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Asthma Phenotypes in Childhood

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Abstract

Introduction: Asthma is no longer thought of as a single disease, but rather a collection of varying symptoms expressing different disease patterns. One of the ongoing challenges is understanding the underlying pathophysiological mechanisms that may be responsible for the varying responses to treatment.

Areas Covered: This review provides an overview of our current understanding of the asthma phenotype concept in childhood and describes key findings from both conventional and data-driven methods.

Expert Commentary: With the vast amounts of data generated from cohorts, there is hope that we can elucidate distinct pathophysiological mechanisms, or endotypes. In return, this would lead to better patient stratification and disease management, thereby providing true personalised medicine.

Keywords: asthma phenotypes, data-driven methods, endotype, machine learning

1 Introduction

Asthma is a common disease which has been rapidly increasing in both prevalence and incidence. The surge of new cases, particularly in the western world, can be in part attributed to rapid changes in lifestyle and environmental exposures. However, the exact extent of this environmental impact is yet to be fully understood. For the most part, asthma starts in early childhood, though some patients can develop more severe disease symptoms either in teenage years or adulthood; the incidence of new cases is lower in adults[1, 2]. The variability in the expression of asthma symptoms observed within a clinical setting has prompted the move away from the concept that asthma is a single entity; it is now generally considered that asthma is an umbrella term for several distinct conditions that share common clinical features such as wheezing, cough, shortness of breath, and variable airflow obstruction[3].

A phenotype is defined as an observable property or trait that arises from the interaction of genes and environmental exposures. Phenotypes are therefore characteristics that can be directly observed and measured (either biochemically or physically)[4]. For example, in clinical terms 'trait' may refer to wheeze or lung function; wheeze can be auscultated and lung function can be measured, e.g. by spirometry. However, these traits can vary drastically in terms of the manner in which they are manifested between different patients, and relating them to underlying mechanisms would be essential to understand the pathology of the disease(s). With such variation in the clinical expression of asthma, the concept of 'endotype' has been proposed[5, 6]. Whereas the term 'phenotype' refers to an external, directly observable characteristic, an 'endotype' indicates a subtype of the disease with a distinct underlying pathophysiologic mechanism, which may in part explain the observed heterogeneity in phenotype manifestation[7]. As shown in Figure 1, our task in understanding asthma is to disentangle the multifarious phenotypes in an attempt to distinguish distinct subtypes which may in turn indicate the presence of distinct endotypes which have distinct causal mechanisms. Multiple 'endotypes' can therefore give rise to the same or similar phenotype[7], and this endotype-phenotype connection itself may not be a static characteristic. A level of complexity is added by the fact that some of the key phenotypes (e.g. eosinophilic inflammation) are highly variable in childhood[8].

The importance of identifying asthma endotypes (or subtype) is primarily for understanding disease mechanisms. Our current treatment guidelines are still guided primarily by symptoms and lung function, yet we have all seen that similar symptoms have different levels of response to commonly used treatments. Deciphering the cause of this heterogeneity would lead to better treatment targeting, and would be a step towards "precision" medicine. Furthermore, there is hope that this knowledge would pave the way for better predictive modelling based on risk factors and disease progression. In other words, if we can correctly categorise children into different subtypes at a young age, we will have insight into the developmental trajectory of the disease in order to apply preventative strategies. However, we have yet to fully discover all the modifiable factors that influence the natural course of the asthma-related diseases.

A wide array of methodologies have been utilised to enhance subtyping of asthma and allergic diseases in childhood. Such methods range from expert investigator-led approaches to identifying patterns and co-occurrence of symptoms which mimics the approach used within a clinical setting, to supervised statistical modelling approaches which aim to test hypothesised frameworks for disease profiles, and unsupervised data-driven statistical methods which take an agnostic view of the data in order to infer structure based

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3 on pattern recognition computer algorithms[9, 10]. Combinations of supervised and
4 unsupervised models allow us to incorporate prior clinical knowledge within a data-driven
5 approach and can also enable us to evaluate the likelihood that our observed data is aligned
6 to prior hypotheses or clinical assumptions. All of these methods have advanced our
7 knowledge in this field in different ways. Subjective expert-driven approaches have been
8 able to describe and externally validate what is seen in clinic, while data driven machine
9 learning approaches are capitalizing on the wealth of data available by seeking to find
10 patterns of disease and then applying that to the general population.

11
12 Our understanding of asthma heterogeneity is constantly evolving. In this review, we
13 present our current knowledge of the subtypes in childhood asthma. We explain the clinical
14 implications of phenotyping and subtyping asthma in childhood, as this is the critical period
15 that is amenable to potential prevention strategies.
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30 **Figure 1:** Schematic drawing of the asthma syndrome. BMI: body mass index
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32 **2 Wheeze phenotypes**

33 The presence or absence of wheeze is one of the key determinants of asthma.
34 Wheezing is associated with airflow obstruction due to airway narrowing. In children, this
35 auscultatory finding is primarily an expression of large airway obstruction. Wheeze can
36 manifest in various ways and at different time points in a child's life. However, it should be
37 noted that not all wheeze can lead to asthma, particularly in those children below the age of
38 3 years. Within the last decade, there has been a surge of data describing various ways of
39 identifying wheeze phenotypes in childhood. At the most general level, phenotypes have
40 been characterised according to age of onset (early vs late), according to severity, or based
41 on triggers (viral, allergen, or other).
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45 **2.1 Wheeze phenotypes based on age of onset and remission (temporal pattern)**

46 Differentiating wheeze phenotypes by age of onset during childhood can give insight
47 into the pattern of disease expression later in adulthood. The ability to predict both the
48 timing (whether a child will develop wheezing early on or later in life) as well as subsequent
49 profile of symptom development may allow us to pre-emptively manage such occurrence
50 and severity. As a result, age of onset of wheeze and its persistence have become key
51 determinants for identifying distinct wheeze subtypes.
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55 **2.1.1 Early onset transient wheeze**

56 The first seminal paper to characterize wheeze and its natural history was by
57 Martinez et al[11] in an unselected birth cohort based in Tucson, AZ. Using a subjective
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3 clinical approach based on the observed patterns of wheeze over time, ‘transient-early
4 onset wheeze’ was defined as wheeze with onset before the age of three years, with
5 subsequent resolution by age six years[11]. The authors hypothesized that transient early
6 wheeze may be triggered by viral infections. These children initially had poorer lung
7 function in infancy which later improved, although remaining lower compared to the control
8 group.
9

10 The Manchester Asthma and Allergy Study (MAAS) used a longitudinal latent class
11 model integrating data from both parental questionnaires and medical records to ascertain
12 children’s wheeze symptoms. This model represented a statistical data-driven approach
13 which assigns children to their most probable latent (unobserved) cluster based on the
14 patterns of wheeze at multiple time-points (Figure 2A). These clusters are hypothesised to
15 represent distinct symptom profiles with distinct underlying pathophysiology. Using
16 complementary data sources enabled the modelling of uncertainty in parental or physician
17 diagnosis of wheeze. Similar to the Tuscan cohort, MAAS also identified a transient early
18 wheeze group (wheezing from age 1-5). However, unlike Tuscan, they found that lung
19 function in these children remained impaired compared to non-wheezers throughout
20 childhood[12].
21
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23 Using a similar statistical approach, but based only on parental reporting of wheeze,
24 Henderson et al[13] of the Avon Longitudinal Study of Parents and Children (ALSPAC) (see
25 figure 2) cohort identified a prolonged early wheezing group (wheezing from 6-54 months).
26 Compared to the findings from the Tucson study, the prolonged-early phenotype is thought
27 to be a more severe form of transient-early wheeze based on observed diminished lung
28 function at age 8-9 years for this group of children. However early-life lung function was not
29 available thus hindering evaluation as to whether there is a distinction in pre-morbid lung
30 function for this group of children compared to the transient early wheezers. Indeed, as
31 lung function measurements are difficult to obtain below the age of 2 years, many
32 institutions are increasingly reluctant on labelling early wheeze as asthma. The results from
33 the ALSPAC have been replicated using similar methodology in other cohorts [12, 14-17].
34 Within the various studies described, the definition and prevalence of early-onset wheeze
35 varied between study groups (in part likely a consequence of the age at which data was
36 collected). For example, the prevalence of early-onset wheeze in the Tucson study[11] was
37 19.9%, and 23.5% in MAAS[18]. Using a solely data-driven approach, the proportion of
38 children in MAAS[19] rose to 29.3%, while ALSPAC reported 42.4%[13].
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41

42 In most studies, the majority of children who wheezed early in infancy have
43 symptom resolution in later childhood [11, 20-23]. Risk factors identified for transient early
44 wheeze include exposure to tobacco smoke, day care attendance, virus infections, and
45 family history of asthma[14, 24, 25]. Results have been inconsistent with regards to sex and
46 position in sibship[25-27].
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55 2.1.2 Persistent wheeze

56 Similar to transient wheezers, children with persistent wheeze start wheezing in
57 early life; however, in contrast to transient wheezers, their symptoms do not resolve, but
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3 continue in later childhood[11]. One of the characteristics of persistent wheeze is
4 diminished lung function by school age, with likely persistence to adulthood. Martinez et al
5 [11] found that compared to controls (non-wheezers), children with persistent wheeze
6 initially had normal lung function, but that lung function significantly worsened by age six
7 years. This was also seen at age 11 years in a follow-up study[29]. These children were more
8 likely to be atopic, have higher IgE levels, and be sensitized early on. Using similar subjective
9 methods to characterise children, study groups from New Zealand[20] and Australia[30],
10 observed that children who were categorised as persistent wheezers continued to wheeze
11 into adulthood and had consistently lower lung function.
12

13
14 Availability of data from primary care medical records in the MAAS cohort[31]
15 allowed stratification of persistent wheeze into two distinct subgroups: persistent
16 controlled and persistent troublesome wheeze. Children with “troublesome” wheeze were
17 more likely to have a high symptom burden despite high doses of inhaled corticosteroids.
18 Belgrave *et al*[12] found that being highly atopic (whether to food or inhalant allergens) and
19 having concurrent eczema were strong predictors of this phenotype. The persistent wheeze
20 identified in ALSPAC showed a similar pattern though with weaker atopy associations[13].
21 Early identification of children who are at risk of persistent troublesome wheeze would
22 allow for better management, and possible prevention to reduce the likelihood of
23 persistence of troublesome symptoms into adulthood.
24

25
26 An intermediate onset wheeze (onset between 18-42 months) was identified in
27 ALSPAC, though given the time of onset, this could be classified as early in other studies.
28 Children in this category were more likely to be atopic (particularly to house dust mite and
29 cat), have poor lung function, and subsequently be at risk of developing asthma in later
30 childhood.
31

32 Atopic sensitization is a well-documented risk factor for both persistent wheezing
33 [11-13] and the persistence of asthma from school-age to late teenage years[32]. However,
34 Simpson et al have demonstrated that atopic sensitisation may not be a simple
35 dichotomous trait, but rather a collection of several different atopic vulnerabilities[33]. Of
36 the four distinct sensitization classes identified in this study, there was a strong association
37 between only one of these classes (assigned as multiple early atopy) and persistent
38 wheezing. Similar structure within the data on sensitisation, and identical association with
39 persistent wheezing and asthma has been reported in the Isle of Wight study[34]. Using a
40 similar approach, similar atopic patterns were identified in the Childhood Asthma
41 Prevention Study (CAPS) from Australia, and asthma at age 8 was associated with mixed
42 food (predominantly peanut) and inhalant sensitization[35]. However, such stratification of
43 atopic sensitization requires the use of complex machine learning models on rich
44 longitudinal data, and cross-sectional biomarkers of different atopic vulnerabilities will need
45 to be discovered if this is to be translated into clinical practice.
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2.1.3 Late onset wheeze

Late onset wheeze is generally described as wheeze with onset after age three years which persists into later childhood. Atopic sensitization is consistently associated with this phenotype of wheeze across the different studies[12-14]. In ALSPAC, this sensitisation was grass pollen induced[13]. However, the association between late onset wheezing, lung function and bronchial hyperresponsiveness has differed between different studies. For example, MAAS and ALSPAC found that late onset wheeze was significantly associated with increased bronchial hyperresponsiveness and lung function impairment at age 6[13, 31] while Prevention and Incidence of Asthma and Mite Allergy (PIAMA)[15] and Southampton Women's Study (SWS)[14] showed such association. Amongst environmental exposures, maternal smoking during pregnancy was risk factor for late onset wheezing in some[11, 36], but not all studies[12, 14].

Little is known on the stability of this phenotype, and further longitudinal follow-up is required to determine whether late-onset wheeze persists into adulthood.

2.2 Wheeze phenotypes based on triggers

Treatment of early childhood wheeze has been generally limited by the lack of evidence for the efficacy of most currently available treatments. To facilitate management of young children with wheezing, the European Task Force[37] proposed a clinical differentiation of early childhood wheezing into two subgroups: 'episodic viral wheeze (EVW)' and 'multiple trigger wheeze (MTW)'. EVW is described as intermittent seasonal wheeze episodes with occasional periods of 'feeling well'. Children labelled with episodic viral wheeze tend to be non-atopic with almost normal lung function, and symptoms tend to resolve by late childhood[38, 39]. Multiple trigger wheeze (MTW) is defined as "wheezing that shows discreet exacerbations, but also symptoms in between episodes[40]." Proposed triggers of MTW includes allergens, exercise, mist, crying, laughter etc. [37]. Of note, the major trigger of MTW are respiratory virus infections, making a clear distinction between EVW and MTW difficult. Both EVW and MTW are defined cross-sectionally at different ages, with severity of symptoms being accounted for by varying frequencies of wheezing episodes (more than three classified as frequent)[41, 42]. This classification was based on expert opinion, rather than solid data, and the implications were that ICS treatment would be more appropriate and effective for the MTW compared to EVW. However, neither of these two proposed "phenotypes" have been shown to be stable. For example, Schultz et al[43] showed that more than 50% of children change their phenotypic classification within 12 months of allocation into one of these two groups; EVW most frequently changed to MTW. However, a few years later, Schultz and Brand showed that regular use of corticosteroids had a modest effect on reducing symptoms in the EVW group[44]. Despite this, it is important to note that a phenotype-driven approach to treatment is still currently limited by our ability to accurately differentiate phenotypes and therefore the clinical utility is yet to be determined[44].

There have been attempts to validate this classification using data-driven techniques. For example, EVW was identified using latent class analysis in two studies from the Trousseau Asthma Program (TAP) [38, 45], while one study from Leicester, UK[39] suggested that the 'transient early wheeze' phenotype was very similar to EVW. A more severe type of EVW characterised by high FeNO levels and strong family history of asthma was described by Kappelle et al[46], and these children were at an increased risk of developing asthma at age five to 10 years, which was found to persist into adulthood[47].

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3 The TAP group identified an atopic MTW in boys that was associated with severe wheezing
4 and allergic comorbidities[45].

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6 There have been attempts to reconcile phenotypes described through temporal
7 patterns of symptoms and those based on triggers. For example, it has been suggested that
8 transient early wheeze may correspond to EVW, and persistent wheeze to MTW [11, 39].
9 However, identifying children as having EVW/MTW is a relatively poor predictor of whether
10 they would subsequently be classified as transient/persistent wheezers, with low positive
11 predictive values[41, 48-50]. Depner and colleagues[16] sought to compare the data-driven
12 wheeze phenotypes (early, transient, intermediate, late-onset, persistent) with the clinical
13 classification of EVW/MTW by using a multi-country cohort of children from birth to 6 years
14 of age and applying a longitudinal latent class model. Their results showed that
15 approximately 60% of children with EVW were found to be within the transient early
16 wheeze class implying that this phenotype is unlikely to encompass a chronic condition with
17 poor lung function, but rather an initial response to viruses that eventually resolves[16].
18 However, the correlation with the LCA classes was poor. In contrast, 60-70% of children with
19 MTW were either in the intermediate, late-onset, or persistent wheeze class. The
20 correlation with the LCA classes was very high. Further to this, a variant of MTW was also
21 identified and labelled recurrent unremitting wheeze (symptoms or wheeze without a cold
22 on multiple occasions). This was characterised by impaired lung function, nonresponse to
23 bronchodilators, and association with smoke exposure in utero. This group was also strongly
24 correlated with late-onset thereby suggesting a distinct disease entity[16].

25
26 In the clinical community there is often an erroneous assumption that transient and
27 EVW are relatively “benign”, and persistent and MTW more troublesome. However, data
28 from Manchester cohort have shown that almost 70% of all inhaled corticosteroids
29 prescribed in the first year of life were prescribed to children in the transient wheeze group,
30 although this class accounted for only one third of children who wheezed in the first
31 year[12]. This would suggest that early-life transient wheezers may have more severe
32 wheezing in infancy compared to those children who wheeze early, but go on to become
33 persistent wheezers, and does not support the notion that transient and EVW are benign.
34 These children may also be at risk of developing COPD in adulthood.

39 40 **3 Phenotypes of severe asthma**

41 The challenges in treatment of severe childhood wheezing/asthma due to high rates
42 of non-responders suggests that children in the most severe category are either not taking
43 their treatment, are undertreated, or do not respond to the currently available treatments.
44 Although quantitatively small, this group of children consume a high proportion of
45 resources[51] and therefore represent a significant economic burden.

46
47 In the US Severe Asthma Research Program (SARP), Fitzpatrick et al[52] used
48 hierarchical clustering to identify four subgroups of severe asthmatic children differing in
49 age of onset, lung function, FeNO and medication use. All subgroups were atopic, however,
50 there was large variation in the magnitude of atopy. It is of note that the definition of
51 asthma severity proposed by the ERS/ATS task force[53] was not fully applicable to any of
52 the subgroups, despite initially using an ATS definition. In contrast, a study in Sweden did
53 not find an association between atopy and severity of asthma[54]. They found that
54 environmental factors, such as smoking, were significant risk factors for the severe asthma
55 phenotype.
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3 The TAP group identified two other severe phenotypes, though within a more
4 heterogeneous asthmatic population: 'asthma with severe exacerbations and multiple
5 allergies', and 'severe asthma with bronchial obstruction'[55]. The first phenotype showed
6 marked eosinophilic and basophilic inflammation, but the baseline FEV₁ values were within
7 normal range, though slightly lower than those for the mild asthmatic group. This is
8 consistent with the observation that children can exacerbate frequently despite high
9 medication use and yet still have relatively normal FEV₁. The second phenotype was
10 characterised by neutrophilia and high BMI. Additionally, this group of children had poorer
11 lung function, though FEV₁ was still within normal limits as depicted by guidelines,
12 confirming that spirometry in children may not be a good marker of severe childhood
13 asthma.
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17 **4 Use of biomarkers to identify phenotypes**

18 The heterogeneity of asthma with regards to symptom expression, response to
19 therapy, and lung function has prompted the search for objective markers with better
20 diagnostic value which are able to distinguish distinct subtypes of asthma. The gold standard
21 for assessing the extent of airway inflammation is through the use of bronchial biopsies,
22 bronchoalveolar lavage, and sputum induction. These techniques, however, are too invasive
23 for children, and there has to be a clear clinical indication with intended benefit for this
24 method of assessment to be employed[56]. As a result, biomarkers in childhood
25 asthma/wheezing have mostly been limited to serum/blood and breath. These biomarkers
26 primarily assess eosinophilic or Th2 inflammation[57].
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30 *4.1 Fractional concentration of exhaled Nitric Oxide (FeNO)*

31 Fractional concentration of Nitric Oxide has been widely used in children as it is non-
32 invasive and relatively simple. Several studies have shown strong correlations between
33 FeNO levels and blood/sputum eosinophils[58], IgE[59-61], and serum eosinophilic cationic
34 protein[62, 63], with higher levels of FeNO denoting Th2-mediated inflammation and good
35 response to inhaled corticosteroids[64]. 'Low' FeNO levels are thought to represent non-
36 eosinophilic asthma subtypes that are less likely to respond to ICS treatment[65]. The
37 optimal threshold to differentiate what constitutes 'high' or 'low' levels of FeNO is still up
38 for debate. The most recent guidelines suggest FeNO <20ppb indicates poor response to
39 inhaled corticosteroids, while FeNO >35ppb indicates good response[66], but that serial
40 measurements should be taken over time for monitoring. However, this recommendation is
41 based on studies that had different cut off points and different positive/negative predictive
42 values with respect to inhaled steroid effect. It is also important to keep in mind that FeNO
43 levels reflect inflammation and not necessarily asthma, and so interpretation of results
44 should be taken within context, particularly in the case of atopic comorbidities. As it stands,
45 rather than identifying subtypes of wheezing, the clinical utility of FeNO is currently limited
46 to that of a screening method for eosinophilic and Th2 mediated inflammation with some
47 indication of steroid response, and may be used as a marker of adherence with ICS
48 treatment.
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53 *4.2 Exhaled Breath Condensate*

54 Exhaled breath condensate (EBC), thought to mirror airway lining fluid[67], is
55 obtained by cooling exhaled air from children breathing normally for 10-15 minutes[68].
56 Potential biomarkers include pH, markers of oxidative stress (8-isoprostane, hydrogen
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peroxide, aldehydes) and airway inflammation (eicosanoids, cytokines). Despite the lack of a standardised method, reference values, or proper validation[69], some interesting results have emerged. For example, 8-isoprostane has been found in increased quantities in both problematic and atopic asthmatic children despite ICS treatment[70, 71]. Th2 Cytokines, such as IL-4, are also increased in asthmatic children, especially those with concurrent atopy[72] and persistent wheeze[73]. This cytokine was also found to be a good marker for assessing asthma control[72]. Additionally, cytokine IL-5 has been shown to predict asthma exacerbations[74]. However, other studies have questioned the utility of EBC (in particular measuring EBC pH) in childhood asthma[75].

4.3 Periostin

Periostin is an emerging biomarker in Th2 inflammation in studies in adults. It is induced by IL-4 and IL-13 in airway epithelial cells and lung fibroblasts and thought to mediate collagen synthesis and fibrillogenesis[76, 77]. It has been suggested that high periostin is associated with good clinical response to corticosteroids in Th2 inflammation[78]. Recently, it has been used in clinical trials as a predictor of response to lebrikizumab (anti IL-13) [79]. However, periostin levels are higher in children compared to those in adults and change developmentally (likely due to bone turnover and growth), and it remains unclear whether periostin will be of use in phenotyping childhood wheezing and asthma.

5 Asthma phenotypes and genetic studies

Approaches for discovering genes connected to asthma have ranged from candidate gene association studies and genome-wide linkage studies, to more recent genome-wide association studies (GWAS). Several large studies (e.g. European GABRIEL consortium[80] and US EVE consortium[81]) identified a number of genetic associates of asthma in children (in particular in the region 17q21). However, the predictive value of these is low, with specificity being 75% and sensitivity only 35%. Other genes (IL33, IL1RL1, IL18R1) have also been implicated in asthma development[82]. Most genetic studies defined “asthma” as parentally or patient-reported “doctor-diagnosed asthma”. Unless genetic studies find better ways to distinguish between different asthma subtypes under this umbrella diagnosis at a population level, it will be difficult (if not impossible) to discover their unique underlying genetic risk factors, as any signal will be diluted by phenotypic heterogeneity[83]. It is worth emphasizing that when a much more precise and specific definition of early-life onset asthma with recurrent, severe exacerbations in pre-school age was used in a GWAS, identified associations had a considerably greater effect size (e.g. in 17q21 region), and novel susceptibility genes such as *CDHR3* (cadherin-related family member 3, rs6967330, C₅₂₉Y) were identified.[84] Subsequent studies have shown that *CDHR3* may be a receptor for rhinovirus-C, and that the same genetic variant which was linked with hospitalizations for early-onset childhood asthma in birth cohort studies also mediates enhanced RV-C binding and replication[85]. These studies provide indirect evidence that we need to move away from using umbrella term of “doctor-diagnosed asthma” in genetic studies, and that investigation of genetic associates of different wheeze phenotypes may render more informative findings. As an example, the ALSPAC investigators extended genetic association studies to include wheeze phenotypes which they identified previously, and found that 17q21 locus was associated with persistent and intermediate wheeze, but not with transient wheeze, atopy or lung function[86]. Combining data from the ALSPAC and the PIAMA

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3 cohort, Savenije et al found that IL1RL1 and IL33 SNPs were associated with intermediate
4 and late-onset wheeze and that this was in the presence of early sensitization, thus
5 suggesting that allergic sensitization, through the IL33-IL1RL1 pathway, may be the key
6 driver to wheeze and subsequent asthma development[87].
7

8 A different approach using transcriptomic analysis of peripheral blood in children
9 with viral induced wheeze and exacerbations has shown that there are distinct microRNA
10 profiles in CD8+ T cells, with reduced regulation of microRNA146a/b and microRNA28-
11 5p[88].
12

13 Although we have been able to enhance our knowledge of genetic associations of
14 wheeze phenotypes and asthma at a population level, we have still not been able to
15 translate this knowledge to an individual level. This is partly due to the heterogeneous
16 nature of childhood wheezing and asthma described above, but is also a consequence of
17 gene-environment interactions whereby the genetic effect on asthma may be modified by
18 certain environmental factors. Classical examples of the role of gene-environment
19 interaction in modifying disease is finding that the impact of environmental endotoxin
20 exposure on non-atopic wheeze and atopic sensitization was dependent on and modified by
21 genetic variants in *CD14* [89, 90], and studies demonstrating that the effect of day care on
22 atopic wheezing is opposite among children with different variants of the *TLR2* gene[91].
23 The approach to understanding asthma within the complex context of gene-environment
24 interactions may be an incentive utilise a candidate gene approach based on sound
25 epidemiological principles of causality[92].
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29 **6 Expert commentary: lack of cohesive methodology for understanding asthma** 30 **phenotypes in childhood**

31 There is clear lack of standardisation in defining childhood wheezing illness and
32 asthma which is leading to the inconsistent findings with respect to the genetic,
33 environmental and physiological risk factors associated with this disease. In the last few
34 years, a plethora of divergent statistical methods have been used in an attempt to
35 understand the natural history of childhood wheezing illness. Although, by definition, all
36 these techniques find patterns within a dataset and categorise them accordingly, there is no
37 unified statistical method, leading to inconsistency in results of studies using different data-
38 driven approaches. This is exacerbated by the problem of inconsistent use of variables in
39 different analyses and inconsistencies in the data collection process itself. Indeed, this could
40 explain the sizeable variation in the proportion of children assigned to these wheeze
41 phenotypes among published studies (see Belgrave et al[83] for table breakdown). This may
42 be a reflection of both the different time points at which data was collected and the
43 inherent symptom patterns among the dataset due to differences in population. Therefore,
44 results from statistical and machine learning approaches need to be interpreted within a
45 larger clinical context, and it needs to be emphasized that although such an approach can
46 be used to generate hypotheses, it remains an exploratory rather than confirmatory
47 approach to understanding subtypes of disease, and therefore clinical interpretation and
48 external epidemiological validation is essential.
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53 The large quantity and ready availability of data, while posing many challenges, also
54 presents an opportunity to understand underlying disease heterogeneity with greater
55 certainty. This is because a quantitatively increased volume of data gives us the ability to
56 distinguish between “data signal” from “noise due to random variation” more accurately.
57 Advances in computational power facilitate data visualisation and pattern recognition in
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3 high-dimensional data with greater speed and accuracy. Combined with increased
4 computational power and advances in statistical methods, the emerging field of systems
5 biology, which combines biomarkers, genomics, metabolomics, proteomics and
6 computational mathematics, may enable better identification of pathophysiology
7 underpinning disease subtypes. Integrating all these components from different cohorts and
8 datasets, while including developmental patterns of symptoms, may initially identify
9 common characteristics on a wider population level, with the ultimate goal of better
10 understanding the disease on an individual level.
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13 **7 Five-year view: clinical implications of defining asthma phenotypes in childhood**

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15 There has been considerable progress in our understanding of the heterogeneity of
16 asthma. Phenotyping asthma has started to provide a framework for further research into
17 subtyping based on specific mechanisms. What has been shown here is that asthma can no
18 longer be considered a single disease. Phenotyping in children can be either based on age of
19 onset, triggers, severity, or symptoms. The clinical relevance of this would then be seen
20 taking it one step further and analysing how each child's disease pattern develops over time
21 and tailoring treatment accordingly. This is in stark contrast to the current approach where
22 it is assumed that one drug treats all.
23

24 Classifying children into groups of similar observable characteristics and features will
25 enable better understanding and subsequent classification into subtypes that represent the
26 genetic, environmental, and biomarker make-up of the disease. Once this has been
27 achieved, we can then follow-up longitudinally over time in order to assess stability,
28 remission, and new onset of disease.
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30 The ultimate aim is to be one step closer to personalised medicine which would
31 provide early prevention and/or tailored treatment leading to more efficient use of
32 resources and more efficacious control of disease in children. However, we are still not
33 ready to apply this to every day clinical practice.
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40 **8 Key Issues**

- 41 • Asthma is not a single disease
- 42 • Various asthma phenotypes have been proposed using subjective and data driven
43 methods
- 44 • Wheeze is the most common manifestation of asthma syndrome, and both cross-
45 sectional and longitudinal studies have enhanced our knowledge on the natural
46 history
- 47 • Using different approaches, wheeze phenotypes have been described using
48 symptoms, triggers, severity, and age of onset
- 49 • Deciphering different subtypes at population level will lead to discovery of the
50 underlying mechanisms
- 51 • The ultimate aim is to enable proper treatment targeting, enhance treatment
52 monitoring, and apply early preventative strategies
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Reference annotations

* Of interest

** Of considerable interest

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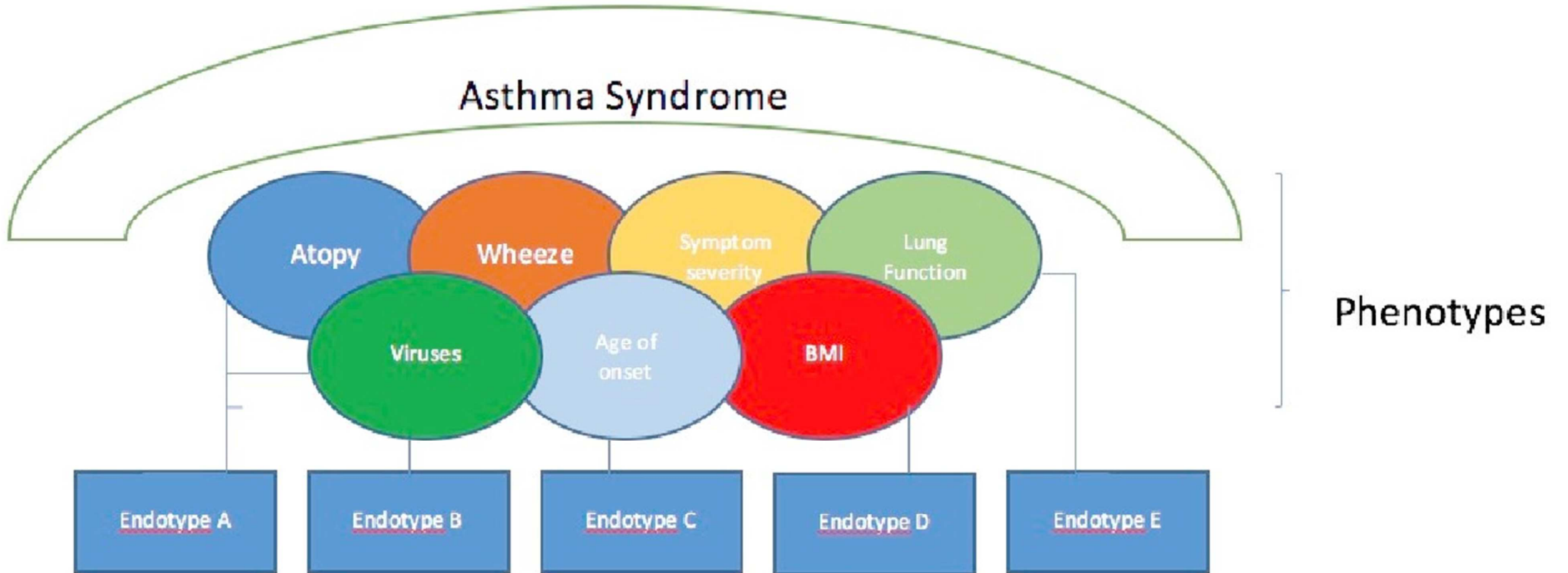
16 Figure Legends:

17 **Figure 1:** Schematic drawing of the asthma syndrome. BMI: body mass index
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21 **Figure 2:** Comparison of wheeze phenotypes from Manchester Asthma and Allergy Study
22 (MAAS) and Avon Longitudinal Study of Parents and Children (ALSPAC).

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