

Onset and Persistence of Childhood Asthma: Predictors From Infancy

Mary D. Klinnert, PhD*; Harold S. Nelson, MD*; Marcella R. Price, MSPH*; Allen D. Adinoff, MD‡; Donald Y. M. Leung, MD, PhD*; and David A. Mrazek, MD, FRCPsych§

ABSTRACT. *Objective.* In a prospective study of children with a family history of asthma, asthma onset by 3 years of age was found previously to be positively associated with variables from the first year of life, including elevated total immunoglobulin E (IgE), frequent respiratory infections, and parenting difficulties. We followed this cohort of genetically at-risk children to investigate the relationship between factors assessed in infancy and asthma, allergy, and psychological status at school age.

Methods. A cohort of 150 children who were at risk for developing asthma were identified prenatally on the basis of the mothers' having asthma. For 28 children, the father had asthma as well, putting them at bilateral genetic risk. Families primarily were middle and upper middle class Caucasians. Parents came to the clinic during the third trimester of pregnancy for assessments of medical and psychosocial functioning. A home visit took place when the infant was 3 weeks old, when parenting risk was assessed before the onset of any asthma symptoms. Parenting difficulties included problems with infant caregiving as well as components of maternal functioning, such as postpartum depression and inadequate marital support. Blood was drawn for serum IgE at 6 months of age. Parents and offspring subsequently came to the clinic multiple times, with the last clinic visit during the child's sixth year. Follow-up at age 6 involved a clinic visit for allergy and psychosocial evaluations, consisting of interviews and a behavior questionnaire. Seventy-seven children received the allergy and psychosocial evaluation, 26 received the psychosocial evaluation in the clinic, and 30 families received telephone interviews and mailed in questionnaires. Additional monitoring of families by telephone and mail was maintained over the next 2 years, until the children were 8, to ensure accurate characterization of the course of illness. Comprehensive medical records were obtained and reviewed for all health care contacts. Children were designated as having asthma when there was documentation in medical records of physician-diagnosed asthma, observed wheezing, and/or prescription of asthma medications during the time period when the child was between 6 and 8 years of age. Parental reports of the occurrence of asthma corroborated the medical record data.

Results. Data regarding asthma status were available for 145 children through 8 years of age. Forty (28%) of the children manifested asthma between 6 and 8 years of age. Among variables previously reported to predict asthma onset by age 3, 3 proved to have significant univariate

relationships with asthma between ages 6 and 8: elevated IgE levels measured when the children were 6 months of age, global ratings of parenting difficulties measured when infants were 3 weeks old, and higher numbers of respiratory infections in the first year of life. Among these offspring of mothers with asthma, paternal asthma showed a significant association with asthma between ages 6 and 8. Eczema in the first year was not significantly related to later asthma. Multiple logistic regression showed that the model that best predicted asthma at ages 6 to 8 from infancy variables included 2 main effects. The adjusted odds ratio for 6-month IgE was 2.15 (1.51, 3.05) and for parenting difficulties was 2.07 (1.15, 3.71). Although socioeconomic status (SES) was not associated with asthma at ages 6 to 8, families of lower SES were more likely to be rated as having parenting difficulties early in the child's life. The mothers of lower SES breastfed for a shorter period of time and were more likely to smoke during their infant's first year. There were more respiratory infections during the first year of life among infants whose mother was rated as having more parenting difficulties. Mothers who reported smoking breastfed their infants for a shorter length of time. Male gender was significantly associated with higher IgE levels when infants were 6 months of age. Laboratory testing was completed for 77 children at age 6. Total serum IgE levels were significantly higher for the children with asthma between ages 6 and 8. Skin-prick testing showed that the children with asthma had significantly more positive skin test reactions than did the children without asthma. Psychosocial interview data at 6 years of age were available for 103 families, and behavioral questionnaires were available for 133 families. On the basis of 6-year interviews, children with asthma were rated as being at greater psychological risk than were the children without asthma. Mothers' Child Behavior Checklist (CBCL) ratings of their children's behavior indicated higher internalizing scores for the children with asthma as compared with the children without asthma. Like the 6-month IgE, 6-year IgE was higher for boys. IgE levels measured at 6 months of age were significantly correlated with 6-year IgE levels. Parenting difficulties measured at 3 weeks were significantly correlated with 6-year measures of maternal depression, CBCL Internalizing score, and Child Psychological Risk (CPR) score. There also were significant correlations among the psychosocial variables assessed when the children were 6 years of age; maternal depression was significantly associated with child CBCL Internalizing score and CPR score, and the last 2 also were significantly correlated. Multiple logistic regression showed that 2 concurrently measured variables entered the model showing the strongest associations with asthma at ages 6 to 8. The adjusted odds ratio for CPR score was 3.21 (1.29–7.96) and for 6-year IgE was 1.71 (1.04–2.80).

Conclusions. This study of the natural history of childhood asthma focused on the development of asthma

From the *National Jewish Medical and Research Center, Denver, Colorado; ‡Colorado Allergy and Asthma Centers, Littleton, Colorado; and §Mayo Clinic, Rochester, Minnesota.

Received for publication Sep 6, 2000; accepted May 4, 2001.

Reprint requests to (M.D.K.) National Jewish Medical and Research Center, 1400 Jackson St, Denver, CO 80206. E-mail: klinnertm@njc.org

PEDIATRICS (ISSN 0031 4005). Copyright © 2001 by the American Academy of Pediatrics.

into the school-age years in a genetically at-risk group of children. The relationships between biological and psychosocial variables in the first year and school-age asthma support the formulation of asthma as beginning early in life, with the developing immune system interacting with environmental influences. The data provide support for the possible contribution of psychosocial factors to asthma onset and persistence into childhood. *Pediatrics* 2001;108(4). URL: <http://www.pediatrics.org/cgi/content/full/108/4/e69>; *pediatric asthma, parenting, IgE allergy, psychosocial problems, risk, respiratory illness*.

ABBREVIATIONS. IgE, immunoglobulin E; SES, socioeconomic status; PRS, Parenting Risk Scale; CPR, Child Psychological Risk; CBCL, Child Behavior Checklist; CI, confidence interval.

Recent investigations of the natural history of childhood asthma have focused on events and mechanisms in the first few years of life that demonstrate the earliest phases of this condition.¹⁻⁴ Evidence clearly indicates that a family history of asthma imposes an increased risk for childhood asthma.^{1,5,6} Asthma results from the genetic predisposition in combination with exposure to environmental stimuli,⁷ such as allergens⁸ and cigarette smoke.^{9,10} Elevated serum immunoglobulin E (IgE) levels measured during the first year of life have been associated with subsequent allergy¹¹ and asthma.¹ The relationship of viral respiratory illnesses in the first years to subsequent asthma remains controversial.^{12,13} In the United States, children from lower socioeconomic status (SES) backgrounds develop higher rates of asthma,¹⁴ a pattern attributed to toxic environmental exposures as well as to poor health behavior.¹⁵

Among environmental influences, increased stress in infancy may contribute to asthma onset,¹⁶ although the mechanism for a stress effect is unknown.¹⁷ Retrospective studies found that increased stress on infants was associated with asthma onset in the first years of life.^{18,19} One prospective study that assessed stressful family life events found no evidence that stress contributed to asthma onset by age 6.²⁰ Questionnaire measures of family life events seem to capture different elements of family life than the stress that is developmentally salient for infants in their first year of life.²

To identify psychosocial as well as biological risk factors for asthma symptoms in the early school-age years, we followed a birth cohort of children who are at genetic risk for asthma to 8 years of age. The status of these children at age 3 is reported elsewhere.²¹ Three variables from the first year of life independently predicted asthma onset by 3 years of age. These were elevated serum IgE (≥ 10 IU/mL) obtained when the children were 6 months old, 8 or more respiratory infections during the first year of life, and parenting difficulties when the infants were 3 weeks of age. Parenting difficulties included problems with infant caregiving as well as components of maternal functioning, such as postpartum depression and inadequate marital support.^{2,22} To our knowledge, this birth cohort study is the only prospective investigation of asthma onset that has ex-

amined the occurrence of psychosocial variables from the prenatal period onward in combination with physiologic variables.

The present report focuses on factors associated with asthma within this birth cohort of children who are at increased risk for the expression of the disease. We focus on the prevalence of asthma between ages 6 and 8 years, on the importance of variables measured prospectively in the first year of life, and on concurrent biological and environmental variables as risk factors for asthma between ages 6 and 8 years.

METHODS

Sample

A cohort of 150 children who are at risk for developing asthma were identified prenatally on the basis of the mothers' having asthma. For 28 of these children, both the mother and the father had asthma. Families were enrolled between July 1985 and June 1987. The SES of the families were upper class (26%), upper middle class (43%), middle class (22%), and lower middle class (7%).²³ Ninety-three percent of the mothers were white. Mothers were an average age of 29 and fathers were 31 at the time of the child's birth. Ninety-four percent of the mothers were married at the time their children were born.

Procedures

The study protocol was approved by the National Jewish Medical and Research Center Institutional Review Board. Consent was obtained from all families at entry to the study. Parents came to the clinic during the third trimester of pregnancy for assessments of medical and psychosocial functioning. A home visit took place when the infant was 3 weeks old. Parents and offspring subsequently came to the clinic multiple times, with the last clinic visit during the sixth year.

For the children's first 2 years of life, information regarding respiratory illnesses was obtained through periodic telephone calls to mothers. When respiratory illnesses were reported, research staff visited the home to corroborate the symptom reports, resulting in a count of respiratory illnesses. In addition, researchers administered nasal washes that were cultured for parainfluenza and respiratory syncytial virus. Information on length of breastfeeding during the first 2 years was acquired, and cigarette smoke exposure and presence of furry pets in the home were monitored at all assessments. Blood samples were obtained when the children were 6, 12, 18, and 24 months of age.

When the children were age 6, an attempt was made to bring all available participants to the clinic for evaluation. Skin-prick testing ($n = 77$) and blood draws ($n = 64$) were conducted, and psychosocial interviews and questionnaires were completed for all children who received the allergy assessment. Twenty-six families came to the clinic for interviews but did not agree to skin testing. Thirty families were interviewed by telephone; 21 had moved from Denver, and the remaining 9 preferred a telephone interview to coming to the clinic. All of these families completed the child behavior questionnaires and returned them by mail. Twelve families refused interviews and questionnaires but gave verbal reports of asthma status and permission to obtain medical records. Four families were lost to follow-up, and 1 child had died from causes unrelated to asthma.

Additional monitoring of families by telephone and mail was maintained during the next 2 years to ensure accurate characterization of the course of illness. During this time, the children were between 6 and 8 years of age. Comprehensive medical records were obtained and reviewed for all health care contacts.

Definition of Asthma

Children were designated as having asthma when there was documentation in medical records of physician-diagnosed asthma, observed wheezing, and/or prescription of asthma medications during the time period when the child was between 6 and 8 years of age. Parental reports of the occurrence of asthma corroborated the medical record data.

Risk Factors Documented in the First Year of Life

Total Serum IgE at 6 Months

Total serum IgE levels were determined for each child using a solid-phase enzyme immunoassay. At 6 months, a level of ≥ 10 IU/mL has been demonstrated to be associated with early-onset asthma.^{1,21} IgE data were log-transformed for statistical analyses then back-transformed and reported as geometric means to allow for meaningful comparisons.

Parenting Difficulties

The Parenting Risk Scale (PRS), described elsewhere,^{2,22} used a semistructured interview and rating methodology.²⁴ Briefly, when the infants were 3 weeks old, an experienced clinician conducted interviews with the mother in the home, with the child present. Parenting risk was rated after the interview, using the 3-point PRS,²⁵ with scale points reflecting no adjustment problems, possible problems, and definite problems.²⁴ The PRS had a broad scope, including evaluation of the parents' psychiatric history, emotional availability for the child, behavioral regulation strategies, knowledge base about infant care, and commitment to child care. Other psychosocial risk factors that were expected to have a negative impact on the relationship between the caregiver and the child were coded, including perinatal maternal depression, using the Perinatal Depression Scale²⁵ and the Quality of Relationship Scale.²⁶ Preliminary analyses showed that the Perinatal Depression Scale and the Quality of Relationship Scale were significantly correlated with the PRS.²² Analyses were conducted with the PRS values. Reliability coefficients for the PRS ratings were consistently greater than 0.87. All 3-week PRS ratings were made prospectively and preceded the onset of any asthma symptoms.

Respiratory Illness

Both respiratory infections and otitis media were coded as recurrent infectious illnesses. These illnesses were documented by monitoring the number of discrete occurrences of upper and lower respiratory tract infections as well as otitis media during the first 12 months of life. The minimal criteria for an upper respiratory illness included acute cough, rhinitis, and congestion. In most cases, the presence of a fever also was documented. Otitis media was coded only when the physician of the child established the diagnosis and prescribed an antibiotic. The overall count was based on the maternal reports corroborated by the researchers' home observations and by medical chart review. For a respiratory illness to be counted as separate, an interim of 10 well days was required.

Eczema

The onset of eczema during the first year of life is known to be associated with the later development of asthma in childhood.²⁷ For a child to be coded as having eczema within the first year of life, symptoms were reported by the mother and photographed by the research team for physician verification. Confirmation of the diagnosis through documentation in the outpatient medical record was required.

Clinical Assessment at Age 6

Skin Testing

Skin-prick testing using bifurcated needles was completed for a panel of local allergens, including cat, dog, dust mite, cockroach, 4 molds, 3 grasses, 5 trees, and 4 weeds (Greer Laboratory, Lenoir, NC). Responses were considered positive with a 3-mm mean wheal.

Total Serum IgE at 6 Years

Total serum IgE levels were determined for each child using a solid-phase enzyme immunoassay. IgE data were log-transformed for statistical analyses then back-transformed and reported as geometric means.

Psychosocial Assessment

Semistructured interviews that were conducted with mothers followed the same format used throughout the longitudinal study,² wherein the mother was asked about family life stresses,

coping strategies, affective functioning, and marital adjustment, as well as child temperament and adjustment. Inquiries regarding the children's adjustment were structured using a standard list of problem behaviors common to young children. On the basis of maternal responses, global ratings of Child Psychological Risk (CPR) were coded. The CPR ratings used a 3-point scale modeled after the PRS from infancy, with scale points reflecting no adjustment problems, possible problems, and definite problems.²⁴ Maternal depression was coded using a 5-point scale that focused on mothers' reports of depressive affect, together with any effects on daily functioning. Family Stress was coded using a 5-point scale that focused on parent reports of stressors, the related subjective experience, and an assessment of the impact on family life. Interviews were conducted by pediatric psychologists in the clinic or by telephone. Interrater reliability coefficients for the 3 interview scales ranged from 0.87 to 1.0.

Child Behavior

Mothers completed the Child Behavior Checklist (CBCL),²⁸ which provides a parent-reported assessment of their child's behavioral functioning across multiple domains. Scores result in empirically derived, broad-band scales: Internalizing (eg, fearfulness, depression), Externalizing (eg, conduct problems), and Total Behavior Problems. This widely used measure has been well standardized and has excellent reliability (test-retest correlation: 0.93; interparent correlation: 0.76; Cronbach's $\alpha = 0.96$).²⁸ This measure has been revised to make it a more appropriate tool for use with a chronically ill population.²⁸

Statistical Analyses

Associations between individual risk factors and the occurrence of active asthma between 6 and 8 years of age were assessed using standard statistical methods. χ^2 analyses were used to compare univariate relationships between risk factors and occurrence of asthma. An independent sample *t* test was used to compare groups when dependent variables had a normally distributed continuous distribution. A Wilcoxon rank sum test was used for such comparisons when data were not normally distributed. Pearson correlations were used for normally distributed data, whereas Spearman correlations were presented for data with skewed distributions. To assess the simultaneous effects of selected risk factors on the occurrence of disease, we performed multiple logistic regression using methods described by Hosmer and Lemeshow.²⁹ For these analyses, the continuous distribution was entered for normally distributed variables; for those with skewed distributions, dichotomized variables were entered. This technique models the log of the odds of getting the disease given a set of risk factors as a linear combination of the risk factors. The advantage of this technique is that the antilog of an individual regression coefficient is interpreted as the relative odds of disease occurrence associated with the corresponding risk factor. In addition, if the best model consists of multiple risk factors, then the estimated odds ratio for each factor is statistically adjusted for the effect of other factors in the model. Alternative logistic regression models that contain combinations of individual risk factors and their interactions were compared using Akaike's information criterion. Odds ratios and their 95% confidence intervals (CI), as well as χ^2 tests for significance of individual coefficients, were computed to summarize the results. Stepwise regression modeling (using 0.10 and 0.05 entrance and removal criteria) was used to select significant factors. Odds ratios and their 95% CI were reported to summarize results.

$P < .05$ was considered statistically significant. All statistical analyses were performed using Version 6.12 of the SAS software system (SAS, Inc, Cary, NC).

RESULTS

Prevalence of Asthma

Information regarding asthma status between ages 6 and 8 was available for 145 of 149 children. Forty children (28%) had documented asthma; 24 (60%) were boys, and 16 (40%) were girls. Fifty percent of the children with asthma were prescribed maintenance medications on an ongoing basis (inhaled

corticosteroids, cromolyn, or theophylline preparations), whereas the other 50% were treated with bronchodilators. Most of the children used their inhalers on an as-needed basis. Among the children who used maintenance medications to control their illness, 14 (70%) had been prescribed at least 1 burst of oral corticosteroids between ages 6 and 8; among the children who used only bronchodilators, 8 (40%) had required oral steroids at least once.

Factors From the First Year of Life

Among variables reported previously to predict asthma onset by age 3²¹ among these genetically at-risk children, 3 proved to have significant univariate relationships with asthma between ages 6 and 8: elevated IgE levels measured when the children were 6 months of age, global ratings of parenting difficulties measured when infants were 3 weeks old, and higher numbers of respiratory infections in the first year of life (Table 1). Although paternal asthma was not an additional predictor for asthma onset at age 3 among these offspring of mothers with asthma, it showed a significant association with asthma between ages 6 and 8. Eczema in the first year, reported previously to bear a significant univariate relationship with early-onset asthma,²¹ was not significantly related to later asthma.

Gender and SES were not significantly associated with asthma between ages 6 and 8. Other variables measured in the first year and not associated with later asthma included cigarette smoke exposure and duration of breastfeeding, as well as evidence for the occurrence of respiratory syncytial virus or parainfluenza viruses.

Relationships Among Demographic and First-Year Variables

Table 2 shows intercorrelations among SES, gender, and risk variables measured during the first year. Although SES was not associated with asthma at ages 6 to 8, families from lower SES backgrounds were more likely to be rated as having parenting difficulties early in the child's life ($P < .02$). The mothers from lower SES backgrounds breastfed for a

shorter period of time ($P < .01$) and were more likely to smoke during their infant's first year ($P < .001$). There were more respiratory infections during the first year of life among infants whose mothers were rated as having more parenting difficulties ($P < .05$). Mothers who reported smoking breastfed their infants for a shorter length of time ($P < .05$). Male gender was significantly associated with higher IgE levels when infants were 6 months of age ($P < .01$).

First-Year Variables Associated With Asthma at Ages 6 to 8

Using multiple logistic regression, 2 of the 4 variables that were significantly associated at the univariate level with asthma at ages 6 to 8 were found to enter a final predictive model (Table 3). The best model included only main effects attributable to each factor; interactions between effects did not significantly improve the fit of the best model. The adjusted odds ratio for 6-month IgE was 2.15 (1.51, 3.05) and for parenting difficulties was 2.07 (1.15, 3.71).

Clinical Assessments at Age 6

Total IgE and Skin Testing

Seventy-seven children participated in clinical assessments when they were 6 years old. Among them, 22 (29%) were classified as having asthma. This subset was similar to the larger group on all measures tested, including gender, proportion of children with asthma, parents' SES at study entry, ethnicity, 6-month IgE level, number respiratory infections in the first year of life, and 3-week ratings of parenting difficulties.

Total serum IgE levels assessed at age 6 were significantly higher for the children with asthma between 6 and 8 (geometric mean: 38.32; 95% CI: 15.6–94.2) as compared with those without asthma (geometric mean: 12.28; 95% CI: 8.9–18.1; $P < .01$). Skin-prick testing showed that the children with asthma had significantly more positive skin test reactions (mean: 4.7; standard error: 0.65) than did the children without asthma (mean: 2.3; standard error: 0.41; $P < .003$).

TABLE 1. Unadjusted Odds Ratios for Variables Associated With Asthma Between Ages 6 and 8

Variable	Unadjusted Odds Ratio	95% CI	P Value	Asthma	No Asthma
Demographic (n = 145)					
Gender (male)	1.85	(0.88–3.88)	.10	60%	45%
SES	0.88	(0.59–1.3)	.55	2.1 (.15)	2.2 (.09)
First year (n = 145)					
6-mo IgE	8.08	(3.10–21.09)	.0001	6.5 (4.0–10.3)	2.3 (1.9–2.7)
Parenting difficulties	2.16	(1.26–3.71)	.005	1.68 (.12)	1.32 (.06)
Respiratory infections	1.12	(1.03–1.22)	.009	8.6 (.72)	6.4 (.40)
Paternal (bilateral) asthma	2.45	(1.08–5.52)	.03	37%	18%
Eczema	2.01	(0.71–5.72)	.18	17.5%	9.5%
Cat exposure	0.76	(0.34–1.67)	.35	27.5%	33.3%
Maternal smoking (packs/d)	1.54	(0.61–3.83)	.35	0.17 (.07)	0.10 (.03)
Sixth year					
6-y IgE (n = 64)	1.83	(1.14–2.93)	.01	38.3 (14.7–99.3)	12.7 (8.9–18.2)
Allergic (≥ 1 positive skin test) (n = 77)	4.7	(1.02–23.1)	.04	91%	67%
Child Psychological Risk (n = 133)	1.84	(1.10–3.07)	.02	1.8 (.13)	1.5 (.07)
CBCL Internalizing (n = 133)	1.05	(1.004–1.09)	.04	52.5 (1.7)	48.7 (.88)
Maternal Depression (n = 133)	1.41	(0.98–2.03)	.07	2.6 (.16)	2.2 (.11)
Family Stress (n = 135)	1.05	(0.69–1.5)	.94	3.1 (.15)	3.1 (.10)

TABLE 2. Spearman Intercorrelations of Demographic, First-Year, and Sixth-Year Variables

	SES	Gender	Parenting Difficulties	6-Month IgE	Respiratory Infections	Maternal Smoking	Breastfed	6-Year IgE	No. Skin Tests	Maternal Depression	CBCL Internalizing
Demographic (<i>n</i> = 150)											
SES	1.0										
Gender	0.04	1.0									
First year (<i>n</i> = 150)											
Parenting difficulties	0.22‡	0.02	1.0								
6-mo IgE	0.07	0.23‡	0.13	1.0							
Respiratory infections	0.05	0.14	0.19†	0.15	1.0						
Maternal smoking	0.29‡	0.00	0.10	0.00	0.04	1.0					
Duration of breastfeeding	0.21‡	0.03	0.08	0.08	0.13	-0.14†	1.0				
Sixth year*											
6-y IgE	0.11	0.27†	0.05	0.42§	0.16	0.04	0.11	1.0			
No. positive skin tests	0.15	0.02	0.02	0.20	0.08	0.06	-0.09	0.47§	1.0		
Maternal depression	0.11	0.06	0.22‡	0.26‡	0.10	0.05	-0.01	0.16	0.03	1.0	
CBCL Internalizing	0.08	0.03	0.21†	0.04	0.15	0.24‡	-0.08	0.06	0.02	0.21†	1.0
Child Psychological Risk	0.06	0.16	0.30§	0.21†	0.30‡	0.07	-0.16	0.17	0.20	0.41§	0.27‡

* *n* = 61–77 for atopy variables; *n* = 133 for psychosocial variables.

† *P* < .05.

‡ *P* < .01.

§ *P* < .001.

TABLE 3. Model With Adjusted Odds Ratios Assessing First-Year Variables Associated With Asthma Between 6 and 8 Years (*n* = 145)

Variable	Adjusted Odds Ratio	95% CI	<i>P</i> Value
6-mo IgE	2.15	(1.51–3.05)	.0001
Parenting difficulties	2.07	(1.15–3.71)	.015

Psychosocial Adjustment

Behavioral measures at 6 years of age were available for 133 families. Among the 6-year interview ratings, children with asthma were rated as being at greater psychological risk than were the children without asthma (*P* < .02; see Table 1). Mothers' CBCL ratings of their children's behavior indicated higher Internalizing scores for the children with asthma as compared with the children without asthma (*P* < .04). There were no differences between groups on the Externalizing scale. There was a trend for 6-year interview ratings of maternal depression levels to be greater for the children with asthma between ages 6 and 8 (*P* < .07). Family Stress assessed at age 6 was not different for the children with and without asthma.

Intercorrelations Between Early and Later Atopy and Psychosocial Variables

Table 2 shows relationships between variables measured in the first year of life and those measured when the children were 6 years of age. Like the 6-month IgE, 6-year IgE was higher for boys (*P* < .05). IgE levels measured at 6 months of age were significantly correlated with 6-year IgE levels (*P* < .001).

Parenting difficulties measured at 3 weeks were significantly correlated with 6-year measures of maternal depression (*P* < .01), CBCL Internalizing score (*P* < .05), and CPR (*P* < .001). There also were significant correlations among the psychosocial variables assessed when the children were 6 years old;

maternal depression was significantly associated with child CBCL Internalizing score (*P* < .05) and CPR (*P* < .001), and the last 2 also were significantly correlated (*P* < .01).

Six-Year Variables Associated With Asthma at Ages 6 to 8

Multiple regression modeling again was used to determine the extent to which the relative contributions of the biological and psychological variables from the sixth year of life were significantly related to concurrent asthma. Two of the 4 variables that were significant at the univariate level entered the model (Table 4). The best model included only main effects attributable to each factor. The adjusted odds ratio for CPR was 3.21 (1.29–7.96) and for 6-year IgE was 1.71 (1.04–2.80).

DISCUSSION

This group of genetically at-risk children was followed from the prenatal period into childhood to evaluate prospectively the contribution of psychosocial variables to childhood asthma in the context of biological risk factors. By 6 to 8 years of age, 28% of the children were experiencing asthma. This prevalence is similar to other studies of the offspring of atopic and asthmatic parents,^{9,11,30} supporting previous estimates of familial risk for asthma. Although all of the children in this study were at risk because their mothers had asthma, those whose father also had asthma were more likely to have asthma at school age. This added risk of a second parent with

TABLE 4. Model With Adjusted Odds Ratios Assessing 6-Year Variables Associated With Asthma Between 6 and 8 Years (*n* = 64)

Variable	Adjusted Odds Ratio	95% CI	<i>P</i> Value
Child Psychological Risk	3.21	(1.29–7.96)	.02
6-y IgE	1.71	(1.04–2.80)	.04

asthma was not demonstrated for the early onset of asthma within the first 3 years of life.²¹

The definition of asthma used in this study was considered carefully. In contrast to many studies that rely on parental report regarding diagnosis or symptoms, here the establishment of the diagnosis required a physician's documenting of wheezing symptoms, prescribing asthma medication, or documenting of the diagnosis of asthma in the medical record. Children in this cohort who had an isolated episode of unsubstantiated wheezing were not classified as having asthma. Given that parents and children often have disparate reports of the children's respiratory functioning,^{31,32} verification of parental report of physician diagnosis using the medical record provided definitive information. In this predominantly middle-class cohort with reasonable access to health care, it is unlikely that there were children who were not medically evaluated in response to significant asthma symptoms.

Three variables assessed for this cohort in the first year of life (elevated serum IgE, frequent respiratory infections, and parenting difficulties) had been shown previously to be independently associated with onset of asthma by 3 years of age.²¹ The same 3 variables that were found to relate to asthma onset at age 3 also were significantly associated with school-age asthma when examined separately; however, only 2 of them entered into a best fit multivariate model predicting later asthma. Elevated serum IgE at 6 months of age maintained a strong relationship with asthma in the school-age years. This is consistent with the findings of others showing high IgE levels from infancy to be associated with persistent wheezing throughout childhood.³³ The significance of allergy in the persistence of these children's asthma symptoms was demonstrated further by the significantly higher IgE levels and number of positive skin tests for children with asthma as compared with those without.

Parenting difficulties similarly maintained a predictive association with the persistence of asthma between ages 6 and 8. Importantly, parenting was assessed when the infants were 3 weeks of age, predating infant respiratory or wheezing illnesses. This global parenting rating is a developmentally sensitive measure that involves assessment of maternal affect and coping, relationship skills and social support, and sensitivity and responsiveness in caregiving.^{2,22} That parenting difficulties rated in the first year of life were significantly and independently associated with asthma at school age is a remarkable and previously unreported finding. The prospective nature of the rating provides strong support for the association, because the ratings of parenting difficulty were made long before either early or later asthma status was known.

The finding of a relationship between early parenting and childhood asthma suggests a number of possible mechanisms. One possibility is that this global rating of parenting difficulties is associated with variables that others have already shown to be associated with increased wheezing or asthma onset in infants. For example, parenting difficulties mea-

sured at 3 weeks of age were significantly correlated with the number of respiratory infections that occurred throughout the remainder of the first year of life. Having frequent respiratory infections in the first year was a significant predictor in this cohort for asthma onset in the first 3 years of life²¹ and as a single factor continued to be associated with asthma that persisted when the sample was 6 to 8 years of age. Indeed, increased psychological stress has been associated with onset of respiratory illnesses for adults³⁴ and for children.³⁵ However, having frequent early respiratory infections did not remain a significant predictor for later asthma when parenting difficulties and elevated IgE were entered with it into a multiple regression model, indicating that having frequent respiratory infections could no longer be considered a significant predictor for asthma at ages 6 to 8 after adjustment for the effects of parenting risk and IgE.

The intercorrelations of variables from the first year of the study also indicate that significantly higher levels of parenting difficulties were rated for families of relatively lower SES. Family risk factors such as maternal depression, lower social support, and less adequate parenting are known to occur more frequently at lower SES levels, although each can be found at any SES level.^{36,37} In this study, relatively lower SES as a single variable had no association with asthma during the 6- to 8-year period. As others have found,³⁸ parental behaviors often studied as predictors for asthma onset—shorter breastfeeding and exposing children to cigarette smoke—were significantly associated with relatively lower SES. However, in this study, these variables were not associated with asthma at ages 6 to 8. These findings cannot speak to the role of SES and asthma in general, because the number of lower SES families in this study was small. However, within this sample, the analyses clearly demonstrate that parenting difficulties measured early in life do not affect the course of asthma as a consequence of lower SES or parenting behaviors that have been suggested previously to account for an SES effect. The data support the supposition that characteristics of the early caregiving environment, independent of SES, are associated with school-age asthma among children who are at familial risk. Furthermore, family stress per se was not associated with asthma at age 6. This negative finding now has been reported several times.^{20,39} Parenting difficulties focus on the emotional caregiving environment, not external stressors that may affect the experience of the infant only through an indirect mechanism.²

If parenting difficulties affect infants in the manner that environmental stress affects adults,⁴⁰ then perhaps the quality of caregiving has an effect on certain aspects of infants' immune systems. Investigators have demonstrated that stress may affect immune functioning in the direction of greater Th2 response among adults⁴¹ and in infants⁴² and subsequently may alter the course of immune-based diseases such as allergies and asthma.⁴³ Infants from the newborn period on have been shown through their behavior, neuroendocrine changes, and resulting physiologic

responses to be highly reactive and sensitive to variations in stimulation,⁴⁴ leading to the suggestion that these early responses are similar in form to stress responses in adults. Furthermore, sensitive and responsive caregiving in early infancy plays a role in buffering reactivity of the hypothalamic-pituitary-adrenal system to potentially stressful events.^{45,46} There is evidence that endogenous glucocorticoids play a role in allergic inflammation⁴⁷ and in airway responses⁴⁸ in adults; in children, low cortisol levels were associated with increased asthma severity.⁴⁹ It is possible that developmentally relevant stressful events and/or the quality of caregiving provided, to the extent that they affect the emotional and physiologic regulation of the infant, could alter the hypothalamic-pituitary-adrenal system or immune functioning in the direction of increased allergic response.⁵⁰

Finally, it may be that parental behavior assessed early in the infant's life is linked to persistent asthma 6 to 8 years later through caregiving responses that are specific to infant illness. Parents who were rated as providing adequate caregiving may have been attentive to their infants' indications of illness and prompt in their responses, possibly leading to more effective medical intervention.⁵¹ Whether through appropriate use of medication, reduction of environmental allergens, or prevention of viral exposure, high parental responsiveness to infant illness could have the effect of reducing amount or duration of inflammation in infants' airways, thus reducing the chances of persistent wheezing. Parents who are high in responsiveness at their infant's birth are likely to be among the more responsive when their child reaches school age. An attractive speculation is that prompt parental detection of illness and appropriate responses during the early childhood years result in decreased asthma between 6 and 8 years of age.

Approximately half of the children received the clinic-based allergy assessment at 6 years. Although there were no differences on baseline variables between the children who participated and those who did not, it still is possible that the data would be different had the entire group been tested. Nevertheless, within the relatively small group with allergy data at both time points, there was a significant relationship between IgE levels in infancy and IgE at age 6. The data from this study also show significant continuity from the first to sixth years of life in the psychosocial variables, which were far more complete. Parenting difficulties rated in the home when the children were 3 weeks old were significantly associated with parent interview-based ratings of maternal depression and CPR when the children were 6 years of age. Furthermore, parenting difficulties rated at 3 weeks were associated with maternal ratings of children's behavior made at age 6. It is possible that this notable continuity was mediated through maternal depression, because one of the components of the global Parenting Difficulties rating was maternal depression. Exposure to maternal depression in the early postpartum months has been demonstrated to have an enduring influence on child psychological adjustment to age 5.⁵² In this study,

there also was a relationship between maternal depression at age 6 and both the maternal interview report of child psychological functioning and maternal ratings of child internalizing behavior. These relationships must be interpreted with caution, because the mother was the informant both about herself and about her child's psychological functioning. Maternal depression has been found to be associated with other informants' assessments of child internalizing problems but also to contribute to biased reporting in mothers' ratings of their children's behavior.⁵³ In fact, it is possible that depressed mothers were biased toward more reporting of asthma symptoms in their children or in seeking more medical attention for their children. It was in part for these reasons that we chose a measure of asthma that depended on physician documentation and on reaching a threshold of symptom severity that was indisputable; we believe that neither reporting bias nor medical care seeking could account for the occurrence of asthma as we have defined it in this study.

CONCLUSION

This study of the natural history of childhood asthma focused on the development of asthma into the school-age years in a genetically at-risk group of children. Early and later elevated IgE levels were shown to be consistent for individuals and were strongly correlated with asthma throughout. The relationships between first-year variables and school-age asthma support the formulation of asthma as beginning in the first year of life, with the developing immune system interacting with environmental influences.⁵⁴ These data provide support for the possible contribution of psychosocial factors to asthma onset and persistence into childhood.

ACKNOWLEDGMENTS

This study was supported by Grants RO1HL53584, USPHS HL-36577, and General Clinical Research Center Grant M01 RR00051; and by the W. T. Grant Foundation and the Developmental Psychobiology Research Group.

REFERENCES

1. Martinez FD, Wright AL, Taussig LM, Holbert CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med*. 1995;332:133-138
2. Klinnert M, Mrazek DA, Mrazek P. Early asthma onset: the interaction between family stressors and adaptive parenting. *Psychiatry*. 1994;57: 51-61
3. Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood: a prospective study. *N Engl J Med*. 1990;323:502-507
4. Van Asperen PO, Kemp AS, Mukhi A. Atopy in infancy predicts the severity of bronchial hyperresponsiveness in later childhood. *J Allergy Clin Immunol*. 1990;85:790-795
5. Sears MR, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. *Arch Dis Child*. 1996;75:392-398
6. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med*. 1998;158:176-181
7. Wiesch D, Meyers D, Bleeker E. Genetics of asthma. *J Allergy Clin Immunol*. 1999;104:895-901
8. Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood: a birth cohort study. *Arch Dis Child*. 1991;66:1050-1053
9. Cogswell JJ, Mitchell EB, Alexander J. Parental smoking, breast feeding,

- and respiratory infection in development of allergic diseases. *Arch Dis Child*. 1987;62:338–344
10. Weitzman M, Gortmaker S, Klein Walker D, Sobol A. Maternal smoking and childhood asthma. *Pediatrics*. 1990;85:505–511
 11. Kjellman N-I, Croner S. Cord blood IgE determination for allergy prediction: a follow-up to 7 years of age in 1651 children. *Ann Allergy*. 1984;53:167–171
 12. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Bjorksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics*. 1995;95:500–505
 13. Glezen WP. Role of respiratory tract infection in childhood asthma: two views. In: Hiatt PWM, Cloutier MMP, eds. *RSV and Asthma: Is There a Link?* New York, NY: American Lung Association, American Thoracic Society; 1998:1–5
 14. Gergen P, Mullally D, Evans R. National survey of prevalence of asthma among children in the United States, 1976–1980. *Pediatrics*. 1988;81:1–7
 15. Oliveti J, Kerckmar C, Redline S. Pre- and perinatal risk factors for asthma in inner city African-American children. *Am J Epidemiol*. 1996;143:570–577
 16. Morgan W, Martinez F. Risk factors for developing wheezing and asthma in childhood. *Pediatr Clin N Am*. 1992;39:1185–1203
 17. Busse WW, Kiekolt-Glaser JK, Coe C, Martin R, Weiss S, Parker S. Stress and asthma. *Am J Respir Crit Care Med*. 1995;151:249–252
 18. Salk L, Grellong B, Straus W, Dietrich J. Perinatal complications in the history of asthmatic children. *Am J Dis Child*. 1974;127:30–33
 19. Johnstone DE, Roghmann KJ, Pless IB. Factors associated with the development of asthma and hay fever in children: the possible risks of hospitalization, surgery, and anesthesia. *Pediatrics*. 1975;56:398–403
 20. Horwood L, Fergusson D, Hons B, Shannon F. Social and familial factors in the development of early childhood asthma. *Pediatrics*. 1985;75:859–868
 21. Mrazek DA, Klinnert MD, Mrazek P, et al. Prediction of early onset asthma in genetically at risk children. *Pediatr Pulmonol*. 1999;27:85–94
 22. Mrazek DA, Mrazek P, Klinnert MD. Clinical assessment of parenting. *J Am Acad Child and Adolesc Psychiatry*. 1995;34:272–282
 23. Hollingshead AB. *Four Factor Index of Social Status*. New Haven, CT: Yale University; 1975
 24. Radke-Yarrow M, Nottelmann E, Martinez P, Fox MB, Belmont B. Young children of affectively ill parents: a longitudinal study of psychosocial development. *J Am Acad Child and Adolesc Psychiatry*. 1992;31:68–77
 25. Mrazek DA, Klinnert MD, Mrazek PJ, Macey T. Early asthma onset: consideration of parenting issues. *J Am Acad Child and Adolesc Psychiatry*. 1991;30:277–282
 26. Klinnert M, Mrazek DA, Mrazek PA. Quality of marital relationship: a clinical rating scale. *Psychiatry*. 1992;55:132–145
 27. Smith J. Epidemiology and natural history of asthma, allergic rhinitis, and atopic dermatitis (eczema). In: Middleton E, Reed C, Ellis E, Adkinson N, Yunginger J, eds. *Allergy: Principles and Practice*. 3rd ed. St Louis: CV Mosby; 1988:891–929
 28. Achenbach TM. *Manual for the Child Behavior Checklist/4–18 and 1991 Profile*. Burlington, VT: Department of Psychiatry, University of Vermont; 1991
 29. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons; 1989:307
 30. Van Asperen PP, Kemp AS. The natural history of IgE sensitization and atopic disease in early childhood. *Acta Paediatr Scand*. 1989;78:239–245
 31. Braun-Fahrlander C, Gassner M, Grize L, et al. Comparison of responses to an asthma symptom questionnaire (ISAAC core questions) completed by adolescents and their parents. SCARPOL-Team. Swiss Study on Childhood Allergy and Respiratory Symptoms with respect to air pollution. *Pediatr Pulmonol*. 1998;25:159–166
 32. Hoek G, Wypij D, Brunekreef B. Self-reporting versus parental reporting of acute respiratory symptoms of children and their relation to pulmonary function and air pollution. *Int J Epidemiol*. 1999;28:293–299
 33. Sherrill D, Stein R, Halonen M, Holberg C, Wright A, Martinez F. Total serum IgE and its association with asthma symptoms and allergic sensitization among children. *J Allergy Clin Immunol*. 1999;104:28–36
 34. Cohen S, Tyrrell DAJ, Smith AP. Psychological stress and susceptibility to common cold. *N Engl J Med*. 1991;325:606–612
 35. Meyer RJ, Haggarty RJ. Streptococcal infections in families: factors altering individual susceptibility. *Pediatrics*. 1962;29:539–549
 36. Sameroff A, Seifer R, Baldwin A, Baldwin C. Stability of intelligence from preschool to adolescence: the influence of social and family risk factors. *Child Dev*. 1993;64:80–97
 37. DeGarmo D, Forgatch M, Martinez CJ. Parenting of divorced mothers as a link between social status and boys' academic outcomes: unpacking the effects of socioeconomic status. *Child Dev*. 1999;70:1231–1245
 38. Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. *J Allergy Clin Immunol*. 1992;90:235–241
 39. Weil C, Wade S, Bauman L, Lynn H, Mitchell H, Lavigne J. The relationship between psychosocial factors and asthma morbidity in inner-city children with asthma. *Pediatrics*. 1999;104:1274–1280
 40. Herbert T, Cohen S. Stress and immunity in humans: a meta-analytic review. *Psychosom Med*. 1993;55:364–379
 41. Marshall G, Agarwal S, Lloyd C, Cohen L, Henninger E, Morris G. Cytokine dysregulation associated with exam stress in healthy medical students. *Brain Behav Immunol*. 1998;12:297–307
 42. Wright R, Kindlon D, Tollerud D, Guevarra L, Tager I, Hanrahan J. Does maternal stress influence polarization of TH2-dominated cytokine production and total IgE in maternal and cord blood? [abstract] *Am J Respir Crit Care Med*. 1999;159:A103
 43. Marshall G, Agarwal S. Stress, immune regulation, and immunity: applications for asthma. *Allergy Asthma Proc*. 2000;21:241–246
 44. Gunnar M. Reactivity of the hypothalamic-pituitary-adrenocortical system to stressors in normal infants and children. *Pediatrics*. 1992;90:491–497
 45. Gunnar MR, Mangelsdorf S, Larson M, Hertzgaard L. Attachment, temperament, and adrenocortical activity in infancy: a study of psychoneuroendocrine regulation. *Dev Psychol*. 1989;25:355–363
 46. Gunnar M. Quality of early care and buffering of neuroendocrine stress reactions: potential effects on the developing human brain. *Prev Med*. 1998;27:208–211
 47. Herrscher R, Kasper C, Sullivan T. Endogenous cortisol regulates immunoglobulin E-dependent late phase reactions. *J Clin Invest*. 1992;90:596–603
 48. Peebles R, Togias A, Bicker C, Diemer F, Hubbard W, Schleimer R. Endogenous glucocorticoids and antigen-induced acute and late phase pulmonary responses. *Clin Exp Allergy*. 2000;30:1257–1265
 49. Landstra A, Boezen H, Postma D, van Aalderen W. A role of serum cortisol levels in children with asthma [abstract]. *Eur Respir J*. 1999;14(suppl):308S
 50. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. *Thorax*. 1998;53:1066–1074
 51. Klinnert M, McQuaid E, Gavin L. Assessing the family asthma management system. *J Asthma*. 1997;34:77–88
 52. Murray L, Sinclair D, Cooper P, Ducourmau P, Turner P, Stein A. The socioemotional development of 5-year-old children of postnatally depressed mothers. *J Child Psychol Psychiatry*. 1999;40:1259–1271
 53. Chilcoat H, Breslau N. Does psychiatric history bias mothers' reports? An application of a new analytic approach. *J Am Acad Child and Adolesc Psychiatry*. 1997;36:971–979
 54. Holgate ST. The cellular and mediator basis of asthma in relation to natural history. *Lancet*. 1997;350(suppl 2):5–9

Onset and Persistence of Childhood Asthma: Predictors From Infancy
Mary D. Klinnert, Harold S. Nelson, Marcella R. Price, Allen D. Adinoff, Donald Y.
M. Leung and David A. Mrazek
Pediatrics 2001;108;e69
DOI: 10.1542/peds.108.4.e69

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/108/4/e69>

References

This article cites 49 articles, 13 of which you can access for free at:
<http://pediatrics.aappublications.org/content/108/4/e69#BIBL>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Onset and Persistence of Childhood Asthma: Predictors From Infancy

Mary D. Klinnert, Harold S. Nelson, Marcella R. Price, Allen D. Adinoff, Donald Y. M. Leung and David A. Mrazek

Pediatrics 2001;108:e69

DOI: 10.1542/peds.108.4.e69

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/108/4/e69>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2001 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

