

Accepted Manuscript

One step forward, two steps back: The enigma of preschool wheeze

Anne M. Fitzpatrick, Ph.D., Leonard B. Bacharier, M.D.



PII: S0091-6749(19)30029-6

DOI: <https://doi.org/10.1016/j.jaci.2019.01.005>

Reference: YMAI 13829

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 20 November 2018

Revised Date: 2 January 2019

Accepted Date: 8 January 2019

Please cite this article as: Fitzpatrick AM, Bacharier LB, One step forward, two steps back: The enigma of preschool wheeze, *Journal of Allergy and Clinical Immunology* (2019), doi: <https://doi.org/10.1016/j.jaci.2019.01.005>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

One step forward, two steps back: The enigma of preschool wheeze

Editorial in response to JACI-D-18-00761_R1 (Oksel et al.)

Anne M. Fitzpatrick, Ph.D.^{1,2}

Leonard B. Bacharier, M.D.³

¹ Emory University Department of Pediatrics, Atlanta, Georgia

² Children's Healthcare of Atlanta, Atlanta, Georgia

³ Washington University Department of Pediatrics, St. Louis, Missouri

Word count = 1,024

Key Words

Asthma

Wheezing

Phenotype

Endotype

Children

Latent class analysis

Preschool

21 **Disclosures:**

22 Anne M. Fitzpatrick:

23 Nothing to disclose

24 Leonard B. Bacharier:

25 Dr. Bacharier reports personal fees from GlaxoSmithKline, personal fees from
26 Genentech/Novartis, personal fees from Merck, personal fees from DBV
27 Technologies, personal fees from Teva, personal fees from Boehringer Ingelheim,
28 personal fees from Sanofi/Regeneron, personal fees from Vectura, personal fees
29 from Circassia, personal fees from AstraZeneca, outside the submitted work.

Wheezing is a common and troubling symptom in preschool children that is associated with significant morbidity and costs both in the United States and worldwide.¹ Indeed, nearly 50% of all children may wheeze at some point during early life.² However, wheezing and respiratory difficulty do not constitute a “syndrome,” defined as a set of symptoms that are linked with a specific pathogenesis (**Figure 1**). Instead, wheezing in preschool children is quite heterogeneous in nature, with many underlying mechanisms that likely contribute to differing temporal disease trajectories. As such, the evidence base remains quite limited. Appropriate identification or classification of preschool children for the purpose of clinical assessment, therapeutic delivery and preventative care is a primary unmet need.

In this issue of the *Journal of Allergy and Clinical Immunology*, Oksel et al.³ aim to refine mathematically-based “phenotyping” (i.e., classification) methods in preschool children with wheezing, which group children into groups with shared observable characteristics. The authors extend a number of prior phenotyping studies of young children with wheezing through examination of multiple sources of variability in phenotype classification. The authors found that sample size, frequency of measurement, timing and distribution of data collection time points, model dimensionality, and a combination of these factors were all critical to the identification of phenotypes by latent class analysis (**LCA**). The final or “ideal” statistical model, which optimized sample size and data collection time points, yielded 6 distinct phenotypes similar to what have been reported previously: 1) never/infrequent wheeze, 2) persistent wheeze, 3) early-onset preschool remitting wheeze, 4) early onset mid-childhood remitting wheeze, 5) school age-onset wheeze, and 6) late childhood-onset wheeze. Interestingly, “never wheezing” and “persistent wheezing” groups were relatively stable in transition analyses across multiple time points (i.e., the probability of remaining in those groups was >80% for each). However,

intermediate wheezing classes were the most sensitive to methodological variations and displayed the highest variability in lung function outcomes at age 23-24 years.³

Primary strengths of the study were the large birth cohort design that captured all children with wheezing regardless of severity and biological risk and the extensive data collection procedures across 14 time points between birth and 16½ years. The final or “ideal” statistical model, which yielded 6 different wheeze phenotypes, also has strong biologic plausibility given observations of lower pre- and post-bronchodilator lung function measures in the persistent wheezing group, which is consistent with independent reports.² The authors therefore conclude that collection of data at critical time points during lung maturation is essential for identification of consistent and reproducible phenotypes in future studies. The authors also assert that utilization of critical versus non-essential time points may counterbalance suboptimal study designs involving smaller sample sizes and less frequent data collection procedures.

The results of the study by Oksel et al.³ highlight several challenges associated with phenotyping of preschool children with wheezing that require some deliberation and consensus before personalized or precision medicine can become a reality.^{4, 5} As stated by the authors, the quest for phenotypes in young children has been extensive; however, there is little agreement on what constitutes a “phenotype” or how to best identify them. Indeed, LCA is a person-centered “top-down” versus as variable-centered “bottom-up” analysis and thus different data sets are expected to yield somewhat different results. Furthermore, although LCA is model-based and allows comparisons to be statistically tested with criteria that permit decision-making about the final model, there is universally-accepted set of criteria for determining the number of latent classes within a dataset. Low-prevalent groups may therefore be ignored even when sample sizes

are quite large. Alternatively, high-prevalent groups can be subject to redundancy with an unnecessarily large number of latent classes.

Second, whereas several studies such as that by Oksel et al.⁵ have focused only on lung function variables, others have also included other observable clinical features such as symptoms and allergic sensitization variables in the phenotype identification models.^{6, 7} There is currently no consensus on which approach is best for the purpose of personalized care delivery. Indeed, some have argued that a “phenotype” *may or may not be* associated with an underlying disease mechanism but provides an opportunity for application of personalized therapy (for example, a patient with persistently low lung function despite therapy attempts).⁸ However, an important goal for time-efficient and resource-efficient clinical care is to refine clinical phenotypes and align them with biological “endotypes” to avoid excessive diagnostic evaluation prior to therapy initiation. In this view, an endotype is a subtype defined by a distinct biological mechanism that links clinical characteristics with a molecular pathway. This would be particularly advantageous in preschool children, in whom routine laboratory, physiologic and imaging studies can be difficult to obtain. Yet unfortunately, alignment with endotypes is still a distant goal. It is still not clear how phenotypic risk factors for asthma (such as family history and allergen exposure) interact in young children, or how these risk factors lead to overt disease. It is also unclear which molecular pathways underlie clinical phenotypes in preschool children and how these phenotype/endotype associations change over time.

Finally, young children are uniquely challenging from both a developmental and research perspective. Animal models are inadequate in recapitulating preschool wheeze and the dynamic nature of this age group prohibits extrapolation of previously-identified phenotypes of wheezing in older children.² While Oksel et al.³ should be commended for their work and their quest to

improve and advance phenotypic identification and application in young children, the relative paucity of research in this population is a significant barrier. It is unclear how older birth cohorts such as the one in the present study generalize to modern-day populations and the most vulnerable populations at highest risk for asthma development and the poorest asthma outcomes. Indeed, the lung function values noted by Oksel et al.³ in early adulthood were remarkably high. While the relatively low prevalence of persistent wheezing in that study was consistent with epidemiologic reports,⁹ children with preschool-onset severe asthma may have a different trajectory that is challenging to identify with a birth cohort design. Therefore as we take “one step forward” with the important insights from this study, we also recognize that we may be further behind than once realized.

Figure Legend. (word count = 60)

Association between phenotypes and endotypes in preschool children with asthma “syndrome.”

A syndrome is a set of symptoms that are linked with a specific pathogenesis (asthma). In our view, asthma syndrome is a heterogeneous “umbrella;” there are many possible “phenotypes” within this syndrome. Each phenotype is also associated with distinct endotypes (biological mechanisms) that can be targeted with personalized approaches.

References

1. Makrinioti H, Klaber R, Watson M. Around the world: preschool wheeze. *Lancet Respir Med* 2017; 5:688-9.
2. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *New Engl J Med* 1995; 332:133-8.
3. Oksel C, Granell R, Mahmoud O, Custovic A, Henderson AJ. Causes of variability in latent phenotypes of childhood wheeze. *J Allergy Clin Immunol*.
4. Belgrave D, Henderson J, Simpson A, Buchan I, Bishop C, Custovic A. Disaggregating asthma: Big investigation versus big data. *J Allergy Clin Immunol* 2017; 139:400-7.
5. Brand PLP, Schultz A. To track or not to track: wheeze phenotypes in preschool children. *Eur Respir J* 2018; 51.
6. Fitzpatrick AM, Bacharier LB, Guilbert TW, Jackson DJ, Szeffler SJ, Beigelman A, et al. Phenotypes of Recurrent Wheezing in Preschool Children: Identification by Latent Class Analysis and Utility in Prediction of Future Exacerbation. *J Allergy Clin Immunol Pract* 2018. doi: 10.1016/j.jaip.2018.09.016.
7. Bacharier LB, Beigelman A, Calatroni A, Jackson DJ, Gergen PJ, O'Connor GT, et al. Longitudinal Phenotypes of Respiratory Health in a High-Risk Urban Birth Cohort. *Am J Respir Crit Care Med* 2018.
8. Fitzpatrick AM, Moore WC. Severe Asthma Phenotypes - How Should They Guide Evaluation and Treatment? *J Allergy Clin Immunol Pract* 2017; 5:901-8.
9. Moorman JE, Akinbami LJ, Bailey CM, Zahran HS, King ME, Johnson CA, et al. National surveillance of asthma: United States, 2001-2010. *Vital Health Stat* 3 2012;1-58.

Variability

Sample sizes for phenotype identification
Frequency and timing of measurement
Distribution of data collection procedures
Statistical modeling considerations

Wheezing/Asthma syndrome

Variable & recurring symptoms, airflow obstruction, bronchial hyper-responsiveness & inflammation

Wheezing/Asthma syndrome

Phenotypes

Observable characteristics such as clinical presentation, symptoms, triggers and allergic features

Phenotype

Phenotype

Endotypes

Subtype defined by a distinct biological mechanism that links clinical characteristics with a molecular pathway

Endotype

Endotype

Endotype

Personalized therapy

