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Phenotypes of wheezing and asthma in preschool children

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Structured Abstract:

Purpose of review: The purpose of this review is to provide an overview of the identified phenotypes of preschool wheezing.

Recent findings: Early life wheezing patterns have been described in multiple populations, with several commonalities found between cohorts. Early life environmental exposures have been found to be differentially associated with preschool wheezing phenotypes and their future trajectories. These include allergen and microbe exposure, environmental tobacco smoke exposure, and maternal stress and depression. Elevated IgE in early life may also influence future asthma risk.

Summary: Preschool wheezing phenotypes are heterogeneous and complex, with trajectories that are related to factors including environmental exposures. More research is needed to characterize these relationships, hopefully leading to targeted prevention strategies.

Keywords

Preschool wheezing; asthma; atopy; asthma predictive index; phenotypes

Introduction

Wheezing is common in the preschool population. Up to 50% of children have at least one episode of wheezing before 3 years of age, but only a minority of these children will have persistent wheezing. Therefore, phenotypic characterization of the patterns and outcomes of these episodes is particularly valuable for characterizing symptoms and assessing future risk, as well as developing strategies for secondary prevention of asthma[1]. This review focuses

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on studies relating to phenotypes of wheezing and asthma in the preschool population which have been published in the past 18 months.

Historic Birth Cohorts

Birth cohort studies have led to significant advances in knowledge regarding early life wheezing phenotypes, in terms of characterizing the trajectory of these symptoms, their clinical outcomes, and factors which may contribute to these trajectories. The initial study characterizing early life wheezing phenotypes was the Tucson Children's Respiratory Study[1]. This observational study of 1246 unselected newborns assessed the presence of wheezing symptoms during the 1st 6 years of life. Four different wheezing patterns, now called phenotypes, at age 6 years were characterized: never wheezed (51.5%), transient early wheezing (wheezing by age 3 years but not between 4 and 6 years of age, 20%), persistent wheezing (wheezing at both ages 0–3 and 4–6 years, 14%) and late-onset wheezing (wheezing onset between 4 and 6 years of age, 15%). Two wheezing phenotypes associated with increased risk of persistent wheezing at 16 years were identified: persistent wheezing and late-onset wheezing[2]

Subsequent studies of other birth cohorts have identified generally similar phenotypes (see Figure 1)[3–5]. Using latent class analysis techniques, the Avon Longitudinal Study of Parents and Children identified two additional phenotypes, prolonged early wheeze and intermediate-onset wheeze(3). Prolonged early wheezers had remission after 69 months, compared with 42 months in the Tucson study, as well as increased airway responsiveness and decreased pulmonary function during school age compared with those of the never/infrequent wheeze phenotype. Intermediate-onset wheezers have symptoms which persist. This phenotype was associated with allergic sensitization, increased airway responsiveness and decreased lung function compared with never/infrequent wheezers. In the Italian Studies of Respiratory Disorders in Childhood study, similar phenotypes were identified in the Tucson study[4]. The main difference was that a greater proportion of children were never wheezers (83% vs 51% in Tucson and 59% in Avon), and fewer were early, transient wheezers (7% vs 20% in Tucson and 16% in Avon).

Predictive Indices

Using data from the Tucson cohort, the Asthma Predictive Index (API) was developed to predict the risk that a child at 3 years of life would continue to have wheezing at 6, 8, 11, and 13 years of age [6]. API status was based on the presence of frequent wheezing in the first 3 years of life, plus major (physician-diagnosed asthma in a parent, physician-diagnosed eczema) and minor criteria (physician-diagnosed allergic rhinitis, wheezing apart from colds and eosinophilia) (see Figure 2). Both stringent and loose indices were developed, with the stringent index requiring early frequent wheezing during the first 3 years of life (score of 3 or above on the 1 to 5 wheezing frequency scale) while the loose index included those who wheezed at any point during that timeframe. A positive stringent or loose index also required the presence of at least 1 major criterion or at least 2 minor criteria. Having a positive stringent API at age 1–3 years increased the likelihood of persistent wheezing between ages

6–13 by 4.3–9.8 times. A negative stringent mAPI predicts that 95% of those children will not have active asthma during the ages of 6–13 years.

The Prevention of Asthma in Kids (PEAK) trial utilized a modified Asthma Predictive Index (mAPI) as an entry criterion[7,8]. The purpose was to identify children at high risk for subsequent asthma in order to test if early initiation of inhaled corticosteroids would alter the course of early life recurrent wheezing. The mAPI was modified from the original, with the addition of allergic sensitization to at least one aeroallergen as a major criterion, and allergic sensitization to milk, eggs, or peanuts as a secondary criterion, whereas allergic rhinitis was removed as a minor criterion (see Figure 2) [3]. Prior studies had identified those sensitizations as significant predictors of childhood asthma. A positive mAPI required meeting the primary criterion of at least 4 wheezing episodes in a year, and at least 1 major or 2 minor criteria.

In a *post hoc* study of a high-risk cohort of newborns enrolled in the Childhood Origins of ASThma cohort (COAST), a positive mAPI significantly increased the probability of asthma at ages 6, 8, and 11 years, with an increase from a 30% pretest probability to 90% posttest probability in some groups[9].

A 2015 systematic review of childhood asthma prediction models identified 12 prediction models which assessed symptomatic children up to 4 years of age, and predicted subsequent development of asthma during school-age (6–12 years)[10]. Children included in the models were selected from varying populations: part from the general population, those attending health-care visits, those reported to have respiratory symptoms by their parents, and those at high risk for asthma. Four models based their predictions on clinical history only, whereas 8 included clinical tests (most commonly specific IgE testing).

Asthma predictors included in one or more of the prediction models were:

1. Demographic factors: age, sex, socioeconomic factors
2. Respiratory symptoms: wheeze, frequent wheeze, wheeze without cold, wheeze with limitations, shortness of breath or dyspnea
3. Number of bronchial obstruction or respiratory tract infection episodes and hospital admissions
4. Comorbid allergy conditions: eczema, allergy (allergic rhinitis and food)
5. Family history of asthma or allergy
6. Eosinophilia
7. Specific and or total IgE, allergen skin prick test results (to foods and aeroallergens)
8. Fractional exhaled nitric oxide (FeNO) levels
9. Preterm birth or post-term delivery

Of these, the data-based predictive factors were age, sex, socioeconomic status, respiratory symptoms, comorbid atopic conditions, specific food and aeroallergen IgE levels, preterm

birth (<37 weeks gestational age) or post-term delivery, and history of respiratory tract infections. The others were based on clinical knowledge and prior literature.

All prediction models were at risk of bias due to missing data, particularly due to loss of follow up. Furthermore, the effect of asthma treatments administered in between the two timeframes was not quantified. Another issue is that socioeconomic status and presence/absence of environmental exposures, such as to tobacco smoke or allergens, were rarely included in the models. In most cases, only aeroallergen sensitization (regardless of extent of sensitization) is included. Assessment of lung function or bronchial hyperresponsiveness was also not included.

No single model had the stand-alone ability to both rule asthma in and out. Models with a higher sensitivity for detection of subsequent asthma also had a lower specificity. The authors hypothesized that this was due to phenotype heterogeneity and the likely modifying role of environmental factors between the preschool and school-age years. Perhaps having two cut off points, one which indicates higher risk and another which indicates low risk, would increase the sensitivity and specificity of future models.

Recent Cohort Studies

Overall, asthma phenotypes, or trajectories of symptom development, appear to be heterogeneous with multifactorial modifying influences. Recent studies have continued to further characterize these phenotypes. In particular, they have expanded the focus to include environmental influences and the impact of early life intervention.

The Canadian Asthma Primary Prevention Study (CAPPS) established a cohort of 545 infants at high-risk for asthma studied from birth to 15 years of age[11]. These children were considered to be at high risk because they had first degree relatives with IgE-mediated allergic diseases[12]. A secondary analysis of this study identified fewer wheeze trajectory phenotypes (low-progressive, early-transient and early-persistent) compared with other cohorts. The low-progressive group had low rates of wheeze initially, and slowly rose to a mid-level frequency of approximately 16% at age 15 years. The early life intervention was avoidance of common allergens (house dust mite, pet allergens, environmental exposure to tobacco smoke), encouragement of breastfeeding or supplementation with a partially hydrolyzed formula. These interventions were found to decrease the risk of persistent wheezing later in life only in the early-persistent wheeze trajectory. Additionally, they found that wheezing during the second, but not first, year of life is a strong asthma risk factor[11]. Similar to other studies, male sex and maternal asthma were associated with the early-persistent trajectory. Those with atopy at 12 months had similarly increased odds ratios of subsequently being in the early-transient or early-persistent groups, when compared with the low-progressive group.

The Urban Environment and Childhood Asthma (URECA) study looked at the contributions of environmental risk factors to varying early life wheezing phenotypes[13]. It included a high-risk, inner-city cohort of 442 children followed between birth and 7 years of age. Children who live in the inner-city are known to have an increased risk of asthma

development and higher morbidity[14–16]. The investigators assessed trajectories of multiple variables[13]. Using latent class mixed models, five phenotypes differentiated by high/low wheezing and high/low atopy were identified. A unique finding in this study is that specific early life environmental exposures were found to be differentiating features for the phenotypes. Amongst children with ‘high wheeze’, high-atopy and low-atopy phenotypes were identified, and both were associated with decreased indoor allergen exposure. The high wheeze – high atopy group had greater disease morbidity. The high wheeze – high atopy and high wheeze – low atopy phenotypes were both associated with an increased frequency of asthma by age 7 years. Prenatal smoke exposure and maternal stress and depression were highest in the high wheeze - low atopy group. The high wheeze-high atopy phenotype was associated with low household dust microbial diversity. This suggests that specific risk factors such as allergen and microbe exposures, maternal stress and depression, and environmental tobacco smoke exposure may be associated with different causal pathways leading to distinct phenotypes.

The French Longitudinal Study of Children (ELFE) birth cohort assessed over 18,000 infants from 2 months to 1 year of age using surveys at 2 months and 1 year of life[17]. 6.5% and 27.5% had at least one episode of wheezing by 2 months and 1 year of age, respectively. This is slightly higher than rates found in other cohorts - 20.4% in the Columbia Center for Children’s Environmental Health cohort and 26% by 18 months of age in the ALSPAC cohort[3,18]. In the ELFE cohort, cough, respiratory distress, excessive bronchial secretion, and maternal smoking during pregnancy were found to be risk factors for wheezing at 1 year of age.

Phenotypes of atopy were further characterized using latent class analysis from two cohorts, Multizentrische Allergiestudie (MAS) and Protection against allergy: Study in Rural Environments (PASTURE) [19]. Those studies included cohorts of healthy German infants and rural European children, respectively, and assessed phenotypes of atopic sensitization during the first 6 years of life. They identified benign, symptomatic, and severe atopy phenotypes. The severe atopy phenotype accounted for 5% of the cohorts but was disproportionally responsible for sensitized asthma rates, accounting for 20%. A unique identifying feature of the severe phenotype is an increased T_H2/T_H1 ratio by 6 years of age. A sharp increase in sensitization to seasonal aeroallergens was seen prior to 3–4 years of age, and this was followed by the development of high serum IgE levels. Notably, these findings were detected prior to the development of asthma symptoms. Specifically, excessive serum IgE production was associated with impaired lung function and increased future asthma risk. These findings could be related, although the relationship is still unclear. The authors hypothesized that severe atopy, as characterized by a sharp increase in serum IgE levels prior to 3–4 years of age, could be a criterion for choosing candidates for anti-IgE therapy.

The Mechanisms of the Development of ALLergy (MeDALL) database was created with an aim to consolidate and maximize utility of the data from 14 European cohorts, with a total of over 44,000 participants[20]. The aim was to have a ‘systems medicine’ approach by linking clinical and phenotypic attributes, and biological samples. Interestingly, IgE sensitization was only found to contribute 38% of the multimorbidity of asthma, rhinitis and eczema.

Monosensitization and polysensitization to aeroallergens was found to represent two different phenotypes, with polysensitization being associated with multimorbidity of allergic diseases and onset during preschool which is earlier than the monosensitization phenotype. A severe allergy phenotype characterized by polysensitization and multimorbidity of allergic diseases was found to include relatively more persistent symptoms, more severe asthma, and higher total and specific IgE levels. They attempted to develop a predictive algorithm for development of asthma in young children by performing a systematic review of predictive models, but were unsuccessful. The authors hypothesized that the interactions with viral infections likely complicated the predictive value of asthma-like symptoms in the preschool years. This database has potential for serving as an external validator of current asthma predictive models.

U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes), part of the Innovative Medicines Initiative, is the largest public-private collaborative asthma initiative in Europe[21]. Its goal is to integrate clinical, biological and ‘omics (i.e. genomics) data via partnerships between industry, academic and patient representatives, to further our understanding of asthma including characterizing phenotypes. Analysis of the 131 preschool children in the cohort identified a milder phenotype and a severe intermittent phenotype, both of which were mostly non-atopic[22]. Analysis of the blood transcriptomic profile showed altered gene expression in adults with asthma, but was poorly defined in preschool age children[23]. These findings reinforce that preschool asthma phenotypes are particularly heterogeneous and difficult to characterize, highlighting the importance of multi-factorial characterization approaches.

Modifying factors for asthma development

Although the pathogenesis and necessary timing of exposures have yet to be clearly elucidated, a few modifying factors have been identified in the preschool group which alter the rates of subsequent wheezing. Farm animal exposure decreased the rates of wheezing during the 1st year of life, whereas presence of an older sibling was associated with increased wheezing incidence[24]. Multiple early sensitizations have been identified as significant asthma risk factors[19,25,26]. Low socioeconomic status, comprised of a composite outcome including factors such as lower parental education levels, occupational class, and household income, was associated with increased asthma rates[27]. Antibiotic use during the first year of life has been linked with the development of transient wheezing and persistent asthma[28]. Maternal smoking is associated with increased rates of wheezing at age 6 years, particularly in nonatopic children[27,29].

Conclusion

Wheezing and asthma phenotypes during the preschool years are heterogeneous, and ongoing modifications occur during the subsequent years which can alter the trajectory of the disease. Increasing knowledge of modifying factors is being elucidated, although more research is needed. As more knowledge is gained, additional aims include improving asthma predictive indices, modifying and preventing future asthma risk, and characterizing economic costs and effects on quality of life associated with each phenotype.

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Key points

- Birth cohorts have provided valuable information about preschool wheezing phenotypes and symptom trajectories.
- Using asthma predictive indices can be helpful for predicting wheezing trajectories.
- Contributing factors of wheezing phenotypes, such as aeroallergen sensitization and early life environmental exposures, have been identified.

	Tucson Children's Respiratory Study[1]	Italian Studies of Respiratory Disorders in Childhood and the Environment[4]	Avon Longitudinal Study of Parents and Children[3]
Initial age:	≤3 years	≤2 years	6-18 months
Final age:	6 years	5-7 years	5-7 years
Phenotypes (%):			
1. *Never wheezers*	51%	83%	59%*
2. *Early, transient wheezers*	20%	7%	16%
3. *Prolonged early wheeze*			9% (wheezing 6-54 months of age, not after 69 months)
4. *Intermediate-onset wheeze*			3% (onset at 18-42 months, persists)
5. *Persistent wheezers*	14%**	4%	7%
6. *Late onset wheezers*	15%	6%	6%

Figure 1: Comparing the historic birth cohorts

*includes infrequent wheezers

**includes atopic and nonatopic sub-phenotypes

	Asthma predictive index (API) [6]	Modified asthma predictive index (mAPI) [7]
Positive index requirements: Wheezing PLUS at least 1 major or 2 minor criteria	Wheezing during first 3 years *Loose*: any wheezing *Stringent*: early frequent wheezing	At least 4 wheezing episodes per year
Major Criteria:	1. Physician-diagnosed asthma in a parent 2. Physician-diagnosed eczema	1. Physician-diagnosed asthma in a parent 2. Physician-diagnosed eczema *3. Allergic sensitization to at least one aeroallergen*
Minor Criteria:	1. Physician-diagnosed allergic rhinitis 2. Wheezing apart from colds 3. Eosinophilia (at least 4%)	*1. Allergic sensitization to milk, eggs, or peanuts* 2. Wheezing apart from colds 3. Eosinophilia (at least 4%)

Figure 2:
Original and modified asthma predictive index criteria