# Data-driven Asthma Phenotypes in Childhood

## Does the Environment Hold the Clue?

For decades, doctors have diagnosed childhood asthma on the basis of medical and family history, physical examination, and if possible, allergy and lung function testing in older children. However, with the currently available clinical tools, we are still not able to accurately predict which children wheezing in preschool will have asthma at school age, and in which children symptoms are of a transient nature (1).

In a seminal article published in 1995, Martinez and coworkers identified different longitudinal patterns of wheeze: transient, persistent, and late onset (2). In the last 10 years, data-driven approaches including latent class and cluster analysis of asthma and wheezing phenotypes in large birth cohorts have confirmed the presence of these wheezing phenotypes (3) and suggested two additional phenotypes: prolonged early wheezing and intermediate-onset wheezing (4, 5). The similarity of these phenotypes observed in different populations is remarkable and suggests that they represent distinct clinical entities. However, there are limitations to these studies, which include low power to detect associations with risk factors for the rare phenotypes because of limited sample sizes in birth cohorts, selective loss to follow-up, and the use of parental-reported symptoms instead of medically confirmed diagnoses.

In this issue of the *Journal*, Sbihi and colleagues (pp. 607–613) present the results of a large, registry-based cluster analysis from the Greater Vancouver area in Canada (6). Through linkage of data registries, they assembled a population-based cohort of more than 65,000 children followed-up from birth to 10 years of age. Group-based trajectory modeling revealed three different asthma trajectories next to a no-asthma group: transient asthma, early-onset asthma before the age of 1 year, and a later asthma onset, before the age of 3 years (6). This analysis, the largest data-driven asthma phenotype analysis published to date, used diagnoses based on physician billing and hospital discharge records and had excellent power. Of all singleton children born in 1999–2002 in the study area, 65,254 (88.9%) could be included in this study, limiting the possibility of selection bias. The asthma patterns observed in this study are very similar to three of the longitudinal wheezing phenotypes that have been observed in birth cohorts. As a consequence, evidence supporting the presence of different longitudinal asthma/wheezing phenotypes is accumulating. However, what can we learn from the identification of these longitudinal phenotypes, in terms of prognosis and genetic and environmental risk factors?

First, there is a strong association of persistent wheezing phenotypes (wheeze $>$ age 3 yr) and school age asthma, with those phenotypes of wheeze persisting into adolescence, showing low lung function growth (7). Second, these wheezing phenotypes likely represent distinct clinical entities that have specific genetic and/or environmental risk factors and interactions with sex (3). For example, genetic variation in the genes encoding interleukin 33 (*IL-33*) and its receptor *IL1RL1* were more strongly associated with intermediate-onset and late-onset wheeze than a doctor's diagnosis of asthma (8). In contrast, the *ORMDL3*/*GSDMB* asthma gene variants on chromosome 17q were associated with transient early wheeze in Central European farmers' children (9), and with persistent and intermediate-onset wheeze in a general population from the United Kingdom (10), suggesting gene–environment interactions in different populations.

In their paper, Sbihi and coworkers focus on environmental factors during pregnancy: maternal exposure to air pollution and residential greenness (6). Although mechanistic support for a causal role of ambient air pollution in the development of asthma is strong, and evidence from prospective cohort studies for such a role is growing (11, 12), residential greenness has only recently been linked to asthma, and findings are mixed (13). An advantage of the study by Sbihi and coworkers over previous studies that relied on incidence or age at onset only is the association with specific longitudinal asthma phenotypes (6). Associations of air pollution with asthma phenotypes were largely limited to $NO_2$, which, in the past, has been suggested as a marker for the complex mixture of traffic-related air pollutants. More recently, however, it has been concluded that $NO_2$, either individually or in combination with other pollutants, may cause adverse health effects (14). Differences in exposure-response patterns were observed for the three different asthma phenotypes, but for none of the phenotypes was a clear dose–response relationship found. Furthermore, the authors acknowledge the lack of complete address histories for the cohort participants and the restriction to maternal residential exposure during pregnancy as limitations of the study. Although the importance of prenatal and early life exposure has been supported by several studies, it cannot be ruled out that exposure later in life is also associated with the progression of asthma, and that changes in exposure, for example, as a result of moving to an address with higher or lower levels of exposure, might be at least partly related to onset or remission of asthma in these children.

Green spaces have been suggested to have beneficial effects on physical and mental health and well-being by increasing physical activity and social contacts and relieving stress (15), and may have beneficial effects on asthma development through overweight (through physical activity) and stress reduction. In contrast, the presence of trees and grasses results in increased pollen exposure, which may increase the risk for allergic asthma. The Normalized Difference Vegetation Index from satellite images that has been used many epidemiological studies, including the study by Sbihi and coworkers, is a very general marker of exposure to greenness and does not provide information about the specific types or of the actual use of green spaces, for example, for physical activity, by the study participants (6). This may explain the lack of associations between asthma and greenness in the present study.

In conclusion, this work strongly underlines the heterogeneity of childhood asthma and underscores the adverse effects of early-life exposure to $NO_2$. It also shows that linking large data sets of health registries may provide important insights into asthma development in the first 10 years of life. Further research is needed to identify

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clinical markers that could be used to diagnose these specific asthma phenotypes in early life. We are therefore still far from applying big data in a personalized way, to improve asthma diagnosis and to provide avenues for prevention of this prevalent, childhood disease. ■

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# Asthma and Prenatal Inflammation

The asthma syndrome comprises various forms, which respond differently to noxious influences during subsequent vulnerable time windows. Some forms of asthma are more or less genetically determined, whereas others are susceptible to exposures encountered in early childhood, such as viral infections and sensitization to food or inhalant allergens (1). Although these latter factors require some time of exposure over the first postnatal years, already the growing fetus may be affected by maternal exposures and conditions during pregnancy, which is illustrated by the effect of in utero smoke exposure on subsequent lung function (1).

These prenatal effects highlight the role of the interface between mother and child; that is, the placenta. Beyond hormone production and exchange of nutrients, metabolites, and gases, the placenta has to maintain tolerance between two mismatched human leukocyte antigen systems.

These complex functions require undisturbed placentation, and any interference with this process such as oxidative stress or hypoxia may derange the homeostasis of metabolism and immunity (2). The quality of placentation thus determines the fate of the pregnancy, ranging continuously from normal development over preeclampsia and fetal growth impairment to miscarriage (3). Preeclampsia is an inflammatory status leading to endothelial damage, which in advanced stages manifests clinically with the characteristic triad of symptoms: hypertension, proteinuria, and edema.