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Maternal sleep quality and diurnal cortisol regulation over pregnancy

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Abstract

Poor sleep in pregnancy is related to adverse neonatal health. Elevated maternal cortisol has been proposed as a pathway, yet the association in pregnancy is not well understood. The goals of the current study were to examine associations between 1) sleep and cortisol, 2) sleep, cortisol, and neonatal outcomes, and 3) variables that could explain these associations. 200 pregnant women completed the Pittsburgh Sleep Quality Index (PSQI) and provided diurnal salivary cortisol samples at two times over pregnancy. Poor sleep quality was associated with greater evening cortisol concentrations at 36 weeks' gestation. This association was mediated by anxiety symptoms. Higher evening cortisol at 36 weeks' gestation was associated with shorter gestation.

Keywords

Sleep; cortisol; pregnancy; birth outcomes

Introduction

Sleep quality and quantity are significantly disrupted in pregnancy. Pregnant women report multiple awakenings, un-refreshing sleep, and more fatigue than non-pregnant individuals (Hedman, Pohjasvaara, Tolonen, Suhonen-Malm, & Myllyla, 2002; Izci et al., 2005). Sleep disturbances increase as pregnancy progresses, with the most sleep disruption reported in the third trimester (Hedman, et al., 2002). Disrupted sleep in pregnancy is a risk factor for adverse neonatal outcomes including preterm birth (Okun, Dunkel Schetter, & Glynn, 2011; Strange, Parker, Moore, Strickland, & Bliwise, 2009), low birth weight (Bonzini et al., 2011; Owusu et al., 2013), small for gestational age (Bonzini, et al., 2011), and stillbirth (Owusu, et al., 2013). Sleep disturbances such as short sleep duration and snoring appear to be associated with adverse perinatal outcomes such as gestational diabetes (Facco, Grobman,

Kramer, Ho, & Zee, 2010), preeclampsia (Owusu, et al., 2013), unplanned Cesarean section, and longer labor duration (Naghi, Keypour, Ahari, Tavalai, & Khak, 2011; O'Brien et al., 2013). Poor sleep quality in pregnancy may also place women at risk for postpartum depression (Okun et al., 2011).

A proposed mechanism linking poor sleep to certain adverse pregnancy outcomes is elevated maternal cortisol production (Okun, Hall, & Coussons-Read, 2007). Cortisol is secreted from the hypothalamic-pituitary-adrenal (HPA) axis in a circadian pattern. The nadir for cortisol occurs around midnight. Cortisol levels begin to rise 2–3 hours after sleep onset, continue to rise upon awakening, peak approximately 30 minutes after awakening (i.e., cortisol awakening response), and then demonstrate a steady decline until the nadir (Van Cauter & Spiegel, 1999). HPA activity changes dramatically over the course of pregnancy. Total cortisol output increases across gestation reaching levels 2–3 times higher at the end of gestation compared to levels observed at the start of pregnancy. Cortisol awakening response and cortisol stress response are attenuated as pregnancy progresses, while circadian cortisol patterns are maintained (Sandman, Davis, Buss, & Glynn, 2011). Higher absolute cortisol levels and greater changes in the diurnal rhythm (such as less pronounced attenuation of the cortisol awakening response over gestation), have been associated with adverse neonatal outcomes including lower birth weight and shorter length of gestation (Buss et al., 2009; Entringer, Buss, Andersen, Chicz-DeMet, & Wadhwa, 2011; Giurgescu, 2009; Wadhwa et al., 2004). Longer term consequences of elevated maternal cortisol levels in utero include programming of infant HPA (dys)regulation, neurodevelopmental problems, and cardiometabolic disease (Duthie & Reynolds, 2013; Stinson et al., 2015).

In non-pregnant samples, sleep and HPA activity have a bidirectional association. Abnormally elevated cortisol levels are associated with changes in sleep architecture, including increases in EEG frequency and wakefulness, decreases in short-wave sleep, and decreases in sleep depth (Antonijevic, 2008; Buckley & Schatzberg, 2005; Friess, V Bardeleben, Wiedemann, Lauer, & Holsboer, 1994). Changes in HPA activity also precede sleep disorders, including insomnia and obstructive sleep apnea (Edwards, Kamat, Tomfohr, Ancoli-Israel, & Dimsdale, 2014). Studies that have examined associations among sleep and diurnal cortisol report mixed findings. Some studies have reported that shorter sleep duration is associated with flatter diurnal cortisol profile (Kumari et al., 2009; Leproult, Copinschi, Buxton, & Van Cauter, 1997; Spiegel, Leproult, & Van Cauter, 1999; Zeiders, Doane, & Adam, 2011). Past studies have also examined effects of sleep on the cortisol awakening response; experimentally restricting sleep in young adults resulted in higher morning cortisol levels in previous studies (Wright et al., 2015), whereas naturally-occurring shorter sleep duration was associated with lower morning cortisol concentrations (Van Lenten & Doane, 2016). A systematic review of sleep and the cortisol awakening response reported a relationship between longer sleep duration (both objectively and subjectively measured) and increased cortisol levels at awakening (Garde, Karlson, Hansen, Persson, & Akerstedt, 2012). Null associations between sleep and diurnal cortisol have also been reported (Castro-Diehl et al., 2015; Federenko et al., 2004; Pruessner et al., 1997), and patterns of results may vary according to sleep measurement (Van Lenten & Doane, 2016).

There are a dearth of studies investigating the association between sleep and diurnal cortisol in pregnancy. In one study, Suzuki and colleagues (1993) reported a trend finding that poor sleepers had attenuated cortisol awakening responses in late pregnancy (Suzuki et al., 1993). Given the importance of maternal cortisol in predicting maternal and neonatal health outcomes, as well as the high prevalence of sleep disturbance in pregnancy, more research is needed on the relationship between maternal sleep quality and cortisol production. The goals of the current study were to examine 1) associations between maternal sleep and diurnal cortisol in pregnancy, 2) maternal medical conditions and psychological symptoms of distress that may mediate the associations between sleep quality and cortisol, and 3) associations among sleep quality, cortisol, and neonatal outcomes.

Methods

Participants

This study was a secondary data analysis of 200 women who participated in a prospective study on the effects of maternal depressive disorder on fetal and infant development, and who provided information on perceived sleep quality in pregnancy (Behavior and Mood in Mothers, Behavior in Infants (BAMBI); R01MH079153). Study eligibility for the parent study was determined through maternal report and review of medical records. Maternal exclusion criteria included age <18 or >40, non-English speaking, non-singleton pregnancy, illicit drug use other than marijuana (meconium confirmed), and involvement with child protective services in pregnancy. Women in the parent study were over-sampled to have experienced a depressive episode in the current pregnancy or to have had a history of major depression; 33% of women in the sample included for these analyses reported a depressive episode in pregnancy. Women were also selected to be at low risk for maternal medical conditions (i.e., gestational diabetes, pre-eclampsia, gestational hypertension) based on review of medical conditions from prior pregnancies. These studies were approved by Women and Infants Hospital and Lifespan Hospital Institutional Review Boards. All women provided written consent prior to their participation.

Procedure

Pregnant women were recruited from obstetric clinics feeding into Women and Infants Hospital, a large tertiary care hospital. Interested women were screened regarding initial study criteria. Included participants for the current analyses completed two maternal interview sessions over pregnancy in the second and third trimesters of pregnancy (session 1: M=24 weeks' (SD=3), and session 2: M=36 weeks' (SD=1) gestation). One hundred and eighty-four women provided both sleep quality and cortisol data at session 1, and 152 women provided both sleep quality and cortisol data at session 2. Eight participants (4%) delivered preterm (< 37 weeks' gestation) and were unable to complete the 36-week study session. At each study session women completed a measure of subjective sleep quality over the previous month and provided information on psychological distress and medical conditions in pregnancy. For three days following each study session, maternal salivary cortisol was sampled by passive drool immediately upon awakening, 30 minutes after awakening, and in the evening (prior to bed). Women were instructed to refrain from eating or drinking anything (other than water) and brushing their teeth for one hour prior to sample

collection. After participants completed the 3 days of saliva collection, study staff retrieved samples from participants' homes and provided payment. Participants stored samples at room temperature until collection by study staff. Participants were instructed to store samples in their refrigerator if retrieval was delayed > 3 days. To verify compliance with saliva sampling protocol, a subset of participants (17%) were given Medication Event Monitoring System (MEMS) caps (AARDEX, Zurich, Switzerland). Women were instructed to place the saliva tube into the MEMS bottle after collection and secure the cap; the cap includes an electronic reader which records the date and time that the bottle is opened. To verify compliance, self-reported sampling times and MEMS cap sampling times were compared. Times differed, on average, by 8 minutes (SD = 5 minutes), suggesting that a subset of participants were adherent to the sampling protocol.

Measures

Subjective Sleep Quality.—Maternal subjective sleep quality was measured at both study sessions using the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI is a self-report measure of subjective sleep quality over the previous month. Global sleep quality scores on the PSQI range from 0 to 21, with higher scores indicating poorer sleep quality. PSQI and its psychometric properties have been validated in pregnant women (Jomeen & Martin, 2007; Skouteris, Wertheim, Germano, Paxton, & Milgrom, 2009). We examined sleep quality as a continuous variable in analyses.

Salivary Cortisol.—Women were asked to provide salivary cortisol samples (passive drool) for three times a day over three days after each study session. Study staff collected saliva samples from participants' homes and returned the samples to the lab where they stored at -80°C until analysis. Samples were shipped to the laboratory of Clemens Kirschbaum, PhD (Dresden University) and analyzed with an immunoassay with time-resolved fluorescence detection. The intra and inter-assay coefficients of variation were < 8%.

Maternal and Infant Characteristics.—Participants provided information on their age, race/ethnicity, marital status, socioeconomic characteristics, number of prior pregnancies, medical conditions, and pre-pregnancy height and weight to compute pre-pregnancy body mass index (BMI). Participants also self-reported new-onset medical conditions during study interviews. Following delivery, a medical chart review was performed in which study staff reviewed all prenatal and delivery notes. Self-reported medical conditions were confirmed by medical chart review, and medical conditions that were not reported by the participant but listed in the medical record were recorded. Birth outcomes were also collected by medical chart review. In particular, we recorded gestational age at birth, birth weight (in grams), and APGAR score at 5 minutes after delivery.

Maternal Psychological Distress.—At each session, symptoms of depression in the previous week were assessed using the Quick Inventory of Depressive Symptomatology (QIDS) (Rush et al., 1986). QIDS scores range from 0–27. Symptoms of anxiety over the past week were assessed at each session using the Hamilton Anxiety Rating Scale (Hamilton, 1959) (HAM-A). HAM-A scores range from 0 to 56. Perceived stress over the

last month was assessed at each study session using the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983), a measure of daily hassles, low perceived control over challenges, and low perceived ability to cope with challenges over the previous month. Perceived Stress scores range from 0 to 40, with higher scores indicating greater stress.

Data Analysis

All analyses were conducted using SPSS v.20 software. Pearson correlations were used to assess associations among sleep quality and continuous variables, and t-tests were used to examine the relation between sleep quality and categorical characteristics. We calculated the cortisol awakening response (CAR) on each day of saliva collection by taking the difference between cortisol values at awakening and 30 minutes after awakening. Morning saliva samples that were < 20 or > 40 minutes apart were omitted from analyses in order to accurately capture the morning awakening response. At 24 weeks, 25 women (12.5% of sample) had data omitted due to non-compliance with collection times, and 29 women (14.5% of sample) had data omitted for non-compliance at the 36 week collection time point. CAR and evening cortisol values were averaged across days to calculate a more stable measure of the diurnal cortisol pattern. Examination of the reliability of the aggregate calculation across collection days using Cronbach's alpha revealed significant variability across days for CAR measures (alphas < .40); however, results from regression analyses did not change when analyses of CAR were performed separately by day. Examination of the reliability of the aggregate calculation across collection days for evening cortisol demonstrated acceptable reliability (alphas > .67), and results from regression analyses did not change when analyses of evening cortisol were performed separately by day. CAR and diurnal cortisol are regulated by different biological processes (Wilhelm, Born, Kudielka, Schlotz, & Wust, 2007) and thus were analyzed separately. Calculated cortisol values were log transformed due to skewed distributions. Raw cortisol values (nmol/L) are presented in Figure 1. All analyses controlled for gestational age and time of day of saliva collection.

Linear regression analyses were performed to assess the association between global sleep quality scores and cortisol. We assessed associations among sleep quality and cortisol at 24 and 36 weeks' gestation in separate models. Linear regression analyses were also performed to examine associations among sleep quality, cortisol, and neonatal outcomes. Analyses were performed to evaluate associations between sleep quality and medical/distress measures, as well as medical/distress measures and cortisol, in order to meet the assumptions of the Baron and Kenny test for mediation (Baron & Kenny, 1986). Finally, stepwise linear regression analyses were performed to evaluate maternal medical conditions and maternal psychological distress as mediators of the associations among sleep quality and cortisol.

Results

Sample characteristics.

Participants were racially and ethnically diverse (44% non-Hispanic White, 16.5% non-Hispanic Black, 27% Hispanic, 5% > 1 race, 3.3% Asian, 3% 'other', 1.4% American Indian), 35% were married, 44% had a high school education or less, and 21% of the sample

reported an annual income of less than \$10,000. Body mass index (BMI) prior to pregnancy was, on average, 26 (SD=6.5). At 24 weeks' gestation, 48% of the sample reported poor sleep quality, and at 36 weeks' gestation, 40% of the sample reported poor sleep quality (according to a cut off score of 5 on the PSQI (Buysse, et al., 1989)).

Covariates.

We examined associations among global sleep quality scores and maternal characteristics. Sleep quality scores were not significantly related to maternal race/ethnicity or medical conditions in pregnancy (p values $> .15$). Sleep quality scores were not significantly associated with maternal pre-pregnancy BMI ($p > .12$). Maternal age was not significantly associated with sleep quality ($p > .26$). Sleep quality assessed at 24 weeks was significantly associated with maternal education ($r = -.16$, $p = .003$) such that women with poorer sleep quality reported lower educational attainment. Sleep quality scores assessed at 24 ($t = 2.71$, $p = .007$) and 36 weeks' gestation ($t = 2.34$, $p = .02$) were associated with marital status; women who were unmarried during the pregnancy reported poorer sleep quality. Gravida was significantly associated with sleep quality at 24 weeks ($r = .17$, $p = .003$) and 36 weeks ($r = .13$, $p = .04$); women with a greater number of prior pregnancies reported poorer sleep quality. Maternal education, gravida, and marital status were included as covariates in regression analyses. Average times of cortisol collection at wake up, 30 minutes after wake up, and bedtime were 7:52 (SD=1:42), 8:26 (SD=1:43), and 22:40 (SD=1:42) at 24 weeks' gestation and 7:52 (SD=1:47), 8:21 (SD=1:48), and 22:48 (SD=1:37) at 36 weeks' gestation. Time of cortisol collection was included as a covariate in analyses.

Associations among maternal sleep quality and cortisol.

Results of regression analyses demonstrated a significant association between sleep quality assessed at 36 weeks' gestation and evening cortisol at 36 weeks' gestation ($\beta = .19$, $p = .02$); poorer sleep quality was significantly associated with elevated evening cortisol levels in late gestation. The association between sleep quality and evening cortisol was not significant at 24 weeks' gestation ($\beta = .09$, $p = .34$). The associations between sleep quality and CAR were non-significant at either gestational time point (β values $< .09$, p values $> .25$). For graphing purposes, we plotted diurnal cortisol patterns at the lowest and highest quartile of the PSQI scores collected at 36 weeks' gestation. See Figure 1.

Mediators of Sleep-Cortisol Association.

We next examined if maternal medical conditions or psychological distress mediated the link between sleep quality and evening cortisol at 36 weeks' gestation. Medical conditions included maternal gestational diabetes, hypertension, preeclampsia, and maternal infection. Psychological distress constructs included maternal depressive symptoms, anxiety symptoms, and perceived stress. Associations among sleep quality and medical conditions were all non-significant (t values < 1.27 , p values $> .21$). We found that subjective sleep quality at 36 weeks was significantly associated with maternal anxiety symptoms ($r = .55$, $p < .001$), and maternal anxiety symptoms were significantly associated with evening cortisol at 36 weeks ($r = .18$, $p = .01$). We then performed stepwise linear regression to examine maternal anxiety as a mediator of the subjective sleep-cortisol association. We found that anxiety significantly mediated the association between sleep quality and cortisol (the association

between sleep quality and evening cortisol became non-significant; $\beta=.12$, $p=.20$). See Figure 2.

Associations among sleep, cortisol, and neonatal outcomes.

We observed a significant association between gestational length and maternal evening cortisol at 36 weeks' gestational age ($r=-.21$, $p=.003$); greater evening cortisol concentrations were associated with shorter gestational length. All other associations among cortisol and neonatal outcomes were not significant. There were no significant associations among subjective sleep quality and neonatal outcomes (β values $<.10$, p values $>.08$).

Discussion

Results from this study revealed that poor subjective sleep quality in pregnancy was associated with higher evening cortisol concentrations in late third trimester. This association was mediated by anxiety symptoms in pregnancy, suggesting that the link between poor subjective sleep quality and higher evening cortisol levels may be due to maternal symptoms of psychological distress. Alternatively, anxiety symptoms may have mediated the association between sleep quality and evening cortisol given the overlapping constructs of sleep and anxiety. Higher evening cortisol concentrations in late gestation were also associated with shorter pregnancy duration, highlighting the importance of understanding factors that may lead to greater cortisol production in pregnancy as they relate to neonatal health.

Previous studies that have examined subjective sleep and diurnal cortisol report mixed associations, and patterns of results may vary by method of sleep measurement and index of diurnal cortisol. It has been proposed that inconsistencies in the literature may also be due to the mediating role of psychological distress (Elder, Wetherell, Barclay, & Ellis, 2014). Studies evaluating maternal sleep quality and HPA activity in pregnancy are scarce, despite findings from previous research in which poor sleep quality was associated with preterm birth (Okun, Dunkel Schetter, et al., 2011; Strange, et al., 2009). Findings of Okun et al. showed an association between disturbed sleep in mid to late pregnancy and higher levels of inflammatory markers, suggesting potential causality of sleep disturbances on adverse neonatal outcomes. Poor sleep in late pregnancy has also been associated with higher rates of Cesarean deliveries and longer labor duration (Naghi, et al., 2011). It is therefore biologically plausible that poor sleep may result in HPA dysfunction and inflammation that could constitute the basis for the development of adverse maternal and neonatal outcomes. Results from this study partially support this proposed pathway; findings demonstrate associations among poor subjective sleep quality and higher cortisol, as well as higher cortisol and shorter gestational length. However, we did not observe direct associations between sleep quality and neonatal health. Findings from this study and the current literature do not establish causality of sleep and adverse pregnancy outcomes, and a reverse directionality is also possible.

There is a normative increase in total cortisol levels across gestation, and circadian rhythms of cortisol secretion are maintained throughout pregnancy. Results of this study suggest that cortisol levels may be abnormally elevated and circadian patterns may be altered as

pregnancy progresses among women who report poor subjective sleep quality. We speculate that poor sleep quality may lead to higher evening cortisol concentrations due to disruptions in the typical circadian decline over the day. Specifically, poor sleep quality may act as a physiological stressor resulting in a shift of the typical circadian phase, delayed HPA quiescence, and delayed HPA axis recovery from early morning cortisol stimulation (Leproult, et al., 1997). Alternatively, poor subjective sleep quality may impact HPA activity in pregnancy via changes in placental CRH secretion over gestation (Irwin, Clark, Kennedy, Christian Gillin, & Ziegler, 2003; Wadhwa, et al., 2004). Elevated CRH has been linked to insomnia and sleep disruption homeostasis in past studies of animals and non-pregnant humans (Buckley & Schatzberg, 2005; Irwin, et al., 2003; Koban, Wei, & Hoffman, 2006; Machado, Tufik, & Suchecki, 2010). Past evidence suggests that a precocious rise in placental CRH may increase the risk for adverse neonatal outcomes including preterm delivery (Sandman et al., 2006). Though no prior data support a direct link between sleep quality and placental function, recent data show an association between sleep disordered breathing and the placenta (Bourjeily et al., 2015; Bourjeily, Curran, & Lambert-Messerlian, 2015; Ravishankar et al., 2015), such that pregnant women with obstructive sleep apnea (OSA) displayed lower levels of plasma protein-A and reduced serum estriol levels compared to pregnant women without OSA. Though this link may be related to intermittent hypoxia and airflow limitation in this disorder, poor sleep associated with sleep disordered breathing may also play a role in altered placental dysfunction. Future studies that examine relationships among placental CRH, maternal cortisol, and maternal sleep over the course of pregnancy are needed, as results from these studies may have important implications for understanding pathways to adverse neonatal outcomes among women who sleep poorly in pregnancy.

The associations among subjective sleep quality in pregnancy and maternal CAR were not significant. Diurnal cortisol and CAR are under different regulatory control (Wilhelm, et al., 2007). It is therefore possible that poor subjective sleep quality may interfere with neurological systems regulating diurnal cortisol secretion (i.e., paraventricular nucleus of the hypothalamus, anterior pituitary) but not systems regulating the awakening response (i.e., hippocampus, hypothalamic suprachiasmatic nucleus (Clow, Hucklebridge, & Thorn, 2010)). Results from this study are in contrast with previous studies reporting a relationship between sleep duration and the CAR (see Garde et al., 2012 for review). In the current study we did not measure sleep duration, and were not able to examine associations between nightly sleep quality and next-day cortisol awakening responses. Therefore, these associations may exist in pregnancy but our data collection methods were unable to capture them. More research is needed to enrich our understanding of multiple components of sleep as well as the daily interplay between sleep and HPA regulation in pregnancy.

The association between maternal sleep quality and cortisol was mediated by maternal anxiety symptoms. Sleep disruption is common among individuals experiencing psychological distress (Akerstedt, 2006), and sleep disruption has predicted symptoms of psychological distress in pregnancy and the postpartum period in previous studies (Goyal, Gay, & Lee, 2009; Skouteris, et al., 2009) but inconsistencies in the literature exist (Dorheim, Bjorvatn, & Eberhard-Gran, 2014; Kamysheva, Skouteris, Wertheim, Paxton, & Milgrom, 2010). Subjectively reported sleep quality has been associated with depressive

symptoms in pregnancy and the postpartum period (Goyal, et al., 2009), however comparable rates of objectively measured sleep disturbance were reported in depressed and nondepressed mothers (Dorheim, Bondevik, Eberhard-Gran, & Bjorvatn, 2009). Thus, patterns of associations may vary according to the subjective vs. objective measurement of sleep. There is some previous evidence to support an indirect association between mood, sleep, and diurnal cortisol; Hoyt et al. found that diurnal cortisol slope and area-under-the curve (but not CAR) mediated the association between self-reported sleep quality and depressive symptoms in a sample of men treated for prostate cancer (Hoyt, Bower, Irwin, Weierich, & Stanton, 2016). Similarly, Ly et al. found that self-reported sleep quality mediated the association between perceived stress and diurnal cortisol in children and adolescents (Ly, McGrath, & Gouin, 2015). Consistent with results from this study, in a recently published abstract, Crowley and colleagues reported that blunted cortisol reactivity to a laboratory stressor predicted increased anxiety symptoms and sleep disturbance in a sample of 14 women in their second trimester of pregnancy (Crowley et al., 2015). The self-reported sleep and anxiety measures used in this study may have evaluated overlapping constructs, leading to the finding that anxiety symptoms mediated the association between subjective sleep and evening cortisol. More research is needed to understand the findings from the current study and to clarify associations between multiple sleep parameters, psychological health, and diurnal cortisol.

Results from this study should be interpreted in light of a number of limitations, most importantly the self-reported nature of the sleep measure. Given the retrospective nature of the measure, subjective sleep quality scores may have systematic errors due to recall bias. Previous studies suggest that women with psychological distress in pregnancy report poorer sleep quality but do not demonstrate sleep problems when measured via actigraphy (Volkovich, Tikotzky, & Manber, 2016). Participants in the parent study were over-sampled to include women experiencing depression in pregnancy and therefore participants may have reported higher rates of sleep disturbances than women in the general population. Future studies are needed that include both subjective sleep measures as well as objective sleep measures (i.e., polysomnography and actigraphy) to further understand associations among sleep, sleep architecture, and maternal HPA regulation in pregnancy. Highlighting the importance of measurement tool, a recent study by Van Lenten & Doane (2016) used both actigraphy and the PSQI for sleep measurement and found that associations between diurnal cortisol and sleep differed if sleep was objectively vs. subjectively measured (Van Lenten & Doane, 2016). Future studies are also needed that examine day to day associations among sleep and diurnal cortisol in order to understand the direction of the association in pregnancy. Given the exploratory nature of this secondary data analysis, we did not correct for multiple comparisons, which is another limitation of this study. Finally, we did not assess for the presence of sleep disorders including obstructive sleep apnea (OSA) or snoring in study participants. These sleep disorders may have served as confounds given some literature supporting an association between OSA and cortisol (Tomfohr, Edwards, & Dimsdale, 2012).

In conclusion, findings from this study demonstrate an association between poor sleep quality and elevated evening cortisol in late third trimester, which was mediated by maternal anxiety symptoms. We also observed an association between higher evening cortisol levels

and shorter gestational length. Results are limited by the retrospective nature of sleep measurement; studies are needed that also include objective measures of sleep and are designed to examine the direction of the association between sleep and cortisol in pregnancy, as well as studies that temporally assess whether this association is mediated by psychological factors. This body of research may yield insight into whether sleep could be a modifiable behavior in pregnancy that could be targeted in interventions aimed at regulating HPA activity and reducing risk for adverse birth outcomes.

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References

- Akerstedt T (2006). Psychosocial stress and impaired sleep. *Scand J Work Environ Health*, 32(6), 493–501. [PubMed: 17173205]
- Antonićević I (2008). HPA axis and sleep: identifying subtypes of major depression. *Stress*, 11(1), 15–27. doi: 10.1080/10253890701378967 [PubMed: 17853067]
- Baron RM, & Kenny DA (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic and statistical considerations. *Journal of Personality and Social Psychology*, 51, 1173–1182. [PubMed: 3806354]
- Bonzini M, Palmer KT, Coggon D, Carugno M, Cromi A, & Ferrario MM (2011). Shift work and pregnancy outcomes: a systematic review with meta-analysis of currently available epidemiological studies. *BJOG*, 118(12), 1429–1437. doi: 10.1111/j.1471-0528.2011.03066.x [PubMed: 21790955]
- Bourjeily G, Curran P, Butterfield K, Maredia H, Carpenter M, & Lambert-Messerlian G (2015). Placenta-secreted circulating markers in pregnant women with obstructive sleep apnea. *Journal of Perinatal Medicine*, 43(1), 81–87. [PubMed: 24846956]
- Bourjeily G, Curran P, & Lambert-Messerlian G (2015). Obstructive sleep apnea is associated with alterations in markers of fetoplacental wellbeing. *Journal of Maternal Fetal Neonatal Medicine*, 28(3), 262–266. [PubMed: 24712853]
- Buckley TM, & Schatzberg AF (2005). On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *J Clin Endocrinol Metab*, 90(5), 3106–3114. doi: 10.1210/jc.2004-1056 [PubMed: 15728214]
- Buss C, Entringer S, Reyes JF, Chiciz-DeMet A, Sandman CA, Waffarn F, & Wadhwa PD (2009). The maternal cortisol awakening response in human pregnancy is associated with the length of gestation. *Am J Obstet Gynecol*, 201(4), 398 e391–398. [PubMed: 19716542]
- Buyse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, & Kupfer DJ (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*, 28(2), 193–213. doi: 10.1016/0165-1781(89)90047-4 [PubMed: 2748771]
- Castro-Diehl C, Diez Roux A, Redline S, Seeman T, Shrager S, & Shea S (2015). Association of Sleep Duration and Quality With Alterations in the Hypothalamic-Pituitary Adrenocortical Axis: The Multi-Ethnic Study of Atherosclerosis (MESA). *Journal of Clinical Endocrinology and Metabolism*, 100(8), 3149–3158. [PubMed: 26046965]
- Clow A, Hucklebridge F, & Thorn L (2010). The cortisol awakening response in context. *International Review of Neurobiology*, 93, 153–175. [PubMed: 20970005]
- Cohen S, Kamarck T, & Mermelstein R (1983). A global measure of perceived stress. *J Health Soc Behav*, 24(4), 385–396. [PubMed: 6668417]
- Crowley S, Morrow A, Schiller C, Stuebe A, Nau S, & Girdler S (2015). Biopsychosocial vulnerability to postpartum depression: A laboratory-based feasibility study of sleep dysregulation, daytime stress reactivity, and anxiety symptomology during pregnancy. Paper presented at the 45th Annual Meeting of the International Society of Psychoneuroendocrinology Edinburgh, Scotland.

- Dorheim S, Bjorvatn B, & Eberhard-Gran M (2014). Can insomnia in pregnancy predict postpartum depression? A longitudinal, population-based study. *PLoS One*, 9(4), e94674. [PubMed: 24732691]
- Dorheim S, Bondevik G, Eberhard-Gran M, & Bjorvatn B (2009). Subjective and objective sleep among depressed and non-depressed postnatal women. *Acta psychiatrica scandinavia*, 119(2), 128–136.
- Duthie L, & Reynolds RM (2013). Changes in the maternal hypothalamic-pituitary-adrenal axis in pregnancy and postpartum: influences on maternal and fetal outcomes. *Neuroendocrinology*, 98(2), 106–115. doi: 10.1159/000354702 [PubMed: 23969897]
- Edwards KM, Kamat R, Tomfohr LM, Ancoli-Israel S, & Dimsdale JE (2014). Obstructive sleep apnea and neurocognitive performance: the role of cortisol. *Sleep Med*, 15(1), 27–32. doi: 10.1016/j.sleep.2013.08.789 [PubMed: 24269133]
- Elder G, Wetherell M, Barclay N, & Ellis J (2014). The cortisol awakening response--applications and implications for sleep medicine. *Sleep Medicine Reviews*, 18(3), 215–224. [PubMed: 23835138]
- Entringer S, Buss C, Andersen J, Chicx-DeMet A, & Wadhwa PD (2011). Ecological momentary assessment of maternal cortisol profiles over a multiple-day period predicts the length of human gestation. *Psychosom Med*, 73(6), 469–474. doi: 10.1097/PSY.0b013e31821fbf9a [PubMed: 21700714]
- Facco FL, Grobman WA, Kramer J, Ho KH, & Zee PC (2010). Self-reported short sleep duration and frequent snoring in pregnancy: impact on glucose metabolism. *Am J Obstet Gynecol*, 203(2), 142 e141–145. doi: 10.1016/j.ajog.2010.03.041 [PubMed: 20510182]
- Federenko I, Wust S, Hellhammer D, Dechoux R, Kumsta R, & Kirschbaum C (2004). Free cortisol awakening responses are influenced by awakening time. *Psychoneuroendocrinology*, 29(2), 174–184. [PubMed: 14604599]
- Friess E, V Bardeleben U, Wiedemann K, Lauer CJ, & Holsboer F (1994). Effects of pulsatile cortisol infusion on sleep-EEG and nocturnal growth hormone release in healthy men. *J Sleep Res*, 3(2), 73–79. [PubMed: 10607111]
- Garde A, Karlson B, Hansen AM, Persson R, & Akerstedt T (Eds.). (2012). *Sleep and salivary cortisol*. Sweden: Benthan Science Publishers.
- Giurgescu C (2009). Are maternal cortisol levels related to preterm birth? *J Obstet Gynecol Neonatal Nurs*, 38(4), 377–390. doi: JOGN1034 [pii] 10.1111/j.1552-6909.2009.01034.x
- Goyal D, Gay C, & Lee K (2009). Fragmented maternal sleep is more strongly correlated with depressive symptoms than infant temperament at three months postpartum. *Archives of Womens Mental Health*, 12(4), 229–237.
- Hamilton M (1959). The assessment of anxiety states by rating. *Br J Med Psychol*, 32(1), 50–55. [PubMed: 13638508]
- Hedman C, Pohjasvaara T, Tolonen U, Suhonen-Malm AS, & Myllyla VV (2002). Effects of pregnancy on mothers' sleep. *Sleep Med*, 3(1), 37–42. [PubMed: 14592252]
- Hoyt M, Bower J, Irwin M, Weierich M, & Stanton A (2016). Sleep Quality and Depressive Symptoms After Prostate Cancer: The Mechanistic Role of Cortisol. *Behavioral Neuroscience*.
- Irwin M, Clark C, Kennedy B, Christian Gillin J, & Ziegler M (2003). Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. *Brain Behav Immun*, 17(5), 365–372. [PubMed: 12946658]
- Izci B, Martin SE, Dundas KC, Liston WA, Calder AA, & Douglas NJ (2005). Sleep complaints: snoring and daytime sleepiness in pregnant and pre-eclamptic women. *Sleep Med*, 6(2), 163–169. doi: 10.1016/j.sleep.2004.12.007 [PubMed: 15716220]
- Jomeen J, & Martin C (2007). Assessment and relationship of sleep quality to depression in early pregnancy. *Journal of Reproductive and Infant Psychology*, 25(97–99).
- Kamysheva E, Skouteris H, Wertheim E, Paxton S, & Milgrom J (2010). A prospective investigation of the relationships among sleep quality, physical symptoms, and depressive symptoms during pregnancy. *Journal of Affective Disorders*, 123(1–3), 317–320. [PubMed: 19822370]
- Koban M, Wei W, & Hoffman G (2006). Changes in hypothalamic corticotropin-releasing hormone, neuropeptide Y, and proopiomelanocortin gene expression during chronic rapid eye movement sleep deprivation of rats. *Endocrinology*, 147(1), 421–431. [PubMed: 16210372]

- Kumari M, Badrick E, Ferrie J, Persi A, Marmot M, & Chandola T (2009). Self-reported sleep duration and sleep disturbance are independently associated with cortisol secretion in the Whitehall II study. *Journal of Endocrinology and Metabolism*, 94(12), 4801–4809.
- Leproult R, Copinschi G, Buxton O, & Van Cauter E (1997). Sleep loss results in an elevation of cortisol levels the next evening. *Sleep*, 20(10), 865–870. [PubMed: 9415946]
- Ly J, McGrath J, & Gouin J (2015). Poor sleep as a pathophysiological pathway underlying the association between stressful experiences and the diurnal cortisol profile among children and adolescents. *Psychoneuroendocrinology*, 57, 51–60. [PubMed: 25889840]
- Machado RB, Tufik S, & Suchecki D (2010). Modulation of Sleep Homeostasis by Corticotropin Releasing Hormone in REM Sleep-Deprived Rats. *Int J Endocrinol*, 2010, 326151. doi: 10.1155/2010/326151 [PubMed: 20628511]
- Naghi I, Keypour F, Ahari SB, Tavalai SA, & Khak M (2011). Sleep disturbance in late pregnancy and type and duration of labour. *J Obstet Gynaecol*, 31(6), 489–491. doi: 10.3109/01443615.2011.579196 [PubMed: 21823845]
- O'Brien LM, Bullough AS, Owusu JT, Tremblay KA, Brincat CA, Chames MC, ... Chervin RD (2013). Snoring during pregnancy and delivery outcomes: a cohort study. *Sleep*, 36(11), 1625–1632. doi: 10.5665/sleep.3112 [PubMed: 24179294]
- Okun M, Dunkel Schetter C, & Glynn LM (2011). Poor sleep quality is associated with preterm birth. *Sleep*, 34(11), 1493–1498. [PubMed: 22043120]
- Okun M, Hall M, & Coussons-Read M (2007). Sleep disturbances increase interleukin-6 production during pregnancy: implications for pregnancy complications. *Reproductive Sciences*, 14(6), 560–567. [PubMed: 17959884]
- Okun M, Luther J, Prather A, Perel J, Wisniewski S, & Wisner K (2011). Changes in sleep quality but not hormones predict time to postpartum depression recurrence. *Journal of Affective Disorders*, 130(3), 378–384. [PubMed: 20708275]
- Owusu JT, Anderson FJ, Coleman J, Oppong S, Seffah JD, Aikins A, & O'Brien LM (2013). Association of maternal sleep practices with pre-eclampsia, low birth weight, and stillbirth among Ghanaian women. *Int J Gynaecol Obstet*, 121(3), 261–265. doi: 10.1016/j.ijgo.2013.01.013 [PubMed: 23507553]
- Pruessner J, Wolf O, Hellhammer D, Buske-Kirschbaum A, von Auer K, Jobst S, ... Kirschbaum C (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sciences*, 61(26), 2539–2549. [PubMed: 9416776]
- Ravishankar S, Bourjeily G, Lambert-Messerlian G, He M, De Paepe M, & Gundogan F (2015). Evidence of Placental Hypoxia in Maternal Sleep Disordered Breathing. *Pediatric and Developmental Pathology*.
- Rush AJ, Giles DE, Schlessler MA, Fulton CL, Weissenburger J, & Burns C (1986). The Inventory for Depressive Symptomatology (IDS): preliminary findings. *Psychiatry Res*, 18(1), 65–87. [PubMed: 3737788]
- Sandman CA, Davis EP, Buss C, & Glynn LM (2011). Prenatal programming of human neurological function. *Int J Pept*, 2011, 837596. doi: 10.1155/2011/837596 [PubMed: 21760821]
- Sandman CA, Glynn L, Schetter CD, Wadhwa PD, Garite TJ, Chicx-DeMet A, & Hobel C (2006). Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (CRH): priming the placental clock. *Peptides*, 27(6), 1457–1463. [PubMed: 16309788]
- Skouteris H, Wertheim E, Germano C, Paxton S, & Milgrom J (2009). Assessing sleep during pregnancy: a study across two time points examining the Pittsburgh Sleep Quality Index and associations with depressive symptoms. *Womens Health Issues*, 19(1), 45–51. [PubMed: 19111787]
- Spiegel K, Leproult R, & Van Cauter E (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet*, 354(9188), 1435–1439. doi: 10.1016/S0140-6736(99)01376-8 [PubMed: 10543671]
- Stinson L, Stroud LR, Buka S, Eaton C, Lu B, Niaura R, & Loucks E (2015). Prospective Evaluation of Associations Between Prenatal Cortisol and Adulthood Coronary Heart Disease Risk: The New England Family Study. *Psychosomatic Medicine*.

- Strange LB, Parker KP, Moore ML, Strickland OL, & Bliwise DL (2009). Disturbed sleep and preterm birth: a potential relationship? *Clin Exp Obstet Gynecol*, 36(3), 166–168. [PubMed: 19860360]
- Suzuki S, Dennerstein L, Greenwood KM, Armstrong SM, Sano T, & Satohisa E (1993). Melatonin and hormonal changes in disturbed sleep during late pregnancy. *J Pineal Res*, 15(4), 191–198. [PubMed: 8120797]
- Tomfohr L, Edwards K, & Dimsdale J (2012). Is obstructive sleep apnea associated with cortisol levels? A systematic review of the research evidence. *Sleep Medicine Reviews*, 16(3), 243–249. [PubMed: 21803621]
- Van Cauter E, & Spiegel K (1999). Circadian and sleep control of hormonal secretions In Turek F & Zee P (Eds.), *Regulation of sleep and circadian rhythms* (pp. 397–425). New York: Marcel Decker.
- Van Lenten S, & Doane L (2016). Examining multiple sleep behaviors and diurnal salivary cortisol and alpha-amylase: Within- and between-person associations. *Psychoneuroendocrinology*, 68, 100–110. [PubMed: 26963376]
- Volkovich E, Tikotzky L, & Manber R (2016). Objective and subjective sleep during pregnancy: links with depressive and anxiety symptoms. *Archives of Womens Mental Health*, 19(1), 173–181.
- Wadhwa PD, Garite TJ, Porto M, Glynn L, Chicz-DeMet A, Dunkel-Schetter C, & Sandman CA (2004). Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. *Am J Obstet Gynecol*, 191(4), 1063–1069. doi: 10.1016/j.ajog.2004.06.070 [PubMed: 15507922]
- Wilhelm I, Born J, Kudielka BM, Schlotz W, & Wust S (2007). Is the cortisol awakening rise a response to awakening? *Psychoneuroendocrinology*, 32(4), 358–366. doi: 10.1016/j.psyneuen.2007.01.008 [PubMed: 17408865]
- Wright K, Drake A, Frey D, Fleshner M, Desouza C, Gronfier C, & Czeisler C (2015). Influence of sleep deprivation and circadian misalignment on cortisol, inflammatory markers, and cytokine balance. *Brain Behavior and Immunity*, 47, 24–34.
- Zeiders K, Doane L, & Adam EK (2011). Reciprocal relations between objectively measured sleep patterns and diurnal cortisol rhythms in late adolescence. *Journal of Adolescent Health*, 48, 566–571. [PubMed: 21575815]

Figure 1. Subjective sleep quality at 36 weeks' gestation predicts evening cortisol at 36 weeks' gestation.

Note: Diurnal cortisol patterns were plotted at the lowest and highest quartile of the Pittsburgh Sleep Quality Index (PSQI) global score collected at 36 weeks' gestation. The PSQI was analyzed as a continuous measure in analyses. * $p < .05$

Figure 2. Maternal anxiety symptoms mediate the association between subjective sleep quality and evening cortisol at 36 weeks' gestation.

Note. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) global score collected at 36 weeks' gestation. Anxiety symptoms were measured at 36 weeks' gestation using the Hamilton Anxiety Rating Scale. * indicates mediation analysis after adjusting for maternal anxiety symptoms.

Table 1.**Maternal and Infant Characteristics**

Maternal Characteristics			
	<i>Mean or %</i>	<i>SD</i>	<i>Range</i>
Maternal Age (years)	26	5	18–40
Gravida	2	2	1–9
Maternal Education (% <High School)	20%		
Race (% Non-Hispanic white)	44%		
Annual Income (% < \$10K)	21%		
Marital Status (% married)	36%		
Pre-pregnancy Body Mass Index	26	6	19–56
PSQI [/] global score 24 weeks	6	4	0–15
PSQI [/] global score 36 weeks	7	4	0–16
Infant Characteristics			
	<i>Mean or %</i>	<i>SD</i>	
Gestational Age at Birth (weeks)	39	2	24–42
Preterm Birth (<36 weeks)	4%		
Birth Weight (grams)	3323	534	600–4620
Low Birth Weight (<2500 grams)	4%		
APGAR score at 5 minutes	9	1	2–10

Note:

[/]PSQI= Pittsburgh Sleep Quality Index