

## POOR SLEEP QUALITY AND ASSOCIATED INFLAMMATION PREDICT PRETERM BIRTH

# Poor Sleep Quality and Associated Inflammation Predict Preterm Birth: Heightened Risk among African Americans

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**Study Objectives:** Poor sleep promotes inflammation. In turn, inflammation is a causal mechanism in term as well as preterm parturition. In the United States, a persistent racial disparity in preterm birth exists, with African Americans showing ~1.5 times greater risk. This study examined associations among sleep quality, serum proinflammatory cytokines, and length of gestation in a racially diverse sample of 138 pregnant women.

**Design:** Observational.

**Measurements:** Women completed the Pittsburgh Sleep Quality Index (PSQI) and other psychosocial and behavioral measures during midpregnancy. Serum levels of interleukin (IL)-6, IL-8, IL-1 $\beta$ , and tumor necrosis factor (TNF)- $\alpha$  were determined by high-sensitivity assays. Birth outcomes were determined via medical record review.

**Results:** Among African American women ( $n = 79$ ), shorter gestation was predicted by poorer overall sleep ( $r_s = -0.35$ ,  $P = 0.002$ ) as well the following PSQI subscales: subjective sleep quality ( $r_s = -0.34$ ,  $P = 0.002$ ), sleep latency ( $r_s = -0.27$ ,  $P = 0.02$ ), and sleep efficiency ( $r_s = -0.27$ ,  $P = 0.02$ ). African American women with poor sleep quality (PSQI > 5) had 10.2 times the odds of preterm birth compared to those with good sleep quality. In contrast, among European American women ( $n = 53$ ), gestational length was not significantly predicted by sleep quality ( $P_s > 0.12$ ). Bootstrapping analyses showed that, among African Americans, IL-8 significantly mediated the association between sleep quality and length of gestation (indirect effect estimate  $-0.029$ ; 95% confidence interval  $-0.06$ ,  $-0.002$ ).

**Conclusions:** The data provide novel evidence that African American women exhibit greater inflammation in response to sleep disturbance than European American women and these effects correspond with length of gestation. Racial differences in susceptibility to sleep induced immune dysregulation may contribute to marked racial disparities in preterm birth.

**Keywords:** African American, gestation, inflammation, race, sleep, pregnancy, preterm, proinflammatory cytokines, PSQI, race

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## INTRODUCTION

In the United States, preterm birth affects 11.5% of deliveries and is the underlying cause of more than one third of infant deaths.<sup>1</sup> A high proportion of surviving preterm infants suffer from severe physical and cognitive consequences, potentially requiring intensive medical and/or educational support throughout the lifespan.<sup>2</sup> The morbidity and mortality associated with preterm birth pose significant drains on the financial and emotional resources of afflicted families, and on the nation as a whole, costing more than \$26 billion annually in the United States.<sup>3</sup>

Inflammation is a causal mechanism in the initiation of preterm as well as term labor.<sup>4</sup> Inflammatory mediators can initiate contractions, encourage cervical ripening, and cause rupture of the membranes.<sup>4,5</sup> Via these mechanisms, inflammation induced by infection or psychological stress may trigger early parturition.<sup>6,7</sup>

Importantly, poor sleep promotes inflammation.<sup>8</sup> For example, in a population-based cohort of more than 5,000 adults, shorter sleep duration was associated with elevations in

interleukin (IL)-6 and C-reactive protein (CRP).<sup>9</sup> Supporting the causal role of poor sleep in such associations, various studies of experimentally induced sleep restriction show resulting increases in circulating inflammatory mediators.<sup>10–12</sup> Notably, the deleterious inflammatory effects of poor sleep appear to be stronger among women than men.<sup>13,14</sup>

In the context of pregnancy, poor sleep quality has been implicated as a risk factor for preterm birth.<sup>15–18</sup> It has been postulated that inflammation may play a causal role in this association.<sup>19,20</sup> Studies to date on sleep and pregnancy outcome have focused primarily on non-Hispanic White and/or Hispanic populations. However, African American women experience preterm birth approximately 1.5 times the rate of European Americans.<sup>21</sup> Moreover, racial differences in sleep have previously been documented, with African Americans showing poorer sleep quality than European Americans, even after adjusting for indicators of socioeconomic status.<sup>22</sup> Thus, representation of African American women in this literature is of importance.

The current study examined associations among sleep quality, serum proinflammatory markers, and length of gestation in a racially diverse sample of 138 women who were assessed in midpregnancy. We focused on the proinflammatory cytokines IL-6, TNF- $\alpha$ , IL-8, and IL-1 $\beta$  based on prior studies linking these markers to sleep quality and/or pregnancy outcomes.<sup>9,11,19</sup> We examined gestational age at delivery as a continuous variable, as well as categorically defined as preterm, early term, term, late term, and postterm per guidelines from the American College of Obstetricians and Gynecologists

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(ACOG).<sup>23</sup> It was hypothesized that (1) poorer sleep quality would be associated with shorter gestation, measured continuously as well as categorically; (2) the relationship between sleep quality and length of gestation would be partially mediated by elevations in serum proinflammatory markers; and (3) the relationship between sleep quality and length of gestation would be moderated by race, with stronger associations among African American women compared to European Americans.

## METHODS

### Study Design

This secondary data analysis used a combined dataset from two concurrent studies examining different aspects of health and risk in pregnancy. Participants for both studies were recruited from The Ohio State University Wexner Medical Center and the surrounding community of Columbus, OH. Both studies were approved by The Ohio State University Biomedical institutional review board. All participants completed informed consent and privacy notifications and received modest compensation for participation.

The first study was a cross-sectional observational design that examined relationships among periodontal disease, race, and the effects of stress among 101 women assessed in mid-pregnancy. The second study examined 56 pregnant women in a longitudinal manner, with assessments during each trimester of pregnancy. For the current analyses, data from the second trimester were used to correspond to the timing of assessment of the first cohort. Thus, eight women who had missing data at the second trimester visit were excluded. In addition, 11 women participated in both protocols; their data were used only once, resulting in a final sample of 138 women.

Exclusion criteria for both samples included chronic health conditions or medications with implications for immune function (including progesterone), diagnosed fetal anomaly, antidepressant use, illicit drug use other than marijuana, or more than two alcoholic beverages per week during pregnancy (per self-report or medical record at time of enrollment). Any woman who reported acute illness (cold- or flu-like symptoms) or antibiotic use within 10 days was rescheduled.

### Demographics

Age, race/ethnicity, education, annual family income, gravidity, and parity were collected by self-report. Prepregnancy body mass index (BMI; kg/m<sup>2</sup>) was calculated using self-reported prepregnancy weight and height measured at the first visit. Gestational age at delivery was determined by medical record review. Gestational age at delivery was examined as a continuous variable. In addition, births were classified as full term ( $\geq 39$  w), early term (37 w, 0 days – 38 w, 6 days), or preterm ( $< 37$  w) based on guidelines from ACOG.<sup>23</sup>

### Psychosocial and Behavioral Measures

Sleep quality was assessed by self-report using the PSQI.<sup>24</sup> A score  $> 5$  is indicative of clinically disturbed sleep. This measure includes seven subscales: subjective sleep quality, sleep latency (time to fall asleep), sleep duration, habitual sleep efficiency (time asleep/time in bed), sleep disturbance, use of sleeping medications, and daytime dysfunction. The PSQI has

high diagnostic sensitivity and specificity in distinguishing good and poor sleepers.<sup>24</sup> Global scores as well as subscale scores show high test-retest reliability across short intervals in adults with insomnia.<sup>25</sup>

The Center for Epidemiological Studies Depression Scale (CES-D) was used to assess depressive symptoms.<sup>26</sup> This is a 20-item measure with high internal consistency. Scores  $\geq 16$  indicate clinically significant depressive symptoms. The 10-item Perceived Stress Scale (PSS) is a well-validated measure that assesses a construct independent of depressive symptomatology.<sup>27</sup> The Revised Prenatal Distress Questionnaire (NUPDQ) is a 17-item measure of pregnancy-specific distress including physical discomforts, financial resources to care for children, and pain during delivery.<sup>28</sup> Finally, women completed the Prenatal Health Behaviors Scale (PHBS), a 24-item measure assessing seven domains of health behaviors.<sup>29,30</sup>

### Serum Proinflammatory Cytokines

Serum levels of IL-6, TNF- $\alpha$ , IL-8, and IL-1 $\beta$  were assayed in duplicate with ultra-sensitive multiplex kits from Meso Scale Discovery (MSD) and electrochemiluminescence methodology using the Sector Imager 2400 (Meso Scale Discovery, 9238 Gaithers Rd., Gaithersburg, Md). Limits of detection were 0.61 pg/mL for IL-6, 2.4 pg/mL for TNF- $\alpha$ , 0.3 pg/mL for IL-8, and 0.61 pg/mL for IL-1 $\beta$ . All values were above the limits of detection. Intra-assay coefficients of variation (CVs) were between 5.21 to 10.66 and the interassay CVs were between 8.4 to 11.17. All samples from the same participant were batched together and assayed on the same plate. Assays for the two studies were conducted at the same time and all plates were from the same lot. Nonfasting blood samples were collected between 8:00 and 16:00 with 63% sampled before 12:00.

### Statistical Analyses

All statistical analyses were conducted using SAS/STAT software version 9.3 (Cary, NC). Demographic characteristics were summarized by means and standard deviations for continuous variables and number and percent for categorical variables, both overall and by race. Differences in participant characteristics by race were assessed using *t* tests for continuous and chi-square tests for categorical variables.

Spearman correlation coefficients (denoted by  $r_s$ ) between gestational age at birth and sleep quality (as indicated by the total PSQI score and subscales) were calculated in the full sample and separately by race (African American and European American). One participant who identified as multiracial without indicating specific races, one Asian, and four Hispanics (one White and three Black) were excluded from analyses by racial subgroup. Spearman correlation coefficients were also calculated between proinflammatory markers and gestational age, and between proinflammatory markers and sleep quality.

Logistic regression models were fit to the outcome of giving birth preterm ( $< 37$  w gestation) and giving birth early term (37 to  $< 39$  w versus full term 39 to  $< 41$  w), with sleep quality and inflammatory markers as the predictors in the models. We adjusted for demographic and psychosocial covariates, selected by the risk factor modeling approach. Covariates were kept in the model if their addition changed the model coefficient for the main risk factor (predictor) by 15% or more.

**Table 1**—Demographic characteristics by race.

	African American (n = 79)	European American (n = 53)	Total (n = 138)
Age, mean (SD)	24.0 (3.9)	23.6 (4.5)	23.8 (4.1)
BMI, mean (SD)	29.1 (8.0)	27.5 (8.5)	28.4 (8.1)
Weeks gestation at assessment	23.1 (2.3)	23.0 (2.6)	23.0 (2.4)
Primigravida	14 (17.7%)	11 (20.8%)	28 (20.3%)
Nullipara	20 (25.3%)	17 (32.1%)	40 (29.0%)
Annual household income			
< \$15,000	57 (72.2%)	30 (56.6%)	89 (64.5%)
\$15,000–\$29,999	20 (25.3%)	13 (23.5%)	37 (26.8%)
\$30,000 or above	2 (2.5%)	10 (18.9%)	12 (8.7%)
Educational attainment			
Some secondary school	22 (27.9%)	11 (20.8%)	33 (23.9%)
High school graduate	26 (32.9%)	11 (20.8%)	39 (28.3%)
Some college	28 (35.4%)	27 (50.9%)	58 (42.0%)
College graduate	3 (3.8%)	4 (7.6%)	8 (5.8%)
Length of gestation, mean (SD)	38.8 (1.7)	39.3 (1.4)	39.0 (1.6)
Preterm birth (< 37 w)	9 (11.4%)	3 (5.7%)	12 (9.1%)

European American women had significantly higher household income than African American women ( $X^2(2) = 10.5, P = 0.01$ ). No other significant differences in demographics between African Americans and European Americans were observed. SD, standard deviation.

**Table 2**—Sleep and psychological factors by race.

	African American (n = 79)	European American (n = 53)	Total (n = 138)
Sleep quality			
Total score, mean (SD)	6.7 (3.9)	7.2 (3.3)	6.9 (3.7)
Clinically disturbed sleep	46 (56.1%)	32 (57.1%)	78 (56.5%)
Sleep subscales, mean (SD)			
Subjective quality	1.1 (0.8)	1.3 (0.7)	1.2 (0.8)
Sleep latency	1.2 (1.0)	1.3 (0.9)	1.3 (1.0)
Sleep duration	0.8 (0.9)	0.8 (0.9)	0.8 (0.9)
Sleep efficiency	1.0 (1.1)	1.1 (1.2)	1.0 (1.1)
Sleep disturbance	1.5 (0.6)	1.5 (0.5)	1.5 (0.6)
Sleep medication	0.3 (0.8)	0.1 (0.6)	0.2 (0.7)
Daytime dysfunction	0.8 (0.7)	1.0 (0.7)	0.9 (0.7)
Depressive symptoms, mean (SD)	13.8 (11.4)	15.1 (9.9)	14.4 (10.7)
Clinically significant symptoms	29 (35.4%)	23 (41.1%)	52 (37.7%)
Perceived stress, mean (SD)	16.1 (8.0)	17.4 (5.7)	16.9 (7.1)
Pregnancy-specific distress, mean (SD)	0.5 (0.3)	0.6 (0.4)	0.6 (0.4)

Wilcoxon rank sum and chi-square tests showed no significant differences between African American and European American women on sleep or psychological factors. SD, standard deviation.

Potential mediating effects of cytokines found to be significantly correlated with both gestational age and sleep quality were tested. Mediation in this model was defined as the indirect effect, which is the product (ab) of (a) the coefficient for the regression of cytokine levels on sleep quality and (b) the coefficient for the regression of gestational age on cytokine levels.<sup>31</sup> Formal tests of the indirect effect were performed using a bootstrapping resampling method to estimate the indirect effect and construct corresponding 95% confidence intervals (CIs) (<http://www.processmacro.org>).

The mediation effect is significant if the 95% CI does not include zero. Ten thousand bootstrapping samples were drawn for each analysis. Sleep subscales were not examined in the mediation analysis.

## RESULTS

### Sample Characteristics

Demographics, sleep, psychological characteristics, and serum cytokine levels are summarized in Tables 1, 2,

**Table 3**—Serum cytokine levels.

	African American (n = 79)	European American (n = 53)	Total (n = 138)
IL-6	1.7 (1.0)	2.1 (1.9)	1.9 (1.4)
TNF- $\alpha$	10.0 (3.4)	10.0 (2.8)	10.0 (3.2)
IL-8	5.3 (3.0)	4.7 (1.7)	5.0 (2.6)
IL-1 $\beta$	0.8 (0.8)	0.6 (0.4)	0.7 (0.6)

Values presented as mean (standard deviation) in pg/mL. IL, interleukin; TNF, tumor necrosis factor.

**Table 4**—Associations between weeks gestation at birth and sleep quality.

	African American (n = 79)	European American (n = 53)	Total (n = 138)
Sleep quality (PSQI measures)			
Total score	-0.35**	-0.13	-0.22*
Sleep Subscales			
Subjective quality	-0.34**	0.08	-0.15
Sleep latency	-0.27*	-0.15	-0.22*
Sleep duration	-0.18	-0.07	-0.12
Sleep efficiency	-0.27*	-0.22	-0.22*
Sleep disturbance	-0.22	-0.06	-0.05
Sleep medication	-0.09	-0.13	-0.08
Daytime dysfunction	-0.21	-0.02	-0.10

Spearman correlations \*\*P < 0.01, \*P < 0.05. PSQI, Pittsburgh Sleep Quality Index.

and 3. Women were assessed between 19–30 w gestation (mean = 23.0  $\pm$  2.4) and were 18–35 y of age (mean = 23.8  $\pm$  4.1). The sample was 57% African American and predominantly from lower socioeconomic backgrounds, with 91% reporting an annual household income < \$30,000. As shown in Tables 1 and 2, African Americans and European Americans were highly similar in terms of demographics, sleep quality, and psychological characteristics, although European Americans had higher household incomes ( $X^2(2) = 10.5, P = 0.01$ ).

### Sleep Quality and Length of Gestation

In the full sample, poorer overall sleep quality (PSQI total score) was associated with shorter gestational age at delivery ( $r_s = -0.22, P = 0.01$ ; Table 4). Analyses of subscales indicated that both greater sleep latency ( $r_s = -0.22, P = 0.01$ ) and poorer sleep efficiency ( $r_s = -0.22, P = 0.01$ ) predicted shorter gestation.

### Sleep Quality and Birth at Full Term, Early Term, and Preterm

Using the risk factor modeling approach, each model below adjusted for age. Women reporting poor quality sleep (PSQI > 5) had higher odds [odds ratio, OR = 4.11 (95% CI = 1.04, 16.25),  $P = 0.04$ ] of giving birth preterm (< 37 w gestation). In a model with sleep as a continuous variable (total PSQI), the odds of preterm birth increased 1.37 times (95% CI = 1.15, 1.64,  $P = 0.001$ ) with each unit increase in PSQI. Sleep quality (total PSQI) was not significantly associated with early term birth compared to full term birth [OR = 1.05 (0.94, 1.18),  $P = 0.38$ ]. The mean PSQI total score was 9.9 in preterm, 6.8 in early-term, and 6.3 in full-term births.

### Sleep Quality and Serum Proinflammatory Cytokines

Analyses of sleep quality and serum proinflammatory cytokines showed that poor sleep quality predicted higher serum IL-8 ( $r_s = 0.23, P = 0.01$ ). Examination of subscales demonstrated that shorter sleep duration ( $r_s = 0.17, P = 0.04$ ), worse sleep efficiency ( $r_s = 0.29, P < 0.001$ ), and greater sleep disturbance ( $r_s = 0.21, P = 0.01$ ) were each predictive of higher IL-8.

Total PSQI scores were not associated with serum IL-6 ( $r_s = 0.04, P = 0.63$ ); however, contrary to prediction, greater sleep latency predicted lower IL-6 ( $r_s = -0.17, P = 0.05$ ). No associations were observed between sleep quality and either TNF- $\alpha$  or IL-1 $\beta$  ( $|r_s| \leq 0.14, P \geq 0.12$ ).

### Serum Proinflammatory Cytokines and Length of Gestation

In the overall sample, higher IL-8 predicted shorter gestation ( $r = -0.22, P = 0.01$ ; Table 5). For each unit increase in IL-8, the odds of preterm birth were 1.23 time higher (95% CI: 1.04, 1.44,  $P = 0.01$ ). IL-8 was not significantly associated with risk of early term birth versus full term birth [OR = 1.12 (95% CI = 0.95, 1.34),  $P = 0.18$ ]. No significant associations between other proinflammatory mediators and length of gestation were observed ( $r_s \leq 0.11, P_s \geq 0.19$ ).

### Demographic and Psychological Correlates

To ensure that observed effects of sleep were not better accounted for by demographic or behavioral covariates of sleep, we examined potential confounds. BMI, income, and education were not significantly associated with IL-8 ( $P_s > 0.22$ ) or sleep quality ( $P_s > 0.07$ ). Poorer sleep quality (total PSQI score) was associated with greater depressive symptoms ( $r_s = 0.49, P < 0.001$ ), greater perceived stress ( $r_s = 0.27, P = 0.01$ ), greater

**Table 5**—Associations of interleukin-8 with gestational age and sleep quality.

	African American (n = 79)	European American (n = 53)	Total (n = 138)
Gestational age at birth	-0.39***	-0.12	-0.22*
Sleep quality (PSQI measures)			
Total score	0.30**	0.13	0.23*
Sleep subscales			
Subjective quality	0.16	-0.12	0.05
Sleep latency	0.17	0.10	0.10
Sleep duration	0.15	0.21	0.17*
Sleep efficiency	0.23*	0.40**	0.29***
Sleep disturbance	0.35**	-0.07	0.21*
Sleep medication	0.06	0.01	0.04
Daytime dysfunction	0.20	-0.26	0.03

Spearman correlations \*\*\*P < 0.001, \*\*P < 0.01, \*P < 0.05.

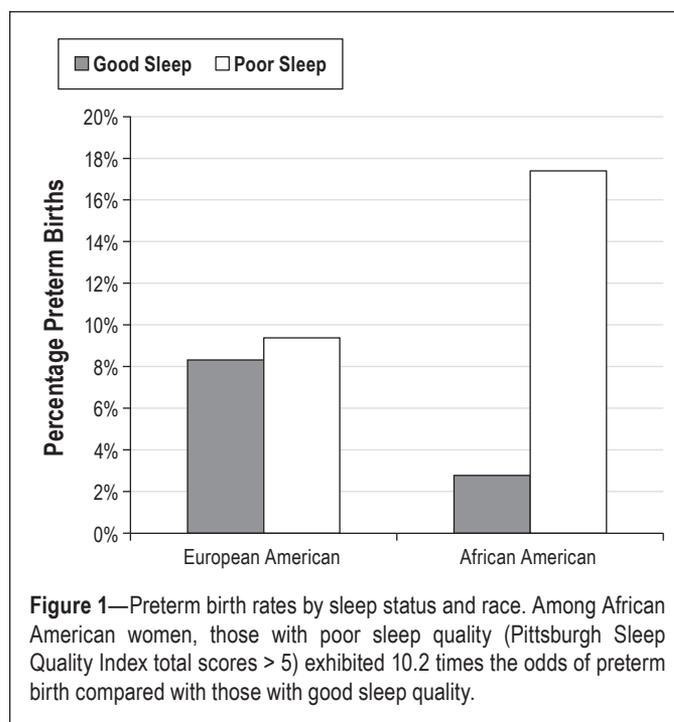
prenatal distress ( $r_s = 0.26$ ,  $P = 0.02$ ), and one subscale on the PHBS indicating less use of prenatal vitamins ( $r_s = -0.19$ ,  $P = 0.04$ ). Depressive symptoms, perceived stress, prenatal distress, and prenatal vitamin use were considered for inclusion in the risk factor model, but none met the criteria for inclusion (i.e., they did not change the model coefficient by 15% or more). In addition, none of these measures were significantly associated with IL-8: depressive symptoms ( $r = 0.05$ ,  $P = 0.57$ ), perceived stress ( $r = 0.01$ ,  $P = 0.94$ ), prenatal distress ( $r = -0.10$ ,  $P = 0.26$ ), or prenatal vitamin use ( $r = -0.11$ ,  $P = 0.25$ ).

### Mediation Analyses

*Post hoc* analyses were performed to examine IL-8 as a possible mediator of the association between sleep quality and gestational age at delivery. IL-8 was found to have a significant mediation effect between sleep quality and length of gestation. Specifically, controlling for age, the bootstrapped indirect effect estimate was  $-0.021$  (95% CI =  $-0.045$ ,  $-0.001$ ). Analyses using preterm birth as a dichotomous outcome variable yielded an indirect effect estimate of  $0.020$  (95% CI =  $-0.017$ ,  $0.067$ ). IL-8 was not a significant mediator in this model.

### Effects of Race

Analyses were next conducted separately for African Americans and European Americans. When examined by racial subgroups, significant associations between poor sleep quality and shortened gestation were observed among African Americans but not European Americans (Table 4). Specifically, among African American women, shorter gestation was predicted by poorer overall sleep ( $r_s = -0.35$ ,  $P = 0.002$ ) as well as the following subscales: poorer subjective sleep quality ( $r_s = -0.34$ ,  $P = 0.002$ ), greater sleep latency ( $r_s = -0.27$ ,  $P = 0.02$ ), and poorer sleep efficiency ( $r_s = -0.27$ ,  $P = 0.02$ ). Among African American women, adjusting for age, those with poor sleep quality (PSQI > 5) had 10.2 (95% CI = 1.1, 91.9,  $P = 0.04$ ) times the odds of preterm birth compared to those with good sleep quality, whereas among European American the odds were 1.6 times higher in those with poor sleep quality (95% CI = 0.2, 11.2,  $P = 0.63$ ) (Figure 1). Compared to full term, early-term birth occurred with 2.3 times higher odds in African American women with poor



sleep quality compared to those with good sleep quality (95% CI = 0.8, 6.2,  $P = 0.12$ ). Among European American women, gestational age examined continuously was not significantly predicted by overall sleep quality ( $r_s = -0.13$ ,  $P = 0.36$ ) or any of the PSQI subscales (subjective sleep quality  $r_s = 0.08$ ,  $P = 0.56$ ; sleep latency  $r_s = -0.15$ ,  $P = 0.30$ ; sleep duration  $r_s = -0.07$ ,  $P = 0.64$ ; sleep efficiency  $r_s = -0.21$ ,  $P = 0.12$ ; sleep disturbance  $r_s = 0.06$ ,  $P = 0.66$ ; sleep medication  $r_s = -0.02$ ,  $P = 0.91$ ; daytime dysfunction  $r_s = -0.13$ ,  $P = 0.36$ ), nor was gestational age examined categorically (overall sleep quality  $P = 0.24$ ; subjective sleep quality  $P = 0.90$ ; sleep latency  $P = 0.92$ ; sleep duration  $P = 0.32$ ; sleep efficiency  $P = 0.09$ ; sleep disturbance  $P = 0.60$ ; sleep medication  $P = 0.15$ ; daytime dysfunction  $P = 0.14$ ). Similarly, when split by race, a significant association between overall sleep quality and IL-8 was present among African American women ( $r_s = 0.30$ ,  $P = 0.01$ ) but not European Americans ( $r_s = 0.13$ ,  $P = 0.35$ ; Table 5).

Based on these results, mediation analyses conducted in the full sample were repeated among African Americans. Consistent with results in the full sample, controlling for age, IL-8 significantly mediated the association between sleep quality and length of gestation as a continuous variable (indirect effect estimate  $-0.027$ ; 95% CI  $-0.065, -0.004$ ). However, no significant mediating effect of IL-8 was observed using preterm birth as a dichotomous variable (indirect effect estimate  $0.034$ ; 95% CI  $= -0.007, 0.140$ ).

## DISCUSSION

This study examined whether poor sleep quality predicted shorter length of gestation, and the possible mediating role of inflammation in this association, in a racially diverse sample of 138 pregnant women. We found that poor sleep quality was significantly associated with shorter gestation overall, as well as greater risk of preterm birth ( $< 37$  w gestation). In addition, a significant mediating role of IL-8 in the association between poor sleep quality and shorter gestation was evidenced when gestational age at delivery was used as a continuous variable.

Notably, significant associations among sleep quality, IL-8, and length of gestation in the overall sample were driven by effects in African American women. When European Americans and African Americans were examined in separate groups, statistically significant associations were observed only among the African Americans. Among African American women, those with poor sleep quality (PSQI  $> 5$ ) had 10.2 times the odds of preterm birth compared to those with good sleep quality. Further, among African American women, IL-8 significantly mediated the association between sleep quality and length of gestation. Importantly, likely reflecting the demographic similarity of the groups, no significant differences in sleep quality were observed by race. Thus, despite similar overall quality of sleep between groups, disturbed sleep had more robust associations with both inflammatory mediators and birth outcomes among African Americans versus European Americans.

These data provide novel evidence that African Americans may exhibit heightened sensitivity to the adverse physiological sequelae of sleep disturbance. This notion is consistent with prior data; for example, in a cross-sectional study of  $> 30,000$  adults, the association between short sleep duration and cardiovascular disease was larger among non-Hispanic Blacks versus non-Hispanic Whites.<sup>32</sup> Similarly, prior data from our group show that, during pregnancy as well as nonpregnancy, African American women show substantially greater inflammatory responses than Whites following exposure to acute psychological stress.<sup>33</sup> Racial differences in susceptibility to sleep induced immune dysregulation may contribute to the marked racial disparity in preterm birth in the United States.

Of note, our results showed that poor sleep in pregnancy was associated with increased risk of preterm birth, but not early term delivery. In their Committee Opinion in 2013, the ACOG emphasized that although the most severe complications occur in babies who are born preterm (prior to 37 w gestation), early-term births (occurring between 37 w, 0 days and 38 w, 6 days gestation) are also not ideal.<sup>23,34</sup> Compared to full-term births, early-term births are characterized by increased risk of neonatal mortality and morbidities including respiratory distress

syndrome, ventilator use, and neonatal intensive care unit admissions.<sup>34–38</sup> Thus, factors that shift delivery timing even in a relatively subtle manner can have a clinically meaningful effect on neonatal outcomes.

As noted, no significant association between sleep and early-term birth was observed in this investigation. However, a mediating effect of IL-8 was only observed with gestational age as a continuous variable. Thus, utilization of the full continuous range of data increased statistical power. This suggests that early-term deliveries contributed to the observed links between poor sleep quality, inflammation, and gestational age at delivery. Continued attention to early-term versus full-term deliveries in future research will enhance the precision of our understanding.

In this study, sleep was assessed in midpregnancy. Subjective as well as objective characteristics of sleep change across gestation. For example, greater sleep duration is commonly observed in the first trimester and poorer sleep quality is more common in late pregnancy.<sup>39–42</sup> However, sleep quality shows within-person consistency; poor sleepers early in gestation tend to also be poor sleepers at mid and late gestation. Thus, although women were assessed in midpregnancy, poor sleep may have exerted the strongest mechanistic effects on birth outcomes at a different stage. For example, sleep disruption in early or late pregnancy may be particularly detrimental because placental development and preparation for birth occur during these periods.<sup>16</sup>

As described, multiple associations between IL-8 and sleep quality as well as shorter gestation were observed. The particular relevance of IL-8 in this context is unknown. Okun and colleagues<sup>41</sup> reported an association between shorter sleep duration and higher serum IL-8 in depressed pregnant women assessed at 20 and 30 w gestation. In addition, elevated serum IL-8 has repeatedly been observed in relation to obstructive sleep apnea.<sup>43</sup> In relation to birth outcomes, elevated serum, intra-amniotic, and cervical IL-8 has been associated with preterm as well as term parturition.<sup>44–47</sup> IL-8, a chemokine, is a potent chemoattractant implicated in endothelial dysfunction.<sup>48</sup> As such, IL-8 plays an important role in the development of atherosclerosis and is implicated in risk of cardiovascular events.<sup>49</sup> Importantly in the context of pregnancy, placental blood flow has been implicated in risk for preterm delivery, as has maternal endothelial dysfunction.<sup>50–52</sup> Thus, although not testable in the current investigation, vascular effects present a potential mechanistic link by which sleep induced elevations in IL-8 may affect birth timing.

The lack of expected associations with other markers is notable. This may be attributable, in part, to the timing of assessment. Cytokine levels change across the course of pregnancy, with different trajectories across markers.<sup>53,54</sup> The association between sleep quality and specific inflammatory markers may likewise vary, highlighting the utility of longitudinal assessment in studies of this type. In addition, as described, in this study blood draws occurred between 08:00 and 16:00. Diurnal variations in serum cytokines occur.<sup>55</sup> Thus, the magnitude of our findings may have been weakened by this variability in the data. In addition, conditions of sleep deprivation can result in shifts in typical diurnal patterns. As multiple sampling timepoints in the same day were not used, this study could

not capture such potential shifts.<sup>55</sup> Finally, other studies have demonstrated effects of poor sleep quality and short sleep duration on stimulated cytokine production as well as cytokine responses to acute stress.<sup>54,56</sup> Thus, other associations may have become apparent if a different approach to assessing inflammatory processes had been used.

Prior studies have linked psychosocial variables including perceived stress, depressive symptoms, and pregnancy-specific distress or anxiety to preterm birth. We did not observe such associations in this sample. Moreover, behavioral correlates of sleep did not appreciably alter the observed relationships between sleep and birth outcomes and thus were not included in our models. Although not observed in this dataset, the possibility remains that sleep may serve as a mediator in the relationship between psychological distress and length of gestation. In addition, psychosocial factors may serve as important moderators; for example Okun et al.<sup>19</sup> reported differences in the association between sleep and proinflammatory cytokines based on depression status. Such moderating effects of psychosocial factors could not be reliably tested in this dataset given the sample size and marked moderating effects of race present.

The current study used self-reported sleep quality, using the PSQImonth, a measure with excellent psychometric properties. This approach has clinical relevance; questionnaire assessment is quick and inexpensive and therefore potentially feasible to implement as a clinical screening tool. Moreover, subjective reports of sleep quality and duration have strong predictive validity for a variety of health outcomes in pregnant as well as non-pregnant samples.<sup>57-60</sup> However, self-rated sleep quality is weakly and inconsistently associated with objective measures such as polysomnography and wrist actigraphy.<sup>61</sup> Objective versus subjective methods capture different and complementary aspects of poor sleep as a construct.

This study focused on pregnant African American and European American women who were predominantly from lower socioeconomic backgrounds. The effects of sleep disturbance may be stronger among lower socioeconomic status groups than the general population due to greater prevalence of sleep disturbance and the additional effect of chronic stress associated with poverty. Thus, generalizability to the larger population is unknown. Relatedly, reflecting our exclusion criteria, this sample had better birth outcomes than seen in the US population overall; for example, only 8% of African Americans delivered preterm, compared to 16–17% in the United States. In addition, power to detect effects was stronger among African Americans versus European Americans due to a slightly larger sample of African Americans as well as higher rates of preterm birth in this group. Our primary analyses used gestational age as a continuous variable, enhancing statistical power. However, a larger overall sample with higher rates of preterm birth would provide the best indication of effects in both groups.

Of note, a key factor that resulted in relatively low rates of preterm birth in this sample was the exclusion of women receiving therapeutic progesterone. This is recommended to women with a history of spontaneous preterm birth, among whom the relative risk of subsequent preterm is 5.64.<sup>62</sup> Inclusion of these women in larger future studies would increase the

overall rate of preterm birth. It could also be information from an empirical standpoint; as progesterone is anti-inflammatory, it could speculatively counteract the inflammatory effects of poor sleep.

With regard to interventions targeting sleep disturbance, cognitive behavioral therapy for insomnia (CBT-I) is a highly effective and evidence-based treatment.<sup>63</sup> A behavioral approach is particularly appropriate for pregnant women, for whom it is desirable to avoid pharmacological therapy. However, a common component of traditional CBT-I is sleep restriction; this technique promotes sleepiness at bedtime, thereby reducing sleep latency and increasing sleep efficiency. Given the inflammatory effects of sleep restriction, as well as possible short-term increases in daytime sleepiness and decreases in psychomotor vigilance,<sup>64</sup> the potential risks of sleep restriction should be weighed against the benefits in pregnant women. Components of CBT-I including stimulus-control therapy, relaxation training, and cognitive restructuring can be effective without the addition of sleep restriction.<sup>65</sup>

In summary, these data support and extend a growing literature linking poor maternal sleep to adverse perinatal health outcomes, including preterm birth but also fetal growth restriction, gestational diabetes, gestational hypertension, longer labor, increased cesarean delivery, and risk for postpartum depression.<sup>57</sup> This study provides novel evidence that the deleterious effects of sleep on length of gestation are more pronounced among African Americans versus European Americans. The role of race in the association between poor sleep and other adverse perinatal health outcomes should be considered in future studies. Moreover, identification and treatment of poor sleep during pregnancy deserves clinical attention, as healthy sleep stands to benefit both maternal and child health.

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