Childhood Wheeze Patterns: What Do They Tell Us?

The relationship between childhood wheeze and increased risk of asthma/lung disease is well established, and latent class analysis (LCA) of wheezing patterns has done an excellent job of categorizing childhood wheeze into different subcategories with differing risks of asthma development and associations with higher or lower levels of pulmonary function (1–3). However, the description of these categories often varies between studies because of sample size, timing, frequency of data collection, and potentially imprecise classification of an individual into a category. In this issue of the *Journal*, Haider and colleagues (pp. 883–893) use a data-driven, novel, dynamic "spell-based" approach and apply partition around medoids (PAM) clustering on these spell indicators to derive wheezing phenotypes, as opposed to applying LCA to the binary question of wheeze versus no wheeze (4). This spell-based approach incorporated six multidimensional longitudinal indicators, including the duration of wheezing episodes. It was applied to data from 7,719 participants from the STELAR (Study Team for Early Life Asthma Research) consortium, an established consortium of five birth cohorts with harmonized data (3). Using this spell-based approach, the authors categorized wheeze into five classes: never (NWZ; 54.1%); early-transient (ETW; 23.7%); late onset (LOW; 6.9%); persistent (PEW; 8.3%); and a novel phenotype, intermittent wheeze (INT; 6.9%). This differed from previous analyses that used LCA, which most often identified four consistent wheeze phenotypes: NWZ, ETW, LOW, and PEW (1–3).

The wheezing phenotypes derived from the dynamic spell-based approach on their surface appear similar to those derived from LCA, but addition of the INT group created more homogeneous phenotypes. For instance, the spell-based NWZ group had no wheezing, whereas in the LCA NWZ group, 10% had occasional wheezing. The spell-based ETW group reported no wheezing after 10 years of age, whereas in the LCA ETW group, some children reported wheeze to age 18 years. Similarly, in the spell-based LOW group, there was no wheezing before the age of 8, whereas in the LCA LOW group, there was wheezing at earlier ages. The PAM spell-based grouping also appeared more stable in terms of children's assignments and predicting asthma and pulmonary function.

The spell-based approach demonstrated that all four wheeze phenotypes compared with the NWZ phenotype were associated with a higher risk of asthma diagnosis and medication use in adolescence, with 3.4% of the ETW class having an asthma diagnosis in the PAM spell-based model versus 8.4% in the LCA binary model, illustrating increased homogeneity in the spell-based approach. Importantly, the majority of asthma risk fell in the LOW, PEW, and INT spell-based classes and relatively little in the NWZ and ETW groups. All four spell-based classes of wheeze were significantly associated with decreases in FEV_1/FVC in adolescence, with the PEW and INT classes being consistently lower than the ETW and LOW groups. Interestingly, the LOW group still showed increased risk of asthma, despite decreases in FEV_1/FVC less than those observed in the INT and PEW groups. The FEV_1/FVC was significantly lower in all wheeze phenotypes compared with the NWZ group, supporting the premise that the children with wheezing phenotypes likely did not reach normal maximum lung function in early adulthood. The FEV_1/FVC was consistently lower in the PEW and INT groups than in the ETW and LOW phenotypes and thus could have the greatest predisposition to chronic obstructive pulmonary disease over time. Of all wheeze phenotypes, the novel INT group was the only phenotype to have a decline in their *z*-score for FEV_1/FVC from ages 8 to 24 in both cohorts, suggesting an early decline in lung function for this group.

Genetic analysis showed that 17q12–21 and *CDHR3* polymorphisms were associated with higher odds of PEW and INT but not with LOW, thus suggesting that LOW is quite different from PEW and INT (4). This is also in contrast to findings from other investigators that demonstrated similar associations between multiple SNPs in the 17q12–21 locus and all LCA wheezing phenotypes (5). This suggests that a more thorough slicing and dicing of wheeze phenotypes will facilitate better genetic linkage and explanations of cause.

Thus, a key finding of this paper is that better wheeze classification will potentially allow better correlation with genetic and epigenetic mechanisms as well as prenatal and postnatal exposures. This can lead to better prevention strategies by prioritizing and modifying the many potential risk factors for wheeze. Although complex, some of these potentially modifiable prenatal factors include preterm deliveries, intrauterine growth restriction, smoking in pregnancy, toxin exposure, placental abnormalities, maternal nutrition, inflammation, stress, obesity, and delivery mode (1). Potential postnatal factors include breastfeeding duration, viral infections, allergen exposures, and the lung–gut microbiome, among others. Greater understanding of wheeze phenotypes will facilitate development of targeted therapies, potentially *in utero* or early in postnatal life, such as vitamin C supplementation during pregnancy, antigenic exposures, and vitamin D supplementation (6–9). Understanding the interaction of specific wheeze phenotypes with specific genotypes has particular promise (10).

This study raises a number of unanswered questions. Will different approaches be needed to prevent the different types of wheeze? How much heterogeneity still resides in these five classes? What are the relative prenatal versus postnatal causes of these classes and the role of environmental pollution? Which of these phenotypes may predispose individuals to chronic obstructive pulmonary disease? How will the novel INT phenotype evolve beyond early adulthood?

Supported by NHLBI grants R01HL105447 and R01HL129060 and NIH grants UH3OD023288 and P51-OD011092 (C.T.M. and E.R.S.).

Originally Published in Press as DOI: 10.1164/rccm.202201-0108ED on February 23, 2022

There are a number of limitations to this paper. To some extent, it represents only an incremental advance over the LCA approach. It relies heavily on imputation, and it may be difficult for other groups to replicate this analytic approach, depending on the needed sample size. The population studied does not appear to be racially diverse. A recent study using LCA showed similar wheeze patterns in White and African American children; however, the African American children were more likely to be in the PEW group (5). A study of 11,000 children showed the incidence rates of asthma among African American children with no family history of asthma were markedly higher than those of non-Hispanic White children during the preschool years (11). Thus, how the wheeze classification described here may change with a more diverse population remains to be determined. The cohorts also did not perform early-life airway function tests that could have helped identify early-life associations with wheeze phenotypes.

Wheeze phenotypes such as lung function trajectories are at least partially established by perinatal factors, allowing the potential for primary prevention with early-life interventions (12). More precise clustering of wheeze phenotypes as described here has the potential to facilitate these strategies. This paper once again demonstrates the importance of longitudinal, diverse birth cohorts to identify the possible genetic, prenatal, and environmental factors associated with different wheeze phenotypes and their association with lung function trajectories, lung disease, and prevention strategies. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Bronchiectasis, the Latest Eosinophilic Airway Disease
What About the Microbiome?

Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous conditions in which biomarkers can help identify individuals who require different management strategies. In asthma, higher type 2 biomarker measurements, including blood eosinophil counts (BECs), can identify individuals with a greater likelihood of a positive corticosteroid response or those with severe asthma who are candidates for biological therapies directed against type 2 inflammation (1).

The Global Initiative for Chronic Obstructive Lung Disease management strategy supports the use of BECs in patients with COPD with increased exacerbation risk to help direct appropriate inhaled corticosteroid (ICS) use (2). The relationship between BEC and ICS effects is continuous; a BEC $<$100 cells/μl identifies individuals with no or little possibility of ICS benefit, with the

Supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC) (D.S.) and the Leicester NIHR BRC (C.B.).

Originally Published in Press as DOI: 10.1164/rccm.202201-0105ED on February 25, 2022