Original Article

Optimum Predictors of Childhood Asthma: Persistent Wheeze or the Asthma Predictive Index?

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What is already known about this topic? The University of Cincinnati Asthma Predictive Index and persistent wheezing phenotypes are associated with physician-diagnosed childhood asthma.

What does this article add to our knowledge? A positive University of Cincinnati Asthma Predictive Index and a persistent wheezing at age 3 were associated with a 13 and 10 times higher odds, respectively, of objectively confirmed asthma in school-age children.

How does this study impact current management guidelines? The University of Cincinnati Asthma Predictive Index predicts objectively confirmed asthma at age 7 and could be used to identify children likely to benefit from early environmental intervention(s) or the use of daily controller therapy.

BACKGROUND: The Asthma Predictive Index (API) and persistent wheezing phenotypes are associated with childhood asthma, but previous studies have not assessed their ability to predict objectively confirmed asthma.

OBJECTIVE: To determine whether the University of Cincinnati API Index (ucAPI) and/or persistent wheezing at age 3 can accurately predict objectively confirmed asthma at age 7.

METHODS: Data from the Cincinnati Childhood Allergy and Air Pollution Study, a high-risk prospective birth cohort, was used. Asthma was defined as parent-reported or physician-diagnosed asthma objectively confirmed by a change in FEV_1 of ≥12% after bronchodilator or a positive methacholine challenge ($PC_{20} \leq 4$ mg/mL); or as prior treatment with daily asthma controller medication(s). Multivariate logistic regression was used to investigate the relationship between confirmed asthma at age 7 and a positive ucAPI (adapted and modified from prior published API definitions) and persistent wheezing at age 3.

RESULTS: At age 7, 103 of 589 children (17.5%) satisfied the criteria for asthma. Confirmed asthma at age 7 was significantly associated with a positive ucAPI (adjusted odds ratio [aOR] 13.3 [95% CI, 7.0-25.2]; $P < .01$) and the persistent wheezing phenotype (aOR 9.8 [95% CI, 4.9-19.5]; $P < .01$) at age 3. Allergic persistent wheezing was associated with a significantly higher risk of asthma (aOR 10.4 [95% CI, 4.1-26.0]; $P < .01$) than nonallergic persistent wheezing (aOR 5.4 [95% CI, 2.04-14.06]; $P < .01$).

CONCLUSION: Both a positive ucAPI and persistent wheeze at age 3 were associated with objectively confirmed asthma at age 7; however, the highest risk was associated with ucAPI. These results demonstrate the ucAPI as a clinically useful tool for predicting future asthma in school-age children. **(J Allergy Clin Immunol Pract 2014;2:709-15)**

Key words: *Asthma; Asthma Predictive Index; Wheezing phenotypes; Persistent wheezing; Atopic persistent wheezing; Nonatopic persistent wheezing; Asthma prediction; Childhood asthma*

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Abbreviations used
aOR- Adjusted odds ratio
API- Asthma Predictive Index
ECAT- Elemental carbon attributable to traffic
ETS- Environmental tobacco smoke
LR- Likelihood ratio
mAPI- Modified Asthma Predictive Index
MCCT- Methacholine Challenge Test
NPV- Negative predictive value
OR- Odds ratio
PPV- Positive predictive value
SN- Sensitivity
SP- Specificity
SPT- Skin prick test
ucAPI- University of Cincinnati Asthma Predictive Index

Asthma is one of the most common chronic diseases in children, the natural history of which is not completely understood.[1,2] Asthma is difficult to diagnose in early childhood because the performance of spirometry maneuvers is not feasible before age 5.[3] A presumptive diagnosis of asthma before school age is based on nonspecific physical findings and clinical features, such as recurrent wheezing or cough. Determining which preschool children are at greatest risk for developing objectively confirmed asthma at school age remains a challenge. Various predictive models and wheezing phenotypes to predict childhood asthma have been identified.

The Asthma Predictive Index (API) is a validated clinical model for childhood asthma originally developed with the Tucson Children's Respiratory Study.[3-7] In this study, parents were asked whether their child had chest wheezing or whistling and to indicate on a Likert scale (1 to 5, from "very rarely" to "on most days") how frequently the child had wheezed; early frequent "wheezers" were defined as children with a score $\geq$3.[4] This API used major (ie, parental asthma and eczema) and minor clinical criteria (ie, allergic rhinitis, wheezing apart from colds and peripheral eosinophilia) to predict asthma later in childhood (ie, age 6 and older) in age 3 early frequent "wheezers."[4] A positive API at age 3 had a sensitivity (SN) of 15% to 28%, specificity (SP) of 96% to 97%, positive predictive value (PPV) of 48% to 52%, and negative predictive value (NPV) of 84% to 92% for predicting physician-diagnosed asthma at age 6 or older.[3] A similar index, the modified API (mAPI) was developed by Guilbert et al[8] in the Prevention of Asthma in Kids (PEAK) trial in 2004. The mAPI uses criteria similar to that of the API to predict childhood asthma, albeit early frequent wheezing was defined as $\geq$4 wheezing episodes per year during the first 3 years. The major criteria of the mAPI added a third criterion of allergic sensitization to $\geq$1 aeroallergen and replaced physician-diagnosed allergic rhinitis in the minor criteria of the original API with allergic sensitization to milk, egg, or peanuts. A positive mAPI at age 3 has an SN of 17% to 19% and SP of 99% to 100% for asthma between ages 6 and 8.[8] Previous studies did not evaluate the predictive value of the API for objectively confirmed asthma by spirometry or methacholine testing.[3-8]

Early wheezing phenotypes also have been studied as a means to predict childhood asthma.[9] In the Tucson prospective birth cohort, Martinez et al[2] showed that children with persistent wheezing at 3 years of age were significantly more likely to have a lower maximal expiratory flow at functional residual capacity at age 6 when compared with those who never wheezed. As with the API, the relationship between early persistent wheezing and objectively diagnosed childhood asthma has not been prospectively evaluated. The aim of this study was to determine if a new asthma predictive index, derived and adapted from the original API and mAPI (herein defined as the "University of Cincinnati API or ucAPI) and persistent wheezing phenotypes determined at age 3 predict the age 7 asthma outcome, objectively confirmed by lung physiologic testing.

METHODS

Study population

Data from the Cincinnati Childhood Allergy and Air Pollution Study, a prospective birth cohort, was used. The hypothesis of the Cincinnati Childhood Allergy and Air Pollution Study was that early life exposure to traffic pollutants increases the risk for allergic disorders during childhood. Recruitment, exposure assessments, and cohort characteristics are described elsewhere.[10-12] Briefly, all women who gave birth between October 2001 and July 2003 in the greater Cincinnati—northern Kentucky area were identified from birth certificate records. Parents who lived either within 400 m (high-traffic pollution exposure cohort) or more than 1500 m (low-traffic pollution exposure cohort) from a major road were screened for allergy symptoms.[12] Those parents who were likely to be atopic based on a report of symptoms of rhinitis had skin prick tests (SPT) to 15 common aeroallergens.[10] Children were eligible for enrollment if they had at least 1 parent who was SPT positive (defined as a wheal $\geq$3 mm larger than the negative control) to at least 1 of the 15 aeroallergens.[10] Parents signed a written informed consent, and the study protocol was approved by the University of Cincinnati Institutional Review Board.

Clinical evaluation

Children underwent clinical evaluations at ages 1, 2, 3, 4, and 7, which included the following: a physical examination; SPT to 15 aeroallergens, cow's milk, and hen's egg; and administration of a modified International Study of Asthma and Allergies in Childhood questionnaire to the parents. Information regarding the child's medical history, exposures to environmental tobacco smoke, pets, breast feeding, day care attendance, and parent's atopic history was collected. Methods for estimating average daily elemental carbon attributable to traffic (ECAT) exposure were previously published.[13,14]

ucAPI and wheezing phenotypes

Children were classified as having an increased risk of future asthma based on a mAPI developed by Castro-Rodriguez et al[4] and Guilbert et al[8] referred to as the "University of Cincinnati API" (ucAPI). A positive ucAPI at age 3 in our study was defined as having 2 or more episodes of wheezing in the previous 12 months at the age 3 clinic visit, and 1 of the 3 major criteria (parental asthma, allergic sensitization to 1 or more aeroallergens, or a history of eczema) or 2 of the 3 minor criteria (wheezing without a cold, physician-diagnosed allergic rhinitis, or allergic sensitization to milk or egg).[15] Persistent wheezing at age 3 was defined as 2 or more episodes of wheezing in the previous 12 months at both the 2- and 3-year clinic visits, or if the parent reported a history of physician-diagnosed asthma in the past 12 months at the age 3 clinic visit.[15] Allergic persistent wheezing was defined as having persistent wheezing (as defined above) with 1 or more SPTs results positive to 15 of the common

aeroallergens in the area. Those children who did not meet these criteria were grouped into the nonallergic persistent wheezing category. The similarities and differences among criteria for the original API, mAPI, and the ucAPI are listed in Table E1 (in this article's Online Repository at www.jaci-inpractice.org).

Asthma outcome

At age 7, all the children completed baseline spirometry and forced exhaled nitric oxide testing (NIOX Flex; Aerocrine Inc, New Providence, NJ) performed by trained technicians according to the American Thoracic Society recommended guidelines.[16,17] Asthma symptoms included parental report of the child having at least 1 of the following: a tight or clogged chest or throat, difficulty breathing or wheezing after exercise, wheezing or whistling in the chest in the previous 12 months, or asthma diagnosed by the child's physician in the past 12 months at the 7-year visit.[16] Those children with these asthma symptoms at age 7, forced exhaled nitric oxide higher than 10 ppb, or a baseline predicted FEV_1 less than 90% and/or an FEV_1 ratio to forced vital capacity less than the lower limit of normal, were further assessed for a change in FEV_1 after receiving levalbuterol. Those with <12% increase in FEV_1 after bronchodilation underwent a methacholine challenge test (MCCT) at a follow-up visit.[16] A modified 4-dose American Thoracic Society methacholine challenge protocol was used with sequential methacholine concentrations of 0.0625, 0.25, 1, and 4 mg/mL.[18] A positive MCCT was defined as a ≥20% decrease in baseline FEV_1 at a cumulative inhaled methacholine concentration of ≤4 mg/mL. Asthma at age 7 hence was defined as either (1) the presence of asthma symptoms (as described above) in the previous 12 months plus either an increase in FEV_1 of ≥12% after bronchodilator or a positive MCCT ($PC_{20} \leq 4$ mg/mL) at the 7-year clinic visit, or (2) regular use of controller medications (ie, inhaled corticosteroid and/or montelukast for the treatment of asthma) in the previous 12 months.

Statistical analysis

Univariate analyses were conducted to assess the relationship between asthma at age 7 and a positive ucAPI, persistent wheezing, and atopic and nonatopic persistent wheezing at age 3 as well as other potential covariates. All dependent and independent variables were dichotomized before analysis based on prior studies of this cohort.[10,19,20] Low socioeconomic status was defined as a household income of <$20,000 per year. Parental report of asthma was defined as either biologic parent ever having been diagnosed with asthma. Exposure to environmental tobacco smoke was defined as having at least 1 smoker in the home from the child's birth to 3 years old. The mean average daily exposure to ECAT was highly skewed for the study population and subsequently was dichotomized by using the 75th percentile (with an average daily exposure to ECAT ≥ 0.41 μg/m^3 [≥75th percentile], which corresponds to a "high" ECAT level).[15]

Pet ownership was defined as the child living with a cat or dog from birth to 3 of age. Breast feeding was defined as ≥4 months of breast feeding from the child's birth to 3 of age.[19] Aeroallergen and food sensitization was defined as the child having at least 1 of 15 aeroallergens positive or a positive test result to either hen's egg or cow's milk at ages 1 or 3 by SPT. Eczema was defined as physician-diagnosed eczema based on physical examination findings consistent with probable or definitive eczema of the child from birth to 3 of age.[20] All covariates with $P < .05$ in the univariate analysis were included in the multivariate logistic regression model. Separate multivariate models were developed for the ucAPI and all 3 persistent wheezing phenotypes. The terms that remain in each final multivariate model were chosen based on backward elimination with a $P < .10$. Statistical analyses were performed by using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Of the 762 children enrolled in the Cincinnati Childhood Allergy and Air Pollution Study cohort, 653 (85.7%) completed the 3-year clinic visit and 617 (81%) completed the 7-year clinic visit. Of these, 589 children had complete data for the asthma outcome variable at age 7 and were included in this analysis. The basic demographics, environmental exposures, and disease status of the subjects included in this analysis are summarized in Table I. The majority were boys (54.8%), 21.2% were African American, and 16.7% were from a household with income <$20,000 per year. At least 1 person smoked in 27.0% of households. Most children were breastfed for at least 4 months (53.1%), attended day care (52.1%), and had at least 1 parent with asthma (40.8%). More children were sensitized to at least 1 aeroallergen at age 3 versus age 1 (41.5% vs 19.0%). Sensitization to both cow's milk and egg white declined from age 1 to age 3. Of the 589 children, 103 (17.5%) met our asthma definition at age 7 (95 based on spirometry or methacholine testing; 8 based on asthma medication use in the previous 12 months). At age 3, 68 children (12.3%) had a positive ucAPI result and 54 (10.6%) had persistent wheezing.

The univariate analysis for associations between asthma at age 7 and a positive ucAPI and persistent wheezing at age 3 are summarized in Table II. The following covariates were significantly associated with an increased risk of asthma at age 7: African American ethnicity, household income of <$20,000 per year, exposure to environmental tobacco smoke, parental asthma, allergic sensitization to aeroallergens at ages 1 and 3, allergic sensitization to egg white at ages 1 and 3, history of eczema, day care attendance, and high exposure to ECAT from birth to 3 of age. Whereas, breastfeeding and dog ownership during the first 3 years of life were associated with a reduced likelihood of asthma at age 7. A positive ucAPI and persistent wheezing at age 3 were both significant predictors of objectively confirmed asthma at age 7 (unadjusted odds ratio [OR] 12.7 and 10.6, respectively; $P < .01$). Furthermore, atopic persistent wheezing at age 3 was associated with a more than 3-fold higher likelihood of asthma at age 7 relative to the nonatopic persistent wheezing phenotype (unadjusted OR 14.6 vs 4.3, respectively; $P < .05$).

In this birth cohort, a positive ucAPI at age 3 had an SN of 44%, SP of 94%, PPV of 60.3%, and NPV of 89.3% for confirmed asthma at age 7 (Table III). A positive API had the highest SN (44%) for asthma compared with the wheezing phenotypes (persistent wheezing, atopic and nonatopic persistent wheezing [SN range, 12.2%-35.9%]). The SP for all 4 phenotypes ranged from 94% to 98%. The positive likelihood ratio (LR^+) for the ucAPI was 7.5, and the negative LR (LR^-) was 0.6 for asthma at age 7. Among the 3 persistent wheezing phenotypes, atopic persistent wheezing had the highest LR^+ of 11.7. The test performance characteristics of the ucAPI defined by using ≥4 wheezing episodes (as used in the mAPI) in the previous 12 months instead of ≥2 wheezing episodes is shown

TABLE I. Characteristics of the cincinnati childhood asthma and air pollution study COHORT

Characteristics of the cohort*	
Total no. children in the cohort at age 7 y, no. (%)	589 (77% of those enrolled at age 1 y; 95% of those enrolled at age 7 y)
Boys, no. (%)	323 (54.8)
African American, no. (%)	124 (21.2)
Household income <$20,000, no. (%)	95 (16.7)
Breast fed for ≥4 mo, no. (%)	312 (53.1)
Exposure to ETS, no. (%)	159 (27.0)
Parental asthma, no. (%)	240 (40.8)
Sensitization to ≥1 aeroallergen, no. (%)	
At age 1	105 (19.0)
At age 3	231 (41.5)
Sensitization to milk, no. (%)	
At age 1	21 (3.8)
At age 3	8 (1.4)
Sensitization to egg, no. (%)	
At age 1	67 (12.2)
At age 3	30 (5.4)
Eczema, no. (%)†	126 (21.6)
Dog ownership, no. (%)‡	244 (41.4)
Cat ownership, no. (%)‡	164 (27.8)
Day care attendance, no. (%)‡	307 (52.1)
Mean (SD) average daily ECAT exposure (μg/m^3)	
At age 3	0.37 ± 0.12
From birth to 3	0.38 ± 0.28
ECAT exposure ≥75th percentile, no. (%)	148 (25.1)
Asthma at age 7, no. (%)	103 (17.5)
Positive ucAPI at 3, no. (%)	68 (12.3)
Persistent wheezing at 3, no. (%)	54 (10.6)
Children with a positive API and persistent wheezing at 3, no. (%)	45 (9.0)

ETS, environmental tobacco smoke.
*Total n = 589 but may differ for each category due to missing data.
†Defined as physician-reported eczema at any age by or before 3.
‡Between birth and age 3.

TABLE II. Univariate associations between asthma at age 7 and the ucAPI, persistent wheezing, and other covariates

	Asthma at 7 y, no. (%)		
Covariate	Yes (n = 103)	No (n = 486)	*P* value
Boys	63 (61.2)	260 (53.5)	.16
African American	33 (32.0)	92 (18.9)	<.01
Household income <$20,000	32 (32.0)	63 (13.4)	<.01
Breast fed for ≥4 mo	42 (40.8)	270 (55.7)	<.01
Exposure to ETS	37 (35.9)	122 (25.2)	.03
Parental asthma	58 (56.3)	182 (37.5)	<.01
Sensitization to ≥1 aeroallergen at age			
1	29 (30.2)	76 (16.7)	<.01
3	52 (56.5)	179 (38.5)	<.01
Sensitization to milk at age			
1	6 (6.32)	15 (3.3)	.14
3	2 (2.17)	6 (1.3)	.39
Sensitization to egg at age			
1	21 (22.1)	46 (10.1)	<.01
3	10 (11.0)	20 (4.3)	.02
Eczema*	34 (33.7)	92 (19.1)	<.01
Dog ownership*	32 (31.1)	212 (43.6)	.02
Cat ownership*	23 (22.3)	141 (29.0)	.17
Day care attendance*	64 (62.1)	243 (50.0)	.025
ECAT exposure ≥75th percentile			
At age 3	32 (33.0)	100 (20.6)	.05
From birth to age 3	34 (33.0)	114 (23.5)	.04
Positive ucAPI at age 3	41 (44.1)	27 (5.86)	<.01
Persistent wheezing at age 3	33 (35.9)	21 (5.02)	<.01
Atopic persistent wheezing at age 3	20 (22.2)	8 (1.9)	<.01
Nonatopic persistent wheezing at age 3	11 (12.2)	13 (3.1)	<.01

ETS, Environmental tobacco smoke.
*Between birth and age 3.

in Table E2 (in this article's Online Repository at www.jaci-inpractice.org). By using ≥4 wheezing episodes, the SN of the ucAPI was 32%, SP was 96%, PPV was 61%, and NPV was 88% for predicting asthma at age 7. The LR^+ for the ucAPI was 7.8, and the LR^- was 0.7 for asthma at age 7. The results of the final multivariate analysis for the association between asthma at age 7 and a positive ucAPI and all of the persistent wheezing phenotypes at age 3 are shown in Table IV. A positive ucAPI at age 3 was associated with a significant risk for objectively confirmed asthma at age 7 (adjusted OR [aOR] 13.3 [95% CI, 7-25.2]; $P < .01$), as was persistent wheezing (aOR 9.8 [95% CI, 4.93-19.52]; $P < .01$). The atopic persistent wheezing phenotype at age 3 was associated with a higher risk of asthma (aOR 10.4 [95% CI, 4.12-26.01]; $P < .01$) than the nonatopic persistent wheezing phenotype (aOR 5.4 [95% CI, 2.04-14.06]; $P < .01$). A household income of <$20,000 per year, sensitization to egg white at age 1, and day care attendance were associated with a higher risk of asthma in all 4 multivariate models. With the ucAPI model, dog ownership was associated with a significantly lower risk for asthma at age 7. The relationship between asthma at age 7 and a positive ucAPI or the persistent wheezing phenotypes was not significantly affected by exposure to high levels of traffic-related air pollution as measured by ECAT from the child's birth to 3 of age in any of the multivariate models. As stated, the original published studies of the API used wheezing severity based on a 1 to 5 scale and mAPI used the ≥4 wheeze per year criterion. Because our study used ≥2 wheezing episodes, we also analyzed the ucAPI with the ≥4 wheeze criterion as with the mAPI; the results of the multivariate analysis remained essentially unchanged (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). Similarly, the multivariate models for the predictors of asthma at age 7 remained unchanged after removal of 8 children who were identified as having asthma based on physician-prescribed daily asthma controller medication, for whom the medication could not be withheld to perform lung physiologic tests at the 7-year clinic visit (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

TABLE III. Clinical phenotype-based SNs, SPs, PPVs, and NPVs for asthma at age 7

Test (no. children with asthma)*	% SN (95% CI)	% SP (95% CI)	% PPV (95% CI)	% NPV (95% CI)	LR^+	LR^-
ucAPI (41)	44 (33.8-54.8)	94.1 (91.6-96.1)	60.3 (47.7-72)	89.3 (86.2-92)	7.5	0.6
Persistent wheezing (33)	35.9 (26.1-46.5)	95 (92.4-96.9)	61.1 (46.9-74.1)	87.1 (83.6-90.0)	7.2	0.7
Atopic persistent wheezing (20)†	22.2 (14.1-32.2)	98.1 (96.3-99.2)	71.4 (51.3-86.8)	85.4 (81.9-88.5)	11.7	0.8
Nonatopic persistent wheezing (11)†	12.2 (6.3-20.8)	96.9 (94.7-98.3)	45.8 (25.6-67.2)	83.7 (80.1-86.9)	3.9	0.9

*At age 3.
†Missing data on results for SPTs for 2 children.

TABLE IV. The aORs for associations of positive ucAPI, persistent wheezing, atopic persistent wheezing, and nonatopic persistent wheezing at age 3 with asthma outcome at age 7 in separate LR models*

	aOR (95% CI) for asthma at 7 y							
Exposure or covariate	ucAPI model	*P*†	Persistent wheezing model	*P*†	Atopic persistent wheezing model	*P*†	Nonatopic persistent wheezing model	*P*†
Positive ucAPI at age 3	13.27 (7.0-25.15)	<.01	‡		‡		‡	
Persistent wheezing at age 3	‡		9.81 (4.93-19.52)	.01	‡		‡	
Atopic persistent wheezing at age 3	‡		‡		10.35 (4.12-26.01)	<.01	‡	
Nonatopic persistent wheezing at age 3	‡		‡		‡		5.36 (2.04-14.06)	<.01
Household income <$20,000	3.64 (1.94-6.82)	<.01	3.61 (1.91-6.81)	<.01	3.62 (1.95-6.75)	<.01	3.61 (1.96-6.68)	<.01
Parental asthma	§		1.87 (1.08-3.23)	.026	2.03 (1.19-3.47)	<.01	2.12 (1.26-3.56)	<.01
Sensitization to egg at age 1	2.82 (1.43-5.57)	<.01	2.92 (1.45-5.90)	<.01	2.61 (1.32-5.16)	.006	2.84 (1.46-5.54)	<.01
Eczema	§		2.06 (1.14-3.74)	.017	2.02 (1.12-3.64)	.02	2.35 (1.34-4.14)	<.01
Day care attendance	1.77 (1.02-3.08)	.042	1.59 (0.91-2.78)	.103	1.81 (1.05-3.11)	.03	1.73 (1.01-2.95)	.04
Dog ownership	0.55 (0.31-0.99)	.045	||		||		||	
ECAT exposure ≥75th percentile from birth to age 3	||		||		||		||	

*The initial multivariate models included all covariates (except when denoted by ‡ or §), including sex; race; exposure to environmental tobacco smoke; breast feeding; sensitization to aeroallergens, egg, and milk at 1 and 3 y of age; cat ownership; and ECAT exposure ≥75th percentile between birth to 3 y of age but were not significant at an alpha of 10%.
†Significant at $P \leq .10$.
‡Not included in the model.
§Not included in the model because it was one of the defining criteria for a positive ucAPI.
||Not significant at $P \leq .10$.

DISCUSSION

This is the first study to show that a positive API (ie, the ucAPI) and persistent wheezing at age 3 were significantly associated with an increased risk of objectively confirmed asthma at age 7. The ucAPI had a higher SN for predicting asthma at age 7 in this study population, which was enriched with individuals from families with atopy, compared with that reported in the population-based Tucson birth cohort study (44% vs 22%, respectively).[5] In addition, this is the first study, to our knowledge, to show that, as early as age 3, children with atopic persistent wheezing had a 2 times greater likelihood of having confirmed asthma at school age than those with nonatopic persistent wheezing. Results from the longitudinal population-based Tucson study showed that a positive API at age 3 is a reliable predictor of physician-reported asthma in children ages 6 to 8.[3,4] However, this is the first to confirm these results in a high-risk birth cohort of children in which the asthma outcome at age 7 was objectively confirmed with FEV_1 reversibility of ≥12% after bronchodilator or a positive MCCT ($PC_{20} \leq 4$ mg/mL). The rigorous asthma definition used in this study uniquely contrasts with prior published studies that evaluated the API or mAPI. In the latter studies, unlike here, the asthma outcomes were defined exclusively by physician or parental reporting of asthma-type symptoms or the use of any asthma medication(s), without additional objective confirmation by physiologic testing.[5-7]

All 3 persistent wheezing phenotypes determined at age 3 were associated with a 5- to 10-fold higher likelihood of asthma, but a positive ucAPI at age 3 was the strongest predictor of objectively confirmed asthma at age 7 (aOR 13.3) in our study. The SN of a positive ucAPI result at age 3 for predicting asthma at age 7 in our study was greater than that of the API in the Tucson cohort (SN, 22%), or that of the mAPI reported in the high-risk atopic Childhood Origins of Asthma birth cohort (SN, 17%-19%).[4,7] However, when comparing the ucAPI with the Prevention and Incidence of Asthma and Mite Allergy risk score, the later yielded a higher SN of 54.5%, and a PPV of 75%, albeit a lower SP, of 78.9%, and an NPV of 60% for parent-reported asthma at age 5 to 6 in a Columbian pediatric population.[6] The SN of a test is

unaffected by the prevalence of disease in the study population.[21] Hence, the disparity in the SN between the above-mentioned cohorts could be attributed to the aforementioned differences in the asthma outcome definition used.[22] In addition, the inherent differences in the risk factors for childhood asthma in this cohort, which is selected for based on parental atopic status, also could explain such differences. Of note, the SN of the ucAPI was reduced from 44% to 32% when 4 or more episodes of wheezing (instead of ≥2 annually) were used to define the ucAPI (Table E2), which suggests that a higher number of reported wheezing episodes is not an essential element of this API criterion.[4,7]

LRs best reflect the diagnostic accuracy of a test. The LR^+ of the stringent API in the Tucson study ranged from 3.0 to 7.4 for asthma between ages 6 to 8, whereas the LR^- ranged from 0.5 to 0.8.[23] The LR^+ of 7.5 and LR^- of 0.6 reported for the ucAPI are comparable with that of the API in the Tucson study and suggest that a positive ucAPI could have a significant effect on the posttest probability. The LRs for the mAPI reported by Chang et al[7] are higher (LR^+ 21-55 and LR^- 0.83-0.84 for asthma between ages 6 and 8). The explanation for the large difference in LRs observed between the latter studies is uncertain but could be partially attributable to differences in the asthma outcome definitions used. These observations suggest that early identification of a child with a positive ucAPI may guide implementation of timely interventions (eg, inhaled corticosteroids, allergen immunotherapy) that could potentially modify their risk for development of allergic asthma.

Results of epidemiologic studies have shown that atopic and nonatopic persistent wheezing phenotypes have varied responses to asthma treatment and long-term outcomes in older children and adolescents; however, very few studies have compared the risk factors for asthma between these 2 phenotypes in preschool-age children.[9,24,25] This is the first study, to our knowledge, to show that, as early as age 3, the atopic persistent wheezing phenotype was associated with a 2 times greater odds of objectively confirmed asthma at age 7 than nonatopic persistent wheezing. For both phenotypes, household income of <$20,000 per year, sensitization to egg white at age 1, eczema, day care attendance, and parental asthma were all comparable risk factors for confirmed asthma at age 7. Although the SP of all 3 persistent wheezing phenotypes to predict asthma at age 7 was high, which suggests that they can aid in the diagnosis of childhood asthma, the low SN may preclude them from being used as a clinically effective screening tool.

In addition, a household income of <$20,000 per year, sensitization to egg white at age 1, and day care attendance were significant risk factors for objectively confirmed asthma at age 7 in all 4 multivariate models in our study. These factors have been reported in other epidemiologic studies and support our findings.[26-31] Dog ownership during the first 3 years of the child's life was protective of asthma at age 7 in the ucAPI multivariate model. A similar protective effect of early dog ownership on frequent wheezing and parent-reported asthma at school age has been reported in other longitudinal birth cohort studies.[32,33] Previous studies indicate that early exposure to traffic-related air pollution is associated with incident asthma after age 7 in an atopic population.[34] In this study, the univariate analysis showed that exposure to high levels of average daily ECAT from birth to 3 of age was a significant risk factor for objectively confirmed asthma at age 7, but this association was not seen in the multivariate analyses.

Limitations of this study are that findings from this high-risk population may not be applicable uniformly to all populations. There also is a potential for recall bias because the persistent wheezing episodes were reported by questionnaire. Our asthma definition did include a small percentage (<8%) of children whose asthma diagnosis was based on receiving a daily asthma controller medication in the previous 12 months at the 7-year clinic visit, which precluded physiologic lung testing. However, the results of the multivariate analysis do not change significantly with removal of these 8 children from the analysis (Table E3). In conclusion, the results of this study demonstrate that the ucAPI and the persistent wheezing phenotype at age 3 can be used to predict the risk of objectively confirmed asthma at age 7. A positive ucAPI was the best overall predictor for asthma at age 7 compared with the other 3 persistent wheezing phenotypes.

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TABLE E1. Major and minor criteria as well as frequent wheezing definitions for the original API, mAPI, and ucAPI

	Original API*	mAPI†	ucAPI
Frequent wheezing	Wheezing score ≥3 on 5 point scale‡	≥4 episodes in a year during the first 3 y	≥2 episodes per year in between ages 2 and 3 y
Parental history of asthma	Major	Major	Major
Physician diagnosed atopic dermatitis	Major	Major	Major
Allergic sensitization to ≥1 aeroallergen	Not used	Major	Major
Allergic sensitization to foods	Not used	Minor (milk, egg or peanuts)	Minor (milk or eggs)
Wheezing unrelated to colds	Minor	Minor	Minor
Blood eosinophils	Minor	Minor	Not used
Physician diagnosed allergic rhinitis	Minor	Not used	Minor

*From Ref 4.
†From Ref 8.
‡The original API defined parental report of "frequent wheezing" by a score ≥3 on a 1 to 5 Likert scale, which ranged from "very rarely" to "on most days" (from Ref 4).

TABLE E2. The ucAPI defined with ≥4 wheezing episodes per year: SN, SP, PPV, and NPV for asthma at age 7

Test (no. with asthma)*	% SN (95% CI)	% SP (95% CI)	% PPV (95% CI)	% NPV (95% CI)	LR^+	LR^-
ucAPI (30)†	32.3 (22.9-42.8)	95.9 (93.6-97.5)	61.2 (46.2-74.8)	87.5 (84.3-90.3)	7.8	0.7

*At age 3.
†ucAPI was defined as ≥4 wheezing episodes in the prior 12 mo (instead of ≥2 wheezing episodes).

TABLE E3. The aORs for associations of positive ucAPI (by using a criterion of ≥4 wheezing episodes per year),* persistent wheezing, atopic persistent wheezing, and nonatopic persistent wheezing at age 3 with asthma outcome at age 7 in separate LR models†

	aOR (95% CI) for asthma at age 7 y							
Exposure or covariate	ucAPI model	*P*‡	Persistent wheezing model	*P*‡	Atopic persistent wheezing model	*P*‡	Nonatopic persistent wheezing model	*P*‡
Positive ucAPI at age 3	14.1 (6.93-28.57)	<.01	§		§		§	
Persistent wheezing at age 3	§		9.81 (4.93-19.52)	<.01	§		§	
Atopic persistent wheezing at age 3	§		§		10.35 (4.12-26.01)	<.01	§	
Nonatopic persistent wheezing at age 3	§		§		§		5.36 (2.04-14.06)	<.01
Household income <$20,000	3.81 (2.06-7.05)	<.01	3.61 (1.91-6.81)	<.01	3.62 (1.95-6.75)	<.01	3.61 (1.96-6.68)	<.01
Parental asthma	||		1.87 (1.08-3.23)	.026	2.03 (1.19-3.47)	<.01	2.12 (1.26-3.56)	<.01
Sensitization to egg at age 1	2.92 (1.48-5.74)	<.01	2.92 (1.45-5.90)	<.01	2.61 (1.32-5.16)	.006	2.84 (1.46-5.54)	<.01
Eczema	||		2.06 (1.14-3.74)	.017	2.02 (1.12-3.64)	.02	2.35 (1.34-4.14)	<.01
Day care attendance	1.57 (1.0-2.69)	0.1	1.59 (0.91-2.78)	.103	1.81 (1.05-3.11)	.03	1.73 (1.01-2.95)	.04
Dog ownership	0.58 (0.32-0.99)	.06	¶		¶		¶	
ECAT exposure ≥75th percentile from birth to age 3	¶		¶		¶		¶	

*ucAPI was defined as ≥4 wheezing episodes in the prior 12 mo (instead of ≥2 wheezing episodes).
†The initial multivariate models included all covariates (except where denoted by § or ||), including sex; race; exposure to environmental tobacco smoke; breast feeding, sensitization to aeroallergens, egg, and milk at 1 and 3 y of age; cat ownership; and ECAT exposure ≥75th percentile between birth and 3 y of age but were not significant at an alpha of 10%.
‡Significant at $P \leq .10$.
§Not included in the model.
||Not included in the model because it was one of the defining criteria for a positive ucAPI.
¶Not significant at $P \leq .10$.

TABLE E4. The aORs for associations of a positive ucAPI (defined by using ≥2 wheezing episodes per year), persistent wheezing, atopic persistent wheezing, and nonatopic persistent wheezing at age 3 with asthma outcome at age 7 (n = 95*) in separate LR models†

	aOR (95% CI) for asthma at 7 y (n = 95*)							
Exposure or covariate	**ucAPI model**	***P*‡**	**Persistent wheezing model**	***P*‡**	**Atopic persistent wheezing model**	***P*‡**	**Nonatopic persistent wheezing model**	***P*‡**
Positive ucAPI at age 3	11.63 (6.6-22.33)	<.01	§		§		§	
Persistent wheezing at age 3	§		8.52 (4.2-17.3)	<.01	§		§	
Atopic persistent wheezing at age 3	§		§		9.7 (3.77-24.94)	<.01	§	
Nonatopic persistent wheezing at age 3	§		§		§		4.72 (1.8-12.72)	<.01
Household income <$20,000	3.27 (1.71-6.25)	<.01	3.36 (1.75-6.67)	<.01	3.31 (1.74-6.31)	<.01	3.45 (1.83-6.50)	<.01
Parental asthma	||		1.96 (1.12-3.45)	.02	2.19 (1.26-3.80)	<.01	2.27 (1.32-3.88)	<.01
Sensitization to egg at age 1	2.63 (1.3-5.32)	<.01	2.61 (1.26-5.41)	.01	2.36 (1.16-4.79)	.02	2.48 (1.24-4.98)	.01
Eczema	||		2.11 (1.15-3.88)	.02	1.98 (1.10-3.64)	.02	2.35 (1.31-4.21)	<.01
Day care attendance	1.99 (1.12-3.52)	.042	1.83 (1.02-3.26)	.103	2.05 (1.16-3.60)	.03	1.95 (1.12-3.40)	.02
Dog ownership	0.6 (0.33-0.99)	.08	¶		¶		¶	
ECAT exposure ≥75th percentile from birth to age 3	¶		¶		¶		¶	

*N = 95 children with asthma after removal of 8 children who were included based on daily use of an asthma controller medication.
†The initial multivariate models included all covariates (except when denoted by § or ||), including sex; race; exposure to environmental tobacco smoke; breast feeding; sensitization to aeroallergens, egg, and milk, at 1 and 3 y of age; cat ownership; and ECAT exposure ≥75th percentile between birth and 3 y of age but were not significant at an alpha of 10%.
‡Significant at P ≤ .10.
§Not included in the model.
||Not included in the model because it was one of the defining criteria for a positive ucAPI.
¶Not significant at P ≤ .10.