New Approaches to Identifying Asthma Phenotypes in Childhood

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This handout has been adapted and updated from the review article:


Heterogeneity of asthma

Despite more than a decade of intensive work using a range of approaches from family linkage and candidate gene association studies through to whole genome association studies, genetic studies of asthma have produced heterogeneous results with little replication. Similarly, data on the role of environmental exposures are inconsistent. One important impediment to better understanding of the genetic and environmental associates of asthma is the lack of universally accepted definition of asthma, which is in part a consequence of asthma not being a single disease, but a collection of several diseases presenting with similar symptoms (which are in recent literature referred to as “asthma endotypes”). This is likely true both for childhood wheezing illness and for asthma in adults. Whilst sharing similar phenotypes (i.e. observable characteristics), these distinct disease entities (endotypes) arise via different pathophysiological mechanisms, and may also be associated with different environmental exposures and different genetic markers. It is important to emphasise that observable characteristics (e.g. sputum inflammatory phenotypes) may not be stable; in contrast, true endotypes should be more stable, as they arise through unique pathophysiological mechanisms.

A further difficulty relevant to paediatric asthma is that the diagnosis is often based on parental reports of wheezing, which is unreliable. Some studies suggest that almost a third of children assigned as “wheezers” in various epidemiological and genetic studies may have never wheezed, but are incorrectly defined as “cases” due to misrepresentation of various respiratory sounds by their parents. Similarly, in adults, only 40% of patients with a primary care physician diagnosis of asthma were confirmed as being asthmatic by a specialist secondary care service. A consequence of this diagnostic shift is a dilution of any true association that would be apparent if a more precise case definition was used.
**Phenotyping and endotyping in paediatric asthma**

Wheezing illness in preschool children in heterogeneous, and the use of term “asthma” to describe all wheezing illness in inappropriate⁹. Using this as a premise, in a seminal publication Martinez et al described “phenotypes” of pre-school wheezing illness based on the temporal patterns wheezing ascertained by answers to a repeated question (the presence of wheezing in the previous 12 months) at age 3 and 6 years, assigning children as Transient Early Wheezers, Late-Onset Wheezers, and Persistent Wheezers¹⁰. In a refinement of this approach using the latent class analysis applied to a large dataset on a current wheezing collected on 7 occasions over a 7-year period, Henderson et al identified six wheezing phenotypes in the ALSPAC birth cohort². Similar findings were reported from the PIAMA study in the Netherlands¹¹.

Rather than relying only on the presence of wheezing within any given 12-month period, in order to capitalises on the wealth of questionnaire data, we used Principle Component Analysis to cluster the answer to multiple questions relating to wheeze and other respiratory symptoms in an “unbiased” way³. In a dimensionality reduction, out of >100 questions we identified 24 as being informative; based on the responses to these questions, we discovered five different clusters³. Of note, the association with commonly used markers of asthma (such as lung function, IgE levels, airway hyper-reactivity and family history) differed between different clusters, suggesting (but not proving) that they may be underpinned by different pathophysiological mechanisms (i.e. that they represent different endotypes). Recent cluster analysis of 315 asthmatic children from France which used 19 variables including personal and family history, sensitisation, inflammatory markers, lung function, severity etc., identified three independent clusters of asthma¹². One of these clusters had characteristics very similar to the clinical phenotype of severe therapy-resistant asthma which can be identified by a structured multidisciplinary assessment of children with problematic severe asthma¹³. Unsupervised cluster analysis of 12 continuous and composite variables from 161 children from the US Severe Asthma Research Program provided similar results compared to the study in adults⁵, but importantly these clusters identified did not corresponded to various definitions of severe asthma suggested by different national and international guidelines¹⁴.

One of the problems of the current cross-sectional approach to unbiased clustering is that the phenotypic variables used to cluster the patients may be unstable⁶; thus, if we are to improve asthma classification and identify true latent endotypes, an added dimension of time is needed to take into account the longitudinal changes. The discovery of novel, latent endotypes of
asthma will thus require complex data-rich longitudinal datasets and application of novel mathematical and statistical approaches.

**Heterogeneity of atopy**

We have recently proposed that not only asthma, but also “atopy” encompasses a number of different endotypes which may differ in their association with asthma\(^\text{15}\). To test this hypothesis, we applied machine learning approach with Bayesian inference to the longitudinally collected dataset from our unselected birth cohort study (Manchester Asthma and Allergy Study); all available skin prick tests and sIgE measurements collected at ages 1, 3, 5 and 8 years were used to cluster the children, taking into account both the timing and of the specific allergens causing sensitization\(^\text{15}\). Most of the children considered “atopic” using conventional definitions were clustered into 4 distinct atopic classes, which on the bases of their characteristics we named “Multiple Early”, “Multiple Late”, “Predominantly Dust Mite” and “Non Dust Mite”\(^\text{15}\). The risk of asthma was highly and significantly increased only amongst children in the “Multiple Early” class (odds ratio of 29.3), but not amongst those in any of the other atopy classes. Furthermore, children in the “Multiple Early” class also had significantly poorer lung function and a markedly increased risk of severe asthma exacerbations compared to the remaining classes\(^\text{15}\). Of note, less than one third of the children assigned as “atopic” using conventional criteria clustered to the Multiple Early class. It is important to emphasise that the clusters could be identified only by using longitudinally collected data. Better understanding of causality and emergence of new diagnostic approaches may offer novel biomarkers to allow practicing physicians more accurate diagnosis based on a single measurement at the time of presentation.

Finally, to test the hypothesis these different classes represent fundamentally different endotypes of atopy with unique genetic associates, we recently compared the results of genome-wide association study using conventional atopy and “Multiple Early” sensitisation class as outcomes\(^\text{16}\). Markedly different patterns of association were observed for the two outcomes, confirming that genetic associations are lost in the noise of poorly defined phenotypes.

**Conclusions**

Novel latent endotypes of atopy and asthma can be defined through the fusion of computational thinking and novel mathematical approaches with biomedical science. These novel endotypes may better reflect the different underlying pathophysiological processes and molecular pathways underpinning asthma endotypes, and may be more relevant for epidemiological, genetic and therapeutic studies.
REFERENCES