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