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Obstructive Sleep Apnea and Severe Maternal-Infant Morbidity/Mortality in the United States, 1998-2009

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Study Objectives: A recent trend in increasing rates of severe maternal morbidity and mortality despite quality improvements has been noted. The goal of this study is to estimate the national prevalence of obstructive sleep apnea (OSA) in pregnant women and examine associations between OSA and pregnancy-related morbidities, including in-hospital maternal mortality.

Design: A retrospective, cross-sectional analysis.

Setting: A nationally representative sample of maternal hospital discharges from 1998-2009.

Patients or Participants: The analytic sample included 55,781,965 pregnancy-related inpatient hospital discharges.

Interventions: N/A.

Measurements and Results: The Nationwide Inpatient Sample (NIS) database was used to identify hospital stays for women who were pregnant or gave birth. Among these women, we determined length of hospital stay, in-hospital mortality, and used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify OSA and other outcome measures. Multivariable logistic regression modeling was used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the associations between OSA and each outcome. The overall rate of OSA was 3.0 per 10,000; however, the rate climbed substantially from 0.7 in 1998 to 7.3 in 2009, with an average annual increase of 24%. After controlling for obesity and other potential confounders, OSA was associated with increased odds of pregnancy-related morbidities including preeclampsia (OR, 2.5; 95% CI, 2.2–2.9), eclampsia (OR, 5.4; 95% CI, 3.3–8.9), cardiomyopathy (OR, 9.0; 95% CI, 7.5–10.9), and pulmonary embolism (OR, 4.5; 95% CI, 2.3–8.9). Women with OSA experienced a more than fivefold increased odds of in-hospital mortality (95% CI, 2.4–11.5). The adverse effects of OSA on selected outcomes were exacerbated by obesity.

Conclusions: Obstructive sleep apnea is associated with severe maternal morbidity, cardiovascular morbidity, and in-hospital death. Targeted interventions may improve pregnancy outcomes in this group.

Keywords: maternal mortality, obstructive sleep apnea, preeclampsia, pregnancy, pulmonary embolus

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INTRODUCTION

In developed countries, recent trends indicate an increase in severe maternal morbidity and, to a lesser extent, maternal mortality.[1-4] The obesity epidemic has garnered considerable attention and has been implicated as a potential cause of this increased morbidity.[5,6] Obesity is a risk factor for the development or exacerbation of some of the most common causes of maternal mortality in the United States, including hemorrhage, hypertensive disorders of pregnancy, cardiovascular conditions, cardiomyopathy, infection, and thrombotic pulmonary embolism.[4,7-9]

One of the proposed pathways linking maternal obesity to poor pregnancy outcomes is through obstructive sleep apnea (OSA), a condition characterized by recurrent episodes of partial or complete airway obstruction, nocturnal hypoxemia, and sleep fragmentation.[10,11] Cardiovascular morbidity, all-cause mortality, and a diminished quality of life are associated with OSA, which is an increasingly common condition.[12-14] The prevalence of OSA among reproductive age women is 0.7–7%, rises to 11–20% among pregnant women, with the highest prevalence observed among obese gravidas.[15-19] Despite increasing trends and potential deleterious effects, the effects of OSA on pregnancy are underinvestigated. Smaller cross-sectional and prospective studies have reported associations between OSA and adverse pregnancy outcomes such as preeclampsia, fetal growth restriction, and preterm delivery, which are similar to the initial published case reports.[19-21] The largest of the most recent studies, a large population-based study from Taiwan, confirmed the association between OSA and pregnancy complications including gestational diabetes, gestational hypertension, and preeclampsia.[21] However, only one study commented on severe maternal morbidity. This study, a prospective study of 175 obese women who underwent portable polysomnography, found a higher-than-expected occurrence of severe morbidity, including maternal death and venous thromboembolism, among the obese women in the cohort.[19] However, the small size of the study limited the ability to evaluate the effect of OSA on less common morbidities.

Therefore, the primary aims of this study were to leverage a large, nationally representative database to estimate the prevalence of OSA among pregnant women in the United States over an 11-y period, and to examine associations between OSA and

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severe clinical and pregnancy-related morbidities, including in-hospital mortality. Considering the common co-occurrence of OSA and obesity, a secondary objective was to assess whether clinically diagnosed maternal obesity modified the effect of OSA on each outcome. We hypothesized that the joint effect of OSA and obesity on pregnancy-related outcomes would be worse than the effect of OSA in the absence of obesity.

METHODS

Study Design and Data Source

We conducted an analysis of pregnancy-related hospital discharges using 1998-2009 annual data from the Nationwide Inpatient Sample (NIS), the largest all-payer, publicly available inpatient database in the United States.[22] The NIS is part of a family of administrative databases developed as part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). Each year the NIS stratifies all non-federal community hospitals from participating states into groups based on five major hospital characteristics: rural/urban location, number of beds, geographic region, teaching status, and ownership. Within each stratum, a 20% sample of hospitals is drawn using a systematic random sampling technique.[22] HCUP includes hospital strata and discharge-level sampling weights with the database so that national frequency and prevalence estimates can be generated while accounting for the complex sampling design of the NIS. In 2010, the NIS had data from 1,051 hospitals in 45 states.

Identifying Maternal Cases and Clinical Conditions

In this study, we were interested in NIS records representing hospital stays for women who were pregnant or gave birth. To identify these discharges, we used a variable (NEOMAT) that HCUP includes with the NIS databases. This variable is used by HCUP to identify maternal and/or neonatal records on the basis of specific International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes.[23] The NIS databases contain ICD-9-CM codes for a patient's principal diagnosis and up to 14 secondary diagnoses (up to 24 beginning in 2009). Maternal cases were those with one or more of the following diagnosis (630–677, 792.3, 796.5, V22.0–V24.2, V27.0–V28.2, V28.6, V61.6–V61.7, V65.11, V72.42) or procedure (72.0–75.37, 75.4–75.99) codes[24] documented during their hospital stay. Among these women, we also used ICD-9-CM codes to identify the primary exposure, OSA, as well as a number of maternal and fetal outcomes including but not limited to gestational diabetes, gestational hypertension, preeclampsia, eclampsia, cardiomyopathy, early-onset delivery, poor fetal growth, and stillbirth. The complete list is presented in Table S1 (supplemental material). We also considered extended length of stay (defined as > 95th percentile, or > 5 days), and in-hospital mortality.

Demographics and Covariates

The NIS also collects information on a limited number of sociodemographic and hospital characteristics. Maternal age in years was classified into five categories: < 20, 20-24, 25-29, 30-34, and ≥ 35 y. Maternal race-ethnicity was first determined by self-reported ethnicity (Hispanic or non-Hispanic [NH]), with the NH group further subdivided by race (white, black, or other). Racial and ethnic disparities in medical comorbidities, severe maternal morbidity, and mortality have been consistently noted.[7,25-27] We, therefore, chose to report these data because they represent a significant confounding variable.[7] A proxy for socioeconomic status, we considered each woman's household income and her primary insurance type. Relative median household income was estimated using the documented ZIP code of residence, and ranked into quartiles by HCUP. We grouped primary payer for each hospital stay into government (Medicare/Medicaid), private (commercial carriers and private health maintenance organizations (HMOs) and preferred provider organization (PPOs), and other sources (including self-pay and no charge). We also considered several hospital characteristics including teaching status (teaching, in which the ratio of full-time equivalent interns and residents to nonnursing home beds is ≥ 0.25, vs. nonteaching), location (urban vs. rural), and region in the United States (Northeast, Midwest, South, or West). We also identified a number of prepregnancy and pregnancy-associated medical comorbidities that are associated with OSA and known or suspected risk factors for the clinical outcomes under study. These conditions were identified using ICD-9-CM codes documented during each hospital stay and include coronary heart disease, chronic renal disease, anemia, lipid metabolism (e.g., hyperlipidemia), hypothyroidism, and disorders of the adrenal glands (Table S1).

Data Analysis

Descriptive statistics were used to calculate the frequency and prevalence of OSA among pregnancy-related discharges. Because national frequency and rate estimates were desired, the discharges in the analyses were weighted to account for the complex sampling design of the NIS. We also calculated the distribution of sociodemographic, perinatal, behavioral, and hospital characteristics, and the rate of selected maternal-fetal-infant outcomes (per 1,000 pregnancy-related discharges) by OSA status.

Using the SURVEYLOGISTIC procedure in SAS (SAS software, version 9.3 (SAS Institute, Inc., Cary, NC), we constructed logistic regression models to calculate odds ratios (OR) and 95% confidence intervals (CI) for the associations between OSA and each outcome. For each association of interest, we constructed a crude (unadjusted) model and three multivariable (adjusted) models. We selected model covariates following a review of the literature, an assessment of biologic plausibility, and based on bivariate analyses. In the first multivariable model, we selected maternal age and race/ethnicity, household income, multiple gestation, tobacco, alcohol, and drug use, primary payer, and rural/urban status to control for variation in sociodemographic, perinatal, behavioral, and hospital-associated characteristics among the OSA groups. In the second model, we added clinically diagnosed obesity (based on selected ICD-9-CM codes, Table S1), a strong comorbidity, and in the third model we also included a composite variable coding for the aforementioned prepregnancy and pregnancy-associated comorbidities, to isolate the independent effect of OSA. In the final model, we assessed the joint effects of OSA and obesity on each outcome by including an interaction term into the model. Trends in rates of OSA and obesity during the study period were assessed using

joinpoint regression. Joinpoint regression begins by modeling annual trend data by fitting a straight line (i.e., zero joinpoints).[28] Using a Monte Carlo permutation test, it then examines whether adding one joinpoint is statistically significant, and if so, incorporates it into the model. This process is repeated until a model of best fit is specified with an optimal number of joinpoints. Each joinpoint in the final model corresponds to a significant increase or decrease in the trend and an annual percent change is calculated to describe how the rate changes within each time interval. The model also estimates the average annual percent change, which describes the trend over the entire study period, even when there are significant changes in the trend over time. Because the NIS sampling design has changed, we used the NIS-Trends files, supplied by HCUP, that consistently define trend weights and data elements over time.[29]

Statistical analyses were performed with SAS software, version 9.3 and the Joinpoint Regression Program (Joinpoint Regression Program, Version 4.0.1; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute).[30] This study has been approved by the institutional review board approval at the University of South Florida.

RESULTS

Among an estimated 55 million pregnancy-related discharges in the United States from 1998-2009, OSA was diagnosed at a rate of 3.0 (95% CI, 2.8–3.2) per 10,000 population. Over this time, the prevalence of OSA in the study population rose dramatically. In 1998, the rate was 0.7 per 10,000 population, and by 2009, it had increased tenfold to 7.3 per 10,000 population, with an average annual increase of 24.4% (95% CI, 22.1–26.8%).

Table 1 presents the distribution of maternal sociodemographic, behavioral, and perinatal characteristics by OSA status. Women in whom OSA had been diagnosed were more likely than other women to be older, in the lowest quartile of household income, have government-funded insurance (Medicare/Medicaid), and use tobacco, alcohol, and illicit drugs during pregnancy. Women with OSA also were more likely to be NH-black (versus NH-white) and have had a previous cesarean section. As hypothesized, women with OSA during pregnancy were more likely to experience adverse clinical conditions and pregnancy-related complications than women with no OSA diagnosis. After adjusting for known/suspected sociodemographic and clinical confounders available in the NIS database, OSA-related discharges had up to a ninefold increased odds of the outcomes under study (Table 2). The strongest associations with clinical conditions were observed for cardiomyopathy (adjusted OR, 9.0; 95% CI, 7.5–10.9), congestive heart failure (adjusted OR, 8.9; 95% CI, 7.5–10.7), and pulmonary edema (adjusted OR, 7.5; 95% CI, 4.6–12.2). Among pregnancy-related factors, OSA was associated with an adjusted OR of 5.4 (95% CI, 3.3-8.9) for eclampsia

Table 1—Distribution of maternal sociodemographic, perinatal, behavioral, and hospital characteristics among pregnancy-related discharges, by obstructive sleep apnea status, Healthcare Cost and Utilization Project - Nationwide Inpatient Sample, 1998-2009

Characteristic	N[a]	OSA %	No OSA %	OR (95% CI)
Overall	55,781,965	100	100	n/a
Maternal age (y)				
< 20	6,197,071	2.7	11.1	0.31 (0.25–0.38)
20 - 24	13,822,023	10.5	24. 8	0.53 (0.47–0.61)
25 - 29	15,001,057	21.3	26. 9	Reference
30 - 34	12,797,406	30.8	22.9	1.70 (1.54–1.88)
≥ 35	7,921,464	34.3	14.2	3.06 (2.76–3.39)
Missing/unknown	42,944	0.5	0.1	7.44 (3.73–14.83)
Maternal race				
White	22,047,327	39.9	39.5	Reference
Black	6,025,913	23.8	10.8	2.18 (1.94–2.45)
Hispanic	9,444,177	7.1	16.9	0.41 (0.34–0.50)
Other	4,079,383	2.8	7.3	0.38 (0.30–0.47)
Missing/unknown	14,185,165	26.4	25.4	1.03 (0.88–1.21)
Previous cesarean section[b]	7,076,933	20.3	12.7	1.76 (1.60–1.93)
Multiple gestation/birth[b]	1,097,921	2.9	2.0	1.50 (1.20–1.88)
Tobacco use[b]	2,009,092	9.0	3.6	2.66 (2.33–3.02)
Alcohol use[b]	96,629	0.4	0.2	2.27 (1.27–4.04)
Drug use[b]	730,909	2.5	1.3	1.94 (1.56–2.41)
Hospital region				
Northeast	9,516,239	15.9	17.1	1.24 (0.97–1.59)
Midwest	12,032,900	29.2	21.6	1.81 (1.46–2.24)
South	20,796,015	36.9	37.3	1.32 (1.09 –1.60)
West	13,436,811	18.0	24.1	Reference
Hospital location				
Rural	6,877,937	7.1	12.4	Reference
Urban	48,763,827	92.9	87.6	1.84 (1.48–2.28)
Hospital teaching status				
Nonteaching	29,501,465	37.8	53.0	Reference
Teaching	26,140,299	62.2	47.0	1.85 (1.62–2.12)
Hospital bed size				
Small	6,100,955	8.0	11.0	0.89 (0.67–1.19)
Medium	14,821,822	21.7	26.6	Reference
Large	34,718,987	70.3	62.4	1.38 (1.18–1.62)
Household income				
Lowest quartile	14,617,169	31.0	26.2	1.48 (1.29–1.71)
Second quartile	14,070,584	25.9	25.2	1.29 (1.13–1.46)
Third quartile	13,294,169	22.8	23.8	1.20 (1.05–1.36)
Highest quartile	12,830,659	18.4	23.0	Reference
Missing/unknown	969,383	2.0	1.7	1.46 (1.09–1.97)
Primary payer				
Medicare/Medicaid	22,249,834	44.4	39.9	1.16 (1.06–1.28)
Private	29,701,613	51.1	53.2	Reference
Other	3,830,518	4.5	6.9	0.68 (0.55–0.85)

[a]Weighted to estimate national frequency; sum of all groups may not add up to the total due to missing data. [b]Reference group is represented by the absence of the condition/characteristic. CI, confidence interval; OR, odds ratio; OSA, obstructive sleep apnea.

Table 2—Outcome rates, adjusted odds ratios, and 95% confidence intervals for the association between obstructive sleep apnea and maternal-infant morbidity and mortality, Healthcare Cost and Utilization Project - Nationwide Inpatient Sample, 1998-2009

	Rate[a]		OR (95% CI)			
Outcomes	**OSA**	**No OSA**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**	**Model 4[e]**
Maternal, pregnancy-related						
Cesarean section[f]	430.51	251.28	2.26 (2.09–2.43)	2.05 (1.87–2.24)	1.29 (1.17–1.42)	1.12 (1.01–1.23)
Gestational diabetes[g]	191.29	45.08	5.03 (4.50–5.62)	3.85 (3.43–4.31)	2.02 (1.79–2.28)	1.89 (1.67–2.14)
Gestational hypertension[h]	65.57	28.36	2.41 (2.04–2.85)	2.35 (1.99–2.77)	1.31 (1.11–1.56)	1.28 (1.08–1.52)
Preeclampsia	133.44	32.74	4.58 (4.05–5.18)	4.44 (3.92–5.03)	2.67 (2.35–3.05)	2.50 (2.19–2.85)
Eclampsia	7.67	1.03	7.56 (4.64–12.32)	7.99 (4.88–13.06)	5.89 (3.58–9.68)	5.42 (3.29–8.92)
Postoperative wound	31.29	4.97	6.47 (5.28–7.93)	5.07 (4.13–6.21)	2.45 (1.98–3.02)	1.89 (1.53–2.34)
Hospital stay > 5 days[i]	189.35	30.07	7.54 (6.85–8.29)	6.75 (6.14–7.41)	4.30 (3.90–4.75)	3.06 (2.76–3.40)
Maternal, clinical conditions						
Acute renal failure	6.44	0.52	12.55 (7.86–20.04)	8.25 (5.16–13.18)	4.90 (3.01–7.98)	2.73 (1.69–4.41)
Pulmonary edema	6.02	0.25	23.85 (15.26–37.28)	18.26 (11.62–28.71)	11.43 (7.00–18.68)	7.50 (4.63–12.15)
Pulmonary embolism and infarction	2.66	0.11	25.46 (13.08–49.55)	16.65 (8.50–32.59)	6.07 (3.04–12.13)	4.47 (2.25–8.88)
Congestive heart failure	64.22	1.01	68.07 (57.52–80.56)	33.41 (28.22–39.56)	13.60 (11.31–16.35)	8.94 (7.45–10.73)
Cardiomyopathy(includes peripartum)	56.42	0.98	61.41 (51.81–72.80)	30.92 (25.96–36.81)	13.16 (10.88–15.91)	9.01 (7.47–10.87)
Stroke	1.22	0.14	8.77 (3.27–23.55)	5.37 (1.99–14.48)	4.24 (1.54–11.71)	2.93 (1.07–8.04)
In-hospital mortality	2.47	0.13	18.41 (8.56–39.61)	11.22 (5.21–24.18)	7.67 (3.50–16.85)	5.28 (2.42–11.53)
Fetal/infant						
Early-onset delivery	101.15	65.33	1.62 (1.43–1.84)	1.40 (1.24–1.61)	1.32 (1.16–1.50)	1.20 (1.06–1.37)
Poor fetal growth	21.88	15.92	1.39 (1.10–1.74)	1.26 (1.01–1.59)	1.28 (1.02–1.62)	1.21 (0.96–1.53)
Stillbirth	8.05	6.29	1.28 (0.84–1.95)	1.04 (0.68–1.58)	1.07 (0.70–1.62)	1.01 (0.66–1.53)

[a]Per 1,000 pregnancy-related discharges. [b]Unadjusted model with the presence of the condition as the outcome, OSA status as the exposure ("No OSA" is the reference group). [c]Model 1 + adjustment for maternal age; race/ethnicity; household income; multiple birth; tobacco, alcohol, and drug use; primary payer; and rural/urban status. [d]Model 2 + additional adjustment for maternal obesity. [e]Model 3 + additional adjustment for clinical comorbidities (coronary heart disease, anemia, hyperlipidemia, hypothyroidism, disorders of the adrenal gland, prepregnancy diabetes, and prepregnancy hypertension). [f]Additional adjustment for previous cesarean section in Models 2-4. [g]All models exclude rather than control for women with prepregnancy diabetes. [h]All models exclude rather than control for women with prepregnancy hypertension. [i]Additional adjustment for discharge disposition status in Models 2-4. CI, confidence interval; OR, odds ratio; OSA, obstructive sleep apnea.

and 2.5 (95% CI, 2.2-2.9) for pre-eclampsia. OSA was also associated with an increased likelihood of gestational diabetes (adjusted OR, 1.9; 95% CI, 1.7–2.1) and gestational hypertension (adjusted OR, 1.3; 95% CI, 1.1–1.5), even after adjusting for clinically diagnosed obesity and common comorbidities.

Pregnant women with an OSA diagnosis were three times as likely as women without an OSA diagnosis to have an extended length of stay (> 5 days) in the hospital. During this time, women with OSA had moderately increased odds of early-onset delivery (adjusted odds ratio, 1.2; 95% CI, 1.1–1.4); however, we did not find any statistically significant increase in the likelihood of poor fetal growth or stillbirth. The most remarkable finding was the association between OSA and maternal mortality. Compared with women without OSA, women with OSA had approximately fivefold higher odds of dying prior to discharge from the hospital, even after adjusting for serious cardiovascular, renal, and metabolic conditions that are known to affect mortality. The estimated 24% annual increase in OSA rates during the study period was mirrored by an average 20% annual increase in clinically diagnosed obesity rates (data not shown). Table 3 presents the results of the analysis for the joint effect of obesity and OSA on severe maternal-infant morbidity/mortality. With the exceptions of cesarean delivery, gestational hypertension, and stillbirth, the adjusted OR of any severe maternal morbidity and mortality were higher among women with OSA than without OSA, regardless of obesity status. Furthermore, the associations between OSA and outcomes, particularly preeclampsia and severe cardiovascular morbidities (congestive heart failure and cardiomyopathy), were stronger in women with comorbid obesity than in women without comorbid obesity. However, the associations between OSA and stroke, pulmonary embolism, acute renal failure, and in-hospital mortality were not significantly increased by a joint diagnosis of obesity.

DISCUSSION

In this study, we found that, in the United States from 1998-2009, the rate of OSA among pregnancy-related discharges increased significantly, and coincided with the rise in obesity rates. We observed strong associations between OSA and increased likelihood not only of morbidities that have an adverse effect on pregnancy outcomes, including preeclampsia, eclampsia, and early-onset delivery, but also of maternal mortality. These associations persisted even after statistical adjustment for potential confounders including clinically diagnosed obesity.

The findings of this investigation are consistent with other studies reporting a higher prevalence of chronic cardiovascular and metabolic medical conditions in subjects with OSA.[19,31] These women are at higher risk of gestational diabetes and hypertensive disorders complicating pregnancy, and are more likely to undergo cesarean delivery.[31] These events/conditions provide a basis for increased severe maternal and infant morbidity and an increased likelihood of maternal death.[4,32,33] There are plausible pathophysiological mechanisms by which OSA can lead to maternal morbidity. OSA is associated with

Table 3—Adjusted odds ratios[a] and 95% confidence intervals for the joint effect of obstructive sleep apnea and obesity on selected clinical outcomes, Healthcare Cost and Utilization Project - Nationwide Inpatient Sample, 1998-2009

	OSA		No OSA		
Outcomes	**With obesity OR (95% CI)**	**Without obesity OR (95% CI)**	**With obesity OR (95% CI)**	**Without obesity OR (95% CI)**	**P value[b]**
Maternal, pregnancy-related					
Cesarean section[c]	1.68 (1.47–1.92)	1.81 (1.62–2.02)	2.60 (2.50–2.69)	Reference	< 0.001
Gestational diabetes[d]	4.13 (3.54–4.82)	3.35 (2.90–3.88)	3.60 (3.48–3.73)	Reference	< 0.001
Gestational hypertension[e]	2.83 (2.24–3.58)	2.01 (1.58–2.56)	3.21 (3.10–3.33)	Reference	< 0.001
Preeclampsia[e]	5.32 (4.43–6.37)	3.41 (2.84–4.10)	2.81 (2.71–2.92)	Reference	< 0.001
Eclampsia[f]	2.93 (0.68–12.66)	10.41 (6.20–17.50)	1.84 (1.62–2.09)	Reference	0.02
Postoperative wound	4.27 (3.25–5.61)	3.03 (2.23–4.12)	2.96 (2.79–3.13)	Reference	< 0.001
Hospital stay > 5 days[g]	3.07 (2.59–3.63)	5.05 (4.47–5.70)	1.86 (1.78–1.95)	Reference	< 0.001
Maternal, clinical conditions					
Acute renal failure	2.77 (1.47–5.23)	3.62 (2.05–6.39)	1.33 (1.16–1.52)	Reference	0.15
Pulmonary edema	5.09 (2.12–12.23)	14.41 (8.72–23.83)	1.72 (1.41–2.10)	Reference	0.002
Pulmonary embolism and infarction	14.06 (6.10–32.40)	8.07 (2.61–24.92)	4.01 (3.21–5.01)	Reference	0.25
Congestive heart failure	19.15 (15.27–24.00)	15.46 (12.16–19.64)	3.02 (2.77–3.29)	Reference	< 0.001
Cardiomyopathy(includes peripartum)	19.12 (15.12–24.18)	15.86 (12.45–20.19)	3.01 (2.76–3.29)	Reference	< 0.001
Stroke	3.02 (0.75–12.16)	3.29 (0.82–13.27)	1.16 (0.85–1.57)	Reference	0.82
In-hospital mortality	7.84 (3.28–18.74)	5.07 (1.63–15.77)	1.44 (1.08–1.93)	Reference	0.91
Fetal/infant					
Early-onset delivery	1.19 (0.98–1.44)	1.30 (1.10–1.53)	1.08 (1.04–1.12)	Reference	0.16
Poor fetal growth	1.02 (0.69–1.51)	1.31 (0.96–1.78)	0.93 (0.88–1.00)	Reference	0.51
Stillbirth	0.62 (0.31–1.25)	1.26 (0.74–2.13)	0.90 (0.85–0.96)	Reference	0.19

[a]Model with the presence of the condition as the outcome, joint OSA-obesity status (OSA and obesity, OSA without obesity, obesity without OSA, and neither OSA nor obesity) as the exposure, adjusted for maternal age; race/ethnicity; household income; multiple birth; tobacco, alcohol, and drug use; primary payer rural/urban status; and clinical comorbidities including coronary heart disease, anemia, hyperlipidemia, hypothyroidism, disorders of the adrenal gland, prepregnancy diabetes, and prepregnancy hypertension ("no OSA, no obesity" is the reference group). [b]P value representing statistical interaction term between OSA and obesity. [c]Additional adjustment for previous cesarean section in model. [d]Model excludes rather than controls for women with prepregnancy diabetes. [e]Model excludes rather than controls for women with prepregnancy hypertension. [f]Additional adjustment for discharge disposition status in model. CI, confidence interval; OR, odds ratio; OSA, obstructive sleep apnea.

increased inflammation, sympathetic traffic, insulin resistance, and oxidative stress.[34,35] Repetitive forced inspiration against a closed upper airway generates a negative intrathoracic pressure gradient which, when transmitted to the heart, can result in significant cardiac dysfunction.[13,14,18,36] Over time, the recurrent hemodynamic stress, hypoxemia, and adrenergic activation lead to chronic systemic inflammation and oxidative vascular injury. These events may have a direct effect on maternal vasculature, resulting in increased endothelial injury and cardiovascular disease. These changes, paired with the physiological demands of pregnancy, increase the risk of morbidity for the pregnant patient. Adverse fetal outcomes may be secondary to worsening maternal health or may be a direct consequence of OSA's effect on placental function via similar pathophysiological mechanisms.

To our knowledge, this is the largest study in the United States to assess the temporal trends in OSA diagnoses during pregnancy, and the only one to analyze the associated perinatal morbidity using nationally representative data. There has been increasing attention paid to the putative adverse effects of sleep disorders on pregnancy. Early literature on the effects of OSA on pregnancy outcomes were limited to case reports and small cohorts.[31] Larger studies have analyzed associations using symptoms of OSA such as habitual snoring or excessive daytime sleepiness instead of a clinical diagnosis of OSA.[36,37] The largest study in the literature used a population-based cohort of 759 Chinese women with confirmed OSA and a comparative group of women without the diagnosis, and the authors reported an increased risk of gestational hypertension (OR, 3.2; 95% CI, 2.1–4.7) and preeclampsia (OR, 1.6; 95% CI, 2.2–11.3) among women with OSA. In that study, OSA also was associated with an increased risk of small-for-gestational age infants.[21] Several small, prospective, observational cohort studies used unattended sleep recordings to identify OSA. Those studies reported significant associations between OSA and preeclampsia, but they were statistically underpowered to evaluate certain severe maternal or fetal outcomes.[19,38,39] The findings of this study support some of that earlier work, but significantly extends the literature by analyzing less common, but clinically relevant (and potentially devastating) outcomes such as eclampsia, stillbirth, and most importantly, maternal mortality.

The magnitude of the observed associations between OSA and grave cardiovascular disease outcomes is significant when examining trends in maternal mortality. Although the causes of maternal mortality have remained the same, there has been a noted increase in cardiovascular disease as a underlying cause of maternal deaths.[4] In our study, the association of cardiovascular disease with OSA was magnified by the presence of obesity. Therefore, in addition to OSA being associated with

maternal mortality, it was also associated with cardiovascular disease, a significant contributor to severe maternal morbidity and mortality. If confirmed, these findings may have significant implications for the prenatal and intrapartum care of those affected with OSA as we continue to strive for safer deliveries, and ultimately, healthy mothers and babies.

Among fetal outcomes, OSA was associated with early-onset delivery, but not fetal growth restriction or stillbirth. The NIS database does not have a link between maternal and infant birth/delivery hospitalizations, which precludes further examination of the etiology for preterm birth and other infant outcomes. However, this mirrors findings previously observed and may be related to medically indicated preterm birth related to comorbid conditions or pregnancy complications.[31] The presence of these conditions would predispose them to medically indicated preterm birth from preeclampsia or suspected fetal compromise.[40]

Strengths and Limitations

The results of this study should be considered in light of several noteworthy limitations. Despite the extensive use of the NIS and other HCUP databases to estimate national prevalence rates of conditions and to investigate potential exposure-outcome associations, the identification of most conditions still relied exclusively on ICD-9-CM codes. As such, these administrative data are subject to errors in coding, which increase false-positive and false-negative diagnoses. For example, the prevalence of obesity in this study was extremely low (1.5%) in comparison with published literature that defines obesity using prepregnancy body mass index. Although cases of mild to moderate obesity were likely misclassified because of this finding, the use of the ICD-9-CM code allowed us to control for and investigate a more severe form of clinically diagnosed obesity that has a significant potential to be associated with OSA and to affect pregnancy outcomes.[41] Also, we expect measurement error associated with covariates included in our models because we used ICD-9-CM codes in hospital records to identify clinical comorbidities (e.g., coronary heart disease, anemia, chronic renal disease) as well as risky behaviors during pregnancy (use of tobacco, alcohol, and drugs). Differential misclassification may exist if knowledge of a woman's OSA status results in a more thorough clinical assessment and documentation of conditions and behaviors in the medical record, relative to women without OSA. However, because these factors are most often positively associated with both OSA and the outcomes investigated in this study, overdiagnosis of behaviors and comorbidities among women with OSA would serve to bias estimates conservatively toward the null in multivariable analyses.

A related concern when relying exclusively on ICD-9-CM codes is that they are updated annually and, thus, change over time. For example, some codes included in the diagnostic definitions for OSA (e.g., 327.23) and obesity (e.g., V85) were introduced in the middle of the study period (October 2005). To assess any effect of differential diagnoses over time on the observed associations, we performed a sensitivity analysis that was restricted to 2006-2009 data during which coding for important study variables was more consistent. Although some measures of effect were reduced slightly, there were no appreciable differences from the analysis on the complete 1998-2009 dataset.

Another limitation relates to the collection of race-ethnicity data in the NIS. Not all states report race-ethnicity data, and there is wide variation in reporting for those that do. Thus, although HCUP attempts to standardize state-specific reports into a single race-ethnicity variable, we were still missing race-ethnicity for one fourth of the study population. Although racial-ethnic disparities were not considered in this study, one's ability to control for the potential confounding effects of maternal race-ethnicity on the OSA-outcome associations was limited. Finally, it is possible that some of the increased prevalence of OSA among pregnancy-related hospitalizations is attributable to heightened clinician awareness of the OSA as opposed to a genuine increasing trend of the magnitude we observed. Despite these limitations, common to nearly every study using HCUP data, the large size and representativeness of the NIS database provided us with the ability to generate national estimates for the frequency and prevalence of OSA among pregnancy-related discharges. We also had the statistical power to evaluate uncommon pregnancy outcomes as well as assess effect modification between OSA and obesity.

CONCLUSIONS

The findings of this study reveal a dramatic increase in a condition that is tied to significant maternal morbidity and mortality, and that also may be detrimental to the developing fetus. The morbidity associated with OSA among its delivery-related hospital discharges implicates OSA as a potential factor in maternal and neonatal health, independently of morbid obesity. Treatment of obesity may potentially decrease this morbidity while also contributing to improvement in OSA-related morbidity. As the pregnant population becomes older and more obese, the rates are likely to rise further. Therefore, future research of perinatal OSA should focus on interventions that improve both OSA and obesity.

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SUPPLEMENTAL MATERIAL

Table S1—List of International Classification of Diseases, Ninth Edition, Clinical Modification codes used to identify selected clinical and behavioral conditions

Condition	International Classification of Diseases, 9th Edition, Diagnosis Code[a]
Exposure	
Obstructive sleep apnea	327.23, 780.53, 780.57
Comorbidity	
Obesity	278.00, 278.01, 278.03, 649.1x, V85.3x, V85.4x, V85.54, 793.91
Prepregnancy hypertension	401x, 402x, 403x, 404x, 405x, 642.0x, 642.1x, 642.2x, 642.7x
Prepregnancy diabetes	249x, 250x, 648.0x
Coronary heart disease	410x, 411x, 412x, 413x, 414x, 429.2
Chronic renal disease	581x, 582x, 583x, 585x, 587x, 646.2x
Anemia	280x, 281x, 282x, 283x, 284x, 285x, 648.2x
Disorders of lipid metabolism (e.g., hyperlipidemia)	272x
Hypothyroidism	243x, 244x
Disorders of the adrenal glands	255x
Perinatal history	
Previous cesarean section	654.2x
Multiple gestation/birth	651x, V27.2, V27.3, V27.4, V27.5, V27.6, V27.7
Behavioral history	
Tobacco use	305.1, 649.0x, 989.84
Alcohol use	291x, 303x, 305.0x, 425.5, 760.71, V11.3
Drug use	292.0x, 292.1x, 292.2x, 292.8x, 304x, 305.2x, 305.3x, 305.4x, 305.5x, 305.6x, 305.7x, 305.9x, 648.3x, 655.5x, 760.72, 779.5, 760.75, 965.00, 965.02, E935.1, E850.1
Maternal outcomes	
Cesarean section[b]	74x
Gestational diabetes	648.8x
Preeclampsia	642.4x, 642.5x
Gestational hypertension	642.3x
Postoperative wound	674.1x, 674.3x, 998.3x, 998.5x
Eclampsia	642.6x
Acute renal failure	584x, 669.3x
Pulmonary edema	518.4
Pulmonary embolism and infarction	415.1x
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 428x
Cardiomyopathy	425x, 674.5x
Stroke	431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91
Fetal outcomes	
Early-onset delivery	644.2x
Poor fetal growth	656.5x
Stillbirth	656.4x, V27.1, V27.3, V27.4, V27.6, V27.7

[a]The code suffix "x" represents all possible codes that follow the stated code prefix. [b]Procedure codes, not diagnostic codes, were used to define cesarean section.