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A longitudinal study of sleep duration in pregnancy and subsequent risk of gestational diabetes: findings from a prospective, multiracial cohort

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BACKGROUND: Both short and prolonged sleep duration have been linked to impaired glucose metabolism. Sleep patterns change during pregnancy, but prospective data are limited on their relation to gestational diabetes.

OBJECTIVE: We sought to prospectively examine the trimester-specific (first and second trimester) association between typical sleep duration in pregnancy and subsequent risk of gestational diabetes, as well as the influence of compensatory daytime napping on this association.

STUDY DESIGN: In the prospective, multiracial *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort, 2581 pregnant women reported their typical sleep duration and napping frequency in the first and second trimesters. Diagnosis of gestational diabetes (n = 107; 4.1%) was based on medical records review. Adjusted relative risks with 95% confidence intervals for gestational diabetes were estimated with Poisson regression, adjusting for demographics, prepregnancy body mass index, and other risk factors.

RESULTS: From the first and second trimester, sleep duration and napping frequency declined. Sleeping duration in the second but not first trimester was significantly related to risk of gestational diabetes. The association between second-trimester sleep and gestational diabetes differed by prepregnancy obesity status (*P* for interaction = .04). Among nonobese but not obese women, both sleeping >8-9 hours or <8-9 hours were significantly related to risk of gestational diabetes: 5-6 hours (adjusted relative risk, 2.52; 95% confidence interval, 1.27—4.99); 7 hours (adjusted relative risk, 2.01; 95% confidence interval, 1.09—3.68); or ≥10 hours (adjusted relative risk, 2.17; 95% confidence interval, 1.01—4.67). Significant effect modification by napping frequency was also observed in the second trimester (*P* for interaction = .03). Significant and positive association between reduced sleep (5-7 hours) and gestational diabetes was observed among women napping rarely/never (adjusted relative risk, 2.48; 95% confidence interval, 1.20—5.13), whereas no comparable associations were observed among women napping most/sometimes.

CONCLUSION: Our data suggest a U-shaped association between sleep duration and gestational diabetes, and that napping and prepregnancy obesity status may modify this association.

Key words: gestational diabetes mellitus, glucose metabolism, napping, pregnancy, sleep patterns

Introduction

Gestational diabetes mellitus (GDM), a common pregnancy complication affecting up to 13% of all pregnancies, is linked to several adverse health outcomes in both women and their children.[1] Identifying modifiable risk factors of GDM is hence critical to prevent the growing burden of GDM and its long-term adverse health sequelae.

Evidence from experimental and observational studies suggests that both reduced and prolonged sleep duration are linked to impaired insulin sensitivity and glucose metabolism.[2,3] Several

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underlying mechanisms have been proposed, including elevated oxidative stress, increased systemic inflammation, dysregulation of energy homeostasis, and chronic activation of the hypothalamic-pituitary-adrenal axis.[2,3] Pregnant women are particularly vulnerable to sleep disturbances, owing to hormonal changes, physical discomfort, or anxiety surrounding childbirth.[4-6] Whether sleep duration during pregnancy contributes to GDM risk is not clear as existing studies have been limited and conflicting.[7-11] Prospective studies are particularly scarce, with only 1 study[8] to date examining sleep duration in early pregnancy in relation to subsequent GDM risk.

In pregnancy, sleep patterns change across gestation.[4,5] In the first trimester, sleep duration tends to increase, with this trend reversing in the second trimester.[4,5] Compared to midpregnancy, napping is also more common toward the beginning and end of pregnancy, which may affect the total sleep exposure in a 24-hour period.[6] Longitudinal assessments of sleeping and napping habits during pregnancy are hence needed to investigate the influence of sleep duration on GDM risk. The trimester-specific association between typical sleep duration and GDM risk, and the influence of compensatory daytime napping on this association has not yet been evaluated. In addition, although obesity is a risk factor for excessive sleepiness,[12] its influence on the association between sleep duration and GDM during pregnancy is unknown.

In this study, our objective was to prospectively examine the trimester-specific association between self-reported sleep duration and subsequent GDM risk in a multiracial cohort of pregnant women. As a secondary objective, we examined whether daytime

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napping modifies the relation between sleep duration and GDM.

Materials and Methods

Study population

This prospective study was conducted on the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies-Singleton Cohort (2009 through 2013), consisting of 2334 nonobese pregnant women[13] and 468 obese pregnant women between the ages of 18-40 years. Sample selection and eligibility criteria have been described in detail previously.[13] Briefly, women with a history of chronic diseases such as hypertension, diabetes, or cancer were excluded. Eligible women were recruited between 8-13 weeks of gestation from 12 participating clinical sites across the United States and followed up throughout pregnancy. Institutional review board approval was obtained from all participating sites including NICHD. All participants provided informed consent.

The analytical population was composed of 2581 women (92.1%) with available medical records and sleep data at enrollment (8-13 weeks); 2% of the analytical sample (n = 51) were lost to follow-up at 16-22 weeks.

Exposure assessment

Structured questionnaires assessed sleep duration and napping frequency during the first (8-13 weeks) and second (16-22 weeks) trimesters. At both visits, participants were asked to indicate their typical sleep duration with possible responses including: ≤5, 6, 7, 8, 9, or ≥10 hours. Participants were also asked: "how often do you get so sleepy during the day or evening that you have to take a nap?" with possible responses including "most of the time," "sometimes," or "rarely or never."

Outcome assessment

GDM diagnosis was abstracted from medical records (n = 107). The diagnosis was based on either the oral glucose tolerance test, using the Carpenter and Coustan diagnostic criteria[14] or indication of medication-treated GDM on the hospital charge diagnosis (n = 12).

Covariates

Several covariates were examined, including sociodemographic variables such as age, race-ethnicity, education, and marital status; gestational age at interview; parity; and known risk factors of GDM including family history of diabetes, prior GDM, and prepregnancy body mass index (BMI) (calculated from self-reported weight and measured height at enrollment, kg/m^2). Participants also reported consumption of caffeinated beverages (coffee/tea/soda/energy drinks) during each trimester (cups) and consumption of alcoholic beverages before pregnancy. Smoking status in the 6 months prior to pregnancy was asked of the obese women; nonobese women who smoked before pregnancy were not eligible for this study.

Statistical analysis

Participant characteristics across sleep duration categories were compared using the χ^2 test for categorical data and 1-way analysis of variance for continuous variables. Poisson regression models (using log-link) with robust variance estimates were used to estimate adjusted relative risks (aRR) and 95% confidence intervals (CI) for the association between typical sleep duration prior to GDM diagnosis and subsequent risk of GDM. Separate models were fitted for sleep duration in the first and second trimester. Typical sleep duration was categorized as 5-6, 7, 8-9, and ≥10 hours, with 8-9 hours as the reference group, to be comparable to prior studies.[8,10] In the multivariable model, analyses were adjusted for a priori selected covariates including age, gestational age at interview, race-ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander), nulliparity (yes, no), education (less, equal to or more than high-school), prepregnancy BMI, marital status (married/living with a partner or not), and family history of diabetes (yes, no). A second model further adjusted for napping frequency (most times, sometimes, rarely/never) at the corresponding trimester.

Caffeine consumption during pregnancy and alcohol consumption before pregnancy were not associated with GDM and hence were not considered in the multivariable models. Due to the small number of women (n = 17) who smoked before pregnancy, smoking status was not included in the multivariable models. In sensitivity analyses we excluded women who smoked before pregnancy (n = 17) and women with prior GDM (n = 32). Additionally, we assessed for effect modification by prepregnancy obesity status (BMI <30.0 vs ≥30.0 kg/m^2), race-ethnicity, family history of diabetes (yes vs no), napping frequency (most/sometimes vs rarely/never), and clinical site.

In sensitivity analyses, missing data (9.7%) were imputed with multiple imputation method,[15] the majority of which stemmed from lack of medical chart abstraction. A total of 100 imputed datasets were created. There were no significant differences in age, race-ethnicity, education, parity, prepregnancy BMI, or family history of diabetes between women who were missing or not missing the medical chart. Women who were non-Hispanic white were more likely to be lost to follow-up at 16-22 weeks; none of the other key variables differed between those who were retained or lost to follow-up.

All tests were 2-tailed and P values $< .05$ were considered statistically significant for main effects and $<.15$ for interactions. Statistical analyses were completed using Software (SAS, Version 9.4; SAS Institute Inc Cary, NC).

Results

From the first to second trimester, the proportion of women sleeping ≤7 hours increased (30.7% vs 36.2%), whereas the proportion of women sleeping ≥10 hours declined (24.4% vs 14.7%) considerably. Compared to the first trimester, fewer women napped most/sometimes (80.4% vs 54.4%) in the second trimester. Sleep duration in the first trimester varied significantly across several sociodemographic and lifestyle characteristics (Table 1). For example, women who were younger, Hispanic, or

TABLE 1
Participant characteristics by sleep duration at 8–13 and 16–22 gestational weeks, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort (2009 through 2013)

	Sleep duration at 8–13 gestational wk						Sleep duration at 16–22 gestational wk					
	Overall	5–6 h	7 h	8–9 h	≥10 h		Overall	5–6 h	7 h	8–9 h	≥10 h	
Characteristics	2581	16%	14.7%	44.8%	24.4%	*P*[a]	2530	15.4%	20.8%	49.1%	14.7%	*P*[a]
Age, y	28.1 (5.5)	28.5 (5.5)	29.4 (5.3)	28.5 (5.3)	26.5 (5.6)	<.0001	28.2 (5.5)	28.8 (5.5)	29.5 (5.2)	28.2 (5.4)	25.5 (5.4)	<.0001
Race/ethnicity						<.0001						<.0001
Non-Hispanic white	27.2	22.5	31.3	34.0	15.4		27.7	19.7	36.5	31.2	11.6	
Non-Hispanic black	27.7	38.0	23.9	19.4	28.5		27.6	40.3	20.2	22	43.3	
Hispanic	28.7	27.4	25.0	28.5	32.3		28.6	27.4	23.2	29.7	33.6	
Asian/Pacific Islander	16.3	12.1	19.7	17.9	13.8		16.2	12.6	20.2	17.1	11.6	
Education						<.0001						<.0001
<High school	11.4	11.1	8.2	9.9	16.2		11.3	11.3	5.3	10.5	22.3	
High-school graduate or equivalent	18.4	21.6	10.8	16.7	24.1		18.3	18.5	11.2	18.4	28.0	
>High school	70.2	67.3	81.1	73.4	59.8		70.4	70.3	83.5	71.2	49.7	
Married/living with partner	74.4	69.0	79.5	79.6	65.2	<.0001	74.4	68.6	80.8	78.3	58.1	<.0001
Nulliparity	46.8	35.3	39.5	48.3	55.9	<.0001	47.0	35.1	46.6	50.0	49.7	<.0001
Smoking before pregnancy	0.7	0.2	0.8	0.9	0.5	.52	0.6	1.3	0.8	0.5	0.3	.26
Family history of diabetes	21.8	28.7	22.9	19.7	20.5	.002	21.8	23.4	20.4	21.8	21.9	.75
Alcoholic beverage consumption before pregnancy	64.6	62.2	71	66	59.8	.002	64.8	62.1	73.2	64.5	57.0	<.0001
Prepregnancy BMI, kg/m^2	25.5 (5.2)	26.3 (5.8)	25.1 (5.0)	25.2 (5.0)	25.5 (5.2)	.001	25.5 (5.2)	26.1 (5.5)	25.2 (5.3)	25.3 (5.1)	25.8 (5.4)	.016
Prepregnancy BMI categories						.03						.02
17.87–24.99 kg/m^2	56.4	51.0	59.4	57.6	56.0		56.5	51.2	60.8	57.2	53.5	
25.0–29.99 kg/m^2	26.5	27.1	26.8	26.7	25.4		26.3	27.9	23.7	27.2	25.5	

Rawal et al. Sleep duration in pregnancy and risk of GDM. Am J Obstet Gynecol 2017.

(continued)

TABLE 1
Participant characteristics by sleep duration at 8–13 and 16–22 gestational weeks, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort (2009 through 2013) *(continued)*

Characteristics	Sleep duration at 8–13 gestational wk						Sleep duration at 16–22 gestational wk					
	Overall	5–6 h	7 h	8–9 h	≥10 h	P^a	Overall	5–6 h	7 h	8–9 h	≥10 h	P^a
	2581	16%	14.7%	44.8%	24.4%		2530	15.4%	20.8%	49.1%	14.7%	
30.00–48.83 kg/m^2	17.1	21.9	13.8	15.7	18.7		17.2	20.9	15.5	15.6	20.9	
Need day nap during corresponding wk												
Most of time	42.9	41.0	34.0	35.4	63.4	<.0001	20.8	27.2	13.9	15.0	43.7	<.0001
Sometimes	37.6	39.1	38.7	42.0	27.7		35.6	31	33.5	38.2	35	
Rarely or never	19.5	19.9	27.4	22.6	8.9		43.5	41.8	52.7	46.9	21.3	
Gestational age during interview, wk	12.7 (1.0)	12.7 (0.9)	12.8 (0.9)	12.7 (1.0)	12.6 (1.0)	.03	19.7 (2.4)	19.7 (2.4)	20.1 (2.5)	19.7 (2.4)	19.4 (2.4)	.001
Caffeinated beverages consumed, cups	0.41 (0.8)	0.46 (0.9)	0.33 (0.7)	0.36 (0.7)	0.37 (0.9)	.08	0.41 (0.8)	0.43 (0.8)	0.40 (0.7)	0.40 (0.8)	0.44 (0.9)	.8

Data are presented as % for categorical variables and mean (SD) for continuous variables.

BMI, body mass index.

[a] *P* values for differences in participant characteristics across categories of sleep duration were obtained by χ^2 test for categorical variables and 1-way analysis of variance for continuous variables.

Rawal et al. Sleep duration in pregnancy and risk of GDM. Am J Obstet Gynecol 2017.

nulliparous were more likely to sleep ≥10 hours, whereas those who were non-Hispanic white, married, or had greater education level were less likely to sleep ≥10 hours. Interestingly, women who reported napping most frequently in the first trimester were also most likely to sleep the most (≥10 hours) in a typical day. Similar sociodemographic and lifestyle patterns were observed with sleep duration in the second trimester, except for family history of diabetes, which was only associated with sleep duration in the first trimester.

First-trimester sleep duration was not associated with subsequent GDM risk (Table 2). In the second trimester, the association between sleep duration and GDM differed by prepregnancy obesity status (P for interaction = .04) with the association only significant among nonobese women. Among the nonobese, both sleeping >8-9 or <8-9 hours was associated with approximately 2-fold higher risk of GDM (Table 2). The associations persisted after adjusting for other GDM risk factors including age, race, prepregnancy BMI, and parity. The associations became slightly attenuated, but were still significant after further adjusting for napping frequency in the second trimester. The highest risk for GDM (aRR, 2.52; 95% CI, 1.27–4.99) was observed among nonobese women who slept 5-6 hours in the second trimester. In sensitivity analyses, we also stratified the analyses by 3 BMI categories (normal weight, overweight, obese); the direction and magnitude of the associations between sleep and GDM were similar among normal-weight and overweight women, which was consistent with a nonsignificant interaction test observed in the multivariable model.

While napping in itself was not associated with GDM risk in either trimester, it significantly modified the sleep-GDM association (P for interaction = .03). GDM risk was not significantly related to sleep duration among women who napped most/sometimes, whereas the association was significant among women who rarely or never napped in the second trimester. Specifically, among women who rarely or never napped in the second trimester, those who slept ≤7

TABLE 2
Gestational diabetes mellitus in association with self-reported sleep duration during first and second trimester of pregnancy, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort (2009 through 2013)

Sleep duration	GDM/total	Unadjusted RR (95% CI)	Model A[a] aRR (95% CI)	Model B[b] aRR (95% CI)
First trimester, 8–13 wk				
All women				
8–9 h	51/1157	1	1	1
5–6 h	16/413	0.88 (0.51–1.52)	0.87 (0.49–1.55)	0.87 (0.49–1.54)
7 h	15/380	0.90 (0.51–1.57)	0.91 (0.51–1.60)	0.90 (0.51–1.60)
≥10 h	25/631	0.90 (0.56–1.44)	1.07 (0.67–1.71)	1.04 (0.65–1.68)
Nonobese				
8–9 h	33/977	1	1	1
5–6 h	11/323	1.01 (0.52–1.97)	1.06 (0.53–2.13)	1.06 (0.53–2.12)
7 h	12/328	1.08 (0.57–2.07)	1.02 (0.52–1.98)	1.02 (0.52–1.98)
≥10 h	16/514	0.92 (0.51–1.66)	1.17 (0.64–2.14)	1.09 (0.59–2.02)
Obese				
8–9 h	18/180	1	1	1
5–6 h	5/90	0.56 (0.21–1.45)	0.60 (0.22–1.62)	0.58 (0.22–1.56)
7 h	3/52	0.58 (0.18–1.88)	0.70 (0.22–2.19)	0.69 (0.22–2.15)
≥10 h	9/117	0.77 (0.36–1.65)	1.00 (0.48–2.05)	1.07 (0.50–2.29)
Second trimester, 16–22 wk				
All women				
8–9 h	44/1242	1	1	1
5–6 h	19/390	1.38 (0.81–2.33)	1.49 (0.87–2.57)	1.51 (0.89–2.60)
7 h	26/526	1.40 (0.87–2.24)	1.37 (0.84–2.22)	1.38 (0.85–2.23)
≥10 h	16/372	1.21 (0.69–2.13)	1.55 (0.89–2.71)	1.49 (0.82–2.68)
Nonobese				
8–9 h	24/1042	1	1	1
5–6 h	14/306	1.99 (1.04–3.79)	2.57 (1.31–5.05)	2.52 (1.27–4.99)
7 h	20/442	1.96 (1.10–3.52)	2.00 (1.09–3.66)	2.01 (1.09–3.68)
≥10 h	12/291	1.79 (0.91–3.54)	2.36 (1.14–4.88)	2.17 (1.01–4.67)
Obese				
8–9 h	20/192	1	1	1
5–6 h	5/81	0.59 (0.23–1.52)	0.61 (0.25–1.47)	0.62 (0.25–1.50)
7 h	6/81	0.71 (0.30–1.71)	0.80 (0.32–1.96)	0.79 (0.32–1.95)
≥10 h	4/77	0.50 (0.18–1.41)	0.72 (0.28–1.86)	0.76 (0.28–2.05)

aRR, adjusted relative risk; *CI*, confidence interval; *GDM*, gestational diabetes mellitus; *RR*, relative risk.

[a] aRR and 95% CI estimated with Poisson regression adjusting for maternal age (years), gestational age at interview (weeks), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander), parity (nulliparous or not), education (less, equal to or more than high school), prepregnancy body mass index (kg/m^2), marital status (married/living with partner vs not), and family history of diabetes (yes/no); [b] aRR and 95% CI estimated with Poisson regression adjusting for variables in model 1 plus napping frequency during corresponding weeks.

Rawal et al. Sleep duration in pregnancy and risk of GDM. Am J Obstet Gynecol 2017.

hours had a significantly higher risk of GDM compared to women who slept 8-9 hours, even after adjusting for other major risk factors of GDM (aRR, 2.48; 95% CI, 1.20–5.13). Among women who rarely or never napped in the second trimester, those sleeping ≥10 hours had a marginally increased risk of GDM, compared to women who slept 8-9 hours

TABLE 3
Gestational diabetes mellitus in association with joint status of self-reported sleep duration and napping frequency at weeks 16–22 of pregnancy, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort (2009 through 2013)

Sleep duration and napping status	GDM/total	Unadjusted RR (95% CI)	Model A[a] aRR (95% CI)
8–9 h and rarely/never	12/582	1	1
5–7 h and rarely/never	26/440	2.61 (1.46–5.62)	2.56 (1.28–5.10)
≥10 h and rarely/never	4/79	2.41 (0.81–7.43)	3.07 (1.02–9.22)
5–7 h and some/most times	19/476	1.95 (0.95–3.95)	2.11 (1.03–4.32)
8–9 h and some/most times	32/660	2.23 (1.22–4.52)	2.21 (1.16–4.24)
≥10 h and some/most times	12/292	2.00 (0.91–4.38)	2.44 (1.12–5.29)

aRR, adjusted relative risk; *CI*, confidence interval; *GDM*, gestational diabetes mellitus; *RR*, relative risk.

[a] aRR and 95% CI estimated with Poisson regression adjusting for maternal age (years), gestational age at interview (weeks), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander), parity (nulliparous or not), education (less, equal to or more than high school), prepregnancy body mass index (kg/m^2) marital status, and family history of diabetes (yes/no).

Rawal et al. Sleep duration in pregnancy and risk of GDM. Am J Obstet Gynecol 2017.

(aRR, 2.90; 95% CI, 0.97–8.70). In the subsample of nonobese women, further stratification by napping frequency (*P* for interaction = .049) revealed that the associations between sleep duration and GDM were not significant among nonobese women who napped most/sometimes, but was strongly significant with a U-shaped association among those who never/rarely napped (data not shown).

When considering the joint effect of sleep duration and napping frequency in the second trimester (Table 3), we observed that the women who slept longer (≥10 hours) and rarely/never napped had the highest risk of GDM (aRR, 3.07; 95% CI, 1.02–9.22). We also examined changes in sleep duration from the first to second trimester in association with GDM risk and found no significant associations. There was no suggestion of effect modification by race-ethnicity, family history of diabetes, or clinical site on the association between sleep duration and subsequent GDM risk (data not shown). In sensitivity analyses we excluded women who smoked before pregnancy (n = 17) or those who had a history of GDM (n = 32), and the results were similar. The analyses with imputed data showed similar results to analyses that excluded women with missing data.

Comment

In this prospective and longitudinal study, we observed a U-shaped association between sleep duration in the second trimester and subsequent risk of GDM, with both less or more sleep than the optimal 8-9 hours per night associated with higher GDM risk. Moreover, our findings suggested that prepregnancy obesity status and napping frequency modified this association, as significant associations were only observed among women who were nonobese prior to pregnancy or napped rarely or never during the second trimester. Our findings did not extend to sleep duration in the first trimester, suggesting that the impact of sleep during pregnancy on GDM risk may be more acute than insidious.

Epidemiological studies on the sleep and GDM association are sparse and have just recently begun to emerge. Findings from the few available studies[7-11] have been inconsistent and provided limited inference due to the retrospective designs and/or small sample sizes. For example, consistent with our study, 2 other studies[8,10] observed a U-shaped association between sleep duration in pregnancy and GDM risk, although the findings were not always significant for both extremes of sleep duration. In a recent study based on a large cohort of Chinese women,[10] both short and prolonged sleep duration were associated with increased GDM risk, but the results were only significant for prolonged sleep duration. However, temporality could not be established from this study,[10] as the sleep duration was assessed concurrently with GDM diagnosis. A second prospective, but small, study[8] found that the association between sleep duration in early pregnancy and GDM was statistically significant for very short sleep duration but insignificant for longer sleep duration. This pilot study,[8] however, had relatively few GDM cases (n = 68) and, as such, inference from this study was hindered by limited statistical power. Studies[7,9] only examining the influence of reduced sleep on GDM have also reported mixed findings. For example, Facco et al[7] reported a positive and significant association between short sleep duration and GDM, yet only had 10 GDM cases and did not distinguish between women who reported short sleep in early pregnancy or the third trimester, making the findings hard to interpret. Another cross-sectional study[9] only found a marginal positive association between short sleep duration and GDM diagnosis at the second trimester. Studies[16,17] evaluating continuous glucose tolerance test measures instead of clinical endpoint of GDM also observed inconsistent findings.

This study extends the previous literature by reporting, for the first time, trimester-specific association between sleep duration in pregnancy and subsequent GDM risk, which is particularly important given the substantial variations in sleep duration across pregnancy. Our findings that the association

between sleep duration and GDM risk varied by trimester, prepregnancy obesity status, and napping frequency may partly explain the inconsistent reports in the literature. One of the novel findings from this study was that the second-trimester sleep duration was associated with an increased GDM risk only among nonobese women. One possible explanation could be that the benefits of optimal sleep are not strong enough to overcome the influence of prepregnancy obesity on GDM risk. In contrast to our study, Qiu et al[8] observed that the magnitude of the association between reduced sleep and GDM risk was greater among overweight/obese women as compared to lean women (<25 kg/m^2); it is worth noting, however, that the majority of women in their overweight/obese group were overweight and not obese. In the present study, we also observed that the association between short sleep duration in the second trimester and GDM risk was only significant among infrequent nappers, providing, for the first time, modest and preliminary evidence that daytime napping may compensate for the adverse effects of insufficient sleep on glucose metabolism.

There are multiple physiological pathways by which sleep disturbances may adversely affect glucose homeostasis. Experimental studies among nonpregnant individuals show that sleep restriction can reduce insulin sensitivity and acute insulin response, which in turn may lead to decreased glucose tolerance.[2,18,19] Sleep deprivation has been linked to elevated oxidative stress and increased inflammatory responses, both of which can affect insulin signaling and adversely impact glucose homeostasis.[3,20,21] Sleep curtailment can also cause increased activation of the sympathetic nervous system, which can disrupt glucose homeostasis and induce insulin resistance by increasing glycogen breakdown and gluconeogenesis.[22] Additional proposed mechanisms are disruption of the hypothalamic-pituitary-adrenal axis, elevations in growth hormone and cortisol levels, and diminished glucose uptake in the brain.[3,23] The mechanisms by which prolonged sleep can adversely influence glucose tolerance are not well understood. One possibility is that excessive sleep allows for less time to be physically active. Increased sedentary time is linked to adverse cardiometabolic outcomes and increased insulin resistance.[24,25] Additionally, both prolonged and reduced sleep could contribute to insulin resistance in pregnancy by dysregulating appetite hormones such as leptin and ghrelin, which may ultimately disrupt energy homeostasis and cause weight gain.[3,23]

Our study had several strengths. To our knowledge, this study is the first to longitudinally examine sleep patterns in pregnancy and investigate trimester-specific associations between sleep duration and subsequent GDM risk. The prospective nature of the present study reduces the possibility of reverse causation. Our follow-up rate was quite high (92.2%), decreasing the probability of selection bias. The study sample also had a good representation of multiple race/ethnicities, and was recruited from 12 clinical centers across the United States. Compared to existing studies, we had a relatively large number of GDM cases that were based on medical records as opposed to self-report. However, we cannot exclude the possibility that some GDM cases were missed on the available medical record or from those lacking the chart abstraction data. Since excessive or insufficient sleep is associated with several chronic diseases such as type 2 diabetes and cardiovascular diseases, an additional strength of this study was that it was conducted among relatively healthy women without major chronic diseases.

Some potential limitations of our study merit discussion. The primary limitation was that sleep duration and napping frequency were self-reported, and thus may be subject to misclassification bias. Self-reported sleep duration is known to be reasonably yet modestly correlated with wrist actigraph-measured sleep duration.[26] However, given the study's prospective design, we expect misclassification if any to be nondifferential, which according to our bias analyses,[27] would yield a bias toward the null. Secondly, our study was focused on the duration of sleep and did not measure other aspects of sleep, such as sleep quality or sleep fragmentation. As such, we could not examine whether coexisting comorbidities, such as sleep apnea, could account for the observed association between sleep duration and GDM. Third, we did not evaluate how dietary and lifestyle factors could influence the association between sleep duration and GDM. Fourth, the prevalence of GDM and prepregnancy obesity in our sample were slightly lower than national estimates,[28,29] presumably due to our relatively healthy cohort. Lastly, due to the lack of data on nap duration, we could not examine whether short or long nap duration had a differential association with GDM risk. Hence, our findings on napping and GDM should be regarded as preliminary.

In summary, the longitudinal and prospective data from our study provide an important contribution to the understanding of the link between sleep duration and GDM risk. Our findings have potential important clinical implications as they suggest that getting an optimal amount of sleep in mid-pregnancy, or compensating for insufficient sleep with daytime napping, may help lower GDM risk, which may ultimately reduce adverse health impacts of GDM on both expecting mothers and their newborns. Future studies that assess sleep quality and include objective measures of nocturnal and daytime sleep duration are needed to extend our findings. ■

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References

1. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2

diabetes: a global perspective. Curr Diab Rep 2016;16:7.
2. Reutrakul S, Van Cauter E. Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes. Ann N Y Acad Sci 2014;1311:151-73.
3. Izci-Balserak B, Pien GW. The relationship and potential mechanistic pathways between sleep disturbances and maternal hyperglycemia. Curr Diab Rep 2014;14:459.
4. Hedman C, Pohjasvaara T, Tolonen U, Suhonen-Malm AS, Myllyla VV. Effects of pregnancy on mothers' sleep. Sleep Med 2002;3:37-42.
5. Lee KA, Zaffke ME, McEnany G. Parity and sleep patterns during and after pregnancy. Obstet Gynecol 2000;95:14-8.
6. Mindell JA, Jacobson BJ. Sleep disturbances during pregnancy. J Obstet Gynecol Neonatal Nurs 2000;29:590-7.
7. Facco FL, Grobman WA, Kramer J, Ho KH, Zee PC. Self-reported short sleep duration and frequent snoring in pregnancy: impact on glucose metabolism. Am J Obstet Gynecol 2010;203:142.e1-5.
8. Qiu C, Enquobahrie D, Frederick IO, Abetew D, Williams MA. Glucose intolerance and gestational diabetes risk in relation to sleep duration and snoring during pregnancy: a pilot study. BMC Womens Health 2010;10:17.
9. Reutrakul S, Zaidi N, Wroblewski K, et al. Sleep disturbances and their relationship to glucose tolerance in pregnancy. Diabetes Care 2011;34:2454-7.
10. Wang H, Leng J, Li W, et al. Sleep duration and quality, and risk of gestational diabetes mellitus in pregnant Chinese women. Diabet Med 2017;34:44-50.
11. Naud K, Ouellet A, Brown C, Pasquier JC, Moutquin JM. Is sleep disturbed in pregnancy? J Obstet Gynaecol Can 2010;32:28-34.
12. Panossian LA, Veasey SC. Daytime sleepiness in obesity: mechanisms beyond obstructive sleep apnea—a review. Sleep 2012;35:605-15.
13. Buck Louis GM, Grewal J, Albert PS, et al. Racial/ethnic standards for fetal growth: the NICHD fetal growth studies. Am J Obstet Gynecol 2015;213:449.e1-41.
14. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. Gestational Diabetes Mellitus. ACOG Practice bulletin no. 137, August 2013 (replaces Gestational diabetes. Practice bulletin no. 30, September 2001). Obstet Gynecol 2013;122:406-16.
15. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci 2007;8:206-13.
16. Herring SJ, Nelson DB, Pien GW, et al. Objectively measured sleep duration and hyperglycemia in pregnancy. Sleep Med 2014;15:51-5.
17. Izci Balserak B, Jackson N, Ratcliffe SA, Pack AI, Pien GW. Sleep-disordered breathing and daytime napping are associated with maternal hyperglycemia. Sleep Breath 2013;17:1093-102.
18. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435-9.
19. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. Diabetes 2010;59:2126-33.
20. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab 2004;89:2119-26.
21. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Arch Intern Med 2006;166:1756-62.
22. Schmid SM, Jauch-Chara K, Hallschmid M, Schultes B. Mild sleep restriction acutely reduces plasma glucagon levels in healthy men. J Clin Endocrinol Metab 2009;94:5169-73.
23. O'Keeffe M, St-Onge MP. Sleep duration and disorders in pregnancy: implications for glucose metabolism and pregnancy outcomes. Int J Obes (Lond) 2013;37:765-70.
24. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, et al. Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis study. JAMA 1998;279:669-74.
25. Assah FK, Brage S, Ekelund U, Wareham NJ. The association of intensity and overall level of physical activity energy expenditure with a marker of insulin resistance. Diabetologia 2008;51:1399-407.
26. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? Epidemiology 2008;19:838-45.
27. Lash T, Fox M, Fink A. Applying quantitative bias analysis to epidemiologic data. New York (NY): Springer-Verlag; 2009.
28. DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007-2010. Prev Chronic Dis 2014;11:E104.
29. Fisher SC, Kim SY, Sharma AJ, Rochat R, Morrow B. Is obesity still increasing among pregnant women? Prepregnancy obesity trends in 20 states, 2003-2009. Prev Med 2013;56:372-8.

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