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Objectively assessed sleep-disordered breathing during pregnancy and infant birthweight

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Abstract

Background: Sleep-disordered breathing (SDB) in pregnancy is associated with adverse maternal outcomes. The relationship between SDB and infant birthweight is unclear. This study's primary aim is to determine if objectively measured SDB in pregnancy is associated with infant birthweight.

Methods: We measured SDB objectively in early (6–15 weeks' gestation) and mid (22–31 weeks' gestation) pregnancy in a large cohort of nulliparous women. SDB was defined as an Apnea-Hypopnea Index 5 and in secondary analyses we also examined measures of nocturnal hypoxemia. We used a modified Poisson regression approach to estimate relative risks (RR) of large-for-gestational-age (LGA: >90th percentile for gestational age) and small-for-gestational-age (SGA: <10th percentile for gestational age) birthweights.

Results: The prevalence of early-pregnancy SDB was nearly 4%. The incidence of mid-pregnancy SDB was nearly 6.0%. The prevalence of LGA and SGA was 7.4% and 11.9%, respectively. Early-pregnancy SDB was associated with a higher risk of LGA in unadjusted models (RR 2.2, 95% CI 1.3–3.5) but not BMI-adjusted models (aRR 1.0, 95% CI 0.6–1.8). Mid-pregnancy SDB was not associated with SGA or LGA. Mid-pregnancy nocturnal hypoxemia (% of sleep time <90% oxygen saturation) and increasing nocturnal hypoxemia from early to mid-pregnancy were associated with a higher risk of LGA in BMI-adjusted models. SDB and nocturnal hypoxemia were not associated with SGA.

Conclusions: SDB in pregnancy was not associated with an increased risk of LGA or SGA birthweight, independent of BMI. Some measures nocturnal hypoxemia were associated with an increase in LGA risk, independent of BMI.

Keywords

abnormal fetal growth; sleep-disordered breathing; sleep apnea; nocturnal hypoxemia

INTRODUCTION

Sleep-disordered breathing (SDB) is common during pregnancy[1,23, 4] and is associated with systemic inflammation, oxidative stress, and increased sympathetic nervous system activity, all of which have been associated with adverse pregnancy and birth outcomes.[2,5] For example, in the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be

(nuMoM2b), early and mid-pregnancy SDB was associated with approximately 95% increased odds of preeclampsia respectively; 46% to 73% increased odds of hypertensive disorders of pregnancy, and 179% to 247% increased odds of gestational diabetes (GDM). However, the relationship between SDB and fetal birthweight is less well understood.

Understanding the relationship between SBD and fetal birth weight is critical because small- and large-for-gestational-age (SGA and LGA, respectively) birthweight is associated with short- and long-term maternal and fetal morbidity and mortality.[6] SGA (i.e., birthweight <10th percentile for gestational age) newborns are predisposed to complications including hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, seizures, sepsis, respiratory distress, and neonatal death.[7] Likewise, LGA (i.e., birthweight 90th percentile for a given gestational age) newborns are at a higher risk for birth trauma, hypoglycemia, respiratory problems, and more likely to have overweight and obese later in life[8] Mothers of LGA newborns are at an increased risk of cesarean birth.

Prior studies examining the relationship between SDB and birthweight found mixed results. For example, Chen et al. examined the association between obstructive sleep apnea (OSA), a type of SDB, and infant birth outcomes, including low birth weight and small-for-gestational-age (SGA), using two nationwide databases in Taiwan. Women with OSA diagnosed in the year before pregnancy had approximately 34% higher odds of SGA and 76% higher odds of low birth weight than age-matched women without OSA. Micheli et al. found that women that reported severe snoring (i.e., frequently or always) had a nearly 3-fold higher risk for low birth weight than women who did not snore.[9] However, two recent meta-analyses did not confirm a relationship between SDB and birthweight or SGA.[4,10] One reason for the inconsistent results is that many prior studies have used subjective or indirect (e.g., ICD-codes) measures of SDB, had small sample sizes, and lacked adjustment for important confounders.

The primary purpose of this analysis was to determine whether objectively measured SDB is associated with SGA and LGA in a large cohort of nulliparous women. We secondarily assessed the association of measures of nocturnal hypoxemia with SGA and LGA.

MATERIALS AND METHODS

Study Design & Population

The nuMoM2b Sleep-Disordered Breathing (nuMOM2b-SDB) study is ancillary to the larger nuMoM2b study. The nuMoM2b was a prospective cohort study aimed at identifying maternal characteristics and environmental factors that are predictive of adverse pregnancy outcomes in nulliparous women.[11] The study enrolled 10,037 nulliparous women (no prior delivery >20 weeks' gestation) with a viable singleton pregnancy at the time of screening (6^0 to 13^6 weeks' gestation; Visit 1) from eight clinical sites. Women were followed throughout pregnancy until the time of delivery. In the nuMoM2b-SDB ancillary study, a subset of participants participated in an in-home sleep apnea study (HST) to obtain objective measures of SDB after Visit 1 (completed HST by 6^0–15^0) and Visit 3 (completed HST between 22^0–31^0). Complete details on HST procedures and scoring have been previously published.[12] The ancillary study's overall aim was to describe the prevalence and characteristics of SDB

during pregnancy and determine its relationship with adverse maternal pregnancy outcomes. Participants were recruited if they were not currently on continuous positive airway pressure treatment for SDB and did not have severe asthma (requiring continuous oral steroid therapy for 14 days) or a condition requiring oxygen supplementation. We did not exclude participants with pre-existing SDB who were not currently on treatment or those with other sleep disorders. 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 AHI >50 events/hour or severe hypoxemia (oxygen saturation of <90% for 10% 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. IRB approval was obtained at each site, and informed consent was obtained from each participant.

Baseline characteristics were similar between nuMoM2b women who did and did not participate in the SDB ancillary study.[13] For this analysis, we excluded women without valid data on SDB assessment at Visit 1 (6 to 15 weeks' gestation) or data on neonatal birth weight.

Primary Exposure: Sleep-Disordered Breathing

Facco et al. described the data collection, analysis, and quality control procedures for the in-home sleep study previously.[12] Briefly, SDB was objectively assessed using the Embletta Gold monitor, a self-administered Level 3 in-home sleep apnea monitor (Broomfield, CO).[12] The monitor assesses SDB by recording nasal airflow waveforms, respiratory effort from abdominal and thoracic inductance plethysmography, the level and duration of oxygen desaturation by pulse oximetry, heart rate, and body position. Participants were instructed on the device's proper placement and asked to wear it overnight for one night after between 6 to 15 weeks' gestation and again for one night between 22 to 31 weeks' gestation. For simplicity, we will refer to Visit 1 and Visit 3 as early and mid-pregnancy hereafter. A central sleep reading center scored all sleep study data by trained scorers blinded to all other data.

SDB was defined by the Apnea-Hypopnea Index (AHI). The AHI was defined as the number of apneas and hypopneas per hour of estimated sleep, which includes all apneas regardless of oxygen desaturation and hypopneas accompanied by 3% oxygen desaturation, divided by estimated sleep time. We used an AHI threshold of 5 to define SDB. SDB that was detected in early pregnancy will be referred to as "early-pregnancy SDB." SDB that was present in late pregnancy, but not early, will be referred to as "mid-pregnancy SDB." SDB present at either visit will be referred to as "SDB ever."

In secondary analyses, in addition to using AHI as a continuous variable to assess SDB severity, we used two additional measures to estimate the nocturnal hypoxemia associated with SDB: the number of oxygen desaturations 3% per hour of estimated sleep (oxygen desaturation index [ODI3]) and the percentage of estimated sleep time below 90% oxygen saturation (ST_{90}).

Primary Outcomes: Neonatal Birthweight

Birthweight was abstracted from medical records. According to gender-specific reference values, large-for-gestational-age (LGA) was defined as a birth weight above the 90th percentile for gestational age.[14] Small-for-gestational-age (SGA) was defined as a birth weight below the 10th percentile for gestational age according to gender-specific reference values.[14]

Statistical Analysis

Chi-square tests were used to compare the distribution of categorical descriptive and medical history characteristics by SDB status (i.e., never, prevalent early, or incident mid-pregnancy). Analysis of variance was used to compare mean levels of continuous variables by SDB status. Linear contrasts were then used to identify between-group differences (e.g., prevalent early vs. incident mid-pregnancy).

Multivariable logistic regression was used to examine the associations of SDB status (i.e., never, early-pregnancy, mid-pregnancy), hypoxemia severity (i.e., defined either by AHI, ODI3, or ST_{90}), and changes in SDB measures from early to mid-pregnancy with LGA and SGA. We used a modified Poisson approach with a robust variance estimator to calculate relative risk with (RRs) and 95% confidence intervals (CI). In analyses that used SDB status as the exposure, women without SDB at either time point (SDB never) served as the reference group. For analyses using continuous SDB and nocturnal hypoxemia severity measures (AHI, ODI3, and ST_{90}) as the exposures, we rescaled the measurements to a mean of 0 and a standard deviation of 1. Thus, RRs for the continuous data are in increments of one standard deviation. For all analyses, Model 1 adjusted for maternal age (years), maternal chronic hypertension (yes/no), and pre-gestational diabetes (yes/no), given their associations with extremes of birth weight and with SDB. Model 2 included all Model 1 covariates as well as maternal BMI (kg/m^2).

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). All analyses were considered statistically significant at an alpha < 0.05.

RESULTS

The sample included 3,114 participants with complete data on SDB status in early pregnancy and birth weight. Of these participants, 2,211 (71.0%) had valid SDB data mid-pregnancy. A higher proportion of participants with missing SDB data mid-pregnancy have obesity, were non-White race, have a male fetus, have two or more children, have an income above the poverty level, have completed college, and were smokers pre-pregnancy than participants with data at both assessments. Also, approximately 13% of participants with missing SDB data mid-pregnancy had SDB in early pregnancy (data not shown).

Approximately 4% (n=114/3,114), 6% (n=132/2,211), and 8% (n=246/3,114) had early-pregnancy SDB, mid-pregnancy SDB, and SDB ever respectively. Seventeen participants with early-pregnancy SDB had resolution in mid-pregnancy. Women with SDB ever were more likely to be older, have obesity, and have chronic hypertension than women without SDB. Women with early-pregnancy SDB were more likely to have obesity, a male fetus, an

income below the poverty level, and less likely to have completed college than women with mid-pregnancy SDB (Table 1).

There were 164 and 273 cases of LGA and SGA births, respectively. Early-pregnancy SDB and SDB ever were associated with a higher unadjusted risk of LGA (Table 2). The relationship between SDB and LGA remained statistically significant in models adjusting for age, chronic hypertension, and pre-gestational diabetes (Figure 1a). After further adjusting for BMI, there were no statistically significant associations between SDB and LGA risk (Figure 1b). Mid-pregnancy SDB was not significantly associated with LGA in unadjusted or adjusted models. Early-pregnancy SDB, mid-pregnancy SDB, or SDB ever were not associated with SGA in unadjusted or adjusted models.

Next, we examined the relationships between fetal growth, SDB severity (AHI as a continuous measure) and nocturnal hypoxemia. Supplemental figure 1 and 2 shows the distribution of each measure in early in mid-pregnancy. Measures of nocturnal hypoxemia were more strongly associated with LGA than SDB severity (Table 3). Specifically, each standard deviation increase in ODI3 in early and mid-pregnancy was associated with a 14% and 16% increased LGA risk, respectively. Likewise, each standard deviation increase in ST_{90} in early and mid-pregnancy was associated with a 7% and 8% increased LGA risk, respectively. Each standard deviation increase in AHI in early and mid-pregnancy was associated with an 11% and 4% increase in the risk of LGA, respectively. However, associations between SDB severity/nocturnal hypoxemia and LGA were attenuated and no longer statistically significant in BMI adjusted models, except for ST_{90} in mid-pregnancy. None of the SDB severity/nocturnal hypoxemia measures in early or mid-pregnancy were associated with SGA (data not shown).

We observed small changes in SDB severity and nocturnal hypoxemia from early to mid-pregnancy, which were associated with LGA risk. Supplemental figure 3 shows the distribution of change in each measure. Specifically, each standard deviation increase in change in AHI, ODI3, and ST90 was associated with a 12%, 17%, 7% increased risk of LGA in models adjusting for age, chronic hypertension, and pre-gestational diabetes, respectively. The relationship between change in AHI across pregnancy and LGA was no longer statistically significant after further adjusting for BMI (Model 2). However, the relationship between ODI3 and ST_{90} change across pregnancy and LGA was unchanged when additionally adjusting for BMI. There was no association of change in SDB severity/ nocturnal hypoxemia from early to late pregnancy with SGA (data not shown).

DISCUSSION

Principal Findings

We examined the association between objectively measured SDB, defined as an AHI 5, in early and mid-pregnancy with SGA and LGA births in a large cohort of nulliparous women. We found that SDB in pregnancy was not associated with SGA. SDB in early pregnancy was associated with a nearly two-fold increase in the risk of LGA when adjusting for maternal age and the presence of chronic hypertension and pre-gestational diabetes. However, when adjusting for BMI, the relationship between early pregnancy SDB and LGA was no longer

observed. Mid-pregnancy SDB was not associated with LGA. Differences in risk estimates seen between early vs. mid-pregnancy SDB and LGA may reflect that women with early-pregnancy SDB have a higher risk profile than women with mid-pregnancy SDB. For example, women with early-pregnancy SDB had higher BMI's than women with mid-pregnancy SDB. The differences in risk may also be due to differences in the duration of exposure to SDB. However, ultimately, when adjusting for BMI, neither early nor mid-pregnancy SDB was associated with LGA. Thus, it is unclear if SDB infers a greater risk of abnormal infant growth than maternal BMI alone. The tight relationship between SDB and obesity and between obesity and adverse pregnancy outcomes, creates a statistical challenge to understanding the independent contribution of each exposure to birthweight. There are strong correlations between higher BMI, the prevalence of sleep apnea, and AHI severity, as well as measures of overnight oxygenation.[15,16] However, there are also data to suggest that sleep apnea may predispose individuals to worsening obesity because of associated sleep deprivation, daytime somnolence, and disrupted metabolism.[17,18] Consistent with prior studies of SDB, we chose to treat BMI as a confounding variable. Our cohort lacked an adequate sample of women without obesity with SDB (20 prevalent early, 59 incident mid-pregnancy) or variation in BMI or AHI to examine the independent relationships more thoroughly. There is a need for additional research that includes samples with adequate variability in BMI and AHI to tease apart their independent relationships with birthweight. Future studies should also consider exploring mediation or effect modification models to understand how these exposures jointly relate to infant birthweight.[19]

Our secondary analyses suggest that some measures that directly quantified overnight hypoxemia, Specifically, ST_{90} in mid-pregnancy and ODI3 and ST_{90} change across pregnancy, were associated with an increase in LGA risk, independent of BMI. Measures of nocturnal hypoxemia were not associated with SGA.

The overall findings from this analysis were similar to those from some prior studies[20–26] but conflicted with others[27–34] For example, Facco et al. reported no association between objectively measured SDB and extremes of birth weight (<5% or >95% for gestational age) in a prospective cohort study of 182 pregnant women.[21] Likewise, Louis et al. found that objectively measured SDB was not associated with mean birthweights or rates of SGA among 175 obese pregnant women.[25]

In contrast, Telerant et al. found that women (n=155) with mild OSA (AHI>5 by in-home sleep apnea testing) in the third trimester had a five-fold increase in the odds of LGA (OR = 5.1, 95% CI 1.3 to 20.0) after adjusting for parity and pre-pregnancy BMI.[29] However, this study excluded women with pre-pregnancy obesity. Bin et al. found that antenatal or pregnancy-associated OSA (identified using ICD10-AM diagnosis codes) was associated with 27% higher odds of LGA in a large population-based study in Australia (n=636,227).[28] Pamidi et al. examined a prospective cohort of 234 pregnant women and found that PSG-determined OSA in the third trimester had a three-fold increase in the odds of SGA, depending on the AHI threshold used to define OSA.[30] The contrasting findings between the current study and these studies may be due to differences in sample characteristics and timing of sleep assessment, as well as the severity of OSA. Specifically, these studies either had a low prevalence of women with obesity or excluded women with obesity. Pamidi et al.

included women into their study who had a predicted birthweight <75th percentile to reduce the potential number of LGA infants, leading to a significant bias in any observed relationship. These differences in sample characteristics between these studies and ours limit comparisons of study findings.

Strengths of this study include its prospective design, the use of objective measures of SDB and the assessment of SDB at multiple time points. We were also able to examine SDB severity as well as quantified overnight oxygen saturation patterns. Our study was significantly larger than most previous reports. Most prior studies had a sample of fewer than 300 women, apart from a few that used medical databases/ICD-9 codes as their method of SDB ascertainment. Despite the larger sample, as noted above, we were limited in our analyses of SDB and BMI by the small number of non-obese women with SDB. Additionally, the clear majority of women with SDB had mild disease (AHI between 5 and 14.9), so we cannot comment on the impact of more severe forms of SDB on birthweight outcomes. Our study was also limited by only having one measure of infant growth (i.e., birthweight). Thus, we were unable to examine associations between SDB, nocturnal hypoxemia, and infant growth trajectories. Additionally, while we found some positive relationships between overnight hypoxemia and LGA indices, those findings should be interpreted with caution, as we did not adjust for multiple comparisons. It should also be noted that overnight hypoxemia may result from SDB but also may be independently the result of from underlying respiratory or cardiac disease (e.g., asthma). Our findings suggest that future research should specifically address the source and characteristics of hypoxemia that may influence fetal growth. Finally, it is possible that the overall lack of effect of SDB on fetal growth demonstrated in this study is a result of opposing effects of SDB on maternal and placental physiology. SDB has been linked to both an increased risk of hypertensive disorders, which are associated with lower birth weight, and to gestational diabetes, which is strongly associated with higher birth weight.

Conclusion

SDB, defined as an AHI 5, in pregnancy was associated with higher unadjusted risk of LGA but not SGA. The association between SDB and LGA was not independent of key covariates, specifically BMI. Some measures of nocturnal hypoxemia were associated with an increase in LGA risk, independent of BMI. Additional studies are needed to determine how SDB severity and other measures of nocturnal hypoxemia may influence fetal growth and development beyond the risk associated with BMI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosure of Funding Received

References

1. Ayyar L, Shaib F, Guntupalli K. Sleep-Disordered Breathing in Pregnancy. Sleep Med Clin. 2018;13(3):349–57. [PubMed: 30098752]

2. Izci-Balserak B, Pien GW. Sleep-disordered breathing and pregnancy: potential mechanisms and evidence for maternal and fetal morbidity. Curr Opin Pulm Med. 2010;16(6):574–82. [PubMed: 20859210]

3. Sarberg M, Svanborg E, Wirehn AB, Josefsson A. Snoring during pregnancy and its relation to sleepiness and pregnancy outcome - a prospective study. BMC Pregnancy Childbirth. 2014;14:15. [PubMed: 24418321]

4. Liu L, Su G, Wang S, Zhu B. The prevalence of obstructive sleep apnea and its association with pregnancy-related health outcomes: a systematic review and meta-analysis. Sleep Breath. 2018.

5. Izci Balserak B Sleep disordered breathing in pregnancy. Breathe (Sheff). 2015;11(4):268–77. [PubMed: 27064321]

6. Hamilton BE, Hoyert DL, Martin JA, Strobino DM, Guyer B. Annual summary of vital statistics: 2010–2011. Pediatrics. 2013;131(3):548–58. [PubMed: 23400611]

7. Fetal Growth Restriction: ACOG Practice Bulletin, Number 227. Obstet Gynecol. 2021;137(2):e16–e28. [PubMed: 33481528]

8. Macrosomia: ACOG Practice Bulletin, Number 216. Obstet Gynecol. 2020;135(1):e18–e35. [PubMed: 31856124]

9. Micheli K, Komninos I, Bagkeris E, Roumeliotaki T, Koutis A, Kogevinas M, Chatzi L. Sleep patterns in late pregnancy and risk of preterm birth and fetal growth restriction. Epidemiology. 2011;22(5):738–44. [PubMed: 21734587]

10. Li L, Zhao K, Hua J, Li S. Association between Sleep-Disordered Breathing during Pregnancy and Maternal and Fetal Outcomes: An Updated Systematic Review and Meta-Analysis. Front Neurol. 2018;9:91. [PubMed: 29892255]

11. Haas DM, Ehrenthal DB, Koch MA, Catov JM, Barnes SE, Facco F, Parker CB, Mercer BM, Bairey-Merz CN, Silver RM, Wapner RJ, Simhan HN, Hoffman MK, Grobman WA, Greenland P, Wing DA, Saade GR, Parry S, Zee PC, Reddy UM, Pemberton VL, Burwen DR, National Heart L, Blood Institute nuMo MbHHSN. Pregnancy as a Window to Future Cardiovascular Health: Design and Implementation of the nuMoM2b Heart Health Study. Am J Epidemiol. 2016;183(6):519–30. [PubMed: 26825925]

12. Facco FL, Parker CB, Reddy UM, Silver RM, Louis JM, Basner RC, Chung JH, Schubert FP, Pien GW, Redline S, Mobley DR, Koch MA, Simhan HN, Nhan-Chang CL, Parry S, Grobman WA, Haas DM, Wing DA, Mercer BM, Saade GR, Zee PC. NuMoM2b Sleep-Disordered Breathing study: objectives and methods. Am J Obstet Gynecol. 2015;212(4):542 e1–127. [PubMed: 25746730]

13. Facco FL, Parker CB, Reddy UM, Silver RM, Koch MA, Louis JM, Basner RC, Chung JH, Nhan-Chang CL, Pien GW, Redline S, Grobman WA, Wing DA, Simhan HN, Haas DM, Mercer BM, Parry S, Mobley D, Hunter S, Saade GR, Schubert FP, Zee PC. Association Between Sleep-Disordered Breathing and Hypertensive Disorders of Pregnancy and Gestational Diabetes Mellitus. Obstet Gynecol. 2017;129(1):31–41. [PubMed: 27926645]

14. Duryea EL, Hawkins JS, McIntire DD, Casey BM, Leveno KJ. A revised birth weight reference for the United States. Obstet Gynecol. 2014;124(1):16–22. [PubMed: 24901276]

15. An HJ, Baek SH, Kim SW, Kim SJ, Park YG. Clustering-based characterization of clinical phenotypes in obstructive sleep apnoea using severity, obesity, and craniofacial pattern. Eur J Orthod. 2019.

16. Sutherland K, Keenan BT, Bittencourt L, Chen NH, Gislason T, Leinwand S, Magalang UJ, Maislin G, Mazzotti DR, McArdle N, Mindel J, Pack AI, Penzel T, Singh B, Tufik S, Schwab RJ, Cistulli PA, Investigators S. A Global Comparison of Anatomic Risk Factors and Their Relationship to Obstructive Sleep Apnea Severity in Clinical Samples. J Clin Sleep Med. 2019;15(4):629–39. [PubMed: 30952214]

17. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? Diabetes Care. 2008;31 Suppl 2:S303–9. [PubMed: 18227501]

18. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK. Interactions between obesity and obstructive sleep apnea: implications for treatment. Chest. 2010;137(3):711–9. [PubMed: 20202954]

19. Spruyt K, Gozal D. A mediation model linking body weight, cognition, and sleep-disordered breathing. Am J Respir Crit Care Med. 2012;185(2):199–205. [PubMed: 22071385]

20. Howe LD, Signal TL, Paine SJ, Sweeney B, Priston M, Muller D, Lee K, Huthwaite M, Gander P. Self-reported sleep in late pregnancy in relation to birth size and fetal distress: the E Moe, Mama prospective cohort study. BMJ Open. 2015;5(10):e008910.

21. Facco FL, Ouyang DW, Zee PC, Strohl AE, Gonzalez AB, Lim C, Grobman WA. Implications of sleep-disordered breathing in pregnancy. Am J Obstet Gynecol. 2014;210(6):559 e1–6. [PubMed: 24373947]

22. Owusu JT, Anderson FJ, Coleman J, Oppong S, Seffah JD, Aikins A, O'Brien LM. Association of maternal sleep practices with pre-eclampsia, low birth weight, and stillbirth among Ghanaian women. Int J Gynaecol Obstet. 2013;121(3):261–5. [PubMed: 23507553]

23. Bourjeily G, Danilack VA, Bublitz MH, Lipkind H, Muri J, Caldwell D, Tong I, Rosene-Montella K. Obstructive sleep apnea in pregnancy is associated with adverse maternal outcomes: a national cohort. Sleep Med. 2017;38:50–7. [PubMed: 29031756]

24. Ko HS, Kim MY, Kim YH, Lee J, Park YG, Moon HB, Kil KC, Lee G, Kim SJ, Shin JC. Obstructive sleep apnea screening and perinatal outcomes in Korean pregnant women. Arch Gynecol Obstet. 2013;287(3):429–33. [PubMed: 23086136]

25. Louis J, Auckley D, Miladinovic B, Shepherd A, Mencin P, Kumar D, Mercer B, Redline S. Perinatal outcomes associated with obstructive sleep apnea in obese pregnant women. Obstet Gynecol. 2012;120(5):1085–92. [PubMed: 23090526]

26. Pien GW, Pack AI, Jackson N, Maislin G, Macones GA, Schwab RJ. Risk factors for sleep-disordered breathing in pregnancy. Thorax. 2014;69(4):371–7. [PubMed: 24262432]

27. Ge X, Tao F, Huang K, Mao L, Huang S, Niu Y, Hao J, Sun Y, Rutayisire E. Maternal Snoring May Predict Adverse Pregnancy Outcomes: A Cohort Study in China. PLoS One. 2016;11(2):e0148732. [PubMed: 26871434]

28. Bin YS, Cistulli PA, Ford JB. Population-Based Study of Sleep Apnea in Pregnancy and Maternal and Infant Outcomes. J Clin Sleep Med. 2016;12(6):871–7. [PubMed: 27070246]

29. Telerant A, Dunietz GL, Many A, Tauman R. Mild Maternal Obstructive Sleep Apnea in Non-obese Pregnant Women and Accelerated Fetal Growth. Sci Rep. 2018;8(1):10768. [PubMed: 30018451]

30. Pamidi S, Marc I, Simoneau G, Lavigne L, Olha A, Benedetti A, Series F, Fraser W, Audibert F, Bujold E, Gagnon R, Schwartzman K, Kimoff RJ. Maternal sleep-disordered breathing and the risk of delivering small for gestational age infants: a prospective cohort study. Thorax. 2016;71(8):719–25. [PubMed: 27084956]

31. Chen YH, Kang JH, Lin CC, Wang IT, Keller JJ, Lin HC. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. Am J Obstet Gynecol. 2012;206(2):136 e1–5. [PubMed: 22000892]

32. O'Brien LM, Bullough AS, Owusu JT, Tremblay KA, Brincat CA, Chames MC, Kalbfleisch JD, Chervin RD. Snoring during pregnancy and delivery outcomes: a cohort study. Sleep. 2013;36(11):1625–32. [PubMed: 24179294]

33. Wilson DL, Howard ME, Fung AM, O'Donoghue FJ, Barnes M, Lappas M, Walker SP. The presence of coexisting sleep-disordered breathing among women with hypertensive disorders of pregnancy does not worsen perinatal outcome. PLoS One. 2020;15(2):e0229568. [PubMed: 32101584]

34. Kidron D, Bar-Lev Y, Tsarfaty I, Many A, Tauman R. The effect of maternal obstructive sleep apnea on the placenta. Sleep. 2019;42(6).

Highlights:

- SDB, defined as an AHI ≥ 5, in pregnancy was not associated with SGA

- Early pregnancy SDB was associated with a twofold increased unadjusted risk in LGA

- BMI attenuated the associations of early pregnancy SDB and LGA

- Mid-pregnancy SDB was not associated with LGA

- Some over overnight hypoxemia measures were associated with an increase in LGA risk
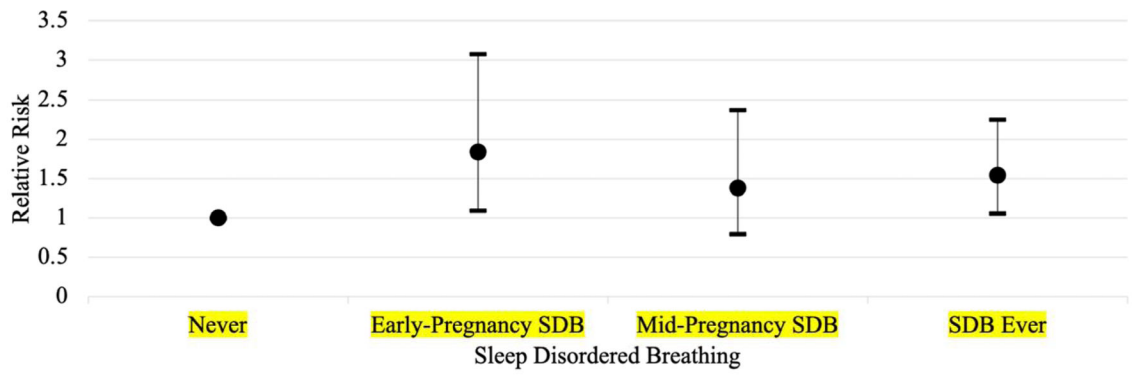
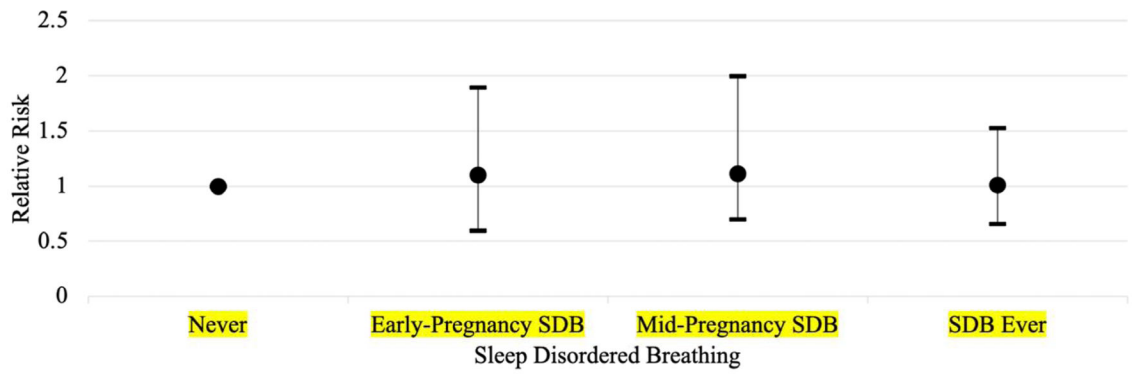|	RR	95% CI	
Never	1.0	Referent	
Early-Pregnancy SDB	1.8	1.1	3.1
Mid-Pregnancy SDB	1.4	0.8	2.4
SDB Ever	1.5	1.1	2.2

Figure 1a -

Model 1 Relative Risk of LGA by SDB status

Model 1: age, pre-gestational diabetes, chronic hypertension

	RR	95% CI	
Never	1.0	Referent	
Early-Pregnancy SDB	1.1	0.6	1.9
Mid-Pregnancy SDB	1.1	0.7	2.0
SDB Ever	1.0	0.7	1.5

Figure 1b -
Model 2 Relative Risk of LGA by SDB status
Model 2: Model 1 and BMI

Table 1

Descriptive characteristics[a] of the sample population by sleep-disordered breathing phenotype

	Sleep-Disordered Breathing			
	Never[b] (n=2079)	Early-Pregnancy SDB (n=114)	Mid-Pregnancy SDB (n=132)	p-value
Age (years)	26.71 ± 5.32	29.61 ± 5.89	29.78 ± 5.14	<0.001
BMI (kg/m2)	25.75 ± 5.78	36.67 ± 8.35	31.15 ± 6.18	<0.001
BMI (categories)				
- Underweight/Normal Weight, %(n)	57 (1167)	7 (8)	18 (24)	<0.001
- Overweight, %(n)	24 (500)	11 (12)	27 (35)	
- Obese, %(n)	19 (387)	82 (92)	55 (72)	
Race/ethnicity				
- non-Hispanic White, %(n)	63 (1320)	58 (66)	63 (83)	0.04
- non-Hispanic Black, %(n)	10 (218)	19 (22)	13 (17)	
- Hispanic, %(n)	18 (369)	12 (14)	13 (17)	
- Asian, %(n)	3 (72)	5 (6)	7 (9)	
- Other, %(n)	5 (100)	5 (6)	5 (6)	
Male Infant, %(n)	51 (1055)	60 (68)	38 (50)	0.002
Gravidity (categories)				
- 1, %(n)	76 (1581)	74 (84)	70 (92)	0.43
- 2, %(n)	17 (360)	20 (23)	23 (31)	
- 3+, %(n)	7 (138)	6 (7)	7 (9)	
Education Status				
- <High School, %(n)	6 (123)	7 (8)	2 (3)	0.01
- High School Grad or GED, %(n)	11 (236)	16 (18)	6 (8)	
- Some College, %(n)	21 (438)	25 (28)	17 (23)	
- Associate Degree or Technical School, %(n)	11 (223)	16 (18)	18 (24)	
- Completed College, %(n)	30 (618)	21 (24)	34 (45)	
- Degree Work Beyond College, %(n)	21 (441)	16 (18)	22 (29)	
Poverty Status[c]				
- >200%, %(n)	68 (1154)	60 (57)	77 (87)	0.11
- 100 to 200%, %(n)	17 (285)	23 (22)	12 (13)	
- <100%, %(n)	15 (256)	17 (16)	12 (13)	
Pre-pregnancy Smoking Status[d], %(n)	15 (318)	26 (30)	21 (28)	0.002
Chronic Hypertension, %(n)	2 (34)	8 (9)	8 (11)	<0.001
Pre-Gestational Diabetes, %(n)	1 (28)	4 (4)	1 (1)	0.14

[a] Values are means ± SD or percentages. Values of polytomous variables may not sum to 100% due to rounding

[b] Never SDB only includes participants with AHI <5 at both assessments

[c] Poverty categories indicate participants household income relative to the 2013 federal poverty guidelines adjusting for household size

[d] Smoked tobacco in the 3 months before pregnancy

Table 2

The Unadjusted relative risk of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) by SDB status

	LGA				SGA			
	Cases	%	RR	95% CI	Cases	%	RR	95% CI
Never (n=2079)	134	6.45	1.00	Referent	250	12.03	1.00	Referent
Early-Pregnancy SDB (n=114)	16	14.04	2.18	1.34 to 3.53	11	9.65	0.80	0.45 to 1.42
Mid-Pregnancy SDB (n=132)	14	10.61	1.65	0.98 to 2.77	12	9.09	0.76	0.44 to 1.31
SDB Ever (n=246)	30	12.2	1.74	1.21 to 2.49	23	9.35	0.78	0.52 to 1.16

Table 3

The adjusted relative risk of a large-for-gestational-age (LGA) by standard deviation change in measures of SDB severity in early and mid-pregnancy

	Mean	SD	Model 1			Model 2		
			RR	95% CI		RR	95% CI	
Early Pregnancy								
AHI	0.95	2.20	1.11	1.04	1.18	0.98	0.88	1.10
ODI3	2.05	3.16	1.14	1.06	1.23	1.00	0.90	1.12
ST_{90}	0.02	0.30	1.07	1.04	1.10	1.03	0.98	1.09
Mid Pregnancy								
AHI	1.82	3.48	1.04	0.99	1.23	1.00	0.86	1.16
ODI3	3.65	4.86	1.16	1.05	1.29	1.05	0.91	1.21
ST_{90}	0.11	1.47	1.08	1.06	1.09	1.08	1.06	1.09

Model 1: Maternal age (continuous), Chronic Hypertension (% yes), Pre-Gestational Diabetes (%yes)

Model 2: Model 1 + BMI (continuous)

Table 4

The relative risk of a large-for-gestational-age (LGA) per standard deviation change in SDB severity from early to mid-pregnancy

	Mean	SD	Model 1			Model 2		
			RR	95% CI		RR	95% CI	
AHI	0.89	2.68	1.12	1.01	1.24	1.08	0.98	1.18
ODI3	1.60	3.84	1.17	1.06	1.28	1.13	1.04	1.23
ST_{90}	0.09	1.40	1.07	1.06	1.08	1.08	1.07	1.09

Model 1: Maternal age (continuous), Chronic Hypertension (% yes), Pre-Gestational Diabetes (%yes)

Model 2: Model 1 + BMI (continuous)