

## Title page

1   **Title:** Sleep duration (24-hour) is associated with birth weight in nulliparous but not in  
2   multiparous women.

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**Word count: 5.007**

**Number of figures: 2**

**Number tables: 4**

## ABSTRACT

**Objective.** To evaluate nightly, napping, and 24-hour sleep duration throughout pregnancy and the associations between these measures and birth weight (BW) z-score among nulliparous and multiparous women. **Methods.** In a prospective cohort of 176 pregnant women followed at a health care center in Rio de Janeiro, Brazil, nightly, napping, and 24-hour sleep duration variables were constructed for each trimester and BW z-score was calculated based on the Intergrowth-21<sup>st</sup> standard. Linear mixed effects (LME) analyses were performed to assess the longitudinal evolution of sleep duration and the best unbiased linear predictors (BLUP) of the random coefficients were estimated. BLUP estimates of sleep duration intercept and slope were included in linear regression models having BW z-score as the outcome. **Results.** Mean hours of nightly sleep decreased over pregnancy in nulliparous women ( $\beta=-0.55$ , 95%CI=-0.83 to -0.27), but the decrease was not statistically significant in multiparous women ( $\beta=-0.19$ , 95%CI=-0.30 to 0.01). 24-hour sleep duration decreased over pregnancy in both multiparous ( $\beta=-0.50$ , 95%CI=-0.76 to -0.25) and nulliparous women ( $\beta=0.77$ , 95%CI=-1.06 to -0.48). Napping sleep duration did not change in either group. Among nulliparous women, both first-trimester 24-hour sleep duration and its change throughout pregnancy were inversely associated with BW ( $\beta=-0.44$ , 95%CI=-0.68 to -0.21;  $\beta=-1.75$ , 95%CI=-3.17 to -0.30, respectively). No associations were detected in multiparous women for nightly and napping sleep duration. **Conclusions.** In nulliparous women, those with greater decreases in sleep duration throughout pregnancy gave birth to newborns with lower BW z-scores.

**Keywords:** sleep; birth weight; pregnancy; parity, cohort.

## Introduction

Pregnancy is a vulnerable period for the development of sleep disturbances, as gestational physiologic and hormonal changes are recognized as possible risk factors for disrupted sleep patterns (Oyiengo et al., 2014). Studies report that short sleep duration is a prevalent issue among pregnant women (Lee et al 2000; Signal et al., 2014; Sivertsen, et al., 2015) and that sleep duration may be additionally influenced by factors such as socioeconomic status (Stringhini et al., 2015), age (Signal et al., 2014), education (Tu et al., 2012), and body mass index (BMI) (Moraes et al., 2013).

Short sleep duration may contribute to undesirable health outcomes for both mother and newborn, such as inadequate gestational weight gain (GWG) (Abeysena et al., 2009; Restall et al., 2014), hypertension (Williams et al., 2010), gestational diabetes (Qiu et al., 2010; O’Keeffe et al., 2013), and preterm birth (Micheli et al., 2011). Other types of sleep disorders such as snoring, breathing pauses, and obstructive sleep apnea have been associated with higher rates of small for gestational age (SGA) births, low birth weight (LBW), and fetal growth restriction (Micheli et al., 2011; Chen et al., 2012; Howe et al., 2015).

Extremes of birth weight (BW) are considered indicators of perinatal morbidity and mortality (Risnes et al., 2011; WHO, 2006; Wilcox, 2001) and have also been associated with an increased risk of cardiovascular diseases in adulthood (Wilcox, 2001; Barker, 1995). In light of these potential health implications, it is important to identify possible modifiable determinants of BW. Few studies have examined the relationship between sleep duration in pregnancy and BW (Abeysena et al., 2009; Micheli et al., 2011; Zafarghandi et al., 2012; Howe et al., 2015), and their results have been inconsistent, likely due to different study designs, statistical approaches, and sample characteristics. One key methodological difference in these studies is the handling of gestational age in relation to BW, even when studies are restricted to term neonates. Studies assessing LBW as an outcome did not adjust for gestational age (Micheli et al., 2011; Zafarghandi et al., 2012) and the ones evaluating the incidence of SGA births (that take into account gestational age at birth) adopted very specific BW references (Abeysena et al., 2009; Micheli et al., 2011; Howe et al., 2015) that limited the generalizability of their results. To remedy this problem, we used a BW z-score based on the International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century

(Intergrowth-21<sup>st</sup>) standards for newborn weight (Villar et al., 2014). The Intergrowth sample was derived from eight geographically defined urban populations in which most of the health and nutrition needs of mothers were met, adequate antenatal care was provided, and there were no major environmental constraints on growth.

We hypothesized that the relationship between sleep duration and BW z-score would differ between nulliparous and multiparous women in contrast to prior studies that considered parity a potential confounder and adjusted for it in their analyses (Micheli et al., 2011; Howe et al., 2015). Specifically, we suspected that the relationship would be weaker among multiparous women. Indeed, Lee et al. (2000) have shown that parous women have shorter sleep duration and reduced sleep efficiency in the preconception period compared to non-parous women, even if their older children are sleeping through the night.

We hypothesized that sleep duration would be inversely associated with BW z-score in this cohort of Brazilian pregnant women. The aim of this study was to 1) describe nightly, napping, and 24-hour sleep duration throughout pregnancy and 2) to evaluate if first trimester sleep and change in sleep throughout pregnancy were associated with BW z-score among nulliparous and multiparous women.

## Methods

### *Setting and participants*

This analysis used data from a prospective cohort study conducted at a public health center in Rio de Janeiro, Brazil, that evaluated maternal and child health during pregnancy and post-partum. Pregnant women were recruited between November 2009 and October 2011, and were evaluated during four follow-up periods: between 5-13 (baseline), 20-26, and 30-36 gestational weeks, and 30-45 days post-partum.

To be included in this study, women had to be aged 20 to 40 years; between 5 and 13 weeks of pregnancy at baseline; and without known infectious or chronic non-communicable diseases, other than obesity. Ninety-two percent (n=299) of women attending the prenatal care clinic who met the eligibility criteria agreed to participate. After the first trimester clinical evaluation, women were excluded on the basis of twin pregnancy (n=4), confirmed presence of infectious or non-communicable disease (except obesity) (n=21), and >13weeks of gestation (n=15). We also excluded women

who declined further prenatal care, who were transferred to other units (n=5), or who experienced miscarriage (n=25) or stillbirth (n=5). In the current analysis, we opted to include only women with information on all variables used in the adjusted analyses, yielding a study sample of 176 pregnant women and their newborns.

#### *Measurements*

BW (g), gestational age at delivery (weeks), and the sex of the newborn (male or female) were obtained at the post-partum interview from the child vaccination booklet, which was filled out at the time of delivery by medical staff. BW z-score adjusted for gestational age at birth and sex was calculated according to the Intergrowth-21<sup>st</sup> standards (Villar et al. 2014). Gestational age was calculated based on data from the first ultrasonography examination if it was performed prior to 24 weeks of gestation. In cases where this measure was unavailable, the date of the last menstrual period was used.

At each trimester visit, women reported their mean sleep duration (hours and minutes) at night and during the day (napping) and based on this information we calculated 24-hour sleep duration. During data collection, the interviewers instructed women to report their average sleep duration over the period between interviews; at the first-trimester interview women reported mean sleep duration since getting pregnant. For our exploratory analysis, we opted to categorize nightly and 24-hour sleep duration as  $\leq 6$  vs.  $> 6$  hours since this dichotomous cut-off point is frequently adopted in studies that assess pregnant women's sleep duration (Signal et al., 2014; Sivertsen, et al., 2015). Our sample size did not allow us to categorize the variable sleep duration into three or more groups.

Maternal body weight (kg) was obtained at baseline and at all follow-up visits using a digital scale (Filizzola PL 150, Filizzola Ltda, Brazil) with a precision of 0.1 kg. Height was measured twice at baseline (mean values were used), using a portable stadiometer with a precision of 0.1 cm (Seca Ltd., Hamburgo, Germany). Height and weight measurements were taken according to standardized techniques (Gordon et al., 1988). Pre-pregnancy weight was self-reported at the first trimester visit and pre-pregnancy BMI was calculated. Women were categorized as under/normal weight ( $<25.0 \text{ kg/m}^2$ ) or as overweight/obese ( $\geq 25.0 \text{ kg/m}^2$ ). Total GWG was calculated as the difference between the last weight measured during pregnancy (mean  $38 \pm 2.3$

gestational weeks) and the reported pre-pregnancy weight. GWG was analyzed in kilograms (kg) and also categorized as insufficient, adequate or excessive according to the guidelines of the Institute of Medicine (IOM, 2009) that considers the pre-pregnancy BMI status.

Data on the following maternal characteristics were collected throughout pregnancy with the application of structured questionnaires: monthly per capita family income (USD\$), depressive symptoms [score of Edinburgh Postnatal Depression Scale (EPDS)], current smoking (no/yes), alcohol consumption (no/yes), and practice of leisure-time physical activity - LTPA (no/yes). Information on maternal age (years), education (years of study), marital status (lives with a partner, does not live with a partner), and planning of pregnancy (no/yes) were collected only at baseline. Women who reported no previous live births were categorized as nulliparous and women reporting at least one previous live delivery were categorized as multiparous. Caloric intake was obtained using a validated semi-quantitative food frequency questionnaire (FFQ) (Sichieri et al., 1998) administered twice in the study: at baseline it inquired about pre-gestational and first-trimester food intake and at the end of the third trimester (last follow-up visit) it inquired about second and third trimester food intake. We identified three dietary patterns (healthy, common-Brazilian and processed) by applying principal component analysis to the data derived from the second FFQ. Specific information on the identification of these dietary patterns may be obtained in Eshriqui et al. (2016).

#### *Statistical analyses*

Maternal characteristics were described according to parity categories and expressed as means and standard deviations (SD) or absolute and relative frequencies (%) for continuous and categorical/binary variables, respectively. Additionally, means of BW z-score were compared between categories of selected variables using unpaired Student's *t* tests and ANOVA.

Scatterplots were constructed in order to graphically represent the longitudinal evolution of sleep duration throughout pregnancy and the associations between 24-hour first-trimester sleep duration and BW z-scores, both according to parity categories.

We performed a two-stage analysis in order to assess the association between sleep duration time trend during pregnancy and BW z-score. First, we constructed linear

mixed effects (LME) models with sleep duration variables as the outcomes to assess the longitudinal evolution of sleep duration throughout pregnancy. We included gestational trimester at sampling as a fixed effect and the gestational week in each follow-up point as a random effect. After the models were run, the best linear unbiased predictors (BLUP) of the random coefficients were estimated. The predicted intercept referred to the mean sleep duration when the time variable was equal to zero (regression intercept) and the predicted slope referred to the trend in sleep duration changes during pregnancy. This approach considers that repeated measures are correlated and allows the estimation of time trend of exposure even for women with missing values across pregnancy, increasing the power of the analysis (Chen et al., 2015). In the second stage, the BLUP estimates of sleep duration intercept and slope were simultaneously included as continuous predictors in a linear regression models having BW z-score as the outcome. We reported estimated effects as regression coefficients ( $\beta$ ) and 95% confidence intervals (95% CI).

Two types of adjusted models were performed aiming to find the best relationship between the main exposure (sleep duration) and the outcome (birth weight), and also to test the effect of potential mediators on this relationship. Model 1 was adjusted for confounding. Potential confounders were selected based on biological plausibility and included one by one in regression models with the sleep duration variable as the predictor and BW z-score as the outcome. If the inclusion of a specific variable generated at least a 10% change in the beta value (compared to the beta from bivariate analysis: sleep duration and BW z-score), the variable was included in the adjusted model. The following variables were considered confounders: woman's age, pre-pregnancy BMI, smoking, EPDS score, total GWG adequacy, LTPA, education, marital status, per-capita family income, planned pregnancy and birth order (the latter only for multiparous women). A second model (model 2) was further adjusted for the mediator, i.e. caloric intake, in addition to those variables considered as confounders in model 1. The modeling approach implemented allows the estimation of different effects that account either for confounding adjustment or mediation effect. Model 1 allows the estimation of the total effect of sleep duration on birth weight, while model 2 provides the direct effect of sleep duration on birth weight. Finally, the indirect effect of sleep duration on birth, i.e. the one mediated by caloric intake can be assessed considering the



absolute differences between beta coefficients from the adjusted models (model 1 and model 2) (Richiardi et al., 2013).

Statistical analyses were performed in Stata Data Analysis and Statistical Software (STATA) version 12.0 (Stata Corp., College Station, TX, USA) and a significance level of  $p < 0.05$  was adopted.

### *Ethical approval*

The Research Ethics Committees of the Municipal Secretariat of Health and Civil Defense of the State of Rio de Janeiro approved the cohort study (Protocol number: 0012.0.249.000-09). All participants signed consent forms, which were obtained freely and spontaneously after all necessary clarifications had been provided.

## **Results**

We evaluated sleep duration of 176, 166 and 173 women in the first, second and third gestational trimesters, respectively. Most women lived with a partner (80.7%) and did not report alcohol consumption (83.0%), smoking (94.3%) or LTPA (95.4%) in early pregnancy. Women were from low socio-economic status families and had an average of US\$ 314.3 of monthly per-capita family income and 8.7 years of schooling. Newborns presented a mean BW of 3281.4g (equivalent to a BW z-score of 0.323 according to the Intergrowth-21<sup>st</sup> standard). There were no significant differences in BW between those born to nulliparous and multiparous women. Multiparous women were older (28.6 vs. 24.5 years,  $p$ -value  $< 0.001$ ), more frequently lived with a partner (88.2 vs. 67.7 %,  $p$ -value = 0.001), and had lower mean years of schooling (7.9 vs. 10.0,  $p$ -value  $< 0.001$ ) and monthly per-capita family income (281.7 vs. 369.7 US\$,  $p$ -value = 0.003) when compared to nulliparous women (**Table 1**).

In the first trimester, nulliparous women reported longer nightly (8.8 vs. 7.7 hours,  $p$ -value  $< 0.001$ ) and 24-hour sleep durations (10.0 vs. 9.0 hours,  $p$ -value = 0.012) than multiparous women. A significant difference was also observed for nightly sleep duration in the second trimester (8.5 vs. 7.8 hours,  $p$ -value=0.012). No significant differences were observed for napping sleep duration in the second trimester or for any of the sleep duration variables in the third trimester (**Table 2**).

Mean nightly sleep duration significantly decreased over the course of pregnancy in nulliparous women ( $\beta=-0.55$ , 95%CI: -0.83 to -0.27), but the decrease was not statistically significant in multiparous women ( $\beta=-0.19$ , 95%CI:-0.30 to 0.01). 24-hour sleep duration also decreased significantly throughout pregnancy in both multiparous ( $\beta=-0.50$ , 95%CI=-0.76 to -0.25) and nulliparous women ( $\beta=-0.77$ , 95%CI=-1.06 to -0.48), but we did not observe significant changes in napping sleep duration in either group (**Figure 1**).

Among multiparous women, those who were overweight or obese before pregnancy and those who gained excessive gestational weight gave birth to newborns with higher BW z-scores compared to newborns of mothers who were normal/underweight before pregnancy (0.73 vs. 0.22 z-score, p-value = 0.009) and who gained insufficient or adequate weight (0.74 vs. -0.04 or 0.46 z-score, p-value = 0.004), respectively. No significant differences in BW z-scores were observed for the other covariates tested (**Table 3**).

Among nulliparous women, first-trimester 24-hour sleep duration was inversely associated with BW z-score ( $\beta=-0.44$ , 95%CI=-0.68 to -0.21) (**Figure 2 and Table 4**) and change in 24-hour sleep duration throughout pregnancy was also negatively associated with BW z-score ( $\beta=-1.75$ , 95%CI=-3.17 to -0.33). The associations identified in model 1 remained statistically significant in model 2 (further adjusted for the mediator). The absolute difference between beta coefficients from model 1 and model 2 was of 6.4% and 10.5%, indicating reductions in the betas of sleep intercept and slope, respectively (**Table 4**).

Regarding nightly sleep duration, there was a trend toward an inverse relationship between the change throughout pregnancy and BW z-score (p-value=0.092). No significant associations with BW z-score were detected for 24-hour or nightly sleep duration in multiparous women or for napping in either group (**Table 4**).

**Table 1.** Characteristics of pregnant women followed at a public health center in Rio de Janeiro, Brazil, 2009-2012.

	Total sample		Nulliparous		Multiparous		
Continuous variables	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	p-value <sup>1</sup>
Age (years)	176	27.1 (5.5)	65	24.5 (4.6)	111	28.6 (5.5)	< 0.001
Education (years of schooling)	176	8.7 (3.0)	65	10.0 (2.3)	111	7.9 (3.1)	< 0.001
Monthly per-capita family income (USD \$)	176	314.2 (195.8)	65	369.7 (189.2)	111	281.7 (193.0)	0.003
Total gestational weight gain (kg)	176	13.3 (5.6)	65	13.7 (5.1)	111	13.0 (5.9)	0.464
Pre-pregnancy BMI (kg/m <sup>2</sup> )	176	24.7 (4.5)	65	24.5 (4.5)	111	24.8 (4.4)	0.607
First-trimester caloric intake (kcal)	175	2423.2 (903.2)	65	2348.6 (1044.4)	110	2467.3 (810.2)	0.402
Second and third-trimester caloric intake (kcal)	168	2375.7 (809.0)	62	2299.6 (751.6)	106	220.3 (841.0)	0.352
Birth weight (grams)	176	3281.4 (529.6)	65	3225.4 (69.5)	111	3314.1 (510.3)	0.284
Birth weight z-score	176	0.3 (1.0)	65	0.1 (1.0)	111	0.4 (1.0)	0.070
Categorical variables	n	%	n	%	n	%	p-value <sup>2</sup>
Cohabitation status							
Lives with a partner	142	80.7	44	67.7	98	88.2	0.001
Does not live with a partner	34	19.3	21	32.3	13	11.7	
First-trimester smoking habit							
No	166	94.3	64	98.5	102	91.9	NA
Yes	10	5.7	1	1.5	9	8.1	
First-trimester alcohol consumption							
No	146	83.0	57	87.7	89	80.2	0.201
Yes	30	17.0	8	12.3	22	19.8	
First-trimester leisure-time physical activity							
No	167	95.4	62	95.4	105	95.5	0.983
Yes	8	4.6	3	4.6	5	4.5	

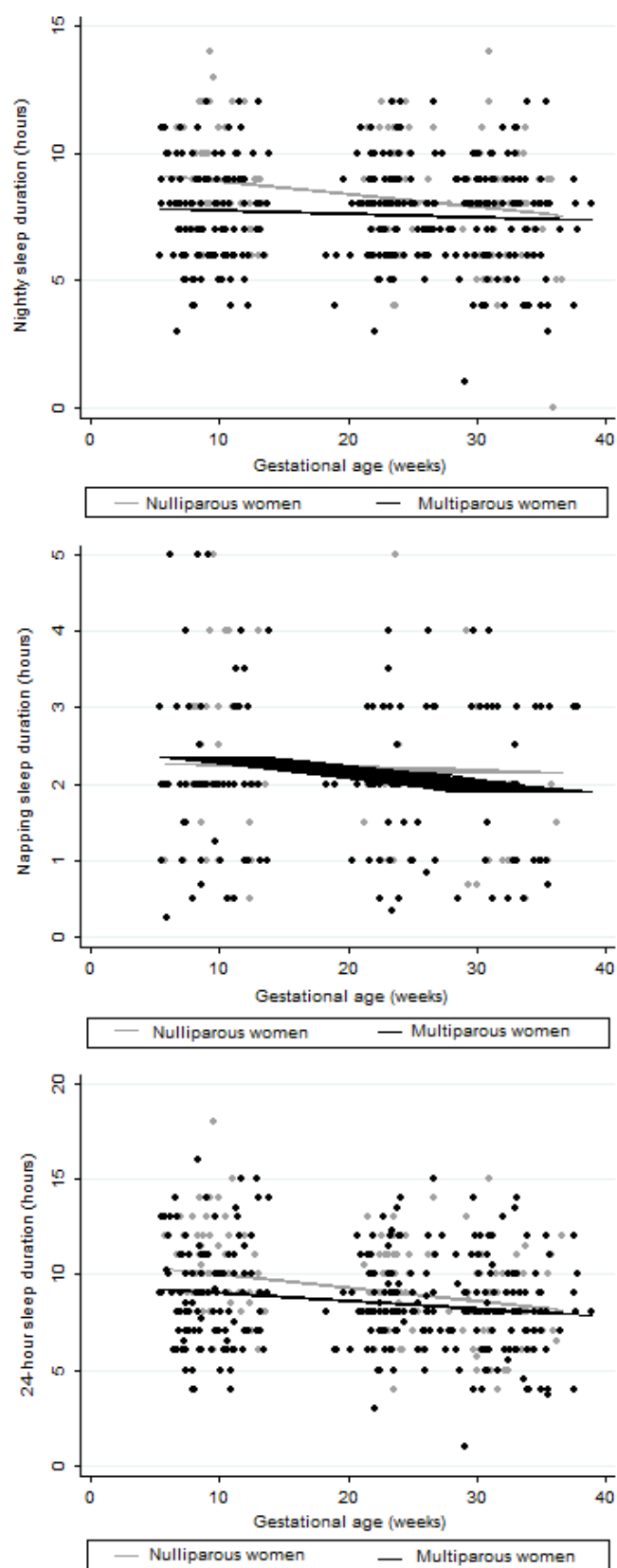
**Notes:** <sup>1</sup> p-value refers to unpaired Student's *t* test comparing nulliparous versus parous women; <sup>2</sup> p-value refers to chi-square test for proportions. **Abbreviations:** SD = standard deviation; BMI = body mass index; NA = not applicable.

**Table 2.** Sleep duration of pregnant women followed at a public health center in Rio de Janeiro, Brazil, 2009-2012.

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	Total sample		Nulliparous		Multiparous		p-value <sup>1</sup>
Sleep duration	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
1 <sup>st</sup> trimester							
Nightly (hours)	176	8.1 (2.0)	65	8.8 (1.9)	111	7.7 (2.0)	<0.001
Napping <sup>2</sup> (hours)	95	2.4 (1.3)	35	2.3 (1.0)	60	2.4 (1.5)	0.684
24-hour (hours)	176	9.4 (2.6)	65	10.0 (2.4)	111	9.0 (2.7)	0.012
2 <sup>nd</sup> trimester							
Nightly (hours)	166	8.1 (1.8)	63	8.5 (1.8)	103	7.8 (1.7)	0.012
Napping <sup>2</sup> (hours)	60	2.0 (0.9)	18	2.2 (0.9)	42	2.0 (0.9)	0.507
24-hour (hours)	166	8.8 (2.1)	63	9.1 (2.0)	103	8.6 (2.2)	0.126
3 <sup>rd</sup> trimester							
Nightly (hours)	173	7.5 (2.1)	64	7.7 (2.2)	109	7.3 (2.0)	0.242
Napping <sup>2</sup> (hours)	63	2.0 (1.3)	24	2.1 (1.7)	39	2.0 (1.0)	0.816
24-hour (hours)	173	8.2 (2.3)	64	8.5 (2.1)	109	8.0 (2.5)	0.222

**Notes:** <sup>1</sup> p-value refers to unpaired Student's *t* test comparing nulliparous and parous women in each pregnancy trimester; <sup>2</sup> missing data for this variable refer to women who reported not to sleep during the day.



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**Figure 1.** Sleep duration throughout pregnancy in a sample of pregnant women followed at a public health center in Rio de Janeiro, Brazil, 2009–2012.

**Notes:** Nightly sleep duration: Unadjusted longitudinal linear regression coefficients (95% confidence intervals) for gestational age in nulliparous and multiparous women, respectively: -0.55 (-0.83 to -0.27) and -0.19 (-0.39 to 0.01). Napping sleep duration: Unadjusted longitudinal linear regression coefficients (95% confidence intervals) for gestational age in nulliparous and multiparous women, respectively: -0.05 (-0.34 to 0.25) and -0.23 (-0.46 to 0.01). 24-hour sleep duration: Unadjusted longitudinal linear regression coefficients (95% confidence intervals) for gestational age in nulliparous and multiparous women, respectively: -0.77 (-1.06 to -0.48) and -0.50 (-0.76 to -0.25).

**Table 3.** Mean birth weight for gestational age and sex (z-score<sup>1</sup>) according to maternal characteristics in a sample of pregnant women and their newborns followed at a public health center in Rio de Janeiro, Brazil, 2009–2012.

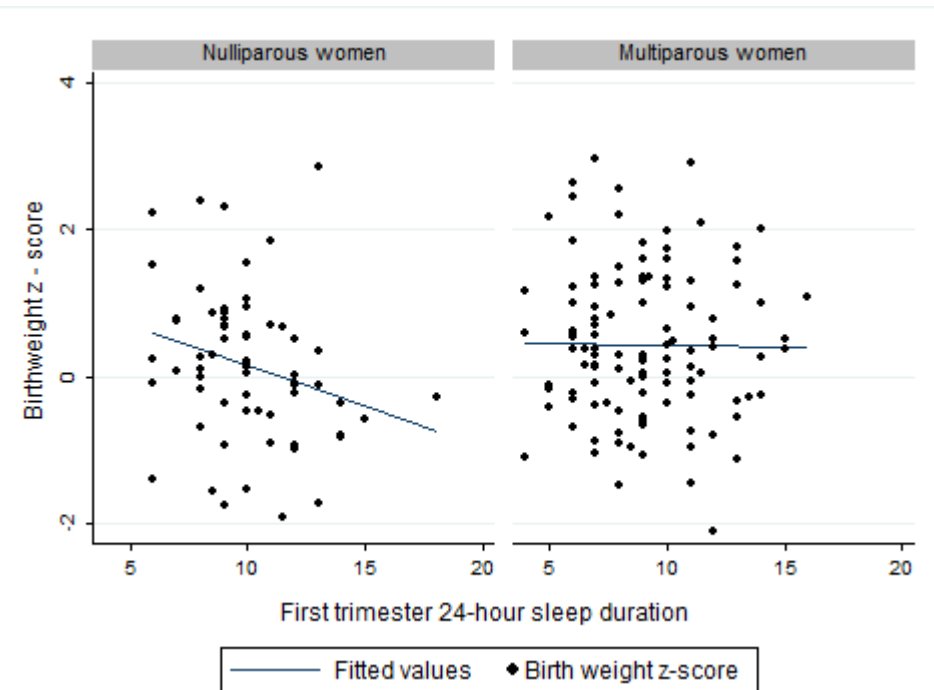
Variables	Nulliparous				Multiparous			
	Birth weight z-score				Birth weight z-score			
	N	%	Mean (SD)	p-value <sup>2</sup>	N	%	Mean (SD)	p-value <sup>2</sup>
First-trimester nightly sleep duration (hours)								
≤ 6	9	13.8	0.48 (1.07)	0.283	33	29.7	0.54 (1.02)	0.454
>6	56	86.2	0.08 (1.02)		78	70.3	0.38 (1.03)	
First-trimester napping sleep duration (hours)								
≤ 1	7	20.0	-0.05 (0.97)	0.982	13	21.7	0.38 (0.84)	0.944
>1	28	80.0	-0.04 (1.12)		47	78.3	0.41 (1.02)	
First-trimester 24-hour sleep duration (hours)								
≤ 6	5	7.7	0.49 (1.42)	0.425	20	18.0	0.57 (1.09)	0.512
>6	60	92.3	0.11 (0.99)		91	82.0	0.40 (1.01)	
Age (years)								
<30	54	83.1	0.17 (1.06)	0.612	64	57.7	0.41 (1.02)	0.823
≥30	11	16.9	-0.01 (0.86)		47	42.3	0.46 (1.04)	
Education (years of schooling)								
<8	9	13.9	0.56 (1.21)	0.180	44	39.6	0.22 (1.08)	0.072
≥8	56	86.1	0.07 (0.99)		67	60.4	0.57 (0.97)	
Monthly per-capita family income (USD \$)								
≤ 300.00	24	36.9	0.04 (1.04)	0.556	76	68.5	0.42 (1.01)	0.846
> 300.00	41	63.1	0.20 (1.02)		35	31.5	0.46 (1.06)	
Marital status								
Lives with a partner	44	67.7	0.22 (1.04)	0.348	98	88.3	0.41 (1.06)	0.639
Does not live with a partner	21	33.3	-0.04 (0.99)		13	11.7	0.56 (0.76)	
First-trimester smoking habit								
No	64	98.5	0.14	NA	102	91.9	0.46 (1.05)	0.327
Yes	1	1.5	-0.02 (NA)		9	8.1	0.11 (0.56)	
First-trimester alcohol consumption								
No	57	87.7	0.13 (1.03)	0.789	89	80.2	0.43 (1.02)	0.942
Yes	8	12.3	0.23 (1.06)		22	19.8	0.45 (1.07)	
Pre-pregnancy leisure time physical activity								
No	62	95.4	0.09 (1.01)	0.103	105	95.5	0.43 (1.03)	0.956
Yes	3	4.6	1.08 (1.07)		5	4.5	0.40 (1.14)	
Pre-pregnancy BMI (kg/m <sup>2</sup> )								
<25.0	39	60	0.02 (1.01)	0.606	65	58.6	0.22 (0.99)	0.009
≥25.0	26	40	0.06 (1.07)		46	41.4	0.73 (1.00)	
Total gestational weight gain <sup>3,4</sup>								

Insufficient	16	24.6	-0.23 (0.95)	0.243	31	27.9	-0.04 (0.89)	0.004
Adequate	18	27.7	0.33 (1.06)		35	31,5	0.46 (0.96)	
Excessive	31	47.7	0.21 (1.03)		45	40.5	0.74 (1.06)	
Depressive symptoms (EPDS score)								
< 11	46	70.8	0.06 (1.01)	0.392	67	60.4	0.48 (1.01)	0.583
≥ 11	19	29.2	0.31 (1.08)		44	39.6	0.37 (1.05)	
Planned pregnancy								
No	32	49.2	0.26 (1.15)	0.363	38	34.2	0.43 (1.11)	0.963
Yes	33	50.8	0.02(0.89)		73	65.8	0.43 (0.99)	

<sup>1</sup>According to the International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (Intergrowth-21<sup>st</sup>) curves. <sup>2</sup>p-value refers to unpaired Student's *t* test; <sup>3</sup>categorized according to IOM, 2009; <sup>4</sup>for this variable, p-values refer to one way ANOVA. **Abbreviations:** SD = standard deviation; NA = not applicable; BMI = body mass index; EPDS = Edinburgh Postnatal Depression Scale.

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**Figure 2.** First trimester 24-hour sleep duration and birth weight Z-score<sup>1</sup> in a sample of pregnant women and their newborns followed at a public health center in Rio de Janeiro, Brazil, 2009–2012.

<sup>1</sup>According to the International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (Intergrowth-21<sup>st</sup>) curves

**Notes:** Unadjusted linear regression coefficients:  $\beta$  (95% confidence interval): Nulliparous = -0.111 (-0.215 to -0.007); Multiparous = -0.006 (-0.078 to 0.067).

**Table 4.** Linear regression between sleep duration time trends during pregnancy and birth weight z-score<sup>1</sup> in a sample of pregnant women and their newborns followed at a public health center in Rio de Janeiro, Brazil, 2009–2012.

Predictors	Birth weight z-score					
	Nulliparous					
	Crude model (n=65)		Adjusted model 1 (n=65) <sup>2</sup>		Adjusted model 2 (n=65) <sup>3</sup>	
	$\beta$ (95% CI)	p-value	$\beta$ (95% CI)	p-value	$\beta$ (95% CI)	p-value
First-trimester nightly sleep duration (intercept)	-0.28 (-0.53 to -0.03)	0.029	-0.27 (-0.58 to 0.05)	0.092	-	-
Variation in nightly sleep duration throughout pregnancy (slope from BLUP)	-0.80 (-2.72 to 1.11)	0.406	-1.10 (-3.14 to 0.94)	0.284	-	-
First-trimester napping sleep duration (intercept) <sup>3</sup>	-0.08 (-0.60 to 0.44)	0.757	-0.20 (-0.77 to 0.37)	0.485	-	-
Variation in napping sleep duration throughout pregnancy (slope from BLUP) <sup>4</sup>	-0.15 (-1.83 to 1.52)	0.856	-0.41 (-2.28 to 1.47)	0.661	-	-
First-trimester 24-hour sleep duration (intercept)	-0.35 (-0.57 to -0.14)	0.069	-0.44 (-0.68 to -0.21)	<0.001	-0.42 (-0.65 to -0.18)	0.001
Variation in 24-hour sleep duration throughout pregnancy (slope from BLUP)	-1.26 (-2.62 to 0.10)	0.002	-1.75 (-3.17 to -0.33)	0.017	-1.56 (-3.00 to -0.13)	0.034
Predictors	Multiparous					
	Crude model (n=111)		Adjusted model <sup>5</sup> (n=111)			
	$\beta$ (95% CI)	p-value	$\beta$ (95% CI)	p-value		
	$\beta$ (95% CI)	p-value	$\beta$ (95% CI)	p-value		
First-trimester nightly sleep duration (intercept)	-0.07 (-0.28 to 0.13)	0.478	-0.01 (-0.24 to 0.22)	0.954	-	-
Variation in nightly sleep duration throughout pregnancy (slope from BLUP)	-1.09 (-2.72 to 0.54)	0.188	-0.75 (-2.47 to 0.97)	0.388	-	-
First-trimester napping sleep duration (intercept) <sup>5</sup>	-0.13 (-0.62 to 0.35)	0.580	0.11 (-0.49 to 0.71)	0.719	-	-
Variation in napping sleep duration throughout pregnancy (slope from BLUP) <sup>6</sup>	-1.05 (-3.08 to 0.99)	0.307	-0.07 (-2.37 to 2.23)	0.949	-	-
First-trimester 24-hour sleep duration (intercept)	-0.09 (-0.25 to 0.07)	0.277	-0.36 (-1.39 to 0.66)	0.483	-	-
Variation in 24-hour sleep duration throughout pregnancy (slope from BLUP)	-0.55 (-1.52 to 0.43)	0.268	-0.02 (-0.19 to 0.15)	0.823	-	-

376 <sup>1</sup>According to the international fetal and newborn growth consortium for the 21<sup>st</sup> Century (Intergrowth-21<sup>st</sup>) curves. <sup>2</sup>Models were adjusted for the following variables: maternal age, pre-  
377 pregnancy Body Mass Index, smoking, Edinburgh Postnatal Depressive Scale Score at baseline, total gestational weight gain adequacy, leisure-time physical activity, education, marital  
378 status, per-capita family income and planned pregnancy. <sup>3</sup>Models were adjusted for the following variables: maternal age, pre-pregnancy Body Mass Index, smoking, Edinburgh Postnatal  
379 Depressive Scale Score at baseline, total gestational weight gain adequacy, leisure-time physical activity, education, marital status, per-capita family income, planned pregnancy and 2<sup>nd</sup>  
380 and 3<sup>rd</sup> trimester caloric intake. <sup>4</sup>For these models the sample size is: 45. <sup>5</sup>Models were adjusted for the following variables: maternal age, pre-pregnancy Body Mass Index, smoking,  
381 Edinburgh Postnatal Depressive Scale Score at baseline, total gestational weight gain adequacy, leisure-time physical activity, education, marital status, per-capita family income, planned  
382 pregnancy and birth order. <sup>6</sup>For these models the sample size is: 74. **Abbreviations:** CI = confidence interval. BLUP = best unbiased linear predictor.

## Discussion

The two main findings in our study regarding sleep duration during pregnancy were that the overall trend among women is to decrease the sleep duration from the first to the third trimester and the higher is the variation in sleep duration throughout pregnancy in nulliparous women, the smaller is the BW z-score of their babies. In other words, the statistically significant association found in our study for the slope from the BLUP is indicating that women who present greater decreases in sleep duration throughout pregnancy give birth to newborns with smaller BW. This significant result was observed only for the variable 24-hour sleep duration and may indicate that in pregnancy studies the variable total sleep duration needs to be considered, independently if women get it from nightly sleep or napping.

In the first trimester, nulliparous women reported longer 24-hour sleep duration than multiparous women, confirming data from Goñi et al. (2014). Multiparous women tended to be less educated and have lower family incomes than nulliparous women in our cohort. Okun et al. (2014) found low socioeconomic status (annual household income) to be associated with poorer sleep quality and fragmented sleep, even after adjustment for potential confounders such as perceived stress and financial strain. Other researchers have also reported negative associations of income and education with sleep quality and sleep duration (Krueger & Friedman, 2009; Soltani et al., 2012).

In a literature review comparing pre-pregnancy and pregnancy sleep habits, Chang et al. (2010) concluded that in early pregnancy there was an increase in sleep duration (compared with the pre-pregnancy period) and that in the third trimester the duration was diminished. Unfortunately, in our study we do not have data regarding the pre-pregnancy period. However, in nulliparous women, 24-hour and nightly sleep duration significantly decreased throughout pregnancy. In multiparous women, we observed a significant decrease in 24-hour sleep duration, but the decrease in nightly sleep duration was not statistically significant. No changes were observed for the duration of napping in the women who reported this habit.

In our study we detected that the higher is the variation in sleep duration throughout pregnancy, smaller is the BW z-score, indicating that women who present greater decreases in sleep duration throughout pregnancy give birth to newborns with smaller BW. Few studies have assessed the associations between sleep duration and BW

and the results are inconsistent. The only previous study we found reporting significant associations between sleep duration and BW was conducted by Abeysena et al. (2009). In a population-based prospective cohort of 690 women in Sri Lanka, the authors observed that sleeping  $\leq 8$  hours during the second or third or both trimesters of pregnancy increased the odds of delivering a SGA newborn ( $< 5^{\text{th}}$  centile according to a customized BW centile chart).

In our sample, sleep duration variables are associated with caloric intake and also with the Healthy dietary pattern score obtained by principal component analysis. Additionally, caloric intake was associated with BW too (results not shown). We observed that caloric intake during pregnancy presented a mediating effect on the association of both sleep variables and BW.

Other studies did not find statistically significant associations between sleep duration and BW. Zafarghandi et al. (2012) evaluated 457 nulliparous pregnant women from Iran and found that women who reported eight or more hours of sleep in late pregnancy (at least 37 weeks gestation) delivered children with lower BW, but the effect was not enough to statistically increase the LBW rate. Similarly, Howe et al. (2015) did not identify associations between sleep duration in late pregnancy (35-37 weeks) or change in sleep duration from pre-pregnancy to late pregnancy and the occurrence of large for gestational age (LGA) or SGA births in a sample of 633 pregnant women from New Zealand. Micheli et al. (2011) did not detect associations between third-trimester sleep duration and birth weight (LBW and fetal growth restriction) in a cohort of 1,091 pregnant women.

We have some hypotheses for the divergences between these previously cited studies and the present results. First, these prior studies assessed associations of sleep duration with LBW, SGA, and fetal growth restriction, well-recognized undesirable pregnancy outcomes, while in our main analysis we detected associations with BW z-score. We believe that the effect of longer sleep duration is beneficial to BW, but depending on model adjustments and sample size, it is not enough to independently decrease the risk of LBW, SGA births and fetal growth restriction. We did not test for potential relationships between sleep duration and LBW/SGA because these outcomes were quite low prevalent in our study, being underpowered to detect possible associations. Additionally, it has already been reported that sleep in early pregnancy is an essential determinant of the physiological alterations that take place during

pregnancy (Okun et al., 2009) and in most of the previously cited studies, sleep duration was assessed only in late pregnancy, with no adjustment made for baseline data (early pregnancy sleep duration).

Considering that studies evaluating associations between sleep duration and BW are still scarce, future studies should be developed, ideally with larger sample sizes, with women with more heterogeneous sleep duration (making it possible to categorize the variable sleep duration into 3 or more groups) and with a higher prevalence of LBW/SGA and macrosomia/LGA.

Our study has two main limitations. First, data on sleep quality is missing, a notable gap, as potential associations between sleep and health are likely a joint effect of duration and quality. Another issue is that our data on sleep duration was self-reported and, thus subject to measurement error. In a literature review, Chang et al. (2010) concluded that objective sleep measures throughout pregnancy tend to be about 30 minutes lower than women's subjective report. Thus, although we may be overestimating sleep duration in our sample, we believe this overestimation is non-differential between parity categories.

Another limitation of our study is the absence of detailed measures on total physical activity of the pregnant women, as this variable is potentially associated with both sleep duration and BW. The available data refers to a variable labeled as LTPA that was self-reported and had as answer options yes or no. Less than 5% of the women studied here reported LTPA engagement. The multiple models were adjusted for this variable in order to minimize potential confounding associated with it, even though the study lacked more accurate measures such as data derived from actigraphy.

Strengths of our study include having repeated measures of sleep duration throughout pregnancy, which allowed us to test the effect of the longitudinal variation in sleep duration using the BLUP technique. Because the BLUP approach considers the correlation among the repeated measures and allows time trends estimations even for women with missing values across pregnancy, we believe the use of BLUP variables provides greater analysis power than assessing each pregnancy point separately. Since BW is substantially impacted by gestational age, the use of sex-specific BW z-scores based on the Intergrowth-21<sup>st</sup> reference may be considered an additional strength of our analyses.

In summary, decrease in sleep duration throughout pregnancy was negatively associated with BW z-score in nulliparous but not in multiparous women. In nulliparous women, those with greater decreases in sleep duration throughout pregnancy gave birth to newborns with lower BW z-scores. We encourage further longitudinal studies assessing sleeping patterns (duration and quality), beginning in early pregnancy (or preferably prior to pregnancy) and assessing differences between nulliparous and multiparous women.

#### **Disclosure Statement**

None

#### **Acknowledgements**

We would like to thank the National Council for Scientific and Technological Development (CNPq) and the Carlos Chagas Filho Foundation for Research Support of Rio de Janeiro State (FAPERJ) for funding this study (grant numbers: CNPq - 471196/2010-0, 304182/2013-3; FAPERJ - E-26/111.400/2010, E-26/110.681/2012, E-26/112.181/2012, E-26/ 111.698/2013). We declare that these funding sources had no involvement in the study conduction.

G.K and M.S. conceived and designed research. A.F-S, D.F and I.E performed data collection. A.F-S analyzed the data. A.F-S, L.K, A.A.F, P.L, M.S and G.K assisted with the interpretation of the results. A.F-S, L.K, I.E, A.C.F, D.F and G.K wrote the manuscript. All authors contributed to subsequent drafts of the manuscript and read and approved the final manuscript submitted for publication.

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