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Low-Normal Gestational Age as a Predictor of Asthma at 6 Years of Age

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ABSTRACT. *Background.* Perinatal factors, including gestational age and birth weight, influence the development of atopy in early life. However, the role of these factors in the development of asthma in later life among children who do not develop perinatal respiratory disease remains unclear.

Methods. Four hundred fifty-four infants who had a history of allergy or asthma in at least 1 parent, were born in the 36th week of gestation or later, and did not develop perinatal respiratory distress were monitored for at least 6 years. Associations between predictor variables and asthma and wheeze were assessed with multivariate logistic regression and repeated-event analyses.

Results. Although we previously observed a relationship between low birth weight and persistent wheeze in the first 1 year of life, we did not observe similar associations between low birth weight and asthma at 6 years of age (odds ratio [OR]: 1.05; 95% confidence interval [CI]: 0.40–2.73). However, a strong relationship was found between low-normal gestational age and asthma at 6 years of age (OR: 4.7; 95% CI: 2.1–10.5). The effects of low-normal gestational age were significantly greater among boys than among girls (boys: OR: 8.15; 95% CI: 2.98–22.3; girls: OR: 1.90; 95% CI: 0.38–13.83). Longitudinal analysis of the relationship between gestational age and wheeze during the 6 years of observation confirmed these gender differences.

Conclusions. Among children at high risk of developing atopic disease, late prematurity might be an important additional determinant of asthma later in life, and these effects are gender specific. *Pediatrics* 2004; 114:e327–e332. URL: <http://www.pediatrics.org/cgi/content/full/114/3/e327>; asthma, gestational age, birth weight, longitudinal studies.

ABBREVIATIONS. IgE, immunoglobulin E; OR, odds ratio; CI, confidence interval.

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There is substantial evidence that perinatal factors contribute to the development of both atopic disease and asthma. Although it is well established that prematurity is a major risk factor for the development of chronic lung disease, as a result of bronchopulmonary dysplasia,^{1,2} and that extremely premature infants more frequently demonstrate persistent airway hyperresponsiveness in early childhood,³ the influence of less extreme prematurity on the development of asthma among otherwise healthy children remains unresolved. Both low birth weight and prematurity were directly associated with the development of wheeze or asthma in several studies,^{4–7} whereas other studies either failed to demonstrate an association^{8–11} or demonstrated inverse relationships.¹² Although several of those studies were prospective,^{6,8} most of the studies that demonstrated important effects included very premature infants (<36 weeks of gestation) in their analyses, making it difficult to separate the effects of prematurity from those associated with mechanical ventilation and respiratory distress syndrome. Moreover, few of those studies examined gender-differing effects, despite evidence of important gender-specific differences in somatic lung development.^{13–16}

The Home Allergens and Asthma Study is a prospective birth cohort study designed to identify the determinants of asthma and allergy among a group of high-risk children. The study was restricted to children born in the ≥36th week of gestation who had at least 1 parent with a history of asthma, allergies, or hay fever. Newborns who required mechanical ventilation were excluded from enrollment. We previously reported that, among these children, low birth weight was a significant determinant of persistent wheeze in the first 1 year of life. The birth cohort has been monitored for >6 years, allowing examination of the relationship between perinatal factors and the development of asthma. This article details our evaluation of the relationship between perinatal factors, including anthropometric measures and gestational age, and asthma at 6 years of age. Because of the gender-specific differences in airway development, we also examined whether effects of perinatal factors differed between boys and girls.

METHODS

Study Cohort

Details of the Home Allergens and Allergy Study protocol were described previously.¹⁷ Briefly, participants were part of a metropolitan Boston prospective birth cohort study designed to examine

relationships between exposure to indoor allergens and development of allergic sensitization and asthma. Five hundred five infants with at least 1 parent with a history of allergy or asthma were recruited between September 1994 and August 1996. Monday through Friday, all mothers who delivered at a large Boston hospital were approached for screening within 48 hours after delivery if they lived within Route 128 (encircling the metropolitan area), were at least 18 years of age, and were able to speak English or Spanish. To reduce the chance of prematurity or respiratory distress syndrome as potential confounders, families were not screened if the child was born before the 36th week of gestation, had a major congenital anomaly, or was in the neonatal intensive care unit. Seven children were excluded from analysis because they were monitored for ≤ 4 months during their first 1 year of life, resulting in a final cohort of 498 children. Anthropometric measurements at birth (birth weight, birth length, and head circumference), the expected date of delivery (due date), and data on postpartum neonatal health status (1- and 5-minute Apgar scores and supplemental oxygen requirements) were extracted from hospital records. Gestational age at birth was determined with reference to the expected due date. The Ponderal index was derived with the following equation: Ponderal index = (birth weight, in grams) $\times$ 100/(birth length, in centimeters).³ To assess the effects of birth weight independent of gestational age, z scores were generated from reference percentiles of birth weight for gestational age for >6.5 million singleton births, available from the National Center for Health Statistics 1999 and 2000 Natality Data Sets.¹⁸ Beginning when the child was 2 months of age, a telephone questionnaire was administered to the child's primary caregiver every 2 months until the child's second birthday. Thereafter, interviews were conducted every 6 months. The study was approved by the institutional review board of the Brigham and Women's Hospital (Boston, MA).

In every survey, we asked whether the child had experienced any wheezing or whistling in the chest since the previous interview. At 6 years of age, we defined asthma as physician-diagnosed asthma and ≥ 1 episode of wheezing in the previous year, allergic rhinitis as physician-diagnosed allergic rhinitis and a history of nasal discharge or sneezing, apart from colds, in the previous year, and eczema as physician-diagnosed eczema and a history of a pruritic rash lasting ≥ 6 months in the previous year. Total serum immunoglobulin E (IgE) levels at 2 years of age were measured with an enzyme-linked immunoassay based on the sandwich technique (UniCap; Pharmacia Diagnostics, Kalamazoo, MI). IgE values were converted to the natural logarithmic scale for analysis.

Statistical Methods

SAS statistical software (SAS Institute, Inc, Cary, NC) was used to evaluate univariate and multivariate associations between predictor variables and asthma at 6 years of age. Birth weight and birth length were assessed as categorical variables, in quartiles. Gestational age at birth was assessed as a 3-category variable (≤ 38.5 weeks [low-normal], >38.5 –40 weeks, and >40 weeks). Data on head circumference at birth were missing for 114 individuals (20.9%) and were not included in the multivariate analysis. Univariate associations between categorical predictor variables and outcome variables were examined by using logistic regression to calculate odds ratios (ORs) and confidence intervals (CIs). On the basis of previously identified predictors of asthma in our cohort, the following variables were considered for inclusion in the multivariate analysis: maternal age, maternal history of asthma (ever or ever with current symptoms [active]),¹⁹ in utero exposure to maternal smoking, season of birth, child's gender, child's ethnicity,¹⁹ annual household income, physician-diagnosed lower respiratory illnesses (croup, bronchitis, bronchiolitis, or pneumonia) in the first 1 year of life, number of older siblings, and day care attendance in the first 1 year of life.²⁰ Stepwise logistic regression was used to study the relationship between gestational age of <38.5 weeks and asthma, with adjustment for potential confounders and examination of interactions. In the final models, we included variables that were significant at $P < .05$ or that satisfied a change in estimate criterion ($\geq 10\%$) in the odds ratio (OR). Evidence for collinearity or confounding of the gestational age-asthma relationship was examined by assessing gestational age risk estimates and SEs in models with and without the following variables: birth weight, birth length, and Ponderal index.

To examine gender-specific associations, we assessed models that included terms for interactions between gestational age and gender. For longitudinal analysis of the relationship between gestational age and wheeze, we used S-PLUS software (version 3.4; Mathsoft, Inc, Cambridge, MA) for proportional-hazards modeling; repeated events for the same child were handled with the method described by Anderson and Gill, with variance adjustment to accommodate correlations between repeated events for the same child.²¹ To examine age-dependent associations, we calculated terms for interactions between the ages of the children at each survey and the variables in the model.

Role of Funding Source

The study sponsors had no role in the study design, data collection, analysis, or interpretation. The study sponsors also had no role in writing or in deciding to submit this article for publication.

RESULTS

We monitored 454 of the 498 study subjects (91%) up to 6 years of age. Subjects who were lost to follow-up monitoring were more likely to come from families of low income. The baseline characteristics of the 454 subjects included in this study are summarized in Table 1. Birth weights were normally distributed and remained so after adjustment for gestational age. Ninety-one children (20.0%) were born at ≤ 38.5 weeks of gestation. As expected, strong correlations ($P < .0001$) were observed between gestational age and birth weight, birth length, and head circumference. There was no evidence of significant

TABLE 1. Baseline Characteristics of Children in the Study Cohort ($n = 454$)

Variable	No. (%) or Mean $\pm$ SD
Female	207 (45.6)
Ethnicity	
White	359 (79.1)
Black	41 (9.0)
Hispanic	22 (4.9)
Asian	26 (5.7)
Other	6 (1.3)
Maternal age, y	33.2 $\pm$ 4.5
Maternal history of asthma	
Ever	132 (29.1)
Active	43 (9.5)
Not available	1 (0.2)
In utero smoke exposure	25 (5.5)
Season of birth	
Winter	112 (24.7)
Spring	130 (28.6)
Summer	99 (21.8)
Fall	113 (24.9)
Household income	
$< \$30,000$	28 (6.2)
$> \$30,000$	415 (91.4)
Not available	11 (2.4)
Daycare attendance in first 1 y of life	218 (48)
LRI in first 1 y of life	120 (26.4)
Gestational age, wk	39.6 $\pm$ 1.4
Gestational age of ≤ 38.5 wk	91 (20.0)
Birth weight, kg*	3.49 $\pm$ 0.49
Birth length, cm*	50.9 $\pm$ 2.9
Head circumference at birth, cm*	34.9 $\pm$ 1.48

Values denote number of subjects, with percentage of cohort in parentheses, or mean $\pm$ SD for cohort. LRI indicates physician-diagnosed lower respiratory infection (croup, bronchitis, bronchiolitis, or pneumonia).

* Numbers missing data for birth weight, birth length, and head circumference at birth were 1 (0.2%), 18 (4.0%), and 114 (20.9%), respectively.

associations between gestational age and ethnicity, household income, maternal age, or in utero smoke exposure (although the prevalence of smoking during pregnancy was only 5.5%). There were no significant differences in gestational age or anthropometric measurements at birth between those who were assessed at 6 years of age and those who were not (data not shown).

Table 2 summarizes the results of the univariate analyses of potential asthma predictors at 6 years of age. As in our previous reports of findings at 4 and 5 years of age, male gender, active maternal asthma, and a history of lower respiratory tract infections during the first 1 year of life were significant predictors of asthma at 6 years of age.^{23,24} Asthma at 6 years of age was not associated with ethnicity, maternal age, in utero smoke exposure, season of birth, household income, day care attendance in the first 1 year of life, or a history of upper respiratory tract infections in the first 1 year of life. In univariate analyses, birth length, birth weight, and head circumference were not associated with asthma at 6 years of age. Although we previously identified low birth weight (1.84 to <3.18 kg) as a predictor of wheeze in the first 1 year of life,¹⁷ we found no association between low birth weight and asthma at 6 years of age, regardless of whether birth weight was adjusted for gestational age. In contrast, low-normal gestational age itself was strongly predictive of asthma at 6 years of age. Infants born at ≤ 38.5 weeks of gestation were 3.5 times more likely to have a diagnosis of asthma at 6 years of age than were infants born between 38.6 and 40.5 weeks ($P = .0009$). Infants born at >40.5 weeks demonstrated a similar

but slightly lower risk of developing asthma, compared with infants born between 38.6 and 40.5 weeks (OR: 0.82; 95% CI: 0.31-2.17; $P = .69$). For the remainder of the analysis, infants born at ≥ 38.5 weeks were considered together. Infants born before or after 38.5 weeks did not differ with respect to other perinatal factors, including type of delivery (vaginal delivery versus cesarean section, scheduled versus emergency delivery), 1- and 5-minute Apgar scores, and postdelivery neonatal oxygen requirements. No significant relationships were observed between gestational age and either eczema or allergic rhinitis at 6 years of age or serum IgE levels at 2 years of age.

In multivariate modeling, low-normal gestational age was significantly associated with asthma at 6 years of age and was the strongest predictor of asthma in all models considered (Table 3). The strength of this association did not differ significantly in models that did or did not include adjustments for anthropometric measurements at birth (z scores for birth weight, birth length, or Ponderal index) or adjustments for rhinitis or eczema (data not shown). Removal of a history of lower respiratory tract infections in the first 1 year of life from the multivariate model had minimal effects on the gestational age effect estimate, which suggests that the effects of low-normal gestational age on asthma are not primarily mediated through increased susceptibility to lower respiratory tract infections (Table 3).

To assess whether the effects of low-normal gestational age were gender specific, we assessed the relationship between low-normal gestational age and asthma at 6 years of age with a stratified analysis (Table 3). The effects of low-normal gestational age

TABLE 2. Univariate Analysis of Predictors of Asthma at 6 Years of Age

Covariate	N	No. (%) with Asthma	OR	95% CI	P Value
Gender					.03
Female	207	11 (5.3)	1.00		
Male	247	27 (10.9)	2.19	1.06–4.52	
Maternal age, y					.30
18–30	103	12 (11.6)	1.00		
30–33	114	7 (6.1)	0.50	0.19–1.30	
33–36	119	7 (5.88)	0.47	0.18–1.24	
>36	118	12 (10.2)	0.85	0.36–2.00	
Maternal history of asthma (active)					.02
No	410	30 (7.3)	1.00		
Yes	43	8 (18.6)	2.90	1.23–6.80	
Child LRI in first 1 y of life					.0003
No	334	18 (5.4)	1.00		
Yes	120	20 (16.7)	3.51	1.79–6.90	
Gestational age, wk					.001
≤ 38.5	91	17 (18.9)	3.52	1.68–7.40	
38.5–40.5	245	15 (6.1)	1.00		
>40.5	118	6 (5.1)	0.82	0.31–2.17	
Weight at birth, kg					.62
3.79 to <4.91	113	9 (8.0)	1.00		
3.46 to <3.79	113	7 (6.2)	0.76	0.27–2.12	
3.18 to <3.46	118	13 (11.0)	1.43	0.59–3.49	
1.84 to <3.18	109	9 (8.3)	1.05	0.40–2.73	
Length at birth, cm					.84
53–58	123	12 (9.8)	1.00		
52	60	4 (6.7)	0.66	0.20–2.14	
50–51	152	11 (7.2)	0.72	0.31–1.70	
34–49	101	9 (8.9)	0.92	0.37–2.27	

P value refers to likelihood ratio P value for univariate models. LRI indicates physician-diagnosed lower respiratory infection (croup, bronchitis, bronchiolitis, or pneumonia).

TABLE 3. Multivariate Analysis of Predictors of Asthma at 6 Years of Age

Variable	OR (95% CI)*			
	Multivariate Model	Model Without LRI	Boys Only (n = 247)	Girls Only (n = 207)
Gestational age of <38.5 wk	4.7 (2.1–10.5)	5.6 (2.5–12.3)	8.15 (2.98–22.31)	1.90 (0.38–9.45)
Male	1.8 (0.8–4.1)	2.2 (1.0–4.9)		
Maternal history of asthma	3.2 (1.2–8.3)	3.5 (1.4–8.9)	4.62 (1.14–18.70)	3.06 (0.68–13.83)
History of LRI in first 1 y of life	2.8 (1.3–5.9)		2.36 (0.92–6.04)	3.73 (1.03–13.47)

LRI indicates physician-diagnosed lower respiratory infection (croup, bronchitis, bronchiolitis, or pneumonia).

* Adjusted for birth length, z score for birth weight, household income, and other variables listed.

on asthma diagnosis and symptoms at 6 years of age differed substantially between boys and girls. Boys of low-normal gestational age were at 8 times greater risk of developing asthma, whereas girls of low-normal gestational age had only a modest increase in risk, ie, ~ 2 . In contrast, there were no significant gender-specific differences in the effects of maternal history of asthma and lower respiratory tract infections in the first 1 year of life (test for interaction, $P > .10$ for both).

Figure 1 summarizes the longitudinal multivariate analysis of the gender-specific effects of low-normal

gestational age on wheezing between 1 and 6 years of age. Among boys, a significant direct association of low-normal gestational age with wheeze was observed very early in life and persisted for the entire period of observation. There was evidence that the magnitude of this effect increased with time (P value for time trend = .07). In contrast, there was no significant relationship between gestational age and wheeze among girls, which suggests that the effects of low-normal gestational age on the development of wheeze differ between boys and girls.

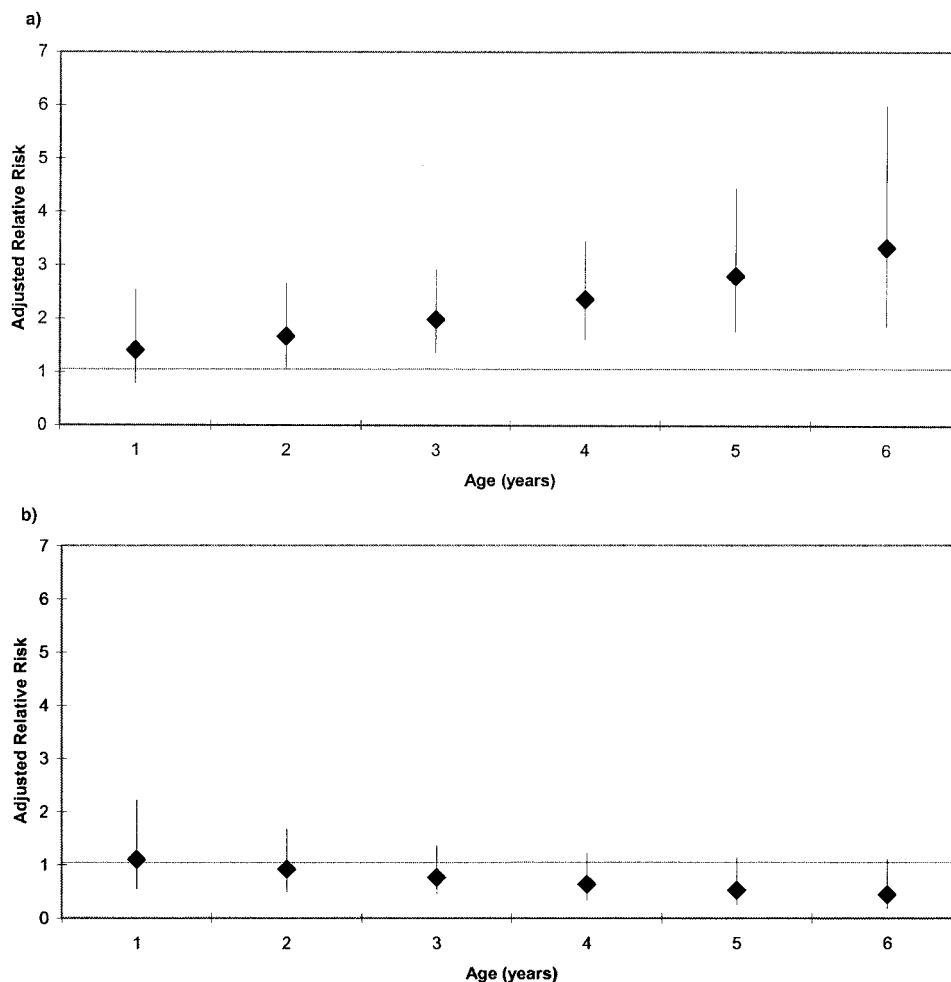


Fig 1. Longitudinal effects of low-normal gestational age on wheezing between the ages of 1 and 6 years among boys (a) and girls (b). Wheezing during the first 1 year of life was not included in the analysis, to avoid misclassification of wheezing associated with lower respiratory tract infections. Findings were based on a proportional-hazards model adjusted for birth length, normalized birth weight, household income, maternal history of asthma, and history of lower respiratory tract infections in the first 1 year of life. The test for time effects was not significant for either boys or girls (Wald χ^2 test P values of .07 and .10, respectively).

DISCUSSION

We have demonstrated a strong direct association between low-normal gestational age and the development of asthma by 6 years of age. These findings are in keeping with those of other studies^{5,6} but extend our understanding of the relationship between gestational age and asthma in several important ways.

First, it is clear from previous studies that children with bronchopulmonary dysplasia and severe respiratory illnesses attributable to extreme prematurity often experience persistent airway hyperresponsiveness and symptoms consistent with asthma.^{3,5} This study differs in that very premature infants and those requiring mechanical ventilation were not enrolled, which enabled us to observe the association between low-normal gestational age and asthma independent of respiratory distress syndrome and the sequelae of mechanical ventilation. Increased incidences of airway hyperresponsiveness have been observed among mothers who deliver prematurely^{3,24} and among siblings of very premature infants.³ Our finding of increased risk of asthma among children born at low-normal gestational age, which we observed even after controlling for maternal history of asthma, suggests that the association of low-normal gestational age with asthma may result in part from factors independent of genetic or environmental influences of maternal asthma.

Second, the effects of low-normal gestational age are largely independent of those related to early-life respiratory tract infections. Although infants born at low-normal gestational age were at higher risk of developing lower respiratory tract infections in the first 1 year of life, low-normal gestational age was strongly related to asthma in multivariate models, regardless of whether lower respiratory tract infections were included in the model. These results suggest that the effects of low-normal gestational age on asthma are mediated primarily not through increased susceptibility to lower respiratory tract infections but through other, undefined pathways. The data also suggest, but do not prove, that the effects of low-normal gestational age may not be mediated primarily through allergic mechanisms, because the strength of the association between early gestational age and asthma did not change with the inclusion of either allergic rhinitis or eczema in the multivariate models. The latter conclusion may not be generalizable to other populations, because gestational age and anthropometric measures at birth have been demonstrated to be important determinants of atopic phenotypes for other groups.^{8,10,12,26}

Finally, we demonstrated gender-specific effects of gestational age on the development of asthma. In this cohort, boys of low-normal gestational age were >4 times as likely to develop asthma as girls of low-normal gestational age. These gender differences may be related to in utero and early-life differences in the late stages of lung development, including hormonal and somatic influences.²⁷ For boys more than girls, low-normal gestational age may increase the risk of dysanapsis (reduced airway-to-lung size),

which is more common among boys and may be associated with increased airway collapsibility, narrowing, and wheeze.^{28–31}

There are several important limitations to this study. First, although we had sufficient power to detect gender-specific differences in the effects of gestational age on asthma, the small number of affected girls precludes our drawing firm conclusions regarding the true effects of perinatal factors on the development of asthma among girls. However, the stability of the estimate of the effects of gestational age on the prevalence of wheeze among girls in the longitudinal analysis suggests that the effects are less important than among boys. Second, gestational age at birth was estimated on the basis of the mother's reported due date. Although it is likely that the majority of these reports were based on ultrasonographic estimates of gestational age, it is possible that some misclassification occurred. Finally, our results may not be generalizable, because we limited our selection of children for inclusion to those with a parental history of atopy, and it is possible that the effects of low-normal gestational age on asthma development are most pertinent for children in this high-risk group.

CONCLUSIONS

We have demonstrated that low-normal gestational age is an important determinant of asthma at 6 years of age in a birth cohort at high risk. This association is independent of anthropometric measurements at birth, does not appear to be related to respiratory tract infections in early life or atopic status, and is not attributable to neonatal respiratory distress syndrome or mechanical ventilation. Importantly, this relationship appears to differ between boys and girls. Our results support the notion that late in utero development can affect lung health in later life.

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