Onset and Persistence of Childhood Asthma: Predictors From Infancy

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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.
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 examined 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 the 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 parental 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. 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, used a semistructured interview and rating methodology. 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, with scale points reflecting no adjustment problems, possible problems, and definite problems. 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 Scale and the Quality of Relationship Scale. Preliminary analyses showed that the Perinatal Depression Scale and the Quality of Relationship Scale were significantly correlated with the PRS. 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. 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, 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 Psychosocial 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. 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.

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 3,21 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).

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
<th>Asthma</th>
<th>No Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic (n = 145)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.85</td>
<td>(0.88–3.88)</td>
<td>.10</td>
<td>60%</td>
<td>45%</td>
</tr>
<tr>
<td>SES</td>
<td>0.88</td>
<td>(0.59–1.3)</td>
<td>.55</td>
<td>2.1 (.15)</td>
<td>2.2 (.09)</td>
</tr>
<tr>
<td>First year (n = 145)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-mo IgE</td>
<td>8.08</td>
<td>(3.10–21.09)</td>
<td>.0001</td>
<td>6.5 (4.0–10.3)</td>
<td>2.3 (1.9–2.7)</td>
</tr>
<tr>
<td>Parenting difficulties</td>
<td>2.16</td>
<td>(1.26–3.71)</td>
<td>.005</td>
<td>1.68 (12)</td>
<td>1.32 (.06)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>1.12</td>
<td>(1.03–1.22)</td>
<td>.009</td>
<td>8.6 (.72)</td>
<td>6.4 (4.0)</td>
</tr>
<tr>
<td>Paternal (bilateral) asthma</td>
<td>2.45</td>
<td>(1.08–5.52)</td>
<td>.03</td>
<td>37%</td>
<td>18%</td>
</tr>
<tr>
<td>Eczema</td>
<td>2.01</td>
<td>(0.71–5.72)</td>
<td>.18</td>
<td>17.5%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Cal exposure</td>
<td>0.76</td>
<td>(0.34–1.67)</td>
<td>.35</td>
<td>27.5%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Maternal smoking (packs/d)</td>
<td>1.54</td>
<td>(0.61–3.83)</td>
<td>.35</td>
<td>0.17 (.07)</td>
<td>0.10 (.03)</td>
</tr>
<tr>
<td>Sixth year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-y IgE (n = 64)</td>
<td>1.83</td>
<td>(1.14–2.93)</td>
<td>.01</td>
<td>38.3 (14.7–99.3)</td>
<td>12.7 (8.9–18.2)</td>
</tr>
<tr>
<td>Allergic (≥1 positive skin test) (n = 77)</td>
<td>4.7</td>
<td>(1.02–23.1)</td>
<td>.04</td>
<td>91%</td>
<td>67%</td>
</tr>
<tr>
<td>Child Psychological Risk (n = 133)</td>
<td>1.84</td>
<td>(1.10–3.07)</td>
<td>.02</td>
<td>1.8 (13)</td>
<td>1.5 (0.7)</td>
</tr>
<tr>
<td>CBCL Internalizing (n = 133)</td>
<td>1.05</td>
<td>(1.004–1.09)</td>
<td>.04</td>
<td>52.5 (1.7)</td>
<td>48.7 (88)</td>
</tr>
<tr>
<td>Maternal Depression (n = 133)</td>
<td>1.41</td>
<td>(0.98–2.03)</td>
<td>.07</td>
<td>2.6 (.16)</td>
<td>2.2 (.11)</td>
</tr>
<tr>
<td>Family Stress (n = 135)</td>
<td>1.05</td>
<td>(0.69–1.5)</td>
<td>.94</td>
<td>3.1 (.15)</td>
<td>3.1 (.10)</td>
</tr>
</tbody>
</table>
TABLE 2. Spearman Intercorrelations of Demographic, First-Year, and Sixth-Year Variables

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

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 old. 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, 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...
asthma was not demonstrated for the early onset of asthma within the first 3 years of life.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 responsivity in caregiving.\textsuperscript{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 measured 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 life\textsuperscript{21} 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 adults\textsuperscript{34} and for children.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{2}

If parenting difficulties affect infants in the manner that environmental stress affects adults,\textsuperscript{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 adults\textsuperscript{41} and in infants\textsuperscript{42} and subsequently may alter the course of immune-based diseases such as allergies and asthma.\textsuperscript{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, 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. There is evidence that endogenous glucocorticoids play a role in allergic inflammation and in airway responses in adults; in children, low cortisol levels were associated with increased asthma severity. 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.

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. Whether through appropriate use of medication, reduction of environmental allergens, or prevention of viral exposure, high parental responsivity 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 responsivity 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 is still 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 deprivation in the early postpartum months has been demonstrated to have an enduring influence on child psychological adjustment to age 5. 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. 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. These data provide support for the possible contribution of psychosocial factors to asthma onset and persistence into childhood.

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