Maternal Weight, Snoring, and Hypertension: Potential Pathways of Associations

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BACKGROUND
Hypertensive disorders of pregnancy (HDP) are linked to excessive maternal weight and frequent snoring. However, pathways between maternal excessive weight, pregnancy-onset snoring, and HDP are only partially estimated. We examined and quantified the total and direct associations between excessive maternal weight and incident HDP and their indirect pathway through pregnancy-onset snoring.

METHODS
Third trimester pregnant women enrolled from prenatal clinics of a large tertiary medical center. Sleep data were collected through a questionnaire. Demographic and pregnancy information and first trimester maternal weight were abstracted from medical charts. After exclusion of women with prepregnancy hypertension and/or chronic snoring, causal mediation analysis was used to estimate the total and direct association between maternal weight and incident HDP and their indirect association through pregnancy-onset snoring. The proportion of the mediated association through pregnancy-onset snoring from the total association of maternal weight and HDP was also quantified.

RESULTS
After excluding those with chronic hypertension and/or snoring, the final sample included 1,333 pregnant women. In adjusted analysis, excessive maternal weight was directly associated with incident HDP; odds ratio (OR) = 1.87 (95% confidence interval (CI) 1.30, 2.70). Pregnancy-onset snoring significantly mediated the association between maternal weight and incident HDP; OR = 1.08 (95% CI 1.01, 1.17). The mediated pathway accounted for 15% of the total association between maternal weight and incident HDP.

CONCLUSIONS
Pregnancy-onset snoring mediates the association between maternal weight and incident HDP in women without prepregnancy snoring or hypertension. These findings demonstrate the relative contributions of excessive maternal weight and pregnancy-onset snoring to incident HDP.

Keywords: blood pressure; body mass index; gestational hypertension; habitual snoring; hypertension; hypertensive disorders of pregnancy; maternal obesity; pre-eclampsia; pregnancy snoring; sleep-disordered breathing.

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BACKGROUND

Hypertensive disorders of pregnancy (HDP) are a group of conditions marked by elevated blood pressure, systolic ≥140 mm Hg and diastolic ≥90 mm Hg, with or without proteinuria.[1] Chronic hypertension, gestational hypertension, and pre-eclampsia, collectively defined as HDP, complicate 5–10% of US pregnancies[2] and contribute to maternal and neonatal morbidity and mortality.[3,4]

Frequent or habitual snoring, defined as snoring at least 3 days/week, is the hallmark symptom of sleep-disordered breathing (SDB), a respiratory dysfunction with associated airway obstruction. Previously, frequent snoring has been linked to adverse pregnancy outcomes, including HDP, gestational diabetes mellitus, preterm birth, and small newborn size.[5–12] In particular, frequent snoring is associated with a 2-fold increased risk of HDP.[5,7,8,13,14] Among pregnant women, with chronic or incident snoring, the prevalence of gestational hypertension ranges from 2- to 3-fold compared with nonsnorers.[8,13] Conversely, pregnant women with hypertension have a much higher snoring prevalence compared with normotensive women.[15,16]

Obesity is an established risk factor for snoring in the general population.[17] Recent data suggest that more than two-thirds of reproductive-age women are overweight or obese[18] and that excessive maternal weight increases the risk of HDP.[19] It is plausible that excessive maternal weight may induce or exacerbate snoring that, in turn, increases the risk for HDP. Further, "bi-directional links" have been proposed between obesity and snoring[20,21] and snoring and

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hypertension.[22,23] Nonetheless, the reported bi-directionality in these associations from cross-sectional studies could mask their temporal aspect. In addition to limitations of small sample sizes and inadequate control for confounding, prior studies had near-universal adjustment for maternal weight in studies on snoring and HDP association rather than investigation of the potential role of pregnancy-onset snoring in the pathway between maternal weight and HDP.

To disentangle the complex associations of maternal snoring, excessive weight, and HDP, this study sought to (i) examine whether pregnancy-onset snoring mediates the temporal pathway between maternal weight and incident HDP and (ii) quantify the total and direct associations between maternal weight and incident HDP and their indirect pathway of association through pregnancy-onset snoring. We hypothesized that pregnancy-onset snoring mediates the association of maternal weight and incident HDP and that the total, direct, and indirect effects—through pregnancy-onset snoring—would be significant.

METHODS

Study population

Third trimester pregnant women receiving care at prenatal clinics of a large tertiary medical center were recruited to this prospective cohort study between March 2008 and December 2010. Women were eligible to be included in this study if they were ≥18 years old and ≥28 weeks pregnant with a single fetus. To account for temporality, we excluded women with chronic, prepregnancy hypertension, and/or chronic, prepregnancy snoring (Figure 1). After all exclusions, the final analytic sample included 1,333 pregnant women.

The study obtained approval from the Institutional Review Board.

Exposure: maternal weight

Maternal weight and height were recorded in medical charts at baseline prenatal care visit during the first trimester. We used these data to calculate body mass index (BMI) (kg/m^2) and then classify women into 2 groups by their baseline weight: (i) underweight or normal weight (BMI <25 kg/m^2) and (ii) overweight or obese (BMI ≥ 25 kg/m^2).

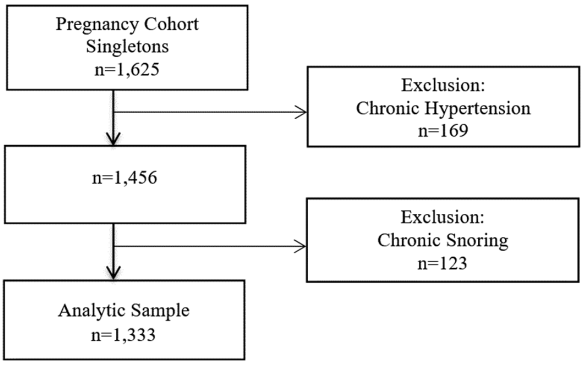

Figure 1. Flowchart of participants in the Sleep Pregnancy Cohort: 2008–2010.

Mediator: pregnancy-onset snoring

Snoring data were collected *via* a questionnaire administered to pregnant women with questions about the frequency of their snoring during pregnancy. Possible responses were "almost daily," "3–4 times per week," "1–2 times per week," "1–2 times per month," or "never." Women were defined as "snorers" if they reported snoring in pregnancy and "non-snorers" if they never or rarely snored. Furthermore, in a subsequent question, women reported the timing of their snoring onset, whether prepregnancy or pregnancy-induced. To examine the temporal relationship between pregnancy-onset snoring and gestational hypertension, women with prepregnancy snoring were excluded from the sample.

Outcome: HDP

Gestational hypertension and pre-eclampsia diagnoses were obtained from medical charts using the International Classification of Diseases, 9th edition (ICD-9). Blood pressure measures were collected from pregnant women receiving care at the University of Michigan prenatal clinics. During their prenatal care visit, pregnant women sat in a quiet room before their blood pressure was taken by trained medical assistants. In all women, blood pressure was measured once using the same protocol. However, if blood pressure reading was abnormal, the medical assistant repeated the measurement to ensure that the reading was valid. Women with a diagnosis of chronic, prepregnancy hypertension were excluded.

Covariates

We selected potential confounders for the exposure, mediator, and outcome, based on prior literature[24–27] and with the use of a directed acyclic graph,[28] a visual representation of the examined associations among maternal weight, pregnancy snoring, and HDP, in addition to their potential confounders (Figure 2).

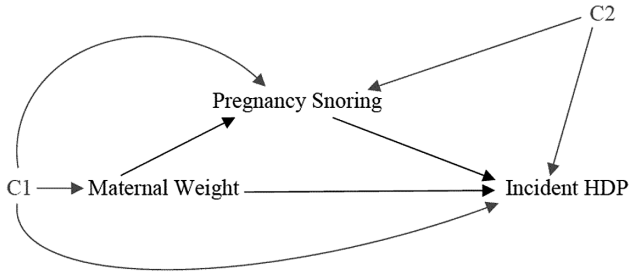

Figure 2. Causal diagram representing direct and indirect (mediated) pathways of associations between maternal weight, pregnancy snoring, and incident hypertensive disorders of pregnancy (HDP).

Maternal characteristics were abstracted from medical charts. Maternal age was analyzed as a categorical variable (<25, 26–29, 30–34, ≥35). Women were classified into 2 racial groups (White, non-White) and 4 education groups ("less than high school," "high school," "some college," and "Bachelor's degree or higher"). Parity, smoking, and history of HDP were binary variables (yes/no).

Statistical analysis

We conducted bivariate analysis to examine potential predictors of the mediator and the outcome, pregnancy-onset snoring, and incident HDP, respectively. In this bivariate analysis, we used a Poisson regression with a log link and robust error variance to calculate risk ratios and 95% confidence intervals (CIs) of incident HDP and pregnancy-onset snoring by respective, potential predictors.

To disentangle associations between excessive maternal weight, pregnancy-onset snoring, and incident HDP, we used a causal diagram to represent potential pathways to incident HDP (Figure 2). Based on the hypothesized causal diagram, we conducted causal mediation analysis using the Valeri and Vanderweele approach,[29] which allows computation of total and direct effects of maternal weight and incident HDP, in addition to their indirect effects through the pathway of pregnancy-onset snoring. We specified logistic regression model to account for the dichotomous exposure, mediator, and outcome (maternal weight, pregnancy-onset snoring, and incident HDP). In adjusted analysis, we concurrently controlled for all potential confounders on the pathways between exposure-outcome, exposure-mediator, and mediator-outcome (Figure 2). We calculated the total, direct, and indirect effects and the 95% CI for those effects. If the indirect effects were statistically significant at $P < 0.05$, we also computed the proportion of the total effect that was mediated by pregnancy-onset snoring. Finally, we tested for the presence of an interaction between maternal weight and pregnancy-onset snoring in relation to incident HDP. In the absence of significant interaction between exposure and mediator, we did not specify interaction in the mediation formula.

We performed sensitivity analysis to estimate and quantify the mediated pathway between maternal weight and incident HDP through frequent snoring. In this analysis, we created an exclusive group to frequent snorers and classified occasional snorers and nonsnorers as controls. All statistical analyses were performed in SAS 9.4 (Cary, NC).

RESULTS

Of the 1,625 pregnant women enrolled, 169 and 123 women with chronic hypertension and/or chronic snoring were excluded, resulting in a final sample with 1,333 pregnant women. In bivariate analyses, risk of incident HDP was associated with prepregnancy BMI, pregnancy-onset snoring, parity, and history of HDP (Table 1). Pregnancy-onset snoring was associated with maternal weight (Table 2).

In unadjusted regression models, excessive maternal weight (BMI ≥ 25) had nearly 2-fold direct and significant association with incident HDP. The magnitude of this association remained unchanged after adjusting for maternal age, race, education, parity, smoking, and history of HDP: OR = 1.87 (95% CI 1.30, 2.70).

Table 1. Risk of incident HDP by maternal characteristics

Maternal and pregnancy characteristics	*N*	HDP *N* (%)	HDP RR (95% CI)
HDP		140 (11)	—
Age			
<25	268	33 (12)	1.32 (0.83, 2.10)
25–29	344	38 (11)	1.19 (0.76, 1.86)
30–34	419	39 (9)	Reference
≥35	302	30 (10)	1.07 (0.66, 1.72)
BMI (categorical)			
<25	752	51 (7)	Reference
25–29.9	302	44 (15)	2.15 (1.44, 3.22)
≥30	269	42 (16)	2.30 (1.53, 3.46)
Pregnancy-onset snoring frequency			
Habitual/frequent	293	44 (15)	1.85 (1.26, 2.73)
Occasional/infrequent	281	31 (11)	1.36 (0.88, 2.10)
Nonsnorers	740	60 (8)	Reference
Gestational diabetes			
Yes	208	21 (10)	0.95 (0.60, 1.52)
No	1,125	119 (11)	Reference
Parity			
0	591	86 (15)	Reference
≥1	736	54 (7)	0.50 (0.36, 0.71)
Education			
Less than high school	107	11 (10)	1.24 (0.65, 2.37)
High school	265	35 (13)	1.60 (1.05, 2.44)
Some college	266	30 (11)	1.36 (0.87, 2.13)
Bachelor's degree or higher	665	55 (8)	Reference
Race/ethnicity			
White	961	107 (11)	Reference
Non-White	372	33 (9)	0.80 (0.54, 1.18)
Smokers			
Yes	146	20 (14)	1.36 (0.85, 2.19)
No	1185	119 (10)	Reference
History of HDP			
Yes	1272	122 (10)	3.18 (1.94, 5.22)
No	59	18 (31)	Reference

Abbreviations: BMI = body mass index; CI = confidence interval; HDP = hypertensive disorders of pregnancy; Non-White = African-American, Asian, or Hispanic; RR = relative risk.

Table 2. Risk of pregnancy-onset snoring by maternal characteristics

Maternal and pregnancy characteristics	*N*	Pregnancy-onset snoring	
		N (%)	RR (95% CI)
Pregnancy-onset snoring		574 (44)	—
Age			
<25	263	102 (39)	0.86 (0.39, 1.10)
25–29	337	134 (40)	0.88 (0.68, 1.10)
30–34	415	187 (45)	Reference
≥35	299	151 (33)	1.12 (0.68, 1.39)
BMI (categorical)			
<25	745	268 (36)	Reference
25–29.9	296	149 (50)	1.40 (1.15, 1.71)
≥30	264	156 (59)	1.64 (1.35, 2.00)
Gestational diabetes			
Yes	205	95 (46)	1.07 (0.86, 1.34)
No	1,109	479 (43)	Reference
Parity			
0	591	249 (42)	Reference
≥1	736	324 (44)	1.04 (0.88, 1.23)
Education			
Less than high school	105	42 (40)	0.93 (0.67, 1.29)
High school	259	114 (44)	1.03 (0.83, 1.28)
Some college	263	120 (46)	1.06 (0.86, 1.32)
Bachelor's degree or higher	658	282 (43)	Reference
Race/ethnicity			
White	947	421 (44)	Reference
Non-White	367	153 (42)	0.94 (0.78, 1.13)
Smokers			
Yes	141	68 (48)	1.12 (0.87, 1.44)
No	1,172	505 (43)	Reference

Abbreviations: BMI = body mass index; CI = confidence interval; Non-White = African-American, Asian, or Hispanic; RR = relative risk.

Pregnancy-onset snoring significantly mediated the pathway between maternal weight and incident HDP: adjusted OR = 1.08 (95% CI 1.01, 1.17). The total associations, i.e., combined direct and indirect associations, of maternal weight and incident HDP through pregnancy-onset snoring pathway were significant: OR = 2.03 (95% CI 1.41, 2.91). Pregnancy-onset snoring mediated 15% of the total association between maternal weight and incident HDP (Table 3).

The sensitivity analysis produced unchanged effect estimates; direct association between maternal weight and HDP (OR = 1.89, 95% CI 1.31, 2.72); indirect association between maternal weight and HDP, through frequent snoring (OR = 1.08, 95% CI 1.00, 1.16). Frequent, pregnancy-onset snoring mediated 14% of the total association between maternal weight and incident HDP.

DISCUSSION

In this large cohort of pregnant women without chronic hypertension and prepregnancy snoring, we have shown significant associations between maternal weight and incident HDP with direct and indirect pathways. Alternative to the direct association pathway from maternal weight to incident HDP, an indirect and significant pathway exists through pregnancy-onset snoring. Furthermore, if induced in pregnancy, maternal snoring—a key symptom of SDB—accounts for about 15% of the total association between maternal weight and incident HDP in pregnant women.

Prior reports have suggested a greater than a 2-fold association between snoring and HDP.[7,13,30] A meta-analysis, associated symptoms of SDB—mostly snoring—with HDP [pooled OR 3.11 (95% CI 2.28, 4.25)].[31] When objectively measured with polysomnography, SDB had a 2-fold association with HDP [pooled OR 2.25 (95% CI 1.13, 4.52)].[31] Similarly, BMI has been linked independently to frequent snoring[32] and also to HDP.[33,34] Frequent snoring and hypertension are known consequence of excessive weight, and hypertension has also been linked to frequent snoring. However, no study, thus far, has examined potential, alternative pathways—beyond direct associations—of maternal weight, pregnancy-onset snoring, and incident HDP. Rather, these studies examined "partial pathways" between (i) maternal weight and pregnancy snoring, (ii) maternal weight and gestational hypertension, or (iii) pregnancy snoring and gestational hypertension, with near-universal control for BMI.

In this study, we used causal mediation analysis to examine the direct association of maternal weight early in pregnancy and incident HDP and their indirect association through pregnancy-onset snoring in a restricted cohort of women without chronic hypertension or prepregnancy snoring. This approach accounts for the temporal aspect of these associations and their 3 potential pathways: (i) maternal weight and HDP, (ii) maternal weight and pregnancy-onset snoring, and (iii) pregnancy-onset snoring and incident HDP. Furthermore, with causal mediation analyses, we are able to quantify the fraction of each pathway—direct and indirect—from the total association. Estimation of the magnitude of these associations may inform and identify priorities for clinical interventions.

Excessive weight is one of the strongest risk factors for frequent snoring. As fat tissue in the neck accumulates, it may cause airway narrowing and resistance that increases the risk of airway obstruction during sleep.[35] Furthermore, excessive weight has also been linked to pre-eclampsia and gestational hypertension. Obesity is characterized with metabolic abnormalities, increased inflammation, and oxidative stress, each of these represents a potential pathway to HDP.[36,37] Similarly, frequent snoring may cause sleep fragmentation and intermittent hypoxia that, in turn, can lead to hypertension through pathways of increased sympathetic activity, oxidative stress, or activation of inflammatory processes.[30]

This large cohort study elucidated the associations among maternal weight, pregnancy-onset snoring, and incident

Table 3. Mediation by pregnancy-onset snoring of the association between maternal weight and HDP

Mediator	OR (95% CI)			Percentage of association mediated %
	Total association	Direct association	Indirect association through mediator	
Pregnancy snoring				
Unadjusted	2.07 (1.47, 2.89)	1.93 (1.37, 2.72)	1.07 (1.00, 1.15)	13
Adjusted[a]	2.03 (1.41, 2.91)	1.87 (1.30, 2.70)	1.08 (1.01, 1.17)	15

Abbreviations: BMI = body mass index; CI = confidence interval; HDP = hypertensive disorders of pregnancy; OR = odds ratio.
[a]Adjusted for maternal age, race, education, parity, smoking, and history of hypertension.

HDP by estimation and quantification of their total, direct, and indirect associations. In addition, we controlled for potential confounders in each of the pathways between maternal weight, pregnancy-onset snoring, and incident HDP. Furthermore, by excluding women with chronic, prepregnancy snoring, or hypertension, this study has provided a temporal perspective to its findings.

As a potential limitation, snoring frequency was self-reported through questionnaires and may have resulted in misclassification of some cases. However, as a key symptom of obstructive sleep apnea, subjective snoring measures in "nonpregnant" populations have been well validated against polysomnography[38,39] but not in "pregnant women". New data show that patient-reported snoring questions are strongly and reliably associated with apnea/hypopnea index (number of apneic events per hour of sleep, apnea/hypopnea index indicates the presence and severity of obstructive sleep apnea).[40] According to this study, patient-reported snoring has 73% sensitivity and 77% specificity with apnea/hypopnea index in pregnancy. Prior studies have shown that symptoms predict outcomes as well as objective measures,[41] and no study, thus far, has failed to associate snoring with objective measures of SDB from polysomnography. Furthermore, validation of SDB-screening tools in pregnancy has not provided significantly better measure of obstructive sleep apnea vs. symptoms alone. Most scales emphasize weight, which in pregnancy will be necessarily high, while some rely on male gender, irrelevant to a study of pregnant women. Finally, the use of questionnaires in this study is similar to symptom-based screening in clinical settings and is affordable and quick to administer to large-scale sample compared with an overnight sleep study.

Another limitation is related to the inclusion of pregnant women with frequent or occasional snoring in 1 study group. Ideally, we would classify women to 3 categories of "frequent snorers," "occasional snorers," and controls. However, current statistical packages for causal mediation are limited to analysis of binary or continuous mediators. Nonetheless, to estimate and quantify indirect pathway between maternal weight and HDP through frequent snoring, we performed sensitivity analysis by creating an exclusive group to frequent snorers and including occasional snorers and nonsnorers in the control group. This sensitivity analysis produced unchanged effect estimates, suggesting that frequent snoring drives the indirect association between maternal weight and incident HDP.

Finally, in addition to maternal weight in early pregnancy, gestational weight gain may also predict pregnancy-onset snoring and incident HDP. However, data on maternal weight gain were not available, and their link to incident HDP was beyond the aims of this study.

In conclusion, maternal weight is associated with incident HDP, directly and indirectly, through pregnancy-onset snoring in women without chronic, prepregnancy snoring, or hypertension. These findings demonstrate the role of maternal weight and pregnancy-onset snoring in incident HDP. Along with clinical recommendations related to excessive weight control in pregnancy and prior to conception, screening for maternal snoring may identify pregnant women at-risk for incident HDP.

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DISCLOSURE

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