studied following birth exhibit a high prevalence of poor sleep quality (64%) and short sleep duration (58%), due mainly to frequent night infant awakenings and feedings. We tested the hypothesis that postpartum sleep loss would predict greater epigenetic age acceleration. We found that 6-month postpartum sleep duration, but not poor sleep quality, predicted 12-month epigenetic aging indexed by IEAA and PEAA, and further, was related to shorter DNAmTL. Furthermore, cross-sectional analyses of self-reported poor sleep quality and sleep duration at 12 months was not related to epigenetic age acceleration at the same time point. These findings suggest that early postpartum sleep loss may be most potent as a contributor to accelerated biological aging.

Declaration of conflicts of interest

Co-author Steve Horvath is a founder of the non-profit Epigenetic Clock Development Foundation which plans to license several patents from his employer UC Regents for the computation of the epigenetic clocks. These patents list SH as inventor. The remaining authors have no conflicts to disclose.

Human subjects protections

The study was approved by the Institutional Review Boards at the University of California, Los Angeles and the Cedars Sinai Medical Center, and all protocols followed the Declaration of Helsinki.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sleh.2021.02.002.

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