

The investigation of asthma phenotypes

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Purpose of review

Asthma is a heterogeneous disease constituted by overlapping separate syndromes. This review discusses recent published data relevant to asthma and severe asthma classification, resting either on the ‘candidate’ approach based on criteria chosen by experts or on the ‘exploratory’ approach based on unsupervised statistical methods.

Recent findings

Following the ‘candidate’ approach, groups of experts recently reviewed the classification of severe asthma to be applicable in low-income, middle-income, and high-income countries and provided a systematic algorithm to diagnose severe refractory asthma. The concept of asthma endotypes involving different biological mechanisms has recently been proposed. Results from the ‘exploratory’ approach support the clinical heterogeneity in severe asthma and the need for new approaches for the classification of asthma severity. The novel childhood and adult asthma phenotypes recently identified using the exploratory approach were supported by first evidence of validity (replication in independent studies, assessment of their discriminative properties, and effect on clinical prognosis).

Summary

Research on asthma phenotypes has increased exponentially in the last year. The main focus has been on severe asthma, likely due to its clinical and socioeconomic burden. Interestingly, many of the phenotypes identified are stable across populations and methodological approaches. Further analyses on the asthma phenotypes are needed to address their stability over time and their relevance from clinical and etiological perspectives.

Keywords

asthma, classification, endotype, phenotype, severe asthma

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Introduction

Evidence is increasing that asthma is a heterogeneous disease constituted by overlapping separate syndromes with probably different, but yet undefined, causes and natural histories. There is a need to identify each of these groups of patients (the so-called asthma phenotypes), whose clinical and prognostic characteristics and responses to treatments may be heterogeneous between groups and homogeneous within each group.

The term phenotype was originally coined together with the term genotype. A modern definition states that the phenotype is ‘the observable and structural and functional characteristics of an organism determined by its genotype and modulated by its environment’ [1]. A recent opinion study on the complexity of chronic obstructive pulmonary disease proposed a definition more focused on prognosis and therapeutic response, stating that a clinical phenotype is ‘a single or combination of disease attributes that describe differences between individuals (...) as they relate to clinically

meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)’ [2]. Such a definition could be extended to other chronic respiratory diseases, such as asthma. The term endophenotype has been proposed from the genetic research for representing specific physiological or biochemical processes closer to gene action and therefore more amenable to genetic analysis [3]. The current review is aimed at appraising the current knowledge and the potential implications of future knowledge about what has been called so far asthma phenotypes.

Why investigating asthma phenotypes?

There are many direct benefits of investigating asthma phenotypes. First, it should provide novel insights in asthma research by increasing the statistical power to detect environmental and genetic risk factors. Despite all the research efforts in asthma genetics in the past decades, most genetic variants identified so far confer relatively small increments in risk, and explain only a small proportion of familial clustering [4,5]. It has been

recognized that the missing explanation could partly reside in the poor asthma phenotype definition mostly used [6,7]. From the genetic research point of view, if current approaches in defining phenotypes are inadequate, the huge currently available genotypic data cannot be optimally used [8]. Recent data support this point, including studies showing that the increased risk of asthma conferred by 17q21 genetic variants is restricted to childhood-onset asthma [9], a finding that has been replicated in the large European GABRIEL Consortium [10]. These considerations also hold for etiologic research on environmental exposures, where proper disease definitions may result in the identification of new risk or protective factors.

The identification of asthma phenotypes should also lead to increasing the understanding of underlying pathobiology that contributes to a particular phenotype [11]. The huge advances in asthma pathology achieved in the last decades have resulted in discussions about whether asthma definition and classification should be revisited but their implications in the clinical practice are still missing.

Finally, from a clinical perspective, distinguishing asthma phenotypes should also lead to the identification of new phenotype-specific treatment. Several already existing examples illustrate this point, including the antiinterleukine-5 therapy, which targets eosinophilic inflammation and is therefore likely to be specifically effective in eosinophilic asthma [12,13].

A review of the asthma phenotypes was published in this journal last year, covering results from the ‘multidimensional phenotyping’ approach, that consists in applying unsupervised statistical methods that group individuals within a population according to similarity of specified variables, and from the ‘molecular phenotyping’ approach that consists in using gene arrays to examine gene expression profiles [14[•]]. The purpose of the present review is to discuss published data in the previous 12 months relevant to the research on asthma phenotypes, with emphasis on phenotypes identified using the ‘multidimensional phenotyping’ approach, also called the ‘exploratory’ approach, and also including recent research on asthma phenotypes using a complementary method, the ‘candidate’ approach. Many articles on asthma phenotypes published this last year have been focused on severe asthma, likely due to its clinical and socioeconomic burden. Consequently, severe asthma phenotypes are largely discussed in the present review.

The candidate approach to identify asthma phenotypes

The ‘candidate’ approach defines simple phenotypes based on criteria chosen by experts, representing one or few components of the disease. Distinct childhood

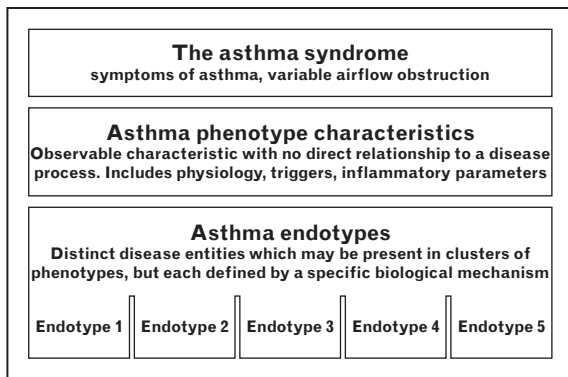
Key points

- Evidence is increasing that asthma and severe asthma are heterogeneous disease constituted by overlapping separate syndromes with probably different, but yet undefined, causes and prognosis.
- Although the exploratory approach, so-called ‘hypothesis-free’ is at an initial step, the novel asthma phenotypes recently identified this way were supported by first evidence of validity.
- Further analyses are needed to address the stability of these phenotypes over time and the relevance of these phenotypes from clinical and etiological perspectives.

and adult asthma phenotypes have been identified for some time. Allergic and nonallergic asthma are probably the most commonly discussed phenotypes. Other phenotypes defined by clinical or physiological categories (i.e. severity, age at onset, and chronic airflow obstruction), by asthma triggers (i.e. viral/multi trigger wheeze, exercise, allergens, occupational allergens, or irritants), by their pathobiology (i.e. eosinophilic and neutrophilic asthma), or their time course (i.e. early transient/persistent/late onset wheeze) have also been proposed and nicely reviewed elsewhere [11,14[•],15,16[•]]. Some of them deserve further explanation for their novelty, and are briefly presented below.

There is increasing evidence that patients with severe asthma form a heterogeneous group. Two studies [17[•],18[•]] published this last year proposed a classification for severe asthma. A meeting of the WHO held in April 2009 in Geneva proposes that a common international approach is needed to define severe, uncontrolled asthma which should be applicable in low-income, middle-income, and high-income countries [17[•]]. The expert group identifies three groups of severe asthma, each carrying different public health messages and challenges: untreated severe asthma characterized by asthma that is easily controlled with appropriate medication and adequate adherence; difficult-to-treat severe asthma – characterized by a partial or poor response to treatment that reflects the presence of factors other than asthma alone, and treatment-resistant severe asthma including those who are partially or poorly controlled despite high a level of recommended treatment (refractory asthma or corticosteroid-resistant asthma) and those for which the highest level of recommended treatment is required to maintain control. In the same line, the recent consensus from the U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) consortium also differentiates ‘severe refractory asthma’ from ‘problematic asthma’ and ‘difficult asthma’ and proposed a stepwise algorithm by which the patient with severe asthma may be identified [18[•]].

Figure 1 Asthma is made up of different endotypes, each characterized by its pathophysiology



Reproduced with permission from [19**].

Following the endophenotypes concept presented above, a group of experts from the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology recently proposed to divide asthma syndrome into asthma 'endotypes' representing distinct disease entities with specific mechanisms (Fig. 1) [19**]. On the basis of seven parameters representing different dimensions of the disease – clinical characteristics, biomarkers, lung physiology, genetics, histopathology, epidemiology, and response to treatment – this group of experts identified six asthma endotypes: aspirine-sensitive asthma, allergic bronchopulmonary mycosis, allergic asthma, asthma-predictive indices-positive preschool wheezers, severe late-onset hypereosinophilic, and asthma in cross-country skiers. Further data are needed to understand the disease process of these proposed endotypes and to determine whether, as expected, specific biological mechanisms are involved in these asthma subgroups.

The candidate approach is simple to understand and its results are easily used in clinical practice. However, this is usually based on classical models of disease that fail to recognize the pathophysiological links between physiological and cellular abnormalities common to different disease labels [20]. The intent to simplify definitions and classifications and making them available to all medical care levels may inhibit the development of new ideas and result in medical care not encompassed with research advances, thus potentially not allowing patients to get the best treatment options.

The exploratory approach to identify asthma phenotypes

The exploratory approach consists in applying unsupervised statistical methods to define asthma phenotypes. Multivariate statistical methods aimed to objectively

identify homogeneous subgroups (or clusters) of patients from a large set of observed data have been applied to unravel the heterogeneity of childhood and adult asthma. The diversity of statistical methods and findings prompts the need for an extensive narrative review.

A cluster analysis was applied to 12 continuous and composite variables from 161 children aged 6 to 17 years enrolled in the American Severe Asthma Research Program (SARP) to identify severe asthma subtypes [21**]. The variables included in the cluster analysis allowed covering personal characteristics (sex, ethnic group), lung function, atopic sensitization, exhaled nitric oxide, asthma characteristics (duration and symptoms frequency), asthma treatment, and healthcare use. Four clusters of asthma were identified: cluster 1 'late-onset symptomatic asthma with normal lung function' ($n = 48$), cluster 2 'early-onset atopic asthma with normal lung function' ($n = 52$), cluster 3 'early-onset atopic asthma with mild airflow limitation' ($n = 32$), and cluster 4 'early-onset atopic asthma with advanced airflow limitation' ($n = 29$). Asthma duration, the number of asthma controller medications and baseline FEV₁ percentage predicted values were identified as the strongest predictors of cluster assignment as these three variables alone resulted in correct classification of 93% of the original patients. These data emphasize that severe asthma is a heterogeneous disorder and point out that the classification identified using the unsupervised approach does not correspond with the definition of asthma severity proposed by current clinical guidelines.

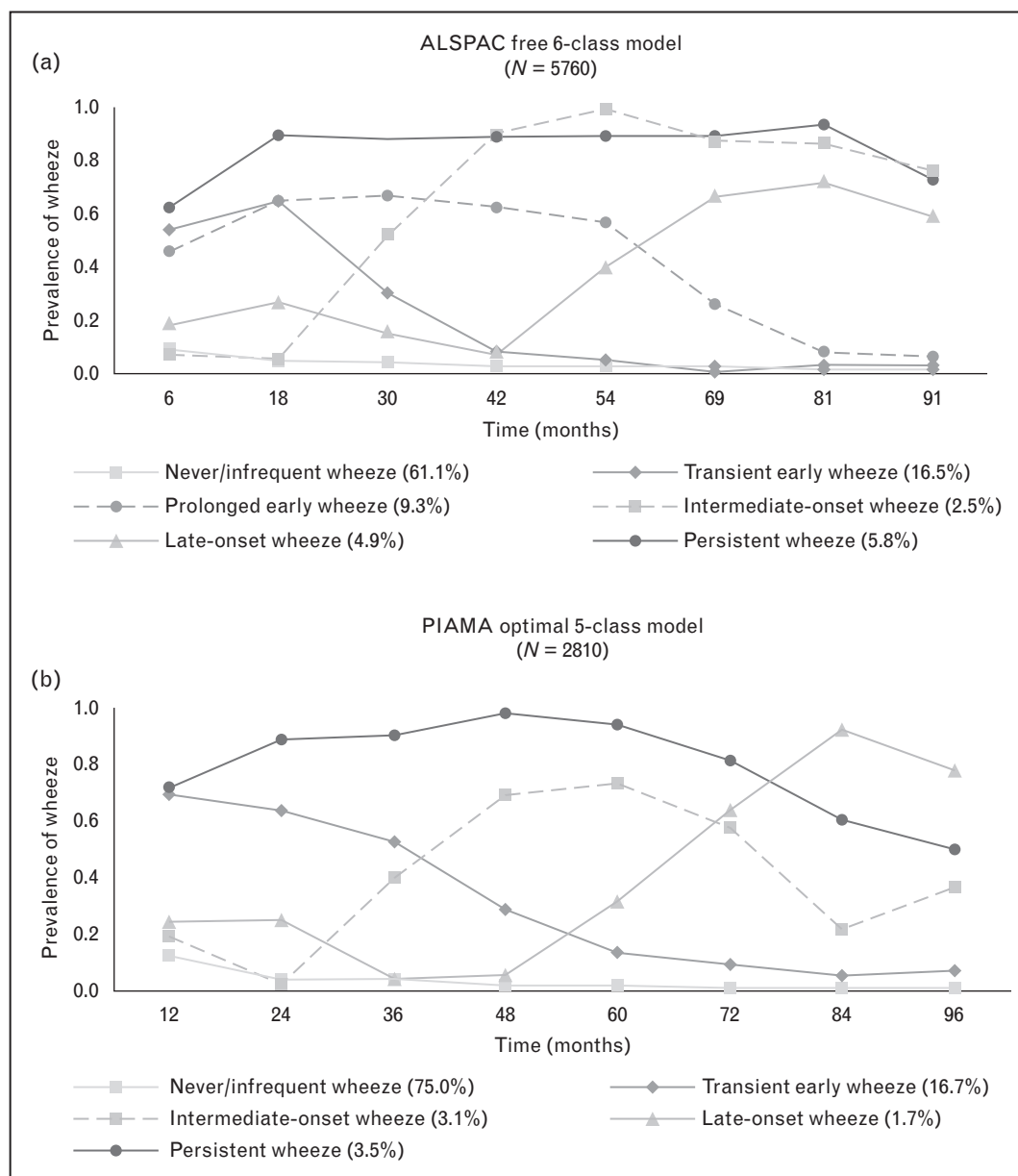
Benton *et al.* [22*] conducted a cluster analysis in an African-American asthma cohort aged 6–20 years (Asthma Severity Modifying Polymorphisms) recruited in an emergency department ($n = 154$). The cluster analysis on seven variables (Asthma Control Test (ACT) score, postbronchodilator FEV₁% predicted, eosinophils from nasal washes, total serum IgE, gender, age of onset, and BMI) identified four groups including cluster 0 composed of six individuals with an extremely mild phenotype, cluster 1 composed mainly of men with high neutrophils counts in their nasal washes ($n = 57$), cluster 2 predominantly composed of women with high BMI and later-onset asthma ($n = 33$), and cluster 3 including children with high eosinophil counts in their nasal washes and lower ACT scores ($n = 58$). The authors reported significant association between tobacco exposure and phenotypic characteristics (lung function, ACT score, and nasal neutrophils) exclusively within some clusters. Although these results should be interpreted cautiously because of the limited sample size, they indicate that cluster analysis may help to detect asthma risk factors in specific subgroups.

In the continuity to the wheezing phenotypes identified by the Longitudinal Latent Class Analysis (LLCA) in the Avon Longitudinal Study of Parents and Children

(ALSPAC, United-Kingdom) [23], Savenije *et al.* [24**] attempted to replicate these phenotypes in a the Netherlands birth cohort, the Prevention and Incidence of Asthma and Mite Allergy (PIAMA). The LLCA, a model-based clustering approach which attempts to explain the association between an outcome assessed at different time points, was applied on wheezing reported at eight time points between 1 and 8 years and identified five wheezing phenotypes in PIAMA which were comparable to 5 of the 6 ones previously identified in ALSPAC: ‘never infrequent wheeze’

(75.0%), ‘intermediate-onset wheeze’ (3.1%), ‘persistent wheeze’ (3.5%), ‘transient early wheeze’ (16.7%), and ‘late onset-wheeze’ (1.7%) (Fig. 2). Interestingly, the ‘intermediate-onset wheeze’ phenotype identified in ALSPAC, a novel phenotype compared with the categories of childhood wheeze previously reported in the Tucson Children Respiratory health Survey (TCRS), was replicated in PIAMA [25]. Importantly, these phenotypes identified in PIAMA showed similar association with asthma, atopy, lung function, and Bronchial HyperResponsiveness (BHR) at 8 years of age compared

Figure 2 Estimated prevalence at each time point from birth to age 8 years for each wheezing phenotype (a) in Avon Longitudinal Study of Parents and Children free 6-class model ($n = 5760$), (b) in the Prevention and Incidence of Asthma and Mite Allergy optimal 5-class model ($n = 2810$)



Reproduced with permission from [24**].

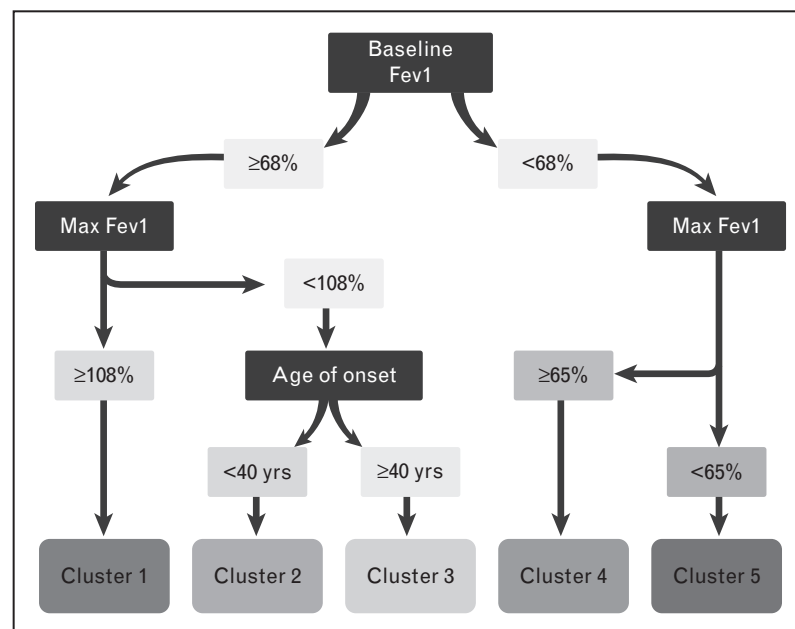
with those found in ALSPAC; children with transient early wheeze had the lowest risk for doctor diagnosed asthma in the last 12 months, children with intermediate-onset wheeze had the highest risk for atopic sensitization and children with persistent wheeze showed the greatest deficit in lung function. The similarity of the phenotypes identified combined with the similarity of the association with asthma, atopy, lung function, and BHR in two independent birth cohorts provide first evidence of validity of the wheezing phenotypes identified.

In adult populations, previous cluster analysis applied in asthmatic population identified asthma sub-phenotypes that exhibit differences in clinical response to treatment [26]. More recently, in a population of 726 patients 12 years of age or older, with persistent asthma recruited in the frame of the Severe Asthma Research Program (SARP), five distinct clinical phenotypes of asthma who differ in clinical, physiologic, and inflammatory parameters have been identified using unsupervised hierarchical cluster analysis on the basis of 34 variables [27^{**}]. Variables were selected to cover demographic data, asthma characteristics (age of onset, duration), asthma symptoms, asthma medications and healthcare use, factors that may confound current asthma control (smoke exposure, sino-pulmonary infection), and important physiologic measures (lung function, atopy). The authors further performed a tree analysis and showed that 80% of patients in the current sample were assigned to the appropriate cluster when using a simple

classification based on three clinical variables (pre and postbronchodilator FEV₁% predicted and age of onset) (Fig. 3). The presence of patients who met the American Thoracic Society definition of severe asthma in all clusters supports the need for new classification of asthma severity.

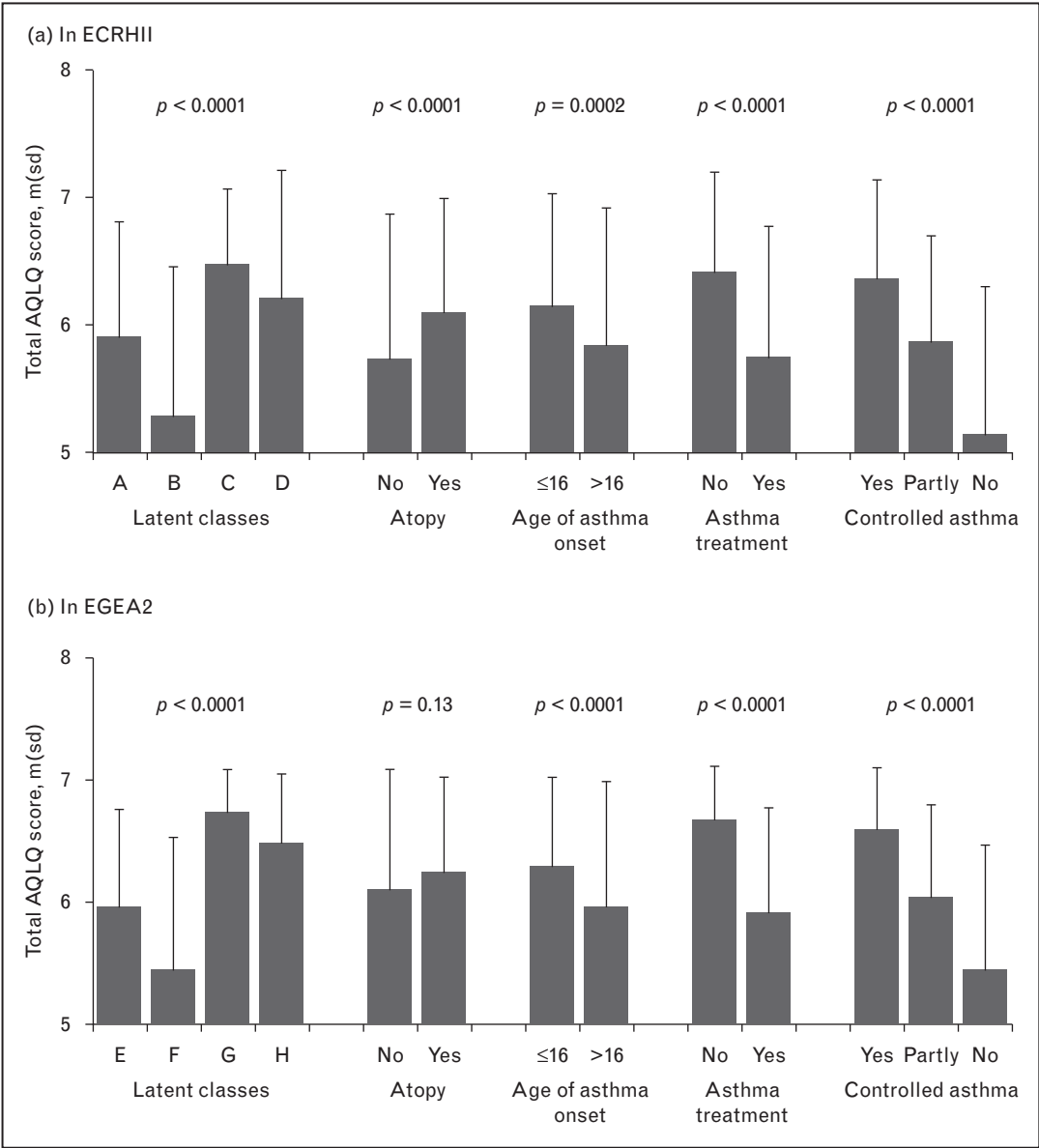
The LCA method has been applied in two adult asthma populations, relying on standardized protocol but different design, the Epidemiological study on Genetics and Environment of Asthma, a French case-control and family based study (EGEA2, $n=641$) and the European Community Respiratory Health Survey, an international population-based study (ECRHSII, $n=1895$) [28^{*}]. In each sample, four asthma phenotypes were distinguished by the LCA resting on 19 variables covering personal characteristics, asthma symptoms, exacerbations and treatment, age of asthma onset, allergic characteristics, lung function, and airway hyperresponsiveness. The phenotypes identified were similar in the two populations and were mainly characterized by the atopic status, the activity of the disease and the age at asthma onset and were labeled 'active treated allergic childhood-onset asthma', 'active treated adult-onset asthma', 'inactive/mild untreated allergic childhood-onset asthma', and 'inactive/mild untreated nonallergic adult-onset asthma'. Interestingly, the asthma phenotypes identified by the LCA discriminated levels of health-related quality of life more efficiently than simple clinical asthma classification (which would have corresponded to a hypothetical candidate approach) (Fig. 4). Furthermore, in

Figure 3 Tree analysis



Using three variables (baseline FEV₁ with a bronchodilator withhold), maximal 'Max' FEV₁ after six to eight puffs of albuterol, and age of onset of asthma), patients can be assigned to the five clusters that range from milder asthma (cluster 1) to more severe disease (clusters 4 and 5). Reproduced with permission from [27^{**}].

Figure 4 Differences on the total AQLQ between the asthma phenotypes identified by latent class analysis and other a priori asthma sub-groups (atopy, age of asthma onset, asthma treatment, and asthma control defined following the Global Initiative for Asthma 2006 guidelines)



Results observed in ECRHII (a) and EGEA2 (b) are presented. Reproduced with permission from [28*].

the EGEA2 study, blood eosinophil and neutrophil counts were strongly associated with the asthma phenotypes (eosinophil count was highest in the ‘active treated allergic childhood-onset asthma’ phenotype and neutrophil count was highest in the ‘active treated adult-onset asthma’).

This exploratory approach, so-called ‘hypothesis-free’ is at an initial step and the difficulty to interpret the results is one main limitation. An intrinsic not-so-obvious limitation is that this approach is not totally hypothesis free, as some key decisions have to be taken: the number and type of variables to be included in the analysis, the population choice, the number of groups to obtain, or the

specific statistical approach to use. So far, these limitations have impeded comparing the findings of the increasing bunch of studies on this topic. A final relevant limitation is the difficulty to immediately apply results of this research into clinical practice. Nevertheless, results provided so far by these approaches provided encouraging results and appear essential in complement of the candidate approach.

Conclusion

Although difficult, the asthma phenotypes identified so far in an unsupervised way will have to be compared

across studies, and further analyses are needed to address the stability of these phenotypes over time and the relevance of these phenotypes from clinical and etiological perspectives. The existing studies were carried out either in a cross-sectional way, by integrating several domains of the disease measured at one point in time, or longitudinally by using a single phenotype assessed at different time points to define 'trajectories' ([24**]). Future research should attempt to identify asthma phenotypes using data from multiple cohort studies to reach large enough sample size and by integrating several domains of the disease repeatedly measured over time. In this context, projects in progress like the MedALL (Mechanisms of the Development of ALLergy) and UBIOPRED programmes should provide novel insights in the identification of childhood asthma phenotypes and severe asthma phenotypes, respectively [18*,29]. Still, other specific asthma phenotypes should not be forgotten.

Future research on asthma phenotypes will help not only to identify the disease risk/protective factors, but also (and maybe mainly) to elaborate on health promotion and prevention policies to prevent or reduce future asthma burden.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

- 1 Rice JP, Saccone NL, Rasmussen E. Definition of the phenotype. *Adv Genet* 2001; 42:69–76.
- 2 Han MK, Agusti A, Calverley PM, *et al.* Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med* 2010; 182:598–604.
- 3 Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003; 160:636–645.
- 4 Weiss ST, Raby BA, Rogers A. Asthma genetics and genomics. *Curr Opin Genet Dev* 2009; 19:279–282.
- 5 Postma DS, Koppelman GH. Genetics of asthma: where are we and where do we go? *Proc Am Thorac Soc* 2009; 6:283–287.
- 6 Manolio TA, Collins FS, Cox NJ, *et al.* Finding the missing heritability of complex diseases. *Nature* 2009; 461:747–753.
- 7 Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008; 8:169–182.
- 8 Freimer N, Sabatti C. The human phenome project. *Nat Genet* 2003; 34:15–21.
- 9 Bouzigon E, Corda E, Aschard H, *et al.* Effect of 17q21 variants and smoking exposure in early-onset asthma. *N Engl J Med* 2008; 359:1985–1994.
- 10 Moffatt MF, Gut IG, Demenais F, *et al.* A large-scale, consortium-based genome-wide association study of asthma. *N Engl J Med* 2010; 363:1211–1221.
- 11 Wenzel SE. Severe asthma in adults. *Exp Lung Res* 2005; 31 (Suppl 1):22.
- 12 Nair P, Pizzichini MM, Kjarsgaard M, *et al.* Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360:985–993.
- 13 Haldar P, Brightling CE, Hargadon B, *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360:973–984.

- 14 Bradding P, Green RH. Subclinical phenotypes of asthma. *Curr Opin Allergy Clin Immunol* 2010; 10:54–59.
- A recent review covering results from the 'multidimensional phenotyping' approach that consists of applying unsupervised statistical methods that group individuals within a population according to similarity of specified variables, and from the 'molecular phenotyping' approach that consists in using gene arrays to examine gene expression profiles.
- 15 Bel EH. Clinical phenotypes of asthma. *Curr Opin Pulm Med* 2004; 10:44–50.
- 16 Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: are they real? *Clin Exp Allergy* 2010; 40:1130–1141.
- A recent review of the research relating to childhood asthma phenotypes, with a focus on the methods used to define and validate them.
- 17 Bousquet J, Mantzouranis E, Cruz AA, *et al.* Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010; 126:926–938.
- This study proposes a global definition of asthma severity applicable in most circumstances in low-income, middle-income, and high-income countries.
- 18 Bel EH, Sousa A, Fleming L, *et al.* Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax* 2010. [Epub ahead of print]
- This study presents the U-BIOPRED international consensus on the definition and diagnosis of severe asthma and produced for the first time a stepwise algorithm by which the patient with truly severe refractory asthma may be identified.
- 19 Lotvall J, Akdis CA, Bacharier LB, *et al.* Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011; 127:355–360.
- This study suggests criteria for defining asthma endotypes on the basis of their phenotypes and putative pathophysiology.
- 20 Wardlaw AJ, Silverman M, Siva R, *et al.* Multidimensional phenotyping: towards a new taxonomy for airway disease. *Clin Exp Allergy* 2005; 35: 1254–1262.
- 21 Fitzpatrick AM, Teague WG, Meyers DA, *et al.* Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011; 127:382–389.
- The first study to apply unsupervised statistical analysis for identifying asthma phenotypes in school-age children with persistent asthma across a wide range of asthma severity. Results emphasize the high heterogeneity of asthma severity.
- 22 Benton AS, Wang Z, Lerner J, *et al.* Overcoming heterogeneity in pediatric asthma: tobacco smoke and asthma characteristics within phenotypic clusters in an African American cohort. *J Asthma* 2010; 47:728–734.
- The first study to apply unsupervised statistical analysis for identifying asthma phenotypes in African American cohort.
- 23 Henderson J, Granell R, Heron J, *et al.* Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; 63:974–980.
- 24 Savenije OE, Granell R, Caudri D, *et al.* Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011. [Epub ahead of print]
- The first study that attempts to replicate, in an independent cohort, wheezing phenotypes previously identified using an unsupervised statistical approach (the longitudinal latent class analysis). The wheezing phenotypes identified were comparable in the two large birth cohorts and were associated with asthma, atopy, lung function, and BHR at 8 years.
- 25 Martinez FD, Wright AL, Taussig LM, *et al.* Asthma and wheezing in the first six years of life: the Group Health Medical Associates. *N Engl J Med* 1995; 332:133–138.
- 26 Haldar P, Pavord ID, Shaw DE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178:218–224.
- 27 Moore WC, Meyers DA, Wenzel SE, *et al.* Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med* 2010; 181:315–323.
- This study identified asthma phenotypes using unsupervised cluster approach in the SARP cohort which includes all levels of asthma severity and propose a simple method for phenotyping of asthma.
- 28 Siroux V, Basagana X, Boudier A, *et al.* Identifying adult asthma phenotypes using a clustering approach. *Eur Respir J* 2011. [Epub ahead of print]
- The first study to apply unsupervised statistical analysis to identify adult asthma phenotypes in two large epidemiological studies relying on standardized protocols but different designs (a European community-based study and a French case-control ad family-based study). The phenotypes identified were similar in both populations and exhibited strong differences in Health Related Quality of Life, even stronger than when using other existing asthma classifications.
- 29 Bousquet J, Anto J, Auffray C, *et al.* MedALL (Mechanisms of the Development of ALLergy): an integrated approach from phenotypes to systems medicine. *Allergy* 2011; 66:596–604.