Maternal Pre-Pregnancy Obesity and Recurrent Wheezing in Early Childhood

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A number of studies have linked obesity with asthma in adults and children. Few longitudinal studies have evaluated the effect of maternal pre-pregnancy obesity on either asthma or early childhood respiratory morbidity, and these have not been in urban, nonwhite populations. We sought to determine whether pre-pregnancy obesity was associated with recurrent wheezing in an urban, nonwhite population. This study includes 1,191 children from the Boston Birth Cohort (1998–present) followed prospectively to a mean age of 3.0 ± 2.4 years with study visits aligned with the pediatric primary care schedule. Multivariate logistic regression was used to evaluate the associations of maternal pre-pregnancy obesity (body mass index ≥ 30) with recurrent wheezing (≥ 4 lifetime episodes). Secondary outcomes included log-transformed cord-blood immunoglobulin E (Phadia), and physician diagnoses of eczema and food allergy. Pre-pregnancy obesity was present in 20.7% of mothers. Of the 1,191 children, 60 (5%) developed recurrent wheezing. Children of obese mothers had an increased risk of recurrent wheezing (adjusted odds ratio, 95% confidence interval: 3.51, 1.68–7.32). These associations persisted even after adjustment for fetal growth status. In contrast, maternal obesity was not associated with eczema or food allergy, and was inversely associated with log cord-blood immunoglobulin E (β , 95% confidence interval: -0.34 , -0.66 to -0.02). In this predominantly urban, multiracial/ethnic birth cohort, maternal pre-pregnancy obesity was associated with an increased risk of recurrent wheezing. This association was not explained by fetal growth or increased atopy. Maternal pre-pregnancy obesity is a prevalent risk factor for respiratory morbidity in this urban, nonwhite population.

Introduction

PRE-PREGNANCY OBESITY AFFECTS 20% of American women of childbearing age.¹ While obesity has been associated with the development of asthma in studies of both adults and children,² only a few studies have evaluated the association of maternal pre-pregnancy obesity with respiratory morbidity in the offspring.^{3–5} A recent Dutch study suggested that maternal pre-pregnancy body mass index (BMI) was a risk factor for asthma and airway reactivity at 8 years of age in children who were at high risk due to a positive family history of asthma.³ Only one of these studies was in an urban population with significant numbers of nonwhite subjects, and this study did not evaluate the role of family history of atopic disease.⁴ Further, in both studies that evaluated young children, questionnaire recall of wheezing⁵ or MD diagnosis of asthma at 3 years⁴ of age was used as

an outcome. These outcomes are problematic due to recall bias and parental misclassification of wheezing^{6–8} as well as diagnostic uncertainty of an asthma diagnosis in young children.⁹

There are a number of question that are not answered in the existing literature. It would be important to confirm the findings of the U.S. study⁴ as to whether maternal obesity is a risk factor for respiratory morbidity in urban, nonwhite populations. These groups have high rates of obesity¹⁰ and also have a disproportionately high burden of asthma morbidity.^{11–13} It is not known whether this association would be modified by atopy in an urban, low-income U.S. population similar to the findings of the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort.¹⁴ Further, it is unclear whether any association of maternal obesity with respiratory morbidity in the offspring is mediated by large for gestational age (LGA) delivery¹⁵ that has been associated

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with wheezing and asthma in early childhood,^{16–19} atopic sensitization, elevated serum immunoglobulin E (IgE),^{20–23} and atopic dermatitis.^{24,25} Similarly, prematurity and low birth weight has been associated with both maternal obesity²⁶ and with wheezing in early life.^{27,28} One of the existing studies evaluated the effect of a high ponderal index⁴ and another evaluated low birthweight,⁵ but none of the studies have evaluated the role of fetal growth overall on the association of maternal obesity on wheezing in early childhood.

We sought to determine whether maternal pre-pregnancy obesity (determined retrospectively by questionnaire at birth) was associated with recurrent wheezing in a prospective, urban, primarily nonwhite birth cohort, and whether the association was mediated via either fetal growth or by atopy.

Materials and Methods

Patient population

The Boston Birth Cohort (BBC) is an ongoing general-population, multi-ethnic cohort that includes subjects from a range of socioeconomic strata that includes inner-city poor up to middle-class subjects, originally initiated in 1998 at the Boston Medical Center to study adverse birth outcomes, particularly preterm birth.^{29,30} Any woman admitted to the Labor and Delivery floor at the Boston Medical Center who delivered a singleton live infant was eligible. The Children's Memorial Hospital (CMH) Institutional Review Board (IRB; CMH IRB approval no. 2004-12324), and the Boston Medical Center IRB (BMC IRB approval no. H-23525) approved the parent study protocol. The Boston Medical Center IRB (BMC IRB approval no. H-23227) and CMH IRB (CMH IRB approval no. 2004-12324) also approved the study protocol and consent process whereby all infants enrolled in the BBC are eligible for the postnatal follow-up study to determine postnatal health outcomes as detailed below.

Data collection and measurements

Recruitment of the birth cohort. Mother–infant pairs were recruited 24 to 48 h postdelivery. After obtaining signed written informed consent, we interviewed subjects using a structured questionnaire. We also reviewed maternal and infant medical records using a standardized abstraction form to obtain clinical data and birth outcomes.

Postnatal follow-up study

Individuals recruited by BBC and who identified themselves as planning to receive primary care at the Boston Medical Center were invited to participate in the postnatal follow-up study, the Children's Health Study (CHS), starting in 2004.³¹

After written informed consent was obtained from the biological mother, visits were scheduled at 6–12 months, 2, 4, and 6 years consistent with the child's pediatric primary care visit schedule. Mothers were interviewed using structured questionnaires at each visit.

Since 2004, there were 3,326 children newly enrolled into the BBC. Of those, 1,569 identified the Boston Medical Center as their preferred site for future pediatric primary care, and thus were eligible for the follow-up study. Of those, 1,190 were approached and 1,116 agreed to participate in the CHS. Approximately 784 children who were born before 2004 also

were approached and 678 agreed to participate, leading to the current CHS enrollment of 1,794 subjects (enrollment of 91% of all those approached). Of those enrolled in the CHS, cord-blood IgE data and key covariate data were available in 1,191 subjects, the sample for this analysis.

Assessment of maternal pre-pregnancy BMI. Maternal pre-pregnancy BMI was calculated by pre-pregnancy weight and height obtained from the maternal postpartum questionnaire interview. Since we had few underweight subjects (3.27%) and there were no differences in the associations between underweight (<18.5) and normal (18.5–24.9) on exploratory analysis, we categorized subjects as control (<25), overweight (25–29.9) and obese (≥30). For comparison, we had a first trimester BMI from the obstetric record with height and weight measured in the obstetric clinic of a subset of subjects ($N = 326$ or 27% of the cohort). The Pearson correlation of first trimester BMI and reported prenatal BMI was 0.87. Individuals who had first trimester BMI measurements available did not differ from those without this information in rates of maternal obesity, demographic, and socioeconomic status (SES) variables.

Assessment of fetal growth. Fetal growth was based on standardized birth weight (SBWT). SBWT is defined as measured birth weight standardized by mean and variance in the stratum of corresponding ethnic group, sex, and gestational week in the reference population using ~15,000 births born at Boston Medical Center during 1998–2003.³² LGA was defined as SBWT >90th percentile of the SBWT in the reference population at the same gestational week. Fetal growth restriction (FGR) was defined as SBWT <10th percentile of the SBWT in the reference population in the same gestational week.

Other clinical variables. Gestational age was assessed based on both the first day of the last menstrual period as recorded in the maternal medical record and early (<20 weeks) prenatal ultrasound. This approach has been used in large hospital-based preterm studies and in our ongoing funded preterm studies.^{29,33,34} Subjects were categorized as having preterm delivery if they were <37 weeks gestation at delivery. Infant race/ethnicity was based on self-report provided by the mother and categorized as nonhispanic black, nonhispanic white, hispanic, or other. Maternal atopy was considered to be present if the mother had reported being diagnosed with any one of the following conditions: atopic dermatitis, allergic rhinitis, or asthma. Pediatric variables, such as the presence of eczema or food allergy, were determined by medical record review of diagnostic codes.

Outcome measures

Given the mean age of our subjects and the natural history of wheezing illness, a physician diagnosis of asthma is less conclusive in this age range.³⁵ Recurrent wheezing (4 or more episodes of medically attended wheezing illness in the subject's lifetime) was the primary outcome. If an individual had a second episodes within the space of 2 weeks or had multiple types of encounters (office, emergency room, or hospitalization) these were counted as a single episode. Four or more episodes of medically attended wheezing illness by age 3 years has been used as a criterion in asthma predictive indices.³⁶ Given our cohort's mean age of 3 years, we felt that with this categorization, individuals classified as recurrent wheezers in our cohort would be similar in level of morbidity to other studies which have used asthma predic-

tive indices in this age range.^{35,36} Episodes were determined prospectively using a unified electronic medical record (with data extracted in an ongoing basis) to evaluate all instances of contact with the Boston Medical Center system for each of the subjects, including well and ill/unscheduled visits (office visits, urgent care, emergency department, and inpatient encounters). This is the most complete and accurate method to assess episodes of wheezing requiring medical attention of CHS subjects who receive their urgent and emergent medical care at Boston Medical Center. This outcome was evaluated both in the cohort as a whole as well as in a secondary analysis limited to those children who were over 2 years of age at time of last follow-up.

To evaluate whether maternal pre-pregnancy BMI was associated with other atopic diseases, we evaluated a number of other secondary outcomes, including cord-blood IgE and also MD diagnosis of eczema, which was determined by standardized medical record abstraction. Cord-blood IgE was included as a marker for the fetal immune response. Cord-blood IgE was determined using a high sensitivity Immunocap method with level of detection of 0.1 kU/L (Phadia) similar to that used for specific IgE determination. For the purposes of this analysis IgE levels were log transformed to normalize the distribution.

Statistical analyses

A total of 1,191 children from the BBC completed at least one postnatal follow-up visit and had cord-blood IgE available. We examined the association of maternal pre-pregnancy overweight and obesity with recurrent wheezing by multivariate logistic regression analysis. Aside from the key determinant variables, demographic variables, and measures of SES, potential confounding variables were retained in the model based on significance (differentially distributed by primary predictor, and $P < 0.2$ for association with the outcome). Infant factors were limited to the child's current age, sex, exposure to tobacco smoke *in utero*, preterm delivery (< 37 weeks of gestation), and ongoing passive smoke exposure in the home (as reported by the parent). We included fetal growth variables (small and LGA), despite lack of significance on uni-variate analyses given their known association with maternal obesity and previously reported associations with asthma and atopy. Gestational diabetes, as documented in the medical record, was not a confounder and has not been consistently associated with wheezing in prior studies. However, based on its previously reported association with maternal obesity, we carried out a sensitivity analysis to evaluate whether inclusion of gestational diabetes modified this association. Other traditional infant risk factors such as breastfeeding, firstborn status, presence of additional smokers in the home other than the mother, and type of delivery (c-section) were not confounders and were excluded. (In keeping with this, sensitivity analyses including these variables did not alter the magnitude, direction, or significance of the association of maternal weight category with recurrent wheezing in the offspring.) Maternal factors included maternal ethnicity (black, white, Hispanic, or other), and SES as measured by highest level of maternal education achieved. For analyses of recurrent wheezing, we also included maternal history of atopic diseases and self-reported MD diagnosis of maternal asthma. We repeated the analyses for recurrent wheezing limited to those children who were > 2 years of age ($N = 655$)

at time of last follow-up. This subgroup analysis was carried out to decrease the potential for residual confounding which may be due to any differences in duration of follow-up between those with recurrent wheezing and those who did not meet our criteria for recurrent wheezing.

We conducted a number of secondary analyses. We performed a zero inflated negative binomial regression on the number of episodes of wheeze to evaluate if the relationship between maternal obesity and wheezing persists when wheezing is evaluated as a count outcome. We carried out analyses to determine if the effect of maternal obesity was mediated by predisposing to atopy in the child. Specifically, we repeated the main analyses for recurrent wheezing with the inclusion of covariates representing manifestations of early life atopy (eczema and log cord-blood IgE levels). To further explore whether maternal obesity had a broad effect on atopic predisposition, we performed multivariate logistic regression analysis to examine the association of maternal overweight and obesity on cord-blood IgE, eczema, and food allergy. Finally, we carried out a subgroup analysis on the children with BMI available in the first year of life to evaluate whether the effect of maternal pre-pregnancy obesity was attenuated by inclusion of child BMI variables (child BMI at 1 year, child BMI at 3 years, and change in child BMI between 1 and 3 years of age). The covariate models for these analyses were similar to the wheezing models described above, but the variable of firstborn status was added due to associations with these outcomes. For this analysis BMI was retained as a categorical variable based on the suggestion of a nonlinear relationship between maternal BMI and cord-blood IgE.

All analyses were performed using statistical software STATA for Windows 9.20 (STATA, College Station, TX).

Results

Demographic characteristics of the cohort

The BBC is a predominantly low-income, multi-ethnic population. Most (59.1%, $N = 704$) mothers were African American, and 21% ($N = 250$) were Latino. Approximately, one-third (30.7%) had not completed high school, but 34.4% had some postsecondary education. The mean age of children at follow-up was 3.0 (standard deviation 2.4) years, with equal numbers of males and females. Of 1,191 mothers, 384 (32.2%) women were overweight and 247 (20.7%) were obese. Four or more episodes of wheezing were present in 60 (5%) of the children.

Table 1 includes the characteristics of the cohort comparing controls to overweight and obese mother-infant dyads. Obese and overweight mothers were more likely to be African American, less likely to have secondary or postsecondary schooling, and more likely to be multiparous and have cesarean section deliveries. Maternal atopy and LGA delivery were both more common in those pregnancies complicated by obesity.

Association of maternal overweight and obesity with wheezing outcomes

The association of maternal pre-pregnancy overweight and obesity with recurrent wheezing is displayed in Table 2. The univariate associations of potential covariates is presented in Supplementary Table S1 (Supplementary Data are available online at www.liebertonline.com/ped). Obesity was associated with recurrent wheezing [odds ratio (OR),

TABLE 1. CHARACTERISTICS OF THE COHORT STRATIFIED BY MATERNAL BODY MASS INDEX CATEGORIES

	Control	Overweight	Obese
	N = 560	N = 384	N = 247
<i>Baseline maternal characteristics</i>			
Age (years), mean $\pm$ SD	27.5 $\pm$ 6.4	30.1 $\pm$ 6.7 ^a	28.7 $\pm$ 6.3 ^b
Race (%)			
Black	53.9 ^b	61.7 ^b	66.8 ^b
White	7.9 ^c	6.3 ^c	3.2 ^c
Hispanic	21.3	20.8	20.6
Other	17.0 ^b	11.2 ^b	9.3 ^b
Education (%)			
< High school	30.1	28.8	34.8
High school	31.4 ^c	39.3 ^c	35.6 ^c
Some college	38.6 ^c	31.9 ^c	29.6 ^c
Maternal atopy (%)	29.7 ^b	28.8 ^b	42.3 ^b
<i>Baseline infant characteristics</i>			
Child's age (years), mean $\pm$ SD	2.9 $\pm$ 2.3	3.0 $\pm$ 2.3	3.2 $\pm$ 2.5
Female sex (%)	53.0	50.3	49.0
Premature birth, <37 weeks of gestation (%)	22.0	26.3	21.1
Firstborn child (%)	48.6 ^a	37.8 ^a	32.8 ^a
C-section delivery	24.7 ^a	36.1 ^a	40.7 ^a
Exclusive breastfeeding (%)	6.3	6.5	3.2
Fetal growth (%)			
FGR	15.5	10.9	10.8
LGA	7.3 ^b	9.4 ^b	16.1 ^b
Passive smoke exposure			
In utero (throughout pregnancy) (%)	9.6	7.3	10.5
Postnatal (%)	13.4	13.1	18.7
Outcomes			
Recurrent wheezing (≥ 4 episodes) (%)	3.2 ^b	4.7 ^b	9.7 ^b
Eczema (%)	42.1	39.0	41.8
Food allergy (%)	7.6	6.9	8.3
Log cord-blood IgE mean $\pm$ SD	-1.6 $\pm$ 2.1	-1.7 $\pm$ 2.2	-1.8 $\pm$ 2.0

Children who have wheezed ≥ 4 times were considered to have recurrent wheezing.

Chi-square test was used for comparison of categorical measures across maternal obesity categories and analysis of variance for comparison of continuous measures.

Fetal growth restriction (FGR) is defined as SBWT <10th percentile of the SBWT in the reference population at the same gestational week.

Large for gestational age (LGA): is defined as SBWT >90th percentile of the SBWT in the reference population at the same gestational week.

Standardized birth weight (SBWT) is defined as birth weight standardized by mean and variance in the stratum of corresponding ethnic group, sex, and gestational week in the reference population using around 15,000 births born at Boston Medical Center during 1998–2003.

^a $P < 0.001$ versus control.

^b $P < 0.01$.

^c $P < 0.05$.

SD, standard deviation; IgE, immunoglobulin E.

95% confidence interval (CI): 3.51, 1.68–7.32]. While the direction of effect was similar for overweight, the associations were not significant for recurrent wheezing (OR, 95% CI: 1.58, 0.75–3.30). We included gestational diabetes mellitus in the model as a sensitivity analysis and found minimal change in the magnitude or significance of the association of maternal obesity with recurrent wheezing (OR, 95% CI: 3.27, 1.50–7.12). When the analysis was restricted to children over 2 years of age, the association with obesity persisted (OR, 95% CI: 3.44, 1.55–7.66). A negative binomial regression evaluating the association of maternal pre-pregnancy obesity with the number of times of wheezing also found a significant relationship ($\beta = 0.62$, 95% CI: 0.27–0.96). In all of the above-described sensitivity analyses, the direction and magnitude of the associations of maternal overweight did not materially change and remained nonsignificant.

The magnitude and significance of the associations of maternal pre-pregnancy obesity with wheezing did not

change when we included 2 markers of fetal and early childhood atopic response, cord-blood IgE level and eczema, in the analysis (Supplementary Table S2). This was true for both analyses including all children (OR, 95% CI: 3.56, 1.64–7.72) as well as analyses including only children over 2 years of age (OR, 95% CI: 3.67, 1.58–8.51). However, as shown in Table 3, inclusion of child BMI variables resulted in an attenuation of the effect of maternal obesity on recurrent wheezing, though the effect remained significant and the odds ratio ranged from 3.24 (inclusion of the child's BMI at 3 years) to 3.87 (inclusion of change in BMI over the first 3 years of life).

Association of maternal overweight and obesity with other atopic outcomes

On linear regression, there was a negative association of maternal obesity with the log of cord-blood IgE (β , 95% CI: -0.34, -0.66 to -0.02). This analysis was also repeated using a more conventional level of detection for IgE of >0.35 kU/L

TABLE 2. ASSOCIATION OF MATERNAL BODY MASS INDEX CATEGORY WITH RECURRENT WHEEZING (≥ 4 EPISODES) ADJUSTING FOR FETAL GROWTH^a

Maternal BMI categories	Total N	Wheeze N (%)	OR	(95% CI)
<i>All children</i>				
Control	560	18 (3.2)	1.00	—
Overweight	384	18 (4.7)	1.58	0.75, 3.30
Obese	247	24 (9.7)	3.51	1.68, 7.32
<i>Only children over 2 years of age at time of follow-up</i>				
Control	302	16 (5.3)	1.00	—
Overweight	212	17 (8.0)	1.77	0.81, 3.87
Obese	141	19 (13.5)	3.44	1.55, 7.66

Basic model for recurrent wheezing is adjusted for children's age, sex, maternal race (black/white/Hispanic/other), maternal education (<high school, high school, >high school), maternal history of atopic diseases (including food allergy, atopic dermatitis, asthma, and hay fever), maternal asthma, premature delivery (<37 weeks), smoking during pregnancy, smoke exposure in the home, FGR, and LGA.

FGR is defined as SBWT <10th percentile of the SBWT in the reference population at the same gestational week.

LGA is defined as SBWT >90th percentile of the SBWT in the reference population at the same gestational week.

^aFetal growth was characterized by use of SBWT. SBWT is defined as birth weight standardized by mean and variance in the stratum of corresponding ethnic group, sex, and gestational week in the reference population using around 15,000 births born at Boston Medical Center during 1998–2003.

BMI, body mass index; CI, confidence interval; OR, odds ratio.

and the overall direction and significance of this finding was unchanged (data available on request). This association (Supplementary Table S3) was not statistically significant for maternal overweight (β , 95% CI: -0.11 , -0.39 to 0.16). There were no associations between maternal pre-pregnancy obesity or overweight with eczema and food allergy (Table 4).

Discussion

In this prospective, urban, primarily nonwhite birth cohort study, we found that maternal pre-pregnancy obesity was prevalent (occurring in 20.7% of the sample) and associated with a nearly 4-fold increase in the risk of recurrent

wheezing in young children. Even after accounting for children's BMI, the risk remained up to 3.2 to 3.9-fold higher. The effect of maternal pre-pregnancy obesity was independent of both LGA and maternal atopy, and there was no evidence of an interaction between maternal obesity and maternal atopy on recurrent wheezing. In keeping with this, maternal pre-pregnancy obesity did not promote an atopic predisposition in the infant as manifested by childhood eczema and actually was associated with a decrease in cord-blood IgE, a marker of the fetal immune response.

Our study confirms the findings by Reichman et al.,⁴ which was also in an urban population with significant numbers of nonwhite subjects. Indeed, we find a higher risk

TABLE 3. ASSOCIATION OF MATERNAL BODY MASS INDEX CATEGORY WITH RECURRENT WHEEZING (≥ 4 EPISODES) ADJUSTING FOR FETAL GROWTH^a

Maternal BMI categories	Total N	Wheeze N (%)	OR	(95% CI)
<i>Model without child BMI</i>				
Control	560	18 (3.2)	1.00	—
Overweight	384	18 (4.7)	1.58	0.75, 3.30
Obese	247	24 (9.7)	3.51	1.68, 7.32
<i>Model with child BMI at 1 year (N = 837)</i>				
Control	380	11 (2.9)	1.00	—
Overweight	287	14 (4.9)	1.67	0.68, 4.05
Obese	170	19 (11.2)	3.77	1.57, 9.07
<i>Model with child BMI at 3 years (N = 946)</i>				
Control	413	17 (4.0)	1.00	—
Overweight	321	18 (5.6)	1.44	0.67, 3.08
Obese	195	23 (11.2)	3.24	1.50, 7.05
<i>Model with change in Child BMI over the first 3 years of life (N = 837)</i>				
Control	380	11 (2.9)	1.00	—
Overweight	287	14 (4.9)	1.70	0.70, 4.12
Obese	170	19 (11.2)	3.87	1.61, 9.31

Basic model for recurrent wheezing is adjusted for children's age, sex, maternal race (black/white/Hispanic/other), maternal education (<high school, high school, >high school), maternal history of atopic diseases (including food allergy, atopic dermatitis, asthma, and hay fever), maternal asthma, premature delivery (<37 weeks), smoking during pregnancy, smoke exposure in the home, FGR, and LGA.

FGR is defined as SBWT <10th percentile of the SBWT in the reference population at the same gestational week.

LGA is defined as SBWT >90th percentile of the SBWT in the reference population at the same gestational week.

^aFetal growth was characterized by use of SBWT. SBWT is defined as birth weight standardized by mean and variance in the stratum of corresponding ethnic group, sex, and gestational week in the reference population using around 15,000 births born at Boston Medical Center during 1998–2003.

TABLE 4. ASSOCIATION OF MATERNAL BODY MASS INDEX CATEGORY WITH EARLY CHILDHOOD ATOPIC DISEASES (ECZEMA AND FOOD ALLERGY)

Maternal BMI	Total N	Case N (%)	OR	(95% CI)
<i>Eczema</i>				
Control	451	190 (42.1)	1.0	—
Overweight	331	129 (39.0)	0.91	0.67, 1.23
Obese	206	86 (41.7)	0.98	0.69, 1.39
<i>Food allergy</i>				
Control	433	33 (7.6)	1.0	—
Overweight	316	22 (7.0)	0.91	0.51, 1.62
Obese	193	16 (8.3)	0.93	0.47, 1.82

Basic model for recurrent wheezing is adjusted for children's age, sex, maternal race (black/white/Hispanic/other), maternal education (<high school, high school, >high school), maternal history of atopic diseases (including food allergy, atopic dermatitis, asthma, and hay fever), parity (0, ≥ 1), premature delivery (<37 weeks), FGR, and LGA.

(as opposed to only a 1.5-fold increased risk) for medically attended episodes of recurrent wheezing than Reichman found for a parent-reported diagnosis of asthma at age 3 years. This finding was robust even after accounting for childhood BMI or change in BMI over the first 3 years of life. Notably, child BMI was not evaluated in both of the studies that evaluated wheezing or asthma in the first few years of life.^{4,5} This suggests that only a portion of the effect is mediated by any association of maternal and child BMI. Also, we expand on their findings by evaluating the role of atopy in the association with early life wheezing. Scholtens et al. found that maternal pre-pregnancy obesity was a risk factor for asthma at 8 years of age only in children who were at high risk due to a positive family history of asthma.³ In our U.S. population, the association between maternal obesity and the likelihood of recurrent wheezing was independent of maternal atopy. However, asthma and recurrent wheezing are not equivalent outcomes, and it is still possible that there may be effect modification by family history of atopy on the association of maternal obesity with the development of asthma by school years.

Our findings also suggest that maternal obesity has effects independent of both LGA and FGR, and may operate via nonatopic mechanisms to increase the rates of early life respiratory morbidity in the offspring. This finding is relevant since prior studies found that LGA was associated not only with asthma,^{16–18,37} but also with sensitization, and IgE levels.^{20–23} We also did not find that FGR resulted in any change in the effect of maternal obesity on recurrent wheezing. This is important since prematurity and low birth weight have been associated with both maternal obesity,²⁶ and with wheezing in early life.^{27,28} One of the existing studies evaluated the effect of a high ponderal index⁴ and another evaluated low birthweight,⁵ but neither of the studies have evaluated the role of both LGA and FGR on the association of maternal obesity on wheezing in early childhood.

We used an outcome of 4 or more episodes of recurrent wheezing requiring medical attention documented in the electronic medical record (EMR), which minimized the possibility of either recall bias and parental misclassification of wheezing^{6–8} or diagnostic uncertainty of an asthma diagnosis in young children.⁹ Medically documented recurrent wheezing is an important outcome for 2 reasons. First, in this

cohort the vast majority of care is captured by the EMR and this is a reliable outcome that helps to evaluate the likelihood that a risk factor will result in morbidity. Second, it allows us to evaluate the effects of early life risk factors on respiratory outcomes without limiting the outcome to those who have either risk factors for asthma or a diagnosis of asthma who represent a minority of the subjects with respiratory symptoms in the first years of life.

Additional studies are needed to understand the possible mechanism underlying the associations we found in this study. One possible mechanism is worth discussion. A pro-inflammatory state associated with adipokine dysregulation has been hypothesized to play a role in the association of asthma and obesity.³⁸ Maternal adipokine disturbances resulting in similar changes in infant levels are unlikely to be responsible for the association we found. Fetal adipokines such as adiponectin are differentially regulated from maternal levels.³⁹ Further, fetal adipokine exposures may have different effects than those seen in adults. For example, cord-blood levels of adiponectin may actually be associated with increased adiposity by 3 years of age,⁴⁰ and along with familial atopy may increase the risk of respiratory morbidity in the first 2 years of life.⁴¹ Although it is also possible that there are local inflammatory and remodeling changes in the fetal airways that are associated with maternal obesity and systemic inflammation, we are not able to evaluate this in the current study.

Despite the lack of a clear mechanism, our results may have significant public health impact. In the United States, obesity is present in 20% of women of childbearing age in the general population, and may be even more prevalent in urban, nonwhite populations.¹⁰ As such, this finding may have relevance to racial health disparities in rates of early childhood wheezing, which remains a prevalent problem with high rates of morbidity.⁴²

This study has the following limitations. First, self-reported BMI is affected by a well-established systematic underreporting of weight by up to 5 pounds.⁴³ If anything, this under reporting of BMI would be nondifferential and bias our findings toward the null hypothesis. Also, the strong correlation with first trimester BMI measured in the obstetric clinic in a subset of subjects provides some validity of this measure. Second, we do not address the outcomes of asthma or persistent wheezing due to the young age of the cohort. This reinforces the need to follow this population over time to determine if maternal BMI is associated with asthma (not just early childhood recurrent wheeze) similar to the findings of the Dutch study by Scholtens et al.³ However, recurrent wheezing is an important endpoint given the level of morbidity in inner-city populations during early childhood.⁴² Third, there are other potential unmeasured confounders, including weight gain during pregnancy, exposure to paternal smoking (if the father lives in another residence), postnatal child diet, and prenatal maternal diet,^{44,45} which may influence levels of immuno-modulatory factors such as vitamin D or folate.^{46–49} However, some studies of these potential confounding factors such as prenatal maternal diet have not found associations with infant wheezing or asthma.^{50–53} This is a predominantly low-income, urban cohort. Other early childhood populations will need to be studied to evaluate the generalizability of our findings.

In conclusion, maternal pre-pregnancy obesity was associated with recurrent wheezing in early childhood. This was

independent of the effects of fetal growth and early life atopy. We feel that given its high prevalence, especially in low-income nonwhite populations, maternal obesity may represent one modifiable risk factor for early childhood respiratory morbidity in these populations.

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Author Disclosure Statement

None of the authors have conflicts of interest to disclose.

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