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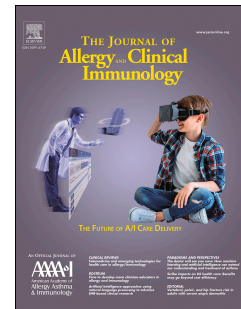
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Preschool wheeze phenotypes from birth cohorts, where do we go from here?

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More than 25 years have passed since Martinez et al. first published results from the Tucson Children's Respiratory Study describing early life wheeze phenotypes and their relationships to persistence of wheeze into school age and lung function.(1) Subsequent birth and early life cohort studies have further advanced understanding of early childhood wheeze phenotypes and their associations with asthma and lung function development. Despite heterogeneity in designs, populations, and analysis strategies between studies several consistent observations have emerged, including an association between maternal asthma and persistent wheezing or asthma.(1,2) Transient wheezing has consistently been associated with male sex, daycare attendance, and having siblings(2), and has been associated with greater airflow obstruction compared to children who never wheezed, perhaps resulting from impaired airway growth that persists to adulthood and may be a risk factor for COPD.(3) Most studies have observed a higher prevalence and longer duration of wheeze among boys until early adolescence. However, there are inconsistencies between studies with regards to associations between early-life breastfeeding, paternal asthma, pet ownership, and birth order as risk factors for wheeze phenotypes. Importantly, despite over 2 decades of research, managing a preschool age child with wheeze and accurately predicting future asthma or lung function remains challenging, impairing decision-making regarding appropriate treatment for an individual child as well as the design of population-level asthma prevention strategies.

In this issue of the *Journal of Allergy and Clinical Immunology*, Dai et al. present data from the CHILd birth cohort wherein they identify wheeze trajectories and examine environmental and genetic factors associated with those trajectories, lung function, and outcomes through age 5 years in over 3,000 Canadian children.(4) Subjects completed detailed high frequency questionnaires from ages 3-60 months, food and aeroallergen testing at 1, 3, and 5 years, and measurement of blood eosinophil counts at 1 and 5 years. Group-based trajectory models (GBTM) was used to classify subjects into wheeze trajectories, whereas most prior studies used latent class analysis approaches. GBTM assume a population is comprised of distinct groups each with a unique trajectory, classify groups of subjects that follow similar trajectories over time, and estimate impacts of factors on trajectory pattern as well as on group membership within each trajectory. The authors identified four distinct wheeze trajectories that are consistent with the Tucson study(1) and more recent Project Viva cohort.(5) All trajectories were associated with increased asthma risk at age 5 years, albeit associations were strongest for intermediate-onset and persistent wheeze phenotypes. Lower lung function was observed at age 5 years among all trajectories as compared to children who never wheezed. Similar to the Tucson cohort, both transient and persistent wheeze phenotypes in CHILd had greater airway obstruction at age 5 years than children without a wheeze history. Interestingly, although the proportions of sexes in each trajectory differed between boys and girls, the patterns were similar between the sexes. Although 36% of the CHILd cohort is reported as multiethnic or "other", the majority of participants are Caucasian, a limitation if results are generalized to non-Caucasians with higher rates of asthma and asthma morbidity.

GBTM used in this study also included a Genetic Risk Score (GRS) for each subject using 4 single nucleotide polymorphisms associated with asthma identified in the largest childhood asthma GWAS study to date(6), followed by an exploratory analysis using an alternative GRS including 42 variants associated with childhood- and adulthood-onset asthma. A child's own genetic asthma risk was associated with greater odds of intermediate-onset wheezing but not with persistent asthma. However, it is premature to rule out possible genetic factors associated with asthma phenotypes that are not

apparent by age 5 years (e.g. adolescent-onset female asthma). After adjusting for asthma genetic risk, only maternal asthma remained a factor associated with persistent wheeze. Similar to previous data(2), this observation confirms that the in utero environment impacts the development of persistent wheeze. This finding supports hypotheses that both genetic and epigenetic factors explain the association between maternal asthma and infant persistent wheeze. However, in addition to the authors' suggestion that maternal-fetal transfer of immune cells or cytokines may modify the early life immune system, other in utero and postnatal environmental factors may explain this observation, including impacts on the infant immune system by the microbiome. A limitation in this CHILD analysis is the lack of inclusion of maternal prenatal and infant postnatal antibiotic use. However, the CHILD study has likely collected data to support future investigations of the impact of the microbiome on asthma evolution. Finally, paternal asthma was only associated with intermediate-onset wheeze, which the authors speculate might reflect airway hyperresponsiveness (AHR) given that AHR has previously been associated with paternal asthma.(7) Since the CHILD cohort has now matured to school age, ideally future follow-up visits will include AHR testing and a GRS enriched for variants associated with AHR.

In this analysis of the CHILD cohort eosinophil counts at age 5 years were higher in intermediate-onset and persistent wheeze as compared to transient and never/infrequent wheeze, suggesting that these trajectories are enriched with children with evolving T2-high asthma. Furthermore, at age 1-year eosinophil counts were highest in the intermediate-onset wheeze group, a finding generally consistent with data from the Tucson cohort(8) demonstrating that inclusion of eosinophil counts in the Asthma Predication Index (API) strengthened the predictive value of the API for asthma in preschool children.

Prior cohort studies have reported conflicting results regarding associations between breastfeeding and other post-natal environmental exposures and early life wheeze trajectories. The CHILD analysis did not observe consistent associations between wheeze trajectories and breastfeeding, pet exposure, NO₂, PM_{2.5}, or prenatal or postnatal smoking. They did observe that daycare attendance was associated with transient wheeze. When stratified by GRS, exclusive breastfeeding at age 3 months was associated with a lower risk of intermediate-onset wheeze in children with a low or moderate GRS, whereas among children with a high GRS breastfeeding was associated with an increased risk of intermediate-onset wheeze, providing a potential explanation for conflicting observations from prior studies.(9). However, the authors are correct that these observations are too preliminary to support changes to public health recommendations around breast feeding infants with asthma genetic risk factors. These results require replication and investigation to probe potential explanatory mechanisms.

Recognition of heterogeneity in asthma based on identification of asthma endotypes with unique underlying pathophysiology (e.g. T2 high vs. T2 low asthma), and development of therapies targeting specific endotypes, has significantly improved albeit primarily for T2-high endotypes.(10) However, our understanding of how early childhood wheeze trajectories relate to asthma endotypes remains limited. Past cohort studies were not optimally designed to serially measure potential biomarkers of evolving asthma endotypes (e.g. exhaled nitric oxide, mass spectrometry of exhaled breath or urine) or collect biospecimens to facilitate mechanistic insights through assessment of immune cell, genetic, epigenetic, proteomic, metabolome and microbiome profiling using systemic samples (e.g. peripheral blood), airway epithelial samples (e.g. nasal brushings), and paired maternal-fetal blood samples. Additionally, high-resolution surveillance of viral infection is lacking from most birth cohort studies. The lack of incorporation of these data into cohorts has resulted from technologic advancements after study launch as well as cost and logistical limitations.

104 The CHILD study has added a tremendous dataset to the literature that has advanced our
105 understanding of early life wheeze trajectories, and the cohort likely includes a plethora of data yet to
106 be analyzed with great potential for further discovery of factors impacting asthma evolution. Going
107 forward it is crucial for birth cohorts to include robust longitudinal collection of biospecimens using
108 acquisition and storage methods that facilitate viral surveillance, assessment of epithelial gene
109 expression, and epigenomic, proteomic, metabolome, microbiome, and immune cell profiling that can
110 be correlated with clinical outcomes and environmental exposure data (**Fig 1**). Increased ethnic diversity
111 of cohorts is also critical. Building cohorts that leverage “big data” computational analysis
112 methodologies will require creativity, collaboration between international teams, and innovative
113 funding mechanisms. However, if we are to truly understand the evolution of childhood asthma and
114 develop robust prediction tools that support precision medicine approaches to guide therapy in young
115 children with wheezing, such approaches will be essential.

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150 **FIG 1.** Improved understanding of determinants of wheeze persistence, school age asthma, and lung
151 function in childhood will require robust longitudinal surveillance of viral infection, airway epithelial
152 gene expression, and epigenomic, proteomic, microbiome, and immune profiling correlated with clinical
153 outcomes, biomarkers and environmental exposure data. *FENO*, fraction of exhaled nitric oxide.

