University of Cincinnati

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I, Priyal Amin , hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research .

It is entitled:

Which is the Optimum Predictor of Childhood Asthma, Persistent Wheezing or the Asthma Predictive Index?

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This work and its defense approved by:

Committee chair: Erin Nicole Haynes, Ph.D.

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Which is the Optimum Predictor of Childhood Asthma, Persistent Wheezing or the Asthma Predictive Index?

A thesis submitted to the
Graduate School
of the University of Cincinnati
in partial fulfillment of the
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Master of Science

In Clinical & Translational Research
In the Department of Environmental Health
Division of Epidemiology & Biostatistics
of the College of Medicine

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by

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ABSTRACT:

Background: The Asthma Predictive Index (API) and persistent wheezing phenotype have been associated with childhood asthma. Previous studies have not assessed their ability to predict objectively confirmed asthma.

Objective: The aim of this study is to determine whether the API and persistent wheezing phenotype at age three can accurately predict asthma confirmed at age seven in a high risk birth cohort.

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 $\geq$ 12% post bronchodilator or a positive methacholine challenge ($PC_{20} \leq 4$ mg/ml); or prior treatment with daily asthma controller medication(s). The API and persistent wheezing were assessed at age three. Multivariate logistic regression was used to investigate the relationship between confirmed asthma at age seven and API and persistent wheezing at age three with adjustment for multiple covariates.

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 API (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 <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 & Clinical Relevance: At age three a positive API was associated with the highest risk of objectively confirmed asthma at age seven. These results validate the API as a clinically useful tool for predicting future asthma in school-age children.

Keywords: Asthma, Asthma Predictive Index (API), wheezing phenotypes, persistent wheezing, phenotype, atopic persistent wheezing, non-atopic persistent wheezing, traffic-related air pollution (TRAP), elemental carbon attributable to traffic (ECAT).

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Table of Contents

LIST OF TABLES:

CHAPTER 1. 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 there are no accurate screening tests (genetic or biochemical markers), and performance of spirometry maneuvers is not generally feasible before age five.[3] A presumptive diagnosis of asthma before school-age is often based on nonspecific physical findings and clinical features such as recurrent wheezing or cough. Determining which pre-school children with these lower respiratory symptoms are at greatest risk for developing objectively confirmed asthma at school-age remains a challenge. Various predictive models and wheezing phenotypes have been identified to help with asthma prediction in young children.

The Asthma Predictive Index (API) is a validated clinical model for childhood asthma that was developed in the Tucson Children's Respiratory Study (TCRS).[4,5,6,7] The API uses factors in the first three years of life to predict asthma in school-age children, where asthma is defined based on physician report or the presence of more than three episodes of wheezing in a 12 month period.[4] While in previous studies, 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 asthma later in childhood, the asthma outcome variable in those studies was not confirmed using objective physiologic methods such as spirometry or methacholine testing.[4]

In addition to the API, early wheezing phenotypes have also been studied as a means to predict childhood asthma.[8] The Tuscon study was the first to examine early childhood wheezing phenotypes. The persistent wheezing phenotype in the TCRS cohort was defined as $\geq$ 1 wheezing episode(s) associated with a lower respiratory tract infection from ages 1-3 years and later at age six.[2] Subsequently, Martinez et al. showed that school-aged children with persistent wheezing were significantly more likely to have diminished lung function at age six when compared to those who never wheezed.[2] However, the relationship between API and persistent wheezing in pre-school age children and objectively diagnosed asthma has not been prospectively evaluated previously.

The purpose of this study was to determine if the API and persistent wheezing phenotypes at age three predict objectively confirmed asthma at age seven in a birth cohort population.

CHAPTER 2. METHODS

2.1 Study Population

Data from the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a prospective birth cohort, was used for this study. The initial hypothesis of the CCAAPS study was that early life exposure to traffic pollutants increases the risk for atopy and allergic disorders during childhood. Details on recruitment, exposure assessments, and cohort characteristics are described elsewhere.[9,10,11] 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 from a major road (low traffic pollution exposure cohort) [11] were screened for allergy symptoms when infants were approximately six months old. Parents who were likely to be atopic were skin prick tested (SPT) to 15 common aeroallergens.[9] Children were eligible for enrollment if they had at least one parent who was SPT positive (defined as having a wheal $\geq$ 3mm bigger than the negative control).[9] Parents signed an written informed consent and the study protocol was approved by the University of Cincinnati Institutional Review Board.

2.2 Clinical Evaluation

Children underwent clinical evaluations at ages 1, 2, 3, 4, and 7 years of age, which included: a physical exam, SPT to 15 aeroallergens, cow's milk and hen's egg, and administration of a modified, age-appropriate version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to the parents to collect relevant information regarding the child's medical history, exposures to environmental tobacco smoke (ETS), pets, breast feeding, daycare attendance and parent's atopic history. Details on calculations for the estimated average daily elemental carbon attributable to traffic (ECAT) exposure for each child can be found elsewhere.[12] Briefly, particulate matter less than 2.5μm ($PM_{2.5}$) was measured in ambient air samples collected at 27 sites in the greater Cincinnati area

from December 2001-2006. The average daily ECAT was measured using Multivariable UNMIX and chemical mass balance models.[13] Each participating child's time-weighted average daily exposure to ECAT (from birth to 6 months, 7-12 months, 13-24 months, and 25-36 months) was determined using a land use regression model by geocoding all addresses where the child spent more than 8 hours per week.[12] Pulmonary function testing (PFT) and/or methacholine challenge test (MCCT) was performed at the seven year visit as described below.[14]

2.3 Asthma Predictive Index (API) 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) proposed by Castro-Rodriguez et al.[4] In our study a positive API at age three was defined as having two or more episodes of wheezing in the previous 12 months at the three year clinic visit (recurrent wheezing) and one of the three major criteria (report of 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).[11] *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.[11] At age three a*llergic persistent wheezing* was defined as having persistent wheezing (as defined above) with one or more SPT positive to 15 of the common aero allergens in the area. Those children not meeting this criterion were grouped into the *non-allergic persistent wheezing* category.

2.4 Asthma Outcome

At age seven all children in the study completed baseline spirometry and a test for exhaled nitric oxide (FeNO) concentration (NIOX Flex; Aerocrine Inc, New Providence, New Jersey) supervised by trained technicians according to American Thoracic Society criteria.[15] Asthma symptoms included parental report of the child having tight or clogged chest or throat, difficulty breathing or wheezing after

exercise, or wheezing or whistling in the chest in the previous 12 months, or a history of physician diagnosed asthma in the past 12 months during the seven year clinic visit.[14] Those children with asthma symptoms, FeNO >10 ppb, or a baseline predicted FEV_1 < 90% and/or an FEV_1 ratio to forced vital capacity less than the lower limit of normal were assessed for airway reversibility by repeat spirometry 15 minutes after 2.5 mg of nebulized levalbuterol. Those with less than 12% increase in FEV_1 post bronchodilation underwent a methacholine challenge test (MCCT) at a follow-up visit. A modified 4-dose ATS methacholine challenge protocol was used with sequential methacholine concentrations of 0.0625, 0.25, 1, and 4 mg/ml.[16] 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 confirmed with 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 a prescribed daily inhaled corticosteroid (ICS) and/or montelukast for the treatment of asthma by their physicians in the previous 12 months.

2.5 Statistical Analysis

Univariate analyses were conducted to assess the associations between asthma at age seven and a positive API, persistent wheezing, and atopic and non-atopic persistent wheezing at age three, as well as other potential covariates including: gender, race, household income, parental history of asthma, exposure to ETS and ECAT, pet ownership, breast feeding, and allergic sensitization to aeroallergens and cow's milk and hen's egg at years one and three. All dependent and independent variables were dichotomized prior to analysis for ease of interpretation and defined as yes/no, high/low or positive/negative based on prior studies of this cohort.[9,17,18] Low socioeconomic status was defined as a household income of < $20k per year. Parental report of asthma (yes/no) was defined as either of the biologic parents ever having been diagnosed by a physician with asthma. Exposure to ETS (yes/no) was defined as having at least one smoker in the home between the ages of six months and three years. The mean average daily exposure to ECAT was highly skewed for the study population, and was subsequently

dichotomized using the 75th percentile (with an average daily exposure to ECAT $\geq$ 0.41μg/m^3 [$\geq$ 75th percentile] corresponding to a 'high' ECAT level).[19] Pet ownership (yes/no) was defined as living with a cat or dog between the ages of six months and three years. Breast feeding (yes/no) was defined as $\geq$ 4 months of breast feeding between six months to three years of age.[17] Aeroallergen and food sensitization (yes/no) 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 and three years. Eczema (yes/no) was defined as a physician report of probable or definitive eczema between ages one to three years.[18] Daycare attendance (yes/no) was based on parental report of whether the child spent time with babysitter(s), daycare providers or relatives between ages six months to three years. All covariates with $p<0.05$ in the univariate analysis were included in the multivariate logistic regression model. Separate multivariate models were developed for API and the persistent wheezing phenotypes. The terms remaining in each final multivariate model (including first order interactions) were chosen based on backward elimination with a p value of < 0.10. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

CHAPTER 3. 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 and were included in this analysis.

Table 1 summarizes the basic demographics, environmental exposures, and disease status of a subset of the CCAAPS cohort included in this analysis. The majority of the subjects 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 (Table 1). Of 589 children, 103 (17.5%) met our asthma definition at the seven year clinic visit (N=95 based on spirometry or methacholine

challenge testing and N=8 based on history of daily asthma medication(s) use in the previous 12 months). Sixty eight children (12.3%) had a positive API and 54 (10.6%) had persistent wheezing at age three.

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 Egg 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 36mo → From age 6-36mo	 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 API 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 1-3 years

^ Between 6months-3 years

Eczema was defined as physician reported eczema at any age by or before 3 years. API= Asthma Predictive Index; ETS= environmental tobacco smoke; ECAT= Elemental Carbon Attributable to Traffic; mo = months

Table 2 summarizes the univariate analysis for associations between asthma at age seven and a positive API and persistent wheezing at age three along with all the other covariates. 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 age six months to three years. In contrast, breastfeeding for at least four months and dog ownership during the first three years of life had a significant protective effect on asthma at age seven. A positive API and the persistent wheezing phenotype at age three were both significantly associated with having asthma at age seven [unadjusted OR = 12.7 and 10.6; $p < 0.01$, respectively]. Furthermore, atopic persistent wheezing at age three was associated with a five fold higher odds of asthma at age seven relative to the non-atopic persistent wheezing phenotype [unadjusted OR = 14.6 vs. 4.3; $p < 0.05$, respectively].

Table II. *Unadjusted* Odds Ratios Measuring Univariate Associations Between Asthma at Age 7 and the Asthma Predictive Index (API), 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 →Between 6mo and 3 years	 32 (33.0%) 34 (33.0%)	 100 (20.6%) 114 (23.5%)	 0.05 0.04
Positive API 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

*Unadjusted OR

Between 1-3 years

^ Between 6months-3 years

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

In our cohort a positive API at age three had a sensitivity (SN) of 44%, specificity (SP) of 94%, PPV of 60.3% and NPV of 89.3% for predicting asthma at age seven (Table 3). A positive API had the highest SN (44%) for asthma compared to the other three wheezing phenotypes [persistent wheezing,

atopic and non-atopic persistent wheezing (SN range: 12.2-35.9%)]. The specificity for all four phenotypes was high ranging from 94-98.1%. Interestingly, the sensitivity and PPV of atopic persistent wheezing were higher than that for non-atopic persistent wheezing in predicting asthma at age seven (SN: 22.2% vs. 12.2%; PPV 71.4% vs. 45.8%, respectively).

Table III. Test 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]
API (41)	44 [33.8-54.8]	94.1 [91.6-96.1]	60.3 [47.7-72]	89.3 [86.2-92]
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]
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]
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]

* At age 3; API: Asthma Predictive Index; ^ Missing data on results for skin prick testing for 2 children.

Table 4 shows the results of the final multivariate analysis for the association between asthma at age seven and a positive API, persistent wheezing, and atopic and non-atopic persistent wheezing phenotypes at age three. A positive API at age three was associated with a significant risk for asthma at age seven [aOR 13.3; 95% CI 7-25.2; $p<0.01$], comparable to that seen for persistent wheezing [aOR = 9.8; 95% CI 4.93-19.52; $p <0.01$]. In addition, 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; $p < 0.01$] or persistent wheezing alone. A household income of <$20k per year, history of parental asthma, sensitization to egg white at age one, history of eczema, and daycare attendance were all associated with a higher odds of asthma in all four multivariate models shown in Table 4. In the API model, dog ownership was associated with a significantly lower risk for asthma at age seven. The relationship between the API or the persistent wheezing phenotypes and asthma at age seven was not significantly affected by high levels of average daily ECAT exposure from age six months to three years in any of the multivariate models.

Table IV. *Adjusted* **Odds Ratios for Associations of Positive API, 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^]**			
	API Model	**Persistent Wheezing Model**	**Atopic Persistent Wheezing Model**	**Non-atopic Persistent Wheezing Model**
Positive API 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 6mo-3years	*	*	*	*

aOR = adjusted odds ratio
^ Significant at p =0.10
- Not included in the model
€ Not included in the model as it was one of the defining criteria for a positive API
* Not significant at the alpha = 0.10 in the multivariate model
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 at 1 and 3 years of age, sensitization to egg and milk at 1 and 3 years of age, cat ownership, and ECAT exposure ≥ 75th percentile between 6mo-3years but were found not to be significant at the 10% level based on backward elimination.

CHAPTER 4. DISCUSSION

This was the first study to show that a positive API and persistent wheezing at age three were significantly associated with an increased risk of objectively confirmed asthma at age seven. The API had

a higher sensitivity for predicting risk of asthma at age seven in our study population enriched with atopic individuals 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 five times greater odds of asthma at school-age than those with non-atopic persistent wheezing.

Results from the longitudinal population based TCRS birth cohort have shown that a positive API is a reliable predictor of future physician-reported asthma in children.[3,4] However, ours is the first study to confirm these results in a high-risk birth cohort of children in which the asthma outcome at age seven was objectively confirmed by FEV1 reversibility of $\geq$ 12% post bronchodilator or a positive MCCT ($PC_{20} \leq 4$ mg/ml). Such a rigorous asthma definition contrasts with previous studies that have evaluated the API or modified API (mAPI) and defined asthma exclusively based on physician or parental-report of asthma-type symptoms or the use of any asthma medication(s), without additional lung physiologic testing.[7,20,21] When comparing the four multivariate predictive models in our study, although the persistent wheezing phenotype and its sub-phenotypes of atopic and non-atopic persistent wheezing determined at age three were associated with a 5-10 fold higher likelihood of asthma, a positive API at age three was the strongest predictor of asthma at age seven (aOR = 13.3). The sensitivity of a positive API for predicting school-age asthma was higher than any of the persistent wheezing phenotypes (44% vs. 12.2-35.9%, respectively). In addition, when compared to the sensitivity of the API in the population-based Tuscon cohort (22%) or that of the mAPI in the atopic Childhood Origins of Asthma (COSTA) birth cohort (11-19%), the sensitivity of a positive API for predicting asthma at age seven in our cohort was higher.[4,7] Since the sensitivity of a test is unaffected by the prevalence of disease in the study population the disparity in sensitivity between cohorts may be attributed to differences in the asthma outcome definitions.[22] Overall, while the PPV is higher here than that reported in other cohorts, the specificity and NPV of the API are comparable to other reports.[23]

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 to date, very few studies have compared the risk factors for asthma between these two phenotypes in pre-school age children.[8, 24, 25] Ours is the first study to show that as early as age three the atopic persistent wheezing phenotype is associated with a 5 times higher odds of asthma at age seven than non-atopic persistent wheezing. For both atopic and non-atopic persistent wheezing phenotypes, household income of <$20k per year, having at least one parent with asthma, sensitization to egg white at age one, childhood history of eczema, and daycare attendance were all comparable risk factors for asthma at age seven with similar odds ratios (Table 4). 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 (Table 3).

In addition to these findings, a household income of <$20k per year, history of sensitization to egg white at age one, and daycare attendance were significantly associated with asthma at age seven in all four multivariate models. These associations with childhood asthma have been previously reported in other epidemiologic studies and support our findings.[26-31] Presence of at least one dog in the household between six months to three years of age was protective of asthma at age seven in the API multivariate model. A similar protective effect of early dog ownership on frequent wheezing and parent-reported asthma at school age has been previously reported in other longitudinal birth cohort studies.[32,33] The lack of a similar association in the persistent wheezing models may be due to small number of dog ownership those groups. Although the results of our univariate analysis showed that exposure to high levels of average daily ECAT from age six months to three years was a significant risk factor for objectively confirmed asthma at age seven, this association did not survive in the multivariate analyses. However, Carlsten et. al. have shown that early exposure to traffic-related air pollution is associated with incident asthma after age seven in an atopic population.[34]

Limitations of this study are that since the data was analyzed in a high-risk population the results cannot be applied universally to all populations and should be interpreted with caution when doing so. Also, there is 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 to include children who may not show positivity on physiologic lung testing due to current use of controller medication(s).

In conclusion, the results of this study support that both a positive API and the persistent wheezing phenotype at age three significantly predict objectively confirmed asthma at age seven in an atopic longitudinal birth cohort. A positive API was the best overall predictor for asthma at age seven compared with the other three persistent wheezing phenotypes.

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