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Sleep disturbances and inflammatory gene expression among pregnant women: Differential responses by race

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A B S T R A C T

Excessive inflammation in pregnancy predicts adverse birth outcomes, including shortened gestational length and lower birthweight, with African American women at greater risk. As substantial racial disparities in sleep quality, and evidence that African Americans have increased vulnerability for sleep-induced inflammatory dysregulation, sleep may be a critical, modifiable health behavior that contributes to racial disparities in birth outcomes. The present study examined sleep disturbance as a predictor of genome-wide transcriptome profiles of peripheral blood samples from 103 pregnant women (33 African American, 70 white) assessed at 18.7 ± 7.2 weeks gestation. We hypothesized that pregnant women with significant sleep disturbances would have gene expression profiles indicating over-expression of inflammatory pathways, with greater effects among African American compared to white women. Promoter-based bioinformatics analyses of differentially expressed genes indicated greater activation of NF-κB, AP1, and CREB transcription factors among African American women with sleep disturbances (all $p < 0.05$), and enhanced activation of AP1, but not NF-κB and reduced CREB activity among white women with sleep disturbances ($p < 0.05$). Differences in glucocorticoid receptor (GR) activity were also observed, in which African American women with sleep disturbances had reduced GR activity ($p < 0.05$), but white women with sleep disturbances showed a trend for enhanced GR activity ($p = 0.11$). Similarly, Interferon Response Factor (IRF) activity was reduced in African American women while increased in white women with sleep disturbances ($p < 0.05$). The current study provides novel evidence for gene expression related to inflammation, glucocorticoids, and anti-viral immunity among pregnant women with sleep disturbances, with differential effects by race. African Americans showed greater breadth and magnitude in these proinflammatory and anti-viral pathways than whites, with divergence in anti-inflammatory glucocorticoid, proinflammatory adrenergic-mediated cAMP, and anti-viral interferon responses. These data elucidate the role of sleep disturbances in intracellular inflammatory and anti-viral immunity in pregnancy and provide a potential target for intervention.

1. Introduction

During pregnancy, the maternal immune system undergoes substantial changes to support fetal development. Overall, pregnancy is characterized by enhanced inflammation, including elevations in serum levels of proinflammatory cytokines and greater ex-vivo LPS-stimulated cytokine production (Gillespie et al., 2016; Christian and Porter, 2014). However, excessive inflammation may be detrimental to sustaining a healthy pregnancy; preterm delivery has been linked with elevations in proinflammatory cytokines in maternal serum and amniotic fluid (Dizon-Townson, 2001; Romero et al., 1990; Romero et al., 1993; Romero et al., 1993; Murtha et al., 2007), and with elevated expression of proinflammatory transcription factors NF-κB and AP1 in circulating leukocytes (Ross et al., 2019). One pathway through which this proinflammatory environment is thought to promote early birth is by triggering contractions, cervical ripening, and rupture of the membranes (Hagberg et al., 2005; Romero et al., 2006). Identification of contributors to inflammation during pregnancy will help target interventions to reduce risk for birth prior to full term. One contributing factor may be poor quality of sleep in pregnancy.

Sleep disturbances have been identified as risk factors for poorer physical health in non-pregnant individuals, and growing evidence suggests a critical role for sleep in perinatal health, including mental and physical outcomes, with inflammation as a key mediator (Christian et al., 2019; Carroll et al., 2019; Irwin et al., 2016; Okun and Coussons-Read, 2007; Okun et al., 2007; Taveras et al., 2011; Blair et al., 2015; Christian et al., 2018; Christian et al., 2016). Our prior data demonstrate that sleep disturbance during pregnancy as well as postpartum is linked with inflammation, including elevations in serum cytokines and exaggerated proinflammatory cytokine production upon ex-vivo

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stimulation of cells with lipopolysaccharide (LPS) (Blair et al., 2015; Christian et al., 2018; Christian et al., 2016). Notably, our data also link these inflammatory sequelae of poor sleep with increased risk for shortened gestation (Blair et al., 2015; Christian et al., 2016). Further, African American women exhibit greater inflammation than white women upon exposure to similar levels of poor sleep, indicating enhanced physiological responses (Blair et al., 2015; Christian et al., 2018; Christian et al., 2016). The current study extends this work to examine intracellular signaling pathways for inflammation associated with sleep disturbances, as well as the counter regulatory (i.e., anti-inflammatory) response initiated through the glucocorticoid receptor. While acute episodes of sleep deprivation have been shown to activate intracellular inflammatory responses in healthy male and female adults (Irwin et al., 2006; Irwin et al., 2010; Carroll et al., 2015), associations of sleep disturbance with inflammatory signaling have not been evaluated in pregnancy.

Another important consideration is that prior studies of racial disparities in perinatal health have generally failed to link differential health outcomes to genetic variants. Instead, there is growing clinical consensus that, as forwarded by the long-standing "weathering hypothesis" (Geronimus, 1992), the psychosocial stress of living in the U.S. as a racial minority plays the predominant role in observed racial disparities. Thus, consistent with the weathering hypothesis, we forward that enhanced vulnerability to negative physiological responses upon exposure to poor sleep is due to enhanced physiological burden related to chronic stressor exposure among African Americans (Christian, in press; Christian, in press).

Racial disparities in birth outcomes in the U.S. are substantial, with 40.5% of births among African Americans occurring prior to full term (13.1% preterm and 27.5% early term) compared to 33.1% of whites (8.9% preterm and 24.2% early term) (Centers for Disease Control. CDC Natality Information: Natality for, 2017). These racial disparities in shortened gestation are not adequately explained by socioeconomic factors, alcohol use, smoking, maternal infection, or access to prenatal care (Okun et al., 2005; Carey et al., 2000; Goldenberg et al., 1996; Ebrahim et al., 1998; Serdula et al., 1991; Mcgrady et al., 1992; Collins and Hawkes, 1997; Shiono et al., 1997; Schoendorf et al., 1992; CDC, Births: Final Data for, 2003; Klebanoff et al., 1991). Sleep may be a critical, modifiable health behavior that contributes to racial disparities in birth outcomes. Indeed, substantial and persistent racial disparities in sleep disturbances are well-documented, with greater prevalence of poor sleep quality, more frequent night time arousals, longer time spent awake during awakenings, shorter overall sleep duration, and reduced slow wave sleep among African Americans compared to whites (Hall et al., 2009; Hale and Do, 2007; Nunes et al., 2008; Mezick et al., 2010; Grandner et al., 2013; Petrov and Lichstein, 2016; Ruiter et al., 2011; Liu et al., 2016; Matthews et al., 2019; Chen et al., 2015). These racial differences are independent of socioeconomic status (Petrov and Lichstein, 2016), and have been observed in pregnant women (Francis et al., 2017). As described, our data demonstrate racial differences in vulnerability to sleep-induced inflammatory dysregulation. Thus, examination of the cellular mechanisms underlying these differences is warranted.

Addressing gaps in the literature, we examined sleep disturbance as a predictor of genome-wide transcriptome profiles of peripheral blood samples from 103 pregnant women (33 African American and 70 white women) assessed at 18.7 ± 7.2 weeks gestation. We hypothesized that, consistent with the demonstrated inflammatory response to sleep disruption in healthy adults, gene expression indicating over-expression of inflammatory pathways, and decreased cellular responses to anti-inflammatory glucocorticoid signaling, would be present among women with poorer sleep quality, with differential effects among African American women as compared to white women.

2. Methods

2.1. Study design

Participants included in the current investigation were recruited as part of a larger ongoing study examining influenza virus vaccine during pregnancy (clinicaltrials.gov number NCT02148874). Women were recruited from the Ohio State University Wexner Medical Center (OSUWMC) Prenatal Clinics, OSU community, and surrounding community of Columbus, Ohio. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorizations were obtained from all participants. Each received modest compensation. The study was approved by the OSU Biomedical Institutional Review Board.

The current study utilized blood samples and demographic data collected at the baseline visit (i.e., prior to influenza virus vaccination). Women included in the current analyses completed the baseline study visit between October 2013 and May 2015.

2.2. Participants

Study participants were pregnant women at less than 30 weeks gestation at study enrollment, who planned to deliver at OSUWMC. Initial study goals were to examine antibody responses to the influenza vaccine, which required women to be seen prior to 30 weeks gestation so that adequate time for a one month follow-up (post-vaccination) could be completed prior to birth. Notably, this assessment timing also is beneficial for the study of sleep; sleep disturbances increase in late relative to mid-pregnancy due to the growth of the baby, which contributes to difficulty finding a comfortable sleeping position, feeling hot, and increased need to urinate that disrupt maternal sleep (Christian et al., 2019). Thus, assessment at mid-pregnancy reduces undesirable variability.

Women diagnosed with chronic conditions that may have implications for their immune function (e.g., cancer, systemic lupus erythematosus) were excluded. Women were also excluded if their self-reported weight and height were consistent with a pre-pregnancy body mass index (BMI) > 50. Women reporting acute illness, such as cold- or influenza-like symptoms, or antibiotic use within ten days of a study visit were rescheduled. For the purpose of these analyses, additional exclusions included stillbirth or multifetal gestation ($n = 4$), gestational hypertension or diabetes ($n = 5$), hard drug use ($n = 9$), medically indicated early delivery due to diabetes, hypertension, liver illness, or infection ($n = 8$), methadone use ($n = 4$), progesterone use ($n = 5$), Asian ancestry ($n = 6$), and blood samples provided but gene data did not meet quality assurance metrics ($n = 9$). After exclusions, the sample size for the present analyses was 103.

2.3. Demographics

Age, race/ethnicity, marital status, education level, annual household income, employment status, and number of prior births (parity) were collected by self-report. Pre-pregnancy body mass index (BMI; kg/m^2) was calculated using self-reported pre-pregnancy weight and measured height at the baseline visit.

2.4. Sleep disturbance

The Pittsburgh Sleep Quality Index (PSQI) was administered to quantify global sleep quality (Buysse et al., 1989). The PSQI captures self-reported typical sleep duration over the past month. A PSQI total score of > 9 has been identified as a significant sleep disturbance in pregnant women (Sedov et al., 2018), and was used as our threshold. Thus, PSQI scores > 9 indicated high sleep disturbance, scores > 5 to 9 indicated moderate sleep disturbance, and scores ≤ 5 indicated no sleep disturbance. Table 1 reports the distribution of scores in the

Table 1
Sample Characteristics.

	Full sample (n = 103)		African Americans (n = 33)		Whites (n = 70)		Group difference	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*t*	*p*
Age (years)	29.52	4.99	26.47	4.58	30.95	4.54	4.66	< 0.001
Pre-pregnancy BMI	26.63	6.77	28.29	7.70	25.85	6.19	−1.73	0.09
Gestation weeks at blood draw	18.65	7.19	19.38	6.60	18.31	7.48	−0.70	0.48
PSQI Total score	5.97	3.29	7.58	3.95	5.21	2.64	−3.59	0.001
	n	%	*n*	%	*n*	%	χ^2	*p*
PSQI Total score							11.24	0.004
No sleep disturbance (≤5)	56	54.4	12	36.4	44	62.9		
Moderate sleep disturbance (> 5–9)	32	31.1	11	33.3	21	30.0		
High sleep disturbance (> 9)	15	14.6	10	30.3	5	7.1		
Marijuana use	7	6.8	7	21.2	0	0	15.93	< 0.001
Tobacco use	9	8.7	8	24.2	1	1.4	14.64	< 0.001
Nulliparous	41	39.8	8	24.2	33	47.1	4.91	0.03
Marital Status							52.17	< 0.001
Married	66	64.1	5	15.2	61	87.1		
Unmarried but in a relationship	26	25.2	18	54.5	8	11.4		
Single	11	10.7	10	30.3	1	1.4		
Income							48.99	< 0.001
< $15,000	20	19.4	18	54.5	2	2.9		
$15,000–29,999	14	13.6	7	21.2	7	10.0		
$30, 000–49,999	15	14.6	4	12.1	11	15.7		
$50,000–74,999	16	15.5	2	6.1	14	20.0		
$75,000–99,999	18	17.5	2	6.1	16	22.9		
$100,000 +	20	19.4	0	0	20	28.6		
Education							36.90	< 0.001
Some high school	4	3.9	3	9.1	1	1.4		
High school graduate	9	8.7	6	18.2	3	4.3		
Some college (2 year)	16	15.5	12	36.4	4	5.7		
Some college (4 year)	6	5.8	3	9.1	3	4.3		
Associate's or technical degree	8	7.8	3	9.1	5	7.1		
Bachelor's degree	26	25.2	4	12.1	22	31.4		
Some graduate school or higher	34	33.0	2	6.1	32	45.7		
Employment status							16.72	< 0.001
Not employed outside the home	29	28.2	18	54.5	11	15.7		
Employed	74	71.8	15	45.5	59	84.3		

current sample.

2.5. Blood sample collection

For gene expression assays, a 3 mL blood sample was collected from each woman in a Tempus™ Blood RNA Tube (Applied Biosystems, CA). Each tube contains 6 mL stabilizing reagent which immediately lyses whole blood cells and stabilizes RNA. Following collection, samples were shaken vigorously for 10 s to ensure that the stabilizing reagent made uniform contact with the sample. Samples were stored at −80 °C until analysis (Mejias et al., 2013).

2.6. Gene expression assays

Blood total RNA was isolated using the RNeasy kit (Qiagen) according to the manufacturer's instructions, and RNA integrity was assessed by using an Agilent 2100 Bioanalyzer (Agilent, Palo Alto, CA). Targets were prepared using the Illumina RNA amplification kit (Ambion, Austin, TX). cRNA targets were hybridized into Illumina Human HT12 V4 beadchips (47,323 probes) and scanned on the Illumina Beadstation 500 as described elsewhere (Mejias et al., 2013). Illumina GenomeStudio software was used for background subtraction and to scale average signal intensities. Raw gene expression data were quantile-normalized (Bolstad et al., 2003) and $\log_2$ transformed prior to analysis using R statistical software. Two outliers were identified based on visual inspection of a boxplot and low correlations ($r < 0.96$) within a correlogram (R package 'corrgram') that included all of the assayed genes.

2.7. Statistical analyses

To identify upstream transcription factors that are represented by the genes differentially expressed in women with high sleep disturbance (PSQI > 9) compared to no sleep disturbance (PSQI ≤ 5), we employed a promoter-based bioinformatics approach using the Transcription Element Listening System (TELiS; http://www.telis.ucla.edu) (Cole et al., 2005) to examine a pre-specified subset of relevant transcription factors from the TRANSFAC database.

To test our *a priori* hypotheses that proinflammatory transcription control pathways would be activated, and glucocorticoid and interferon response elements would be down-regulated, we examined whether putative binding-sites for select transcription factors were over- or under-represented among the core promoter sequences of over- and under-expressed genes (defined as 25% or greater average difference between groups) in women with high sleep disturbance and moderate sleep disturbance versus no sleep disturbance (reference group), taking into account the need to avoid false negative thresholds as previously described (Tabassum et al., 2013; Norris and Kahn, 2006; Cole et al., 2003). All analyses were adjusted for assay batch, age, race (except for the subgroup analyses), pre-pregnancy BMI, weeks gestation at time of blood draw, time of day of blood draw, self-reported use of marijuana, and self-reported use of tobacco after finding out about pregnancy. We then proceeded to test our *a priori* hypotheses using TELiS with a significance threshold of $p < 0.05$ for the proinflammatory transcription factor families, nuclear factor kappa-B (NFκB), activator protein-1 (AP1), and the adrenergic-responsive cAMP response element binding protein (CREB) family, the generally anti-inflammatory glucocorticoid receptor (GR), and innate anti-viral interferon response factor (IRF) family (Takahashi et al., 2001; Akerfelt et al., 2007; Zhao, 2013;

Gomez-Pastor et al., 2017; de Nadal et al., 2011). Detailed methods of TELiS are further described in (Cole et al., 2005) following bioinformatics guidelines (Tabassum et al., 2013; Norris and Kahn, 2006; Cole et al., 2003). This analysis identifies transcription factor binding motifs (TFBMs) that are over- or under-represented within the core promoter sequences of genes that are differentially expressed among women with high sleep disturbance and moderate sleep disturbance compared to no sleep disturbance.

3. Results

As shown in Table 1, the present sample consisted of women aged 18–35 years, with a mean age of 29.52 years (SD = 4.99). Women were predominantly in their 2nd trimester with a mean of 18.65 (SD = 7.19) weeks gestation at study enrollment, and a mean pre-pregnancy BMI of 26.63 (SD = 6.77). Participants were 68.0% white and 32.0% African American, with a range of educational attainment and annual household income. In addition, 39.8% of the participants were nulliparous, or had not given birth previously. A small percentage of participants reported using marijuana (6.8%) or tobacco (8.7%) since finding out they were pregnant. Of note, approximately 7% of white women had high sleep disturbance (PSQI > 9), compared to 31% of African American women. Other differences by race are noted, with significant differences in age, income, education, employment status, and prevalence of sleep disturbance. African American women were on average younger, had lower income and education, less likely to work outside the home, and reported more sleep disturbances (ps < 0.05). Among those with sleep disturbances, there were no significant differences by race in income, χ^2 = 8.63, p = 0.07, or education, χ^2 = 6.12, p = 0.29.

3.1. Sleep disturbance and gene expression

We first examined the difference in gene expression in the full sample, and found that only 32 genes met the threshold of 25% differential expression (i.e., 1.25 fold) or greater between women with high sleep disturbance (PSQI > 9) compared to no sleep disturbance (PSQI ≤ 5). Two genes met this threshold when comparing women with moderate sleep disturbance (PSQI > 5 – 9) and no sleep disturbance. Among white women with high versus no sleep disturbance, 654 genes differed in average expression level by 25% or more, with 35.3% of those genes (n = 231) relatively up-regulated and 64.7% (n = 423) relatively down-regulated (genes listed in Supporting Information Table 1). Among African American women with high vs. no sleep disturbance, 229 genes differed in average expression level by 25% or more, with 41.5% (n = 95) relatively up-regulated and 58.5% (n = 134) relatively down-regulated (genes listed in Supporting Information Table 1). There were also genes that met the threshold of 25% differential expression or greater between women with moderate sleep disturbance (PSQI > 5–9) compared to no sleep disturbance (PSQI ≤ 5) (188 genes in African American women; 19 in white women; genes listed in Supporting Information Table 2).

3.2. Transcription factor activity among pregnant women with sleep disturbance versus no sleep disturbance by race

Promoter-based bioinformatics analysis (TELiS) was applied to identify common transcription factors among genes associated with sleep disturbance, by quantifying the prevalence of specific transcription factor binding motifs (TFBM) in gene promoter sequences. Analyses revealed different patterns of TFBM prevalence among the sleep disturbance-related genes in African American women and white women. Specifically, African American women with high sleep disturbance showed significantly elevated proinflammatory NF-κB, AP1, and CREB transcription factor activity (ps < 0.05; Fig. 1) compared to those with no disturbance, whereas white women with high sleep disturbance exhibited a non-significant trend toward elevated NF-κB

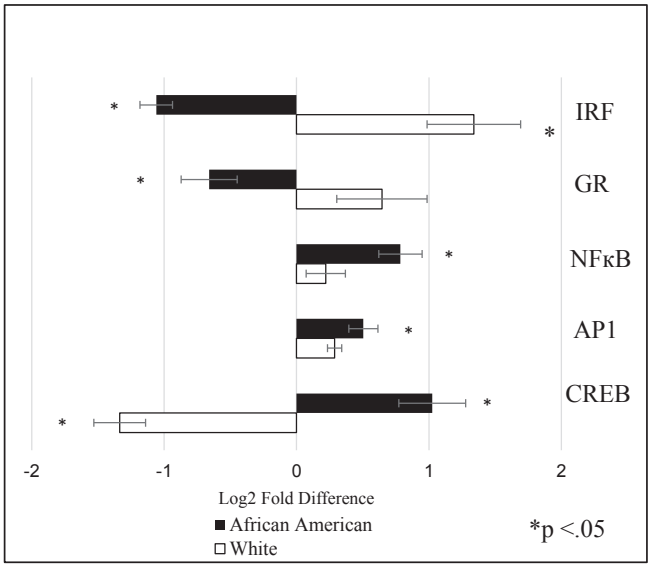

Fig. 1. TFBM in pregnant women with high sleep disturbance compared to no disturbance by race.

(p = 0.18), significantly reduced CREB (p < 0.001), and similarly significant elevations in AP1 (p < 0.001) activity compared to those with no disturbance. With regard to the generally anti-inflammatory glucocorticoid receptor (GR), African American women with high sleep disturbance exhibited reduced activity (p < 0.05), while white women showed no significant difference based on sleep disturbance (p = 0.11). IRF activity was significantly decreased in African American women with high sleep disturbance (p < 0.05), and inversely elevated in white women with high sleep disturbance (p < 0.05) compared to no sleep disturbance.

4. Discussion

Our analyses of inflammatory and anti-viral gene expression profiles in African American and white women during pregnancy revealed distinct effects of sleep disturbance. Among African American women, sleep disturbances were associated with up-regulated activity of proinflammatory transcription factors NF-κB, AP1, and CREB, and down-regulated activity of anti-inflammatory glucocorticoid responses and anti-viral Interferon Response Factors (IRF). For white women, however, these differences were much less pronounced, with the majority of inflammatory transcription factors (NFκB, AP1) found to predict birth outcomes in a prior report (Ross et al., 2019) trending modestly upward but failing to reach statistical significance. However, white women with sleep disturbances did show a modest trend toward up-regulation of the glucocorticoid receptor (GR) and significantly down-regulated CREB, suggesting a potential elevated responsivity of immune cells to the anti-inflammatory effect of cortisol and decreased adrenergic response to sleep disturbance. This same pattern was inverted in African American women with sleep disturbances, with GR activity down-regulated and CREB up-regulated. This race-related difference in GR and CREB activity under conditions of sleep disturbance could potentially contribute to the greater proinflammatory activity observed in the African American women. As such, this study identifies race-related differences in glucocorticoid signaling activity and adrenergic-responsive cAMP response element binding protein as potential pathways through which race-related differences in proinflammatory signaling might arise in the context of sleep disruption during pregnancy. NF-κB transcription factor regulates gene expression of inflammatory cytokines and chemokines under a multitude of conditions including cell stress, activation of Damage-Associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs)

(Liu et al., 2017; Glass and Saijo, 2010). AP1/JUN transcription factor activates the expression of proinflammatory cytokines and cell differentiation, and CREB is activated in response to cAMP, indicating cellular metabolic activation, a key pathway activated by β-adrenergic receptors (Irwin and Cole, 2011).

Divergent innate anti-viral immune responses to sleep disturbance, as were seen with IRF, could signal differential viral surveillance and susceptibility to infection in pregnancy between African American and white women, although further research is warranted to better understand the immune system response under challenge. These effects are consistent with our prior data showing greater reactivation of latent Epstein Barr Virus (EBV) among African American compared to white women during pregnancy and postpartum—an effect that was further exacerbated among those reporting greater perceived racial discrimination (Christian et al., 2012).

Taken together, our findings identify sleep quality as a potentially important and modifiable behavioral target in pregnancy that might alter the inflammatory environment in a clinically relevant manner, particularly for African American women. As reviewed, excessive inflammation is thought to be detrimental to sustaining a healthy pregnancy, as it has been associated with increased risk for delivery prior to full term (Hagberg et al., 2005; Romero et al., 2006; Dizon-Townson, 2001; Romero et al., 1990; Romero et al., 1993; Romero et al., 1993; Murtha et al., 2007). The current data lend support to emerging evidence that sleep disturbance is a contributor to inflammatory activity in pregnancy.

These data are consistent with prior reports of elevated circulating inflammatory markers among pregnant (Okun et al., 2007; Blair et al., 2015; Christian et al., 2016; Christian, 2012) and non-pregnant (Irwin et al., 2016) adults with sleep disturbance. Our findings provide further clinical evidence that sleep disturbances are associated with up-regulation of proinflammatory transcription control pathways, down-regulation of anti-viral transcription pathways, and reduced glucocorticoid sensitivity in African American women, all of which were less pronounced or reversed in white women. These racial disparities in transcription of inflammatory factors under conditions of insufficient sleep may underlie some of the racial disparities in birth outcomes. Indeed, our prior work identified that poor sleep in African Americans to be associated with increased risk for preterm birth, and suggested a possible mediational pathway through inflammation (Blair et al., 2015).

These data extend our prior work demonstrating greater inflammatory dysregulation under conditions of poor sleep among African American pregnant women as compared to white women when measured at the level of serum cytokines or ex-vivo LPS-stimulated cytokine production (Blair et al., 2015; Christian, 2012). Furthermore, these gene expression results provide mechanistic insight into the pathways by which poor sleep may contribute to disproportionately higher rates of shortened gestation among African American women. Thus, targeting sleep disturbance, as well as related down-stream inflammatory sequelae, represent promising future avenues of investigation.

Consistent with the weathering hypothesis (Geronimus, 1992), we forward that the differences observed hererin are likely attributable to environmental factors rather than genetic variants. Chronic stress related to racial minority status (e.g., racial discrimination) is causally implicated in birth outcomes (Blair et al., 2015; Christian et al., 2012; Muglia and Katz, 2010; Giscombe and Lobel, 2005; Christian, 2012; Christian et al., 2013) and is clearly implicated in sleep parameters (Francis et al., 2017; Grandner et al., 2012; Tomfohr et al., 2012). Indeed, greater vigilance to perceived and actual threat among African American women, as a result of chronic discrimination exposure, increases stress appraisal (Himmelstein et al., 2015) and elevates risk for subthreshold and clinical insomnia (Bethea et al., 2019). Further characterization of how stress, and the parallel adrenergic-mediated inflammatory transcription factor CREB, and discrimination might contribute to sleep disturbances in pregnant African American women is an important future research direction.

Critically, this study included a focus on African American women. Despite marked and intractable racial disparities in health, African American women notably lack representation in transcriptomics studies. In this study, we statistically examined cohorts of African Americans and whites separately to provide the clearest evidence with regard to the presence of transcription factors of interest, while controlling for key potential confounds. Nevertheless, replication in larger samples is needed to confirm findings and strengthen confidence.

The current investigation focused on maternal peripheral blood, which provides advantages in relation to early identification of risk given that sample procurement during pregnancy is non-invasive. However, placental samples greatly advance our understanding of both predictive and mechanistic pathways in birth outcomes as well as child development (e.g., Miller et al., 2017). Indeed, there is a paucity of research investigating the effect of sleep disturbances in pregnancy on child health and developmental outcomes. Thus, inclusion of both placental and peripheral markers, as well as child outcomes, in future studies would be advantageous. Although the current study proposes that sleep disturbances that give rise to inflammation, particularly among African American women, may drive poorer birth outcomes, the current study was not designed to test this hypothesis, and future well-powered study designs are needed. In addition, the current results were determined using Illumina HT12 BeadKits. RNAseq technology is now available, which would provide even more sensitive data in future related studies.

In conclusion, the current study provides novel evidence for differences in expression of genes related to inflammation among pregnant women with sleep disturbances. Consistent with prior work, these pathways were of both greater breadth and magnitude among African American women than among white women, and point to a possible role of reduced glucocorticoid signaling activity and enhanced adrenergic-responsive inflammatory activation as potential pathways through which sleep disturbances might contribute to racial differences in pregnancy outcomes. Interventions that target sleep disturbances in pregnancy may not only improve sleep but also offer biological benefit, and further research that investigates the impact of improving sleep in pregnancy on inflammatory and birth outcomes is warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.04.065.

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