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Sleep Disordered Breathing in Pregnancy and Post-Delivery: Associations with Cardiometabolic Health

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TITLE: Sleep Disordered Breathing in Pregnancy and Post-Delivery: Associations with Cardiometabolic Health

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ABSTRACT

Rationale: Knowledge gaps exist regarding health implications of sleep disordered breathing (SDB) identified in pregnancy and/or post-delivery.

Objective: To determine whether SDB in pregnancy and/or post-delivery is associated with hypertension (HTN) and metabolic syndrome (MS).

Methods: The nuMoM2b Heart Health Study (n=4,508) followed participants initially recruited during their first pregnancy. Participants returned for a visit 2-7 years after pregnancy. This study examined a subgroup who underwent SDB assessments during their first pregnancy (n=1,964) and a repeat SDB assessment post-delivery (n=1,222). Two SDB definitions were considered: apnea-hypopnea index (AHI) ≥5; oxygen desaturation index (ODI) ≥5. Associations between SDB and incident HTN and MS were evaluated with adjusted risk ratios (aRR).

Results: The aRR for MS given an AHI ≥5 during pregnancy was 1.44 (95% CI 1.08, 1.93), but no association with HTN was found. ODI ≥5 in pregnancy was associated with both an increased risk for HTN (aRR 2.02, 95% CI 1.30, 3.14) and MS (aRR 1.53, 95% CI 1.19, 1.97). Participants with an AHI ≥5 in pregnancy that persisted post-delivery were at higher risk for both HTN (aRR 3.77, 95% CI 1.84, 7.73) and MS (aRR 2.46, 95% 1.59, 3.76). Similar associations were observed for persistent post-delivery ODI ≥5.

Conclusions: An AHI ≥5 in pregnancy was associated with an increased risk of MS. An ODI ≥5 in pregnancy was significantly associated with both HTN and MS. Participants with persistent elevations in AHI and ODI both during pregnancy and at 2-7 post-delivery were at the highest risk for HTN and MS.

Introduction

Sleep disordered breathing (SDB) characterized by recurrent apneas and hypopneas, intermittent hypoxemia, and sleep disruption, is increasingly recognized in pregnancy. Pregnant individuals are at increased risk for SDB, predominantly obstructive sleep apnea (OSA), compared to their non-pregnant counter-parts, due to physical and hormonal changes that occur during pregnancy.(1, 2) A meta-analysis of 33 studies found that the pooled overall prevalence of SDB during pregnancy was 15% (95% CI 12–18%).(3)

While epidemiologic data from cohorts of middle-aged and older adults indicate that SDB is associated with adverse cardiometabolic outcomes,(4-6) less is known about how SDB in pregnancy and in the post-delivery period impacts maternal health. In pregnancy, increases in inflammation, oxidative stress, and sympathetic nervous system activity, all of which can be exacerbated by SDB, can lead to adverse maternal health events.(2, 7) Indeed, SDB in pregnancy has been associated with a 2-3-fold increased risk for preeclampsia and gestational diabetes mellitus (GDM).(3, 8) These and other adverse pregnancy outcomes (APOs) are risk factors for later development of hypertension (HTN) and metabolic disease.(9-12) The post-partum period is also of unique relevance regarding SDB epidemiology given the likely impact of post-partum weight retention on SDB risk.(13-15) Thus, there is a critical need to elucidate whether SDB identified in pregnancy and/or in the post-delivery period is associated with cardiovascular and metabolic health in young adults.

The Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be Heart Health Study (nuMoM2b-HHS) was a post-delivery follow-up study of participants initially recruited during their first pregnancy to the parent nuMoM2b study. A subset of women in the parent study underwent evaluation for SDB during their first pregnancy (“nuMoM2b SDB Substudy”), and were offered a repeat assessment post-delivery.(16-18) We utilized the nuMoM2b data to address the knowledge gap that exists regarding health implications of SDB identified in

pregnancy and/or post-delivery. Specifically, our objective was to determine whether SDB in pregnancy and/or post-delivery is associated with hypertension (HTN) and metabolic syndrome.

Methods

Details of the nuMoM2b study, and the nuMoM2b-SDB Substudy have been previously published.(18) (16) Inclusion criteria for the nuMoM2b study were nulliparity (no prior delivery ≥20 weeks' gestation) and a viable singleton pregnancy at screening (6^0–13^6 weeks' gestation). Participants were excluded from the nuMoM2b-SDB Substudy if they were currently using continuous positive airway pressure (CPAP) treatment for SDB, had severe asthma, or required oxygen supplementation.

nuMoM2b-HHS Methods

The complete methods of the follow-up nuMoM2b-HHS are described elsewhere.(17) Briefly, contacts/interviews began at least 6 months after delivery. An in-person nuMoM2b-HHS visit was conducted 2 to 7 years after the index pregnancy ended. Participants were asked to fast for 8 hours before the visit. Blood pressure (BP), anthropometric measurements, and biological specimens were collected using standardized protocols. Participants in the nuMoM2b-HHS were eligible to participate in a follow-up assessment of SDB if they had participated in the nuMoM2b-SDB Substudy while pregnant.

nuMoM2b-HHS Outcomes (see online supplement for additional details)

Incident HTN was defined as HTN that developed after the index pregnancy, as determined by BP measurement (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) or use of an antihypertensive medication for BP control at the 2- to 7-year post-delivery visit.

Metabolic syndrome (MS) was defined as the presence of 3 of the following 5 criteria: elevated waist circumference (≥88 cm (non-Asian) or ≥80 cm (Asian)); elevated triglycerides (≥150 mg/dL) or use of a triglyceride-lowering medication; elevated fasting glucose (≥100 md/dL) or use of a glucose-lowering medication; elevated BP (systolic BP ≥130 mm Hg or a diastolic BP ≥85 mm Hg) or use of an antihypertensive medication; and reduced high-density lipoprotein levels (<50 mg/dL) or use of medications known to increase HDL.(19)

SDB Assessments (see online supplement for additional details)

SDB was assessed at all exams using the same model (Embletta-Gold device Embla, Broomfield, CO) Level 3 home sleep apnea test (HSAT).(18) Studies were conducted twice during pregnancy, first between 6^0-15^0 weeks of pregnancy and then again between 22^0-31^0 weeks, and then at the 2-7 year follow-up visit. Sleep studies were scored by a central reading center by trained polysomnologists blinded to all other data. Event definitions, scoring reliability and the quality control protocol were previously published.(18) Two SDB definitions were considered: (1) Apnea Hypopnea Index (AHI): the number of apneas and hypopneas per hour of estimated sleep, inclusive of all apneas plus hypopneas accompanied by ≥3% oxygen desaturation; and (2) Oxygen-Desaturation Index (ODI): the number of oxygen desaturations ≥3% from the pre-event baseline per hour of estimated sleep.

Statistical Analyses (see online supplement for additional details)

For our primary analyses we defined SDB using dichotomous AHI and ODI metrics: SDB by AHI (SDB-AHI) was defined as an AHI≥5, SDB by ODI (SDB-ODI) was defined as an ODI≥5. Among participants with valid early and mid-pregnancy sleep study data, SDB in pregnancy was defined as an AHI≥5 in either early or mid-pregnancy (versus AHI<5 in both early and mid-pregnancy). A similar categorization was used to define SDB during pregnancy by ODI. In secondary analyses, we separately considered SDB that was present in early pregnancy or mid-pregnancy. To examine exposure-response relationships we also grouped participants at early and mid-pregnancy into four categories based on their AHI or ODI values: =0, 0-4.9, 5-14.9 and

≥15 events per hour.(20) Post hoc tests using orthogonal contrasts were used to assess the exposure-response relationships for linear and quadratic trends in risk on the log scale across the SDB categories.

In a similar fashion, a secondary analysis was performed using the AHI and ODI data obtained at the 2-7 year follow-up visit. We also examined the trajectory of SDB (by both definitions) in pregnancy and at the follow-up visit by defining 4 groups: those with no SDB at either time point, those with SDB in pregnancy that persisted at the 2-7 year follow-up, those with SDB in pregnancy that resolved at follow-up, and those with new onset SDB at the 2-7 year follow-up visit.

Baseline characteristics of the index pregnancy and cardiovascular characteristics at the 2-7 year follow-up visit were summarized according to SDB status during pregnancy. Similarly, cardiovascular characteristics at the 2-7-year follow-up visit were also summarized by SDB status at follow-up.

Analyses during pregnancy were restricted to participants who had an early or mid-pregnancy sleep study with adequate data and attended the in-person nuMoM2b-HHS cardiovascular assessment. Participants with baseline chronic HTN in pregnancy were excluded from the HTN analyses; likewise, those with preexisting diabetes were excluded from the MS analyses.

Crude and adjusted risk ratios (RR) and 95% confidence intervals (CI) were estimated using Poisson regression with robust standard errors to relate SDB to incident HTN and MS.(21) P-values from likelihood ratio tests were reported. Adjustment covariates chosen *a priori* included: age and body mass index (BMI) in early pregnancy, self-identified race, and years from delivery of the index pregnancy to the HHS follow-up visit. Similar methods were used for the cross-sectional analyses of SDB in the post-delivery period, with age and BMI at the time of the HHS follow up visit and race used as adjustment covariates. In all our adjusted analyses BMI was included as a linear and a quadratic term.

We also considered having a hypertensive disorder of pregnancy (HDP, i.e., gestational hypertension and preeclampsia) during the index pregnancy as a mediator in the associations of SDB during pregnancy with HTN post-delivery and HDP or GDM during pregnancy as a mediator in the associations of SDB during pregnancy with MS post-delivery.

All tests were performed at a nominal significance level of α=05. All single degree-of-freedom tests were two-sided. No correction was made for multiple comparisons. Analyses were performed using SAS 9.4 (Cary, NC). Some of the results of these studies have been previously reported in the form of an abstract.(22)

Results

A total of 4,508 participants attended a nuMoM2b-HHS in-person visit between February 4, 2014 and October 9, 2017. Among these 1,964 had a HSAT from the index pregnancy with 1,863 having adequate sleep study data available (406 with early pregnancy data only; 92 with mid-pregnancy data only; 1,365 with both early and mid-pregnancy data, Figure 1). Median (interquartile range) time between delivery of the index pregnancy and the HHS in-person visit was 36 (28-42) months.

Among nuMoM2b-HHS participants who had both early and mid-pregnancy sleep study data, 127 (9.3%) had an AHI≥5 at either the early or mid-pregnancy SDB assessment. Baseline characteristics according to AHI category during pregnancy for the nuMoM2b-HHS participants are presented in Table 1. Participants with an AHI≥5 in pregnancy were older, had higher BMIs in early pregnancy, and had a lower rate of weight gain in pregnancy.

A repeat sleep study at the 2-7 year follow-up visit was conducted on 1,222 of the 1,964 participants who completed a sleep study during pregnancy. The participants who did not complete the follow-up sleep assessment were less likely to be non-Hispanic White and had a longer latency from delivery to the HHS follow-up (see supplement Table S1). Adequate follow-up sleep study data were available on 1,069 participants (Figure 2). SDB defined as an AHI≥5 was found in 133 of the 1069 (12.4%) participants with follow-up sleep data when studied at a

median (interquartile range) of 32 (13) months post-delivery. Of the 844 participants with SDB data from all timepoints (i.e., at both the early and mid-pregnancy visits, and at the follow-up visit), 710 (84.1%) did not have SDB-AHI during pregnancy or at follow-up, 49 (5.8%) had SDB-AHI in pregnancy that persisted at follow-up, 22 (2.6%) had SDB-AHI in pregnancy that resolved at follow-up, and 63 (7.5%) had new-onset SDB-AHI detected at the 2-7 year follow-up visit.

Cardiovascular and metabolic characteristics and outcome rates at the 2-7 year follow-up visit based on AHI status in pregnancy are presented in Table 2. Participants with SDB-AHI in pregnancy had higher BMIs; larger waist circumference; higher systolic and diastolic BP, triglyceride levels and fasting blood glucose; and lower HDL-C levels at 2-7 years post-delivery. At follow-up, incident HTN was more common in participants with an SDB-AHI during pregnancy (15.7% vs. 6.2 %, p<0.0001), as was MS (40.2% vs. 14.2%, p<0.0001).

Table 3 provides crude and adjusted risks ratios (aRR) for incident HTN and MS, related to AHI in pregnancy. In adjusted analyses, SDB-AHI in pregnancy (early or mid) was not associated with the risk of incident HTN. Similarly, SDB-AHI in early pregnancy was not associated with a statistically significant increased HTN risk, although the mid-pregnancy SDB-AHI point estimate was of borderline significance (aRR 1.73, 95% CI 0.99, 3.01, p=0.091). AHI grouping by AHI=0 (referent), 0<AHI<5, 5≤AHI<15 and AHI≥15 did not reveal a statistically significant linear or quadratic trend in incident HTN risk with increasing AHI in either early or mid-pregnancy.

The adjusted risk for MS given SDB-AHI in pregnancy was 1.44 (95% CI 1.08, 1.93). Separate analyses of AHI ≥5 in early-pregnancy or AHI ≥5 in mid-pregnancy with MS were not statistically significant. There was, however, a significant linear trend suggesting an exposure-response relationship between increasing AHI in mid-pregnancy and the risk of MS (p=0.043). Participants in the highest AHI group (≥15) had an aRR for MS of 2.32(95% CI 1.11, 4.86).

Tables 4 gives crude and adjusted risk ratios relating ODI in pregnancy to incident HTN and MS diagnosed at 2-7 year follow-up. In adjusted analyses, SDB-ODI in pregnancy (early or mid), was associated with an increased risk for incident HTN (aRR 2.02, 95% CI 1.30, 3.14). A

similar statistically significant risk was observed separately for ODI≥5 at mid-pregnancy but not early pregnancy.

In adjusted analyses, SDB-ODI in pregnancy was associated with an increased risk of MS (aRR 1.53, 95% CI 1.19, 1.97). This risk was also separately observed for both early and mid-pregnancy and the risk increased with increasing categories of ODI severity. Notably, participants with an ODI≥15 in mid-pregnancy had an aRR of 2.57(95% CI 0.82, 8.01) for MS (p=0.02 for linear trend).

To better understand the relationships between SDB in pregnancy and MS, we examined the individual components of MS in relation to the presence of SDB-AHI or SDB-ODI in pregnancy. In adjusted analyses, an SDB-AHI in pregnancy was associated with elevated triglycerides and reduced HDL. SDB-ODI in pregnancy was associated with elevated triglycerides and elevated BP (data shown in Tables S2 and S3 in the supplement).

Given the associations between AHI and ODI in pregnancy and hypertensive disorders of pregnancy and GDM, and the relationship between these pregnancy complications and later life cardiometabolic disease, we performed a mediation analysis aimed at assessing the controlled direct effect of SDB in pregnancy on HTN and MS at the 2-7 year follow-up. In these analyses we did not observe a statistically significant controlled direct effect (AHI only, without mediation or interaction) between SDB-AHI and the outcomes. Similarly, no direct effect was observed for SDB-ODI on HTN risk at 2-7 year follow-up. However, the controlled direct effect of SDB-ODI in pregnancy on MS was statistically significant. A total excess aRR of 0.60 (95% CI: 0.10, 1.09) was observed with SDB-ODI in pregnancy and the proportion explained by mediation and/or interaction was estimated at ≤11% with 95% confidence (data in Supplement Tables S4 and S5).

Cardiovascular and metabolic characteristics and outcome rates at 2-7 year follow-up by current SDB status by AHI are detailed in the supplement (Table S6). In summary, participants with an SDB-AHI at the 2-7 year follow-up had higher BMIs; larger waist circumferences; higher systolic and diastolic BP, triglyceride levels, and fasting blood glucose levels; and lower HDL-C

levels. Incident HTN was more common in participants with a post-delivery SDB-AHI (19.5% vs. 5.3 %, p<0.0001), as was MS (44.4% vs 14.0%, p<0.0001).

Table 5 gives crude and adjusted risk ratios relating SDB by AHI and ODI status at the 2-7 year follow-up to incident HTN and MS. In adjusted analyses, an SDB-AHI post-delivery was associated with an increased likelihood of HTN (aRR 2.01, 95% CI 1.17, 3.46) and MS (aRR 1.51, 95% CI 1.14, 2.00). Similarly, SDB-ODI was associated with increased risks for incident HTN (aRR 1.75, 95% CI 1.05, 2.92) and MS (aRR 1.60, 95% CI 1.21, 2.12). There were statistically significant linear trends suggesting exposure-response relationships between increasing values of AHI and risk of incident HTN and MS, and between increasing values of ODI and risk of incident HTN.

Among participants with data across all time points (826 participants), Table 6 examines the relationship between SDB trajectory by AHI and ODI criteria from pregnancy to the 2-7 year follow-up visit in relation to risk of incident HTN and MS. Rates of both outcomes differed by SDB trajectory. Participants with persistent SDB, defined using either the AHI or ODI, had the highest risk for incident HTN and MS (aRR's ranging from 2.3 to 3.8).

Given that the relationships between our outcomes were stronger for ODI in pregnancy compared to AHI, we sought to understand how AHI and ODI related to each other in the larger pregnancy dataset. As expected, AHI and ODI were strongly correlated (Spearman correlation coefficients at early and mid-pregnancy visits were 0.79 and 0.84, respectively). The median (interquartile range) for the difference (delta) between ODI and AHI in early and mid-pregnancy were 0.65 (1.47) and 1.16 (2.11), respectively. A larger ODI-AHI delta was seen with higher BMI in pregnancy (additional data on ODI-AHI delta can be found in the online supplement).

Discussion

In this analysis of objectively-assessed SDB in pregnancy and at a 2-7 year follow-up visit in a large U.S. cohort, we found that SDB measured during pregnancy and in the 2 to 7 year post-delivery period was associated with HTN and MS. Associations of SDB in pregnancy

were generally stronger when SDB was defined using the ODI, which quantified the frequency of drops in oxygen saturation of at least 3%, than the AHI, which was defined by a combination of changes in airflow and oxygen saturation. Participants with persistent elevations in AHI or ODI during pregnancy and 2-7 year follow-up visits were at more than 3-fold increased risk for incident HTN and more than a 2-fold increased risk for MS. Our data suggest that the simpler measure of ODI can identify those at increased risk just as well, if not better, than AHI.

In non-pregnant populations that have been followed after a SDB diagnosis, such as the Wisconsin Sleep Cohort, increasing AHI has been linked to higher rates of incident HTN.(23) In our prospective analysis of SDB in pregnancy, we did not find an association between AHI in pregnancy and incident HTN. However, there was an association between the ODI in pregnancy and incident HTN. AHI and ODI are very tightly correlated, but we found that the ODI tended to be slightly higher than AHI, meaning that there were oxygen desaturation events that were not associated with clearly evident respiratory events (apneas and hypopneas). In our analysis, the difference between ODI and AHI during pregnancy could not be explained by an asthma diagnosis or restless legs syndrome symptoms (see supplement). However, it was correlated with BMI, as was AHI. It may be that there were subtle respiratory flow events that did not reach the amplitude criteria for hypopnea but impaired ventilation, leading to oxygen desaturations. Other researchers found that the difference between AHI and ODI increases progressively with obesity level and similarly postulated that higher BMI may result in desaturation events even in the absence of notable changes in breathing amplitude as measured during routine sleep studies.(24)

Our data demonstrated a relationship between pregnancy ODI and MS, and a weaker association (demonstrated only in analysis of AHI in early or mid-pregnancy) between pregnancy AHI and MS. This association has been reported in prior cohorts, but this is the first large prospective study in young women to confirm this association.(25) It is important to note that unlike the HTN analyses, we cannot assert that the MS was incident in the follow-up period as we do not have assessments of fasting blood glucose and lipids pre-pregnancy for

comparison. Furthermore, how best to interpret this relationship between SDB and MS is complicated by the very tight relationship of both SDB and MS with BMI. Yet, even after adjustment for BMI (linear and quadratic), the associations between SDB measures and MS remained statistically significant. Also, notably, in our mediation analysis we considered pregnancy complications and found that ODI ≥5 in pregnancy had a significant controlled direct effect on MS risk unrelated to the impact of HDP and GDM.

In our cross-sectional analyses of AHI and ODI at the 2-7 year follow-up period, we demonstrated strong associations between AHI and ODI with both HTN and MS. We found significant exposure-response relationships between increasing AHI values and higher rates of both outcomes, and a significant exposure-response relationship between increasing ODI and incident HTN. When we examined these associations in relation to prior sleep data from pregnancy, we found that participants who had persistent SDB (defined either by AHI or ODI) were at the highest risk.

A major strength of this study is the combined prospective and cross-sectional design from pregnancy through 2-7 years of follow-up in which the pregnancy AHI and ODI results were blinded to the care providers, investigators, and participants (unless an urgent alert was identified-see online supplement for details). This limited the possibility of ascertainment bias. Our SDB ascertainment was optimized using an independent and blinded central reading center. We were able to control for important confounding factors including BMI (BMI in early pregnancy for prospective analysis, BMI at HHS visit for cross sectional analysis) and we had objective assessments of cardiovascular and metabolic outcomes at the 2-7 year follow-up visit. However, given the observational and voluntary nature of the study and moderate adjusted risk ratios, the possibility of residual confounding due to selection bias and unmeasured confounders cannot be definitively excluded. Additionally, given sample size limitations, we were unable to perform a meaningful analysis considering the impact of intercurrent pregnancies on the HTN and MS risk. Also, we do not have objective SDB data from all of our participants at the 2-7 year follow-up. While it was offered to most nuMoM2b-SDB Substudy

participants, only 62.2% repeated sleep testing at the 2-7 year follow-up assessment. We also recognize the limitations of utilizing a Level 3 HSAT for measuring AHI. Unattended home sleep apnea testing may modestly under-estimate the AHI/ODI values due to over-estimation of sleep time, leading to some degree of misclassification bias.(26) Unlike full PSG, our home sleep testing procedures did not employ electroencephalogram (EEG) so that events associated with arousals (without desaturations) were not ascertained. Finally, because many analyses were done and adjustment for multiple statistical testing was not performed, chance alone might be responsible for some statistically significant results.

Although we found associations with AHI, ODI and incident HTN and MS, we cannot conclude that universal screening for and treatment of SDB in pregnancy and/or in the post-delivery period would reduce the risks of these adverse outcomes. The most widely prescribed treatment for SDB is continuous positive air pressure (CPAP). The benefit of treatment with CPAP has been reliably demonstrated when excessive daytime sleepiness and sleep quality are used as endpoints.(27, 28) CPAP has also been demonstrated in randomized, controlled trials to reduce blood pressure.(29, 30) However, data conflict regarding whether treatment of SDB can reduce the risk of developing HTN, other cardiovascular disease, or diabetes.(31-34) This is especially true for milder forms of SDB (AHI<30), which our study confirms represent the vast majority of SDB cases in young pregnant persons.

In summary, in this prospective analysis of objectively assessed SDB in pregnancy, ODI but not AHI ≥5 in pregnancy was associated with incident HTN 2-7 years after the index pregnancy. Both AHI and ODI were associated with MS, though associations were stronger for ODI in pregnancy. AHI and ODI ≥5 at 2-7 years post-delivery were both strongly associated with both incident HTN and MS, and participants who had persistent AHI and ODI elevations (present at pregnancy and post-delivery visit) were at the highest risk for these adverse outcomes. Further longitudinal studies are needed to examine the temporal or causal relationships between SDB and cardiometabolic risk, to determine if simple oximetry monitoring

396 can reliably be used to identify individuals at risk, and to study if treatment with CPAP during or
397 after pregnancy can modify these risks.

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TITLE: Sleep Disordered Breathing in Pregnancy and Post-Delivery: Associations with Cardiometabolic Health

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ABSTRACT

Rationale: Knowledge gaps exist regarding health implications of sleep disordered breathing (SDB) identified in pregnancy and/or post-delivery.

Objective: To determine whether SDB in pregnancy and/or post-delivery is associated with hypertension (HTN) and metabolic syndrome (MS).

Methods: The nuMoM2b Heart Health Study (n=4,508) followed participants initially recruited during their first pregnancy. Participants returned for a visit 2-7 years after pregnancy. This study examined a subgroup who underwent SDB assessments during their first pregnancy (n=1,964) and a repeat SDB assessment post-delivery (n=1,222). Two SDB definitions were considered: apnea-hypopnea index (AHI) ≥5; oxygen desaturation index (ODI) ≥5. Associations between SDB and incident HTN and MS were evaluated with adjusted risk ratios (aRR).

Results: The aRR for MS given an AHI ≥5 during pregnancy was 1.44 (95% CI 1.08, 1.93), but no association with HTN was found. ODI ≥5 in pregnancy was associated with both an increased risk for HTN (aRR 2.02, 95% CI 1.30, 3.14) and MS (aRR 1.53, 95% CI 1.19, 1.97). Participants with an AHI ≥5 in pregnancy that persisted post-delivery were at higher risk for both HTN (aRR 3.77, 95% CI 1.84, 7.73) and MS (aRR 2.46, 95% 1.59, 3.76). Similar associations were observed for persistent post-delivery ODI ≥5.

Conclusions: An AHI ≥5 in pregnancy was associated with an increased risk of MS. An ODI ≥5 in pregnancy was significantly associated with both HTN and MS. Participants with persistent elevations in AHI and ODI both during pregnancy and at 2-7 post-delivery were at the highest risk for HTN and MS.

Introduction

Sleep disordered breathing (SDB) characterized by recurrent apneas and hypopneas, intermittent hypoxemia, and sleep disruption, is increasingly recognized in pregnancy. Pregnant individuals are at increased risk for SDB, predominantly obstructive sleep apnea (OSA), compared to their non-pregnant counter-parts, due to physical and hormonal changes that occur during pregnancy.(1, 2) A meta-analysis of 33 studies found that the pooled overall prevalence of SDB during pregnancy was 15% (95% CI 12–18%).(3)

While epidemiologic data from cohorts of middle-aged and older adults indicate that SDB is associated with adverse cardiometabolic outcomes,(4-6) less is known about how SDB in pregnancy and in the post-delivery period impacts maternal health. In pregnancy, increases in inflammation, oxidative stress, and sympathetic nervous system activity, all of which can be exacerbated by SDB, can lead to adverse maternal health events.(2, 7) Indeed, SDB in pregnancy has been associated with a 2-3-fold increased risk for preeclampsia and gestational diabetes mellitus (GDM).(3, 8) These and other adverse pregnancy outcomes (APOs) are risk factors for later development of hypertension (HTN) and metabolic disease.(9-12) The post-partum period is also of unique relevance regarding SDB epidemiology given the likely impact of post-partum weight retention on SDB risk.(13-15) Thus, there is a critical need to elucidate whether SDB identified in pregnancy and/or in the post-delivery period is associated with cardiovascular and metabolic health in young adults.

The Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be Heart Health Study (nuMoM2b-HHS) was a post-delivery follow-up study of participants initially recruited during their first pregnancy to the parent nuMoM2b study. A subset of women in the parent study underwent evaluation for SDB during their first pregnancy ("nuMoM2b SDB Substudy"), and were offered a repeat assessment post-delivery.(16-18) We utilized the nuMoM2b data to address the knowledge gap that exists regarding health implications of SDB identified in

pregnancy and/or post-delivery. Specifically, our objective was to determine whether SDB in pregnancy and/or post-delivery is associated with hypertension (HTN) and metabolic syndrome.

Methods

Details of the nuMoM2b study, and the nuMoM2b-SDB Substudy have been previously published.(18) (16) Inclusion criteria for the nuMoM2b study were nulliparity (no prior delivery ≥20 weeks' gestation) and a viable singleton pregnancy at screening (6^0–13^6 weeks' gestation). Participants were excluded from the nuMoM2b-SDB Substudy if they were currently using continuous positive airway pressure (CPAP) treatment for SDB, had severe asthma, or required oxygen supplementation.

nuMoM2b-HHS Methods

The complete methods of the follow-up nuMoM2b-HHS are described elsewhere.(17) Briefly, contacts/interviews began at least 6 months after delivery. An in-person nuMoM2b-HHS visit was conducted 2 to 7 years after the index pregnancy ended. Participants were asked to fast for 8 hours before the visit. Blood pressure (BP), anthropometric measurements, and biological specimens were collected using standardized protocols. Participants in the nuMoM2b-HHS were eligible to participate in a follow-up assessment of SDB if they had participated in the nuMoM2b-SDB Substudy while pregnant.

nuMoM2b-HHS Outcomes (see online supplement for additional details)

Incident HTN was defined as HTN that developed after the index pregnancy, as determined by BP measurement (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) or use of an antihypertensive medication for BP control at the 2- to 7-year post-delivery visit.

Metabolic syndrome (MS) was defined as the presence of 3 of the following 5 criteria: elevated waist circumference (≥88 cm (non-Asian) or ≥80 cm (Asian)); elevated triglycerides (≥150 mg/dL) or use of a triglyceride-lowering medication; elevated fasting glucose (≥100 md/dL) or use of a glucose-lowering medication; elevated BP (systolic BP ≥130 mm Hg or a diastolic BP ≥85 mm Hg) or use of an antihypertensive medication; and reduced high-density lipoprotein levels (<50 mg/dL) or use of medications known to increase HDL.(19)

SDB Assessments (see online supplement for additional details)

SDB was assessed at all exams using the same model (Embletta-Gold device Embla, Broomfield, CO) Level 3 home sleep apnea test (HSAT).(18) Studies were conducted twice during pregnancy, first between 6^0-15^0 weeks of pregnancy and then again between 22^0-31^0 weeks, and then at the 2-7 year follow-up visit. Sleep studies were scored by a central reading center by trained polysomnologists blinded to all other data. Event definitions, scoring reliability and the quality control protocol were previously published.(18) Two SDB definitions were considered: (1) Apnea Hypopnea Index (AHI): the number of apneas and hypopneas per hour of estimated sleep, inclusive of all apneas plus hypopneas accompanied by ≥3% oxygen desaturation; and (2) Oxygen-Desaturation Index (ODI): the number of oxygen desaturations ≥3% from the pre-event baseline per hour of estimated sleep.

Statistical Analyses (see online supplement for additional details)

For our primary analyses we defined SDB using dichotomous AHI and ODI metrics: SDB by AHI (SDB-AHI) was defined as an AHI≥5, SDB by ODI (SDB-ODI) was defined as an ODI≥5. Among participants with valid early and mid-pregnancy sleep study data, SDB in pregnancy was defined as an AHI≥5 in either early or mid-pregnancy (versus AHI<5 in both early and mid-pregnancy). A similar categorization was used to define SDB during pregnancy by ODI. In secondary analyses, we separately considered SDB that was present in early pregnancy or mid-pregnancy. To examine exposure-response relationships we also grouped participants at early and mid-pregnancy into four categories based on their AHI or ODI values: =0, 0-4.9, 5-14.9 and

≥15 events per hour.(20) Post hoc tests using orthogonal contrasts were used to assess the exposure-response relationships for linear and quadratic trends in risk on the log scale across the SDB categories.

In a similar fashion, a secondary analysis was performed using the AHI and ODI data obtained at the 2-7 year follow-up visit. We also examined the trajectory of SDB (by both definitions) in pregnancy and at the follow-up visit by defining 4 groups: those with no SDB at either time point, those with SDB in pregnancy that persisted at the 2-7 year follow-up, those with SDB in pregnancy that resolved at follow-up, and those with new onset SDB at the 2-7 year follow-up visit.

Baseline characteristics of the index pregnancy and cardiovascular characteristics at the 2-7 year follow-up visit were summarized according to SDB status during pregnancy. Similarly, cardiovascular characteristics at the 2-7-year follow-up visit were also summarized by SDB status at follow-up.

Analyses during pregnancy were restricted to participants who had an early or mid-pregnancy sleep study with adequate data and attended the in-person nuMoM2b-HHS cardiovascular assessment. Participants with baseline chronic HTN in pregnancy were excluded from the HTN analyses; likewise, those with preexisting diabetes were excluded from the MS analyses.

Crude and adjusted risk ratios (RR) and 95% confidence intervals (CI) were estimated using Poisson regression with robust standard errors to relate SDB to incident HTN and MS.(21) P-values from likelihood ratio tests were reported. Adjustment covariates chosen *a priori* included: age and body mass index (BMI) in early pregnancy, self-identified race, and years from delivery of the index pregnancy to the HHS follow-up visit. Similar methods were used for the cross-sectional analyses of SDB in the post-delivery period, with age and BMI at the time of the HHS follow up visit and race used as adjustment covariates. In all our adjusted analyses BMI was included as a linear and a quadratic term.

We also considered having a hypertensive disorder of pregnancy (HDP, i.e., gestational hypertension and preeclampsia) during the index pregnancy as a mediator in the associations of SDB during pregnancy with HTN post-delivery and HDP or GDM during pregnancy as a mediator in the associations of SDB during pregnancy with MS post-delivery.

All tests were performed at a nominal significance level of α=05. All single degree-of-freedom tests were two-sided. No correction was made for multiple comparisons. Analyses were performed using SAS 9.4 (Cary, NC). Some of the results of these studies have been previously reported in the form of an abstract.(22)

Results

A total of 4,508 participants attended a nuMoM2b-HHS in-person visit between February 4, 2014 and October 9, 2017. Among these 1,964 had a HSAT from the index pregnancy with 1,863 having adequate sleep study data available (406 with early pregnancy data only; 92 with mid-pregnancy data only; 1,365 with both early and mid-pregnancy data, Figure 1). Median (interquartile range) time between delivery of the index pregnancy and the HHS in-person visit was 36 (28-42) months.

Among nuMoM2b-HHS participants who had both early and mid-pregnancy sleep study data, 127 (9.3%) had an AHI≥5 at either the early or mid-pregnancy SDB assessment. Baseline characteristics according to AHI category during pregnancy for the nuMoM2b-HHS participants are presented in Table 1. Participants with an AHI≥5 in pregnancy were older, had higher BMIs in early pregnancy, and had a lower rate of weight gain in pregnancy.

A repeat sleep study at the 2-7 year follow-up visit was conducted on 1,222 of the 1,964 participants who completed a sleep study during pregnancy. The participants who did not complete the follow-up sleep assessment were less likely to be non-Hispanic White and had a longer latency from delivery to the HHS follow-up (see supplement Table S1). Adequate follow-up sleep study data were available on 1,069 participants (Figure 2). SDB defined as an AHI≥5 was found in 133 of the 1069 (12.4%) participants with follow-up sleep data when studied at a

median (interquartile range) of 32 (13) months post-delivery. Of the 844 participants with SDB data from all timepoints (i.e., at both the early and mid-pregnancy visits, and at the follow-up visit), 710 (84.1%) did not have SDB-AHI during pregnancy or at follow-up, 49 (5.8%) had SDB-AHI in pregnancy that persisted at follow-up, 22 (2.6%) had SDB-AHI in pregnancy that resolved at follow-up, and 63 (7.5%) had new-onset SDB-AHI detected at the 2-7 year follow-up visit.

Cardiovascular and metabolic characteristics and outcome rates at the 2-7 year follow-up visit based on AHI status in pregnancy are presented in Table 2. Participants with SDB-AHI in pregnancy had higher BMIs; larger waist circumference; higher systolic and diastolic BP, triglyceride levels and fasting blood glucose; and lower HDL-C levels at 2-7 years post-delivery. At follow-up, incident HTN was more common in participants with an SDB-AHI during pregnancy (15.7% vs. 6.2 %, $p<0.0001$), as was MS (40.2% vs. 14.2%, $p<0.0001$).

Table 3 provides crude and adjusted risks ratios (aRR) for incident HTN and MS, related to AHI in pregnancy. In adjusted analyses, SDB-AHI in pregnancy (early or mid) was not associated with the risk of incident HTN. Similarly, SDB-AHI in early pregnancy was not associated with a statistically significant increased HTN risk, although the mid-pregnancy SDB-AHI point estimate was of borderline significance (aRR 1.73, 95% CI 0.99, 3.01, $p=0.091$). AHI grouping by AHI=0 (referent), $0<AHI<5$, $5\leq AHI<15$ and $AHI\geq 15$ did not reveal a statistically significant linear or quadratic trend in incident HTN risk with increasing AHI in either early or mid-pregnancy.

The adjusted risk for MS given SDB-AHI in pregnancy was 1.44 (95% CI 1.08, 1.93). Separate analyses of AHI ≥5 in early-pregnancy or AHI ≥5 in mid-pregnancy with MS were not statistically significant. There was, however, a significant linear trend suggesting an exposure-response relationship between increasing AHI in mid-pregnancy and the risk of MS ($p=0.043$). Participants in the highest AHI group (≥15) had an aRR for MS of 2.32(95% CI 1.11, 4.86).

Tables 4 gives crude and adjusted risk ratios relating ODI in pregnancy to incident HTN and MS diagnosed at 2-7 year follow-up. In adjusted analyses, SDB-ODI in pregnancy (early or mid), was associated with an increased risk for incident HTN (aRR 2.02, 95% CI 1.30, 3.14). A

similar statistically significant risk was observed separately for ODI≥5 at mid-pregnancy but not early pregnancy.

In adjusted analyses, SDB-ODI in pregnancy was associated with an increased risk of MS (aRR 1.53, 95% CI 1.19, 1.97). This risk was also separately observed for both early and mid-pregnancy and the risk increased with increasing categories of ODI severity. Notably, participants with an ODI≥15 in mid-pregnancy had an aRR of 2.57(95% CI 0.82, 8.01) for MS (p=0.02 for linear trend).

To better understand the relationships between SDB in pregnancy and MS, we examined the individual components of MS in relation to the presence of SDB-AHI or SDB-ODI in pregnancy. In adjusted analyses, an SDB-AHI in pregnancy was associated with elevated triglycerides and reduced HDL. SDB-ODI in pregnancy was associated with elevated triglycerides and elevated BP (data shown in Tables S2 and S3 in the supplement).

Given the associations between AHI and ODI in pregnancy and hypertensive disorders of pregnancy and GDM, and the relationship between these pregnancy complications and later life cardiometabolic disease, we performed a mediation analysis aimed at assessing the controlled direct effect of SDB in pregnancy on HTN and MS at the 2-7 year follow-up. In these analyses we did not observe a statistically significant controlled direct effect (AHI only, without mediation or interaction) between SDB-AHI and the outcomes. Similarly, no direct effect was observed for SDB-ODI on HTN risk at 2-7 year follow-up. However, the controlled direct effect of SDB-ODI in pregnancy on MS was statistically significant. A total excess aRR of 0.60 (95% CI: 0.10, 1.09) was observed with SDB-ODI in pregnancy and the proportion explained by mediation and/or interaction was estimated at ≤11% with 95% confidence (data in Supplement Tables S4 and S5).

Cardiovascular and metabolic characteristics and outcome rates at 2-7 year follow-up by current SDB status by AHI are detailed in the supplement (Table S6). In summary, participants with an SDB-AHI at the 2-7 year follow-up had higher BMIs; larger waist circumferences; higher systolic and diastolic BP, triglyceride levels, and fasting blood glucose levels; and lower HDL-C

levels. Incident HTN was more common in participants with a post-delivery SDB-AHI (19.5% vs. 5.3 %, p<0.0001), as was MS (44.4% vs 14.0%, p<0.0001).

Table 5 gives crude and adjusted risk ratios relating SDB by AHI and ODI status at the 2-7 year follow-up to incident HTN and MS. In adjusted analyses, an SDB-AHI post-delivery was associated with an increased likelihood of HTN (aRR 2.01, 95% CI 1.17, 3.46) and MS (aRR 1.51, 95% CI 1.14, 2.00). Similarly, SDB-ODI was associated with increased risks for incident HTN (aRR 1.75, 95% CI 1.05, 2.92) and MS (aRR 1.60, 95% CI 1.21, 2.12). There were statistically significant linear trends suggesting exposure-response relationships between increasing values of AHI and risk of incident HTN and MS, and between increasing values of ODI and risk of incident HTN.

Among participants with data across all time points (826 participants), Table 6 examines the relationship between SDB trajectory by AHI and ODI criteria from pregnancy to the 2-7 year follow-up visit in relation to risk of incident HTN and MS. Rates of both outcomes differed by SDB trajectory. Participants with persistent SDB, defined using either the AHI or ODI, had the highest risk for incident HTN and MS (aRR's ranging from 2.3 to 3.8).

Given that the relationships between our outcomes were stronger for ODI in pregnancy compared to AHI, we sought to understand how AHI and ODI related to each other in the larger pregnancy dataset. As expected, AHI and ODI were strongly correlated (Spearman correlation coefficients at early and mid-pregnancy visits were 0.79 and 0.84, respectively). The median (interquartile range) for the difference (delta) between ODI and AHI in early and mid-pregnancy were 0.65 (1.47) and 1.16 (2.11), respectively. A larger ODI-AHI delta was seen with higher BMI in pregnancy (additional data on ODI-AHI delta can be found in the online supplement).

Discussion

In this analysis of objectively-assessed SDB in pregnancy and at a 2-7 year follow-up visit in a large U.S. cohort, we found that SDB measured during pregnancy and in the 2 to 7 year post-delivery period was associated with HTN and MS. Associations of SDB in pregnancy

were generally stronger when SDB was defined using the ODI, which quantified the frequency of drops in oxygen saturation of at least 3%, than the AHI, which was defined by a combination of changes in airflow and oxygen saturation. Participants with persistent elevations in AHI or ODI during pregnancy and 2-7 year follow-up visits were at more than 3-fold increased risk for incident HTN and more than a 2-fold increased risk for MS. Our data suggest that the simpler measure of ODI can identify those at increased risk just as well, if not better, than AHI.

In non-pregnant populations that have been followed after a SDB diagnosis, such as the Wisconsin Sleep Cohort, increasing AHI has been linked to higher rates of incident HTN.(23) In our prospective analysis of SDB in pregnancy, we did not find an association between AHI in pregnancy and incident HTN. However, there was an association between the ODI in pregnancy and incident HTN. AHI and ODI are very tightly correlated, but we found that the ODI tended to be slightly higher than AHI, meaning that there were oxygen desaturation events that were not associated with clearly evident respiratory events (apneas and hypopneas). In our analysis, the difference between ODI and AHI during pregnancy could not be explained by an asthma diagnosis or restless legs syndrome symptoms (see supplement). However, it was correlated with BMI, as was AHI. It may be that there were subtle respiratory flow events that did not reach the amplitude criteria for hypopnea but impaired ventilation, leading to oxygen desaturations. Other researchers found that the difference between AHI and ODI increases progressively with obesity level and similarly postulated that higher BMI may result in desaturation events even in the absence of notable changes in breathing amplitude as measured during routine sleep studies.(24)

Our data demonstrated a relationship between pregnancy ODI and MS, and a weaker association (demonstrated only in analysis of AHI in early or mid-pregnancy) between pregnancy AHI and MS. This association has been reported in prior cohorts, but this is the first large prospective study in young women to confirm this association.(25) It is important to note that unlike the HTN analyses, we cannot assert that the MS was incident in the follow-up period as we do not have assessments of fasting blood glucose and lipids pre-pregnancy for

comparison. Furthermore, how best to interpret this relationship between SDB and MS is complicated by the very tight relationship of both SDB and MS with BMI. Yet, even after adjustment for BMI (linear and quadratic), the associations between SDB measures and MS remained statistically significant. Also, notably, in our mediation analysis we considered pregnancy complications and found that ODI ≥5 in pregnancy had a significant controlled direct effect on MS risk unrelated to the impact of HDP and GDM.

In our cross-sectional analyses of AHI and ODI at the 2-7 year follow-up period, we demonstrated strong associations between AHI and ODI with both HTN and MS. We found significant exposure-response relationships between increasing AHI values and higher rates of both outcomes, and a significant exposure-response relationship between increasing ODI and incident HTN. When we examined these associations in relation to prior sleep data from pregnancy, we found that participants who had persistent SDB (defined either by AHI or ODI) were at the highest risk.

A major strength of this study is the combined prospective and cross-sectional design from pregnancy through 2-7 years of follow-up in which the pregnancy AHI and ODI results were blinded to the care providers, investigators, and participants (unless an urgent alert was identified-see online supplement for details). This limited the possibility of ascertainment bias. Our SDB ascertainment was optimized using an independent and blinded central reading center. We were able to control for important confounding factors including BMI (BMI in early pregnancy for prospective analysis, BMI at HHS visit for cross sectional analysis) and we had objective assessments of cardiovascular and metabolic outcomes at the 2-7 year follow-up visit. However, given the observational and voluntary nature of the study and moderate adjusted risk ratios, the possibility of residual confounding due to selection bias and unmeasured confounders cannot be definitively excluded. Additionally, given sample size limitations, we were unable to perform a meaningful analysis considering the impact of intercurrent pregnancies on the HTN and MS risk. Also, we do not have objective SDB data from all of our participants at the 2-7 year follow-up. While it was offered to most nuMoM2b-SDB Substudy

participants, only 62.2% repeated sleep testing at the 2-7 year follow-up assessment. We also recognize the limitations of utilizing a Level 3 HSAT for measuring AHI. Unattended home sleep apnea testing may modestly under-estimate the AHI/ODI values due to over-estimation of sleep time, leading to some degree of misclassification bias.(26) Unlike full PSG, our home sleep testing procedures did not employ electroencephalogram (EEG) so that events associated with arousals (without desaturations) were not ascertained. Finally, because many analyses were done and adjustment for multiple statistical testing was not performed, chance alone might be responsible for some statistically significant results.

Although we found associations with AHI, ODI and incident HTN and MS, we cannot conclude that universal screening for and treatment of SDB in pregnancy and/or in the post-delivery period would reduce the risks of these adverse outcomes. The most widely prescribed treatment for SDB is continuous positive air pressure (CPAP). The benefit of treatment with CPAP has been reliably demonstrated when excessive daytime sleepiness and sleep quality are used as endpoints.(27, 28) CPAP has also been demonstrated in randomized, controlled trials to reduce blood pressure.(29, 30) However, data conflict regarding whether treatment of SDB can reduce the risk of developing HTN, other cardiovascular disease, or diabetes.(31-34) This is especially true for milder forms of SDB (AHI<30), which our study confirms represent the vast majority of SDB cases in young pregnant persons.

In summary, in this prospective analysis of objectively assessed SDB in pregnancy, ODI but not AHI ≥5 in pregnancy was associated with incident HTN 2-7 years after the index pregnancy. Both AHI and ODI were associated with MS, though associations were stronger for ODI in pregnancy. AHI and ODI ≥5 at 2-7 years post-delivery were both strongly associated with both incident HTN and MS, and participants who had persistent AHI and ODI elevations (present at pregnancy and post-delivery visit) were at the highest risk for these adverse outcomes. Further longitudinal studies are needed to examine the temporal or causal relationships between SDB and cardiometabolic risk, to determine if simple oximetry monitoring

396 can reliably be used to identify individuals at risk, and to study if treatment with CPAP during or
397 after pregnancy can modify these risks.

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Figure 1
Inclusion in Analysis of Sleep Study Results During Pregnancy in Association with Hypertension and Metabolic Syndrome 2-7 Years Post-Delivery

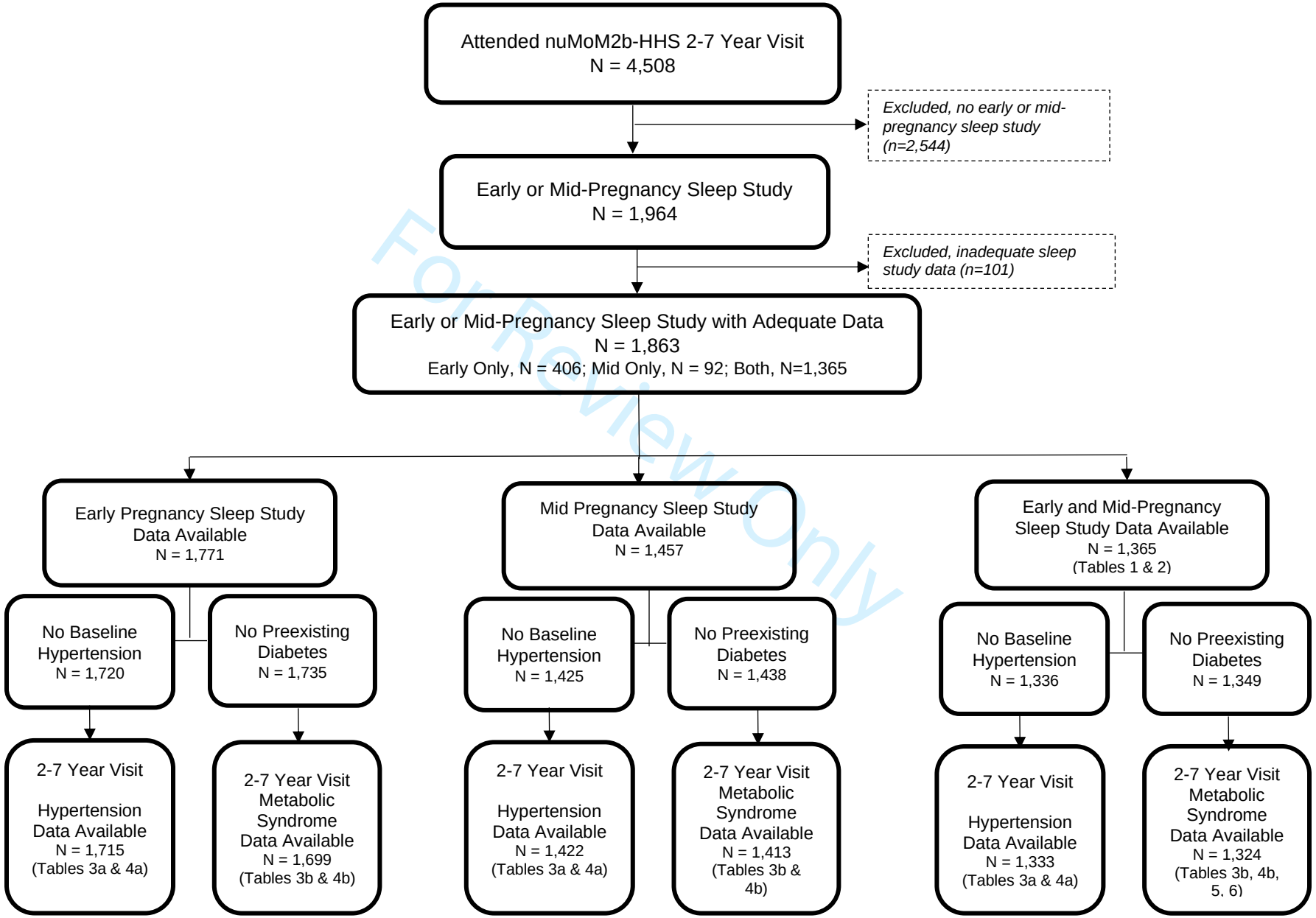
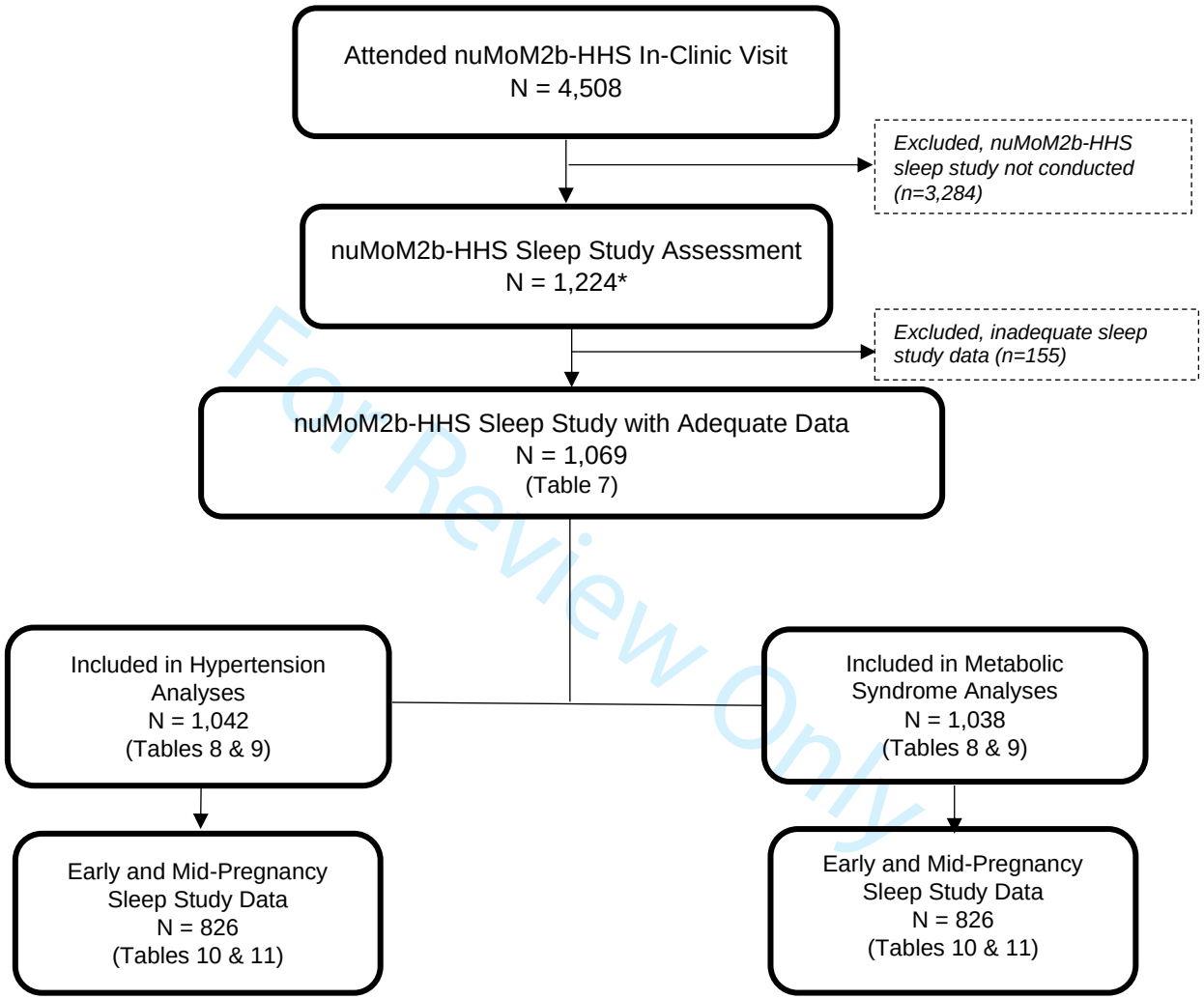


Figure 2. Enrollment and Inclusion in Analysis of nuMoM2b-HHS Sleep Study Data



*There were 2 participants who completed a nuMoM2b-HHS HSAT who did not have a HSAT during pregnancy

Table 1

Characteristics of nuMoM2b Participants with Mid or Early Pregnancy Sleep Study and Cardiovascular Assessment at 2-7 Year Follow-up according to Apnea-Hypopnea Index (AHI)[1/] Categories

Characteristics	AHI < 5 in Early and Mid-pregnancy (N = 1,238)	AHI ≥ 5 in Early or Mid-pregnancy (N = 127)	p-value[2/]
Maternal age in early pregnancy, in years			
Mean (standard deviation)	26.6 (5.2)	29.8 (5.8)	<.0001
Category: n (%)			<.0001
13-21	234 (18.9)	11 (8.7)	
22-35	939 (75.8)	93 (73.2)	
>35	65 (5.3)	23 (18.1)	
Maternal race: n (%)			0.5663
White Non-Hispanic	810 (65.4)	83 (65.4)	
Black Non-Hispanic	133 (10.7)	18 (14.2)	
Hispanic	199 (16.1)	16 (12.6)	
Asian	34 (2.7)	5 (3.9)	
Other	62 (5.0)	5 (3.9)	
BMI in early pregnancy, in kg/m^2			
Mean (standard deviation)	25.9 (5.9)	33.5 (8.2)	<.0001
Category: n (%)			<.0001
<25	680 (55.8)	18 (14.4)	
25 to <30	295 (24.2)	29 (23.2)	
≥30	244 (20.0)	78 (62.4)	
Smoked during pregnancy: n (%)	74 (6.0)	11 (8.7)	0.2332
Rate of weight gain from early to mid-pregnancy, in kg per week			
Mean (standard deviation)	0.49 (0.22)	0.42 (0.26)	0.0011

Abbreviations: AHI = Apnea-Hypopnea Index; BMI = body mass index.

[1/] Including all apneas and hypopneas w/ ≥3% oxygen desaturation / hour

[2/] p-values are shown for chi-square tests for AHI and the categorical baseline characteristics and from ANOVA F-tests for AHI and continuous baseline characteristics.

Table 2

Cardiovascular Characteristics at 2-7 Years After nuMoM2b Index Pregnancy, According to Apnea-Hypopnea Index (AHI)[1/] Categories

Cardiovascular Characteristic 2-7 Years After nuMoM2b Index Pregnancy	AHI < 5 in Early and Mid-pregnancy (N = 1,238)	AHI ≥ 5 in Early or Mid-pregnancy (N = 127)	p-value[2/]
BMI, in kg/m^2			
N	1,225	126	
Mean (SD)	27.0 (7.1)	35.2 (9.0)	<.0001
Category: n (%)			<.0001
<25	599 (48.9)	17 (13.5)	
25 to <30	314 (25.6)	19 (15.1)	
≥30	312 (25.5)	90 (71.4)	
Waist circumference over iliac crest, in cm			
N	1,230	127	
Mean (SD)	94.6 (15.1)	111.6 (19.3)	<.0001
≥88 cm (non-Asian) or ≥80 cm (Asian): n (%)	768 (62.4)	115 (90.6)	<.0001
Systolic blood pressure, in mmHg			
N	1,235	127	
Mean (SD)	110.8 (10.8)	116.1 (12.2)	<.0001
Diastolic blood pressure, in mmHg			
N	1,235	127	
Mean (SD)	71.7 (9.5)	77.4 (9.8)	<.0001
Hypertension: n (%)			
140≤SBP/90≤DBP, or antihypertensive medication	76 (6.2)	20 (15.7)	<.0001
Triglycerides, in mg/dL			
N	1,223	127	
Mean (SD)	93.0 (60.6)	134.5 (83.8)	<.0001
≥150 mg/dL or on lipid-lowering medication: n (%)	124 (10.1)	41 (32.3)	<.0001

Table 2 (continued)

Cardiovascular Characteristics 2-7 Years After nuMoM2b Index Pregnancy, According to Apnea-Hypopnea Index (AHI)[1/] Categories

Cardiovascular Characteristic 2-7 Years After nuMoM2b Index Pregnancy	AHI < 5 in Early and Mid-pregnancy (N = 1,238)	AHI ≥ 5 in Early or Mid-pregnancy (N = 127)	p-value[2/]
HDL-C, in mg/dL			
N	1,223	127	
Mean (SD)	55.6 (12.7)	49.6 (11.5)	<.0001
<50 mg/dL or on HDL-raising medication: n (%)	405 (33.1)	73 (57.5)	<.0001
Blood glucose (fasting), in mg/dL			
N	1,220	127	
Mean (SD)	89.9 (14.9)	96.4 (25.2)	<.0001
≥100 mg/dL or on glucose-lowering medication: n (%)	175 (14.3)	31 (24.4)	0.0027
Metabolic Syndrome[3/]: n (%)	172 (14.2)	51 (40.2)	<.0001
Time from delivery to HHS cardiovascular assessment, in years			
N	1,236	127	
Mean (SD)	3.0 (0.8)	2.9 (0.8)	0.1812

Abbreviations: AHI = Apnea-Hypopnea Index; BMI = body mass index; SD = standard deviation

[1/] Including all apneas and hypopneas w/ ≥3% oxygen desaturation / hour

[2/] p-values are shown for chi-square tests for AHI and the categorical baseline characteristics and from ANOVA F-tests for AHI and continuous baseline characteristics.

[3/] Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication.

Table 3
Crude and Adjusted Risk Ratios[1/] for Incident Hypertension and Metabolic Syndrome[2/] at 2-7 Year Follow-up According to Apnea-Hypopnea Index (AHI)[3/] in Early and Mid-Pregnancy

AHI Characteristic	n/N (%)	Crude Risk Ratios		Adjusted Risk Ratios	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Incident Hypertension					
Early or Mid-Pregnancy					
AHI<5 in both early and mid-pregnancy (referent)	67/1215 (5.5)	1.00	0.0402	1.00	0.3344
AHI≥5 in early or mid-pregnancy	14/118 (11.9)	2.15 (1.25, 3.71)		1.39 (0.75, 2.56)	
Early Pregnancy					
AHI<5 (referent)	96/1647 (5.8)	1.00	0.0463	1.00	0.6015
AHI≥5	10/68 (14.7)	2.52 (1.38, 4.62)		1.21 (0.61, 2.41)	
AHI=0 (referent)	18/391 (4.6)	1.00	0.1280	1.00	0.9606
0<AHI<5	78/1256 (6.2)	1.35 (0.82, 2.22)	*Trend tests:*	1.03 (0.63, 1.68)	*Trend tests:*
5≤AHI<15	9/63 (14.3)	3.10 (1.46, 6.60)	*0.3931 linear*	1.26 (0.55, 2.88)	*0.8631 linear*
AHI≥15	1/5 (20.0)	4.34 (0.71, 26.55)	*0.9702 quadratic*	1.11 (0.19, 6.61)	*0.8672 quadratic*
Mid-pregnancy					
AHI<5 (referent)	72/1308 (5.5)	1.00	0.0070	1.00	0.0908
AHI≥5	17/114 (14.9)	2.71 (1.66, 4.43)		1.73 (0.99, 3.01)	
AHI=0 (referent)	9/189 (4.8)	1.00	0.0547	1.00	0.3871
0<AHI<5	63/1119 (5.6)	1.18 (0.60, 2.34)	*Trend tests:*	0.86 (0.44, 1.69)	*Trend tests:*
5≤AHI<15	14/100 (14.0)	2.94 (1.32, 6.55)	*0.1325 linear*	1.43 (0.62, 3.30)	*0.3511 linear*
AHI≥15	3/14 (21.4)	4.50 (1.37, 14.77)	*0.7140 quadratic*	1.92 (0.49, 7.60)	*0.5638 quadratic*
Metabolic Syndrome					
Early or Mid-Pregnancy					
AHI<5 in both early and mid-pregnancy (referent)	165/1200 (13.8)	1.00	<.0001	1.00	0.0211
AHI≥5 in early or mid-pregnancy	48/124 (38.7)	2.82 (2.16, 3.66)		1.44 (1.08, 1.93)	

Early Pregnancy					
AHI<5 (referent)	260/1630 (16.0)	1.00	<.0001	1.00	0.1214
AHI≥5	32/69 (46.4)	2.91 (2.20, 3.84)		1.28 (0.95, 1.73)	
AHI=0 (referent)	43/383 (11.2)	1.00	<.0001	1.00	0.4454
0<AHI<5	217/1247 (17.4)	1.55 (1.14, 2.11)	*Trend tests:*	1.07 (0.80, 1.43)	*Trend tests:*
5≤AHI<15	29/63 (46.0)	4.10 (2.78, 6.05)	*0.1141 linear*	1.38 (0.92, 2.07)	*0.5643 linear*
AHI≥15	3/6 (50.0)	4.45 (1.91, 10.40)	*0.4084 quadratic*	1.25 (0.50, 3.13)	*0.7232 quadratic*
Mid-pregnancy					
AHI<5 (referent)	178/1292 (13.8)	1.00	<.0001	1.00	0.0754
AHI≥5	45/121 (37.2)	2.70 (2.06, 3.53)		1.33 (0.99, 1.79)	
AHI=0 (referent)	13/189 (6.9)	1.00	<.0001	1.00	0.1497
0<AHI<5	165/1103 (15.0)	2.17 (1.26, 3.74)	*Trend tests:*	1.31 (0.78, 2.21)	*Trend tests:*
5≤AHI<15	37/107 (34.6)	5.03 (2.80, 9.03)	*0.0053 linear*	1.64 (0.91, 2.97)	*0.0432 linear*
AHI≥15	8/14 (57.1)	8.31 (4.15, 16.62)	*0.4603 quadratic*	2.32 (1.11, 4.86)	*0.8503 quadratic*

Abbreviations: AHI = Apnea-Hypopnea Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) in early pregnancy, race, and time from delivery to HHS cardiovascular assessment.

[2/] Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication. Analyses are adjusted for age and BMI in early pregnancy, race, and time from delivery to HHS cardiovascular assessment.

[3/] Including all apneas and hypopneas w/ ≥3% oxygen desaturation / hour

Table 4
Crude and Adjusted Risk Ratios[1/] for Incident Hypertension and Metabolic Syndrome[2/] at 2-7 Year Follow-up
Oxygen Desaturation Index (ODI)[3/] in Early and Mid-Pregnancy

ODI Characteristic	n/N (%)	Crude Risk Ratios		Adjusted Risk Ratios	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Incident Hypertension					
Early or Mid-Pregnancy					
ODI<5 in both early and mid-pregnancy (referent)	41/984 (4.2)	1.00	<.0001	1.00	0.0041
ODI≥5 in early or mid-pregnancy	40/349 (11.5)	2.75 (1.81, 4.18)		2.02 (1.30, 3.14)	
Early Pregnancy					
ODI<5 (referent)	82/1521 (5.4)	1.00	0.0048	1.00	0.2918
ODI≥5	24/194 (12.4)	2.29 (1.49, 3.53)		1.32 (0.81, 2.13)	
ODI=0 (referent)	5/141 (3.5)	1.00	0.0220	1.00	0.6595
0<ODI<5	77/1380 (5.6)	1.57 (0.65, 3.82)	*Trend tests:*	1.30 (0.53, 3.19)	*Trend tests:*
5≤ODI<15	21/174 (12.1)	3.40 (1.32, 8.80)	*0.1462 linear*	1.73 (0.63, 4.75)	*0.5806 linear*
ODI≥15	3/20 (15.0)	4.23 (1.09, 16.36)	*0.7345 quadratic*	1.41 (0.33, 6.11)	*0.5015 quadratic*
Mid-pregnancy					
ODI<5 (referent)	47/1094 (4.3)	1.00	<.0001	1.00	0.0013
ODI≥5	42/328 (12.8)	2.98 (2.00, 4.44)		2.16 (1.41, 3.30)	
ODI=0 (referent)	4/57 (7.0)	1.00	0.0002	1.00	0.0092
0<ODI<5	43/1037 (4.1)	0.59 (0.22, 1.59)	*Trend tests:*	0.50 (0.18, 1.39)	*Trend tests:*
5≤ODI<15	35/287 (12.2)	1.74 (0.64, 4.70)	*0.0605 linear*	1.09 (0.39, 3.08)	*0.3663 linear*
ODI≥15	7/41 (17.1)	2.43 (0.76, 7.77)	*0.2666 quadratic*	1.37 (0.40, 4.74)	*0.2533 quadratic*
Metabolic Syndrome					
Early or Mid-Pregnancy					
ODI<5 in both early and mid-pregnancy (referent)	106/972 (10.9)	1.00	<.0001	1.00	0.0014
ODI≥5 in early or mid-pregnancy	107/352 (30.4)	2.79 (2.19, 3.54)		1.53 (1.19, 1.97)	

Early Pregnancy					
ODI<5 (referent)	219/1505 (14.6)	1.00	<.0001	1.00	0.0188
ODI≥5	73/194 (37.6)	2.59 (2.08, 3.22)		1.35 (1.06, 1.70)	
ODI=0 (referent)	10/137 (7.3)	1.00	<.0001	1.00	0.0456
0<ODI<5	209/1368 (15.3)	2.09 (1.14, 3.85)	*Trend tests:*	1.49 (0.82, 2.71)	*Trend tests:*
5≤ODI<15	63/173 (36.4)	4.99 (2.66, 9.35)	*0.0021 linear*	2.02 (1.07, 3.81)	*0.0917 linear*
ODI≥15	10/21 (47.6)	6.52 (3.09, 13.76)	*0.1995 quadratic*	1.77 (0.82, 3.78)	*0.1362 quadratic*
Mid-pregnancy					
ODI<5 (referent)	121/1083 (11.2)	1.00	<.0001	1.00	0.0031
ODI≥5	102/330 (30.9)	2.77 (2.19, 3.49)		1.48 (1.15, 1.90)	
ODI=0 (referent)	3/54 (5.6)	1.00	<.0001	1.00	0.0148
0<ODI<5	118/1029 (11.5)	2.06 (0.68, 6.28)	*Trend tests:*	1.38 (0.47, 4.04)	*Trend tests:*
5≤ODI<15	82/286 (28.7)	5.16 (1.69, 15.74)	*<.0001 linear*	1.94 (0.65, 5.75)	*0.0214 linear*
ODI≥15	20/44 (45.5)	8.18 (2.60, 25.75)	*0.6269 quadratic*	2.57 (0.82, 8.01)	*0.9481 quadratic*

Abbreviations: ODI = Oxygen Desaturation Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) in early pregnancy, race, and time from delivery to HHS cardiovascular assessment.

[2/] Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication. Analyses are adjusted for age and BMI in early pregnancy, race, and time from delivery to HHS cardiovascular assessment.

[3/] Number of desaturations ≥3% per hour sleep

Table 5

Crude and Adjusted Risk Ratios[1/] for Incident Hypertension[2/] and Metabolic Sydrome[3/] at 2-7 Year Follow-up According to Apnea-Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI)[4/] at the Follow-up Assessment

Sleep Characteristic	Outcome n/N (%)	Crude Risk Ratios		Adjusted Risk Ratios	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
AHI					
Incident Hypertension					
AHI<5 (referent)	45/918 (4.9)	1.00	0.0008	1.00	0.0271
AHI≥5	21/124 (16.9)	3.45 (2.13, 5.60)		2.01 (1.17, 3.46)	
AHI=0 (referent)	4/118 (3.4)	1.00	0.0048	1.00	0.0580
0<AHI<5	41/800 (5.1)	1.51 (0.55, 4.14)	*Trend tests:*	1.11 (0.39, 3.15)	*Trend tests:*
5≤AHI<15	11/94 (11.7)	3.45 (1.14, 10.49)	*0.0015 linear*	1.67 (0.50, 5.57)	*0.0131 linear*
AHI≥15	10/30 (33.3)	9.83 (3.31, 29.19)	*0.3869 quadratic*	4.18 (1.19, 14.76)	*0.2783 quadratic*
Metabolic Syndrome					
AHI<5 (referent)	122/911 (13.4)	1.00	<.0001	1.00	0.0073
AHI≥5	54/127 (42.5)	3.18 (2.45, 4.12)		1.51 (1.14, 2.00)	
AHI=0 (referent)	11/116 (9.5)	1.00	<.0001	1.00	0.0073
0<AHI<5	111/795 (14.0)	1.47 (0.82, 2.65)	*Trend tests:*	1.00 (0.57, 1.75)	*Trend tests:*
5≤AHI<15	34/96 (35.4)	3.73 (2.00, 6.97)	*<.0001 linear*	1.32 (0.71, 2.46)	*0.0079 linear*
AHI≥15	20/31 (64.5)	6.80 (3.66, 12.65)	*0.5670 quadratic*	2.14 (1.11, 4.15)	*0.1936 quadratic*
ODI					
Incident Hypertension					
ODI<5 (referent)	28/695 (4.0)	1.00	0.0002	1.00	0.0349
ODI≥5	38/347 (11.0)	2.72 (1.70, 4.35)		1.75 (1.05, 2.92)	
ODI<5 (referent) §	28/695 (4.0)	1.00	0.0004	1.00	0.0244
5≤ODI<15	23/279 (8.2)	2.05 (1.20, 3.49)	*Trend tests:*	1.52 (0.86, 2.68)	*Trend tests:*
ODI≥15	15/68 (22.1)	5.48 (3.08, 9.74)	*0.0010 linear 0.5825 quadratic*	2.89 (1.50, 5.57)	*0.0080 linear 0.6403 quadratic*
Metabolic Syndrome					
ODI<5 (referent)	71/689 (10.3)	1.00	<.0001	1.00	0.0009

ODI≥5	105/349 (30.1)	2.92 (2.22, 3.83)		1.60 (1.21, 2.12)	
ODI=0 (referent)	2/22 (9.1)	1.00	<.0001	1.00	0.0014
0<ODI<5	69/667 (10.3)	1.14 (0.30, 4.35)	*Trend tests:*	0.74 (0.20, 2.79)	*Trend tests:*
5≤ODI<15	68/280 (24.3)	2.67 (0.70, 10.18)	*<.0001 linear*	1.10 (0.29, 4.16)	*0.3061 linear*
ODI≥15	37/69 (53.6)	5.90 (1.55, 22.52)	*0.4812 quadratic*	1.57 (0.41, 6.01)	*0.4813 quadratic*

Abbreviations: AHI = Apnea-Hypopnea Index; ODI = Oxygen Desaturation Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) at the time of the HHS cardiovascular assessment, and race.

[2/] Women with baseline hypertension are excluded from the hypertension analyses.

[3/] Women with preexisting diabetes are excluded from the metabolic syndrome analyses. Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication.

[4/] AHI= all apneas and hypopneas w/ ≥3% oxygen desaturation / hour; ODI = Number of desaturations ≥3% per hour sleep

[§] There were no women in the ODI=0 with hypertension, so the ODI=0 group was combined with the 0<ODI<5 group for this analysis.

Table 6

Crude and Adjusted Risk Ratios[1/] for Incident Hypertension[2/] and Metabolic Sydrome[3/] at 2-7 Year Follow-up According to Apnea-Hypopnea Index (AHI) Oxygen Desaturation Index (ODI)[4/] During the nuMoM2b Pregnancy and at the Follow-up Assessment

Sleep Characteristic	Outcome n/N (%)	Crude Risk Ratios		Adjusted Risk Ratios	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
AHI					
Incident Hypertension[§]					
Never: AHI<5 in early and mid-pregnancy and post-delivery (referent)	31/702 (4.4)	1.00	0.0130[§]	1.00	0.0327[§]
New Onset: AHI<5 in early and mid-pregnancy; AHI≥5 post-delivery	8/59 (13.6)	3.07 (1.48, 6.37)		2.18 (1.07, 4.48)	
Resolved: AHI≥5 in early or mid-pregnancy; AHI<5 post-delivery	0/20 (0.0)	*not applicable*		*not applicable*	
Persistent: AHI≥5 in early or mid-pregnancy; AHI≥5 post-delivery	10/45 (22.2)	5.03 (2.64, 9.60)		3.77 (1.84, 7.73)	
Metabolic Syndrome					
Never: AHI<5 in early and mid-pregnancy and post-delivery (referent)	81/697 (11.6)	1.00	<.0001	1.00	0.0033
New Onset: AHI<5 in early and mid-pregnancy; AHI≥5 post-delivery	20/60 (33.3)	2.87 (1.90, 4.33)		1.81 (1.18, 2.80)	
Resolved: AHI≥5 in early or mid-pregnancy; AHI<5 post-delivery	4/22 (18.2)	1.56 (0.63, 3.89)		1.12 (0.49, 2.54)	
Persistent: AHI≥5 in early or mid-pregnancy; AHI≥5 post-delivery	24/47 (51.1)	4.39 (3.11, 6.22)		2.46 (1.59, 3.79)	
ODI					
Incident Hypertension					
Never: ODI<5 in early and mid-pregnancy and post-delivery (referent)	15/468 (3.2)	1.00	0.0029	1.00	0.0401
New Onset: ODI<5 in early and mid-pregnancy; ODI≥5 post-delivery	9/144 (6.3)	1.95 (0.87, 4.36)		1.69 (0.76, 3.74)	
Resolved: ODI≥5 in early or mid-pregnancy; ODI<5 post-delivery	5/68 (7.4)	2.29 (0.86, 6.11)		1.81 (0.71, 4.60)	
Persistent: ODI≥5 in early or mid-pregnancy; ODI≥5 post-delivery	20/146 (13.7)	4.27 (2.25, 8.13)		2.94 (1.50, 5.77)	
Metabolic Syndrome					
Never: ODI<5 in early and mid-pregnancy and post-delivery (referent)	38/468 (8.1)	1.00	<.0001	1.00	0.0004
New Onset: ODI<5 in early and mid-pregnancy; ODI≥5 post-delivery	28/143 (19.6)	2.41 (1.54, 3.78)		1.93 (1.24, 3.01)	
Resolved: ODI≥5 in early or mid-pregnancy; ODI<5 post-delivery	9/65 (13.8)	1.71 (0.87, 3.36)		1.17 (0.62, 2.18)	
Persistent: ODI≥5 in early or mid-pregnancy; ODI≥5 post-delivery	54/150 (36.0)	4.43 (3.06, 6.43)		2.42 (1.59, 3.67)	

Abbreviations: AHI = Apnea-Hypopnea Index; ODI = Oxygen Desaturation Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) in early pregnancy, race, and time from delivery to HHS cardiovascular assessment.

[2/] Women with baseline hypertension are excluded from the hypertension analyses.

[3/] Women with preexisting diabetes are excluded from the metabolic syndrome analyses. Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication.

[4/] AHI= all apneas and hypopneas w/ ≥3% oxygen desaturation / hour; ODI = Number of desaturations ≥3% per hour sleep

§ None of the 20 participants with AHI≥5 during the nuMoM2b pregnancy and AHI<5 at the 2-7 year assessment had hypertension at the follow-up assessment. To compute relative risk estimates and an upper bound on the p-value for differences between the AHI categories, one observation among the 20 was categorized as having hypertension, such that the observation selected resulted in the smallest estimate of adjusted relative risk for this group compared to the referent group.

Sleep Disordered Breathing in Pregnancy and at 2-7 Years Follow-Up: Associations with Hypertension and Metabolic Syndrome: Online Data Supplement

Additional Details on Enrollment Criteria for the nuMoM2n Sleep Disordered Breathing (SDB) Substudy and the nuMoM2b-HHS Visit

The SDB Substudy to the parent nuMoM2b Study was initiated about six months after enrollment began for the parent study. Once initiated, all women enrolled in the parent study were eligible for a sleep study in pregnancy unless 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. Women were administered informed consent separately for the substudy. Baseline characteristics were similar between nuMoM2b women who participated in the SDB Substudy and those who did not.(1)

Women were eligible for the in-person nuMoM2b-HHS visit if 2-7 years have elapsed since their nuMoM2b pregnancy ended and they were not currently pregnant. Until late in the recruitment effort, they were also required to be at least 6 months postpartum from any subsequent pregnancy.

Additional Details on Outcome Measures

Incident HTN was defined as HTN that developed after the index pregnancy, as determined by BP measurement (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) or use of an antihypertensive medication for BP control at the 2- to 7-year post-delivery visit. For the BP measurements, following a standard protocol, research personnel recorded 3 standardized BP measurements using calibrated automatic devices that were the same at each site. With the participant seated, BP measurements were recorded, and the average of the last 2 systolic and diastolic pressures were used for analysis. (2)

Additional Details on Statistical analyses

Baseline characteristics of the index pregnancy and cardiovascular characteristics at the 2-7 year follow-up visit were summarized according to SDB status during pregnancy. Using means and standard deviations for continuous variables, and frequencies for categorical variables. Chi square tests assessed associations with categorical characteristics and analysis of variance F-tests were used for continuous measurements.

Analyses during pregnancy were restricted to participants who had an early or mid-pregnancy sleep study with adequate data and attended the in-person nuMoM2b-HHS cardiovascular assessment. Participants with baseline HTN were excluded from the HTN analyses; likewise, those with preexisting diabetes were excluded from the metabolic syndrome analyses.

Crude and adjusted risk ratios (RR) and 95% confidence intervals (CI) were estimated using Poisson regression with robust standard errors to relate SDB in -pregnancy and post-delivery to incident HTN and

metabolic syndrome.(3) In addition, p-values from likelihood ratio tests were reported. Adjustment covariates chosen *a priori* included: age and body mass index (BMI) in early pregnancy (both continuous), self-identified race (categorized as non-Hispanic White, non-Hispanic Black, Hispanic, Asian, other), and years from delivery of the index pregnancy to the HHS cardiovascular assessment (continuous). Similar methods were used for the cross-sectional analyses of SDB in the post-delivery period, with age and BMI at the time of the HHS visit and race used as adjustment covariates. In all our adjusted analyses BMI was included as a linear and a quadratic term.

We also considered having a hypertensive disorder of pregnancy (HDP) during the index pregnancy as a mediator in the associations of SDB during pregnancy with HTN post-delivery and HDP or GDM during pregnancy as a mediator in the associations of SDB during pregnancy with metabolic syndrome post-delivery. The associations of hypertensive disorders of pregnancy (HDP) and HDP or GDM with SDB in pregnancy were estimated using Poisson regression, as described in the paper; and four-way decompositions of total excess relative risk were computed using the method of VanderWeele(4) to estimate how much of the SDB risk was mediated by the pregnancy complication, how much was due to interaction between the pregnancy complication and the SDB risk factor, how much was due to both mediation and interaction together, and how much was a direct effect of the SDB. Mediation models were adjusted for age and BMI in early pregnancy, race/ethnicity, and years from delivery of the index pregnancy to the HHS cardiovascular assessment.

All tests were performed at a nominal significance level of $\alpha = 05$. All single degree-of-freedom tests were two-sided. No correction was made for multiple comparisons. Analyses were performed using SAS 9.4 (Cary, NC).

Additional Details on Sleep Study Scoring and Urgent Alerts:

Sleep studies were scored by a central reading center by trained polysomnologists blinded to all other data. Event definitions, scoring reliability and the quality control protocol were previously published.(5) Two SDB definitions were considered: (1) Apnea Hypopnea Index (AHI): the number of apneas and hypopneas per hour of estimated sleep, inclusive of all apneas plus hypopneas accompanied by ≥3% oxygen desaturation; and (2) Oxygen-Desaturation Index (ODI): the number of oxygen desaturations ≥3% from the pre-event baseline per hour of estimated sleep.

Apnea: amplitude (peak to trough) of the nasal pressure signal flat for ≥10 seconds; 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% reduction of amplitude in the nasal pressure signal or the respiratory sum channel (if no nasal pressure signal) for ≥10 seconds.

Apnea-Hypopnea Index (AHI): number of apneas and hypopneas per hour of estimated sleep, defined in this analysis as all apneas regardless of oxygen desaturation and hypopneas accompanied by ≥3% oxygen desaturation.

Oxygen-Desaturation Index (ODI): number of oxygen desaturations ≥3% per hour of estimated sleep.

After receipt at the Sleep Reading Center, studies were identified that met "urgent alert" criteria based on an AHI >50 events/hour or severe hypoxemia (baseline oxygen saturation <88%, oxygen saturation of <90% for ≥10% of sleep time) or marked abnormalities in heart rate.

Additional Data on Relationship between AHI and ODI in Pregnancy:

As expected, AHI and ODI were strongly correlated (Spearman correlation coefficients at early and mid-pregnancy visits were 0.79 and 0.84, respectively). Median (interquartile range) AHI at early and mid-pregnancy visits were 0.32 (0.10-0.93) and 0.65 (0.21-1.92), respectively; median (interquartile range) ODI at early and mid-pregnancy visits were 1.10 (0.30-2.50) and 2.10 (0.80-4.50), respectively. The median (interquartile range) for the difference (delta) between ODI and AHI in early and mid-pregnancy were 0.65 (1.47) and 1.16 (2.11), respectively.

Higher ODI-AHI delta was associated with non-Hispanic ethnicity and higher BMI in early pregnancy and was associated with higher BMI in mid-pregnancy (data not shown). Given possible associations between asthma and restless legs syndrome with oxygen desaturation, we examined these variables (asthma by self-report, restless legs by validated questionnaire) in relation to the ODI-AHI delta but found no significant relationships (data not shown).(6) A re-examination of representative sleep tracings of those with the highest ODI-AHI differences suggested that some of the desaturation events included in the ODI were not included in the AHI due to only subtle evidence of airflow reduction. Finally, we acknowledge that signal artifact cannot be ruled out as a plausible contributor.

We ran models additionally adjusting for average oxygen saturation preceding sleep onset and found similar results (data in Supplement Tables: S7a,S7b, S8a, S8b).

We also ran a sensitivity analyses for AHI and ODI in relation to HTN and metabolic syndrome excluding the 6 women (1 in early, 5 in mid-pregnancy) who met urgent alert criteria based on oxygen saturation data (oxygen saturation during sleep of <90% for >10% of sleep time or baseline oxygen saturation prior to sleep onset of <88%) and found similar results (data not shown).

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Supplemental Table S1
Characteristics of nuMoM2b Participants with a Mid or Early Pregnancy Sleep Study and a Cardiovascular Assessment 2-7 Years After the Index Pregnancy by Conduct of a Sleep Study at the 2-7 Year Assessment

Characteristics	Sleep Study Conducted 2-7 Years Postpartum (N = 1,222)	Sleep Study Not Conducted 2-7 Years Postpartum (N = 742)	p-value[1/]
Maternal age in early pregnancy, in years			
Mean (standard deviation)	26.5 (5.4)	27.0 (5.8)	0.0587
Category: n (%)			0.1861
13-21	253 (20.7)	160 (21.6)	
22-35	896 (73.3)	523 (70.5)	
>35	73 (6.0)	59 (8.0)	
Maternal race: n (%)			0.0027
White Non-Hispanic	777 (63.6)	436 (58.8)	
Black Non-Hispanic	160 (13.1)	125 (16.8)	
Hispanic	206 (16.9)	107 (14.4)	
Asian	25 (2.0)	29 (3.9)	
Other	54 (4.4)	45 (6.1)	
BMI in early pregnancy, in kg/m^2			
Mean (standard deviation)	26.9 (6.7)	26.9 (6.7)	0.9635
Category: n (%)			0.2392
<25	598 (49.6)	375 (51.1)	
25 to <30	286 (23.7)	188 (25.6)	
≥30	321 (26.6)	171 (23.3)	
Smoked during pregnancy: n (%)	90 (7.4)	57 (7.7)	0.7958
Rate of weight gain from early to mid-pregnancy, in kg per week			
Mean (standard deviation)	0.47 (0.24)	0.49 (0.24)	0.0826
Early Pregnancy AHI[2/] Category: n (%)			0.1886
AHI=0	253 (21.8)	146 (24.0)	
0<AHI<5	866 (74.5)	432 (71.1)	
5≤AHI<15	42 (3.6)	26 (4.3)	
AHI≥15	2 (0.2)	4 (0.7)	
Mid-Pregnancy AHI[2/] Category: n (%)			0.6932
AHI=0	131 (13.0)	62 (13.8)	
0<AHI<5	798 (79.1)	343 (76.6)	
5≤AHI<15	71 (7.0)	38 (8.5)	
AHI≥15	9 (0.9)	5 (1.1)	
Time from Delivery to nuMoM2b-HHS Cardiovascular Assessment, in years			
N	1,219	741	
Mean (SD)	2.8 (0.7)	3.2 (0.9)	<.0001

Abbreviations: AHI = Apnea-Hypopnea Index; BMI = body mass index.
[1/] p-values are shown for chi-square tests for AHI and the categorical baseline characteristics and from ANOVA F-tests for AHI and continuous baseline characteristics.
[2/] Including all apneas and hypopneas with ≥3% oxygen desaturation / hour.

Supplemental Table S2

Crude and Adjusted Risk Ratios[1/] for the Components of Metabolic Sydrome[2/] at 2-7 Year Follow-up

According to Apnea-Hypopnea Index (AHI)[3/] in Early or Mid-Pregnancy
Among Women Without Preexisting Diabetes

Metabolic Syndrome Component / AHI Category	Metabolic Syndrome Component	Crude Risk Ratios		Adjusted Risk Ratios	
	n/N (%)	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Elevated waist circumference					
AHI<5 in both early and mid-pregnancy (referent)	742/1200 (61.8)	1.00	<.0001	1.00	0.8300
AHI≥5 in early or mid-pregnancy	112/124 (90.3)	1.46 (1.36, 1.57)		0.99 (0.92, 1.06)	
Elevated triglycerides or associated medication					
AHI<5 in both early and mid-pregnancy (referent)	121/1200 (10.1)	1.00	<.0001	1.00	0.0012
AHI≥5 in early or mid-pregnancy	39/124 (31.5)	3.12 (2.29, 4.25)		1.93 (1.37, 2.73)	
Elevated fasting glucose or associated medication					
AHI<5 in both early and mid-pregnancy (referent)	165/1200 (13.8)	1.00	0.0254	1.00	0.6767
AHI≥5 in early or mid-pregnancy	28/124 (22.6)	1.64 (1.15, 2.34)		1.09 (0.73, 1.64)	
Elevated blood pressure or associated medication					
AHI<5 in both early and mid-pregnancy (referent)	126/1200 (10.5)	1.00	<.0001	1.00	0.0688
AHI≥5 in early or mid-pregnancy	34/124 (27.4)	2.61 (1.88, 3.63)		1.46 (1.00, 2.14)	
Reduced HDL-C or associated medication					
AHI<5 in both early and mid-pregnancy (referent)	399/1200 (33.3)	1.00	<.0001	1.00	0.0013
AHI≥5 in early or mid-pregnancy	71/124 (57.3)	1.72 (1.45, 2.05)		1.40 (1.16, 1.68)	

Abbreviations: AHI = Apnea-Hypopnea Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) in early pregnancy, race, and time from delivery to HHS cardiovascular assessment.

[2/] Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication.

[3/] Including all apneas and hypopneas w/ ≥3% oxygen desaturation / hour

Supplemental Table S3
Crude and Adjusted Risk Ratios[1/] for the Components of Metabolic Sydrome[2/] at 2-7 Year Follow-up According to Oxygen Desaturation Index (ODI)[3/] in Early or Mid-Pregnancy Among Women Without Preexisting Diabetes

Metabolic Syndrome Component / ODI Category	Metabolic Syndrome Component n/N (%)	Crude Risk Ratios		Adjusted Risk Ratios	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Elevated waist circumference					
ODI<5 in both early and mid-pregnancy (referent)	563/972 (57.9)	1.00	<.0001	1.00	0.8979
ODI≥5 in early or mid-pregnancy	291/352 (82.7)	1.43 (1.33, 1.53)		1.00 (0.93, 1.07)	
Elevated triglycerides or associated medication					
ODI<5 in both early and mid-pregnancy (referent)	77/972 (7.9)	1.00	<.0001	1.00	<.0001
ODI≥5 in early or mid-pregnancy	83/352 (23.6)	2.98 (2.24, 3.96)		2.03 (1.51, 2.74)	
Elevated fasting glucose or associated medication					
ODI<5 in both early and mid-pregnancy (referent)	123/972 (12.7)	1.00	0.0026	1.00	0.4157
ODI≥5 in early or mid-pregnancy	70/352 (19.9)	1.57 (1.20, 2.05)		1.13 (0.84, 1.52)	
Elevated blood pressure or associated medication					
ODI<5 in both early and mid-pregnancy (referent)	84/972 (8.6)	1.00	<.0001	1.00	0.0074
ODI≥5 in early or mid-pregnancy	76/352 (21.6)	2.50 (1.88, 3.32)		1.58 (1.15, 2.18)	
Reduced HDL-C or associated medication					
ODI<5 in both early and mid-pregnancy (referent)	309/972 (31.8)	1.00	<.0001	1.00	0.1508
ODI≥5 in early or mid-pregnancy	161/352 (45.7)	1.44 (1.24, 1.67)		1.12 (0.96, 1.31)	

Abbreviations: ODI = Oxygen Desaturation Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) in early pregnancy, race, and time from delivery to HHS cardiovascular assessment.

[2/] Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication.

[3/] Number of desaturations ≥3% per hour sleep

Supplemental Table S4
Assessment of SDB Risk on Hypertension 2-7 Years After nuMoM2b Pregnancy Mediated by Hypertensive Disorder of Pregnancy[1/]
With Adjustment for Age, BMI (Linear and Quadratic), Race/Ethnicity, and Time from Delivery to Follow-up Visit

SDB	Total Excess Relative Risk (95% CI)	Components[2/] of Excess Relative Risk (95% CI) Associating SDB with Hypertension				Proportion of Total Eliminated (95% CI)
		Controlled Direct Effect	Interaction with HDP	Interaction & Mediation with HDP	Pure Indirect Effect	
AHI≥5 in early pregnancy (versus AHI<5)	0.10 (-0.80, 1.00)	0.02 (-0.90, 0.94)	0.04 (-0.24, 0.32)	0.01 (-0.05, 0.07)	0.03 (-0.05, 0.12)	0.81 (-6.77, 8.40)
AHI≥5 in mid pregnancy (versus AHI<5)	0.53 (-0.44, 1.49)	0.25 (-0.70, 1.19)	0.13 (-0.13, 0.39)	0.08 (-0.10, 0.27)	0.06 (-0.02, 0.15)	0.53 (-0.56, 1.62)
AHI≥5 in early or mid-pregnancy (versus AHI<5 in early and mid-pregnancy)	0.25 (-0.61, 1.10)	0.07 (-0.77, 0.91)	0.08 (-0.17, 0.33)	0.04 (-0.09, 0.17)	0.06 (-0.02, 0.14)	0.73 (-1.88, 3.34)
ODI≥5 in early pregnancy (versus ODI<5)	0.35 (-0.39, 1.08)	0.36 (-0.39, 1.11)	-0.03 (-0.25, 0.19)	0.00 (-0.02, 0.02)	0.01 (-0.05, 0.08)	-0.05 (-0.76, 0.67)
ODI≥5 in mid pregnancy (versus ODI<5)	1.06 (0.04, 2.09)	0.76 (-0.17, 1.69)	0.26 (-0.05, 0.57)	0.03 (-0.06, 0.13)	0.01 (-0.02, 0.04)	0.28 (-0.05, 0.62)
ODI≥5 in early or mid-pregnancy (versus ODI<5 in early and mid-pregnancy)	0.93 (-0.05, 1.92)	0.64 (-0.24, 1.53)	0.25 (-0.06, 0.57)	0.03 (-0.07, 0.12)	0.01 (-0.02, 0.04)	0.31 (-0.07, 0.69)

Abbreviations: AHI = Apnea-Hypopnea Index; BMI=body mass index; CI=confidence interval; HDP = hypertensive disorder of pregnancy; ODI - Oxygen Desaturation Index; SDB = sleep disordered breathing.

[1/] Hypertensive disorder of pregnancy includes antepartum gestational hypertension, preeclampsia, and eclampsia.

[2/] Components defined as: controlled direct effect (effect due to SDB only, without mediation or interaction), interaction only (effect due to interaction only), interaction & mediation (mediated interaction; effect due to both mediation and interaction), pure indirect effect (effect due to mediation only), portion eliminated (% effect due to either mediation or interaction). Ref: VanderWeele 2014.

Supplemental Table S5
Assessment of SDB Risk on Metabolic Syndrome 2-7 Years After nuMoM2b Pregnancy
Mediated by Hypertensive Disorder of Pregnancy[1/] or Gestational Diabetes
With Adjustment for Age, BMI (Linear and Quadratic), Race/Ethnicity, and Time from Delivery to Follow-up Visit

SDB	Total Excess Relative Risk (95% CI)	Components[2/] of Excess Relative Risk (95% CI) Associating SDB with Metabolic Syndrome				Proportion of Total Eliminated (95% CI)
		Controlled Direct Effect	Interaction with HDP/GDM	Interaction & Mediation with HDP/GDM	Pure Indirect Effect	
AHI≥5 in early pregnancy (versus AHI<5)	0.34 (-0.27, 0.94)	0.36 (-0.33, 1.06)	-0.03 (-0.17, 0.11)	-0.01 (-0.06, 0.04)	0.02 (-0.01, 0.05)	-0.07 (-0.56, 0.43)
AHI≥5 in mid pregnancy (versus AHI<5)	0.40 (-0.14, 0.94)	0.44 (-0.18, 1.05)	-0.05 (-0.16, 0.07)	-0.03 (-0.11, 0.05)	0.04 (-0.01, 0.08)	-0.10 (-0.51, 0.32)
AHI≥5 in early or mid-pregnancy (versus AHI<5 in early and mid-pregnancy)	0.54 (-0.04, 1.12)	0.61 (-0.06, 1.27)	-0.07 (-0.19, 0.06)	-0.04 (-0.12, 0.04)	0.04 (-0.01, 0.09)	-0.12 (-0.44, 0.20)
ODI≥5 in early pregnancy (versus ODI<5)	0.43 (-0.01, 0.87)	0.50 (0.01, 0.99)	-0.07 (-0.18, 0.03)	-0.01 (-0.04, 0.02)	0.01 (-0.01, 0.04)	-0.17 (-0.45, 0.12)
ODI≥5 in mid pregnancy (versus ODI<5)	0.56 (0.08, 1.04)	0.64 (0.12, 1.15)	-0.08 (-0.19, 0.03)	-0.03 (-0.07, 0.02)	0.03 (-0.01, 0.07)	-0.14 (-0.39, 0.10)
ODI≥5 in early or mid-pregnancy (versus ODI<5 in early and mid-pregnancy)	0.60 (0.10, 1.09)	0.67 (0.14, 1.20)	-0.08 (-0.19, 0.04)	-0.02 (-0.06, 0.02)	0.02 (-0.01, 0.06)	-0.12 (-0.36, 0.11)

Abbreviations: AHI = Apnea-Hypopnea Index; BMI=body mass index; CI=confidence interval; GDM = gestational diabetes mellitus; HDP = hypertensive disorder of pregnancy; ODI = Oxygen Desaturation Index; SDB = sleep disordered breathing.

[1/] Hypertensive disorder of pregnancy includes antepartum gestational hypertension, preeclampsia, and eclampsia.

[2/] Components defined as: controlled direct effect (effect due to SDB only, without mediation or interaction), interaction only (effect due to interaction only), interaction & mediation (mediated interaction; effect due to both mediation and interaction), pure indirect effect (effect due to mediation only), portion eliminated (% effect due to either mediation or interaction). Ref: VanderWeele 2014.

Supplemental Table S6 (continued on next page)
Cardiovascular Characteristics at the 2-7 Year Assessment According to Apnea-Hypopnea Index (AHI)[1/] Categories at the follow-up Assessment

Cardiovascular Characteristic 2-7 Years After nuMoM2b Index Pregnancy	AHI < 5 at 2-7 Year Assessment (N = 936)	AHI ≥ 5 at 2-7 Year Assessment (N = 133)	p-value[2/]
BMI, in kg/m^2			
N	933	131	
Mean (SD)	26.7 (6.6)	36.1 (8.6)	<.0001
Category: n (%)			<.0001
<25	450 (48.2)	11 (8.4)	
25 to <30	249 (26.7)	19 (14.5)	
≥30	234 (25.1)	101 (77.1)	
Waist circumference over iliac crest, in cm			
N	936	133	
Mean (SD)	93.9 (14.4)	113.9 (18.4)	<.0001
≥88 cm (non-Asian) or ≥80 cm (Asian): n (%)	575 (61.4)	125 (94.0)	<.0001
Systolic blood pressure, in mmHg			
N	936	133	
Mean (SD)	110.9 (10.6)	115.2 (13.0)	<.0001
Diastolic blood pressure, in mmHg			
N	936	133	
Mean (SD)	71.6 (9.3)	77.8 (10.6)	<.0001
Hypertension Definitions: n (%)			
HHS (140≤SBP/90≤DBP, or antihypertensive medication)	50 (5.3)	26 (19.5)	<.0001
AMA 2018 (130≤SBP/80≤DBP, or antihypertensive medication)	178 (19.0)	59 (44.4)	<.0001
MetSyn (130≤SBP/85≤DBP, or antihypertensive medication)	94 (10.0)	41 (30.8)	<.0001
Triglycerides, in mg/dL			
N	931	133	
Mean (SD)	93.8 (61.6)	142.8 (82.2)	<.0001
≥150 mg/dL or on lipid-lowering medication: n (%)	99 (10.6)	47 (35.3)	<.0001
HDL-C, in mg/dL			
N	931	133	
Mean (SD)	55.3 (12.4)	49.1 (10.5)	<.0001
<50 mg/dL or on HDL-raising medication: n (%)	330 (35.4)	71 (53.4)	<.0001

Blood glucose (fasting), in mg/dL			
N	929	133	
Mean (SD)	91.5 (24.8)	97.8 (27.5)	0.0071
≥100 mg/dL or on glucose-lowering medication: n (%)	138 (14.9)	37 (27.8)	0.0002
Metabolic Syndrome[3/]: n (%)	130 (14.0)	59 (44.4)	<.0001
Time from delivery to HHS cardiovascular assessment, in years			
N	933	133	
Mean (SD)	2.9 (0.7)	2.7 (0.6)	0.0776

Abbreviations: AHI = Apnea-Hypopnea Index; BMI = body mass index; SD = standard deviation

[1/] Including all apneas and hypopneas w/ ≥3% oxygen desaturation / hour

[2/] p-values are shown for chi-square tests for AHI and the categorical baseline characteristics and from ANOVA F-tests for AHI and continuous baseline characteristics.

[3/] Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication.

Supplemental Table S7a: Sensitivity Analysis Adjusting for Baseline Oxygen Saturation
Crude and Adjusted Risk Ratios[1/] for Incident Hypertension at 2-7 Years Postpartum
According to Apnea-Hypopnea Index (AHI)[2/] in Early and Mid-pregnancy
Among Women Without Baseline Hypertension

AHI Characteristic	Hypertension 2-7 Years After Index nuMoM2b Pregnancy	Crude Risk Ratios		Adjusted Risk Ratios	
	n/N (%)	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Early Pregnancy					
AHI<5 (referent)	96/1647 (5.8)	1.00	0.0463	1.00	0.5023
AHI≥5 (versus AHI<5)	10/68 (14.7)	2.52 (1.38, 4.62)		1.31 (0.63, 2.75)	
AHI=0 (referent)	18/391 (4.6)	1.00	0.1280	1.00	0.8967
0<AHI<5 (versus AHI=0)	78/1256 (6.2)	1.35 (0.82, 2.22)	*Trend tests:*	1.08 (0.65, 1.78)	*Trend tests:*
5≤AHI<15 (versus AHI=0)	9/63 (14.3)	3.10 (1.46, 6.60)	*0.3931 linear*	1.38 (0.57, 3.35)	*0.6036 linear*
AHI≥15 (versus AHI=0)	1/5 (20.0)	4.34 (0.71, 26.55)	*0.9702 quadratic*	1.73 (0.28, 10.86)	*0.8760 quadratic*
Mid-pregnancy					
AHI<5 (referent)	72/1308 (5.5)	1.00	0.0070	1.00	0.0838
AHI≥5 (versus AHI<5)	17/114 (14.9)	2.71 (1.66, 4.43)		1.80 (1.00, 3.24)	
AHI=0 (referent)	9/189 (4.8)	1.00	0.0547	1.00	0.3504
0<AHI<5 (versus AHI=0)	63/1119 (5.6)	1.18 (0.60, 2.34)	*Trend tests:*	0.81 (0.41, 1.60)	*Trend tests:*
5≤AHI<15 (versus AHI=0)	14/100 (14.0)	2.94 (1.32, 6.55)	*0.1325 linear*	1.42 (0.59, 3.40)	*0.3857 linear*
AHI≥15 (versus AHI=0)	3/14 (21.4)	4.50 (1.37, 14.77)	*0.7140 quadratic*	1.79 (0.44, 7.31)	*0.5676 quadratic*

Abbreviations: AHI = Apnea-Hypopnea Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) in early pregnancy, race, time from delivery to HHS cardiovascular assessment, and average oxygen saturation preceding sleep onset.

[2/] Including all apneas and hypopneas w/ ≥3% oxygen desaturation / hour

Supplemental Table S7b: Sensitivity Analysis Adjusting for Baseline Oxygen Saturation
Crude and Adjusted Risk Ratios[1/] for Metabolic Sydrome[2/] at 2-7 Years Postpartum
According to Apnea-Hypopnea Index (AHI)[3/] in Early and Mid-pregnancy
Among Women Without Preexisting Diabetes

AHI Characteristic	Metabolic Syndrome n/N (%)	Crude Risk Ratios		Adjusted Risk Ratios	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Early Pregnancy					
AHI<5 (referent)	260/1630 (16.0)	1.00	<.0001	1.00	0.2821
AHI≥5 (versus AHI<5)	32/69 (46.4)	2.91 (2.20, 3.84)		1.20 (0.87, 1.65)	
AHI=0 (referent)	43/383 (11.2)	1.00	<.0001	1.00	0.5878
0<AHI<5 (versus AHI=0)	217/1247 (17.4)	1.55 (1.14, 2.11)	*Trend tests:*	1.01 (0.75, 1.36)	*Trend tests:*
5≤AHI<15 (versus AHI=0)	29/63 (46.0)	4.10 (2.78, 6.05)	*0.1141 linear*	1.25 (0.82, 1.91)	*0.7816 linear*
AHI≥15 (versus AHI=0)	3/6 (50.0)	4.45 (1.91, 10.40)	*0.4084 quadratic*	0.80 (0.27, 2.41)	*0.3808 quadratic*
Mid-pregnancy					
AHI<5 (referent)	178/1292 (13.8)	1.00	<.0001	1.00	0.1210
AHI≥5 (versus AHI<5)	45/121 (37.2)	2.70 (2.06, 3.53)		1.29 (0.95, 1.75)	
AHI=0 (referent)	13/189 (6.9)	1.00	<.0001	1.00	0.1529
0<AHI<5 (versus AHI=0)	165/1103 (15.0)	2.17 (1.26, 3.74)	*Trend tests:*	1.39 (0.81, 2.39)	*Trend tests:*
5≤AHI<15 (versus AHI=0)	37/107 (34.6)	5.03 (2.80, 9.03)	*0.0053 linear*	1.67 (0.90, 3.11)	*0.0373 linear*
AHI≥15 (versus AHI=0)	8/14 (57.1)	8.31 (4.15, 16.62)	*0.4603 quadratic*	2.47 (1.14, 5.32)	*0.8857 quadratic*

Abbreviations: AHI = Apnea-Hypopnea Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) in early pregnancy, race, time from delivery to HHS cardiovascular assessment, and average oxygen saturation preceding sleep onset.

[2/] Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication.

[3/] Including all apneas and hypopneas w/ ≥3% oxygen desaturation / hour

Supplemental Table S8a: Sensitivity Analysis Adjusting for Baseline Oxygen Saturation
Crude and Adjusted Risk Ratios[1/] for Incident Hypertension at 2-7 Years Postpartum
According to Oxygen Desaturation Index (ODI)[2/] in Early and Mid-pregnancy
Among Women Without Baseline Hypertension

ODI Characteristic	Hypertension 2-7 Years After Index nuMoM2b Pregnancy	Crude Risk Ratios		Adjusted Risk Ratios	
	n/N (%)	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Early Pregnancy					
ODI<5 (referent)	82/1521 (5.4)	1.00	0.0048	1.00	0.1122
ODI≥5 (versus ODI<5)	24/194 (12.4)	2.29 (1.49, 3.53)		1.59 (0.95, 2.68)	
ODI=0 (referent)	5/141 (3.5)	1.00	0.0220	1.00	0.3471
0<ODI<5 (versus ODI=0)	77/1380 (5.6)	1.57 (0.65, 3.82)	*Trend tests:*	1.45 (0.58, 3.59)	*Trend tests:*
5≤ODI<15 (versus ODI=0)	21/174 (12.1)	3.40 (1.32, 8.80)	*0.1462 linear*	2.29 (0.80, 6.57)	*0.2856 linear*
ODI≥15 (versus ODI=0)	3/20 (15.0)	4.23 (1.09, 16.36)	*0.7345 quadratic*	2.27 (0.51, 10.16)	*0.5986 quadratic*
Mid-pregnancy					
ODI<5 (referent)	47/1094 (4.3)	1.00	<.0001	1.00	0.0008
ODI≥5 (versus ODI<5)	42/328 (12.8)	2.98 (2.00, 4.44)		2.35 (1.50, 3.69)	
ODI=0 (referent)	4/57 (7.0)	1.00	0.0002	1.00	0.0063
0<ODI<5 (versus ODI=0)	43/1037 (4.1)	0.59 (0.22, 1.59)	*Trend tests:*	0.48 (0.17, 1.34)	*Trend tests:*
5≤ODI<15 (versus ODI=0)	35/287 (12.2)	1.74 (0.64, 4.70)	*0.0605 linear*	1.11 (0.38, 3.29)	*0.3093 linear*
ODI≥15 (versus ODI=0)	7/41 (17.1)	2.43 (0.76, 7.77)	*0.2866 quadratic*	1.52 (0.41, 5.67)	*0.2042 quadratic*

Abbreviations: ODI = Oxygen Desaturation Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) in early pregnancy, race, time from delivery to HHS cardiovascular assessment, and average oxygen saturation preceding sleep onset.

[2/] Number of destaturations ≥3% per hour sleep

Supplemental Table S8b: Sensitivity Analysis Adjusting for Baseline Oxygen Saturation
Crude and Adjusted Risk Ratios[1/] for Metabolic Sydrome[2/] at 2-7 Years Postpartum
According to Oxygen Desaturation Index (ODI)[3/] in Early and Mid-pregnancy
Among Women Without Preexisting Diabetes

ODI Characteristic	Metabolic Syndrome n/N (%)	Crude Risk Ratios		Adjusted Risk Ratios	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Early Pregnancy					
ODI<5 (referent)	219/1505 (14.6)	1.00	<.0001	1.00	0.0826
ODI≥5 (versus ODI<5)	73/194 (37.6)	2.59 (2.08, 3.22)		1.27 (0.98, 1.64)	
ODI=0 (referent)	10/137 (7.3)	1.00	<.0001	1.00	0.1165
0<ODI<5 (versus ODI=0)	209/1368 (15.3)	2.09 (1.14, 3.85)	*Trend tests:*	1.44 (0.79, 2.62)	*Trend tests:*
5≤ODI<15 (versus ODI=0)	63/173 (36.4)	4.99 (2.66, 9.35)	*0.0021 linear*	1.87 (0.97, 3.60)	*0.3095 linear*
ODI≥15 (versus ODI=0)	10/21 (47.6)	6.52 (3.09, 13.76)	*0.1995 quadratic*	1.41 (0.62, 3.21)	*0.0851 quadratic*
Mid-pregnancy					
ODI<5 (referent)	121/1083 (11.2)	1.00	<.0001	1.00	0.0049
ODI≥5 (versus ODI<5)	102/330 (30.9)	2.77 (2.19, 3.49)		1.49 (1.14, 1.95)	
ODI=0 (referent)	3/54 (5.6)	1.00	<.0001	1.00	0.0111
0<ODI<5 (versus ODI=0)	118/1029 (11.5)	2.06 (0.68, 6.28)	*Trend tests:*	2.01 (0.52, 7.78)	*Trend tests:*
5≤ODI<15 (versus ODI=0)	82/286 (28.7)	5.16 (1.69, 15.74)	*<.0001 linear*	2.88 (0.74, 11.28)	*0.0067 linear*
ODI≥15 (versus ODI=0)	20/44 (45.5)	8.18 (2.60, 25.75)	*0.6269 quadratic*	3.77 (0.92, 15.51)	*0.4806 quadratic*

Abbreviations: ODI = Oxygen Desaturation Index; CI = confidence interval

[1/] Poisson regression models are used for the analyses with robust error covariance used to compute confidence intervals and to test for trends. P-values are based on likelihood ratio tests. Analyses are adjusted for age and BMI (linear and quadratic) in early pregnancy, race, time from delivery to HHS cardiovascular assessment, and average oxygen saturation preceding sleep onset.

[2/] Metabolic syndrome is defined based on the presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication.

[3/] Number of destaturations ≥3% per hour sleep