Published in final edited form as:
J Allergy Clin Immunol. 2008 April ; 121(4): 878–84.e6. doi:10.1016/j.jaci.2008.01.030.

Prematurity, Chorioamnionitis and the Development of Recurrent Wheezing: a Prospective Birth Cohort Study

Rajesh Kumar, MD[1], **Yunxian Yu, MD, PhD**[2], **Rachel E. Story, MD, MPH**[1], **Jacqueline A. Pongracic, MD**[1], **Ruchi Gupta, MD**[2], **Colleen Pearson, BA**[3], **Kathryn Ortiz, BA**[3], **Howard C. Bauchner, MD**[3], and **Xiaobin Wang, MD, MPH, ScD.**[2]

[1]Division of Allergy, Children's Memorial Hospital,Chicago, IL

[2]The Mary Ann and J. Milburn Smith Child Health Research Program, Children's Memorial Hospital and Children's Memorial Research Center,Chicago, IL

[3]Department of Pediatrics, Boston University School of Medicine, and Boston Medical Center

Abstract

Background—Prematurity (<37 weeks) has been inconsistently associated with asthma and wheezing. Chorioamnionitis may promote both prematurity and inflammatory pathways in infants' airways.

Objective—To investigate the relationship of prematurity and chorioamnionitis with the development of early childhood recurrent wheezing.

Methods—The Boston Birth Cohort (n=1096) were followed prospectively from birth to a mean age of 2.2±2 years. Perinatal and postnatal clinical data and placental pathology were collected. The primary outcome was recurrent wheezing (≥2 physician documented episodes). Secondary outcomes included physician diagnosed asthma, food allergy and eczema. Preterm children were grouped by gestational age into moderately (33-36.9 weeks) and very preterm (<33 weeks) with and without chorioamnionitis, and compared to term children without chorioamnionitis (reference group). Chorioamnionitis was diagnosed either by intrapartum fever or by placental histology findings. Logistic regression models were preformed to investigate the independent and joint associations of degree of prematurity and chorioamnionitis.

Results—Prematurity was associated with recurrent wheezing (OR:1.7, 95%CI:1.2-2.6). However, when subjects were grouped by degree of prematurity with or without chorioamnionitis, the highest risk of wheezing (OR:4.0, 95%CI:2.0-8.0) and physician diagnosed asthma (OR:4.4 95%CI:2.2-8.7) was present in the very preterm children with chorioamnionitis. The effect on both wheezing (OR:5.4, 95%CI:2.4-12.0) and asthma (OR:5.2, 95%CI:2.3-11.9) was greater in African Americans. Neither prematurity nor chorioamnionitis were associated with food allergy or eczema.

Conclusions—We found a strong joint effect of prematurity and chorioamnionitis on early childhood wheezing. This effect was stronger in African Americans.

Correspondence should be addressed to: Rajesh Kumar, MD, Children's Memorial Hospital, 2300 Children's Plaza, box #60, Chicago Illinois, USA 60614, Tel: 773 – 327- 3710, Fax: 773 – 327 - 3790, rkumar@childrensmemorial.org.

Clinical Implications—Chorioamnionitis may increase the risk of recurrent wheezing in very low birth weight infants.

Keywords

Chorioamnionitis; prematurity; recurrent wheezing

Introduction

A limited number of studies have explored the role of prenatal factors on the development of respiratory morbidity or later asthma.[1-5] At least one study suggests that either programming in-utero or immunological changes determined in-utero affect the risk for respiratory diseases.[6] Given that a significant proportion of those who develop asthma in childhood wheezed in early life, [7] investigation of prenatal and early life factors is important to better understand etiology of recurrent wheezing and possibly later development of asthma.

In this context, we chose to evaluate the role of prematurity and associated chorioamnionitis on recurrent wheezing in early life. Preterm births (<37 weeks of gestation) account for 12.5% of all births in the US and prematurity has been identified as a risk factor for asthma in many[8-11] but not all studies.[12, 13] A major limitation of previous studies, which may have led to inconsistent findings, is that they did not consider the underlying pathogenesis of preterm birth. A great proportion of high risk preterm births are associated with chorioamnionitis.[14-16] In this regard, febrile episodes in pregnancy (especially the third trimester) have also been associated with subsequent development of asthma in offspring.[17, 18] Chorioamnionitis as a potential risk factor for wheezing illness becomes even more important since like asthma,[19, 20] prematurity and chorioamnionitis disproportionately affect the African American community. (IOM report 2006) This co-morbid epidemic has not been evaluated as a contributor to asthma health disparities.

The purpose of this study was to evaluate the association between prematurity and wheezing accounting for the presence of perinatal chorioamnionitis utilizing subjects enrolled in the Boston Birth Cohort, a large-scale, multi-ethnic, inner city population[21] based study, which includes both term and preterm children.

Methods

Patient Population

The Boston Birth Cohort was initiated in 1998 and recruitment is ongoing at the Boston University Medical Center (BUMC). It consists of mother-infant pairs enrolled from a range of socio-economic strata that includes inner city poor up to middle class subjects. It is a multi-ethnic population, and the three major racial groups are black (56%), white (11%), and Hispanic (20%).

The Boston Birth Cohort was originally designed to study adverse birth outcomes, particularly preterm birth and intra-uterine fetal growth restriction. The inclusion and exclusion criteria of the parent study are as follows: Any woman admitted to the Labor and Delivery floor at BMC who delivered a singleton live infant and met our case (gestational age <37 weeks or birthweight <2,500 grams) or control (gestational age >= 37 weeks with birthweight >=2,500 grams) criteria was eligible.[21] For the purposes of this follow-up study, preterm status was solely determined by gestational age not by “case” status as defined in the parent study. A small percentage of women (<1%) with pregnancies that involved in vitro fertilization, multiple gestation, chromosomal abnormalities or major birth defects, or women with congenital or acquired uterine lesions, or incompetent cervix were excluded.

The Children's Memorial Hospital (CMH) Institutional Review Board (IRB), the Boston University Medical Center (BUMC) IRB, and the Massachusetts Department of Public Health approved the parent study protocol. Under a separate CMH and BUMC IRB approved study protocol and consent process. all infants enrolled in the Boston Birth Cohort are eligible for the postnatal follow-up study.

Data Collection and Measurements

Recuitment of the Birth Cohort—For the parent study, mother-infant pairs were recruited 24 to 48 hours post-delivery. After obtaining signed written informed consent, we interviewed subjects using a standardized questionnaire to gather epidemiologic data. We also reviewed maternal and infant medical records using a standardized abstraction form to obtain clinical data including ultrasound findings, placental pathology reports, laboratory reports, pregnancy complications, labor and delivery course, and birth outcomes.

Postnatal Follow-up Study—In the postnatal follow-up study, after written informed consent was obtained from the biological mother, visits were conducted at 6-12 mo, 2 yr, 4 yr, and 6 yr in alignment with the child's pediatric primary care visit schedule. Mothers were interviewed using standardized postnatal health questionnaires to gather important postnatal epidemiologic data. We also reviewed the study child's medical record using a standard medical record abstraction form to obtain clinical data including type and date of visits, clinical diagnosis including ICD 9 codes, and growth parameters.

Assessment of Gestational Age—Precise estimation of gestational age is essential for defining degree of prematurity. In this cohort, gestational age was assessed based on both the first day of the last menstrual period (LMP) 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.[21]

Determination of Presence of Chorioamnionitis—For this study, chorioamnionitis was considered present if the pregnancy was associated with either the presence of intrapartum fever (>38 degrees centigrade)[22] based on review of medical record or by the presence of placental histological changes associated with chorioamnionitis. A detailed description of placental pathology criteria has been published by our group elsewhere.[23] Briefly, all placentas sent for pathology were reviewed by the hospital's perinatal pathologist, and a subset were independently reviewed by a second pathologist to confirm reliability. The presence and location of inflammation was reported using well-established algorithms, e.g., types of inflammatory cells were identified and reported to designate acute versus chronic inflammation, and the location of inflammatory infiltrate was denoted in these reports to specify decidual, chorionic, amnionic, chorionic plate, and umbilical cord involvement. These guidelines for histologic reporting were consistent with recommendations developed by the College of American Pathologists and have been used consistently in the literature to classify types of placental infection [24 25].

Outcome Measures

The primary outcome was recurrent wheezing (>=2 episodes of physician documented wheezing). Secondary outcomes included physician diagnosis of asthma, eczema and/or food allergy. These outcomes were determined by standardized abstraction of the medical record. The follow up of these children and determination of the outcomes were greatly facilitated by the fact that approximately 60% of subjects who are recruited in the Boston Birth Cohort continue pediatric primary care at BUMC and 38% continue at a BUMC affiliated neighborhood health center. The availability of a unified electronic medical record allows for abstraction of data with efficiency and accuracy.

Statistical Analyses

We used a Chi square test to compare the baseline characteristics of term and preterm children in terms of demographic measures, SES measures, and maternal and in-utero risk factors and complications of pregnancy. We also carried out this analysis comparing children whose mothers did and did not meet our criteria for chorioamnionitis.

Potential confounding variables included infant and maternal factors. Infant factors included child's current age and sex, breast feeding, infection during pregnancy, preterm delivery, postnatal passive smoking, and type of delivery. Maternal factors included maternal ethnicity, maternal smoking during pregnancy, maternal asthma and maternal atopy, stress during pregnancy, parity, and SES as measured by highest level of maternal education achieved. To determine the best fitted and most parsimonious model, we performed a two step process. Firstly, certain variables which have been strongly associated with early childhood wheezing in the literature were retained in the model regardless of significance. These included tobacco smoke exposure in utero, postnatal passive smoke exposure, breastfeeding, maternal asthma, and the child's age. This resulted in three variables which were not statistically significant being kept in the model (intrapartum antibiotics, breastfeeding and postnatal passive smoking). Secondly, the other variables listed were retained in the model depending on the level of significance in the bivariate analyses. The use of a backwards stepwise regression model, forcing inclusion of the covariates felt to be important from the literature were used as a tool to assist in this selection process.

This process resulted in the inclusion of the following covariates: child's age and sex, post-natal passive smoke exposure, maternal ethnicity, presence of maternal atopic diseases, maternal education, maternal smoking postnatally, intrapartum antibiotics, and breastfeeding status. Of note, all variables which differed between those with and without chorioamnionitis (delivery type, antibiotic use, and gestational age) were accounted for in our models. (Gestational age group was used to stratify the comparision groups and the other 2 variables were included in the model.)

We carried out an initial logistic regression analysis to evaluate the effects of prematurity overall (<37 weeks gestation) on the outcomes, with adjustment for chorioamnionitis and the other covariates listed above. We further evaluated how the variables of degree of prematurity and chorioamnionitis jointly affect the risk of early childhood wheezing. Using term pregnancies (> =37 weeks) without chorioamnionitis as the reference group, the moderate preterm (33 to 36.9 weeks) and very preterm (<33 weeks) were further stratified by the presence of chorioamnionitis. Finally, we performed race-specific analysis to determine if these associations were consistent in African American children. For this subgroup analysis we removed the variable of maternal ethnicity.

Two other secondary analyses were carried out using the same covariates. The first divided the deliveries into spontaneous and medically indicated deliveries to evaluate the role of other perinatal morbidities on wheezing. The other secondary analysis evaluated the joint effect of fever and placental inflammation on the odds of recurrent wheezing or asthma. This was carried out to evaluate the relative impact of these two variables which were used to construct the chorioamnionitis variable.

All analyses were carried out using statistical software SAS for Windows 8.20 (SAS Institute, NC).

Results

This analysis included 771 term and 325 preterm infants enrolled from the Boston Birth Cohort who completed of at least one postnatal follow-up study visit. Recruitment from the Boston Birth Cohort to the follow up study has been approximately 90% of those approached. No differences in key variables including birthweight, gestation and prevalence of chorioamnionitis have been found from those infants yet to be enrolled in the follow up study. (data not shown).

The mean age of children at the point of last follow up was 2.2 ± 2.0 years. Baseline characteristics of the study children, including demographic measures, SES measures, and maternal/in-utero factors are displayed in Table I, stratified by term and preterm birth. As compared to the term children, preterm children had higher frequencies of maternal cigarette smoking during pregnancy, cesarean sections, prenatal antibiotic and steroid use, and chorioamnionitis as well as other pregnancy complications. Preterm children also had a higher frequency of wheezing (19.7 % vs. 10.2% in term infants) and a slightly higher prevalence of maternal asthma (15.7 vs. 11.2 in term infants). We also compared subjects with and without chorioamnionitis in Table E1. Subjects with chorioamnionitis were similar to those without chorioamnionitis in demographic variables, SES variables, and maternal in-utero factors; but had lower mean gestational age, more frequent delivery by c-section, and a higher frequency of antibiotic use.

Table E2 displays the results of a stepwise logistic regression to evaluate major covariates, in addition to prematurity and chorioamnionitis, for the outcomes of interest. We evaluated the association of prematurity overall (<37 weeks gestational age) with recurrent wheezing. We found that prematurity was associated with increased risk of recurrent wheezing (OR: 1.7, 95%CI:1.2-2.6), even after adjusting for child's age, gender, breastfeeding, postnatal exposure to maternal cigarette smoking, and chorioamnionitis as well as maternal ethnicity, education, prenatal smoke exposure and history of atopy. In contrast, prematurity did not seem to increase the risk of eczema (OR:0.6, 95%CI:0.5-0.9) or food allergy (OR:0.8, 95%CI:0.4-1.5).

We further evaluated the joint association of degree of prematurity and presence of chorioamnionitis with the outcomes of interest as shown in Table IIa. Our data suggest a joint effect when gestational age and chorioamnionitis are combined. With the exception of the moderately preterm group, children with chorioamnionitis had an increased risk of recurrent wheezing compared to term children without chorioamnionitis. Of note, the moderately preterm group with chorioamnionitis had smaller numbers of subjects. Children who were very preterm and had chorioamnionitis had the highest risk of recurrent wheezing (OR:4.0, 95%CI:2.0-8.0). Similarly, in this group the likelihood of physician diagnosed asthma was increased (OR:4.4 95%CI:2.2-8.7). Neither prematurity nor chorioamnionitis were associated with an increased risk of food allergy or eczema. There was no evidence of a statistically significant effect modification of chorioamnionitis on the associations of prematurity with the outcomes studied. Specifically, this is evidence of a joint effect of these variables, but not an interaction.

Finally, we evaluated if the above associations were consistently observed if restricted to African American children. As shown in Table IIb, we found a similar association which was greater in magnitude than that seen in the analysis of all the study subjects. For example, African American children who were very preterm with chorioamnionitis had a 5.4- fold increased risk of recurrent wheezing (OR:5.4, 95%CI:2.4-12.0) and a 5.2-fold increased risk of physician diagnosed asthma (OR:5.2, 95%CI:2.3-11.9). Again, neither prematurity nor chorioamnionitis were associated with food allergy or eczema.

As a secondary analysis, deliveries were divided into spontaneous births and medically indicated deliveries to evaluate whether other perinatal morbidities confounded the effect of chorioamnionitis on wheezing. As expected, both hypertensive disorders (including preeclampsia, eclampsia, HELLP), and other morbidities (including gestational diabetes, abruption placenta, placenta previa or incompetent cervix) were more common in medically indicated deliveries (Table E3). However, the relationships of wheezing and asthma with chorioamnionitis and prematurity persisted despite stratification by type of delivery (Table E4).

Finally, for this analysis a total of 36 children had chorioamnionitis determined by maternal fever alone, 106 children had chorioamnionitis defined by placental histopathology alone (sub-clinical chorioamnionitis), and 30 children had chorioamnionitis determined by both. We further examined this classification in two ways. Firstly, we evaluated the proportion of elevated white counts at delivery by these variables. All the groups which would have been identified as chorioamnionitis in our main analysis had a higher proportion of elevated white counts at delivery (>15000 by Gibbs Criteria)[22] than individuals who do not meet our criteria of chorioamnionitis. (Table E5) Second, we carried out a subgroup analysis using groupings defined by maternal fever and placental pathology in preterm infants with available data on both placental pathology and peripartum fever. As noted in the Table E6, those with placental inflammation and no fever showed higher risk of asthma compared to those without inflammation and fever. A similar trend was observed for the outcome of recurrent wheezing, but was not significant due to the smaller sample size in the subgroup analysis. The group at highest risk were those with both inflammation and fever. Our data indicates that placental inflammation appears to be a more sensitive and robust risk factor for wheezing or asthma than fever alone.

Discussion

In-utero events can affect early life immune responses,[26, 27] the development of atopic diseases in the offspring,[2-5] and even result in epigenetic effects on subsequent generations.[6] To date, no prospective studies have examined the joint effect of prematurity and chorioamnionitis in relation to the development of respiratory morbidity and atopic diseases in early childhood. In this study, we found that while prematurity was associated with recurrent wheezing in this cohort of children in the first few years of life, this association was greatly augmented by the severity of prematurity and presence of chorioamnionitis. The children who were very preterm and had chorioamnionitis had the greatest risk of recurrent wheezing. Furthermore, this association was much stronger in African American children. Our findings provide new information to a long-standing clinical and public health challenge, that is, increased risk of respiratory morbidities in African American children.

There were a number of features of our cohort which allowed us to carry this study out. We carried out a thorough evaluation of prenatal factors including placental pathology which provided a very sensitive indicator of intrauterine infection or inflammation. Ours is one of the few prospective studies with large enough numbers to allow stratification by severity of prematurity and presence of chorioamnionitis. Our study also has significant minority representation, with a high frequency of African Americans. Like asthma,[28, 29] prematurity and chorioamnionitis disproportionately affect the African American community (IOM report 2006). Our findings underscore the importance of examining the role of in-utero factors on the later development of respiratory morbidities. They also raise questions about whether the persistent and high prevalence of prematurity and chorioamnionitis, especially in African Americans, are linked in a causal fashion to the asthma epidemic and ethnic disparity in respiratory outcomes.

Caution is needed in interpreting our findings because of a number of potential limitations. Although we have shown associations with physician diagnosed asthma, we focused on recurrent wheezing given the average age of the children (around 2 years). It would be important to evaluate if the associations persist as we continue to follow these children and if increased rates of recurrent wheezing correlate with increased rates of asthma diagnoses at later ages. We were not able to follow all of the patients in the initial cohort as recruitment into the follow up cohort is ongoing. Subjects already enrolled in the follow up study showed no differences from those not yet recruited in key variables including birth-weight, gestation and percent of the cohort with chorioamnionitis.

This study focused on two prominent prenatal factors (prematurity and chorioamnionitis). While our analyses attempted to adjust for many potential covariates, we need to recognize that there are many other important prenatal factors that could affect the associations, such as intrapartum antibiotics and mode of delivery. Intrapartum antibiotics and mode of delivery can affect types of commensal organisms present in the mother[30] and infant[31] , and atopic disease prevalence.[32-34] However, we do not feel that mode of delivery or intrapartum use of antibiotics influenced our findings; intrapartum antibiotics was included as a covariate in our analyses. Also, modification of the commensal flora by antibiotics or mode of delivery should affect allergic diseases in general, not just wheezing. Since a significant proportion of the diagnoses of chorioamnionitis were made by histological diagnosis alone and represent subclinical inflammation, these mothers would not have had a clinical indication to receive intera-partum antibiotics. Notably, subclinical chorioamnionitis, determined by placental pathology, makes up the majority of our cases, and our analyses suggest that this is a stronger determinant than maternal fever alone. Finally, our findings compare subjects of similar gestational age, thereby decreasing any differential distribution of delivery mode. While we have controlled for modifiable risk factors such as smoking and breastfeeding in the analysis, we have insufficient sample size to stratify by all of these variables or evaluate interactions between all of these variables in addition to our main variables of interest, prematurity and chorioamnionitis. Further studies with increased sample size may be able to address these potential interactions.

Other potential mechanisms which need to be considered include possibilities such as increased susceptibility to early life respiratory infections and pneumonias such as RSV and the impact of these events on our findings. Also, further studies are needed to determine if the effects associated with chorioamnionitis are due to the administration of antipyretics in the perinatal period.

Several important points merit further discussion with respect to the prior literature. Prematurity has been associated with later childhood asthma in a number of studies[3, 9-11] While the effect of gestational age has not been consistent in all studies[12, 13], a recent meta-analysis of 19 studies reported that preterm infants are more likely than term infants to develop asthma, with preterm infants having a 7% increased risk[8]. One potential reason for discrepant results in the literature is that these studies did not evaluate the causes of prematurity. As emphasized in the 2006 IOM (Institute of Medicine) report, chorioamnionitis is a major pathway leading to the development of preterm birth.[14-16] The potential role of chorioamnionitis as a cause of respiratory morbidity has been evaluated in only a few studies to date. In these studies, febrile episodes in pregnancy (especially the third trimester) were associated with subsequent development of asthma in offspring.[17, 18] In keeping with the fact that chorioamnionitis is much more common in very preterm infants,[35] we found our greatest effect in this group of infants.

Secondly, we did not find an association of prematurity and chorioamnionitis with atopic dermatitis or food allergy. This is also consistent with other published studies. A number of

studies of prematurity suggest either no association with atopic diseases[36] or decreased risk of atopic outcomes including atopic dermatitis[37], and allergic rhinitis.[38] The differential associations for respiratory morbidities vs. non-respiratory atopic diseases suggest differential pathways of disease promotion. In our study, chorioamnionitis increased the risk of wheezing and physician diagnosed asthma, but not atopy. While this outcome is important in itself, it may or may not equate to asthma later in life. If it does predispose to persistent asthma, it would suggest that some prenatal factors may lead to asthma via non-atopic pathways such as fetal programming or epigenetic effects in-utero. However, the biological links between prematurity or chorioamnionitis and wheezing are not well established.

Finally, there is some biological rationale for our findings. Chorioamnionitis is associated with a strong pro-inflammatory response with increased levels of TNF-α, IL-6, and IL-8.[39, 40] These inflammatory cytokines may be a response to infection and also a trigger for premature delivery. Specifically, human decidual cells increase the production of delivery promoting factors such as PGE2 and PGF2 in response to inflammatory cytokines including IL1a, IL1b, and TNF-α.[41] In animal models, administration of a PDE4 inhibitor prevents preterm delivery.[42] Some of the same cytokines which are a response to infection may be involved in chronic respiratory disease development. Of these inflammatory cytokines, TNF-alpha variants have been found to be associated with recurrent wheezing after RSV bronchiolitis.[43] IL-8 levels were increased in children who developed wheezing illnesses in response to Rhinovirus,[44] and in another cohort, individuals who wheezed with Rhinovirus were at additional risk of persistent wheezing till follow up at age 3 years.[45] Thus, the same cytokines which are generated as part of the inflammatory response to chorioamnionitis may play a role in asthma and responses to respiratory viral illness.

In summary, we found a strong joint effect of prematurity and chorioamnionitis on early childhood recurrent wheezing. This effect was even stronger in African Americans. Further investigation is warranted to evaluate if the associations persist as we continue to follow these children to older age and if increased rates of recurrent wheezing correlate with increased rates of later asthma. Our findings remain to be confirmed by future studies in other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source(s) of support: The parent study is in part supported by the March of Dimes PERI grants (PI: Wang, 20-FY02-56), NIEHS (PI: Wang, R21 ES011666), and NICHD (PI: Wang, R01 HD041702). The follow-up study is in part supported by Food Allergy Project.

References

1. Gilliland FD, Li YF, Dubeau L, et al. Effects of glutathione S-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. Am J Respir Crit Care Med 2002;166(4):457–63. [PubMed: 12186820]
2. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. Am J Respir Crit Care Med 2001;163(2):429–36. [PubMed: 11179118]
3. Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health 2004;94(1):136–40. [PubMed: 14713711]

4. Lannero E, Wickman M, Pershagen G, Nordvall L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). Respir Res 2006;7:3. [PubMed: 16396689]
5. Magnusson LL, Olesen AB, Wennborg H, Olsen J. Wheezing, asthma, hayfever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. Clin Exp Allergy 2005;35(12): 1550–6. [PubMed: 16393320]
6. Li YF, Langholz B, Salam MT, Gilliland FD. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. Chest 2005;127(4):1232–41. [PubMed: 15821200]
7. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med 2005;172(10):1253–8. [PubMed: 16109980]
8. Jaakkola JJ, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: a systematic review and meta-analysis. J Allergy Clin Immunol 2006;118(4):823–30. [PubMed: 17030233]
9. Schwartz J, Gold D, Dockery DW, Weiss ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States. Association with social class, perinatal events, and race. Am Rev Respir Dis 1990;142(3):555–62. [PubMed: 2389907]
10. von Mutius E, Nicolai T, Martinez FD. Prematurity as a risk factor for asthma in preadolescent children. J Pediatr 1993;123(2):223–9. [PubMed: 8345417]
11. Yuan W, Fonager K, Olsen J, Sorensen HT. Prenatal factors and use of anti-asthma medications in early childhood: a population-based Danish birth cohort study. Eur J Epidemiol 2003;18(8):763–8. [PubMed: 12974551]
12. Rasanen M, Kaprio J, Laitinen T, Winter T, Koskenvuo M, Laitinen LA. Perinatal risk factors for asthma in Finnish adolescent twins. Thorax 2000;55(1):25–31. [PubMed: 10607798]
13. Steffensen FH, Sorensen HT, Gillman MW, et al. Low birth weight and preterm delivery as risk factors for asthma and atopic dermatitis in young adult males. Epidemiology 2000;11(2):185–8. [PubMed: 11021618]
14. Chellam VG, Rushton DI. Chorioamnionitis and funiculitis in the placentas of 200 births weighing less than 2.5 kg. Br J Obstet Gynaecol 1985;92(8):808–14. [PubMed: 4027203]
15. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342(20):1500–7. [PubMed: 10816189]
16. Mueller-Heubach E, Rubinstein DN, Schwarz SS. Histologic chorioamnionitis and preterm delivery in different patient populations. Obstet Gynecol 1990;75(4):622–6. [PubMed: 2314782]
17. Xu B, Pekkanen J, Jarvelin MR, Olsen P, Hartikainen AL. Maternal infections in pregnancy and the development of asthma among offspring. Int J Epidemiol 1999;28(4):723–7. [PubMed: 10480702]
18. Calvani M, Alessandri C, Sopo SM, et al. Infectious and uterus related complications during pregnancy and development of atopic and nonatopic asthma in children. Allergy 2004;59(1):99–106. [PubMed: 14674941]
19. Akinbami LJ, LaFleur BJ, Schoendorf KC. Racial and income disparities in childhood asthma in the United States. Ambul Pediatr 2002;2(5):382–7. [PubMed: 12241134]
20. Roberts EM. Racial and ethnic disparities in childhood asthma diagnosis: the role of clinical findings. J Natl Med Assoc 2002;94(4):215–23. [PubMed: 11991334]
21. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. Jama 2002;287(2):195–202. [PubMed: 11779261]
22. Gibbs RS, Blanco JD, St Clair PJ, Castaneda YS. Quantitative bacteriology of amniotic fluid from women with clinical intraamniotic infection at term. J Infect Dis 1982;145(1):1–8. [PubMed: 7033397]
23. Gupta M, Mestan KK, Martin CR, et al. Impact of clinical and histologic correlates of maternal and fetal inflammatory response on gestational age in preterm births. J Matern Fetal Neonatal Med 2007;20(1):39–46. [PubMed: 17437198]
24. Benirschke, K.; K, P.; Baergen, R. Pathology of the human placenta. New York: Springer; 2000.
25. Langston C, Kaplan C, Macpherson T, et al. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med 1997;121(5):449–76. [PubMed: 9167599]

26. Noakes PS, Hale J, Thomas R, Lane C, Devadason SG, Prescott SL. Maternal smoking is associated with impaired neonatal toll-like-receptor-mediated immune responses. Eur Respir J 2006;28(4):721–9. [PubMed: 16870663]
27. Noakes PS, Holt PG, Prescott SL. Maternal smoking in pregnancy alters neonatal cytokine responses. Allergy 2003;58(10):1053–8. [PubMed: 14510725]
28. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. Pediatrics 2002;110(2 Pt 1):315–22. [PubMed: 12165584]
29. Turkeltaub PC, Gergen PJ. Prevalence of upper and lower respiratory conditions in the US population by social and environmental factors: data from the second National Health and Nutrition Examination Survey, 1976 to 1980 (NHANES II). Ann Allergy 1991;67(2 Pt 1):147–54. [PubMed: 1867453]
30. Benn CS, Thorsen P, Jensen JS, et al. Maternal vaginal microflora during pregnancy and the risk of asthma hospitalization and use of antiasthma medication in early childhood. J Allergy Clin Immunol 2002;110(1):72–7. [PubMed: 12110824]
31. Penders J, Thijs C, van den Brandt PA, et al. Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. Gut 2007;56(5):661–7. [PubMed: 17047098]
32. McKeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. Am J Respir Crit Care Med 2002;166(6):827–32. [PubMed: 12231492]
33. Rusconi F, Galassi C, Forastiere F, et al. Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. Am J Respir Crit Care Med 2007;175(1):16–21. [PubMed: 16998092]
34. Marra F, Lynd L, Coombes M, et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest 2006;129(3):610–8. [PubMed: 16537858]
35. Goldenberg RL, Andrews WW, Hauth JC. Choriodecidual infection and preterm birth. Nutr Rev 2002;60(5 Pt 2):S19–25. [PubMed: 12035853]
36. de Martino M, Donzelli GP, Galli L, et al. Food allergy in preterm infants fed human milk. Biol Neonate 1989;56(6):301–5. [PubMed: 2611300]
37. Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: historical follow up by record linkage. Bmj 1997;314(7086):1003–8. [PubMed: 9112844]
38. Braback L, Hedberg A. Perinatal risk factors for atopic disease in conscripts. Clin Exp Allergy 1998;28(8):936–42. [PubMed: 9756196]
39. Murtha AP, Sinclair T, Hauser ER, Swamy GK, Herbert WN, Heine RP. Maternal serum cytokines in preterm premature rupture of membranes. Obstet Gynecol 2007;109(1):121–7. [PubMed: 17197597]
40. Jacobsson B, Mattsby-Baltzer I, Hagberg H. Interleukin-6 and interleukin-8 in cervical and amniotic fluid: relationship to microbial invasion of the chorioamniotic membranes. Bjog 2005;112(6):719–24. [PubMed: 15924526]
41. Mitchell MD, Edwin S, Romero RJ. Prostaglandin biosynthesis by human decidual cells: effects of inflammatory mediators. Prostaglandins Leukot Essent Fatty Acids 1990;41(1):35–8. [PubMed: 2251294]
42. Schmitz T, Souil E, Herve R, et al. PDE4 inhibition prevents preterm delivery induced by an intrauterine inflammation. J Immunol 2007;178(2):1115–21. [PubMed: 17202375]
43. Goetghebuer T, Isles K, Moore C, Thomson A, Kwiatkowski D, Hull J. Genetic predisposition to wheeze following respiratory syncytial virus bronchiolitis. Clin Exp Allergy 2004;34(5):801–3. [PubMed: 15144474]
44. Gern JE, Martin MS, Anklam KA, et al. Relationships among specific viral pathogens, virus-induced interleukin-8, and respiratory symptoms in infancy. Pediatr Allergy Immunol 2002;13(6): 386–93. [PubMed: 12485313]
45. Lemanske RF Jr, Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol 2005;116(3):571–7. [PubMed: 16159626]

Abbreviations used

MD diagnosis	physician diagnosis
BUMC	Boston University Medical Center
CDC	Centers for Disease Control
IOM	Institute of Medicine
OR	odds ratio

Table I

Baseline Characteristics of Boston Birth Cohort by Gestational age.

Characteristic	Term	Preterm	P value
N	771	325	
Demographic measures			
Sex: Males (%)	384(49.8)	158(48.6)	0.72
Age, years (mean ± SD)	2.2 ± 2.0	2.2 ± 2.0	0.74
Overall Age, years (mean ± SD)	2.2 ± 2.0		
Age <3 years (%)	467(60.6)	195(60.0)	0.86
>=3 years	304(39.4)	130(40.0)	
Maternal race/ethnicity (%)			
AA	477(61.9)	206(63.4)	0.392
White	47(6.1)	26(8.0)	
Hispanic	154(20.0)	65(20.0)	
Asian/Pacific Islander	18(2.3)	4(1.2)	
Other	75(9.7)	24(7.4)	
SES measures			
Annual household income (%)			
<$15k	226(47.2)	107(52.7)	0.40
$15k~30k	164(34.2)	64(31.5)	
>=$30k	89(18.6)	32(15.8)	
Maternal education level (%)			
<High school	230(29.8)	103(31.7)	0.53
High school	267(34.6)	118(36.3)	
>High school	274(35.5)	104(32.0)	
Maternal / in utero factors			
Maternal ever smoking (%)	101(13.1)	76(23.4)	<0.001
Postnatal Passive smoking (%)	141(18.3)	90(27.7)	<0.001
Maternal asthma (%)	86(11.2)	51(15.7)	0.04
Any maternal atopic disease (%)	204(26.5)	102(31.4)	0.10
High stress during pregnancy (%)	152(19.7)	64(19.7)	0.99
Breast feed (%)			
Breast only	46(6.0)	26(8.0)	0.08
Bottle only	122(15.8)	66(20.3)	
Both	603(78.2)	233(71.7)	
Delivery by C-section (%)	226(29.3)	132(40.6)	<0.001
First child (nulliparity) (%)	319(41.4)	144(44.3)	0.43
Placental evidence of chorioamnionitis (%)	88(11.4)	84(25.8)	<0.001
Intrapartum Antibiotic use (%)	99(15.4)	104(32.0)	<0.001
Steroid use (%)	3(0.4)	109(33.5)	<0.001
Complications during pregnancy* (%)	82(10.6)	100(30.8)	<0.001
≥ 2 episodes of wheezing (%)	79(10.2)	64(19.7)	<0.001

*Complications during pregnancy includes Chronic Hypertension, Preeclampsia, eclampsia, HELLP(hemolysis, elevated liver enzymes and low platelets syndrome), Diabetes (gestational diabetes), Abruption placentia or Incompetent Cervix.

J Allergy Clin Immunol. Author manuscript; available in PMC 2010 November 29.

Table IIa

The joint association of degree of prematurity with chorioamnionitis and recurrent wheezing, asthma, eczema, and food allergy.

Chorioamnionitis	Degree of Prematurity (weeks of gestation)	TotalN	Case %	OR (95%CI)	p
	Wheezing[#]				
No	>=**37**	683	9.2	1.0	--
	33~36.9	178	15.7	1.7(1.0-2.9)	0.03
	<**33**	63	22.2	2.7(1.3-5.5)	0.005
Yes	>=**37**	88	18.2	2.0(1.1-3.8)	0.03
	33~36.9	32	15.6	1.3(0.4-3.6)	0.67
	<**33**	52	32.7	4.0(2.0-8.0)	0.0001
	Asthma				
No	>=**37**	683	12.9	1.0	--
	33~36.9	179	13.5	1.0(0.6-1.7)	0.95
	<**33**	63	19	1.6(0.8-3.5)	0.18
Yes	>=**37**	88	17.0	1.2(0.6-2.2)	0.67
	33~36.9	32	21.9	1.4(0.6-3.6)	0.47
	<**33**	52	42.3	4.4(2.2-8.7)	0.0000
	Eczema				
No	>=**37**	683	32.1	1.0	--
	33~36.9	178	23.6	0.6(0.4-0.9)	0.02
	<**33**	63	23.8	0.7(0.4-1.2)	0.20
Yes	>=**37**	88	43.2	1.5(0.9-2.4)	0.07
	33~36.9	32	25.0	0.6(0.3-1.4)	0.24
	<**33**	52	37.2	0.9(0.5-1.7)	0.74
	Food allergy				
No	>=**37**	683	6.3	1.0	--
	33~36.9	178	5.6	0.8(0.4-1.7)	0.55
	<**33**	63	3.2	0.4(0.1-1.9)	0.25
Yes	>=**37**	88	5.7	0.7(0.3-2.0)	0.53
	33~36.9	32	3.1	0.4(0.1-2.8)	0.34
	<**33**	52	5.8	0.8(0.2-2.7)	0.67

Covariates adjusted in the model:

Infant factors - Child's age and sex, breastfeeding, postnatal passive smoking.

Maternal factors - maternal ethnicity, maternal atopic diseases, maternal smoking during pregnancy, antibiotics, and maternal educational status.

[#] Wheezing, episodes of wheezing >=2;

Table IIb

The joint association of degree of prematurity and chorioamnionitis with recurrent wheezing and asthma among African American children.

Chorioamnionitis	Degree of Prematurity (weeks of gestation)	Total, N	Case %	OR (95%CI)	p
	Wheezing[#]				
No	**>=37**	423	10.4	1.0	--
	33~36.9	103	16.5	1.7(0.9-3.3)	0.10
	<33	43	30.2	3.8(1.7-8.5)	0.0009
Yes	**>=37**	54	20.4	2.0(0.9-4.3)	0.09
	33~36.9	23	21.7	1.8(0.6-5.3)	0.31
	<33	37	42.3	5.4(2.4-12.0)	0.0000
	Asthma				
No	**>=37**	423	14.7	1.0	--
	33~36.9	103	13.6	0.9(0.5-1.8)	0.74
	<33	43	23.3	1.9(0.8-4.4)	0.45
Yes	**>=37**	54	22.2	1.3(0.6-2.9)	0.45
	33~36.9	23	30.4	2.0(0.7-5.7)	0.18
	<33	37	51.4	5.2(2.3-11.9)	0.0001

Covariates adjusted in the model:

Infant factors - Child's age and sex, breastfeeding, postnatal passive smoking.

Maternal factors - maternal atopic diseases, maternal smoking during pregnancy, antibiotics, and maternal educational status.

[#]Wheezing, episodes of wheezing >=2;