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Recurrent Wheeze in Early Childhood and Asthma Among Children at Risk for Atopy

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ABSTRACT

OBJECTIVES. Little is known about the natural history of wheezing disorders among children at risk for atopy. We examined the relation between early wheeze and asthma at 7 years of age among children with parental history of asthma or allergies followed from birth.

METHODS. Information on wheeze was collected bimonthly from birth to age 24 months and every 6 months thereafter. Recurrent early wheeze was defined as ≥ 2 reports of wheezing in the first 3 years of life. Frequent early wheeze was defined as ≥ 2 reports of wheezing per year in the first 3 years of life. At 7 years of age, asthma was defined as physician-diagnosed asthma and wheezing in the previous year.

RESULTS. Of the 440 participating children, 223 (50.7%) had ≥ 1 report of wheeze before 3 years old, 111 (26.0%) had recurrent early wheeze, and 12 (2.7%) had frequent early wheeze. Whereas only 31 (13.9%) of 223 children with ≥ 1 report of wheeze developed asthma at 7 years of age, 24 (21.6%) of 111 children with recurrent early wheeze developed asthma at 7 years of age. Among the 12 children with frequent early wheeze, 6 (50%) had asthma at 7 years of age. After adjustment for other covariates, recurrent early wheeze in children at risk for atopy was associated with a fourfold increase in the odds of asthma at 7 years of age, and frequent early wheeze was associated with an ~ 12 -fold increase in the odds of asthma at 7 years of age. Most (94%) of the children without frequent early wheeze did not develop asthma at 7 years of age.

CONCLUSIONS. The absence of recurrent early wheeze indicates a very low risk of asthma at school age among children with parental history of asthma or allergies. Early identification of children who will develop asthma at school age is difficult, even in children at risk for atopy. However, children with parental history of asthma or allergies who have frequent early wheeze, in particular, are at greatly increased risk of asthma and merit close clinical follow-up.

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Key Words

wheeze, asthma, atopy, parental asthma, early childhood

Abbreviations

OR—odds ratio

CI—confidence interval

LRI—lower respiratory illness

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WHEEZING DISORDERS ARE common in childhood, especially in the early years. A birth cohort study of children not selected on the basis of a parental history of atopy showed that early onset wheeze seems to follow a transient course for a majority of children, with no associated long-term consequences.¹⁻³ However, that study also identified a small subset of children with early onset wheeze who continued to wheeze beyond the early years ("persistent wheeze"). Children with persistent wheeze were more likely than those with transient early wheeze to be atopic and to have a family history of allergies.¹

Little is known about the natural history of wheezing disorders among children at high risk for atopy. Additional understanding of the relationship between early onset wheeze and asthma in children at risk for atopy has significant epidemiological and clinical implications, because data have shown a strong association between persistent early onset wheeze and asthma-related morbidity, including frequent relapse of symptoms, increased airway responsiveness, and reduced pulmonary function.^{1,4-6} We examined the relation between early onset wheeze and asthma at 7 years of age in a prospective birth cohort study of children with a parental history of asthma or allergies.

METHODS

The children included in this analysis were a subset of the 505 term infants with a parental history of allergy or asthma who were recruited between September 1994 and August 1996 for the Epidemiology of Home Allergens and Asthma Study, an ongoing longitudinal birth cohort study. Detailed inclusion criteria have been described previously.⁷ In brief, inclusion criteria were residence within Route 128 (encircling the Boston metropolitan area); history of asthma, allergies, or hay fever in either parent; maternal age ≥ 18 years; and maternal ability to speak English or Spanish. Families were not screened if the child's gestational age was < 36 weeks, if he/she had a congenital anomaly, or if he/she was hospitalized in the NICU. Of the 505 children, 7 were excluded because they were followed for < 4 months during their first year of life. The study was approved by the Institutional Review Board of the Brigham and Women's Hospital.

We administered telephone questionnaires to the child's caretaker every 2 months during the first 24 months of life and every 6 months thereafter. The questionnaire was based on that of the American Thoracic Society-Division of Lung Diseases questionnaire,⁸ with questions on physician-diagnosed asthma and wheeze taken from the International Study of Asthma and Allergies in Childhood questionnaire.⁹ At every interview, we asked: "Since we last spoke with you on [date given], has your child had wheezing or whistling in the chest?" Recurrent early wheeze was defined as ≥ 2 reports of

wheezing in the first 3 years of life. Frequent early wheeze was defined as ≥ 2 reports of wheezing per year in the first 3 years of life (the child had to have ≥ 2 reports of wheezing every single year from birth to 3 years of age). At 7 years of age, asthma was defined as physician-diagnosed asthma and wheezing in the previous year. Because of the possibility of diagnostic bias by physicians, we also examined recurrent wheeze (≥ 2 reports of wheezing in the previous year) as an alternative definition of asthma at 7 years of age.

At a mean age of 7.4 years (range: 6.5–10.1 years), allergy skin testing was performed in 248 children, and IgEs specific to common allergens were measured in an additional 23 children. Allergy skin testing was performed on the volar aspect of the lower arms. Pricks were made ~ 5 cm apart using Morrow-Brown needles (Allerguard, Topeka, KS). The allergens tested (Hollister Steir Labs, Buffalo, NY) included common indoor (cat dander, dog dander, cockroach [*Blattella germanica*], house dust mite [*Dermatophagoides pteronyssinus* and *D farinae*], and mouse) and outdoor (ragweed, tree, *Aspergillus*, *Alternaria*, grass, *Cladosporium*, and *Penicillium*) allergens. Glycerinated saline and histamine were used as the negative and positive controls, respectively. Skin tests to specific allergens were considered positive if the mean diameter of the wheal was ≥ 3 mm after subtraction of the saline control wheal. Serum from 23 children who declined skin testing was assayed for IgE to the allergens listed above using the UniCAP 250 system (Pharmacia & Upjohn, Kalamazoo, MI). IgEs to specific allergens were considered positive at a level ≥ 0.35 IU/mL.

The following variables were considered for inclusion in the multivariate models, as described previously^{7,10,11}: child's gender, smoke exposure, day care attendance in the first year of life, annual household income ($< \$30\,000$ vs $\geq \$30\,000$), ethnicity/race, parental report of physician-diagnosed lower respiratory illnesses (LRIs; bronchiolitis, bronchitis, croup, or pneumonia) in the first year of life, recurrent nasal catarrh (< 3 vs ≥ 3 episodes of parental report of runny nose) in the first year of life, physician-diagnosed eczema before the age of 3 years, maternal history of asthma (ever), and paternal history of asthma (ever).

Statistical Analysis

The χ^2 test was used to compare between-group proportions. An unpaired *t* test was used to compare between-group means. The sensitivity, specificity, positive predictive value, and negative predictive value of the wheeze variables for asthma at 7 years of age were calculated as described previously.¹² For example, sensitivity was defined as the probability that children with asthma at 7 years of age had recurrent early wheeze, specificity as the probability that children without asthma at 7 years of age had no recurrent early wheeze, positive predictive

value as the probability that a child with recurrent early wheeze developed asthma at 7 years of age, and negative predictive value as the probability that a child without recurrent early wheeze developed asthma at 7 years of age.

Stepwise logistic regression was used to study the relation between early onset wheeze and asthma and recurrent wheeze at the age of 7 years, while adjusting for potential confounders and examining interactions. In the final models, we included variables that were significant at $P < .05$ or that satisfied a change in estimate criterion ($\geq 10\%$) in the odds ratio (OR). All of the analyses were performed using SAS, version 8 (SAS Institute, Cary, NC).

RESULTS

The characteristics of the study participants have been described in detail elsewhere.^{10,13} Of the 498 participating children, 440 (88.4%) were followed up to 7 years of age. Table 1 summarizes the main characteristics of these 440 children. Of these children, 218 had a history of asthma in either parent, with approximately equal numbers of children having a maternal as compared with a paternal history of asthma. Gender, parental history of asthma, and reports of early onset wheeze were similar between subjects who dropped out and subjects who remained in the study at 7 years of age. Study participants who had follow-up at 7 years of age were more likely to be white and to have a family annual income of $\geq \$30\,000$.

Of the 440 participating children, 223 (50.7%) children had ≥ 1 report of wheeze before the age of 3 years. Of these 223 children, only 31 (13.9%) had asthma and 24 (10.8%) had recurrent wheeze at 7 years of age. In univariate analysis, we found that having ≥ 1 report of wheeze before 3 years of age was associated with asthma

(OR: 2.7; 95% CI: 1.3–5.3) but not with recurrent wheeze (OR: 1.7; 95% CI: 0.8–3.3) at 7 years of age. The association between having ≥ 1 report of wheeze before 3 years of age and asthma or recurrent wheeze at 7 years of age did not appreciably change after adjusting for gender, maternal asthma, paternal asthma, and household income (data not shown).

Tables 2 and 3 summarize the results of the univariate and multivariate analyses of the relation between wheeze in early childhood (recurrent early wheeze and frequent early wheeze) and asthma and recurrent wheeze at 7 years of age. Of the 440 study participants, 111 (26.0%) had recurrent early wheeze, and 12 (2.7%) had frequent early wheeze. Of the 111 children with recurrent early wheeze, 24 (21.6%) had asthma, and 18 (16.2%) had recurrent wheeze at 7 years of age. Recurrent early wheeze was associated with a fourfold increase in the odds of asthma (Table 2) and an approximate threefold increase in the odds of recurrent wheeze (Table 3) at 7 years of age. Of the 12 children with frequent early wheeze, 6 (50%) had asthma, and 6 (50%) had recurrent wheeze at 7 years of age. Children with frequent early wheeze had an ~ 11 -fold increase in the odds of asthma and a 13-fold increase in the odds of recurrent wheeze at 7 years of age.

As calculated from the data shown in Table 2, recurrent early wheeze had a sensitivity of 55.8%, a specificity of 77.3%, a positive predictive value of 21.6%, and a negative predictive value of 94.0% for asthma at 7 years of age. Frequent early wheeze had a sensitivity of 14.3%, a specificity of 98.5%, a positive predictive value of 50.0%, and a negative predictive value of 91.5% for asthma at 7 years of age.

The associations between early onset wheeze and asthma or recurrent wheeze at 7 years of age were unchanged in multivariate analyses adjusting for other covariates. After adjusting for gender, paternal asthma, maternal asthma, and household income, recurrent early wheeze was associated with a fourfold increase in the odds of asthma (Table 2) and an approximate threefold increase in the odds of recurrent wheeze at 7 years of age (Table 3). After adjusting for gender, paternal asthma, maternal asthma, and household income, children with frequent early wheeze were ~ 12 times more likely to have asthma (Table 2) and 13 times more likely to have recurrent wheeze at 7 years of age than children without frequent early wheeze (Table 3).

Our results suggest that maternal and paternal asthma confer independent risks for asthma at 7 years of age (Table 2). For example, paternal asthma and maternal asthma were each associated with an approximately twofold increase in the odds of asthma at 7 years of age in a multivariate model (model 3, Table 2). Although the association between maternal asthma and childhood asthma was not statistically significant, the strength of the association between maternal asthma and childhood

TABLE 1 Characteristics of Children in the Cohort ($n = 440$)

Characteristics	<i>n</i> (%)
Gender	
Male	240 (54.6)
Female	200 (45.5)
Race/ethnicity	
White	351 (79.8)
Black	36 (8.2)
Hispanic	21 (4.8)
Other	32 (7.3)
Household income	
<\$30 000	27 (6.1)
$\geq \$30\,000$	403 (91.6)
Unknown	10 (2.3)
Maternal history of asthma, ever	130 (29.6)
Paternal history of asthma, ever	100 (23.2)
Both parents with history of asthma, ever	12 (2.7)
Physician-diagnosed eczema, first 3 years of life	195 (44.3)
Physician-diagnosed LRI, first year of life	117 (26.6)
Recurrent nasal catarrh (≥ 3 episodes), first year of life	371 (84.3)

TABLE 2 Univariate and Multivariate Models of the Relation Between Early Wheeze and Asthma at Age 7 Years

Predictors	Asthma Outcome (n = 43) No. (%) ^a		OR (95% CI)				
			Unadjusted	Adjusted			
	No	Yes		Model 1 ^b	Model 2 ^b	Model 3 ^b	Model 4 ^b
Recurrent early wheeze (≥ 2 reports of wheezing in the first 3 years of life)							
No	297 (94.0)	19 (6.0)	1.00	1.00	1.00	1.00	1.00
Yes	87 (78.4)	24 (21.6)	4.3 (2.3–8.2)	4.1 (2.1–8.2)	4.5 (2.3–8.8)	4.2 (2.1–8.3)	4.6 (2.4–9.1)
Gender (female = ref)				2.1 (1.0–4.4)	2.3 (1.1–4.7)	2.3 (1.1–4.7)	2.4 (1.1–5.1)
Paternal history of asthma, ever				1.5 (0.7–3.1)	—	1.8 (0.8–3.9)	—
Maternal history of asthma, ever				—	1.5 (0.7–3.0)	1.8 (0.8–3.9)	—
Both parents with asthma, ever				—	—	—	4.1 (0.8–22.4)
Frequent early wheeze (≥ 2 reports of wheezing per year in the first 3 years of life)							
No	389 (91.5)	36 (8.5)	1.00	1.00	1.00	1.00	1.00
Yes	6 (50.0)	6 (50.0)	10.8 (3.3–35.2)	11.7 (3.5–39.4)	10.6 (3.2–35.7)	11.8 (3.4–40.6)	11.1 (3.3–37.2)
Gender (female = ref)				2.0 (1.0–4.2)	2.1 (1.0–4.3)	2.1 (1.0–4.4)	2.2 (1.1–4.7)
Paternal history of asthma, ever				1.9 (0.9–4.0)	—	2.3 (1.1–5.0)	—
Maternal history of asthma, ever				—	1.3 (0.7–2.7)	1.8 (0.8–3.8)	—
Both parents with asthma, ever				—	—	—	3.6 (0.7–18.5)

Ref indicates reference; —, variable not included in model.

^a The total *n* for each of the groups presented in the table is different because of variable missingness in response to the wheeze questionnaire.

^b All models were adjusted for annual household income and gender, in addition to the variables listed in each column.

TABLE 3 Univariate and Multivariate Models of the Relation Between Early Wheeze and Recurrent Wheeze at Age 7 Years

Predictors	Recurrent Wheeze Outcome (n = 38) No. (%) ^a		OR (95% CI)				
			Unadjusted	Adjusted			
	No	Yes		Model 1 ^b	Model 2 ^b	Model 3 ^b	Model 4 ^b
Recurrent early wheeze (≥ 2 reports of wheezing in the first 3 years of life)							
No	293 (93.6)	20 (6.4)	1.00	1.00	1.00	1.00	1.00
Yes	93 (83.9)	18 (16.2)	2.8 (1.4–5.6)	2.9 (1.4–5.8)	2.8 (1.4–5.7)	2.9 (1.4–5.8)	2.8 (1.4–5.7)
Gender (female = ref)				2.0 (1.0–4.3)	2.1 (1.0–4.4)	2.1 (1.0–4.5)	2.0 (0.9–4.1)
Paternal history of asthma, ever				1.0 (0.4–2.2)	—	1.1 (0.5–2.5)	—
Maternal history of asthma, ever				—	1.4 (0.6–2.9)	1.4 (0.6–3.1)	—
Both parents with asthma, ever				—	—	—	NA ^c
Frequent early wheeze (≥ 2 reports of wheezing per year in the first 3 years of life)							
No	392 (92.9)	30 (7.1)	1.00	1.00	1.00	1.00	1.00
Yes	6 (50.0)	6 (50.0)	13.1 (4.0–43.0)	13.1 (3.9–44.1)	13.0 (3.8–44.1)	13.0 (3.8–44.5)	12.7 (3.8–42.8)
Gender (female = ref)				2.2 (1.0–4.8)	2.1 (1.0–4.7)	2.2 (1.0–4.8)	2.1 (0.9–4.5)
Paternal history of asthma, ever				1.3 (0.6–3.0)	—	1.4 (0.6–3.3)	—
Maternal history of asthma, ever				—	1.1 (0.5–2.5)	1.3 (0.5–2.9)	—
Both parents with asthma, ever				—	—	—	NA ^c

Ref indicates reference; —, variable not included in model.

^a The total *n* for each of the groups presented in the table is different because of variable missingness in response to the wheeze questionnaire.

^b All models were adjusted for annual household income and gender, in addition to the variables listed in each column.

^c Unable to produce statistical results because of infrequent observations.

asthma was similar to the association between paternal asthma and childhood asthma. In addition, there was a nonstatistically significant trend for an ~ 3.5 -fold increase in the odds of asthma in children who had both parents with asthma (model 4, Table 2). Because none of the children who had recurrent wheeze at 7 years of age had both parents with asthma, risk estimates could not be calculated (model 4, Table 3).

We also found that boys were approximately twice as

likely to have asthma (Table 2) and recurrent wheeze (Table 3) at the age of 7 years as girls. In this cohort, there were no significant differences in recurrent early wheeze, frequent early wheeze, eczema, maternal history of asthma, or paternal history of asthma between boys and girls.

We did not find significant differences in gender, ethnicity, annual household income, eczema in the first 3 years of life, recurrent nasal catarrh, maternal asthma,

and paternal asthma between those with and without recurrent early wheeze. Similar results were obtained for the comparison of children with and without frequent early wheeze.

Having ≥ 1 physician-diagnosed LRI in the first year of life was more frequently reported in subjects with recurrent early wheeze than in those without (44.1% vs 20.3%; $P < .001$). Subjects with frequent early wheeze were more likely to report ≥ 1 physician-diagnosed LRI in the first year of life than those without frequent early wheeze (50.0% vs 25.7%; $P = .06$). Having ≥ 1 physician-diagnosed LRI in the first year of life was not a significant predictor of asthma or recurrent wheeze at 7 years of age in multivariate analyses that adjusted for either recurrent early wheeze or frequent early wheeze. In addition, having ≥ 1 physician-diagnosed LRI in the first year of life did not confound or modify the relationship between early onset wheeze and either asthma or recurrent wheeze at 7 years of age.

We assessed allergen sensitization (by allergy skin testing [$n = 248$] or measurement of allergen-specific IgE [$n = 23$]) in 271 (54.4%) of the 498 study participants. Of these 271 children, 149 (55%) were sensitized to ≥ 1 allergen (atopic) at school age. Of the 43 children with asthma at 7 years of age, 30 underwent assessment of allergen sensitization (some parents refused to have their children tested because of known allergies). Significant proportions of children with recurrent wheezing (76.9%) and asthma (73.3%) at 7 years of age were atopic at school age. Of the 64 children with recurrent early wheeze who underwent assessment of allergen sensitization, 56.3% were atopic at school age. Of the 9 children with frequent early wheeze who underwent assessment of allergen sensitization, 55.6% were atopic. Although we had limited statistical power, we did not find a significant association between our measures of early onset wheeze and allergen sensitization at school age. We did not find any modification of the effect of early onset wheeze on asthma or recurrent wheeze at 7 years of age by gender, maternal asthma, or paternal asthma.

DISCUSSION

In our study, approximately half of the children with parental history of asthma or allergies had ≥ 1 episode of wheezing before 3 years of age. However, 86.1% of children with parental history of asthma or allergies who had any wheezing before 3 years of age did not go on to have asthma at 7 years of age. Among these children, only those who had more frequent wheezing before 3 years of age had an increased risk of asthma at 7 years of age. For example, children with frequent early wheeze (≥ 2 episodes of wheeze per year in the first 3 years of life) had a 12-fold increase in the odds of asthma at 7 years of age.

Our results suggest that wheezing before 3 years of

age is more frequent in children at risk for atopy than in children not selected on the basis of parental history of atopy.¹ However, our findings are similar to those studies of children not selected on the basis of parental history of atopy in that having any wheeze before 3 years of age is a poor predictor of asthma.¹ In a birth cohort study of children who were not selected on the basis of a parental history of atopy, Martinez et al¹ reported that approximately one-third (33.6%) of study participants had ≥ 1 report of wheezing before 3 years of age. Of the children who had ≥ 1 report of wheezing before the age of 3 years, 13.7% had persistent wheeze (defined as having ≥ 1 lower respiratory tract illness with wheezing during the first 3 years of life and wheezing at 6 years of age). Among children with IgE measurements in that study, children with persistent wheeze were more likely to have a maternal history of asthma and elevated total serum IgE levels in infancy and at the age of 6 years.

Few studies have examined the natural history of wheezing disorders among children at risk for atopy. Rhodes et al¹⁴ followed British subjects with parental history of asthma or hay fever from birth to 22 years of age. Prospective information on wheeze (obtained every 3 months during the first year of life, every year from years 1–5, and then at ages 11 and 22 years) was available for 58 of the 100 participating subjects. Of the 18 children who had ≥ 1 report of wheezing before 2 years of age, 6 (37.5%) had a report of wheezing at either 11 or 22 years of age. Of the 11 children who had ≥ 3 reports of wheezing before the age of 5 years, 10 (90.9%) had a report of wheezing at either 11 or 22 years of age. There was no assessment of the relation between wheeze before 3 years of age and asthma at ages 11 and 22 years. In contrast to those results, we found that half of the children with parental history of asthma, hay fever, or allergies who had frequent early wheeze went on to have asthma at 7 years of age. In the study by Rhodes et al,¹⁴ several factors (small sample size, infrequent follow-up of children between the ages of 1 and 5 years, and marked loss of follow-up [42%] of study participants) likely resulted in significant overestimation of the risk of asthma at age 11 and 22 years among children with parental history of asthma or hay fever. However, our results and those of Rhodes et al¹⁴ suggest that children with parental history of asthma or hay fever who wheeze frequently in early childhood are at markedly increased risk of subsequent asthma.

Although many studies have shown an association between maternal asthma and childhood asthma, few have shown an association of paternal asthma to childhood asthma, especially in school-aged children.^{15,16} In a previous cross-sectional analysis of 217 siblings of the index children from this at-risk birth cohort, Litonjua et al¹¹ showed that the risk of childhood asthma before the age of 5 years was strongly associated with a maternal

history of asthma. However, in agreement with our findings, maternal and paternal asthma were associated with similar risks among children older than 5 years of age. Unlike the findings from a recent study,¹⁷ we did not find interactions between gender and maternal or paternal history of asthma in their effect on asthma risk.

In keeping with previous findings from other investigators, we showed that asthma at the age of 7 years was more commonly observed in boys than girls. The higher asthma prevalence in boys at a young age has been explained by dysanapsis of the normal lungs in boys, that is, smaller airway size relative to lung volume.¹⁸ Current evidence suggests that the asthma prevalence in girls increases during puberty. Some investigators have suggested that this transition may be partially related to increased production of female sex hormones.^{19,20} Additional follow-ups of these children into their teenage years is needed to help elucidate the gender-specific differences in environmental, immunologic, and developmental factors influencing asthma prevalence in girls and boys.

Our findings further illustrate the difficulties of early identification of children who will develop asthma at school age among children with early wheeze, even in children at high risk for atopy. Among children not selected on the basis of parental history of asthma or allergies, Castro-Rodríguez et al²¹ developed an index to predict asthma at school age. Similar to our findings for the sensitivity and specificity of recurrent early wheeze for the diagnosis of asthma at 7 years of age, those investigators found that their index had a sensitivity of 56.6% and a specificity of 80.8% for predicting asthma at 6 years of age. However, that index was more complicated than our definition of recurrent early wheeze, because it included any wheeze before 3 years of age and either 1 of 2 major criteria (doctor-diagnosed eczema or a parental asthma) or 2 of 3 minor criteria (doctor-diagnosed allergic rhinitis, wheezing apart from colds, or eosinophilia $\geq 4\%$).²¹ Similar to our findings in children with parental history of asthma or allergies, the use of more frequent wheeze before 3 years of age in the study by Castro-Rodríguez et al²¹ resulted in reduced sensitivity (16.3% at 8 years of age) but increased specificity (96.7% at 8 years of age) for predicting asthma at school age.

Among children with parental history of asthma or allergies, we found that recurrent early wheeze had a very high negative predictive value for asthma at 7 years of age. This is an important finding for clinicians, because 94% of children with parental history of atopy who had no recurrent early wheeze did not go on to develop asthma at 7 years of age. Although we found that frequent early wheeze had a relatively low sensitivity for asthma at school age (eg, few children with asthma at 7 years of age had frequent early wheeze), it was associated with a greatly increased risk of asthma at

school age. In addition, frequent early wheeze had a very high specificity for asthma at school age because of a very low proportion of “false positives” (eg, few children without asthma at school age had frequent early wheeze).

Selection bias is an unlikely explanation for our findings, because we had a relatively low proportion of subjects lost to follow-up (11.6%) from birth to 7 years of age. In addition, there were no differences in reports of early onset wheeze, and parental history of asthma and gender were similar between subjects who dropped out and subjects who remained in the study at 7 years of age.

CONCLUSIONS

In summary, we found that the absence of recurrent early wheeze indicates a very low risk of asthma at school age among children with parental history of asthma or allergies. Among children with parental history of asthma or allergies, early identification of children who will develop asthma at school age in children with early wheeze is difficult. However, children with parental history of asthma or allergies who have recurrent early wheeze, in general, and frequent early wheeze, in particular, are at significantly increased risk of asthma and merit close clinical follow-up.

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