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Maternal short sleep duration is associated with increased levels of inflammatory markers at 3 years postpartum

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ABSTRACT

The purpose of this study was to examine the association of short sleep duration among women in the first year postpartum with inflammation at 3 years postpartum. We studied 479 women in Project Viva, a prospective cohort. At 6 months and 1 year postpartum, women reported the number of hours they slept in a 24-hour period, from which we calculated a weighted average of daily sleep. We used multivariable median regression analyses to predict the independent effects of short sleep duration (≤5 vs >5 h/d) on markers of inflammation, for example, interleukin 6 (IL-6) and C-reactive protein at 3 years postpartum. Women's mean (SD) hours of daily sleep in the first year postpartum was 6.7 (0.96) hours. After adjusting for age, race/ethnicity, education, parity, pre-pregnancy body mass index, excessive gestational weight gain, and gestational age at delivery, we found that postpartum sleep ≤5 h/d was associated with elevated IL-6 (β, 0.25 pg/mL; 95% confidence interval, 0.14-0.43) compared with >5 h/d. Although postpartum sleep ≤5 h/d appeared to also be associated with elevated C-reactive protein (β 0.15 mg/dL; 95% confidence interval, –0.08 to 0.52), these results did not reach statistical significance. Short sleep duration in the first year postpartum is associated with elevated levels of the proinflammatory marker, IL-6, at 3 years postpartum.

1. Introduction

Mounting epidemiologic evidence indicates that short (<5 h/day) duration of sleep is a risk factor for obesity, type 2 diabetes mellitus, coronary heart disease, hypertension, and all-cause mortality in adults independent of other measured risk factors [1-7]. Sleep loss [8] and circadian misalignment [9] have also been associated with markers of metabolic dysfunction and with adverse levels of adipokines. A group that may be at particularly high risk for the adverse effects of short sleep duration and sleep loss is women in the postpartum period.

Substantial sleep restriction and reduced sleep quality in the postpartum period have been well documented and found to be associated with women's physical and mental health [10,11]. Emerging evidence also suggests that postpartum sleep restriction is associated with greater adiposity and excessive postpartum weight retention 1 and 3 years after delivery [12,13]. Although studies have found a cross-sectional association between sleep disturbances during pregnancy

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with increased markers of inflammation [14], no existing studies have prospectively examined the effects of *postpartum* short sleep duration on inflammatory status. Such information would help support interventions to improve sleep quality and quantity in the postpartum period.

The purpose of this study was to examine the longitudinal association of short sleep duration in the first year postpartum with markers of inflammation at 3 years postpartum. We hypothesized that short sleep duration would be associated with elevated markers of inflammation, measured as higher levels of C-reactive protein (CRP) and interleukin-6 (IL-6).

2. Methods and procedures

2.1. Study subjects

The subjects for this study were participants in Project Viva, a prospective cohort study of gestational factors and offspring health [15]. We recruited women who were attending their initial prenatal visit at 8 obstetrical offices of a multispecialty group practice in Massachusetts. Eligibility criteria included fluency in English, gestational age less than 22 weeks at the initial prenatal clinical appointment, and singleton pregnancy. Details of recruitment and retention procedures are available elsewhere [15].

Of the 2128 participating women who gave birth, 1579 were invited to a 3-year follow-up examination because they had completed dietary questionnaires during pregnancy. We excluded 818 women from the current analysis because they had delivered another child since the birth of the index child 3 years previously, they had type 1 or type 2 diabetes mellitus, or they did not attend the 3-year visit. Of the remaining 761 women, 586 had measures of sleep duration at 6 months and 1 year; 480 provided a blood sample at 3 years postpartum. We included 479 women with CRP or IL-6 levels in the current analysis.

After obtaining informed consent, we performed in-person study visits with the mother immediately after delivery and at 6 months and 3 years postpartum. Mothers completed mailed questionnaires at 1 and 2 years postpartum. Institutional review boards of participating institutions approved the study.

2.2. Main exposure: maternal postpartum sleep duration

At 6 months and 1 year postpartum, we asked women to report hours of sleep duration within a 24-hour period using the question: "In the past month, how many hours of sleep do you get in an average 24-hour period?" Response options were in integers for hours of sleep at each period. We calculated a weighted average of sleep duration from 6 months to 1 year as the mean of 6-month and 1-year values.

2.3. Main outcomes: markers of inflammation

We tested all blood samples for CRP and IL-6. Blood samples were collected by trained phlebotomists and transferred within 24 hours for storage in liquid nitrogen freezers. Sample testing was performed at the Children's Hospital Boston Clinical Chemistry Laboratory. We assessed CRP using an immunoturbidimetric high-sensitivity assay on a Hitachi 911 analyzer and reagents and calibrators from Denka Seiken (Niigata, Japan). Plasma IL-6 was measured by ultrasensitive ELISA. Inter- and intra-assay coefficients of variation for our biosamples ranged from 2% to 10%.

2.4. Study covariates

Using a combination of self-administered questionnaires and interviews, we also collected information about maternal age, education, parity, household income, and race/ethnicity. Mothers reported their pre-pregnancy weight and height. We calculated gestational weight gain as the difference between the last weight before delivery and the self-reported pre-pregnancy weight. We categorized gestational weight gain as inadequate, adequate, or excessive for pre-pregnancy BMI categories using the new Institute of Medicine guidelines [16]. At 3 years postpartum, we measured women's weight to the nearest 0.1 kg using a research quality scale, measured height to the nearest 0.1 cm using a stadiometer, and calculated body mass index as kilograms divided by the square of height in meters. At 3 years postpartum we also assessed maternal total physical activity (walking, moderate, and vigorous activity, hours per week) and television viewing (hours per week).

2.5. Statistical analysis

Our main exposure of interest was maternal short sleep duration defined as an average daily sleep duration from 6 months to 1 year ≤5 h/d (vs >5 h/d).

We first performed univariate analyses to assess the distribution of all variables included in the analyses. We then used bivariate analyses to examine the association of our exposure of interest with study covariates and outcomes. We used multiple regression models to assess the independent effects of short sleep duration on our main outcomes. We used median regression [17] because the distributions of the CRP and IL-6 were nongaussian. In multivariable models, we included only those covariates that were of a priori interest or confounded associations of sleep duration with our outcomes. Model 1 was unadjusted. Model 2 was adjusted for maternal age, race/ethnicity, education, parity, pre-pregnancy BMI, excessive gestational weight gain, and gestational age at delivery. To examine the confounding effects of maternal BMI, total physical activity, and television viewing at the time of cytokine measurement at 3 years postpartum, we also added these variables to model 1 in subsequent models. We report regression estimates (β) and 95% confidence intervals (CIs) for the main exposure. We performed data analyses with SAS version 9.2 (SAS Institute, Cary, NC).

3. Results

Characteristics of study participants are shown in Table 1. The mean (SD) of daily sleep duration from 6 months to 1 year was 6.7 hours (0.97 hours); 74 (13%) women were sleeping ≤5 h/d. Mean (SD) for pre-pregnancy BMI was 24.9 kg/m^2 (5.2 kg/m^2). Means, standard deviations, medians, and interquartile range of CRP and IL-6 are shown in Table 2.

Table 1 – Unadjusted and bivariate associations of maternal characteristics with short sleep duration from 6 months to 1 year postpartum

Sociodemographic characteristic	N	Overall	Average daily sleep duration (h/d), 6 mo to 1 y postpartum		P[a]
			≤5 h (n = 68)	>5 h (n = 411)	
			Mean (SD) or %		
Maternal age at 3 y postpartum (y)	479	37.8 (5.1)	38.7 (4.1)	37.7 (5.3)	.09
Gestational age at delivery (wk)	479	39.4 (2.0)	39.4 (2.6)	39.5 (1.9)	.80
Pre-pregnancy BMI (kg/m^2)	479	24.9 (5.2)	25.3 (5.6)	24.9 (5.2)	.55
BMI at 3 y postpartum (kg/m^2)	470	26.3 (6.2)	27.2 (6.5)	26.2 (6.2)	.21
Total physical activity at 3 y postpartum (h/wk)	452	7.1 (6.8)	6.9 (6.7)	7.1 (6.9)	.79
Television viewing at 3 y postpartum (h/wk)	452	9.7 (8.4)	10.3 (9.3)	9.6 (8.2)	.54
Institute of Medicine gestational weight gain category					.95
Adequate/inadequate	218	46	46	46	
Excessive	257	54	54	54	
Race/ethnicity					.04
White	356	74	71	75	
Black	55	11	10	12	
Hispanic	30	6	10	6	
Asian	19	4	0	5	
Other	19	4	9	3	
Parity					.15
1	132	28	24	28	
2	236	49	44	50	
3+	111	23	32	22	
College graduate					.49
No	145	30	34	30	
Yes	334	70	66	70	
Household income					.34
< $40 000/y	52	11	15	11	
≥ $40 000/y	401	89	85	89	

Data from 479 participants in Project Viva who presented for follow-up at 3 years postpartum without an intervening birth.
[a] *P* from *t* test for continuous and χ^2 for categorical characteristics.

Sleep duration ≤5 h/d was associated with higher levels of IL-6 at 3 years postpartum (Table 2). In multivariable analyses adjusted for maternal age, race/ethnicity, education, parity, pre-pregnancy BMI, excessive gestational weight gain, and gestational age at delivery, we found that postpartum sleep ≤5 h/d was associated with elevated IL-6 (β 0.25 pg/mL; 95% CI, 0.14-0.43) at 3 years postpartum (Table 3). Although postpartum sleep ≤5 h/d appeared to also be associated with elevated CRP (β 0.15 mg/dL; 95% CI, −0.08 to 0.52), these results did not reach statistical significance (Table 3).

Models adjusted for maternal BMI at 3 years postpartum instead of pre-pregnancy BMI and excessive gestational weight gain showed similar effect estimates for IL-6 (β 0.21 pg/mL; 95% CI, 0.09-0.40) and CRP (β 0.07 pg/mL; 95% CI, −0.04 to 0.35). Further adjustment for total physical activity and TV viewing at 3 years postpartum minimally changed the effect estimates for IL-6 (β 0.32 pg/mL; 95% CI, 0.05-0.57) and CRP (β 0.20 pg/mL; 95% CI, −0.15 to 0.87).

4. Discussion

In this prospective study of women, we found that short sleep duration in the first year postpartum was associated with higher levels of the proinflammatory marker IL-6 and appeared to also be associated with higher CRP levels at

Table 2 – Unadjusted and bivariate associations of maternal inflammatory markers at 3 years postpartum with short sleep duration from 6 months to 1 year postpartum among 479 participants

Inflammatory markers at 3 y postpartum	Overall		Average daily sleep duration (h/d), 6 m to 1 y postpartum				P[a]
			≤5 h		>5 h		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
CRP (mg/dL)	2.3 (5.7)	0.7 (0.3, 2.1)	2.4 (4.3)	0.9 (0.4, 2.4)	2.3 (5.9)	0.7 (0.3, 2.1)	.25
IL-6 (pg/mL)	1.6 (3.0)	0.9 (0.5, 1.5)	2.1 (3.4)	1.1 (0.7, 1.8)	1.5 (2.9)	0.8 (0.5, 1.4)	.01

IQR indicates interquartile range.
[a] *P* values are from Wilcoxon rank sum test for nonnormally distributed variables.

Table 3 – Inflammatory markers at 3 years postpartum, by average daily sleep duration from 6 months to 1 year postpartum among 479 participants

	Average daily sleep duration (h/d), 6 mo to 1 y postpartum		P
	≤5 h	>5 h	
	Effect estimate (95% CI)		
CRP (mg/dL)[a]			
Model 1. Unadjusted	0.12 (–0.10 to 0.88)	0.00 (ref)	.60
Model 2. Multivariable adjusted[b]	0.15 (–0.08 to 0.52)	0.00 (ref)	.39
IL-6 (pg/mL)[a]			
Model 1. Unadjusted	0.29 (–0.02 to 0.68)	0.00 (ref)	.12
Model 2. Multivariable adjusted[b]	0.25 (0.14 to 0.43)	0.00 (ref)	.01

[a] Effect estimates are from multivariable median regression. Estimates reflect the difference from the median of each outcome associated with sleep duration ≤5 h/d.
[b] Model 2 is adjusted for maternal age, race/ethnicity, education, parity, pre-pregnancy BMI, excessive gestational weight gain, and gestational age at delivery.

3 years postpartum independent of maternal sociodemographic characteristics. Our observed estimates were independent of pre-pregnancy BMI and excessive gestational weight gain.

Previous studies have found that short sleep duration is associated with increased risk of coronary heart disease [18] and incident diabetes [1]. The mechanisms relating sleep duration to adverse cardiometabolic outcomes are not clear, but one possible explanation is the effects of sleep restriction on inflammation. Experimental studies and prospective cohort studies of adults have shown associations of sleep restriction with increases in the proinflammatory cytokines, IL-6, and CRP [4,19-21]. Studies among pregnant women have also related short sleep duration and poor sleep efficiency in both mid and late pregnancy to higher stimulated levels of IL-6 [14]. Elevations in both CRP and IL-6 predict an increased risk for adverse cardiometabolic outcomes such as myocardial infarction and diabetes [22,23]. However, it is not known if the associations of sleep duration and inflammation extend to women in the postpartum period. In this study we found that short sleep duration in the first postpartum year was associated with higher IL-6 at 3 years postpartum. The association was robust to adjustment for a wide range of potential confounders. Thus, it is possible that sleep curtailment in the first year postpartum might lead to elevations in inflammatory markers that could increase women's risks of adverse cardiometabolic outcomes. To our knowledge, our study is the first to report associations of maternal *postpartum* sleep duration and inflammation.

Although we found that short sleep duration was associated with higher levels of CRP, these results did not reach statistical significance. Plasma CRP is a marker of systemic inflammation induced by proinflammatory cytokines in the liver [24]. Its production is influenced by tumor necrosis factor α (TNF-α) and IL-6, both of which are upstream of CRP [25]. Thus, the levels of CRP depend on both TNF-α and IL-6 activity. We observed a relationship between short sleep duration and higher levels of IL-6 but did not have data on TNF-α or circulating soluble TNF-α receptor II, the circulating levels of which reflect TNF-α activity. Thus, it is possible that the effects of short sleep duration on IL-6 are proportionally stronger than those on TNF-α and/or that their effects on CRP lag behind the IL-6 elevations. Longer-term follow-up could reveal stronger associations.

Several limitations of this study deserve mention. First, although we had measures of total sleep duration, we did not have direct measures of sleep (eg, from actigraphs) nor did we have measures of snoring or of other signs of obstructive sleep apnea. Thus, we are not able to determine whether our observed effects were independent of snoring and obstructive sleep apnea, both of which have been found to be associated with adverse inflammatory biomarkers [4,26]. Second, we did not have measures of sleep during pregnancy or beyond 1 year postpartum. Thus, it is possible that postpartum sleep is a marker of sleep at 3 years. In addition, we did not measure inflammatory biomarkers before pregnancy to control for differences in these measures that may have preceded changes in postpartum sleep. Fourth, although women in the study had diverse racial/ethnic backgrounds, their education and income levels were relatively high. Our results may not be generalizable to more socioeconomically disadvantaged populations. Finally, in any observational study, it is possible that unmeasured characteristics might explain the observed associations between exposure and outcome.

5. Conclusions

Short sleep duration in the first year postpartum is associated with higher levels of inflammatory markers at 3 years postpartum. Given the adverse physiological effects of chronic inflammation, our findings suggest that there is significant public health impact among the sizable number of women who experience prolonged sleep curtailment in the first postpartum year.

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