Prenatal, Perinatal, and Early Childhood Factors Associated with Childhood Obstructive Sleep Apnea

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Objectives To investigate prenatal, perinatal, and early childhood factors, including cord and early childhood plasma leptin, on a clinical diagnosis of obstructive sleep apnea (OSA) among children in the Boston Birth Cohort.
Study design We conducted a secondary analysis of 2867 mother–child pairs from the Boston Birth Cohort who were enrolled between 1998 and 2014 at Boston Medical Center and followed from birth to age 16 years. Child's OSA was defined based on clinical diagnoses documented in the medical record. Plasma leptin was measured in cord and early childhood blood samples. Logistic regression was used to examine individual and combined effects of early life factors on the risk of OSA, adjusting for potential confounders.
Results The mean age of the study children was 6.39 years (SD = 3.77); 49.3% were girls, and 209 (7.3%) had ever been diagnosed with OSA. Four significant risk factors for OSA were identified: maternal obesity/diabetes during pregnancy (OR, 1.63; 95% CI, 1.21-2.21; P = .001), preterm/low birth weight (OR, 1.74; 95% CI, 1.30-2.32; P < .001), early childhood obesity (OR, 1.89; 95% CI, 1.37-2.62; P < .001), and high leptin levels in early childhood (OR, 1.94; 95% CI, 1.22-3.09; P = .005). The presence of all these 4 risk factors significantly amplified the odds of OSA by about 10 times (OR, 9.95; 95% CI, 3.42-28.93; P < .001) compared with those lacking these factors.
Conclusions Our findings, if further confirmed, provide new insight into the early life risk factors of pediatric OSA and underscore the need for early screening and prevention of OSA among children with those risk factors. *(J Pediatr 2019;212:20-7)*.

Obstructive sleep apnea (OSA), the most severe condition of sleep-disordered breathing,[1] is characterized by the recurrence of partial or complete upper airway obstruction with intermittent nocturnal hypoxia, disrupted normal ventilation, or disordered sleep patterns.[2] OSA affects 1%-5% of all children worldwide.[3] Without early recognition and timely treatment, OSA in children can lead to long-term complications, including cognitive and neuropsychological deficits,[2,4,5] behavioral abnormalities,[6,7] poorer social interactions and performance,[2] metabolic disorders,[8] reduced life quality for both children and their families,[9] and long-term adverse cardiovascular outcomes.[10]

Childhood overweight and obesity are major risk factors for childhood OSA.[11] With the increasing prevalence of childhood overweight and obesity, the problem of childhood OSA may become more common. Other risk factors for childhood OSA reported in previous studies have included preterm and low birth weight of the child,[12,13] maternal race,[12-14] low socioeconomic status,[12,14,15] maternal smoking during pregnancy,[15] and mild preeclampsia.[16] However, these studies were limited due to small sample sizes,[12] measurement of childhood OSA by self-reports,[13-15] a focus on a narrow age range, cross-sectional or retrospective data collection, and a lack of controls for potential cofounding variables.[12-16] Moreover, leptin, known as a marker of adiposity, plays an important role in upper airway obstruction.[17] Some studies found leptin level was higher among children with OSA,[18,19] but 1 study found no relation between leptin and OSA.[20] Considering the discrepancy, the relation between leptin and OSA is worth further exploring.

Prior studies have not examined the connection between maternal obesity or diabetes during pregnancy and a child's risk of OSA. This question is important, given that pregnancy overweight or obesity is highly prevalent in the US.[21] We previously reported that more than one-half the mothers in the Boston Birth

BBC	Boston Birth Cohort
BMI	Body mass index
EMR	Electronic medical record
ICD-9	*International Classification of Diseases, Ninth Revision*
OSA	Obstructive sleep apnea
PTB	Preterm birth

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Cohort (BBC) entered pregnancy overweight or obese, which is a major risk factor for childhood obesity.[22] Furthermore, studies have not examined how the combination of maternal obesity or diabetes, preterm birth (PTB) or low birth weight, plasma leptin levels, and childhood obesity affects the risk of childhood OSA. These factors occur sequentially over the developmental stages (prenatal, perinatal, and postnatal) and are interdependent, so examining individual and combined associations with pediatric OSA may shed light on potential intergenerational and life course pathways leading to pediatric OSA.

We evaluated the association between prenatal, perinatal, and early childhood characteristics and clinical diagnosis of childhood OSA as documented in the electronic medical records (EMR) and examined whether the presence of multiple risk factors (maternal obesity/diabetes, preterm/low birth weight birth of the child, early childhood leptin levels, and childhood obesity) jointly elevate the risk of childhood OSA.

Methods

We conducted a secondary analysis of 2867 mother–infant pairs from the BBC, a predominantly urban, low-income, minority sample with a high prevalence of maternal obesity, PTB, and child obesity. The study was approved by the Institutional Review Boards of Boston University Medical Center and the Johns Hopkins School of Public Health. Written informed consent was obtained from all study mothers.

Participants

As shown in **Figure 1** (available at www.jpeds.com), a total of 8502 mothers who gave birth at the Boston Medical Center between October 1998 and June 2014 along with their newborns were enrolled in the BBC.[23] Eligible for inclusion at initial enrollment were all mothers who delivered preterm (<37 weeks) or low birth weight (<2500 g) infants; mothers who delivered term (≥37 weeks) normal birth weight (≥2500 g) infants were matched by maternal age and parity and recruited at a ratio of 1:2.[23] Exclusion criteria for the initial enrollment included multiple gestation pregnancies, pregnancies from in vitro fertilization, deliveries resulting from trauma, and infants with major birth defects.[23] Cord blood was collected at delivery. A face-to-face maternal interview was conducted using a structured questionnaire. Maternal and child medical records were extracted to obtain pertinent clinical information.

The 2867 mother–child pairs who had ≥1 postnatal care visit from 2004 to 2014 at Boston Medical Center and had a complete EMR were included in this study. The length of postnatal follow-up was from birth up to 16 years (with a median of 5.79 years [interquartile range, 3.33-8.83 years]). The baseline characteristics of the 2867 BBC mother–child pairs included in this study vs the 5627 BBC mother–child pairs excluded were comparable (**Table I**; available at www.jpeds.com). As a sensitivity analyses, we restricted the analyses to children born in 2004 and later and obtained similar results (**Tables II** and **III**; available at www.jpeds.com).

Measures

Outcome: Childhood OSA. The child EMRs contained physician primary or secondary diagnoses for each clinic visit using the *International Classification of Diseases, Ninth Revision* (ICD-9). The outcome for this study was defined as the child ever having a diagnosis of OSA (according to the ICD-9 code) in the EMR during the postnatal follow-up period. The first diagnosis was used to define the age and event of OSA diagnosis. For those without diagnoses of child OSA until the end of the follow-up period, we used their last visits and records in the EMRs to calculate their age. In total, 209 children were identified as having ≥1 diagnosis of child OSA during the follow-up period: 192 children with ICD-9 code 327.23 and 17 children with ICD-9 code 786.03.

Prenatal and Perinatal Characteristics. Maternal prepregnancy body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. We initially divided maternal BMI into 4 groups: underweight (<18.5 kg/m^2), normal weight (18.5-25.0 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (≥30 kg/m^2) (using IOM recommendations, 2013). Owing to the small proportion of underweight mothers (4.5%), the underweight group was combined with the normal weight group for a total of 3 groups. In additional comparisons, the overweight group showed no statistically significant difference in the odds of childhood OSA compared with the normal weight group (OR, 1.38; 95% CI, 0.97-1.97; $P = .072$); thus, we combined the underweight, normal weight, and overweight groups into the "non-obesity" group. Maternal diabetes was assessed based on maternal medical records and defined as either pregestational diabetes or gestational diabetes. Collinearity existed between maternal obesity and diabetes, so we generated a composite variable indicating the status of maternal obesity and/or diabetes during pregnancy: women who had maternal obesity and/or diabetes and women who had neither.

Maternal demographic characteristics included smoking during pregnancy, age, race/ethnicity, and parity. Smoking behavior was classified into 2 groups: smoking within 6 months before pregnancy or during pregnancy, and otherwise. Mothers' race/ethnicity was categorized into 4 groups: Hispanic, non-Hispanic black, white, and other (which included Asian, Pacific Islander, and >1 race/ethnicity). Maternal age was grouped into tertiles as category variables. Maternal parity was defined as 2 groups: 0 or ≥1.

Gestational Age, Birth Weight, and Postnatal Characteristics. Gestational age and birth weight were obtained from maternal and newborn medical records. Gestational age was calculated based on "the first day of the last menstrual period and early prenatal ultrasonographic results."[23] PTB was defined as a gestational age of <37 weeks, and term birth was defined as a gestational age of ≥37 weeks. Low birth

weight was categorized as infant's birth weight of <2500 g, and normal birth weight was categorized as infant's birth weight of ≥2500 g. Owing to the high correlation between PTB and low birth weight, we combined them in a new variable: infants with PTB or low birth weight were categorized as the "either PTB or low birth weight" vs "no PTB, no low birth weight." Infant's sex was obtained from the EMR. Gestational age-specific birth weight was defined into 3 groups according to the United States Birth Weight Reference: small for gestational age (<10th percentile), average for gestational age (≥10th percentile to ≤90th percentile), and large for gestational age (>90th percentile).[24]

Childhood Characteristics. Because the mean age of all study children was 6.39 ± 3.77 years, we used the mean of 6 years as a cut point to divide the sample for sensitivity analysis, with about 50% children in each group. Child's height and weight were measured during the pediatric well-child visits by trained pediatric staff. Child BMI was calculated by weight in kilograms divided by the squared recumbent length or standing height in meters. The World Health Organization's growth chart[25] was used to calculate the age- and sex-specific BMI standardized z-scores for children ≤2 years of age. US national reference data[26] were used to calculated the age- and sex-specific BMI z-scores for children >2 years of age. Child overweight was defined as an age- and sex-specific BMI of ≥85th percentile and <95th percentile. **Figure 2** (available at www.jpeds.com) illustrates child BMI's predictive margins of the probability of childhood OSA with the 95% CI.

There were some missing data for child height and weight; we adopted several methods to replace the missing data. For those with several height and weight measures at different ages, we used linear interpolation for each subject to calculate height and weight at 1 year before the first clinical diagnosis of childhood OSA. For the remaining cases, we replaced the missing data with height and weight from a different clinic visit if the age difference between that visit and the diagnosis of childhood OSA was <2 years. Finally, we used the age- and sex-specific series mean to replace the remaining missing data. Furthermore, we conducted a sensitivity analysis (**Tables IV** and **V**; available at www.jpeds.com) on child height and weight without replacing the missing data. The results showed similar patterns as those found when we replaced the missing data, although they had a lower OR owing to the limited sample size of childhood OSA cases. We also conducted a sensitivity analysis (**Tables VI** and **VII**; available at www.jpeds.com) on child BMI z-score at 1 year of age or 2 years of age without replacing the missing data to consider the temporal relationship between child BMI and OSA. The results showed similar trends when we replaced the missing data.

Plasma Leptin Levels. Cord leptin levels were assessed in cord blood collected at delivery, and early childhood leptin levels were assessed in venous blood collected at follow-up visits. Plasma leptin levels were measured using sandwich immunoassays based on flow metric xMAP technology on Luminex 200 machines (Luminex Corp, Austin, Texas).[20] To make the results easy to interpret, cord leptin levels and childhood leptin levels were grouped into tertiles as category variables.

Statistical Analyses

In our analysis, we first examined the bivariate association of a clinical diagnosis of child OSA with each categorical covariate, using the χ^2 test to identify statistically significant relationships. We then assessed the unadjusted and adjusted (including all other covariates) association between childhood OSA and the majority of risk factors except leptin, using logistic regression models. We then limited the sample size to those with early childhood leptin levels, and estimated the unadjusted and adjusted (including all other covariates) association between childhood OSA and early childhood leptin levels by using several logistic regression models. Finally, the combinations of the 3 major risk factors (maternal obesity/diabetes, premature birth, and childhood obesity) and the estimated odds of having OSA were measured at the mean of other covariates in the logistic regression model, stratified by early childhood leptin tertiles. Covariates included in our analysis were selected first based on review of the literature and then using backward stepwise model selection.

Statistical analyses were conducted using Stata (version 14.0; Stata Corp, College Station, Texas) and SAS (version 9.4; SAS Institute, Cary, North Carolina). Statistical tests were 2-sided and a P value of $< .05$ was considered to be statistically significant.

Results

A total of 209 children (7.3%) with a clinical diagnosis of OSA were identified and compared with 2658 children (92.7%) without a clinical diagnosis of OSA. The mean age of all child participants was 6.39 ± 3.77 years, and 49.3% were girls. The mean age was 6.51 ± 3.80 years for those children without a clinical diagnosis of OSA. The mean age at children's first clinical diagnosis of OSA was 4.79 years (range, 0.10-12.69 years). The incidence of clinically diagnosed OSA by age groups is shown in **Figure 3** (available at www.jpeds.com). The majority of childhood OSA cases were first diagnosed before age 6.

Table VIII summarizes prenatal, perinatal, and early childhood characteristics by OSA status. Compared with their peers, children diagnosed with OSA were more likely to be born either preterm or with low birth weight, with childhood overweight or obesity, younger (<6 years), with higher early childhood leptin levels, with mothers who were either obese or experienced pregestational/gestational diabetes during pregnancy ($P < .05$). There were no statistically significant differences in maternal age, parity, maternal smoking during pregnancy, child's sex, or cord leptin levels between those with and without a clinical diagnosis of OSA in childhood ($P \geq .05$).

Table VIII. Prenatal, perinatal, and early childhood factors by first clinical diagnosis of OSA in childhood (n = 2867)

Variables	OSA diagnosis		*P* value
	No (n = 2658)	Yes (n = 209)	
Child's sex			.314
Female	1317 (49.55%)	96 (45.93%)	
Male	1341 (50.45%)	113 (54.07%)	
Child's age, years			<.001*
<6	1341 (50.45%)	142 (67.94%)	
≥6	1317 (49.55%)	67 (32.06%)	
Child's BMI			.007†
Normal	1647 (61.96%)	115 (55.02%)	
Overweight	445 (16.74%)	30 (14.35%)	
Obesity	566 (21.30%)	64 (30.63%)	
Birth outcome			<.001*
No PTB, No LBW	1731 (65.12%)	109 (52.15%)	
Either PTB or LBW without child obesity	743 (27.95%)	70 (33.50%)	
Either PTB or LBW with child obesity	184 (6.93%)	30 (14.35%)	
Maternal obesity and diabetes			<.001*
No obesity, no diabetes	1946 (73.21%)	126 (60.29%)	
Either obesity or diabetes	712 (26.79%)	83 (39.71%)	
Maternal smoking during pregnancy			.993
No	2365 (88.98%)	186 (89.00%)	
Yes	293 (11.02%)	23 (11.00%)	
Race/ethnicity			.041‡
Black	1730 (65.09%)	128 (61.24%)	
White	203 (7.64%)	13 (6.22%)	
Hispanic	545 (20.50%)	59 (28.23%)	
Other	180 (6.77%)	9 (4.31%)	
Maternal age (tertile), years			.906
Low	889 (33.45%)	67 (32.06%)	
Middle	884 (33.25%)	72 (34.45%)	
High	885 (33.30%)	70 (33.49%)	
Parity			.917
0	1129 (42.48%)	88 (42.11%)	
≥1	1529 (57.52%)	121 (57.89%)	
Cord leptin (tertile), ng/mL§			.154
Low	323 (32.69%)	35 (41.18%)	
Middle	329 (33.30%)	29 (34.12%)	
High	336 (34.01%)	21 (24.70%)	
Early childhood leptin (tertile), ng/mL¶			.018‡
Low	457 (34.34%)	30 (23.26%)	
Middle	443 (33.28%)	44 (34.11%)	
High	431 (32.38%)	55 (42.64%)	

LBW, low birth weight.
*$P \leq .001$.
†$P < .01$.
‡$P < .05$.
§There are 1794 missing values for cord leptin.
¶There are 1407 missing values for early childhood leptin.

Table IX. Unadjusted and adjusted association of prenatal, perinatal, and early childhood factors with first clinical diagnosis of OSA in childhood (n = 2867)

Variables	Unadjusted model		Adjusted model*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Maternal obesity and diabetes				
No obesity, no diabetes	1		1	
Either obesity or diabetes	1.80 (1.35-2.41)	<.001†	1.63 (1.21-2.21)	.001†
Birth outcome				
No PTB, No LBW	1		1	
Either PTB or LBW	1.71 (1.29-2.27)	<.001†	1.74 (1.30-2.32)	<.001†
Child obesity				
No	1		1	
Yes	1.63 (1.20-2.22)	.002‡	1.89 (1.37-2.62)	<.001†
Race/ethnicity				
Black	1		1	
White	0.87 (0.48-1.56)	.631	0.84 (0.45-1.57)	.587
Hispanic	1.46 (1.06-2.02)	.021§	1.47 (1.06-2.05)	.022§
Other	0.68 (0.34-1.35)	.268	0.66 (0.33-1.34)	.253
Maternal age (tertile), years				
Low	1		1	
Middle	1.08 (0.77-1.53)	.660	1.05 (0.73-1.51)	.807
High	1.05 (0.74-1.49)	.785	0.97 (0.66-1.43)	.874
Parity				
0	1		1	
≥1	1.02 (0.76-1.35)	.917	0.99 (0.72-1.37)	.964
Maternal smoking during pregnancy				
No	1		1	
Yes	1.00 (0.64-1.57)	.993	0.94 (0.58-1.53)	.811
Child's sex				
Female	1		1	
Male	1.16 (0.87-1.53)	.314	1.16 (0.87-1.54)	.321
Child's age, years				
<6	1		1	
≥6	0.48 (0.36-0.65)	<.001†	0.43 (0.31-0.59)	<.001†

*Adjusted model was controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†$P \leq .001$.
‡$P < .01$.
§$P < .05$.

Table IX presents the unadjusted and adjusted associations between prenatal, perinatal, and early childhood factors with a first clinical diagnosis of OSA in childhood, except for the plasma leptin levels. After adjusting for all the covariates, the odds that a mother with either obesity or diabetes had a child with a diagnosis of childhood OSA were 63% higher than the odds of a mother without obesity or diabetes (OR, 1.63; 95% CI, 1.21,2.21; $P = .001$). Children with either PTB or low birth weight still showed an increased risk of OSA (OR, 1.74; 95% CI, 1.30-2.32; $P < .001$). Those children who were obese showed an increased risk of a clinical diagnosis of OSA compared with children who were not obese (OR, 1.89; 95% CI, 1.37-2.62; $P < .001$).

Then we limited the sample size to those with early childhood leptin levels. **Table X** presents the unadjusted associations between early childhood leptin levels with a first clinical diagnosis of OSA in childhood. Compared with those with low early childhood leptin levels, children with high leptin levels had a higher risk for childhood OSA (OR, 1.94; 95% CI, 1.22-3.09; $P = .005$), children with middle leptin levels did not show statistically significant association with OSA (OR, 1.51; 95% CI, 0.93-2.45; $P = .092$). After adjusting for maternal obesity or diabetes, birth outcomes, child obesity, and all the covariates, children with high leptin levels still had a higher risk for childhood OSA (OR, 2.08; 95% CI, 1.25-3.45; $P = .005$) compared with those with low leptin levels.

Table X. Unadjusted and adjusted association of early childhood plasma leptin levels (tertiles) with first clinical diagnosis of OSA in childhood (n = 1460)

	Early childhood plasma leptin levels (tertile)*			
	Middle		High	
Variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Unadjusted model	1.51 (0.93-2.45)	.092	1.94 (1.22-3.09)	.005†
Adjusted model‡				
Model I	1.69 (1.03-2.76)	.036§	2.57 (1.58-4.17)	<.001¶
Model II (with child obesity)	1.63 (0.99-2.66)	.053	2.22 (1.34-3.67)	.002†
Model III (with maternal obesity and diabetes)	1.64 (1.00-2.68)	.051	2.38 (1.46-3.89)	.001¶
Model IV (with birth outcome)	1.73 (1.06-2.84)	.029§	2.56 (1.57-4.17)	<.001¶
Model V (with cord leptin)**	1.35 (0.70-2.60)	.369	1.58 (0.82-3.02)	.169
Model VI (with child obesity, maternal obesity and diabetes, and birth outcomes)	1.60 (0.97-2.63)	.065	2.08 (1.25-3.45)	.005†

*Low early childhood plasma leptin level group was the reference group.
†$P < .01$.
‡Adjusted models: model I was controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age; model II was controlled for variables in model I plus child obesity; model III was controlled for variables in model I plus maternal obesity and diabetes; model IV was controlled for variables in model I plus birth outcome; model V was controlled for variables in model I plus cord leptin; model VI was controlled for variables in model I plus child obesity, maternal obesity and diabetes, and birth outcomes.
§$P < .05$.
¶$P \leq .001$.
**n = 850 for model V.

Figure 4 (available at www.jpeds.com) and **Table XI** (available at www.jpeds.com) present the combined association of maternal obesity or diabetes, premature birth or low birth weight, and childhood obesity with child risk of OSA stratified by early childhood plasma leptin levels. Our findings showed that obese children who were born preterm or low birth weight, with high early childhood leptin levels, and mothers with obesity or diabetes during pregnancy had the highest risk of OSA in childhood, with a strikingly high odds ratio of 11.34 compared with the group of children who had none of these 4 risk factors. This finding is further illustrated in **Figure 5**, where the combination of the 4 factors amplified the risk of childhood OSA about 10 times (OR, 9.95; 95% CI, 3.42-28.93; $P < .001$). Seven other groups also showed higher risks of a clinical diagnosis of OSA in childhood compared with the reference group, the ORs ranged from 2.93 to 8.64 (**Figure 5**).

We conducted additional analyses on the role of small, average, and large for gestational age variables and their combination with gestational age (term vs preterm) (**Tables XII** and **XIII**; available at www.jpeds.com). Compared with those born term average for gestational age, children born term small for gestational age and children born preterm average for gestational age still showed an increased risk of childhood OSA after adjusting for all the covariates.

The odds that a mother with either obesity or diabetes had a child with high cord leptin levels were 93% higher than the odds of a mother without obesity or diabetes (OR, 1.93; 95% CI, 1.45-2.55; $P < .001$) (**Tables XIV** and **XV**; available at www.jpeds.com).

Sensitivity analyses were conducted to assess the robustness of our study findings across age strata (child's age <6 years and ≥6 years) and subgroups defined by other prenatal, perinatal and early childhood factors. The results are presented in **Tables XVI** to **XIX** (available at www.jpeds.com). The results for children aged <6 years showed the same results as the results for children from all age groups. Our results for the ≥6 years' age group demonstrated similar trend, but did not reach statistical significance, likely because most OSA cases were first diagnosed when children were <6 years of age.

Discussion

This study was a secondary analysis of a prospective birth cohort study and examined multiple early life risk factors of OSA, including mother's obesity or diabetes during pregnancy, PTB or low birth weight, early childhood leptin levels, and early childhood obesity, individually and in combination. We found that these risk factors individually were each associated with a greater odds of childhood OSA and, more important, a combination of all 4 risk factors could lead to about a 10 times higher risk of OSA.

The finding that children whose mothers experienced obesity or diabetes during pregnancy had a high risk of a clinical diagnosis of OSA is important from an early risk assessment and prevention perspective. Previous studies of this relationship were limited; in the only previous population-based study, of 613 school-aged American children, Calhoun et al showed that maternal weight gain during pregnancy was associated with slightly greater odds (OR, 1.02) of having a child with polysomnography-confirmed sleep-disordered breathing.[27] We speculate that the link between maternal obesity/diabetes during pregnancy with offspring higher risk of OSA may be operated via 2 pathways—maternal obesity/diabetes during pregnancy increases the risk of childhood obesity and mothers with obesity/diabetes may be at high risk of OSA themselves and then transmit this risk to

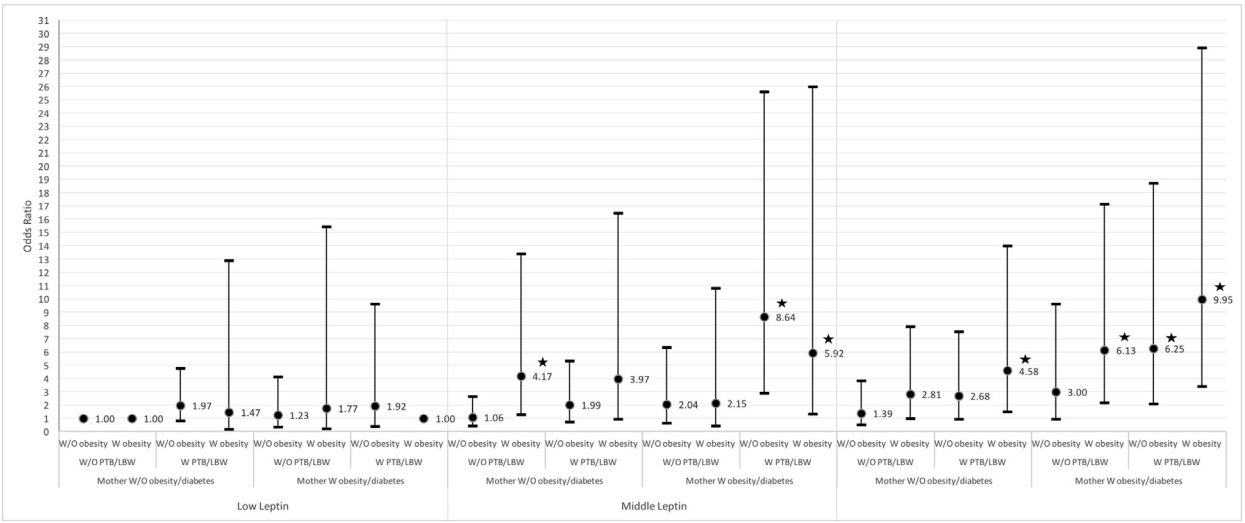

Figure 5. Combined association of maternal obesity/diabetes, PTB and low birth weight, and childhood obesity with first clinical diagnosis of OSA in childhood, stratified by early childhood leptin tertiles. Controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age. *W*, with; *W/O*, without. ★$P < .05$. The first group is the reference group. The OR of the second and eighth groups cannot be estimated owing to the small sample sizes.

their offspring. This notion is supported by a population-based study conducted in Sweden by Sundquist et al indicating that a family history of OSA was closely associated with childhood OSA.[28]

The data reported here also indicate that being born preterm or low birth weight was associated with a higher risk of clinical diagnosis of OSA in childhood. This study finding is in line with a population-based cohort study by Rosen et al, which indicated that children born preterm were 3-5 times more likely to having sleep-disordered breathing in childhood.[13] Our study findings are also in accordance with another retrospective longitudinal study[15] which found that young adults who were born with very low birth weight had a greater risk (OR, 2.2) of sleep-disordered breathing symptoms. In contrast, the finding of a population-based cohort study focused of children aged 2.5-6.0 years by Raynes Greenow et al differs somewhat with our findings.[29] They showed that children born preterm had an increased risk of childhood OSA even after adjusting for potential confounders, although this was not true for children born with low birth weight; however, they analyzed the association without controlling for childhood BMI, which might have biased their finding toward the null. The potential mechanism underlying the association between childhood prematurity and pediatric OSA may be that prematurity has a long-term adverse influence on upper airway size and development of respiratory control,[30-32] which increases the risk of childhood OSA.

Childhood obesity has proved to be the most important and independent risk factor for childhood OSA,[11] which our study findings support. It has been reported worldwide that children with overweight or obesity have an increased risk of OSA compared with normal weight children, with an increased risk that ranges from 3- to 5-fold.[30,33] There is evidence that obesity and OSA may interact to amplify serious clinical consequences, including insulin resistance, increased proinflammatory cytokines, increased leptin, decreased adiponectin, and fatty liver diseases.[34-36] Concurrent with the epidemiologic evidence, 2 potential mechanisms that underlie the association of obesity and OSA have been partially elucidated. One of the potential pathways may be related to the fact that OSA is now considered to be a chronic inflammatory disease that may promote both local and systemic inflammation, which is similar to obesity.[37-39] The other theoretical model indicates that both childhood obesity and OSA are closely connected to altered gut microbiota and an elevated translocation of bacterial lipopolysaccharides,[40-42] which can lead to metabolic dysfunction, especially insulin resistance, in the long term.

Plasma leptin levels have been shown to be increased among individuals with OSA compared with those without OSA,[17] which our findings support.[18,19] It has been shown that plasma leptin is a marker of adiposity and has an effect on suppressing appetite and increase metabolism.[43] However, plasma leptin levels are still high among the obese individuals, which is due to the leptin resistance at the central nervous system.[43] Berger et al proved that in obese mice intranasal leptin bypassed the leptin resistance and alleviate sleep-disordered breathing.[44] Although further investigation on human is needed to verify the correlation, leptin may become an important therapy for OSA.

The combination of maternal obesity/diabetes, PTB/low birth weight, early childhood leptin levels, and childhood obesity significantly amplified the risk of childhood OSA in our study sample. In fact, these factors covary in a sequential way. Thus, the presence of each risk factor forms a chain

(mom obesity/diabetes > PTB > child obesity > plasma leptin levels) to heighten the odds of OSA. So far, only a few previous studies have examined the effects of all these 4 conditions in a large prospective birth cohort from birth up to childhood. Most studies have examined the association of prenatal and perinatal factors with OSA, but without considering childhood obesity.[12,29] As noted, childhood obesity and early childhood leptin levels have been shown to be the most important risk factors for childhood OSA.

Our study had several limitations. First, although a clinical diagnosis of OSA is reliable, it may have led to underdiagnosis of OSA, because the majority of children with OSA have mild symptoms and may not seek medical attention.[45] As such, mild OSA cases may be misclassified into controls, which may bias the results toward the null. Furthermore, we did not have polysomnogram confirmation of OSA, which might increase the potential uncertainty of the diagnosis. However, most previous studies determined OSA cases by self-report, which might suffer from recall bias and diagnosis uncertainty. Second, the initial study on which this secondary analysis was based focused only on those children who continued their pediatric care at Boston Medical Center, which might have led to selection bias. However, baseline maternal characteristics were comparable between the included and excluded samples. Moreover, a propensity score matching was conducted to decrease the potential selection bias by balancing covariates and obtained similar results (**Table XX**; available at www.jpeds.com). Third, maternal BMI during pregnancy was assessed by self-reported height and weight in questionnaires, which might have been subject to recall bias. Nevertheless, Wang et al used the same BBC data to compare a subset of self-reported maternal BMI data with those identified in medical records to show that there was a high agreement between the maternal BMI data from these 2 sources.[22] Fourth, there were some missing data for child height and weight, for which we adopted several methods to replace the missing data. The sensitivity analysis indicated the feasibility of the missing data replacement methods. Last, although this was among the largest birth cohort study of pediatric OSA, the study sample size in the stratified analyses became small (**Table X**), which might lead to decreased power and wide CIs.

Overall, this study showed that the combination of 4 factors greatly amplified the risk of OSA by about 10 times. The findings, if further confirmed, may have important clinical and public health implications on early screening and prevention of OSA among children with these early life risk factors, which may, in turn, help to decrease OSA and its consequences later in life. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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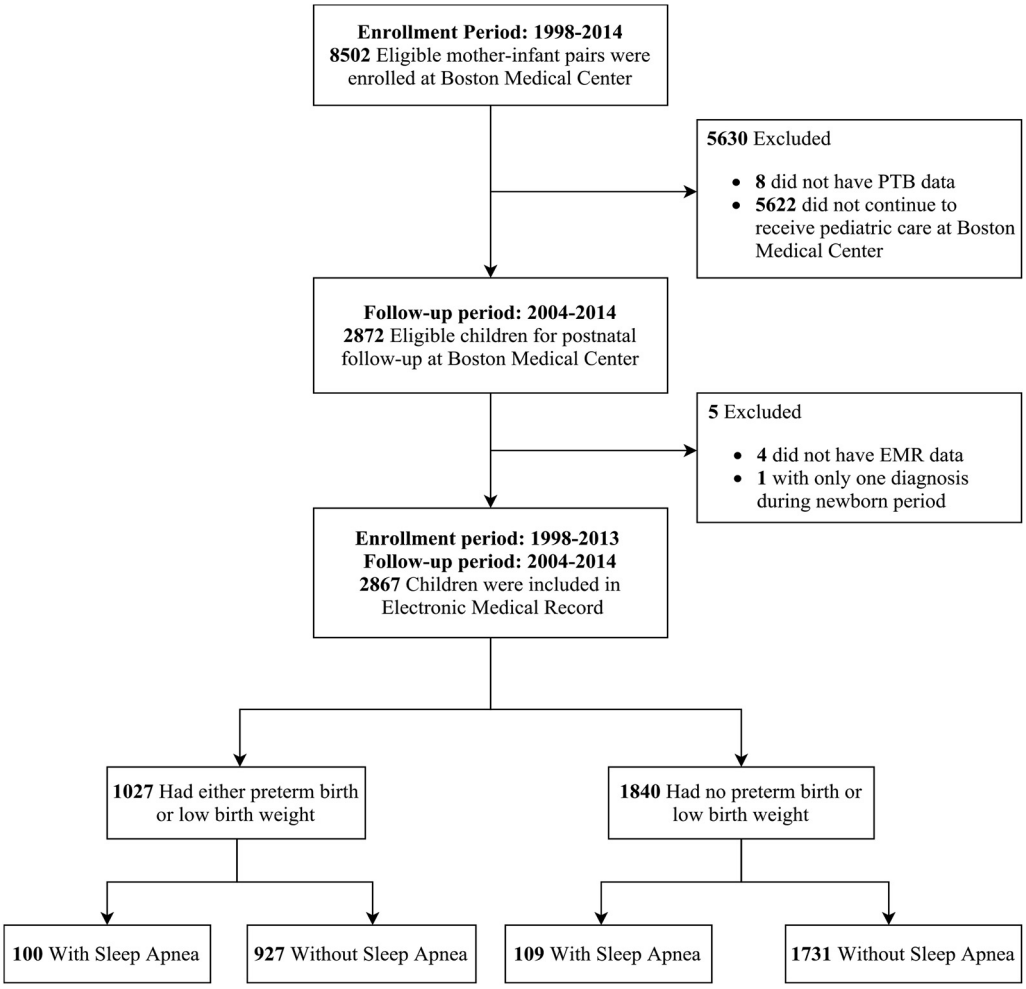

Figure 1. Flow chart of the study participants.

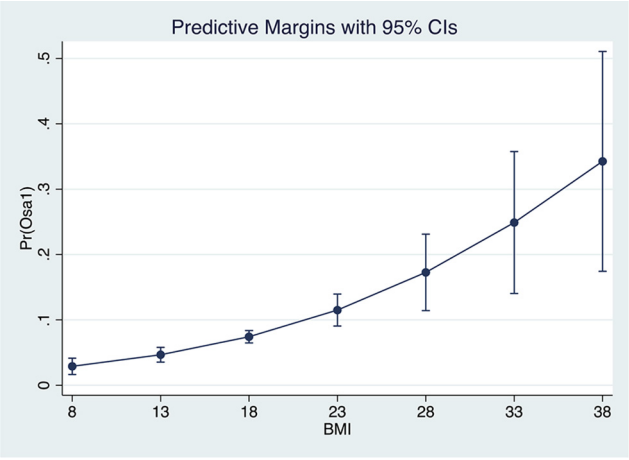

Figure 2. Child BMIs predictive margins of the probability of childhood OSA [Pr(OSA1)]. with 95% CI. Controlled for maternal obesity/diabetes, PTB/low birth weight, maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.

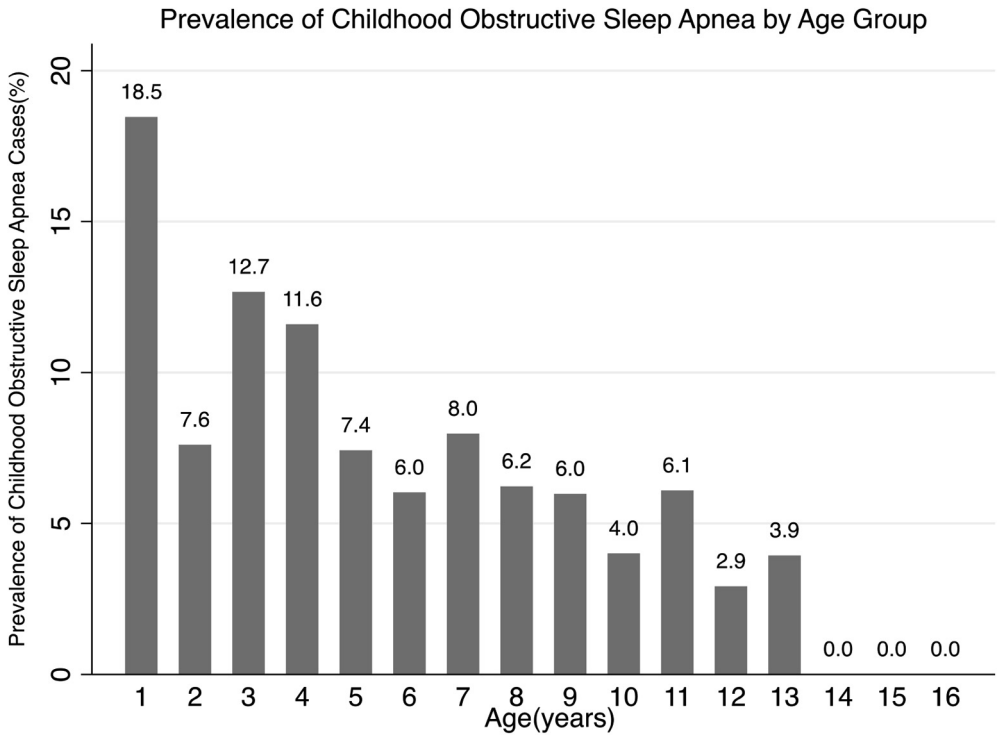

Figure 3. Incidence of childhood OSA by age group.

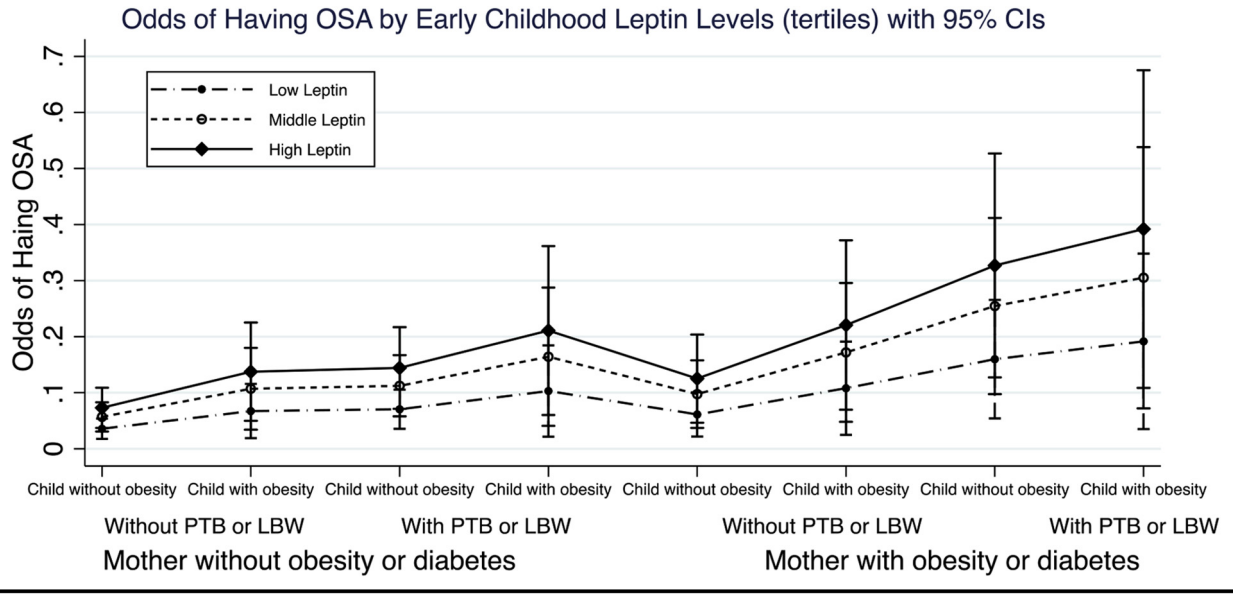

Figure 4. Combined association of maternal obesity/diabetes, PTB, and childhood obesity with first clinical diagnosis of childhood OSA stratified by early childhood plasma Leptin levels (tertile). Controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age. *LBW*, low birth weight.

Table I. Comparison of the baseline characteristics of the included and excluded sample (n = 8494)

Variables	Total birth cohort (n = 8494)	
	Included (n = 2867)	Excluded (n = 5627)
PTB		
No	2044 (71.29%)	4139 (73.56%)
Yes	823 (28.71%)	1488 (26.44%)
Low birth weight		
No	2086 (72.76%)	4191 (74.49%)
Yes	781 (27.24%)	1435 (25.51%)
Maternal obesity		
No	2180 (76.04%)	4586 (81.50%)
Yes	687 (23.96%)	1041 (18.50%)
Maternal diabetes		
No	2644 (92.22%)	5275 (93.74%)
Yes	223 (7.78%)	352 (6.26%)
Maternal smoking during pregnancy		
No	2551 (88.98%)	4910 (87.26%)
Yes	316 (11.02%)	717 (12.74%)
Race/ethnicity		
Black	1858 (64.81%)	2522 (44.82%)
White	216 (7.53%)	789 (14.02%)
Hispanic	604 (21.07%)	1818 (32.31%)
Other	189 (6.59%)	498 (8.85%)
Maternal age (tertile), years		
Low	901 (31.43%)	1933 (34.35%)
Middle	949 (33.10%)	1881 (33.43%)
High	1017 (35.47%)	1813 (32.22%)
Parity		
0	1217 (42.45%)	2437 (43.31%)
≥1	1650 (57.55%)	3190 (56.69%)

Table II. Sensitivity analysis (children born in 2004 or after): Prenatal, perinatal, and early childhood factors by first clinical diagnosis of OSA in childhood (n = 2191)

Variables	OSA diagnosis		*P* value
	No (n = 2037)	Yes (n = 154)	
Child's sex			.228
Female	1002 (49.19%)	68 (44.16%)	
Male	1035 (50.81%)	86 (55.84%)	
Child's age			<.001*
<6	1295 (63.57%)	129 (83.77%)	
≥6	742 (36.43%)	25 (16.23%)	
Child obesity			.020†
No	1652 (81.10%)	113 (73.38%)	
Yes	385 (18.90%)	41 (26.62%)	
Birth outcome			<.001*
No PTB, No LBW	1338 (65.68%)	77 (50.00%)	
Either PTB or LBW without child obesity	571 (28.04%)	57 (37.01%)	
Either PTB or LBW with child obesity	128 (6.28%)	20 (12.99%)	
Maternal obesity and diabetes			.001*
No obesity, no diabetes	1475 (72.41%)	93 (60.39%)	
Either obesity or diabetes	562 (27.59%)	61 (39.61%)	
Maternal smoking during pregnancy			.592
No	1810 (88.86%)	139 (90.26%)	
Yes	227 (11.14%)	15 (9.74%)	
Race/ethnicity			.093
Black	1228 (63.23%)	92 (59.74%)	
White	166 (8.15%)	10 (6.49%)	
Hispanic	434 (21.31%)	45 (29.22%)	
Other	149 (7.31%)	7 (4.55%)	
Maternal age (tertile), years			.749
Low	679 (33.33%)	53 (34.42%)	
Middle	682 (33.48%)	47 (30.52%)	
High	676 (33.19%)	54 (35.06%)	
Parity			.470
0	881 (43.25%)	62 (40.26%)	
≥1	1156 (56.75%)	92 (59.74%)	

LBW, low birth weight.
*$P \leq .001$.
†$P < .01$.

Table III. Sensitivity analysis (children born in 2004 or after): Unadjusted and adjusted association of prenatal, perinatal, and early childhood factors with first clinical diagnosis of OSA in childhood (n = 2191)

	Unadjusted model		Adjusted model*	
Variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Maternal obesity and diabetes				
No obesity, no diabetes	1		1	
Either obesity or diabetes	1.72 (1.23-2.41)	.002†	1.56 (1.10-2.22)	.013‡
Birth outcome				
No PTB, No LBW	1		1	
Either PTB or LBW	1.91 (1.38-2.66)	<.001§	1.92 (1.37-2.69)	<.001§
Child obesity				
No	1		1	
Yes	1.56 (1.07-2.26)	.020§	1.91 (1.29-2.84)	.001§
Race/ethnicity				
Black	1		1	
White	0.84 (0.43-1.65)	.619	0.90 (0.44-1.85)	.779
Hispanic	1.45 (1.00-2.11)	.050	1.43 (0.97-2.09)	.071
Other	0.66 (0.30-1.44)	.297	0.69 (0.31-1.52)	.355
Maternal age (tertile), years				
Low	1		1	
Middle	0.88 (0.59-1.33)	.548	0.80 (0.52-1.24)	.323
High	1.02 (0.69-1.52)	.908	0.85 (0.54-1.34)	.496
Parity				
0	1		1	
≥1	1.13 (0.81-1.58)	.470	1.18 (0.81-1.72)	.397
Maternal smoking during pregnancy				
No	1		1	
Yes	0.86 (0.50-1.49)	.592	0.77 (0.43-1.40)	.396
Child's sex				
Female	1		1	
Male	1.22 (0.88-1.70)	.229	1.21 (0.86-1.69)	.268
Child's age				
<6	1		1	
≥6	0.34 (0.22-0.52)	<.001§	0.30 (0.19-0.47)	<.001§

*Adjusted model was controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†$P < .01$.
‡$P < .05$.
§$P \leq .001$.

Table IV. Sensitivity analysis (without BMI imputation): Prenatal, perinatal, and early childhood characteristics by clinical diagnosis of OSA in childhood (n = 640)

	OSA Diagnosis		
Variables	**No (n = 584)**	**Yes (n = 56)**	***P* value**
Child's sex			.382
Female	286 (48.97%)	24 (42.86%)	
Male	298 (51.03%)	32 (57.14%)	
Child's age			<.001*
<6	389 (66.61%)	51 (91.07%)	
≥6	195 (33.39%)	5 (8.93%)	
Birth outcome			.093
No PTB, No LBW	369 (63.18%)	29 (51.79%)	
Either PTB or LBW	215 (36.82%)	27 (48.21%)	
Child obesity			.591
No	476 (81.51%)	44 (78.57%)	
Yes	108 (18.49%)	12 (21.43%)	
Maternal obesity and diabetes			.010†
No obesity, no diabetes	428 (73.29%)	32 (57.14%)	
Either obesity or diabetes	156 (26.71%)	24 (42.86%)	
Maternal smoking during pregnancy			.330
No	505 (86.47%)	51 (91.07%)	
Yes	79 (13.53%)	5 (8.93%)	
Race/ethnicity			.527
Black	361 (61.82%)	37 (66.07%)	
White	58 (9.93%)	4 (7.14%)	
Hispanic	117 (20.03%)	13 (23.21%)	
Other	48 (8.22%)	2 (3.57%)	
Maternal age (tertile), years			.301
Low	174 (29.79%)	12 (21.43%)	
Middle	193 (33.05%)	28 (32.14%)	
High	217 (37.16%)	26 (46.43%)	
Parity			.232
0	257 (44.01%)	20 (35.71%)	
≥1	327 (55.99%)	36 (64.29%)	

*$P \leq .001$.
†$P < .05$.

Table V. Sensitivity analysis (without BMI imputation): Crude and adjusted association of prenatal, perinatal, and early childhood factors with clinical diagnosis of OSA in childhood (n = 640)

	Unadjusted model		Adjusted model*	
Variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Child's sex				
Female	1		1	
Male	1.28 (0.74-2.23)	.383	1.15 (0.65-2.05)	.624
Child's age, years				
<6	1		1	
≥6	0.20 (0.08-0.50)	.001†	0.17 (0.06-0.46)	<.001†
Birth outcome				
No PTB, No LBW	1		1	
Either PTB or LBW	1.60 (0.92-2.77)	.095	1.64 (0.92-2.91)	.094
Child obesity				
No	1		1	
Yes	1.20 (0.61-2.35)	.591	1.85 (0.88-3.88)	.106
Maternal obesity and diabetes				
No obesity, no diabetes	1		1	
Either obesity or diabetes	2.06 (1.18-3.60)	.012‡	1.50 (0.83-2.71)	.182
Maternal smoking during pregnancy				
No	1		1	
Yes	0.63 (0.24-1.62)	.334	0.57 (0.20-1.60)	.287
Race/ethnicity				
Black	1		1	
White	0.67 (0.23-1.96)	.467	0.82 (0.25-2.63)	.733
Hispanic	1.08 (0.56-2.11)	.812	1.14 (0.57-2.29)	.707
Other	0.41 (0.09-1.74)	.225	0.45 (0.10-1.97)	.288
Maternal age (tertile), years				
Low	1		1	
Middle	1.35 (0.63-2.89)	.436	1.33 (0.59-2.97)	.488
High	1.74 (0.85-3.54)	.129	1.36 (0.61-3.03)	.452
Parity				
0	1		1	
≥1	1.41 (0.80-2.50)	.233	1.28 (0.67-2.45)	.462

N (%): cases in each group (percent of cases).
*Adjusted model has controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†$P \leq .00$.
‡$P < .05$.

Table VI. Sensitivity analysis (child's BMI z-score at 1 year of age ±3 months without BMI imputation): Crude and adjusted association of prenatal, perinatal, and early childhood factors with clinical diagnosis of OSA in childhood (n = 1841)

	Unadjusted model		Adjusted model*	
Variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Child's sex				
Female	1		1	
Male	1.16 (0.87-1.53)	.312	1.45 (0.98-2.13)	.063
Child's age				
<6	1		1	
≥6	0.49 (0.37-0.67)	<.001†	0.42 (0.27-0.65)	<.001†
Maternal obesity and diabetes				
No obesity, no diabetes	1		1	
Either obesity or diabetes	1.80 (1.35-2.41)	<.001†	1.85 (1.25-2.74)	.002‡
Birth outcome				
No PTB, No LBW	1		1	
Either PTB or LBW	1.71 (1.29-2.27)	<.001‡	1.80 (1.21-2.66)	.003‡
Child obesity				
No	1		1	
Yes	2.88 (1.84-4.51)	<.001†	2.79 (1.76-4.44)	<.001†
Maternal smoking during pregnancy				
No	1		1	
Yes	1.00 (0.64-1.57)	.995	0.73 (0.37-1.45)	.370
Race/ethnicity				
Black	1		1	
White	0.87 (0.48-1.56)	.632	0.97 (0.43- 2.16)	.932
Hispanic	1.46 (1.06-2.02)	.021§	1.95 (1.24-3.08)	.004‡
Other	0.68 (0.34-1.35)	.268	0.67 (0.26-1.71)	.399
Maternal age (tertile), years				
Low	1		1	
Middle	1.08 (0.77-1.53)	.660	1.36 (0.81-2.28)	.243
High	1.05 (0.74-1.48)	.790	1.50 (0.88-2.57)	.139
Parity				
0	1		1	
≥1	1.01 (0.76-1.35)	.921	0.88 (0.57-1.35)	.547

N (%): cases in each group (percent of cases).
*Adjusted model has controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†$P \leq .00$.
‡$P < .01$.
§$P < .05$.

Table VII. Sensitivity analysis (child's BMI z-score at 2 year of age ±3 months without BMI imputation): Crude and adjusted association of prenatal, perinatal, and early childhood factors with clinical diagnosis of OSA in childhood (n = 1446)

	Unadjusted model		Adjusted model*	
Variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Child's sex				
Female	1		1	
Male	1.16 (0.87-1.53)	.312	1.16 (0.77-1.73)	.485
Child's age				
<6	1		1	
≥6	0.49 (0.37-0.67)	<.001†	0.32 (0.20-0.51)	<.001†
Maternal obesity and diabetes				
No obesity, no diabetes	1		1	
Either obesity or diabetes	1.80 (1.35-2.41)	<.001†	1.58 (1.03-2.41)	.036‡
Birth outcome				
No PTB, No LBW	1		1	
Either PTB or LBW	1.71 (1.29-2.27)	<.001†	1.80 (1.19-2.74)	.006§
Child obesity				
No	1		1	
Yes	1.77 (1.05-3.00)	.033‡	1.77 (1.02-3.06)	.041‡
Maternal smoking during pregnancy				
No	1		1	
Yes	1.00 (0.64-1.57)	.995	1.42 (0.75-2.68)	.278
Race/ethnicity				
Black	1		1	
White	0.87 (0.48-1.56)	.632	1.12 (0.49-2.59)	.785
Hispanic	1.46 (1.06-2.02)	.021‡	1.53 (0.93-2.54)	.097
Other	0.68 (0.34-1.35)	.268	0.29 (0.07-1.22)	.092
Maternal age (tertile), years				
Low	1		1	
Middle	1.08 (0.77-1.53)	.660	1.12 (0.66-1.90)	.679
High	1.05 (0.74-1.48)	.790	1.21 (0.69-2.12)	.503
Parity				
0	1		1	
≥1	1.01 (0.76-1.35)	.921	0.90 (0.57-1.42)	.652

N (%): cases in each group (percent of cases).
*Adjusted model has controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†$P \leq .00$.
‡$P < .05$.
§$P < .01$.

Table XI. Combined association of maternal obesity/diabetes, PTB, and childhood obesity with first clinical diagnosis of childhood OSA stratified by early childhood plasma leptin levels (tertile) (n = 1460)

			Adjusted model*			
Maternal obesity or diabetes	PTB or LBW	Child obesity	Odds†	95% CI—low	95% CI—upper	*P* value
Low early childhood plasma leptin levels						
Mother without obesity or diabetes	Without PTB or LBW	Child without obesity	0.035	0.017	0.053	<.001‡
		Child with obesity	0.068	0.019	0.118	.006§
	With PTB or LBW	Child without obesity	0.071	0.036	0.106	<.001‡
		Child with obesity	0.102	0.021	0.182	.013¶
Mother with obesity or diabetes	Without PTB or LBW	Child without obesity	0.061	0.022	0.101	.002§
		Child with obesity	0.108	0.025	0.192	.011¶
	With PTB or LBW	Child without obesity	0.162	0.055	0.269	.003§
		Child with obesity	0.193	0.036	0.351	.016¶
Middle early childhood plasma leptin levels						
Mother without obesity or diabetes	Without PTB or LBW	Child without obesity	0.056	0.030	0.082	<.001‡
		Child with obesity	0.109	0.035	0.183	.004§
	With PTB or LBW	Child without obesity	0.112	0.058	0.167	<.001‡
		Child with obesity	0.162	0.040	0.284	.009§
Mother with obesity or diabetes	Without PTB or LBW	Child without obesity	0.097	0.037	0.158	.002§
		Child with obesity	0.173	0.048	0.297	.007§
	With PTB or LBW	Child without obesity	0.258	0.099	0.418	.001‡
		Child with obesity	0.308	0.073	0.542	.010¶
High early childhood plasma leptin levels						
Mother without obesity or diabetes	Without PTB or LBW	Child without obesity	0.072	0.037	0.108	<.001‡
		Child with obesity	0.141	0.051	0.230	.002§
	With PTB or LBW	Child without obesity	0.145	0.072	0.218	<.001‡
		Child with obesity	0.209	0.060	0.359	.006§
Mother with obesity or diabetes	Without PTB or LBW	Child without obesity	0.126	0.046	0.205	.002§
		Child with obesity	0.223	0.071	0.375	.004§
	With PTB or LBW	Child without obesity	0.333	0.129	0.537	.001‡
		Child with obesity	0.397	0.110	0.684	.007§

*Adjusted model has controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†Odds indicates the odds of having childhood OSA. The OR is the ratio of 2 odds.
‡$P \leq .001$.
§$P < .01$.
¶$P < .05$.

Table XII. The role of small, average, and large for gestational age variables and their combination with gestational age (term vs preterm) by first clinical diagnosis of OSA in childhood (n = 2867)

	OSA Diagnosis		
Variables	No (n = 2658)	Yes (n = 209)	*P* value
Gestational age-specific birth weight			.039*
Average for gestational age	1885 (93.41%)	133 (6.59%)	
Small for gestational age	594 (91.67%)	54 (8.33%)	
Large for gestational age	179 (89.05%)	22 (10.95%)	
Gestational age-specific birth weight and PTB			.032*
Average for gestational age, TB	1338 (94.29%)	81 (5.71%)	
Small for gestational age, TB	433 (91.74%)	39 (8.26%)	
Large for gestational age, TB	137 (89.54%)	16 (10.46%)	
Average for gestational age, PTB	547 (91.32%)	52 (8.68%)	
Small for gestational age, PTB	161 (91.48%)	15 (8.52%)	
Large for gestational age, PTB	42 (87.50%)	6 (12.50%)	

TB, term birth.
*$P < .05$.

Table XIII. Unadjusted and adjusted* association of the combination of small, average, and large for gestational age variables with gestational age (term vs preterm) by first clinical diagnosis of OSA in childhood (n = 2867)

	Outcome: OSA diagnosis	
	OR (95% CI)	*P* value
Unadjusted model		
Average for gestational age, TB	1	
Small for gestational age, TB	1.49 (1.00-2.21)	.050
Large for gestational age, TB	1.93 (1.10-3.39)	.022†
Average for gestational age, PTB	1.57 (1.09-2.26)	.015†
Small for gestational age, PTB	1.54 (0.87-2.73)	.141
Large for gestational age, PTB	2.36 (0.97-5.71)	.057
Adjusted model†		
Average for gestational age, TB	1	
Small for gestational age, TB	1.68 (1.11-2.53)	.013†
Large for gestational age, TB	1.52 (0.85-2.72)	.159
Average for gestational age, PTB	1.54 (1.07-2.23)	.021†
Small for gestational age, PTB	1.63 (0.90-2.92)	.105
Large for gestational age, PTB	1.96 (0.79-4.85)	.145

Average for gestational age, TB was the reference group.
*Controlled for child obesity, maternal obesity and diabetes, maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†$P < .05$.

Table XIV. Cord leptin levels by maternal obesity or diabetes (n = 1073)

Variables	Maternal obesity/diabetes		*P* value
	No (n = 794)	Yes (n = 279)	
Cord leptin (tertile), ng/mL			<.001*
Low	290 (36.52%)	68 (24.37%)	
Middle	271 (34.13%)	87 (31.18%)	
High	233 (29.35%)	124 (44.45%)	

*$P \leq .001$.

Table XV. Unadjusted association of maternal obesity or diabetes with cord leptin levels (n = 1073)

Variables	Maternal obesity/diabetes	
	OR (95% CI)	*P* value
Cord leptin (tertile), ng/mL		
Low	1	
High or middle	1.79 (1.31-2.43)	<.001*
Cord leptin (tertile), ng/mL		
Middle or low	1	
High	1.93 (1.45-2.55)	<.001*

*$P \leq .001$.

Table XVI. Sensitivity analysis (child's age <6 years): Prenatal, perinatal, and early childhood characteristics by clinical diagnosis of OSA in childhood (n = 1501)

Variables	OSA diagnosis		*P* value
	No (n = 1376)	Yes (n = 125)	
Maternal obesity and diabetes			.001*
No obesity, no diabetes	987 (71.73%)	72 (57.60%)	
Either obesity or diabetes	389 (28.27%)	53 (42.40%)	
Birth outcome			.001*
No PTB, No LBW	897 (65.19%)	63 (50.40%)	
Either PTB or LBW	479 (34.81%)	62 (49.60%)	
Child obesity			<.001*
No	1185 (86.12%)	93 (74.40%)	
Yes	191 (13.88%)	32 (25.60%)	
Maternal smoking during pregnancy			.260
No	1208 (87.79%)	114 (91.20%)	
Yes	168 (12.21%)	11 (8.80%)	
Race/ethnicity			.090
Black	838 (60.90%)	80 (64.00%)	
White	145 (10.54%)	7 (5.60%)	
Hispanic	289 (21.00%)	33 (26.40%)	
Other	104 (7.56%)	5 (4.00%)	
Maternal age (tertile), years			.579
Low	438 (31.83%)	37 (29.60%)	
Middle	484 (35.17%)	41 (32.80%)	
High	454 (32.99%)	47 (37.60%)	
Parity			.495
0	616 (44.77%)	52 (41.60%)	
≥1	760 (55.23%)	73 (58.40%)	
Child's sex			.668
Female	677 (49.20%)	59 (47.20%)	
Male	699 (50.80%)	66 (52.80%)	

*$P \leq .001$.

Table XVII. Sensitivity analysis (child's age <6 years): Crude and adjusted association of prenatal, perinatal, and early childhood factors with clinical diagnosis of OSA in childhood (n = 1501)

	Unadjusted model		Adjusted model*	
Variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Maternal obesity and diabetes				
No obesity, no diabetes	1		1	
Either obesity or diabetes	1.87 (1.29-2.71)	.001†	1.71 (1.16-2.51)	.007‡
Birth outcome				
No PTB, No LBW	1		1	
Either PTB or LBW	1.84 (1.28-2.66)	.001†	1.87 (1.29-2.73)	.001†
Child obesity				
No	1		1	
Yes	2.13 (1.39-3.28)	.001†	2.12 (1.36-3.28)	.001†
Maternal smoking during pregnancy				
No	1		1	
Yes	0.69 (0.37-1.32)	.263	0.73 (0.37-1.44)	.363
Race/ethnicity				
Black	1		1	
White	0.51 (0.23-1.12)	.092	0.65 (0.28-1.50)	.316
Hispanic	1.20 (0.78-1.83)	.411	1.26 (0.81-1.95)	.311
Other	0.50 (0.20-1.27)	.147	0.53 (0.21-1.35)	.185
Maternal age (tertile), years				
Low	1		1	
Middle	1.00 (0.63-1.59)	.991	0.99 (0.61-1.62)	.982
High	1.23 (0.78-1.92)	.376	1.07 (0.64-1.79)	.793
Parity				
0	1		1	
≥1	1.14 (0.79-1.65)	.495	1.05 (0.69-1.59)	.825
Child's sex				
Female	1		1	
Male	1.08 (0.75-1.56)	.668	1.09 (0.75-1.58)	.661

N (%), Cases in each group (percent of cases).
*Adjusted model has controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†$P \leq .00$.
‡$P < .01$.

Table XVIII. Sensitivity analysis (child's age ≥ 6 years): Prenatal, perinatal, and early childhood characteristics by clinical diagnosis of OSA in childhood (n = 1367)

	OSA diagnosis		
Variables	No (n = 1300)	Yes (n = 67)	*P* value
Maternal obesity and diabetes			.179
No obesity, no diabetes	969 (74.54%)	45 (67.16%)	
Either obesity or diabetes	331 (25.46%)	22 (32.84%)	
Birth outcome			.568
No PTB, No LBW	840 (64.62%)	41 (61.19%)	
Either PTB or LBW	460 (35.38%)	26 (38.81%)	
Child obesity			.002*
No	924 (71.08%)	36 (53.73%)	
Yes	376 (28.92%)	31 (46.27%)	
Maternal smoking during pregnancy			.592
No	1171 (90.08%)	59 (88.06%)	
Yes	129 (9.92%)	8 (11.94%)	
Race/ethnicity			.413
Black	899 (69.15%)	42 (62.69%)	
White	62 (4.77%)	2 (2.99%)	
Hispanic	263 (20.23%)	19 (28.36%)	
Other	76 (5.85%)	4 (5.97%)	
Maternal age (tertile), years			.339
Low	456 (35.08%)	25 (37.31%)	
Middle	406 (31.23%)	25 (37.31%)	
High	438 (33.69%)	17 (25.38%)	
Parity			.593
0	520 (40.00%)	29 (43.28%)	
≥1	780 (60.00%)	38 (56.72%)	
Child's sex			.190
Female	650 (50.00%)	28 (41.79%)	
Male	650 (50.00%)	39 (58.21%)	

*$P < .01$.

Table XIX. Sensitivity analysis (child's age ≥6 years): Crude and adjusted association of prenatal, perinatal, and early childhood factors with clinical diagnosis of OSA in childhood (n = 1367)

	Unadjusted model		Adjusted model*	
Variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Maternal obesity and diabetes				
No obesity, no diabetes	1		1	
Either obesity or diabetes	1.43 (0.85-2.42)	.181	1.34 (0.78-2.31)	.294
Birth outcome				
No PTB, No LBW	1		1	
Either PTB or LBW	1.16 (0.70-1.92)	.569	1.15 (0.69-1.93)	.587
Child obesity				
No	1		1	
Yes	2.12 (1.29-3.47)	.003†	1.98 (1.19-3.28)	.009†
Maternal smoking during pregnancy				
No	1		1	
Yes	1.23 (0.58-2.63)	.592	1.29 (0.59-2.84)	.527
Race/ethnicity				
Black	1		1	
White	0.69 (0.16-2.92)	.615	0.70 (0.16-3.10)	.641
Hispanic	1.55 (0.88-2.70)	.126	1.57 (0.89-2.77)	.121
Other	1.13 (0.39-3.23)	.824	1.21 (0.42-3.51)	.722
Maternal age (tertile), years				
Low	1		1	
Middle	1.12 (0.64-1.99)	.690	1.13 (0.62-2.06)	.687
High	0.71 (0.38-1.33)	.283	0.72 (0.36-1.42)	.338
Parity				
0	1		1	
≥1	0.87 (0.53-1.43)	.593	0.88 (0.51-1.51)	.635
Child's sex				
Female	1		1	
Male	1.39 (0.85-2.29)	.192	1.39 (0.84-2.30)	.202

N (%): cases in each group (percent of cases).
*Adjusted model has controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†$P < .01$.

Table XX. Sensitivity analysis (propensity score): Adjusted association of prenatal, perinatal, and early childhood factors with first clinical diagnosis of OSA in childhood before and after propensity score matching

	Before matching (n = 2867)		After matching (n = 2862)*	
Variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Maternal obesity and diabetes				
No obesity, no diabetes	1		1	
Either obesity or diabetes	1.63 (1.21-2.21)	.001†	1.63 (1.21-2.20)	.001†
Birth outcome				
No PTB, No LBW	1		1	
Either PTB or LBW	1.74 (1.30-2.32)	<.001†	1.74 (1.30-2.32)	<.001†
Child obesity				
No	1		1	
Yes	1.89 (1.37-2.62)	<.001†	1.89 (1.37-2.62)	<.001†
Race/ethnicity				
Black	1		1	
White	0.84 (0.45-1.57)	.587	0.84 (0.45-1.57)	.580
Hispanic	1.47 (1.06-2.05)	.022‡	1.47 (1.05-2.05)	.023‡
Other	0.66 (0.33-1.34)	.253	0.68 (0.34-1.36)	.273
Maternal age (tertile), years				
Low	1		1	
Middle	1.05 (0.73-1.51)	.807	1.04 (0.72-1.50)	.818
High	0.97 (0.66-1.43)	.874	0.97 (0.66-1.43)	.873
Parity				
0	1		1	
≥1	0.99 (0.72-1.37)	.964	0.99 (0.72-1.36)	.961
Maternal smoking during pregnancy				
No	1		1	
Yes	0.94 (0.58-1.53)	.811	0.95 (0.59-1.54)	.833
Child's sex				
Female	1		1	
Male	1.16 (0.87-1.54)	.321	1.16 (0.87-1.54)	.318
Child's age, years				
<6	1		1	
≥6	0.43 (0.31-0.59)	<.001†	0.43 (0.31-0.59)	<.001†

*Adjusted model was controlled for maternal age, parity, race/ethnicity, maternal smoking during pregnancy, child's sex, and child's age.
†$P \leq .001$.
‡$P < .05$.