
Relationship between childhood atopy and wheeze: what mediates wheezing in atopic phenotypes?

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Background: The nature of the relationship between childhood wheeze and atopy remains uncertain.

Objective: To characterize childhood wheeze among atopic phenotypes in a longitudinal birth cohort study.

Methods: A whole population birth cohort (N = 1,456) was recruited in 1989. Children were seen at birth and at 1, 2, 4, and 10 years of age to obtain information on asthma and allergic disease development and relevant risk factors for these states. Skin prick testing at ages 4 (n = 980) and 10 (n = 1,036) years was used to define atopic phenotypes. Wheezing in these states was characterized, and logistic regression was used to identify independent risk factors for wheeze onset in different atopic phenotypes.

Results: Wheeze ever occurred in 37% of never atopics, 38% of early childhood atopics, 65% of chronic childhood atopics, and 52% of delayed childhood atopics. Chronic childhood atopics had significant wheezing morbidity and bronchial hyperresponsiveness. Their wheezing was associated with male sex, early eczema, family history of eczema, and early tobacco exposure. Never atopic wheeze was related to maternal asthma, parental smoking, and respiratory tract infections. Exclusive breastfeeding protected against early childhood atopic wheeze. Maternal asthma, family history of urticaria, and dog ownership increased delayed childhood atopic wheeze.

Conclusions: In many respects, chronic childhood atopy is the atopic phenotype associated with the most significant forms of childhood wheezing. In such children, heritable drive, allergens, and synergy with other environmental triggers seem to be crucial determinants of wheeze onset. Where such sensitization is absent, numerous environmental factors plus genetic predisposition may assume importance for wheezing.

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INTRODUCTION

A body of work^{1,2} has accumulated suggesting a close association between childhood asthma and atopic status. However, the recognition of wheezing as a heterogeneous disorder has led to the identification of various wheezing phenotypes throughout life, both atopic and nonatopic.^{3,4} Thus, Martinez et al⁵ found a substantial proportion of nonatopic early transient wheeze in association with viral illness in infancy. We recently found that even at 10 years of age, almost 50% of current wheezing is nonatopic.⁶ Although an important associated feature of childhood asthma and wheezing, the precise contribution of atopic sensitization to the development of these states is unclear. Indeed, some researchers⁷ have suggested a population-attributable risk of less than 50% for atopy toward asthma.

So how can we better understand the relationship between childhood atopy and wheeze? A longitudinally defined phenotypic classification of childhood atopy,⁸ based on atopic sensitization at 4 and 10 years of age, may offer some insight

into this matter (Table 1). Characterization of wheezing in such atopic phenotypes, along with identification of early-life influences for onset of that wheeze, could yield further insight into the association of atopy and wheeze. In this article, we characterize associations of wheeze with atopic phenotypes during the first decade of life and describe early-life risk factors that might mediate wheeze development in such states.

METHODS

A whole population birth cohort was established on the Isle of Wight, England, in 1989 to prospectively study the natural history of childhood wheeze and allergy. Approval for the study was obtained from the local research ethics committee. Of 1,536 children born between January 1, 1989, and February 28, 1990, informed consent was obtained to enroll 1,456 individuals. Enrollment took place at birth when information was recorded on asthmatic or allergic family history (parental or sibling), household pets present during pregnancy, smoking habit during pregnancy, and birth weight. Social class was also defined (using the Registrar General's classification: professional occupations, managerial and technical occupations, skilled occupations [nonmanual or manual], partly skilled occupations, and unskilled occupations).

Children were followed up at the ages of 1 (n = 1,167; 80.2%), 2 (n = 1,174; 80.6%), 4 (n = 1,218; 83.7%), and 10 (n = 1,373; 94.3%) years. At each follow-up visit, detailed

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Table 1. Patterns of Atopic Sensitization for the Childhood Atopic Phenotypes*

	Childhood atopic phenotype			
	Never	Early	Chronic	Delayed
Atopic at age 4 y	No	Yes	Yes	No
Atopic at age 10 y	No	No	Yes	Yes

* The presence or absence of atopic sensitization at skin prick testing was defined by at least 1 allergen test response greater than 3 mm from a panel of common food allergens and aeroallergens.

questionnaires were completed by the investigator (an allergist) with the parents for every child regarding allergic symptoms and diagnoses. Exposure to relevant environmental factors (domestic pets and tobacco smoke) was noted. Method of feeding was obtained at 1 and 2 years of age. A history of recurrent chest infections (>1 in the past year) was evaluated at 1 and 2 years of age. Current wheeze was recorded as occurring on at least 1 occasion in the previous 12 months. Diagnosed asthma was defined at 1, 2, and 4 years of age as 3 or more separate episodes of wheeze in the previous 12 months, each lasting at least 3 days. At 10 years of age, currently diagnosed asthma was defined as a combination of current wheeze plus ever diagnosed as having asthma. Investigators' diagnoses of eczema (chronic or chronically relapsing itchy dermatitis lasting >6 weeks with characteristic morphologic features and distribution), recurrent nasal symptoms or rhinitis (recurrent nasal discharge or blockage with attacks of sneezing and itchy eyes), and food allergy (history of vomiting, diarrhea, colic, or rash within 4 hours of ingesting a particular food on ≥ 2 occasions) were made each time. Details of lifetime asthma treatment (short- or long-acting inhaled bronchodilators, inhaled corticosteroids, sodium cromoglycate, theophyllines, leukotriene antagonists, and antihistamines) were recorded at 10 years of age.

Skin prick tests (SPTs), performed by research nurses, were offered to all the children. Panels of common inhaled and food allergens were used at 4 years of age (Biodiagnostics, Reinbek, Germany) and at 10 years of age (ALK-Abelló, Hørsholm, Denmark). The former panel comprised house dust mite (*Dermatophagoides pteronyssinus*), grass pollen mix, cat and dog epithelia, *Alternaria alternata*, *Cladosporium herbarum*, milk, hen's egg, soya, cod, wheat, and peanut. The latter panel included house dust mite (*D pteronyssinus*), grass pollen mix, tree pollen mix, cat and dog epithelia, *A alternata*, *C herbarum*, milk, hen's egg, soya, cod, and peanut. On both occasions, histamine and physiologic saline were used as positive and negative controls, respectively. Any SPT reaction with a mean wheal diameter of at least 3 mm greater than the negative control was regarded as positive, and the child was described as atopic. At 10 years of age, nonspecific bronchial hyperresponsiveness (BHR) was measured at methacholine bronchial challenge in children with past or current wheeze (n = 484) and in never

wheezers (controls) (n = 300). The methods have been previously described.⁹

Data were double entered into a statistical software program (SPSS v10.0; SPSS Inc, Chicago, IL). Atopic phenotypes were assigned in children with SPT at both 4 and 10 years of age (n = 823). Thus, never atopic were nonatopic at both ages, early childhood atopics were atopic at 4 years of age only, chronic childhood atopics were atopic at both ages, and delayed childhood atopics were atopic at 10 years of age only. Differences in proportions between groups were tested using χ^2 analysis with Bonferroni correction for multiple comparisons. Bronchial hyperresponsiveness was categorized by provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% per American Thoracic Society guidelines,¹⁰ with categories 3 and 4 considered definite BHR.

Risk factors for wheeze onset in each atopic phenotype were identified at univariate analysis by comparing wheeze ever and never wheezed within that state. To obtain the independent effect of risk factors with trends for significance at univariate testing ($P < .2$), separate logistic regression models were created for wheezing in never atopics, early childhood atopics, chronic childhood atopics, and delayed childhood atopics. Stepwise backward (likelihood ratio) logistic regression was used for this purpose. Where more than 1 risk factor could explain a particular exposure of interest, only the most relevant was entered into the model.

RESULTS

Of the original birth cohort (N = 1,456), 1,218 (83.7%) and 1,373 (94.3%) were reevaluated by questionnaire at 4 and 10 years of age, respectively. The SPT was conducted in 980 children at 4 years of age and in 1,036 at 10 years of age. Atopy was found in 19.7% (193/980) of the children at 4 years of age and in 26.9% (279/1,036) at 10 years of age. A total of 823 children underwent SPT at both 4 and 10 years of age and thus were eligible for evaluation of atopic phenotype. Children included in this phenotypic analysis were representative, in terms of demographic and disease characteristics, of those seen at the largest follow-up visit (10 years) (data not shown).

Among children with defined atopic phenotypes, 340 had prospectively recorded wheeze ever in the first decade of life. Of these children, 57.6% (n = 196) were never atopic, 25.6% (n = 87) were chronic childhood atopic, 13.2% (n = 45) were delayed childhood atopic, and 3.5% (n = 12) were early childhood atopic. The prevalence of lifetime wheeze was highest in chronic childhood atopics (65%), followed by delayed childhood atopics (52%), early childhood atopics (38%), and never atopics (37%). Diagnosed asthma rates changed relatively little throughout the first decade of life for never atopics and delayed childhood atopics but peaked at the age of 4 years and declined thereafter in early childhood atopics (Fig 1). Conversely, asthma diagnoses rose steadily in chronic childhood atopics. This phenotype also showed significantly elevated disease severity in terms of specialist

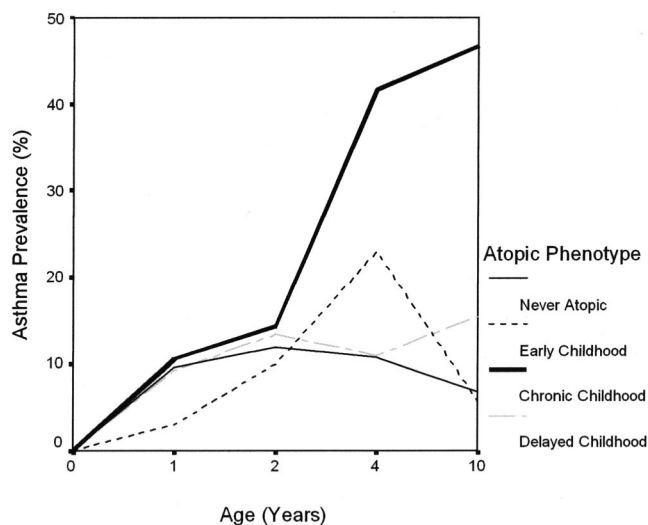


Figure 1. Changing prevalence of diagnosed asthma for the atopic phenotypes during the first decade of life.

referral, hospitalization, and current wheezing morbidity at the age of 10 years (Table 2) plus the highest lifetime asthma treatment use (Table 3). In contrast, delayed childhood atopics had less morbidity with lower treatment needs, and early childhood and never atopics had the lowest measures of these indices. Furthermore, definite BHR was detected most often at the age of 10 years in chronic childhood atopics and to a lesser extent in delayed childhood atopics (Fig 2).

Risk Factors for Wheezing in the Childhood Atopic Phenotypes

Factors showing statistical significance in univariate testing for wheeze ever in each phenotype are given in Table 4.

Significantly increased wheezing risk in never atopics was associated with male sex, low birth weight, recurrent chest infections, and nasal symptoms in infancy, plus parental tobacco smoking in the first 4 years of life. Allergic family history in the form of maternal asthma and urticaria, plus sibling food allergy, was also significant. Exclusive breastfeeding in the first 3 months of life and high social class at birth conferred reduced risk of wheeze in never atopics. Exclusive breastfeeding in the first 3 months of life was the only significant factor in early childhood atopics, showing a protective effect against wheeze ever. Wheezing in chronic childhood atopics was associated with male sex, recurrent chest infections in infancy, eczema throughout early life, and parental smoking at 4 years old. Allergic family history in the form of asthma and eczema was also associated with wheezing in this state. Increased wheeze in delayed childhood atopics was associated with recurrent chest infections in infancy, maternal asthma, and family history of urticaria.

Adjusted Risk Factors for Wheezing in the Childhood Atopic Phenotypes

To establish the independent effects of early-life risk factors on these phenotypes, logistic regression analysis was used (Table 5). With never atopic wheeze, independent significance was found for recurrent nasal symptoms plus recurrent chest infections in infancy, parental smoking in infancy, and maternal asthma. For early childhood atopic wheeze, a significant protective effect was found for exclusive breastfeeding in the first 3 months of life. For chronic childhood atopic wheeze, independent significance was found for male sex, eczema at 4 years of age, parental smoking at 4 years of age, and family history of eczema. For delayed childhood atopic wheeze, independent significance was found for maternal asthma, family history of urticaria, and dog ownership at 4 years of age.

Table 2. Wheezing Morbidity Associated With the Childhood Atopic Phenotypes*

	Childhood atopic phenotype			
	Never	Early	Chronic	Delayed
Specialist (pediatric) referral	17/511 (3.3)	0/33	21/134 (15.7)†	4/82 (4.9)
Hospital admission	19/511 (3.7)	1/33 (3.0)	27/134 (20.1)†	9/82 (11.0)‡
Wheeze frequency at age 10 y (>4 episodes in 12 mo)	22/533 (4.1)	2/35 (5.7)	33/136 (24.3)†	11/91 (12.1)§
Sleep disturbance at age 10 y (waking from sleep because of wheeze >1/wk)	3/558 (0.5)	0/35	11/136 (8.1)†	2/91 (2.2)
Nocturnal cough at age 10 y	67/560 (12.0)	4/35 (11.4)	48/137 (35.0)†¶	24/91 (26.4)†
Exercise-induced wheeze at age 10 y	43/560 (7.7)	1/35 (2.9)	54/137 (39.4)† #	15/91 (16.5)‡

* Data are given as number/total number (percentage). Comparisons were performed using χ^2 analysis with Bonferroni correction for multiple comparisons.

† $P < .001$ vs never atopic.

‡ $P = .04$ vs never atopic.

§ $P = .006$ vs never atopic.

¶ $P = .04$ vs early childhood atopic.

|| $P < .001$ vs early childhood atopic.

$P < .001$ vs delayed childhood atopic.

Table 3. Asthma Treatment in the Childhood Atopic Phenotypes*

	Childhood atopic phenotype			
	Never	Early	Chronic	Delayed
Ever treated for wheezing†	120/515 (23.3)	5/33 (15.2)	90/134 (67.2)‡§¶	36/83 (43.4) #
Inhaled corticosteroids	42/508 (8.3)	1/33 (3.0)	60/134 (44.8)‡§**	15/80 (18.8)††
Inhaled bronchodilators	114/512 (22.3)	5/33 (15.2)	88/134 (65.7)‡§**	34/82 (41.5)‡§§
Any prophylactic medication ever‡‡	57/508 (11.2)	1/33 (3.0)	68/134 (50.7)‡§**	17/80 (21.3)
Oral corticosteroids	17/511 (3.3)	0/33	39/134 (29.1)‡§**	7/82 (8.5)

* Data are given as number/total number (percentage). Testing was performed using χ^2 analysis with Bonferroni correction for multiple comparisons.

† Refers to ever needing any form of therapy for wheezing (ie, short-acting bronchodilators, any prophylactic medications, or oral corticosteroids).

‡ $P < .001$ vs never atopic.

§ $P < .001$ vs early childhood atopic.

¶ $P = .006$ vs delayed childhood atopic.

|| $P = .006$ vs never atopic.

$P = .02$ vs early childhood atopic.

** $P < .001$ vs delayed childhood atopic.

†† $P = .02$ vs never atopic.

‡‡ Includes inhaled corticosteroids, long-acting β -agonists, sodium cromoglycate, theophyllines, leukotriene antagonists, and antihistamines.

§§ $P = .04$ vs early childhood atopic.

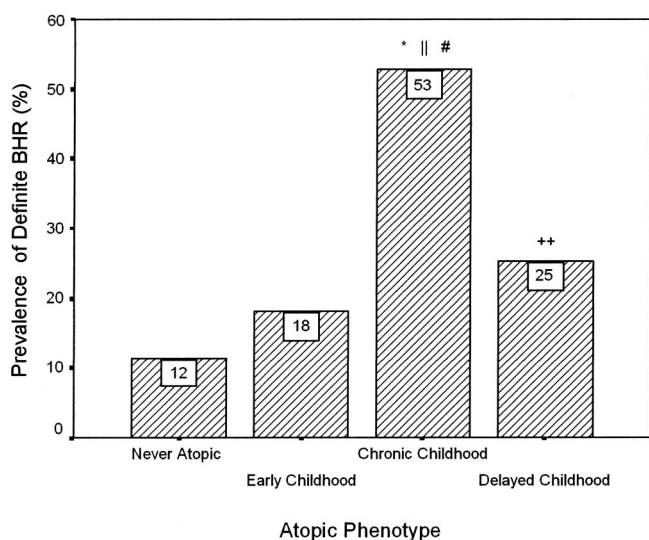


Figure 2. Prevalence of definite bronchial hyperresponsiveness (BHR) for the atopic phenotypes at 10 years of age. Definite BHR is defined as a provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% of less than 4 mg/mL at methacholine bronchial challenge. Asterisk indicates $P < .001$ vs never atopic; double plus sign, $P = .01$ vs never atopic; parallels, $P = .02$ vs early childhood atopic; and number sign, $P < .001$ vs delayed childhood atopic.

DISCUSSION

Complex interactions of genetic predisposition and environmental influence probably mediate the development of wheezing and asthma. The role of atopic sensitization in this process is not fully understood. Previously, our group¹¹ reported early-life atopy to be a key predictor of long-term persistence of early-life wheezing. However, we also identified a substantial burden of

nonatopic wheeze at 10 years of age.⁶ By now presenting a phenotypic description of childhood atopy, we tried to further clarify these relationships and identify influential factors for wheeze development in the presence or absence of atopic sensitization. Our classification found that most childhood wheezing is actually never atopic, although the highest prevalence of wheeze in any one phenotype occurred among chronic childhood atopics. As they aged, this chronically sensitized group was increasingly diagnosed as having asthma, demonstrating the highest wheezing morbidity, asthma therapy needs, and prevalence of BHR at 10 years of age. The contribution of heredity and environment to the genesis of wheeze was found to be variable between this and the other childhood atopic phenotypes. Where chronic or delayed atopic sensitization was present, the effect of allergic heredity seemed to predominate over environment, with the latter assuming more importance among never and transiently sensitized early childhood atopic states.

Our chronic childhood atopics emerged as having the highest risk of clinically relevant wheeze and asthma. Accordingly, we demonstrated enhanced BHR in such individuals. Bronchial hyperresponsiveness is an important feature of asthmatic disease. Intrinsic associations between IgE and BHR were previously reported in the Dunedin cohort,¹² regardless of allergic symptoms. We recently confirmed strong associations between atopy and BHR.¹³ We showed¹⁴ that the presence of BHR itself does not always imply wheezing symptoms but that atopy may be a key element for wheeze expression in those with BHR. Although using different defining criteria, our present atopic classification extends previous characterization of early persistent atopy reported by Peat et al¹⁵ in Australia and Sherrill and coworkers¹⁶ in the United States. We found that wheezing in chronic childhood atopics was associated with a constellation of largely heritable factors, including male sex, allergic family

Table 4. Significant Univariate Risk Factors for Wheeze Development in the Atopic Phenotypes*

Phenotype and risk factor	Prevalence in		OR (95% CI)	P value
	Wheeze	Never wheeze		
Never atopic†				
Social class I-III at birth	45/124 (36.3)	89/184 (48.4)	0.61 (0.38–0.97)	.04
Male sex	102/196 (52.0)	138/335 (41.2)	1.55 (1.09–2.21)	.02
Exclusively breastfed first 3 mo of life	51/178 (28.7)	124/314 (39.5)	0.62 (0.41–0.91)	.02
Low birth weight (<2.5 kg)	14/192 (7.3)	9/324 (2.8)	2.75 (1.17–6.49)	.02
Recurrent chest infections at age 1 y	31/190 (16.3)	6/335 (1.8)	10.69 (4.37–26.15)	<.001
Recurrent chest infections at 2 y	54/178 (30.3)	13/335 (3.9)	10.79 (5.69–20.46)	<.001
Parental smoking at age 1 y	82/189 (43.4)	111/334 (33.2)	1.54 (1.07–2.22)	.02
Parental smoking at age 2 y	75/171 (43.9)	112/329 (34.0)	1.51 (1.04–2.21)	.03
Parental smoking at age 4 y	91/196 (46.4)	109/335 (32.5)	1.80 (1.25–2.58)	.001
Maternal asthma	43/177 (24.3)	41/318 (12.9)	2.17 (1.35–3.49)	.001
Maternal urticaria	20/177 (11.3)	20/318 (6.3)	1.90 (0.99–3.63)	.05
Sibling food allergy	27/177 (15.3)	29/318 (9.1)	1.79 (1.03–3.14)	.04
Nasal symptoms at age 1 y	35/190 (18.4)	23/335 (6.9)	3.06 (1.75–5.36)	<.001
Nasal symptoms at age 2 y	52/178 (29.2)	28/335 (8.4)	4.53 (2.73–7.49)	<.001
Early childhood atopic‡				
Exclusively breastfed first 3 mo of life	1/11 (9.1)	11/20 (55.0)	0.08 (0.01–0.77)	.02
Chronic childhood atopic§				
Male sex	56/87 (64.4)	20/46 (43.5)	2.35 (1.13–4.87)	.02
Recurrent chest infections at age 2 y	18/80 (22.5)	0/46	–	.001
Parental smoking at age 4 y	36/87 (41.4)	9/46 (19.6)	2.90 (1.25–6.75)	.01
Family history of asthma	57/86 (66.3)	18/43 (41.9)	2.73 (1.29–5.80)	.008
Family history of eczema	47/86 (54.7)	15/43 (34.9)	2.25 (1.06–4.80)	.03
Eczema at age 1 y	32/83 (38.6)	7/46 (15.2)	3.50 (1.40–8.75)	.006
Eczema at age 2 y	29/80 (36.3)	6/46 (13.0)	3.79 (1.44–10.02)	.005
Eczema at age 4 y	35/87 (40.2)	8/46 (17.4)	3.20 (1.33–7.67)	.007
Rhinitis at age 4 y	23/87 (26.4)	5/46 (10.9)	2.95 (1.04–8.37)	.04
Delayed childhood atopic¶				
Recurrent chest infections at age 2 y	10/41 (24.4)	0/39	–	.001
Maternal asthma	13/41 (31.7)	4/39 (10.3)	4.06 (1.19–13.84)	.02
Family history of urticaria	16/41 (39.0)	4/39 (10.3)	5.60 (1.67–18.78)	.003

Abbreviations: CI, confidence interval; OR, odds ratio.

* Comparison of prevalence (χ^2 test) for various risk factors in each atopic phenotype with and without wheezing is shown. Only statistically significant risk factors are given. Trends for significance ($P < .2$ but $> .05$) are given below.

† For never atopics, eczema at 1 year of age, food allergy at 1 year of age, rhinitis at 4 years of age, sibling asthma, and parental smoking at birth showed positive trends for significance.

‡ For early childhood atopics, cat ownership at birth showed positive trends for significance.

§ For chronic childhood atopics, food allergy at 2 years of age and parental smoking at 1 year of age showed positive trends for significance.

¶ For delayed childhood atopics, maternal rhinitis plus dog ownership at birth and at 4 years of age showed positive trends for significance.

history, and early-life allergic comorbidity, plus environment in the guise of parental smoking.

Associations between male sex and wheezing in chronic childhood atopics are noteworthy. Male predominance among wheezing children in early life is well documented.¹⁷ In the present analysis, though, male sex assumed independent significance for wheezing only among chronic childhood atopics. The effect of sex on wheeze development, therefore, seems peculiar to this phenotype. This could reflect the impact of chronic allergen-induced airway inflammation on sex-related airflow limitation in boys.¹⁸ Alternatively, it may signal an as yet unknown mechanism by which chronic atopy and wheeze frequently manifest together as comorbid states

in males. An intriguing consideration is whether this sex relationship for wheeze in chronic atopics alters with time. Sex predominance for wheezing has been previously observed^{19,20} to change from male to female near puberty.

We previously found²¹ that early-life environmental factors, including smoking exposure, chest infections, and low social class, contributed to earlier clinical manifestation of persistent childhood wheeze in our population. In this article, the only environmental effect of significance for wheezing in chronic childhood atopics was exposure to tobacco smoke at the age of 4 years. This extends previous findings associating parental smoking with childhood atopy²² and asthma.²³ A synergistic effect of tobacco smoke exposure and allergen

Table 5. Early-Life Risk Factors for Wheeze Ever in Atopic Phenotypes*

Phenotype and risk factor	OR (95% CI)	P value
Never atopic†		
Recurrent chest infections at age 2 y	9.26 (3.15–27.18)	<.001
Maternal asthma	2.89 (1.30–6.44)	.009
Parental smoking at age 2 y	2.12 (1.10–4.09)	.02
Nasal symptoms at age 1 y	2.61 (1.01–6.77)	.048
Early childhood atopic‡		
Exclusive breastfeeding in first 3 mo of life	0.09 (0.01–0.93)	.04
Chronic childhood atopic§		
Male sex	3.11 (1.23–7.89)	.02
Eczema at age 4 y	3.48 (1.24–9.75)	.02
Family history of eczema	3.08 (1.21–7.83)	.02
Parental smoking at age 4 y	2.95 (1.04–8.35)	.04
Delayed childhood atopic¶		
Family history of urticaria	5.12 (1.29–20.38)	.02
Maternal asthma	4.68 (1.15–19.11)	.03
Dog ownership at age 4 y	3.40 (1.08–10.71)	.04

Abbreviations: CI, confidence interval; OR, odds ratio.

* Factors entered into each regression model were those showing trends for significance in univariate analysis ($P < .2$). For each phenotype, logistic regression models used the outcomes of wheeze/never wheeze to identify independently significant factors. Factors demonstrating statistical significance at the final step of each regression model are included in this table.

† For never atopic, factors entered into the regression model were social class I to III at birth; exclusive breastfeeding in the first 3 months of life; parental smoking at birth and 1, 2, and 4 years of age; recurrent chest infections at 1 and 2 years of age; low birth weight; maternal/sibling asthma; sibling food allergy; eczema/nasal symptoms/food allergy at 1 year of age; nasal symptoms at 2 years of age; rhinitis at 4 years of age; and male sex.

‡ For early childhood atopic, factors entered into the regression model were exclusive breastfeeding in the first 3 months of life and cat ownership at birth.

§ For chronic childhood atopic, factors entered into the regression model were male sex, recurrent chest infections at 2 years of age, parental smoking at 1 and 4 years of age, family history of asthma, family history of eczema, eczema at 1, 2, and 4 years of age, food allergy at 2 years of age, and rhinitis at 4 years of age.

¶ For delayed childhood atopic, factors entered into the regression model were recurrent chest infections at 2 years of age, dog ownership at birth and at 4 years of age, maternal asthma, maternal rhinitis, and family history of urticaria.

sensitization or exposure on airway epithelium might provide one cause for wheezing in the setting of chronic atopy. In a similar manner, Green et al²⁴ reported an apparent synergism of high allergen and viral exposure in the setting of atopy that resulted in increased asthma hospitalization.

Early childhood atopics seem to be a small subgroup with weak, quickly waning early-life atopic sensitization lacking strong genetic predisposition. The only effect of note for wheezing in such children was a protective effect of breastfeeding. Breastfeeding did not assume importance for wheeze

onset in atopic phenotypes, which may partly explain the conflicting literature^{25,26} on the importance of infant feeding in asthma development. Thus, studies investigating this relationship in early childhood might have reflected early childhood atopy-related wheeze and reported a protective effect,²⁵ whereas those with longer follow-up to later childhood or early adult life did not show such protection.²⁶

The other form of atopic sensitization defined was the delayed childhood atopic with a strong heritable tendency to wheezing. Dog exposure in early childhood was also associated with increased wheezing in this small specific group of atopic children. This furthers the debate over whether animal exposures in childhood increase or decrease the risk of wheezing illness. Another study²⁷ has suggested protective effects of earlier dog exposure against wheezing but not atopy. The timing of such animal exposures in childhood may prove crucial regarding their positive or negative effect on wheezing. Furthermore, the mechanisms behind such relationships remain unclear; for example, we previously showed⁸ dog sensitization to be less prevalent than house dust mite, grass, and cat sensitization at 10 years of age among delayed childhood atopics. In this context, it is also important to note that despite only showing late-onset sensitization, delayed childhood atopics showed constant asthma prevalence throughout childhood that changed little despite the onset of atopic sensitization. This implies that, in some situations, although atopy is associated with the genesis of wheeze or asthma, this is not necessarily in a causal manner.

An important finding of this study is the demonstration of substantial nonatopic wheeze and asthma that remained a constant presence, with not insignificant treatment needs. Maternal asthma proved to be an important factor for wheeze onset in this phenotype. This is in line with past findings²⁸ from the Tucson cohort linking maternal asthma with that in children not sensitized to the major local aeroallergen (*Alternaria*). Environmental factors, including upper and lower respiratory tract infections in infancy and tobacco smoke exposure in infancy, all held significance for wheezing in never atopics. A role for respiratory pathogens in nonatopic wheeze has been proposed by Von Mutius et al.²⁹ Thus, environment seems highly important for never atopic wheeze, perhaps even more so than for chronic atopic wheeze. Indeed, recently, Eduard et al³⁰ found that certain environmental exposures increased the risk of nonatopic asthma but decreased that of atopic asthma in a farming environment.

It seems likely that multiple triggers affect the airway to mediate the development of asthmatic disease in predisposed individuals. Inherited susceptibility to disease seems fundamental to atopic and nonatopic wheeze. The search for candidate genes for asthma has already highlighted a polygenic nature. In turn, it is probable that a variety of genes exert importance for wheeze onset in our different atopic phenotypes. From the present findings we propose a differential model of childhood wheeze development varying by atopic status. In chronic atopic sensitization, a strong genetically mediated tendency interacts with several environmental triggers, prime among which are

aeroallergen exposures, in a synergistic manner to propel the disease process and lead to wheezing. With more variable or absent atopic sensitization, environmental factors, such as respiratory pathogens, tobacco smoke exposure, pet exposure, and infant feeding method, assume clearer importance for wheezing in conjunction with genetic predisposition to disease.

CONCLUSIONS

Not all childhood wheezing is atopic, although that associated with chronic sensitization may be most clinically relevant in terms of asthma. One might speculate that persistent allergen-mediated atopic inflammation is more potent than that associated with other environmental exposures, hence the higher indices of wheezing morbidity, BHR, and rising asthma prevalence in childhood found in chronic childhood atopics. However, it may be more accurate to regard such allergen sensitization as one of many factors affecting the airway in the development of childhood wheezing disorders. Rather than being the primary cause of asthma in most children, we propose that atopy acts in conjunction with a probable inherited or virally induced BHR to increase the likelihood of persistent clinical asthma in childhood. Future researchers will need to focus further on such intricate relationships.

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