

# Childhood Asthma-Predictive Phenotype

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**Wheezing is a fairly common symptom in early childhood, but only some of these toddlers will experience continued wheezing symptoms in later childhood. The definition of the asthma-predictive phenotype is in children with frequent, recurrent wheezing in early life who have risk factors associated with the continuation of asthma symptoms in later life. Several asthma-predictive phenotypes were developed retrospectively based on large, longitudinal cohort studies; however, it can be difficult to differentiate these phenotypes clinically as the expression of symptoms, and risk factors can change with time. Genetic, environmental, developmental, and host factors and their interactions may contribute to the development, severity, and persistence of the asthma phenotype over time. Key characteristics that distinguish the childhood asthma-predictive phenotype include the following: male sex; a history of wheezing, with lower respiratory tract infections; history of parental**

**asthma; history of atopic dermatitis; eosinophilia; early sensitization to food or aeroallergens; or lower lung function in early life.** © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:664-70)

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## ASTHMA PHENOTYPES: CHILDHOOD ASTHMA-PREDICTIVE PHENOTYPE

Wheezing is a fairly common symptom in early life, but only some toddlers will experience continued wheezing symptoms in later childhood.<sup>1</sup> From epidemiologic data, several early childhood wheezing phenotypes were described based on the natural history and risk factors associated with each. Appropriate identification of young children at high risk to develop persistent asthma could lead to the development of effective prevention and therapeutic strategies.

## DEMOGRAPHICS

Although almost 50% of children report wheeze in the first year of life, only 40% of these children will continue to wheeze in later childhood.<sup>1</sup> Wheezing phenotypes were defined to identify the characteristics and risk factors associated with children who experience continued wheezing in later childhood and others into adolescent and adulthood.

## CLINICAL CHARACTERISTICS Wheezing phenotypes

Several wheezing phenotypes were developed. It can be difficult to differentiate these phenotypes clinically because the expression of symptoms and risk factors can change with time.

**Tucson Children's Respiratory Study classification.** In this study, 4 different wheezing phenotypes were classified among 1246 newborns observed for the development of lower respiratory tract infections based on the occurrence of wheezing symptoms during the first 3 years of life and again at 6 years of life (Table 1).<sup>1</sup> These phenotypes included the following:

- Never wheezers (51%): healthy children without wheezing.
- Early, transient wheezers (20%): onset of wheezing before age 3 years with resolution by 6 years of age.
- Persistent wheezers (14%): onset of wheezing before age 3 years with sustained wheezing at age 6 years.
- Late-onset wheezers (15%): onset of wheezing between 3 and 6 years of age.

Thus, children in the persistent and late-onset wheezing groups may represent 2 asthma-predictive phenotypes, that is,

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Abbreviations used  
API- Asthma Predictive Index  
RV- Rhinovirus

those children who are most likely to experience asthma-like symptoms that persist into later childhood, adolescence, and adult life (Figure 1).

Further evaluation of the cohort led to further refinement of the persistent wheezing phenotype:

- Nonatopic persistent wheezing phenotype: the first episode of wheezing occurs in the first year of life<sup>2</sup> and the wheezing episodes become less frequent by early adolescence,<sup>3</sup> and most outgrow their symptoms. Children with this phenotype have a lower level of prebronchodilator lung function and enhanced airway reactivity.<sup>3</sup>
- IgE-associated and/or atopic persistent wheezing phenotype: is characterized by wheezing, which usually starts in the second year of life and persists into later adolescence.<sup>4</sup> It remains to be seen if this phenotype will persist into adulthood. Risk factors associated with atopic wheeze include parental asthma, male sex, atopic dermatitis, eosinophilia at 9 months, early sensitization to food or aeroallergens, and a history of wheezing with lower respiratory tract infections.<sup>1,5</sup>

**The Italian Studies of Respiratory Disorders in Childhood and the Environment classification.** The Italian Studies of Respiratory Disorders in Childhood and the Environment was a longitudinal birth cohort of 16,333 children that identified similar phenotypes but with different frequencies, as did the Tucson study.<sup>1,6</sup> The age that differentiated early transient wheezing from persistent wheezing was age 2 years rather than 3 years. In differing from the Tucson study, 83% had never wheezed, 7% had early transient wheezing, 4% had persistent wheezing, and 6% had late-onset wheezing.

**Avon Longitudinal Study of Parents and Children classification.** In the Avon Longitudinal Study of Parents and Children,<sup>7</sup> a longitudinal birth cohort of 6265 children, the occurrence of wheeze in these children was measured by a parental report at yearly intervals from age 6 months to 7.5 years. By using a latent class analysis, the investigators identified 6 phenotypes, 4 of which had patterns similar to those identified in the Tucson study.<sup>1</sup> Data were collected at more time points and shorter intervals, and included lung function, which led to the identification of 2 additional subphenotypes (prolonged early wheeze and intermediate-onset wheeze):

- Never or infrequent wheeze (59%).
- Transient early wheeze (16%): wheezing at 6 to 18 months, remitting after 42 months.
- Prolonged early wheeze (9%): wheezing at 6 to 54 months, remitting after 69 months; characterized by increased airway responsiveness and lower school-aged lung function compared with the never or infrequent wheeze phenotype.
- Intermediate-onset wheeze (3%): wheezing onset between ages 18 and 42 months that persists into later childhood; these children are characterized by allergic sensitization, higher levels of airway responsiveness, and lower lung function compared with the never or infrequent wheeze phenotype.

- Late-onset wheeze (6%): infrequent wheezing from 6 to 42 months but frequent after 42 months.
- Persistent wheeze (7%): wheezing from 6 months onward.

The intermediate onset, late-onset, and persistent wheeze groups also may represent asthma-predictive phenotypes.

**New Zealand classification.** Risk factors that are associated with sustained wheezing from childhood (age 9 years) to adulthood were evaluated in a New Zealand longitudinal study. More than 1 in 4 children had wheezing that persisted from childhood to adulthood or who had relapsed after remission. The factors that predicted persistence or relapse were sensitization to house-dust mites, airway hyperresponsiveness, early age at onset, female sex (after puberty), and personal smoking exposure.<sup>8</sup> In those with persistent asthma, lung function was decreased through childhood and adulthood in a comparatively similar pattern.

**Melbourne classification.** Data attained from a cohort of 378 children with asthma in Melbourne, Australia, evaluated every 7 years from age 7 years through 35 years showed a link between asthma and other atopic conditions. The presence of an atopic condition in childhood augmented the risk of severe asthma in later life, whereas severe asthma in childhood predicted an increased risk of atopic eczema or allergic rhinitis in later life.<sup>9</sup> Consequently, analysis of these data indicated that children whose symptoms start in early life are at greater risk for the development of persistent chronic airflow limitation and continued severe symptoms.

**Symptomatic classification.** Epidemiologic phenotypes are limited by their retrospectively defined periods of wheeze. Thus, phenotypes based upon temporal patterns of wheeze were created, which can be applied prospectively and may be more practical when making treatment decisions. Other names, for example, episodic (viral) wheeze, also were proposed to describe the phenotype for children who primarily wheeze with viral infections alone. In contrast, the term multiple-trigger wheeze phenotype is used for children who wheeze when exposed to a variety of triggers rather than solely with viral infections.<sup>10</sup> Subsequently, airway function was observed to be lower in multiple triggers than episodic wheeze, which suggests that these are distinct phenotypes.<sup>11</sup> However, some children classified into 1 of these 2 clinically based phenotypes switched into the other phenotype in the following year,<sup>12</sup> which suggests that these phenotypes may be inconsistent over time. A 2014 study found a high correlation between the epidemiology defined latent class analysis phenotypes and clinically defined wheeze phenotypes.<sup>13</sup> Accordingly, clinical phenotypes may be useful asthma definitions for future epidemiologic studies.

**Additional perinatal and early childhood exposures associated with asthma.** Genetic, environmental, developmental, and host factors and their interactions may contribute to the development, severity, and persistence of the asthma phenotype over time.<sup>14,15</sup> Atopic disease,<sup>1,7,16-18</sup> reduced lung function,<sup>1,7,17-19</sup> viral infections,<sup>20-22</sup> and frequent wheeze<sup>1,23,24</sup> appear to be key risk factors. Other risk factors present *in utero* and at the time of delivery associated with increasing risk of asthma include a family history of atopic disease, black race<sup>25</sup>; male sex<sup>26</sup>; passive tobacco smoke exposure<sup>27</sup>; low birth weight; caesarean section delivery<sup>28,29</sup>; and maternal consumption of milk, eggs, and wheat during pregnancy.<sup>30</sup> Factors associated with increased risk of asthma after birth and in later childhood include respiratory

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