Original Research

Association Between Sleep-Disordered Breathing and Hypertensive Disorders of Pregnancy and Gestational Diabetes Mellitus

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OBJECTIVE: To estimate whether sleep-disordered breathing during pregnancy is a risk factor for the development of hypertensive disorders of pregnancy and gestational diabetes mellitus (GDM).

METHODS: In this prospective cohort study, nulliparous women underwent in-home sleep-disordered breathing assessments in early (6–15 weeks of gestation) and midpregnancy (22–31 weeks of gestation). Participants and health care providers were blinded to the sleep test results. An apnea–hypopnea index of 5 or greater was used to define sleep-disordered breathing. Exposure–response relationships were examined, grouping participants into four apnea–hypopnea index groups: 0, greater than 0 to less than 5, 5 to less than 15, and 15 or greater. The study was powered to test the primary hypothesis that sleep-disordered breathing occurring in pregnancy is associated with an increased incidence of preeclampsia. Secondary outcomes were rates of hypertensive disorders of pregnancy, defined as preeclampsia and antepartum gestational hypertension, and GDM. Crude and adjusted odds ratios and 95% confidence intervals (CIs) were calculated from univariate and multivariate logistic regression models.

RESULTS: Three thousand seven hundred five women were enrolled. Apnea–hypopnea index data were available for 3,132 (84.5%) and 2,474 (66.8%) women in early and midpregnancy, respectively. The corresponding prevalence of sleep-disordered breathing was 3.6% and 8.3%. The prevalence of preeclampsia was 6.0%, hypertensive disorders of pregnancy 13.1%, and GDM 4.1%. In early and midpregnancy the adjusted odds ratios for

preeclampsia when sleep-disordered breathing was present were 1.94 (95% CI 1.07–3.51) and 1.95 (95% CI 1.18–3.23), respectively; hypertensive disorders of pregnancy 1.46 (95% CI 0.91–2.32) and 1.73 (95% CI 1.19–2.52); and GDM 3.47 (95% CI 1.95–6.19) and 2.79 (95% CI 1.63–4.77). Increasing exposure–response relationships were observed between apnea–hypopnea index and both hypertensive disorders and GDM.

CONCLUSION: There is an independent association between sleep-disordered breathing and preeclampsia, hypertensive disorders of pregnancy, and GDM.

Sleep-disordered breathing conditions are characterized by abnormal respiratory patterns and abnormal gas exchange during sleep.[1] Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing. In reproductive-aged women, epidemiologic studies suggest a 2–13% prevalence of OSA.[2,3]

Pregnancy is associated with changes that promote OSA such as increased body weight and upper airway edema.[4] Frequent snoring, a cardinal symptom of OSA, is endorsed by 15–25% of pregnant women.[5,6] Health outcomes linked to OSA in the nonpregnant population such as hypertension and insulin-resistant diabetes have correlates in pregnancy (preeclampsia, gestational diabetes).[7–9] Obstructive sleep apnea has been linked to enhanced inflammatory and oxidative stress responses, endothelial damage, and metabolic derangements.[10,11] These same biologic pathways have been associated with adverse pregnancy outcomes suggesting a mechanistic link between OSA exposure in pregnancy and adverse outcomes.[12]

Several cross-sectional and retrospective studies suggest that sleep-disordered breathing may increase the risk of developing hypertensive disorders and gestational diabetes mellitus (GDM) during pregnancy, but most of these studies relied on self-reported symptoms (eg, snoring) as the exposure variable or suboptimally controlled for body mass index (BMI, calculated as weight (kg)/[height (m)]^2).[13–15] There are limited and conflicting data from small prospective observational cohorts.[16–18] Addressing this knowledge gap is clinically relevant because hypertensive disorders of pregnancy and GDM are associated with maternal and perinatal morbidity and have long-term health consequences for both mothers and children.[17,19] The Sleep Disordered Breathing Substudy of the Nulliparous Pregnancy Outcomes Study was a multicenter, prospective cohort study. The objective was to estimate whether sleep-disordered breathing during pregnancy is a risk factor for the development of hypertensive disorders of pregnancy and GDM of pregnant women.

MATERIALS AND METHODS

Details of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) parent and Sleep Disordered Breathing Substudy methods have been previously published.[20,21] Briefly, the nuMoM2b parent study was conducted at eight clinical sites and managed by an independent data coordinating center. Inclusion criteria for the parent study were nulliparity (no prior delivery 20 weeks of gestation or greater) and a viable singleton pregnancy at the time of screening (6–13 6/7 weeks of gestation). Women were excluded from the Sleep Disordered Breathing Substudy if they were currently on continuous positive airway pressure (CPAP) treatment for sleep-disordered breathing, had severe asthma requiring continuous oral steroid therapy for more than 14 days, or experienced a condition requiring oxygen supplementation. The Sleep Disordered Breathing Substudy was designed and powered to test the primary hypothesis that sleep-disordered breathing occurring early or appearing later in pregnancy is associated with an increased incidence of preeclampsia. Secondary aims were to examine the association between sleep-disordered breathing and gestational hypertension and GDM.

For the nuMoM2b Sleep Disordered Breathing Substudy, level 3 home sleep tests were performed using a six-channel monitor that was self-applied by the participant twice during pregnancy, first between 6 and 15 weeks of gestation and then again between 22 and 31 weeks of gestation. Sleep study data were downloaded at the study site and electronically transmitted to a central sleep reading center. The scoring and quality control protocol has been previously published.[20] Sleep studies were scored using the following definitions:

Apnea: amplitude (peak to trough) of the nasal pressure signal flat for 10 seconds or greater; if accompanied by effort on either respiratory band (obstructive apnea); if accompanied by complete absence of effort on both respiratory bands (central apnea).

Hypopnea: scored based on 30% or greater reduction of amplitude in the nasal pressure signal or the respiratory sum channel (if no nasal pressure signal) for 10 seconds or greater.

Apnea–hypopnea index: number of apneas and hypopneas per hour of estimated sleep, defined in this analysis as all apnea as regardless of oxygen desaturation and hypopneas accompanied by 3% or greater oxygen desaturation.

All apnea and hypopnea events were annotated and later linked with oxygen saturation values. Participants, investigators, and care providers were blinded to the sleep test results unless urgent alert criteria were identified. Urgent alert studies included those with an apnea–hypopnea index greater than 50 events per hour or severe hypoxemia (oxygen saturation of less than 90% for 10% or greater of sleep time). Criteria for urgent alerts were developed by expert consensus from members of the study team and approved by the Advisory and Safety Monitoring Board. Institutional Review Board approval was obtained at each site and informed consent was obtained from each participant.

For our primary analyses, apnea–hypopnea index was treated as a dichotomous variable with an apnea–hypopnea index of 5 or greater defining the presence of sleep-disordered breathing. To examine exposure–response relationships between increased apnea–hypopnea index and pregnancy outcomes we also ran analyses grouping participants into four apnea–hypopnea index groups: 0, greater than 0 to less than 5, 5 to less than 15, and 15 or greater events per hour. The cutoff points of 5 to less than 15 and 15 or greater represent mild and moderate-to-severe sleep-disordered breathing, respectively.

For any participant with hypertension, proteinuria, or a related condition documented in the chart, a detailed chart review was required by a site investigator or a staff member certified for abstraction of complicated charts. Appendix 2, available online at http://links.lww.com/AOG/A905, outlines our study definitions of hypertensive disorders. Cases that presented atypically and were difficult to classify according to study criteria were adjudicated by the principal investigators and final classification was reached by consensus. As part of chart abstraction, the onset of the hypertensive disorder (gestational age; antepartum, intrapartum, postpartum) was ascertained. For analysis, preeclampsia was defined as all cases of mild, severe, or superimposed preeclampsia or eclampsia regardless of the timing of onset. A hypertensive disorder related to pregnancy was defined as all cases of preeclampsia and antepartum gestational hypertension.

Gestational diabetes mellitus was defined by one of the following glucose tolerance testing (GTT) criteria: 1) fasting 3-hour 100-g GTT with two abnormal values: fasting 95 mg/dL or greater, 1-hour 180 mg/dL or greater, 2-hour 155 mg/dL or

greater, 3-hour 140 mg/dL or greater; 2) fasting 2-hour 75-g GTT with one abnormal value: fasting 92 mg/dL or greater, 1-hour 180 mg/dL or greater, 2-hour 153 mg/dL or greater; or 3) nonfasting 50-g GTT 200 mg/dL or greater if no fasting 3-hour or 2-hour GTT was performed. In addition to GTT data, chart abstractors recorded if a diagnosis of GDM was made during the course of clinical care. If no GTT data were available, the information from chart abstraction was used for GDM classification. Women with pregestational diabetes were excluded from analysis of GDM.

A detailed description of our sample size calculation has been previously published.[20] In summary, we aimed to enroll 3,630 women in the Sleep Disordered Breathing Substudy anticipating that this would yield approximately 180 women (5%) with sleep-disordered breathing in early pregnancy and 360 (10%) in late pregnancy. With these assumptions, and setting the type I error at two-sided $\alpha=0.05$, the target sample size yields at least 80% power to detect a relative risk of 2.0 (1.8) for preeclampsia for women with sleep-disordered breathing in early (late) pregnancy, assuming a 7% incidence of preeclampsia among the unexposed.[22,23]

Descriptive statistics were used to characterize the study population by apnea–hypopnea index category. Chi square tests assessed associations with characteristics that were categorical and analysis of variance F-tests were used for continuous measurements. Crude and adjusted odds ratios and 95% confidence intervals were calculated from univariate and multivariate logistic regression models to relate level of sleep-disordered breathing in early and midpregnancy to hypertensive disorders of pregnancy and to GDM. Adjustment covariates included maternal age (21 or younger, 22–35, and older than 35 years), BMI (less than 25, 25 to less than 30, 30 or greater), chronic hypertension (yes, no), and for midpregnancy, rate of weight gain per week between early and midpregnancy assessments, treated as a continuous variable. These covariates were selected before analysis of results based on data supporting an association between these variables and both sleep-disordered breathing and the adverse pregnancy outcomes of interest.[24,25] To avoid overfitting, other potential covariates first were evaluated for confounding on the relationship of sleep-disordered breathing (apnea–hypopnea index 5 or greater) with hypertensive disorders of pregnancy and with GDM using a criteria of greater than 10% modification in the sleep-disordered breathing odds ratio by inclusion of the potential covariate. The interactions of BMI with hypertensive disorders

of pregnancy on sleep-disordered breathing and with GDM on sleep-disordered breathing were investigated for early and midpregnancy assessments. Exposure–response relationships were assessed in post hoc tests for linear and quadratic trends in the log-odds across the apnea–hypopnea index categories using orthogonal contrasts. For all analyses, women with pregnancy losses before 20 weeks of gestation were excluded.

All tests were performed at a nominal significance level of $\alpha=0.05$. All single degree-of-freedom tests were two-sided. No correction was made for multiple comparisons. Analyses were conducted using SAS 9.3/9.4.

RESULTS

A total of 3,705 women participating in the nuMoM2b parent study were enrolled in the Sleep Disordered Breathing Substudy between March 2011 and September 2013 (Fig. 1). Baseline characteristics were similar between nuMoM2b women who participated in the Sleep Disordered Breathing Substudy and those who did not (Appendix 3, available online at http://links.lww.com/AOG/A905). Apnea–hypopnea index distributions in early and midpregnancy are presented in Figure 2. The prevalence of sleep-disordered breathing (apnea–hypopnea index 5 or greater) in early and midpregnancy was 3.6% and 8.3%, respectively. In both early and midpregnancy, the majority of sleep-disordered breathing cases was mild (5 apnea–hypopnea index or less and less than 15). Urgent alerts for an apnea–hypopnea index greater than 50 or severe hypoxemia occurred in only six patients (one in early and five in midpregnancy). In women with sleep-disordered breathing, the vast majority of apneic events were obstructive (Appendix 4, available online at http://links.lww.com/AOG/A905), indicating that almost all participants identified with sleep-disordered breathing had OSA.

Characteristics of the participants according to the apnea–hypopnea index at baseline are shown in Table 1. In early pregnancy, older age, higher BMI, larger neck circumference, non-Hispanic black race–ethnicity, smoking, and chronic hypertension were all associated with increased apnea–hypopnea index. Similar findings were seen with the midpregnancy apnea–hypopnea index (Appendix 5, available online at http://links.lww.com/AOG/A905).

Among the 3,306 women included in the analysis (Fig. 1), hypertensive disorders data were available on 3,304 participants; hypertensive disorders of pregnancy occurred in 433 (13.1%); specifically preeclampsia occurred in 199 (6.0%). The most common
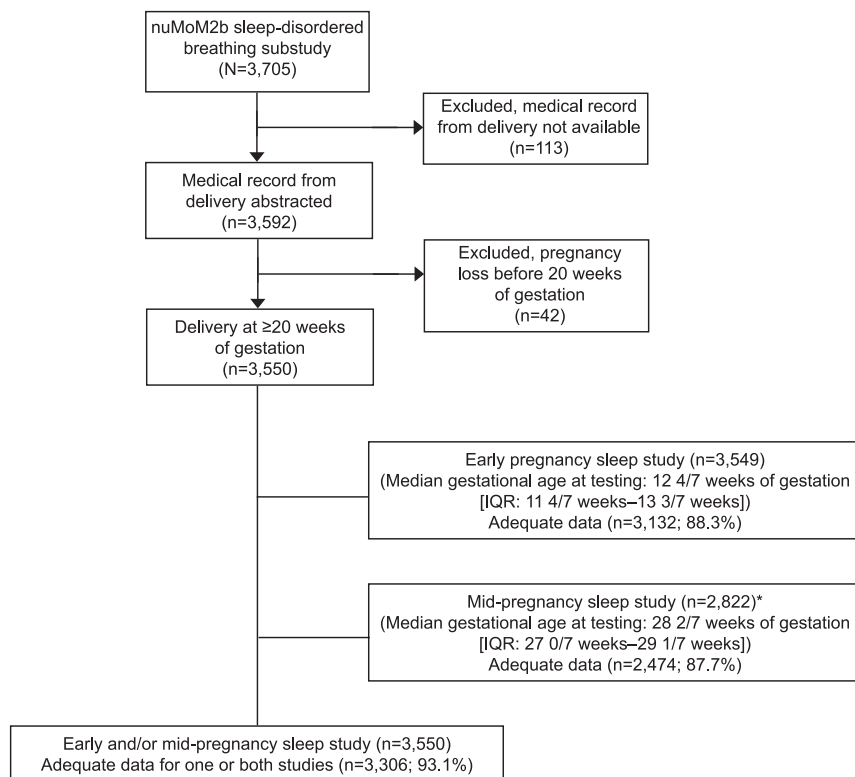
Fig. 1. Flowchart showing enrollment in Disordered Breathing Study within the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) Sleep Disordered Breathing Substudy and inclusion in analysis. *For the 728 women (3,550−2,822) without sleep studies in midpregnancy, 30 had a preterm birth before the sleep study could be completed, 86 missed the study visit (including the sleep assessment), and 612 had the study visit but did not participate in the midpregnancy sleep study. In planning the study, it was assumed that 25% would refuse the second sleep study. The participation rate in the midpregnancy sleep study was higher than expected. IQR, interquartile range.

Facco. Sleep-Disordered Breathing and Pregnancy Outcomes. Obstet Gynecol 2017.
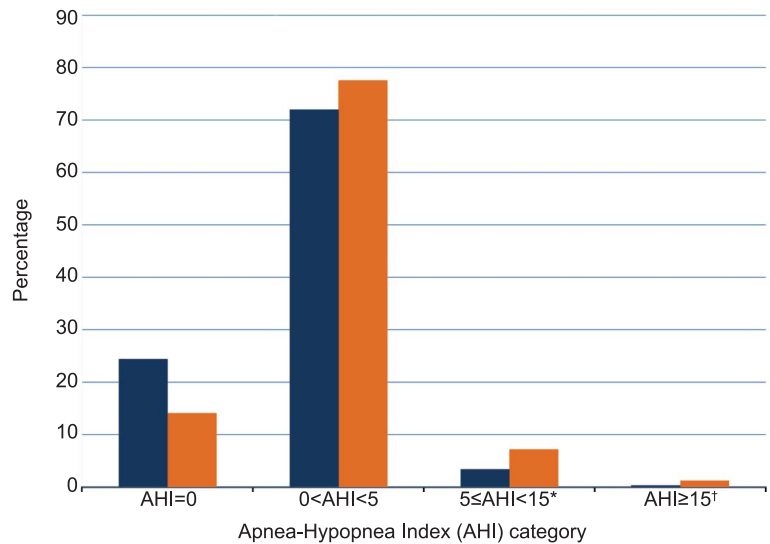
Fig. 2. The distributions of the women by apnea–hypopnea index (AHI) category in early and mid-pregnancy are presented, giving a point estimate (95% confidence interval). *Mild sleep-disordered breathing. †Moderate or severe sleep-disordered breathing.

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	AHI=0	0<AHI<5	5≤AHI<15*	AHI≥15†
Early pregnancy	24.4% (22.9–25.9)	72.0% (70.4–73.6)	3.4% (2.7–4.0)	0.3% (0.1–0.5)
Mid-pregnancy	14.1% (12.7–15.5)	77.6% (75.9–79.3)	7.2% (6.1–8.2)	1.2% (0.7–1.6)

diagnosis was antepartum gestational hypertension (n=234 [7.1%]) followed by severe preeclampsia (n=96 [2.9%]), mild preeclampsia (n=86 [2.6%]), superimposed preeclampsia (n=14 [0.4%]), and eclampsia (n=3).

Gestational diabetes mellitus occurred in 134 of 3,245 women without pregestational diabetes (4.1%). The median gestational age in weeks at the time of GDM testing was 27 with an interquartile range of 25–28. Of the patients with GDM, 55% (n=74) were diet-controlled; 36% (n=48) required treatment with insulin, an oral hypoglycemic, or both; and in 9% of patients (n=12), information on therapy modality was not available.

Table 2 presents crude and adjusted odds ratios for preeclampsia and hypertensive disorders of pregnancy according to apnea–hypopnea index in early and midpregnancy. We found a statistically significant association between sleep-disordered breathing (apnea–hypopnea index 5 or greater) during pregnancy and preeclampsia. In early pregnancy analyses, the adjusted odds ratio (OR) for preeclampsia when sleep-disordered breathing was present compared with absent was 1.94 (95% confidence interval [CI] 1.07–3.51); and in midpregnancy was 1.95 (95% CI 1.18–3.23). Statistically significant linear trends were observed between increasing apnea–hypopnea index and the rate of preeclampsia in unadjusted analyses (early P=.02 and midpregnancy P=.001), but the trend did not remain statistically significant in the adjusted analyses.

The adjusted OR for hypertensive disorders of pregnancy (preeclampsia and antepartum gestational hypertension) when sleep-disordered breathing was present compared with absent in early pregnancy did not reach statistical significance (adjusted OR 1.46, 95% CI 0.91–2.32), but in midpregnancy, the adjusted analysis was statistically significant (adjusted OR 1.73, 95% CI 1.19–2.52). Statistically significant linear trends were observed between increasing apnea–hypopnea index and the rate of all hypertensive disorders in unadjusted analyses (early and midpregnancy) and remained significant for midpregnancy apnea–hypopnea index in the adjusted analyses (P<.001).

We examined the timing between the sleep study and the diagnosis of a hypertensive disorder. Hypertensive complications were diagnosed between 45 and 229 days after the early pregnancy sleep study and from 44 days before to 113 days after the midpregnancy sleep study. Only 4.1% of hypertension diagnoses were made before the midpregnancy sleep-disordered breathing assessment; 91.7% of hypertension diagnoses were made more than 2 weeks after the midpregnancy assessment.

Table 3 presents the crude and adjusted ORs for GDM according to apnea–hypopnea index in early and midpregnancy. For sleep-disordered breathing present (apnea–hypopnea index 5 or greater) compared with absent, the adjusted OR for GDM was 3.47 (95% CI 1.95–6.19) and 2.79 (95% CI 1.63–4.77) in early and midpregnancy, respectively. In adjusted

Table 1. Baseline Characteristics of Participants Completing the Early Pregnancy Sleep Study According to the Apnea–Hypopnea Index in Early Pregnancy

Baseline Characteristics	Failed Study* (n=417)	All Apneas and Hypopneas With 3% or Greater Oxygen Desaturation/h (AHI)				P[†]
		0 (n=764)	Greater Than 0 to Less Than 5 (n=2,254)	5 to Less Than 15 (n=105)	AHI 15 or Greater (n=9)	
Maternal age (y)	25.8±5.7	25.7±5.5	27.1±5.5	29.2±5.8	34.0±5.8	<.001
Category						<.001
13–21	120 (28.8)	218 (28.5)	417 (18.5)	11 (10.5)	0 (0.0)	
22–35	275 (65.9)	513 (67.1)	1,686 (74.8)	77 (73.3)	5 (55.6)	
Older than 35	22 (5.3)	33 (4.3)	151 (6.7)	17 (16.2)	4 (44.4)	
Maternal race						.05
White non-Hispanic	227 (54.4)	434 (56.8)	1,406 (62.4)	63 (60.0)	3 (33.3)	
Black non-Hispanic	104 (24.9)	106 (13.9)	265 (11.8)	18 (17.1)	4 (44.4)	
Hispanic	51 (12.2)	156 (20.4)	396 (17.6)	13 (12.4)	1 (11.1)	
Asian	10 (2.4)	28 (3.7)	83 (3.7)	6 (5.7)	0 (0.0)	
Other	25 (6.0)	40 (5.2)	104 (4.6)	5 (4.8)	1 (11.1)	
BMI (kg/m^2)	27.0±6.3	24.4±5.4	26.8±6.5	36.3±8.6	45.6±11.3	<.001
Category						<.001
Less than 25	195 (47.4)	496 (65.9)	1,112 (49.8)	8 (7.8)	0 (0.0)	
25 to less than 30	109 (26.5)	182 (24.2)	573 (25.7)	12 (11.7)	0 (0.0)	
30 or greater	107 (26.0)	75 (10.0)	546 (24.5)	83 (80.6)	9 (100.0)	
Smoked during 3 mo before pregnancy	102 (24.5)	125 (16.4)	383 (17.0)	30 (28.6)	0 (0.0)	.03
Chronic hypertecnsion	14 (3.4)	11 (1.4)	50 (2.2)	7 (6.7)	2 (22.2)	<.001
Pregestational diabetes mellitus	6 (1.4)	13 (1.7)	33 (1.5)	4 (3.8)	0 (0.0)	.23
Neck circumference (cm)	33.3±3.1	32.3±2.5	33.0±2.8	36.5±4.6	40.2±3.2	<.001
Category						<.001
Less than 34	234 (61.6)	563 (77.3)	1,425 (65.8)	23 (22.8)	0 (0.0)	
34–36.5	92 (24.2)	127 (17.4)	512 (23.6)	32 (31.7)	0 (0.0)	
Greater than 36.5	54 (14.2)	38 (5.2)	230 (10.6)	46 (45.5)	9 (100.0)	

AHI, apnea–hypopnea index; BMI, body mass index.

Data are mean±standard deviation or n (%) unless otherwise specified.

* Tests comparing baseline characteristics of women with failed studies compared with those with adequate data found significant differences at P<.05 for: age (continuous and categorical), race, smoking status, and neck circumference (continuous).

[†] P values are shown for χ^2 tests for AHI and the categorical baseline characteristics and from analysis of variance F-tests for AHI and continuous baseline characteristics. As a result of the small number of women with AHIs of 15 or greater, the AHI 5 to less than 15 and 15 or greater categories were combined for these tests.

analyses for both early and midpregnancy, GDM rates increased with increasing apnea–hypopnea index (P values for linear trend .001 and <.001, respectively). When we repeated all analyses excluding women whose GDM status was ascertained only through chart abstraction (without a confirmatory GTT), the direction, magnitude, and statistical significance of effects did not change (data not shown). We examined the timing of the sleep study relative to GTT testing. Only 93 women (3.2%) completed GTT testing before the early pregnancy home sleep test; 96.4% of women had testing done more than 1 week after the sleep test. With respect to midpregnancy, 61.7% of GTT testing was done before the midpregnancy home sleep test, which was expected given the gestational age window for the study visit (22–31 weeks of gestation).

Both race–ethnicity and smoking were considered for covariate adjustment to the analyses presented in Tables 2 and 3. Neither met the criteria for inclusion as a confounder. Specifically, adding either variable to a univariate model with sleep-disordered breathing (apnea–hypopnea index 5 or greater) for hypertensive disorder of pregnancy and for GDM modified the crude ORs by 0.0–2.6% and 0.4–4.1%, respectively. Adding either variable to the multivariate models shown in the tables modified the adjusted ORs by 0.0–1.4% and 0.3–1.1%, respectively.

Given the clear relationship between sleep-disordered breathing and BMI, we also ran analyses with BMI as a continuous variable and considered the interaction between apnea–hypopnea index and BMI. Adjusting for BMI as a continuous variable (linear and quadratic terms) did not alter the

Table 2. Crude and Adjusted* Odds Ratios for Preeclampsia and Hypertensive Disorder of Pregnancy (Study Definition)[†] According to the Apnea–Hypopnea Index in Early and Midpregnancy

All Apneas and Hypopneas With 3% Oxygen Desaturation/h (AHI)	n/N (%)	Crude OR		Adjusted OR	
		Estimate (95% CI)	P	Estimate (95% CI)	P
Preeclampsia					
Early pregnancy (n=3,131)					
Less than 5 (referent)	170/3,017 (5.6)	1.00	<.001	1.00	.03
5 or greater	16/114 (14.0)	2.73 (1.58–4.74)		1.94 (1.07–3.51)	
0 (referent)	42/763 (5.5)	1.00	.004	1.00	.16
Greater than 0 to less than 5	128/2,254 (5.7)	1.03 (0.72–1.48)	Trend tests:	0.96 (0.66–1.39)	
5 to less than 15	14/105 (13.3)	2.64 (1.39–5.02)	.02 linear	1.79 (0.89–3.61)	
15 or greater	2/9 (22.2)	4.90 (0.99–24.34)	.50 quadratic	2.74 (0.51–14.73)	
Midpregnancy (n=2,472)					
Less than 5 (referent)	114/2,266 (5.0)	1.00	<.001	1.00	.01
5 or greater	26/206 (12.6)	2.73 (1.73–4.29)		1.95 (1.18–3.23)	
0 (referent)	15/347 (4.3)	1.00	<.001	1.00	.06
Greater than 0 to less than 5	99/1,919 (5.2)	1.20 (0.69–2.10)	Trend tests:	1.01 (0.57–1.78)	
5 to less than 15	21/177 (11.9)	2.98 (1.50–5.94)	.001 linear	1.83 (0.86–3.89)	
15 or greater	5/29 (17.2)	4.61 (1.54–13.76)	.68 quadratic	2.95 (0.91–9.58)	
Hypertensive disorder of pregnancy					
Early pregnancy (n=3,131)					
Less than 5 (referent)	378/3,017 (12.5)	1.00	<.001	1.00	.11
5 or greater	28/114 (24.6)	2.27 (1.46–3.53)		1.46 (0.91–2.32)	
0 (referent)	79/763 (10.4)	1.00	<.001	1.00	.29
Greater than 0 to less than 5	299/2,254 (13.3)	1.32 (1.02–1.72)	Trend tests:	1.16 (0.88–1.53)	
5 to less than 15	25/105 (23.8)	2.71 (1.63–4.49)	.02 linear	1.62 (0.94–2.79)	
15 or greater	3/9 (33.3)	4.33 (1.06–17.65)	.80 quadratic	2.17 (0.52–9.14)	
Midpregnancy (n=2,472)					
Less than 5 (referent)	266/2,266 (11.7)	1.00	<.001	1.00	.004
5 or greater	51/206 (24.8)	2.47 (1.76–3.48)		1.73 (1.19–2.52)	
0 (referent)	28/347 (8.1)	1.00	<.001	1.00	.004
Greater than 0 to less than 5	238/1,919 (12.4)	1.61 (1.07–2.43)	Trend tests:	1.31 (0.86–1.99)	Trend tests:
5 to less than 15	40/177 (22.6)	3.33 (1.97–5.61)	<.001 linear	1.98 (1.12–3.48)	<.001 linear;
15 or greater	11/29 (37.9)	6.96 (2.99–16.19)	.58 quadratic	4.27 (1.74–10.45)	.30 quadratic

OR, odds ratio; CI, confidence interval; AHI, apnea–hypopnea index.

* Early and midpregnancy AHI results were adjusted for maternal age (21 or younger, 22–35, and older than 35 years), body mass index (less than 25, 25 to less than 30, 30 or greater), and chronic hypertension (yes, no) as determined in early pregnancy. The midpregnancy results were also adjusted for rate of weight gain from early pregnancy to midpregnancy (as a continuous variable, linear on the log-odds scale). The adequacy of a linear term for rate of weight gain was investigated using AHI (dichotomized: less than 5, 5 or greater), body mass index categories, linear rate of change in weight, and quadratic rate of change in the model. The quadratic term was not significant and was not considered further. The adjusted analyses for early and midpregnancy included N_e=3,093 and N_m=2,413 observations, respectively. P values from logistic regression are given for general association with AHI categories. For a significant test of general association with the four-category AHI, post hoc tests are given for linear and quadratic trends in the log-odds across AHI categories using orthogonal contrasts.

[†] Preeclampsia includes mild, severe, and superimposed preeclampsia and eclampsia. Hypertensive disorder of pregnancy includes mild, severe, and superimposed preeclampsia and eclampsia plus antepartum gestational hypertension.

direction, magnitude, or statistical significance of effects (data not shown). For both hypertensive disorders and GDM, the interaction of BMI and sleep-disordered breathing was nonsignificant (early pregnancy: P=.90 and P=.31, respectively; and midpregnancy: P=.61 and P=.95, respectively).

Furthermore, we considered that weight gain from early to midpregnancy could be an intermediate

Table 3. Crude and Adjusted* Odds Ratios for Gestational Diabetes According to the Apnea–Hypopnea Index in Early and Midpregnancy for Women Without Pregestational Diabetes

All Apneas and Hypopneas With 3% Oxygen Desaturation/h (AHI)	GDM	Crude OR		Adjusted OR	
		Estimate (95% CI)	P	Estimate (95% CI)	P
Early pregnancy (n=3,075)					
Less than 5 (referent)	107/2,965 (3.6)	1.00	<.001	1.00	<.001
5 or greater	21/110 (19.1)	6.30 (3.77–10.53)		3.47 (1.95–6.19)	
0 (referent)	21/750 (2.8)	1.00	<.001	1.00	<.001
Greater than 0 to less than 5	86/2,215 (3.9)	1.40 (0.86–2.28)	Trend tests:	1.13 (0.69–1.85)	Trend tests:
5 to less than 15	17/101 (16.8)	7.03 (3.57–13.84)	<.001 linear	3.50 (1.64–7.44)	.001 linear
15 or greater	4/9 (44.4)	27.77 (6.96–110.89)	.17 quadratic	8.44 (1.90–37.60)	.34 quadratic
Midpregnancy (n=2,432)					
Less than 5 (referent)	69/2,231 (3.1)	1.00	<.001	1.00	<.001
5 or greater	27/201 (13.4)	4.86 (3.04–7.79)		2.79 (1.63–4.77)	
0 (referent)	2/347 (0.6)	1.00	<.001	1.00	<.001
Greater than 0 to less than 5	67/1,884 (3.6)	6.36 (1.55–26.07)	Trend tests:	4.96 (1.20–20.51)	Trend tests:
5 to less than 15	22/173 (12.7)	25.12 (5.84–108.17)	<.001 linear	12.62 (2.80–56.81)	<.001 linear
15 or greater	5/28 (17.9)	37.49 (6.90–203.79)	.11 quadratic	15.64 (2.67–91.60)	.13 quadratic

GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval; AHI, apnea–hypopnea index.
Data are n/N (%) unless otherwise specified.
* Early and midpregnancy AHI results were adjusted for maternal age (younger than 21, 22–35, and older than 35 years), body mass index (less than 25, 25 to less than 30, 30 or greater), and chronic hypertension (yes, no) as determined in early pregnancy. The midpregnancy results were also adjusted for rate of weight gain from early pregnancy to midpregnancy (as a continuous variable, linear on the log-odds scale). The adequacy of a linear term for rate of weight gain was investigated using AHI (dichotomized: less than 5, 5 or greater), body mass index categories, linear rate of change in weight, and quadratic rate of change in the model. The quadratic term was not significant and was not considered further. The adjusted analyses for early and midpregnancy included N_e=3,037 and N_m=2,374 observations, respectively. P values from logistic regression are given for general association with AHI categories. For a significant test of a general association with the four-category AHI, post hoc tests are given for linear and quadratic trends in the log-odds across AHI categories using orthogonal contrasts.

variable in the causal pathway between apnea–hypopnea index and pregnancy outcomes. However, the direction, magnitude, and significance of effects were similar to those in Tables 2 and 3 when we excluded weight gain as a covariate in the midpregnancy models (Appendices 6 and 7, available online at http://links.lww.com/AOG/A905).

DISCUSSION

In this prospective analysis of objectively assessed sleep-disordered breathing in pregnancy, the prevalence of sleep-disordered breathing was 3.6% and 8.3% in early pregnancy and midpregnancy, respectively. Nearly all participants in this cohort identified as sleep-disordered breathing-positive (apnea–hypopnea index 5 or greater) had a nocturnal respiratory pattern consistent with OSA. There was an independent association between sleep-disordered breathing and preeclampsia, hypertensive disorders of pregnancy, and GDM after adjustment for age, BMI, chronic hypertension, and pregnancy-related weight gain. Increasing exposure–response relationships were

observed between apnea–hypopnea index and pregnancy-related hypertension and GDM.

Before this report, the largest studies evaluating sleep-disordered breathing and pregnancy-related hypertension have been retrospective or cross-sectional and limited by the quality of sleep-disordered breathing exposure and pregnancy outcome assessment.[26] Data from smaller prospective cohorts, using objective assessments of sleep-disordered breathing, have yielded conflicting results.[16–18] Louis et al[16] reported on a cohort of 175 obese women and demonstrated that women with sleep-disordered breathing (apnea–hypopnea index 5 or greater) were more likely to develop preeclampsia (adjusted OR 3.5, 95% CI 1.3–9.9). However, two other small studies failed to demonstrate a positive association between sleep-disordered breathing and pregnancy-related hypertension.[17,18] In our large prospective study, in which sleep-disordered breathing was diagnosed using objective criteria and confounding variables carefully considered, we found an association between sleep-disordered breathing and preeclampsia and pregnancy-related hypertension. In adjusted analyses, an early pregnancy apnea–hypopnea index of 5 or

greater was associated with preeclampsia. In mid-pregnancy, an apnea–hypopnea index of 5 or greater was associated with the development of preeclampsia and the composite of preeclampsia and antepartum gestational hypertension. In regard to our midpregnancy apnea–hypopnea index data, because rapid weight gain and extravascular fluid retention may result in an increase in apnea–hypopnea index, we additionally adjusted for weight gain between visits in the mid-pregnancy analyses. We also examined the timing of the midpregnancy sleep assessment in relation to hyper-tension diagnosis and found that 91.7% of diagnoses were made more than 2 weeks after the midpregnancy sleep test. In summary, the associations and dose–response relationships observed in this study among apnea–hypopnea index, preeclampsia, and pregnancy-related hypertension could potentially signify a causal link between sleep-disordered breathing exposure in pregnancy and the subsequent development of hyper-tensive disorders of pregnancy.

Our data regarding the association between sleep-disordered breathing and GDM are robust. By excluding women with pregestational diabetes and defining GDM, we optimized case ascertainment. We observed increasing apnea–hypopnea index with increasing incidence of GDM in both early and mid-pregnancy, independent of important covariates. The early pregnancy apnea–hypopnea index data (6–15 weeks of gestation) predated the GTT testing by more than 1 week in more than 96% of our cohort.

A major strength of this study is the prospective design in which the apnea–hypopnea index results were blinded to the care providers, investigators, and participants. This limited the possibility of ascertain-ment bias. Our sleep-disordered breathing ascertain-ment was optimized using an independent and blinded central reading center. We were able to con-trol for important confounding factors including BMI and weight gain, and we evaluated the interaction between apnea–hypopnea index and BMI. We did observe a lower than expected rate of sleep-disordered breathing in early pregnancy (early preg-nancy 3.6% observed compared with 5% expected, midpregnancy 8.3% compared with 10%), but despite the lower rates, we detected statistically significant differences in our primary outcome. The observed differences were substantially greater than what we powered to detect. Nonetheless, given the observa-tional and voluntary nature of the study and moderate adjusted ORs (particularly for association with hypertensive disorders), the possibility of residual confounding resulting from selection bias and unmea-sured or unknown confounders cannot be definitively

excluded. Finally, we recognize the limitations of uti-lizing a level 3 home sleep apnea test for measuring apnea–hypopnea index. Although a full in-laboratory polysomnogram is considered the gold standard for the objective measurement of sleep-related breathing disorders, it is often not feasible to use a full polysom-nogram for large sleep-related studies given the cost and limited availability of sleep laboratory space as well as difficulties recruiting a larger number of par-ticipants in research requiring such in-laboratory monitoring. Data indicate that unattended home sleep testing can reliably detect sleep-disordered breathing at substantively lower cost compared with in-laboratory polysomnogram.[27] Furthermore, most in-surers now routinely require home sleep tests as the first-line diagnostic modality for the majority of pa-tients with suspected sleep-disordered breathing and without certain comorbidities.[28,29] Unattended home sleep testing may modestly underestimate the apnea–hypopnea index as a result of this overestimation of sleep time.[30] However, studies were scored after ed-iting movement and artifact, reducing the effect of wake time on the apnea–hypopnea index estimates.

Although we found an association with sleep-disordered breathing preceding the development of both pregnancy-related hypertensive disorders and GDM, we cannot conclude that universal screening for and treatment of sleep-disordered breathing in pregnancy would reduce the risks of these adverse outcomes. The most widely prescribed treatment for sleep-disordered breathing is CPAP during sleep. The benefit of treatment with CPAP has been consistently demonstrated when excessive daytime sleepiness and sleep quality are used as endpoints.[31,32] However, even in nonpregnant populations, data conflict regard-ing whether treatment of sleep-disordered breathing can reduce the risk of developing hypertension or diabetes.[33–35] This is especially true for milder forms of sleep-disordered breathing (apnea–hypopnea index less than 30), which our study confirms represents the vast majority of sleep-disordered breathing cases in young pregnant women. Pregnancy is an ideal sce-nario in which to better understand the role of CPAP as a preventive strategy for reducing cardiometabolic morbidity because the timeframe needed to measure outcomes after initiating therapy is significantly con-tracted. To date, studies examining the effect of CPAP treatment on pregnancy have been small and limited in the scope of endpoints.[36–42]

In summary, in this prospective analysis of objectively assessed sleep-disordered breathing in pregnancy, the prevalence of sleep-disordered breath-ing was 3.6% in early pregnancy and increased to

8.3% in midpregnancy. The majority of sleep-disordered breathing cases identified were mild. Our data demonstrate that even modest elevations of apnea–hypopnea index in pregnancy are associated with an increased risk of developing hypertensive disorders and an increased incidence of GDM. These findings are important because sleep-disordered breathing is a risk factor that is amenable to therapeutic intervention. The underlying mechanistic pathways linking sleep-disordered breathing and adverse pregnancy outcomes are likely multifactorial. Sleep-disordered breathing is linked to oxidative stress, autonomic dysfunction, inflammation, endothelial damage, and altered hormonal regulation of energy expenditure.[11] These same biologic pathways have been associated with adverse pregnancy outcomes.[12] Further research should help to establish whether screening for and treating sleep-disordered breathing in pregnancy can mitigate the risk and consequences of hypertensive disorders of pregnancy and GDM.

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