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Respiratory phenotypes during childhood and early life exposures

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It is widely accepted that childhood asthma is not a single disease, but a heterogeneous condition with multiple dimensions which involve atopy or allergic sensitization, poor lung function, airway responsiveness and a variety of symptoms. For the most common symptom, wheezing, a number of distinct patterns of early childhood wheezing have been identified and consolidated by using data-driven approaches (1). Similarly, distinct patterns for allergic sensitization (2) and lung function (3) using data from several birth cohorts have recently been reported.

Here, Bacharier and colleagues have combined distinct trajectories of wheezing and allergic sensitization together with pulmonary function measures in a single model using data from 442 participants from the URECA birth cohort, a well followed up high risk population (4).
The study identified five respiratory phenotypes from birth to 7 years mainly differentiated by patterns of wheezing and allergic sensitization: low wheeze-low atopy; low wheeze-high atopy; transient wheeze-low atopy; high wheeze-low atopy and high wheeze-high atopy. Differences in lung function variables were less pronounced with the greatest impairment in lung function seen in the two high wheeze phenotypes. Phenotype-specific crude associations with potentially modifiable early life environmental exposures were also reported.

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In a pioneering study that involved categorizing 826 children with wheeze data collected at three and six years of age, Martinez et al. (5) reported four mutually-exclusive wheezing phenotypes (no wheezing, transient early wheezing, late-onset wheezing and persistent wheezing). This finding was confirmed in several independent cohort studies (6,7) and later extended using data-driven approaches to include more intermediate phenotypes (1, 8-12). In some of these studies phenotype-specific associations with atopy and lower lung function were reported (8, 10). Furthermore, several different phenotypes of atopic sensitization which differ in their relation with asthma presence and severity have been identified throughout childhood in different population-based birth cohorts (2, 13).

It has been reported that different phenotypes of childhood wheezing have different environmental associations (5, 11, 14) and similarly, different phenotypes of allergic sensitization differ in their environmental risk factors (15); Although the effect of most environmental factors is likely to vary across subjects with different genetic predispositions, the underlying mechanisms driving gene-environment interactions remain uncertain.

One of the strongest points of the study presented by Bacharier and colleagues is the availability of deep phenotyping: wheezing reports available annually from birth to 7 years, allergic sensitization (specific skin prick test or IgE) available at year 2, 3, 5 and 7 and lung function measures (mean and standard deviation FEV_1/FVC) available annually from 3 to 7 years. The methods used are based on repeated objective measures which are often unavailable in large birth cohorts. Bacharier and colleagues have conducted the first study to combine wheezing, atopy and lung function longitudinal data in a single model; first by

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identifying distinct trajectories for wheezing and allergic sensitization using latent class mixed models and second by combining these two sets of trajectories together with repeated lung function measures in a single clustering model. The resulting 5 distinct respiratory phenotypes were mainly characterised by patterns of wheeze and atopy; the transient wheeze-low atopy phenotype supports previous results reporting no associations between the early wheezing phenotypes and atopy or specific allergen sensitisation (8).

The combination of deep phenotyping and sophisticated methodology represents a major strength of this study which optimises the use of the available repeated measures. This approach provides deep characterization of this high-risk population with exclusive crude associations reported for maternal stress, depression, prenatal tobacco smoke exposure and high wheeze-low atopy phenotype, indoor allergens and low wheeze phenotypes and low household microbial richness and high wheeze-high atopy phenotype. However, there are limitations in this study, the small sample size (n=442) might have influenced the optimal number of phenotypes identified, furthermore the classification of participants into 5 respiratory phenotypes means the associations with early environmental factors might have been underpowered. An attempt was made to identify lung function trajectories, however the age window for this study (0 to 7 years) might just be too early to distinguish distinct lung function patterns. A recent study using longitudinal measures of lung function from two population-based birth cohorts identified four distinct lung function trajectories extending from early school age (5 years) into adulthood (24 years) (3). BMI trajectories were identified in the first phase of the modelling approach (distinct longitudinal trajectories) but were not included

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in the second phase (clustering of trajectory and objective variables) because they did not contribute to the resolution of the resultant phenotypes.

Children living in the inner-city are more likely to develop asthma and to experience more severe asthma symptoms than children from general populations. In the USA, people from African-American communities living in deprived communities are at particular risk (16). These differences might have shaped the resulting phenotypes which cannot be generalised to the general population. Replication of these findings in a larger birth cohort from a general population would be ideal but will be challenging given the richness of data required. However, the fact that previously identified key exposures such as maternal stress and depression, prenatal tobacco smoke exposure, indoor allergens and the microbiome have also been identified in this study might suggest a common pathway of disease for both general and high-risk populations.

It is becoming more evident that symptoms such as wheezing, the presence of allergic sensitization and lung function all interplay in the risk of distinct forms of childhood asthma. Furthermore, different genetic and environmental risk factors, and the interaction of these, contribute to the risk of distinct respiratory phenotypes. The next step is to causally associate these phenotypes with underlying mechanisms, driven by distinct molecular, genetic, environmental, and demographic characteristics. This will enable us to define and refine asthma endotypes with the ultimately goal being to develop mechanism-based strategies to prevent childhood asthma.

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