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Pre- and Perinatal Risk Factors for Asthma in Inner City African-American Children

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The relations between pre- and perinatal risk factors and asthma were investigated using a case-control study of 262 African-American children aged 4–9 years, both asthmatic and nonasthmatic, all of whom resided in a poor urban area and received health care at a local hospital-based clinic. Risk factors were ascertained through review of obstetric, perinatal, and pediatric records. Asthmatic children had significantly lower birth weights and gestational ages than nonasthmatic children and were more likely to have required oxygen supplementation and positive pressure ventilation after birth than nonasthmatics ($p < 0.05$). The mothers of asthmatic children were more likely to have smoked during pregnancy (50% vs. 27%), to have gained less weight during pregnancy (26.3 pounds (11.9 kg) vs. 34.5 pounds (15.7 kg)), and to have had no prenatal care (12% vs. 2%) than mothers of nonasthmatic children. Multiple logistic regression demonstrated that the strongest independent predictors of asthma were maternal history of asthma (adjusted odds ratio (OR) = 9.7), lack of prenatal care (OR = 4.7), history of bronchiolitis (OR = 4.7), positive pressure ventilation at birth (OR = 3.3), low maternal weight gain (<20 pounds (<9 kg)) (OR = 3.4), and maternal smoking during pregnancy (OR = 2.8). These data suggest that pre- and perinatal exposures may increase susceptibility to asthma in inner city children. *Am J Epidemiol* 1996;143:570–7.

asthma; blacks; child; prenatal care; prenatal exposure delayed effects; risk factors

Asthma is a prevalent chronic disease, affecting 5–12 percent of the US population, and it is associated with substantial morbidity and economic cost (1). Over the past decade, the morbidity and mortality associated with asthma have increased, with the greatest increases having occurred in persons under 35 years of age (2–7). This increase in asthma morbidity, including hospitalizations, emergency room visits, and days of school lost, as well as mortality, appear to affect poor urban African-Americans disproportionately (8–15). The basis for excess asthma morbidity in the inner city is not well understood, but it may include factors associated with poor access to medical care, psychosocial stressors, and adverse indoor and outdoor environmental exposures.

Increased asthma prevalence in African-Americans as compared with Caucasians is apparent for children between the ages of 1 and 3 years (2). Thus, exposures that occur early in life may be particularly important in influencing susceptibility to asthma. Elucidation of the role of specific environmental exposures could be important in the development of interventions aimed at reducing excess morbidity.

Previous studies have related pre- and perinatal factors, such as low birth weight, maternal age, and maternal smoking, to the later development of wheezing illnesses, asthma, and reduced lung function (16–23). However, previous relations between prenatal factors and respiratory disease may have been partly confounded by socioeconomic status or race. To minimize the effects of confounding, we assessed the relations between pre- and perinatal exposures and asthma in a study population restricted to African-Americans living in impoverished inner city census tracts. In this high risk population, we performed a case-control study to test the hypothesis that pre- and perinatal stressors are associated with an increased risk of developing asthma which is independent of race per se.

MATERIALS AND METHODS

Cases and controls were identified using rosters of patients followed during the previous year at the Rainbow Babies and Children's Hospital continuity care

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Abbreviations: FEV_1, forced expiratory volume in 1 second; OR, odds ratio.

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clinic, University Hospitals, Cleveland, Ohio. Of all of the inner city African-American children with physician-diagnosed asthma between the ages of 4 and 9 years who were followed in the clinic, approximately 50 percent had also been born at University Hospitals. These children were selected as cases (n = 131). An inner city residence was defined as a residence in a census tract in the Greater Cleveland area with more than 40 percent of the population living below the poverty level (1990 data). The control group was chosen from the list of patients followed for well-child care who were born at University Hospitals (>1,000 patients), resided in the same census tracts as the cases (matched according to age (±1 month), race, and sex), and had no history of recurrent respiratory problems. The control selected for each case was the patient born closest to the subject who met the above criteria for matching.

A patient was defined as asthmatic if the medical record indicated a physician diagnosis of asthma in addition to the presence of wheezing or coughing symptoms in the previous 12 months that had resulted in the use of asthma medication (e.g., beta agonists, steroids, or theophylline). Subjects were excluded from the study if they had a history of bronchopulmonary dysplasia, cystic fibrosis, or anatomic lung anomaly or if they had required supplemental oxygen or mechanical ventilation for more than 14 days after birth.

Using a single instrument, demographic data and information on relevant "exposures" were extracted from prenatal clinic and maternal obstetric records. These records consisted of standard forms used by the medical staff for recording prenatal and perinatal data. The maternal obstetric records required the attending nurse or physician to complete sections on medical history (specifically including asthma history); age at delivery; insurance status; marital status; weight prior to pregnancy (reported) and at the time of birth (measured); height; tobacco, ethanol, and illegal drug use during pregnancy; time of rupture of membranes and of delivery; type of delivery; and last menstrual period and estimated date of conception. The standardized birth record provided data on Apgar scores at 5 minutes, birth weight and length, requirements for resuscitation in the delivery room, and type of infant feeding (breast or bottle) at the time of discharge from the nursery. If "suctioning for meconium" was recorded in the medical record, this was noted without an attempt to differentiate between thin and thick meconium. Prenatal care was defined as having made at least one prenatal care visit to a health care provider. Childhood risk factors and symptoms (history of bronchiolitis prior to 2 years of age, reported history of allergies or eczema, and history of wheezing) were obtained from review of the pediatric clinic records.

Statistical methods

The significance of sets of risk factors in differentiating asthmatic groups from nonasthmatic groups was assessed by multivariate analysis of covariance, with the asthma status of the child used as the independent variable. Variable sets were as follows: insurance status, marital status, smoking history, alcohol history, prenatal care, age at delivery, weight gain during pregnancy, and maternal history of asthma (designated "maternal variables"); birth weight, birth length, and gestational age ("birth size" variables); bronchiolitis, eczema, and allergies (variables related to early childhood risks/atopy); and delivery mode, Apgar scores, meconium status, and ventilatory or oxygen support (delivery variables). The overall significance of each variable set was assessed with Hotelling's T^2 (Statistical Package for the Social Sciences, version PC 4.1; SPSS, Inc., Chicago, Illinois). Each variable set was highly significant ($p < 0.001$), suggesting the appropriateness of further statistical analyses of individual risk factors. These factors were then assessed with two-tailed unpaired t tests and contingency table analysis (1 df). Multiple logistic regression was used to formulate a prediction equation relating likelihood of asthma to selected pre- and perinatal risk factors (maternal history of asthma, bronchiolitis, maternal smoking during pregnancy, prenatal care, low maternal gestational weight gain (<20 pounds (<9 kg)), use of oxygen at birth, positive pressure ventilation (bag mask or mechanical) at birth, prematurity (<37 weeks' gestation), low birth weight (<2,500 g), and low 5-minute Apgar scores (<7)). Adjusted odds ratios were calculated from the parameter coefficients obtained in the final logistic regression model. Analyses (univariate and logistic regression) were also stratified by bronchiolitis, maternal asthma, and prematurity in order to further assess possible confounding or effect modification.

RESULTS

The study population consisted of 131 asthmatic subjects and 131 control subjects born between August 31, 1983, and January 1, 1989, with a mean age at the time of chart review of 6.7 years (standard deviation, ±1.7). Subject characteristics are presented in table 1. The majority of children from each group were insured by Medicaid. Asthmatic children were more likely to have had documented bronchiolitis prior to age 2 years and a documented history of allergic rhinitis or con-

TABLE 1. Demographic factors and previous medical conditions in asthmatic and nonasthmatic children aged 4–9 years, Cleveland, Ohio, 1993–1994

	Children with asthma (n = 131)	Controls (n = 131)
Sex (% male)	63.4	63.4
Mean age (years) at chart review	6.7 (1.7)‡	6.7 (1.7)
Health insurance status (%)		
Self-pay	7.6	3.8
Medicaid	86.3	88.5
Private	6.1	7.6
Bronchiolitis prior to age 2 years (%)	38.2	9.9*
Allergic rhinitis/conjunctivitis (%)	28.2	8.4*
Eczema (%)	41.2	29.8†

* $p < 0.001$.
† $p = 0.053$.
‡ Numbers in parentheses, standard deviation.

junctivitis. There was a trend toward increased eczema in the children with asthma ($p = 0.053$).

Differences in maternal risk factors between asthmatic and control subjects are shown in table 2. Mothers of asthmatic children were significantly more likely to have asthma themselves than the mothers of control subjects. They were also significantly more likely to have received no prenatal care, and were less likely to have been married at the time of delivery. Mothers of asthmatic children were more likely to have smoked during pregnancy and to have smoked in higher amounts. The frequencies of self-reported alcohol consumption and illegal drug use were somewhat higher in the mothers of asthmatics than among the control mothers, but these differences did not reach statistical significance. Mothers of asthmatic children were more likely to have gestational weight gains of <20 pounds (mean weight gain = 12.7 pounds (5.8 kg); interquartile range, 9–17 pounds (4–8 kg)) and lower mean weights at the time of delivery.

Table 3 shows the distribution of risk factors associated with delivery and the perinatal period. There was no difference in mode of delivery or the occurrence of prolonged rupture of the membranes between the asthmatic children and the control group. Children with asthma were significantly more likely to have 5-minute Apgar scores below 7, to have required positive pressure ventilation, and to have required oxygen after birth than the nonasthmatic children. Prematurity and low birth weight and length were also more frequent among the asthmatic children than among the control children. Controls were more likely to have been suctioned for meconium below the vocal cords than the asthmatic children. Children with asthma were less likely to have been breast-fed during early infancy.

Logistic regression analysis (see "Materials and Methods") demonstrated that the strongest independent predictors of asthma were maternal history of asthma (adjusted odds ratio (OR) = 9.7), bronchiolitis prior to 2 years of age (OR = 4.7), lack of prenatal care (OR = 4.7), positive pressure ventilation at birth (OR = 3.3), low maternal weight gain during pregnancy (OR = 3.4), and maternal smoking during pregnancy (OR = 2.8) (table 4). After adjustment for these factors, prematurity and birth weight were not significant predictors of asthma.

TABLE 2. Maternal risk factors in 262 mothers of asthmatic and nonasthmatic children, Cleveland, Ohio, 1993–1994

	Children with asthma (n = 131)	Children without asthma (n = 131)	p value
Mean maternal age (years) at delivery	23.0 (60)*	23.7 (5.2)	NS†
Maternal asthma history (%)	22.9	2.3	<0.001
No prenatal care (%)	11.5	2.3	0.003
Married at delivery (%)	9.2	22.9	0.002
Smoking during pregnancy (%)	50.4	26.9	<0.001
1–10 cigarettes/day	10.1	15.4	
11–20 cigarettes/day	22.5	8.5	
>20 cigarettes/day	17.8	2.3	
Alcohol use during pregnancy (%)	11.9	5.6	0.091
Mean maternal height (inches‡)	62.8 (8.4)	61.2 (12.7)	NS
Mean maternal weight at delivery (pounds§)	168.8 (37.8)	179.7 (36.6)	0.031
Mean gestational weight gain (pounds)	26.3 (16.4)	34.5 (15.0)	<0.001
Mothers who gained <20 pounds (%)	43.1	14.5	<0.001

* Numbers in parentheses, standard deviation.
† NS, not significant.
‡ To convert inches to millimeters, multiply by 254 and divide by 10.
§ To convert pounds to kilograms, multiply by 454 and divide by 1,000.

TABLE 3. Delivery-related and perinatal risk factors for asthma in African-American children aged 4–9 years, Cleveland, Ohio, 1993–1994

	Children with asthma (n = 131)	Controls (n = 131)	p value
Prolonged rupture of membranes (>12 hours) (%)	28.2	20.2	NS*
Delivered by cesarean section (%)	25.2	23.7	NS
5-minute Apgar score <7 (%)	7.6	2.3	0.047
Oxygen administered in the delivery room (%)	51.9	38.2	0.025
Positive pressure ventilation (bag mask or mechanical ventilation) (%)	19.2	3.8	<0.001
Suctioned for meconium below vocal cords at birth (%)	10.8	20.6	0.029
Mean gestational age (weeks)	38.2 (3.4)†	39.2 (2.4)	0.008
Premature birth (<37 weeks) (%)	24.6	13.7	0.026
Mean birth weight (g)	2,915 (741)	3,145 (480)	0.003
Mean birth length (cm)	47.6 (4.4)	49.0 (2.3)	0.016
Birth weight <2,500 g (%)	20.6	9.9	0.016
Being breast-fed at time of discharge from nursery (%)	23.7	34.4	0.057

* NS, not significant.
† Numbers in parentheses, standard deviation.

TABLE 4. Adjusted odds ratios for asthma among children aged 4–9 years, Cleveland, Ohio, 1993–1994*

	Odds ratio	95% CI†
No prenatal care	4.66	1.12–19.51
Weight gain <20 pounds	3.42	1.72–6.79
Maternal smoking during pregnancy	2.82	1.53–5.20
Positive pressure ventilation in delivery room	3.25	1.03–10.24
Maternal history of asthma	9.68	2.57–36.49
Bronchiolitis prior to age 2 years	4.71	2.18–10.20

* Odds ratios were based on multiple stepwise logistic regression analysis using asthma as the outcome variable and maternal asthma history, bronchiolitis, maternal smoking, lack of prenatal care, gestational weight gain <20 pounds, use of oxygen at birth, prematurity (<37 weeks), birth weight <2,500 g, and 5-minute Apgar score <7 as predictor variables. Variables with a p value of <0.05 were retained.
† CI, confidence interval.

It is possible that the above risk factors may have differentially operated in subsamples who differed according to their "intrinsic" susceptibility to asthma (i.e., those with a maternal history of asthma), those who may have been most vulnerable to perinatal exposures (i.e., premature infants), or those who later experienced a serious respiratory illness (i.e., bronchiolitis). Therefore, analyses were stratified according to prematurity, maternal history of asthma, bronchiolitis, and maternal smoking (table 5). These analyses demonstrated similar relations between asthma and lack of prenatal care, maternal smoking, mechanical ventilation, and low weight gain in all substrata.

DISCUSSION

Susceptibility to asthma is determined by genetic risk factors that influence atopy, as well as by environmental exposures that cause sensitization or airway irritation and/or inflammation. In this study, the strong association between maternal history of asthma and asthma susceptibility (OR = 9.7) confirms the results of previous studies that have suggested the importance of familial factors in predisposing people to asthma. This study also suggests the importance of environmental factors, including those that occur in utero and during early childhood, in increasing asthma risk. Specifically, in analyses restricted to African-American children from the inner city, asthma was significantly increased in children born to mothers who did not receive prenatal care and who had poor weight gain and smoked during pregnancy. Thus, risk factors that predict adverse pregnancy outcomes are also significant independent predictors for the development of asthma during childhood.

Mothers of asthmatic children were three times more likely to have weight gains under 20 pounds, and they had lower mean weights at the time of delivery than the mothers of controls; the mean birth weight of the asthmatic children also was significantly lower than that of the nonasthmatic children. Poor maternal nutrition and low birth weight have previously been noted to predict the development of lung disease during childhood and adulthood (20, 24). In a prospective study of more than 5,000 men aged 59–70 years in Great Britain, forced expiratory volume in 1 second and mortality due to chronic obstructive airways dis-

TABLE 5. ***Distribution of selected risk factors for asthma in asthmatic (AS) and nonasthmatic (NAS) children aged 7–9 years, according to prematurity, maternal asthma history, bronchiolitis, and maternal smoking, Cleveland, Ohio, 1993–1994***

	No.	No prenatal care		Maternal smoking		Positive pressure ventilation		Maternal weight gain <20 pounds		Birth weight (g)
		No.	%	No.	%	No.	%	No.	%	
Premature birth										
No										
NAS	113	2	2	32	29	5	4	16	14	3,231
AS	99	11	11	50	52	13	13	38	38	3,194
Yes										
NAS	18	1	6	2	11	0	0	3	17	2,603
AS	32	4	12	15	47	12	36	19	58	2,060
Maternal history of asthma										
No										
NAS	128	3	2	34	27	5	4	19	15	3,142
AS	101	10	10	52	52	17	17	39	39	2,904
Yes										
NAS	3	0	0	0	0	0	0	0	0	3,276
AS	30	5	17	13	45	8	27	18	60	2,953
Bronchiolitis										
No										
NAS	118	3	3	31	26	3	3	17	14	3,150
AS	81	11	14	39	49	14	17	29	36	2,980
Yes										
NAS	13	0	0	3	25	2	15	2	15	3,101
AS	50	4	8	26	52	11	22	28	56	2,812
Maternal smoking										
No										
NAS	96	2	2			4	4	12	13	3,155
AS	64	5	8			8	13	31	48	2,939
Yes										
NAS	34	1	3			1	3	6	18	3,142
AS	65	9	14			16	25	26	40	2,913

ease were both significantly related to birth weight (24). Similarly, low birth weight was significantly associated with reduced lung function in a study of more than 5,000 British children aged 5–11 years (20). Studies of animals have shown that nutritional deprivation during gestation may result in specific abnormalities in lung development, such as a decreased ratio of lung size to body size and decreased lecithin content and surface activity of lung extracts (25). Whether low maternal weight gain and/or low birth weight are markers for nutritional deprivation, and whether this predisposes to airway hyperreactivity and asthma, are not known.

The mechanisms by which lack of prenatal care predisposes to the birth of an asthmatic child also are unclear. Absence of prenatal care, a problem that disproportionately affects poor African-Americans (26, 27), is a well established risk factor for low birth weight and prematurity (28). However, even after adjustment for maternal weight gain, birth weight, and prematurity, absence of prenatal care remained a significant independent risk factor for asthma. (Low birth weight and prematurity are not presented in the final logistic regression model because of their low significance after consideration of prenatal care, low weight gain, and maternal smoking.) Thus, there are probably aspects of prenatal care apart from those that directly influence maternal nutrition and prematurity that also favorably influence asthma risk. Lack of prenatal care also may be a marker for a particularly disrupted social environment (29). Although all of the subjects in this study lived in the same impoverished area and the majority met Medicaid eligibility requirements, there probably were some differences in the distribution of psychosocial stressors among subjects which may have paralleled their differences in prenatal care. Lack of prenatal care may be a surrogate for increased psychosocial stressors that broadly adversely influence the health of the mother and/or fetus.

Children with asthma were significantly more likely to have been born to mothers who smoked than were the nonasthmatic children. In-utero exposure to to-

bacco smoke increases the risk of intrauterine growth retardation and prematurity (30, 31). In-utero tobacco smoke exposure also may influence lung development, as suggested by the reduced size-corrected forced expiratory flow rates observed among infants of mothers who smoke (17, 22). Mothers who smoke during pregnancy are likely to also smoke after the birth of their children. Numerous studies have shown that exposure to passive cigarette smoke in childhood leads to an increased incidence of lower respiratory tract illness and diminished pulmonary function (17, 22, 32–37); airway reactivity also may be heightened among asthmatic children exposed to passive smoking (38). Thus, it is possible that passive smoking during early childhood also contributed to the increased asthma risk observed among children of smoking mothers.

In a group of predominantly middle-class Caucasian subjects, lower maternal age has been associated with an increased incidence of wheezing illness during the first year of life (18). In contrast, no relation between maternal age and asthma was observed in our sample of poor African-Americans. It is possible that in our high risk population, an influence of maternal age was obscured by a stronger impact of other adverse factors (e.g., maternal weight gain and smoking) or by the close matching of cases and controls on socioeconomic status. Nevertheless, the two studies are consistent in suggesting that increased maternal and fetal stress, caused by a variety of factors, may adversely influence lung development and increase asthma risk.

The presence of meconium at birth was inversely related to the chance of developing asthma. Meconium aspiration is associated with significant morbidity and mortality due to lung disease in the newborn period (39). However, the presence of meconium in the amniotic fluid at birth occurs often in association with increased fetal maturity (40). This may indicate that fetal maturity is a more important factor in protecting infants from the development of asthma than the potentially deleterious effects of small amounts of aspirated meconium.

The occurrence of respiratory illnesses during early infancy and childhood may predispose people to respiratory illness later in life. Many preterm infants have persistent respiratory morbidity after surviving neonatal respiratory distress such as bronchopulmonary dysplasia (41). In addition, numerous studies have demonstrated an increased 10-year incidence of recurrent wheezing following viral lower respiratory tract illnesses in infancy (42–46). In our study, the need for positive pressure ventilation at delivery and the occurrence of bronchiolitis prior to 2 years of age were both significant independent predictors of asthma. In this cross-sectional study, it is difficult to assess whether these risk factors directly predisposed children to asthma or rather were markers for children with compromised lung function who were predisposed to problems both in early infancy and in later childhood. Additionally, we cannot exclude the possibility that bronchiolitis was preferentially diagnosed in the asthmatic children as compared with the nonasthmatic children.

Similarly to what has been reported in other populations, maternal history of asthma and atopy (history of allergies and eczema) were more common in asthmatic children than in the nonasthmatic children. We had postulated that subjects with these "intrinsic host" risk factors may have had different susceptibilities to the influences of adverse pre- and perinatal exposures. However, stratified analyses did not demonstrate significant differences in the influences of pre- and perinatal factors on asthma risk among subsets of children with and without a family history of asthma. Similarly, a history of bronchiolitis or prematurity did not cause significant effect modification.

The roles of pre- and perinatal risk factors were the focus of this study. Early life environmental exposures, in addition to environmental tobacco smoke, undoubtedly also play important roles in asthma pathogenesis. Although the role of exposure to allergens (e.g., cockroaches, mites, cats, molds, etc.) and other irritants (nitrogen dioxide) could not be assessed in this study, it is unlikely in this population of subjects of similar socioeconomic status living in the same neighborhoods that such exposures were significant confounders (i.e., related to both asthma occurrence and to pre-/perinatal factors).

The study subjects were all born at a single hospital located within their community and received their primary health care from this hospital's continuity care clinic. The extent to which the observations made in these subjects are generalizable to children with more varied health care (i.e., children born at a different facility than the one providing their primary pediatric care) is not clear. However, significant selection biases resulting in a distorted frequency of asthmatic versus nonasthmatic children with adverse pre- and perinatal exposures were unlikely, suggesting the internal validity of the findings. The subjects all resided within census tracts defined by >40 percent of the population living below the poverty level, and the majority of mothers received Medicaid and were unmarried. A plot of the residence of each participant on a city map did not indicate any differences in the distribution of the residential locations of cases and controls (data not shown). However, despite the similarity of residential patterns, there probably were differences in environmental and psychosocial variables that were not mea-

sured. Additionally, the assessment of other variables, e.g., drug and alcohol use, may have been subject to misclassification bias due to inaccurate reporting. Thus, it is possible that some of the risk factors identified in this study (e.g., absent prenatal care) were surrogates for other exposures. Nevertheless, the findings of this study emphasize the potential importance of pre- and perinatal risk factors in asthma pathogenesis. Specifically, these data provide further support for programs aimed at wider provision of prenatal care, including maternal nutritional support and strategies for smoking cessation, to favorably influence pregnancy outcome as well as to reduce asthma risk during childhood. Furthermore, the risk factors that emerged in this study, which were unexplained by obvious biases, may help us to identify subsets of children within inner city populations who are at greatest risk for asthma, and thus are most likely to benefit from early and/or aggressive intervention.

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