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ORIGINAL ARTICLE

Association between sleep disordered breathing in early pregnancy and glucose metabolism

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Abstract

Study Objectives: To examine the association between maternal sleep disordered breathing (SDB) and glucose metabolism in early gestation.

Methods: Women with body mass index (BMI) ≥27 kg/m^2 and singleton pregnancies underwent in-home sleep study (HSAT) and homeostatic model assessment (HOMA) in early pregnancy. Insulin resistance (HOMA-IR) and β-cell function (HOMA %B) were derived. Exclusion criteria included pregestational diabetes, use of continuous positive airway pressure and chronic steroid therapy. We performed linear regression analyses to evaluate the association between continuous measures of SDB (respiratory event index (REI), and oxygen desaturation index (ODI)) and glucose metabolism parameters (HOMA-IR and HOMA %B). Analyses were adjusted for a set of a priori selected variables which included gestational age, maternal age, BMI, ethnicity, race, and parity.

Results: One hundred and ninety-two pregnant women with median (interquartile range) BMI of 35.14 (8.30) kg/m^2 underwent HSAT and HOMA assessment at 11.14 (3) and 15.35 (4.14) gestational weeks, respectively. REI and ODI, as continuous values, were associated with HOMA-IR after adjusting for covariates. OSA (obstructive sleep apnea) diagnosis (REI > 5 events per hour) was not associated with HOMA-IR after adjusting for BMI ($p \geq 0.05$). None of the parameters were associated with HOMA %B ($p > 0.07$).

Conclusions: SDB and insulin resistance are associated in early pregnancy, with a dose response association between respiratory event index severity and insulin resistance. Further studies are needed to establish if pregnant women with overweight and obesity may benefit from early SDB screening to improve glucose metabolic outcome.

Clinical trials: NCT02412696, Positive Airway Pressure, Sleep Apnea, and the Placenta (PAP-SAP) https://clinicaltrials.gov/ct2/show/NCT02412696?term=Bourjeily&draw=2&rank=2 and NCT02917876, Predictors of De-novo Development of Obstructive Sleep Apnea in Pregnancy (Predictors) https://clinicaltrials.gov/ct2/show/NCT02917876?term=Bourjeily&draw=2&rank=1

Statement of Significance

Maternal sleep disordered breathing (SDB) is recognized as a risk factor for gestational diabetes in late gestation. However, the association with glucose metabolism in early pregnancy remains poorly understood, limiting potential interventions to improve pregnancy outcomes. This is the first study to our knowledge demonstrating a dose response association in early pregnancy between maternal sleep disordered severity and insulin resistance, a precursor for gestational diabetes. This association moves the field forward as it indicates that interventions aimed at the prevention of gestational diabetes in pregnancy may need to be initiated in early pregnancy, or possibly even prior to conception. Further studies are needed to establish if pregnant women may benefit from early SDB screening and interventions to improve glucose metabolic outcome.

Key words: maternal sleep disordered breathing; obstructive sleep apnea; pregnancy; maternal overweight; maternal obesity; insulin resistance; sleep study; gestational diabetes; glucose metabolism; β-cell function; HOMA

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Introduction

Sleep disordered breathing (SDB) is common in pregnancy and has been associated with abnormal glucose metabolism and gestational diabetes mellitus (GDM), which is defined as glucose intolerance diagnosed in pregnancy [1]. Gestational diabetes affects 7%–18% of pregnancies, and women with GDM have a sevenfold increased risk of developing type 2 diabetes later in life [2, 3]. In the general population, obstructive sleep apnea (OSA) is associated with type 2 diabetes and the relationship between the two disorders is thought to be bidirectional [4]. Evidence from animal and human studies supports that SDB is independently associated with insulin resistance and glucose intolerance, leading to onset of type 2 diabetes among nonpregnant patients [5, 6]. Although the exact underlying mechanisms are yet to be determined, it is thought that intermittent hypoxia, recurrent airflow limitations, and arousals, which characterize SDB, trigger a cascade of events, such as increased sympathetic and hypothalamic-pituitary-adrenal activation, oxidative stress, and inflammation, which ultimately negatively affect glucose metabolism [4]. In addition, there is evidence in the general population that type 2 diabetes exacerbates the onset of SDB or can contribute to the worsening of SDB symptoms [4]. Underlying mechanisms have been investigated and animal models suggest that insulin resistance is associated with a decrease in ventilatory response, which improves with insulin therapy [7].

Data from our laboratory and other groups have shown that both snoring [8] and OSA in pregnancy [9–11] are associated with an increased risk for GDM after adjusting for potential confounders such as maternal age and body mass index (BMI). Moreover, SDB is common in pregnant women with GDM and impacts 17%–72% of women with the diagnosis [1, 12]. Biological plausibility favors SDB leading to GDM, rather than the reverse, given that the short duration of exposure to GDM would be unlikely to predispose to SDB. However, it is also possible that GDM and SDB coexist and share similar risk factors. A temporal relationship was demonstrated between a diagnosis of SDB at 12 weeks' gestation and a diagnosis of GDM in later pregnancy. [9] However, it remains unclear whether women with SDB in early pregnancy start the pregnancy at a higher risk for GDM or whether they develop the risk after the exposure in pregnancy. A better understanding of the timing of this relationship is key to furthering our understanding of timing -in relation to pregnancy- of interventions aimed at improving outcomes of GDM in women with SDB.

Hence, the aim of the current study is to examine whether OSA diagnosis and severity of SDB in early pregnancy are associated with insulin resistance in early pregnancy. We hypothesize that objective measures of SDB, and SDB severity, in early pregnancy are associated with higher insulin resistance, after controlling for confounding factors.

Methods

This is a cross-sectional study based on baseline characteristics of participants enrolled in two prospective studies listed as clinical trials (PAP-SAP: NCT02412696 and Predictors: NCT02917876), and enriched for OSA positivity. Briefly, these two studies present similar inclusion and exclusion criteria and study methods at the first research visits, which included in-home sleep apnea testing (HSAT), followed by homeostatic model assessment (HOMA) (Figure 1). We recruited women with singleton pregnancies from community and hospital-based obstetric practices with risk factors for obstructive sleep apnea such as BMI equal or above 27 kg/m^2 and habitual snoring defined as self-reported snoring >3 days per week. Women were excluded from the presented analysis if they were on chronic steroid therapy, used of continuous positive airway pressure (CPAP) at enrollment, or had a history of pregestational diabetes (Figure 1). For PAP-SAP, participants who were diagnosed with OSA in early pregnancy were randomized to treatment and followed to delivery. For Predictors study, women were tested for OSA in early pregnancy. Those who met criteria for OSA only completed a baseline evaluation which included HOMA testing (see below) while women who were negative for OSA were followed until delivery and had repeat evaluations in late pregnancy. Demographics and medical history were collected at enrollment. For the study presented here, we included only baseline data collected in early pregnancy, given that, following the first research visits, some participants started OSA treatment which may impact glucose metabolism [13]. The study was approved by the Institutional Review Board, and all participants signed an informed consent prior to participating.

In-home sleep apnea monitoring

Testing for SDB was performed using an in-home level III recording device, Nox T3 (Carefusion, San Diego, CA, USA). This device utilizes built-in sensors including a pressure transducer allowing the recording of nasal pressure, a microphone for true audio-recording capabilities, and a three-dimensional acceleration sensor for measuring body position and activity. The external sensor options used included electrocardiography and dual abdominal/ thoracic respiratory inductance plethysmography belts. The Nox-T3 device also supports wireless Bluetooth connectivity allowing for Bluetooth pulse oximeter recording capabilities. Nox T3 auto-score has been validated against in-laboratory polysomnography and has shown high specificity and sensitivity in the identification of SDB [14], however studies were scored by an experienced polysomnography technician and supervised by the investigative team. Diagnosis of OSA was defined as REI >5 events/hour using the ASSM's recommended hypopnea scoring (3% desaturation) rule [15].

Homeostatic model assessment

Homeostatic model assessment is used to yield an estimate of insulin resistance, sensitivity and β-cell function [16]. HOMA is a structural model of steady state insulin and glucose domains, constructed from physiological dose responses of glucose uptake and insulin production. Among the nonpregnant population, the relationship between glucose and insulin reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback mechanism between the liver and β cells. Insulin resistance and pancreatic beta-cell dysfunction, identified as fundamental measures to the pathogenesis of diabetes mellitus, are assessed by the HOMA model in the HOMA-IR (homeostatic model assessment-insulin resistance) and the HOMA-B% (homeostatic model assessment-insulin resistance β-cell function) measures, respectively. The HOMA model can utilize either insulin or C-peptide. Compared to other measures

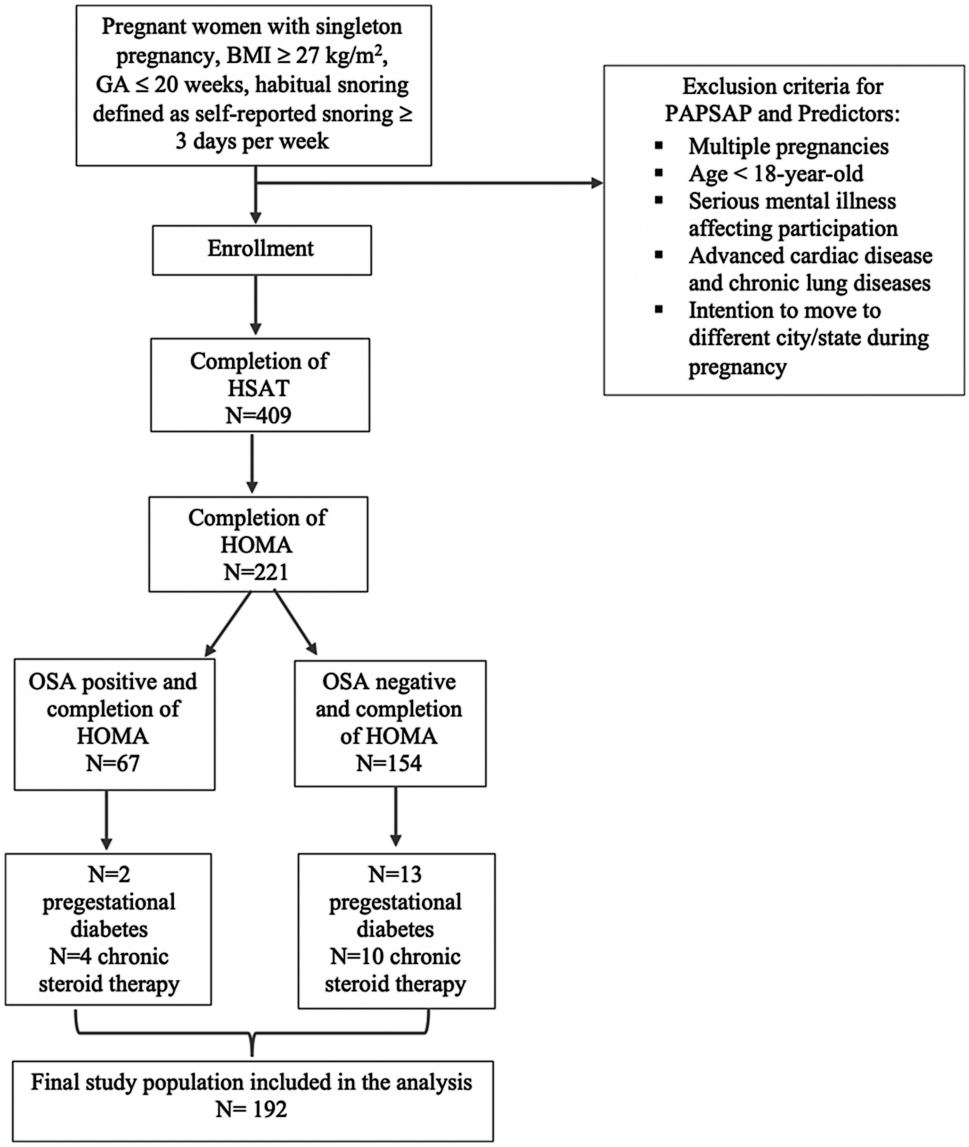

Figure 1. Study population selection. Note. BMI, body mass index; GA, gestational age; HOMA, homeostatic model assessment; HSAT, home sleep apnea testing.

of insulin sensitivity, HOMA has the advantage of requiring a single, fasting plasma sample assayed for insulin or C-peptide, and glucose. C-peptide is a measure of insulin secretion and, unlike insulin, is not significantly cleared by the liver, therefore it is thought that C-peptide is a more accurate marker of pancreatic insulin secretion than peripheral insulin. [17, 18] Insulin sensitivity measured by the HOMA model using C-peptide and glucose correlated strongly with insulin sensitivity measured via the oral glucose tolerance test in pregnant women in the HAPO study, $r = 0.676$, $p < 0.001$ [19]. Similarly, this model has also been validated during pregnancy to calculate beta-cell function [20] and insulin resistance [13, 21, 22].

For this study, we measured fasting glucose and C-peptide, and used the HOMA2 software (HOMA2 calculator v2.2.3) provided by the Diabetes Trials Unit (DTU) (https://www.dtu.ox.ac.uk/homacalculator/) [23]. The HOMA2 calculator is a mathematical model based on nonlinear equations simulating the physiological processes that influence circulating glucose and insulin or C-peptide levels, to estimate beta-cell function and insulin sensitivity or insulin resistance, the latter being the reciprocal measure of insulin sensitivity [18, 23].

Morning blood was obtained via venipuncture, following an 8-h fast, and tested for glucose and C-peptide [24]. Glucose testing consisted of blood collection in a heparinized tube via venipuncture following an 8-h fast. The sample was spun for 10 min at 3,500 rpm and separated from cells. Glucose concentrations below 45 mg/dL were excluded as they did not represent a steady state [18]. The specimen was checked for acceptability and loaded onto the 5800 analyzer (Beckman Coulter, Inc., Brea, CA, USA). Serum was also collected for C-peptide measurements, transported at room temperature for testing and processed via immunoassay.

Statistical analysis

To test our hypothesis, we performed linear regression analyses to evaluate the associations among continuous measures of SDB (respiratory event index (REI) and oxygen desaturation

index (ODI)) and glucose metabolism parameters (HOMA-IR and HOMA-%B); we used univariate analysis of variance to examine if glucose metabolism parameters differed according to diagnosis of OSA, defined as REI values ≥5 events/h.

Prior to analyses, both respiratory parameters during sleep and insulin resistance indicators were log transformed due to significant skewness (>2). Continuous variables were reported as median and interquartile range (IQR) and categorical variables were reported as frequency and percentage value. Demographic characteristics of the study population were compared by Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. All models adjusted for gestational age at HOMA testing, maternal age, body mass index, parity, ethnicity, and race. Covariates were selected a priori; in both low-risk pregnancies and pregnancies complicated by maternal diabetes, there is a decrease in insulin sensitivity with advancing gestational age [25] and the amount of decrease is greater in pregnancies complicated by maternal obesity [26]. In addition, the incidence of gestational diabetes and type 2 diabetes varies among women from different racial, ethnic backgrounds and parity. [27, 28]

Data were analyzed by using IBM SPSS Statistic 25 and *p*-values <0.05 were considered statistically significant.

Results

Study population

We enrolled 409 women with singleton pregnancies who underwent in-home sleep apnea testing in early pregnancy from June 2015 to March 2020 (Figure 1). Among those, 221 also completed HOMA assessment at a median of 15 weeks of gestation and had fasting glucose values above 45 mg/dL. Twenty-nine subjects were excluded due to chronic therapy with steroids or history of pregestational diabetes, and 192 participants were eligible for analysis. Of note, none of the subjects who completed HSAT and HOMA were on CPAP at enrollment or had fasting glucose levels <45 mg/dL. Among the final study population, 61 (32%) participants were diagnosed with OSA based on REI values ≥5 events/h. Demographic characteristics are presented in Table 1. Participants diagnosed with OSA were older, had a higher BMI and were more likely to be multipara, compared to those without a diagnosis of OSA. Sleep respiratory parameters are presented in Table 2. Virtually all respiratory events were obstructive, and the sleep hypoxemia was minimal in both groups. Median respiratory event index was in the mild category for OSA (below 15 events/h) and 10 women had REI values above 15 events/h (Table 2). Glucose parameters are presented in Table 3. Women with a diagnosis of OSA exhibited higher glucose and C-peptide values and a higher degree of insulin resistance compared to women without OSA.

Association between SDB and glucose metabolism

Respiratory events index and oxygen desaturation index were associated with HOMA-IR and this remained statistically significant after adjusting for a priori determined covariates ($B = 0.17$, $p = 0.051$, and $B = 0.31$, $p = 0.001$, respectively) (Table 4). A representation of the relationship between REI and HOMA-IR parameters, expressed as log values, is shown in Figure 2. Figure 3 illustrates the trend in HOMA-IR by REI category (REI < 1, ≥1 REI < 5, ≥5 REI < 15 and REI ≥ 15) to represent the dose response association between respiratory event index severity and insulin resistance. HOMA-IR differed by OSA diagnosis ($F = 11.14$, $p = 0.001$), however the difference was attenuated after adjusting for covariates ($F = 3.47$, $p = 0.064$).

When examining the magnitude of change described, we found that for each 10 unit increase in REI there was a 0.3 unit increase in HOMA-IR and a 4 unit increase in fasting glucose levels.

When examining the association between measures of SDB with insulin secretion, there did not appear to be any significant associations between REI and HOMA %B ($p > 0.34$) or between ODI and HOMA %B ($p = 0.073$).

A total of 42 women had fasting glucose levels ≥95 mg/dL. Elevated glucose levels were found in 20/61 (32.8%) in the OSA group and in 22/131 (16.8%) in the non-OSA group. Both REI and ODI were associated with fasting glucose levels after adjusting for the same covariates, $B = 0.22$, $p = 0.012$ and $B = 0.27$, $p = 0.003$, respectively.

Table 1. Demographic characteristics of the study population

Variable	OSA positiveREI ≥5(n = 61)	OSA negativeREI <5(n = 131)	P-value
Maternal age (years)	34 (6)	30 (8)	<0.001
BMI at enrollment (kg/m^2)	39.72 (10.83)	33.91 (6.44)	<0.001
Gestational age at HSAT (weeks)	11 (2.43)	11.14 (3.43)	0.589
Gestational age at HOMA (weeks)	14.14 (3.29)	15.57 (3.93)	0.027
Ethnicity			
Hispanic or Latina	11 (18%)	42 (32%)	0.056
Unknown	4 (7%)	4 (3%)	
Race			
White	36 (59%)	68 (52%)	0.437*
Black	10 (16.4%)	20 (15%)	
Asian, American Indian, or Alaska Native	3 (5%)	5 (4%)	
More than one race	8 (13%)	15 (11%)	
Unknown/not reported	4 (6.6%)	23 (18%)	
Nulliparous	8 (13%)	37 (28%)	0.027

Continuous variables are reported as median (interquartile range). Categorical variables are reported as frequency (percentage). *p*-value derived with Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. BMI, body mass index; HOMA, homeostatic model assessment; HSAT, home sleep apnea testing; OSA, obstructive sleep apnea, defined as respiratory event index ≥5 events/h; REI, respiratory event index.
*White and nonwhite categories were compared.

Table 2. Sleep respiratory parameters of the study population

Variable	OSA positiveREI ≥5(n = 61)	OSA negativeREI <5(n = 131)
REI (events/h)	7.7 (6.8)	0.8 (1.55)
Number (%) of participants per REI category*		
<1	NA	72 (37.5%)
≥1–<5	NA	59 (30.7%)
≥5–<15	51 (26.6%)	NA
≥15	10 (5.2%)	NA
Hypopnea index (events/h)	6.6 (6)	0.8 (1.5)
Apnea index (events/h)	0.6 (2.2)	0 (0.1)
Apnea total (number of events)	4 (11)	0 (1)
Apnea obstructive	4 (10)	0 (0)
Apnea mixed	0 (0)	0 (0)
Apnea central	0 (1)	0 (0)
ODI	16 (12)	4.36 (4.39)
Time spent <SpO_2 90%	0.3 (1)	0 (0)

Continuous variables are reported as median (interquartile range). Categorical variables are reported as frequency (percentage). NA, not applicable; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; REI, respiratory event index.
* Percentage values of number of participants per each REI category are calculated among the final study population of 192 participants.

Table 3. Glucose metabolism parameters of the study population

Variable	OSA positiveREI ≥5(n = 61)	OSA negativeREI <5(n = 131)	P-value
Glucose(mg/dL)	91 (12)	86 (10)	<0.001
C-peptide	2.01 (0.88)	1.56 (0.835)	<0.001
HOMA %B	118.6 (43.9)	112.6 (37.85)	0.3843
HOMA-IR	1.45 (0.73)	1.11 (0.645)	<0.001

Continuous variables are reported as median (interquartile range) and p-value was derived with Mann–Whitney U-test. HOMA %B, β-cell function; HOMA-IR, insulin resistance; OSA, obstructive sleep apnea; REI, respiratory event index.

Table 4. Linear regression models of respiratory events index and oxygen desaturation index predicting insulin resistance

Model	Covariates	β	SE	R^2	P-value
REI and HOMA-IR					
1	Unadjusted	0.27	0.021	0.075	<0.001
2	Adjusted by age, race, ethnicity, parity, GA at HOMA	0.25	0.025	0.075	0.003
3	Model 2 + BMI	0.17	0.026	0.11	0.051
ODI and HOMA-IR					
1	Unadjusted	0.32	0.02	0.10	<0.001
2	Adjusted by age, race, ethnicity, parity, GA at HOMA	0.36	0.023	0.13	<0.001
3	Model 2 + BMI	0.31	0.024	0.15	0.001

REI, ODI, and HOMA-IR values were significantly skewed, therefore log transformed values were included in analyses. BMI, body mass index; GA, gestational age; HOMA-IR, homeostatic model assessment-insulin resistance; REI, respiratory event index; ODI, oxygen desaturation index.

Discussion

Main findings

We investigated the association between SDB and glucose metabolism in early pregnancy in a large cohort of women with singleton pregnancies who were overweight or obese, without a history of pregestational diabetes. Our results demonstrate that objective measures of SDB are associated with an increase in insulin resistance in early pregnancy, after controlling for factors affecting glucose metabolism, such as maternal BMI, age, race, ethnicity, parity, and gestational age at insulin resistance assessment. Further, there was also a significant association between objective measures of SDB and fasting blood glucose levels. While the association between SDB and glucose metabolism in the late second and third trimester of pregnancy has been already described [8, 9, 21, 29], to our knowledge, this is the first study investigating a possible association in early pregnancy with insulin resistance, a precursor for gestational diabetes.

Our results are consistent with a previous study by Farabi et al. [21] that reported a positive correlation between number of apneas and hypopneas per hour of sleep and hepatic insulin resistance in late pregnancy, among 18 women with singleton pregnancy and obesity without pregestational or gestational diabetes. However, while all participants in that study were on a fixed eucaloric diet before data collection, their results did not adjust for maternal BMI. In this study, the association between OSA diagnosis [15] and insulin resistance was attenuated after adjusting for maternal BMI, while continuous values of respiratory event index were not affected by covariates. These findings may be related to the limitations of the REI cutoff extrapolated from the general population for a diagnosis of OSA in pregnancy. [30, 31] Indeed, the REI is a less than ideal measure of SDB, especially in the pregnant population, as the prevalence of subtle airflow limitation and events of sympathetic activation are quite common [30, 31]. Similar associations were demonstrated between ODI and insulin resistance. In addition, we demonstrated that SDB measures were associated with glucose levels after adjusting for covariates. These findings are consistent with previous studies which investigated this association in pregnant women with and without gestational diabetes [21, 29].

The change demonstrated in insulin resistance measures is clinically significant. HOMA-IR values in the adult population are affected by age, sex, ethnicity, BMI, and underlying morbidities [32]. Hence, several threshold values, with varying sensitivity, have been proposed to define the risk for developing diabetes [32], with a narrow range of normal. A recent, large prospective cohort study among women with normal glucose tolerance in early pregnancy defined the normal range of HOMA-IR

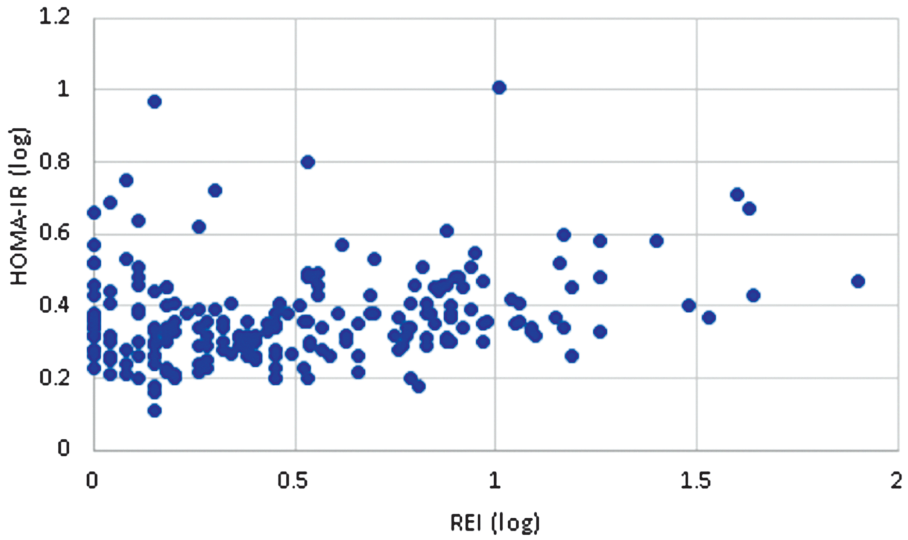

Figure 2. Association between respiratory event index (REI) and insulin resistance (HOMA-IR). Note. All values presented in this figure were log transformed due to significant skewness. HOMA, homeostatic model assessment; HOMA-IR, insulin resistance; REI, respiratory event index.

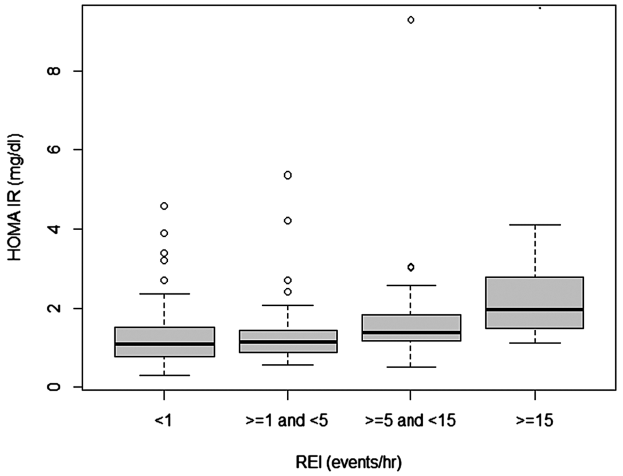

Figure 3. Respiratory event index (REI) categories and insulin resistance (HOMA-IR). Note. REI and HOMA-IR data were log transformed for analyses due to significant skewness; however raw values are shown in the figure for clinical context. HOMA-IR, homeostatic model assessment for insulin resistance; REI, respiratory event index.

between 0.48 and 1.76, and demonstrated a significant increase in the risk for gestational diabetes at values above the 75th centile cutoff of 1.76, after adjusting for maternal age and BMI [33]. Therefore, a 0.3 increase in HOMA-IR, related to maternal SBD in early pregnancy, may significantly affect glucose metabolism, given the narrow normal reference range of HOMA-IR values.

In our study, neither REI nor ODI showed a significant association with HOMA %B, which is a parameter of pancreatic β-cell function and therefore, insulin secretion. This result is consistent with findings from previous studies among nonpregnant healthy adults reporting that the initial effects of intermittent hypoxia and sleep fragmentation on glucose metabolism are a decrease in insulin sensitivity rather than β-cell function impairment, even in healthy volunteers without obesity [6, 34]. However, while there is evidence from the nonpregnant population that exposure to SDB leads to abnormal pancreatic β-cell function and onset of type 2 diabetes [35], it is unclear whether the duration of the exposure to SDB in these young women plays a role in the impact on pancreatic function.

Our data provide insight into the relationship of breathing parameters during sleep and insulin resistance using HOMA-IR, a measure that has been linked to the development of gestational diabetes and the risk of hypertensive disorders of pregnancy [36, 37]. HOMA has been validated against the hyperinsulinemic-euglycemic clamp, the gold standard measure of insulin resistance in early and late pregnancy [16], and was found to correlate with glucose disposal rate in nondiabetic populations [38, 39]. However, though HOMA is a rapid and simple measure of insulin resistance and sensitivity that only involves a fasting blood test, insulin resistance and sensitivity measured by HOMA correlates less well with the hyperinsulinemic-euglycemic clamp than an oral glucose tolerance test [40]. The underlying reason is that HOMA, compared to the other methods, mainly detects changes in hepatic insulin sensitivity, while it is less accurate in estimating peripheral insulin sensitivity and therefore may underestimate total body insulin sensitivity [40]. Therefore future studies in pregnancy complicated by SDB may consider the oral glucose tolerance test to derive insulin resistance. On the other hand, some physiological changes occurring in early pregnancy, at 12–14 weeks of gestation, compared to the period before conception, include an increase in both insulin sensitivity and insulin secretory response, suggesting that early pregnancy may have an independent effect on insulin resistance [41]. However, these changes were taken into account in the inclusion of gestational age in the list of covariates. Despite these physiological changes, our study did demonstrate an association, in early pregnancy, between SDB and lower levels of insulin sensitivity, and this association persisted after adjusting for covariates including gestational age. Therefore, our results support that maternal sleep disordered breathing is associated with an increase in insulin resistance in early gestation, despite the physiological changes of early pregnancy leading to an increase in insulin sensitivity. Early pregnancy insulin resistance has been associated with the development of gestational diabetes in later pregnancy [42]. Further, the trajectory of insulin

sensitivity and Beta-cell function during pregnancy has been linked to various trajectories of metabolic risk in the postpartum period [43]. Given the associations demonstrated here, the contribution of SDB, a potentially modifiable risk factor, to the long-term risk, needs to further elucidated.

Clinical and research implications

Our results bring multiple clinical and research implications. This study extends our understanding of the association of SDB and GDM to indicate that SDB is associated with a precursor of GDM, about 10 weeks before screening for GDM typically occurs in the general pregnant population. This finding argues that SDB and the risk for GDM coexist, or that the risk for the development of GDM in women with SDB actually starts prior to pregnancy. Hence, any trials aiming at examining the effect of treatment of SDB on the prevention of GDM in pregnancy should target women very early in pregnancy or even prior to conception. Although our results build evidence to screen for SDB in pregnancy, further studies would need to establish which pregnant women (universal screening in pregnancy versus screening of specific high-risk pregnancy categories) would most benefit from screening strategies, and what methodology and diagnostic criteria should be employed [44]. Furthermore, different phenotypes have been suggested in gestational diabetes. While some pregnant women may have the diagnosis mainly on the basis of defects in insulin sensitivity, others may have it because of defects in insulin secretion, and a third group may have both [45]. Our study suggests that SDB may fit within the phenotype that exhibits defects in insulin sensitivity rather than insulin secretion. This observation is supported by the fact that the decreased insulin sensitivity phenotype of GDM, and SDB, have both been associated with similar sets of adverse outcomes [8, 46–48]. Hence, future studies need to focus on better phenotyping and endotyping of these disorders to further understand this relationship, and examine whether abnormalities in glucose metabolism are mediators of some of the adverse perinatal outcomes associated with SDB.

Strengths and limitations

Our study has several strengths, including a relatively large sample size of women with overweight and obesity, objective assessment of SDB in early pregnancy, comprehensive measures of glucose metabolism and the exclusion of glucose values that suggested a nonsteady state, and statistical adjustment for multiple confounding factors. Ethnic and racial diversity of our sample supports generalizability of our findings.

There are also limitations that should be considered in the interpretation of our results. Our data did not include weight gain from time of pregnancy, as prepregnancy weight is subject to recall bias and we did not have reliable access to prepregnancy weight. Instead, our models adjusted for maternal obesity by using maternal BMI. Though this parameter can be less accurate in estimating obesity in pregnancy compared to nonpregnant populations [49], it performs better in early pregnancy. Our hypothesis was not tested in pregnant women with a normal or low BMI. Although we excluded women with a history of pregestational diabetes based on both medical record review and patient history, our participants did not undergo systematic early pregnancy diabetes screening by laboratory methods [50]. In addition, REI distribution in our sample precluded our ability to establish an REI threshold that would be associated with a significant rise in insulin resistance. In order to test whether the difference in timing of home sleep testing and HOMA testing could have influenced our findings, we compared HOMA-IR measured at 11 versus 15 weeks in both groups and found no significant differences (results not shown).

This study did not examine outcomes of developing gestational diabetes in the index pregnancy as some of the participants started CPAP therapy after completion of early pregnancy data presented here. Since the use of CPAP may affect glucose metabolism [13], we decided to not investigate. Our results support that a 10 unit increase in REI is associated with a 0.3 unit increase in HOMA-IR, suggesting a dysregulation in glucose metabolism. However, longitudinal studies linking the type and degree of metabolic dysregulation among women with sleep disordered breathing to short term gestational diabetes development in late pregnancy and longer term outcomes (type II diabetes and cardiovascular disease) are needed.

Conclusion

Our results demonstrate that, among pregnant women with overweight and obesity, objectively determined SDB is associated with an increase in insulin resistance, but not insulin secretion, in early pregnancy, after controlling for multiple factors. Further studies are needed to further investigate the association and its impact on the development of gestational diabetes, and to establish whether early-gestation or pregestational treatment of SDB would improve glucose metabolic outcomes in pregnancy.

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