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Association of Birth Weight With Asthma-Related Outcomes at Age 2 Years

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Abstract

Summary. Background: Although lower birth weight associated with prematurity raises the risk of asthma in childhood, few prospective studies have examined higher birth weight, and few have separated the two components of birth weight, fetal growth and length of gestation.

Objective. To examine the associations of fetal growth and length of gestation with asthma-related outcomes by age 2 years.

Methods. We studied 1,372 infants and toddlers born after 34 weeks' gestation in Project Viva, a prospective cohort study of pregnant mothers and their children. The main outcome measures were parent report of (1) any wheezing (or whistling in the chest) from birth to age 2 years, (2) recurrent wheezing during the first 2 years of life, and (3) doctor's diagnosis of asthma, wheeze or reactive airway disease ("asthma") by age 2. We calculated gestational age from the last menstrual period or ultrasound examination, and determined birth weight for gestational age z-value ("fetal growth") using US national reference data.

Results. Infants' mean birth weight was 3,527 (SD, 517; range, 1,559–5,528) grams. By age 2 years, 34% of children had any wheezing, 14% had recurrent wheezing, and 16% had doctor-diagnosed asthma. After adjusting for several parent, child, and household characteristics in logistic regression models, we found that infants with birth weight $\geq 4,000$ g were not more likely to have any wheezing (odds ratio (OR), 0.91; 95% confidence interval (CI): 0.62, 1.34) or doctor-diagnosed asthma (OR, 0.80; 95% CI: 0.49, 1.31) than infants with birth weight 3,500–3,999 g. In models examining length of gestation and fetal growth separately, neither the highest nor the lowest groups of either predictor were associated with the three outcomes. Boys had a higher incidence of asthma-related outcomes than girls, and exposure to passive smoking, parental history of asthma, and exposure to older siblings were all associated with greater risk of recurrent wheeze or asthma-related outcomes at age 2 years.

Conclusion. Although male sex, exposure to smoking, parental history of asthma, and exposure to older siblings were associated with increased risk of wheezing and asthma-related outcomes in this prospective study of children born after 34 weeks gestation, fetal growth and length of gestation were not.

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Keywords

asthma; birth weight; fetal growth; length of gestation; wheezing

INTRODUCTION

Asthma, the most common cause of chronic childhood disease in the US, is the diagnosis most frequently resulting in admission to pediatric hospitals, and accounts for over \$6 billion in health care costs per year.¹ The diagnosis of asthma is difficult in infants and toddlers given their age and the frequency of isolated wheezing for other reasons (e.g., respiratory infections). Nevertheless, evidence suggests that half of all cases of childhood asthma are diagnosed by age 3 years, and 80% of all childhood asthma cases are diagnosed by 5.^{2,3} Thus, it is important to investigate possible early-life risk factors for asthma incidence.

Obesity appears to be a risk factor for childhood asthma,^{4–6} and birth weight is directly associated with body mass index (BMI) in childhood,⁷ so it makes sense to examine the association between birth weight and asthma. Although several investigators have found a relationship between lower birth weight and incident asthma,^{8–10} the opposite extreme, the relationship between higher birth weight and risk of asthma, remains understudied.^{11–14} In addition, most studies model the birth weight–asthma association using birth weight as a single, continuous term or as a dichotomous variable (i.e., low birth weight: yes/no). Either approach precludes observation of a curvilinear association. Finally, many previous studies have either retrospectively collected gestational age data or have not adjusted for gestational age. It is important to distinguish the relative contributions of fetal growth and length of gestation, because they suggest different etiologies, that is, the impact of lung immaturity versus nutritional or hormonal “fetal programming.”^{15,16}

The purpose of this study was to examine the associations of birth weight, especially higher birth weight, and of fetal growth and length of gestation separately, with incidence of asthma-related outcomes at age 2 years among a prospective cohort of pregnant women and their offspring.

METHODS

Subjects/Study Design

Study subjects were participants in Project Viva, a prospective observational cohort study of gestational diet, pregnancy outcomes, and offspring health. We have previously reported details of recruitment and follow up through pregnancy.¹⁷ Of the 2,128 women who delivered a live infant, 303 mothers subsequently disenrolled from the study and we excluded 45 infants whose gestational age at birth was less than 34 weeks. At the time of analysis, data were available for 1,372 participants (77% of those eligible) who had completed the 2-year survey and were not missing data for our main exposures. Although we did not measure the reasons why mothers disenrolled, we were able to compare sociodemographic and anthropometric characteristics between the 1,372 participants in our study and the full 2,083 participants who delivered full term, live births. We found only small differences between the two. For example, the subjects that contributed to our analyses are slightly more educated (28% vs. 35% <college education) have slightly higher household incomes (11% vs. 14% <\$40,000/year), and have slightly higher birth weights for gestational age z-values (0.23 vs. 0.18), but do not differ on mean birth weight or gestational age.

We collected demographic and health history information via interviews and self-administered questionnaires at two time points in pregnancy, and at 6, 12, and 24 months after delivery.

Measurements

Main Exposure—We obtained infant birth weight from the hospital clinical record. We calculated gestational age from the last menstrual period and if the estimate of gestational age from the second trimester ultrasound differed by more than 10 days, we used the ultrasound instead. Approximately 12% (N = 59 or 1,372) of gestational ages were based on ultrasound information. For the rest, we calculated gestational age from the last menstrual period. We determined birth weight for gestational age z-value (“fetal growth”) by use of US national reference data.¹⁸ In statistical analyses, we examined the risk of asthma-related outcomes within quartiles of fetal growth, and within pre-specified categories of birth weight (1,500 to <3,000 g, 3,000 to <3,500 g, 3,500 to <4,000 g, and ≥4,000 g) and gestational age at birth (34 to <37 weeks, 37 to <39 weeks, 39 to <41 weeks, and ≥41 weeks).

Outcome Measures—The main outcome measures were (1) any wheezing (or whistling in the chest) by age 2 years defined as parent’s report of wheezing symptoms anytime from birth to age 2 years, (2) recurrent wheezing by age 2 years defined as parent’s report of wheezing symptoms in both the first and second years of life, and (3) parent’s report of a doctor diagnosis of asthma, wheeze or reactive airway disease (“asthma”) at anytime between birth and age 2 years. We considered the third outcome as doctor-diagnosed “asthma”. In analyses incorporating the recurrent wheeze outcome, we excluded 204 children who had wheezing reported in the first or second year of life, but not both, and 67 children with missing data. Thus, the sample size for recurrent wheeze was reduced to 1,101.

Other Measures—Mothers self-reported information about maternal age, height, pre-pregnancy BMI, household income, passive smoking exposure in the first year of life, duration of breastfeeding, maternal and paternal history of asthma, and the number of children under the age of 12 living in the household.

Statistical Analysis

We used multiple logistic regression models to examine the associations between birth weight, and in separate models fetal growth and length of gestation, with our main outcomes. Because we hypothesized a U-shaped relationship between predictors and outcomes, the reference group for each predictor was the third of the four categories. We report odds ratios and 95% confidence intervals for our main exposure and covariates. We investigated for effect modification by sex using multiplicative interaction terms and stratification. We performed all analyses using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

Study Participant Characteristics

The study group was 74% white, 12% black, 6% Hispanic, 5% Asian, and 4% multiracial or other. The mean age of mothers was 32.5 (median, 32.6; range, 16.7–44.8) years at enrollment. Reflecting a generally employed and insured population, 72% of the mothers had a college degree, and 61% had a total household income >\$70,000. The mothers’ mean pre-pregnancy BMI was 24.7 (median, 23.5; range, 15.2–47.4) kg/m²; the mean reported duration of breastfeeding was 6.2 (median, 6.0; range, 0–12) months. Approximately 55% of participants had other children under the age of 12 living in the household; 16% of mothers and 15% of fathers had a previous history of doctor-diagnosed asthma.

The mean birth weight for infants was 3,527 (median, 3,515; SD, 517; range, 1,559–5,528) grams, and the mean birth weight for gestational age z-score was 0.23 (median, 0.21; SD, 0.95; range, –2.58 to 2.58). The mean gestational age was 39.6 (median, 39.8; SD, 1.45; range, 34.1–42.7) weeks. By age 2, 34% of parents reported their children had any wheezing, 14% reported

recurrent wheezing in the first and second years of life and 16% reported doctor-diagnosed asthma in their children (13% reported doctor-diagnosed wheezing or reactive airway disease and 8% reported doctor-diagnosed asthma).

Multivariate Analyses

In models adjusting for child's sex and passive exposure to smoking during the first year of life, and mother's age, pre-pregnancy BMI, breastfeeding duration, household income, number of children under 12 years of age living in the household, and maternal and paternal history of asthma, we found that infants with birth weight $\geq 4,000$ g were not more likely to have doctor-diagnosed asthma at 2 years of age (OR, 0.80; 95% CI: 0.49, 1.31) than infants whose birth weights were 3,500 to $<4,000$ g. In addition, infants whose birth weights were in the first (1,500 to $\leq 3,000$ g) and second (3,000 to $\leq 3,500$ g) categories were not more likely to have doctor-diagnosed asthma, with odds ratios of 0.75 (95% CI: 0.43, 1.31) and 1.19 (95% CI: 0.81, 1.73), respectively. The associations between birth weight and any wheezing and recurrent wheezing were likewise null (data not shown).

In models examining length of gestation and fetal growth separately, neither the highest nor the lowest group of either predictor was associated with the three outcomes (Table 1). Infants in the second lowest quartile of fetal growth appeared more likely to have recurrent wheeze at age 2 (OR, 2.04; 95% CI: 1.16, 3.59). This finding was likely due to chance given that the same infants were not at elevated risk of any wheezing or doctor-diagnosed asthma at age 2 years, and that infants in the lowest fetal growth quartile were also not at elevated risk of any of our asthma-related outcomes.

Thus, we did not observe a U-shaped relationship between birth weight or fetal growth and our asthma-related outcomes (Table 1). In sex-stratified models, girls in the lowest category of gestational age had an elevated risk of both recurrent wheezing (OR, 2.87; 95% CI: 0.97, 8.47) and doctor-diagnosed asthma (OR, 2.78; 95% CI: 1.08, 7.13). Boys in the lowest category of gestational age were not at elevated risk of either outcome (OR, 0.49; 95% CI: 0.13, 1.86 and OR, 0.43; 95% CI: 0.13, 1.36, respectively). In no other category of gestational age was there a difference between boys and girls and the *P*-values for the multiplicative interaction terms between sex and gestational age were 0.10 and 0.07, respectively. There was no evidence of sex differences in the association of fetal growth with either outcome.

We found that boys had a higher incidence of asthma-related outcomes than girls, and exposure to passive smoking, parental history of asthma, exposure to older siblings, and lower household income were all associated with greater risk of recurrent wheeze or asthma-related outcomes at age 2 years.

DISCUSSION

In this prospective study of children born after 34 weeks gestation, we did not find that children with higher birth weights were at greater risk of any wheezing, recurrent wheezing, or of doctor-diagnosed asthma, wheeze, or reactive airways in the first 2 years of life. In addition, we did not observe definitive associations of fetal growth or length of gestation with these asthma-related outcomes, nor did we observe a curvilinear association between birth weight and our asthma-related outcomes.

Our findings of a null association between the highest birth weights and recurrent wheeze and asthma at 2 years of age are in contrast to two population-based cohort studies that found a direct association between high birth weight and risk of emergency visits and hospitalizations for asthma among 10–12 year old children.^{11,12} However, our results of a null association confirm those of a recent retrospective cohort study by Dik et al.¹⁹ who examined data from

170,960 children at age 6. In multivariate models adjusted for gestational age, the relative risk of asthma was 1.01 (95% CI: 0.97, 1.05) for children whose birth weight was $\geq 3,800$ g compared to those whose birth weight was 3,500–3,790 g. That study was limited, however, by adjustment for a limited number of confounders.

In the present study, we attempted to address limitations of previous studies, which have included analysis of birth weight as a continuous or dichotomous variable and in some studies, small sample sizes and retrospective collection of anthropometric and gestational age data. An additional strength of our study was the ability to adjust for multiple socioenvironmental confounders. Consistent with previous studies, we found other socioenvironmental factors, such as exposure to passive smoking and maternal and paternal history of asthma, to be associated with greater risk of recurrent wheeze or asthma-related outcomes at age 2 years.

Although some studies suggest lower birth weight is a risk factor for childhood asthma,^{8–10} others do not.^{20–22} Some authors have suggested that this association may be due primarily to preterm births,^{22,23} although others have observed increased asthma prevalence among full term infants with low birth weight.²⁴ Few previous studies have adjusted for gestational age in an attempt to isolate the effect of fetal growth from prematurity. In our study, we examined fetal growth independent of gestational age, and we restricted the analysis to infants born after 34 weeks' gestation to exclude prematurity as a cause of respiratory disease. We did not find any definitive association between length of gestation and our asthma-related outcomes. Our unexpected findings of differences between boys and girls in the lowest category of gestational age need to be confirmed in future studies.

In conclusion, although male sex, exposure to smoking, parental history of asthma, and exposure to older siblings were associated with increased risk of wheezing and asthma-related outcomes at age 2 years, neither birth weight nor its two components, fetal growth and length of gestation, were associated with asthma-related outcomes in this US-based cohort of pregnant women and their offspring. Limitations of this study include a relatively early age of measurement of our outcomes and a lack of sensitivity and specificity of doctor diagnosis of asthma and related symptoms at age 2 years. Follow up to later ages may reveal associations between fetal growth or length of gestation and asthma-related outcomes. In addition, the population we studied was generally insured and well educated. Our results may not be generalizable to more socioeconomically disadvantaged populations. Further studies should also examine the role of postnatal growth in predicting asthma, as both overweight and asthma develop in common during the preschool years.^{2,25}

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Ethics approval: Institutional review boards of participating institutions (Harvard Pilgrim Health Care and Brigham and Women's Hospital, both in Boston, MA) approved the study. All procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki.

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TABLE 1

Odds of Any Wheezing, Recurrent Wheezing, and of Doctor Diagnosis of Asthma, Wheezing or Reactive Airway Disease During the First 2 Years of Life. Data From Multivariate Analyses of 1,372 Mother-Child Pairs Participating in Project Viva.*

Model covariates	N (%) or mean (SD)	Any wheezing (N = 409)		Persistent wheezing** (N = 150)		Doctor diagnosis of asthma, wheezing or reactive airway disease (N = 214)	
		OR	95% CI	OR	95% CI	OR	95% CI
Main predictors:							
Birth weight for gestational age z-score (quartile)	341 (25)						
1st (lowest) quartile	340 (25)	1.04	0.71, 1.52	1.41	0.78, 2.55	1.03	0.64, 1.65
2nd quartile	336 (24)	1.15	0.79, 1.67	2.04	1.16, 3.59	1.09	0.68, 1.73
3rd quartile	354 (26)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
4th (highest) quartile		0.98	0.68, 1.41	1.46	0.84, 2.55	0.90	0.57, 1.41
Gestational age							
34 to <37 weeks	73 (5)	1.25	0.69, 2.28	1.19	0.53, 2.66	1.12	0.55, 2.28
37 to <39 weeks	284 (21)	0.92	0.66, 1.29	0.75	0.45, 1.24	0.86	0.56, 1.31
39 to <41 weeks	763 (56)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
≥41 weeks	252 (18)	0.88	0.62, 1.26	0.87	0.51, 1.47	1.03	0.66, 1.60
Maternal variables:							
Mother's age (years)	32.5 (4.9)	0.98	0.96, 1.01	0.95	0.91, 0.99	0.99	0.95, 1.02
Mother's pre-pregnancy BMI (kg/m ²)	24.7 (5.3)	1.01	0.98, 1.04	1.02	0.98, 1.05	1.04	1.01, 1.07
Income:							
≤\$40,000	157 (11)	1.77	1.14, 2.75	1.33	0.70, 2.51	1.56	0.93, 2.61
\$40,001–\$70,000	286 (21)	1.04	0.74, 1.46	1.51	0.96, 2.38	1.35	0.90, 2.03
>\$70,000	832 (61)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
Don't know or missing	97 (7)	0.99	0.56, 1.77	0.97	0.45, 2.09	0.93	0.46, 1.88
Passive exposure to smoking (hours per week)	0.27 (1.32)	1.12	1.01, 1.23	1.14	1.02, 1.27	1.04	0.94, 1.15
Child Variables:							
Child's sex							
Boy	711 (52)	1.80	1.38, 2.35	1.89	1.29, 2.78	1.52	1.10, 2.12
Girl	661 (48)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
Breastfeeding duration							
<9 months	801 (63)	1.49	1.13, 1.96	1.42	0.94, 2.14	1.26	0.88, 1.79
≥9 months	465 (37)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
Children under the age of 12 years living in home							
>1	724 (55)	1.45	1.11, 1.90	1.85	1.24, 2.76	1.57	1.11, 2.20
1	597 (45)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
Parental History of Asthma							
Mother's history of asthma (yes vs. no)	225 (16)	2.14	1.53, 2.99	2.33	1.48, 3.68	2.58	1.77, 3.76
Father's history of asthma (yes vs. no)	201 (15)	1.70	1.21, 2.40	2.14	1.36, 3.38	1.90	1.27, 2.84

* Numbers may not add up to 1,372 because of missing values. Bold type indicates that confidence limits exclude one.

** Sample size for recurrent wheeze outcome is 1,101 after excluding 204 children who had wheezing reported in the first or second year of life, but not both, and 67 children with missing data.