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Optimum predictors of childhood asthma: persistent wheeze or the asthma predictive index?

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Abstract

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 (ucAPI) and/or persistent wheezing at age three can accurately predict objectively confirmed asthma at age seven.

Methods—Data from the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a high risk prospective birth cohort, was used. Asthma was defined as: parent-reported or physician-diagnosed asthma objectively confirmed by a change in FEV1 of ≥ 12% post bronchodilator or a positive methacholine challenge (PC_{20} ≤ 4 mg/ml); or prior treatment with daily asthma controller medication(s). Multivariate logistic regression was used to investigate the relationship between confirmed asthma at age seven and a positive ucAPI (adapted and modified from prior published API definitions) and persistent wheezing at age three.

Results—At age seven, 103 of 589 (17.5%) children satisfied the criteria for asthma. Confirmed asthma at age seven was significantly associated with a positive ucAPI (adjusted [a]OR=13.3; 95% CI [7.0–25.2]; p<0.01) and the persistent wheezing phenotype (aOR = 9.8 [4.9–19.5]; p

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<0.01) at age three. Allergic persistent wheezing was associated with a significantly higher risk of asthma (aOR = 10.4 [4.1–26.0]; p<0.01) than non-allergic persistent wheezing (aOR = 5.4 [2.04–14.06]; p <0.01).

Conclusions—Both a positive ucAPI and persistent wheeze at age 3 years were associated with objectively confirmed asthma at age seven; however the highest risk was associated with ucAPI. These results demonstrate that the ucAPI as a clinically useful tool for predicting future asthma in school-age children.

Keywords

Asthma; Asthma Predictive Index (API); wheezing phenotypes; persistent wheezing; atopic persistent wheezing; non-atopic persistent wheezing; asthma prediction; childhood asthma

Introduction

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

Early wheezing phenotypes have also been studied as a means to predict childhood asthma.[9] In the Tucson prospective birth cohort Martinez et al. showed that children with persistent wheezing at three years were significantly more likely to have lower VmaxFRC (maximal expiratory flow at functional residual capacity) at age six when compared to those who never wheezed.[2] 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 three 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 (CCAAPS), a prospective birth cohort, was used. The hypothesis of the CCAAPS 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 – July 2003 in the Greater Cincinnati/Northern Kentucky area were identified from birth certificate records. Parents living either within 400 m (high traffic pollution exposure cohort) or greater than 1,500 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 report of symptoms of rhinitis were skin prick tested (SPT) to 15 common aeroallergens.[10] Children were eligible for enrollment if they had at least one parent who was SPT positive (defined as a wheal ≥ 3mm bigger than the negative control) to at least one 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 years, which included: a physical exam, SPT to 15 aeroallergens, cow's milk and hen's egg, and administration of a modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to the parents. Information regarding the child's medical history, exposures to environmental tobacco smoke (ETS), pets, breast feeding, daycare attendance and parent's atopic history was collected. Methods for estimating average daily elemental carbon attributable to traffic (ECAT) exposure have been previously published.[13,14]

University of Cincinnati Asthma Predictive Index (ucAPI) and Wheezing Phenotypes

Children were classified as having an increased risk of future asthma based on a modified version of the *Asthma Predictive Index* (API) developed by Castro-Rodriguez et al and Guilbert et al. referred to as the "*University of Cincinnati API*" (ucAPI).[4,8] A positive ucAPI at age three in our study was defined as having two or more episodes of wheezing in the previous 12 months at the three year clinic visit, and one of the three major criteria (parental

asthma, allergic sensitization to one or more aeroallergen, or history of eczema) or two of the three minor criteria (wheezing without a cold, physician-diagnosed allergic rhinitis, or allergic sensitization to milk or egg).[15] *Persistent wheezing* at age three was defined as two or more episodes of wheezing in the previous 12 months at both the two and three year clinic visits, or if the parent reported a history of physician diagnosed asthma in the past 12 months at the three year clinic visit.[15] *Allergic persistent wheezing* was defined as having persistent wheezing (as defined above) with one or more SPT positive to 15 of the common aeroallergens in the area. Those children not meeting these criteria were grouped into the *non-allergic persistent wheezing* category. The similarities and differences among criteria for the original API, modified API and the ucAPI are listed in Table E1.

Asthma Outcome

At age seven all children completed baseline spirometry and exhaled nitric oxide (FeNO) testing (NIOX Flex; Aerocrine Inc., New Providence, N.J.), performed by trained technicians according to the American Thoracic Society (ATS) recommended guidelines.[16,17] Asthma symptoms included parental report of the child having at least one 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 seven year visit.[16] Those children with these asthma symptoms at age seven, FeNO of greater 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 post bronchodilation underwent a methacholine challenge test (MCCT) at a follow-up visit.[16] A modified 4-dose ATS 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 seven was hence 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% post bronchodilator or a positive MCCT (PC_{20} ≤ 4 mg/ml) at the seven year clinic visit; or 2) regular use of controller medications (i.e. inhaled corticosteroid (ICS) 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 seven and a positive University of Cincinnati API (ucAPI), persistent wheezing, and atopic and non-atopic persistent wheezing at age three, as well as other potential covariates. All dependent and independent variables were dichotomized prior to analysis based on prior studies of this cohort.[10,19,20] Low socioeconomic status was defined as a household income of < $20k per year. Parental report of asthma was defined as either biologic parent ever having been diagnosed with asthma. Exposure to ETS was defined as having at least one smoker in the home from birth to three years. The mean average daily exposure to ECAT was highly skewed for the study population, and was subsequently dichotomized using the 75^{th} percentile (with an average daily exposure to ECAT ≥ 0.41μg/m^3 [≥ 75^{th} percentile]

corresponding to a 'high' ECAT level).[15] Pet ownership was defined as living with a cat or dog from birth to three years. Breast feeding was defined as ≥ 4 months of breast feeding from birth to three years of age.[19] Aeroallergen and food sensitization was defined as having at least one of 15 aeroallergens positive or a positive test to either hen's egg or cow's milk at ages one or three years by skin prick testing. Eczema was defined as physician diagnosed eczema based on physical exam findings consistent with probable or definitive eczema from birth to three years.[20] All covariates with $p<0.05$ in the univariate analysis were included in the multivariate logistic regression model. Separate multivariate models were developed for the ucAPI and all three persistent wheezing phenotypes. The terms remaining in each final multivariate model were chosen based on backward elimination with a $p < 0.10$. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, N.C.).

Results

Of the 762 children enrolled in the CCAAPS cohort, 653 (85.7%) completed the age three clinic visit and 617 (81%) completed the seven year clinic visit. Of these, 589 children had complete data for the asthma outcome variable at age seven and were included in this analysis.

Table I summarizes the basic demographics, environmental exposures, and disease status of the subjects included in this analysis. The majority were male (54.8%), 21.2% were African American, and 16.7% were from a household with income <$20k per year. At least one person smoked in 27.0% of households. Most children were breastfed for at least four months (53.1%), attended daycare (52.1%), and had at least one parent with asthma (40.8%). More children were sensitized to at least one aeroallergen at age three vs. age one (41.5 vs. 19.0%). Sensitization to both cow's milk and egg white declined from age one to age three. Of the 589 children, 103 (17.5%) met our asthma definition at age seven (95 based on spirometry or methacholine testing; 8 based on asthma medication use in the previous 12 months). At age three, 68 children (12.3%) had a positive University of Cincinnati API (ucAPI) and 54 (10.6%) had persistent wheezing.

Table II summarizes the univariate analysis for associations between asthma at age seven, and a positive ucAPI and persistent wheezing at age three. The following covariates were significantly associated with an increased risk of asthma at age seven: African American ethnicity, household income of <$20k per year, exposure to ETS, parental asthma, allergic sensitization to aeroallergens at ages one and three, allergic sensitization to egg white at ages one and three, history of eczema, daycare attendance, and high exposure to ECAT from birth to three years. Whereas, breastfeeding and dog ownership during the first three years of life were associated with reduced likelihood of asthma at age seven. A positive ucAPI and persistent wheezing at age three were both significant predictors of objectively confirmed asthma at age seven [unadjusted OR = 12.7 and 10.6, respectively; $p <0.01$]. Furthermore, atopic persistent wheezing at age three was associated with a greater than three-fold higher likelihood of asthma at age seven relative to the non-atopic persistent wheezing phenotype [unadjusted OR = 14.6 vs. 4.3, respectively; $p <0.05$].

In this birth cohort, a positive ucAPI at age three had a sensitivity (SN) of 44%, specificity (SP) of 94%, PPV of 60.3% and NPV of 89.3% for confirmed asthma at age seven (Table III). A positive API had the highest SN (44%) for asthma compared to the wheezing phenotypes [persistent wheezing, atopic and non-atopic persistent wheezing (SN range: 12.2–35.9%)]. The specificity for all four phenotypes ranged from 94–98%. The positive likelihood ratio (LR^+) for the ucAPI was 7.5, and the negative likelihood ratio (LR^-) was 0.6 for asthma at age 7. Amongst the three persistent wheezing phenotypes, atopic persistent wheezing had the highest LR^+ of 11.7.

Table E2 in the Online Repository shows the test performance characteristics of the ucAPI defined using ≥ 4 wheezing episodes (as used in the mAPI) in the previous twelve months instead of ≥ 2 wheezing episodes. Using ≥ 4 wheezing episodes, the sensitivity of the ucAPI was 32%, specificity 96%, PPV 61%, and NPV was 88% for predicting asthma at age 7. The positive likelihood ratio (LR^+) for the ucAPI was 7.8, and the negative likelihood ratio (LR^-) was 0.7 for asthma at age 7.

Table IV shows the results of the final multivariate analysis for the association between asthma at age seven and a positive ucAPI and all of the persistent wheezing phenotypes at age three. A positive ucAPI at age three was associated with a significant risk for objectively confirmed asthma at age seven [aOR 13.3; 95% CI 7–25.2; p<0.01], as was persistent wheezing [aOR = 9.8; 95% CI 4.93–19.52; p<0.01]. The atopic persistent wheezing phenotype at age three was associated with a higher risk of asthma [aOR 10.4; 95% CI 4.12–26.01; p <0.01] than the non-atopic persistent wheezing phenotype [aOR 5.4; 95% CI 2.04–14.06; p < 0.01]. A household income of <$20k per year, sensitization to egg white at age one and daycare attendance were associated with a higher risk of asthma in all four multivariate models. In the ucAPI model, dog ownership was associated with a significantly lower risk for asthma at age seven. The relationship between asthma at age seven 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 birth to three years in any of the multivariate models. As stated, the original published studies of the API used wheezing severity based on a 1–5 scale and mAPI used ≥ 4 wheeze per year criterion. Since ours used ≥ 2 wheezing episodes, we also analyzed the ucAPI with the ≥ 4 wheeze criterion as in the mAPI; the results of the multivariate analysis remained essentially unchanged (see Table E3 in the Online Repository). Similarly, the multivariate models for the predictors of asthma at age 7 remained unchanged after removal of eight children who were identified as having asthma based on physician prescribed daily asthma controller medication, in whom the medication could not be withheld to perform lung physiologic tests at the 7 year clinic visit (see Table E4 in the Online Repository).

Discussion

This is the first study to show that a positive API (i.e., the ucAPI) and persistent wheezing at age three are significantly associated with an increased risk of objectively confirmed asthma at age seven. The ucAPI had a higher sensitivity for predicting asthma at age seven in this study population, which was enriched with individuals from atopic families, compared to that reported in the population-based Tucson birth cohort study (44% vs. 22%,

respectively).[5] In addition, this is the first study to show that as early as age three, children with atopic persistent wheezing have a two times greater likelihood of having confirmed asthma at school-age than those with non-atopic persistent wheezing.

Results from the longitudinal population based Tucson study have shown that a positive API at age 3 is a reliable predictor of physician-reported asthma in children ages 6–8 years.[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 seven was objectively confirmed with FEV_1 reversibility of ≥ 12% post bronchodilator or a positive MCCT (PC_{20} ≤ 4 mg/ml). The rigorous asthma definition used in this study uniquely contrasts with prior published studies evaluating 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.[6,7,21]

All three persistent wheezing phenotypes determined at age three were associated with a 5–10 fold higher likelihood of asthma, but a positive ucAPI at age three was the strongest predictor of objectively confirmed asthma at age seven (aOR = 13.3) in our study. The sensitivity of a positive ucAPI at age 3 for predicting asthma at age seven in our study was greater than that of the API in the Tuscon cohort (sensitivity = 22%), or that of the mAPI reported in the high-risk atopic Childhood Origins of Asthma (COSTA) birth cohort (sensitivity = 17–19%).[4,7] However, when comparing the ucAPI to the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) risk score, the later yielded higher sensitivity of 54.5%, and PPV of 75%, albeit a lower specificity of 78.9%, and a NPV of 60% for parent-reported asthma at age 5–6 in a Columbian pediatric population.[22] The sensitivity of a test is unaffected by the prevalence of disease in the study population.[23] Hence the disparity in the sensitivity between the above mentioned cohorts could be attributed to the aforementioned differences in the asthma outcome definition used.[24] In addition, the inherent differences in the risk factors for childhood asthma in this cohort, which is selected for based on parental atopic status could also explain such differences. Of note, the sensitivity of the ucAPI was reduced from 44% to 32% when 4 or more episodes of wheezing (instead of ≥ 2 annually) was used to define the ucAPI (Table E2), suggesting that a higher number of reported wheezing episodes is not an essential element of this API criterion.[4,7]

Likelihood ratios (LRs) best reflect the diagnostic accuracy of a test. The positive likelihood ratio (LR^+) of the stringent API in the Tuscan study ranged from 3.0 – 7.4 for asthma between ages 6–8, while the negative likelihood ratio (LR^-) ranged from 0.5–0.8.[25] The LR^+ of 7.5 and LR^- of 0.6 reported for the ucAPI are comparable to that of the API in the Tuscon study, and suggest that a positive ucAPI could have a significant effect on the post-test probability. The LRs for the mAPI reported by Cheng et al. are higher (LR^+ = 21–55 and LR^- =0.83–0.84 for asthma between ages 6–8).[7] 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 (e.g., inhaled corticosteroids, allergen immunotherapy) that could potentially modify their risk for development of allergic asthma.

Epidemiologic studies have shown that atopic and non-atopic 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 two phenotypes in pre-school age children.[9, 26, 27] This is the first study to show that as early as age three the atopic persistent wheezing phenotype is associated with a 2 times higher odds of objectively confirmed asthma at age seven than non-atopic persistent wheezing. For both phenotypes, household income of <$20k per year, sensitization to egg white at age one, eczema, daycare attendance, and parental asthma were all comparable risk factors for confirmed asthma at age seven. While the specificity of all three persistent wheezing phenotypes to predict asthma at age seven was high, suggesting that they can aid in the diagnosis of childhood asthma, the low sensitivity may preclude them from being used as a clinically effective screening tool.

In addition, a household income of <$20k per year, sensitization to egg white at age one, and daycare attendance were significant risk factors for objectively confirmed asthma at age seven in all four multivariate models in our study. These have been reported in other epidemiologic studies and support our findings.[28–33] Dog ownership during the first three years of life was protective of asthma at age seven 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.[34,35] Previous studies indicate that early exposure to traffic-related air pollution is associated with incident asthma after age seven in an atopic population.[36] In this study, the univariate analysis showed that exposure to high levels of average daily ECAT from birth to three years was a significant risk factor for objectively confirmed asthma at age seven, 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 is also a potential for recall bias since the persistent wheezing episodes were reported by questionnaire. Our asthma definition did include a small percent (<8%) of children whose asthma diagnosis was based on receiving a daily asthma controller medication in the previous 12 months at the seven year clinic visit precluding physiologic lung testing. However, the results of the multivariate analysis do not change significantly with removal of these eight children from the analysis (Tables E3).

In conclusion, the results of this study demonstrate that the ucAPI and the persistent wheezing phenotype at age three can be used to predict the risk of objectively confirmed asthma at age seven. A positive ucAPI was the best overall predictor for asthma at age seven compared with the other three persistent wheezing phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

API	Asthma Predictive Index
mAPI	Modified Asthma Predictive Index
ucAPI	University of Cincinnati Asthma Predictive Index
CCAAPS	Cincinnati Childhood Allergy and Air Pollution Study
ECAT	Elemental Carbon Attributable to Traffic
ETS	Environmental tobacco smoke
FeNO	Forced exhaled Nitric Oxide
ICS	Inhaled corticosteroid
MCCT	Methacholine Challenge Test
$PM_{2.5}$	Particulate matter less than 2.5μm
PFT	Pulmonary Function Testing
SPT	Skin prick test

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Highlights Box

1. What is already known about this topic?
   - The University of Cincinnati Asthma Predictive Index (ucAPI) and persistent wheezing phenotypes are associated with *physician diagnosed* childhood asthma.
2. What does this article add to our knowledge?
   - A positive ucAPI and persistent wheezing at age three are associated with a 13 and 10 times higher odds, respectively, of *objectively confirmed* asthma in school-age children.
3. How does this study impact current management guidelines?
   - The ucAPI 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.

Table I

Characteristics of the Cincinnati Childhood Asthma and Air Pollution Study Cohort

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

* Total N = 589 but may differ for each category due to missing data.

^ Between birth-3 years

Eczema was defined as physician reported eczema at any age by or before 3 years.

ucAPI= Adapted Asthma Predictive Index; ETS= environmental tobacco smoke; ECAT= Elemental Carbon Attributable to Traffic.

Table II

Univariate Associations between Asthma at Age 7 and the University of Cincinnati Asthma Predictive Index (ucAPI), Persistent Wheezing and Other Covariates

Covariate	Asthma at 7 years		P value
	Yes n =103 (%)	No n= 486 (%)	
Gender: Male	63 (61.2%)	260 (53.5%)	0.16
Race: African American	33 (32.0%)	92 (18.9%)	<0.01
Household income < $20K	32 (32.0%)	63 (13.4%)	<0.01
Breast fed for ≥ 4mo	42 (40.8%)	270 (55.7%)	<0.01
Exposure to ETS	37 (35.9%)	122 (25.2%)	0.03
Parental asthma	58 (56.3%)	182 (37.5%)	<0.01
Sensitization to ≥ 1 aeroallergen at: → 1 year → 3 years	29 (30.2%) 52 (56.5%)	76 (16.7%) 179 (38.5%)	<0.01 <0.01
Sensitization to Milk at: → 1 year → 3 years	6 (6.32%) 2 (2.17%)	15 (3.3%) 6 (1.3%)	0.14 0.39
Sensitization to Egg at: → 1 year → 3 years	21 (22.1%) 10 (11.0%)	46 (10.1%) 20 (4.3%)	<0.01 0.02
Eczema^	34 (33.7%)	92 (19.1%)	<0.01
Dog ownership^	32 (31.1%)	212 (43.6%)	0.02
Cat ownership^	23 (22.3 %)	141 (29.0%)	0.17
Daycare attendance^	64 (62.1%)	243 (50.0%)	0.025
ECAT exposure ≥ 75th percentile: →At 3 years →From birth-3 years	32 (33.0%) 34 (33.0%)	100 (20.6%) 114 (23.5%)	0.05 0.04
Positive ucAPI at 3 years	41 (44.1%)	27 (5.86%)	<0.01
Persistent wheezing at 3 years	33 (35.9%)	21 (5.02%)	<0.01
Atopic persistent wheezing at 3years	20 (22.2%)	8 (1.9%)	<0.01
Non-atopic persistent wheezing at 3years	11 (12.2%)	13 (3.1%)	<0.01

^Between birth-3 years

ETS= Environmental tobacco smoke; ECAT= Elemental Carbon Attributable to Traffic.

Table III

Clinical Phenotype Based Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Values for Asthma at age 7.

Test* (No. with asthma)	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	Positive Predictive Value (%) [95% CI]	Negative Predictive Value (%) [95% CI]	Likelihood Ratio	
					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
Non-Atopic 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; ucAPI: University of Cincinnati Asthma Predictive Index; LR+: positive likelihood ratio; LR−: negative likelihood ratio.

^Missing data on results for skin prick testing for 2 children.

Table IV

Adjusted Odds Ratios for Associations of Positive ucAPI, Persistent Wheezing, Atopic Persistent Wheezing and Non-atopic Persistent Wheezing at Age 3 With Asthma Outcome at Age 7 in Separate Logistic Regression Models.

Exposure/Covariate	**aOR (95% CI) for Asthma at 7 years [p-value^]**			
	ucAPI Model	**Persistent Wheezing Model**	**Atopic Persistent Wheezing Model**	**Non-atopic Persistent Wheezing Model**
Positive ucAPI at 3 years	13.27 (7.0–25.15) <0.01	-	-	-
Persistent Wheezing at 3 years	-	9.81 (4.93–19.52) <0.01	-	-
Atopic Persistent Wheezing at 3 years	-	-	10.35 (4.12–26.01) <0.01	-
Non-atopic Persistent Wheezing at 3 years	-	-	-	5.36 (2.04–14.06) <0.01
Household income < $20K	3.64 (1.94–6.82) <0.01	3.61 (1.91–6.81) <0.01	3.62 (1.95–6.75) <0.01	3.61 (1.96–6.68) <0.01
Parental Asthma	€	1.87 (1.08–3.23) 0.026	2.03 (1.19–3.47) <0.01	2.12 (1.26–3.56) <0.01
Sensitization to Egg at 1year	2.82 (1.43–5.57) <0.01	2.92 (1.45–5.90) <0.01	2.61 (1.32–5.16) 0.006	2.84 (1.46–5.54) <0.01
Eczema	€	2.06 (1.14–3.74) 0.017	2.02 (1.12–3.64) 0.02	2.35 (1.34–4.14) <0.01
Daycare attendance	1.77 (1.02–3.08) 0.042	1.59 (0.91–2.78) 0.103	1.81 (1.05–3.11) 0.03	1.73 (1.01–2.95) 0.04
Dog ownership	0.55 (0.31–0.99) 0.045	*	*	*
ECAT exposure ≥ 75th percentile from birth-3years	*	*	*	*

ucAPI: University of Cincinnati API
aOR = adjusted odds ratio

^Significant at p ≤ 0.10

- 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 ≤ 0.10

The initial multivariate models included all covariates (except when denoted by - or €), including gender, race, exposure to environmental tobacco smoke, breast feeding, sensitization to aeroallergens, egg and milk at 1 and 3 years of age, cat ownership, and ECAT exposure ≥ 75th percentile between birth to 3years of age but were not significant an alpha of 10%.