ORIGINAL ARTICLE

Clinical and Epidemiologic Phenotypes of Childhood Asthma

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Abstract

Rationale: Clinical and epidemiologic approaches have identified two distinct sets of classifications for asthma and wheeze phenotypes.

Objectives: To compare epidemiologic phenotype definitions identified by latent class analysis (LCA) with clinical phenotypes based on patient histories, diagnostic work-up, and treatment responses. To relate phenotypes to genetic and environmental determinants as well as diagnostic and treatment-related parameters.

Methods: LCA was performed in an international multicenter birth cohort based on yearly questions about current wheeze until age 6 years. Associations of wheeze classes and clinical phenotypes with asthma-related characteristics such as atopy, lung function, fraction of exhaled nitric oxide, and medication use were calculated using regression models.

Measurements and Main Results: LCA identified five classes, which verified the clinically defined wheeze phenotypes with high sensitivity and specificity; the respective receiver operating characteristics curves displayed an area under the curve ranging from 84% (frequent wheeze) to 85% (asthma diagnosis) and 87% (unremitting wheeze) to 97% (recurrent unremitting wheeze). Recurrent unremitting wheeze was the most specific and unremitting wheeze at least once the most sensitive definition. The latter identified a subgroup of children with decreased lung function, increased genetic risk, and *in utero* smoke exposure (odds ratio, 2.03; 95% confidence interval, 1.12–3.68; $P = 0.0191$), but without established asthma diagnosis and treatment.

Conclusions: Clinical phenotypes were well supported by LCA analysis. The hypothesis-free LCA phenotypes were a useful reference for comparing clinical phenotypes. Thereby, we identified children with clinically conspicuous but undiagnosed disease. Because of their high area under the curve values, clinical phenotypes such as (recurrent) unremitting wheeze emerged as promising alternative asthma definitions for epidemiologic studies.

Keywords: childhood asthma; phenotypes; latent class analysis; epidemiology

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*A complete list of members may be found before the beginning of the References.

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At a Glance Commentary

Scientific Knowledge on the Subject: Childhood asthma phenotypes have been defined by two different approaches. From a clinically oriented perspective, classification has been based on patient histories, diagnostic techniques, and treatment responses, whereas the hypothesis-free approach by latent class analysis (LCA) has been used by epidemiologists. So far these approaches have not been compared systematically.

What This Study Adds to the Field: We found that clinical definitions such as unremitting wheeze, recurrent unremitting wheeze, multitrigger wheeze, and, with reservations, also a reported asthma diagnosis, are well supported by LCA based on longitudinal data on current wheeze during the first 6 years of life. Unremitting wheeze at least once is the most sensitive, whereas recurrent unremitting wheeze is the most specific phenotype, when compared to LCA classes. Applying the sensitive phenotype definition of unremitting wheeze, we identified a group of patients with impaired lung function but without adequate diagnosis and treatment.

Asthma is a highly variable disease, in terms of presentation, disease progression over time, and response to therapy (1). Recurrent lower respiratory symptoms associated with cough, wheezing, and reversible airway obstruction support a diagnosis of asthma. A proper asthma diagnosis, however, cannot be based on a single common feature (1, 2). It has long been recognized that distinct subsets of the above characteristics are seen in some patients with asthma but not in others. Nevertheless, features suggestive of asthma run together and have elicited a search for common phenotypes following two main approaches: The clinical approach classifies clinical phenotypes based on a wealth of experience in patient histories, diagnostic techniques, and treatment responses, whereas the epidemiologic approach identifies asthma phenotypes by unsupervised, hypothesis-free statistical methods in population samples (3).

Two major clinical phenotypes have been distinguished with respect to their triggers: The first phenotype can be subdivided into the two variants multi(ple)-trigger wheeze, with a focus on episodes of wheeze being elicited by various triggers besides infections (4), and unremitting wheeze, which is defined by symptoms such as wheeze or cough at night or due to exercise also occurring between distinct episodes (5). The other major phenotype, episodic viral wheeze, is commonly triggered by infections, with the child being well between episodes (4). Beyond this dichotomy, severity of symptoms has been addressed by a higher frequency of wheezing episodes (usually more than three per year) resulting in the use of frequent wheeze as a distinct phenotype (6–8).

Epidemiologic studies often operate with long-term trajectories such as the triad of early transient, persistent, and late-onset wheeze (9). This classification has been confirmed in different cohort studies by latent class analysis (LCA) as a data-driven approach (10, 11).

So far, clinical and epidemiologic classifications have hardly been compared systematically. Therefore, we intended to evaluate both sets of definitions and their interrelations with respect to environmental determinants, family history of atopy, genetic risk factors, sensitization to specific allergens, fraction of exhaled nitric oxide (Fe_{NO}), lung function parameters, and medication use.

Methods

Study Design and Population

The Protection against Allergy—Study in Rural Environments (PASTURE) has been set up as a prospective birth cohort including children from rural areas, comprising children who live and do not

Table 1: Definition of Clinical Phenotypes Used

Clinical Phenotype	Definition
Asthma diagnosis	A physician's diagnosis of asthma at least once per lifetime or recurrent diagnoses of spastic, obstructive, or asthmatic bronchitis as reported by the parents at age 6 yr
Multitrigger wheeze	At least 2 out of 6 different triggers (cold, effort, dust, animals, grass, other) reported to elicit wheeze during at least one follow-up period between age 3 and 6 yr
Unremitting wheeze (at least once)	Having symptoms between distinct wheezing episodes or having wheeze without a cold during at least one follow-up period between age 1 and 6 yr
Recurrent unremitting wheeze	Having symptoms between distinct wheezing episodes or having wheeze without a cold during at least two follow-up periods between age 1 and 6 yr
Frequent wheeze	Having wheeze on a monthly basis during at least one follow-up period between age 1 and 6 yr
Episodic wheeze	Having distinct wheezing episodes concomitantly with a cold, but no symptoms between those distinct wheezing episodes between age 1 and 6 yr

For details, *see* the online supplement.

live on farms, in five European countries: Austria, Finland, France, Germany, and Switzerland. The study design has been described earlier (12). In brief, pregnant women were contacted in the third trimester of pregnancy. Families living on and running livestock farms were assigned to the farm study group. For the reference study group, families from the same rural areas, but not living on a farm, were recruited. The study was approved by the ethical committees of the participating institutions, and written informed consent was obtained from the children's parents or guardians.

Questionnaires

Questionnaires were administered at the end of pregnancy and when the children were 2, 12, 18, 24, 36, 48, 60, and 72 months of age. Questionnaires were based on items from the International Study of Allergy and Asthma in Childhood (ISAAC) (13), the Asthma Multicenter Infants Cohort Study (AMICS) (14), the ALEX (Allergy and Endotoxin) study (15), the PARSIFAL (Prevention of Allergy Risk factors for Sensitization In children related to Farming and Anthroposophic Lifestyle) study (16), and the American Thoracic Society questionnaire (17).

Parents were asked at all time points "How often has your child wheezed during the last 12 months?" or during the respective time period between questionnaire intervals. The possible answer categories were: never, less than once a month, once a month, and at least twice a month. Children with any wheeze at the respective time point were classified as wheezers.

Clinical phenotypes were defined as displayed in Table 1 based on clinically relevant information collected by the questionnaires. LCA classes add up to 100% because LCA assigns each child only to one class. In contrast, the clinical phenotypes are not mutually exclusive (i.e., a child can be classified within different phenotypes [e.g., a child may have unremitting wheeze and also an asthma diagnosis]). Control subjects used in the regression models were defined as children without an asthma diagnosis and without wheeze at any time point.

Genetic Determinants

Genotyping was performed at the Centre National de Génotypage, Evry, France, using the iPLEX Gold technology. Of all 939 children with available DNA samples, 896 passed all quality checks. The single-nucleotide polymorphism (SNP) rs7216389 was selected to cover a major known risk locus (chromosome *17q21*) for childhood asthma (18–20) and was coded for its risk allele (T).

Specific IgE in Serum Samples

Specific immunoglobulin E (sIgE) levels for 6 food and 13 common inhalant allergens were assessed in children at the age of 4.5 and 6 years in peripheral blood by the Allergy Screen test panel for atopy (Mediwiss Analytic, Moers, Germany) in one central laboratory. The levels of allergen-specific IgE were dichotomized at RAST class 2 (sIgE $\geq$ 0.7 kU/L), and other cut-off values corresponding to RAST class 1 or 3 (sIgE $\geq$ 0.35 kU/L and sIgE $\geq$ 3.5 kU/L, respectively) were explored.

Fe_{NO} Measurements and Lung Function

At the age of 6 years, 799 children were contacted for Fe_{NO} measurements, lung function testing, and medication use. Exhaled air was collected in triplicate, and Fe_{NO} was measured as described previously (21). After exclusion of 12 participants with reported intake of inhaled steroids in the week before the field visit, 737

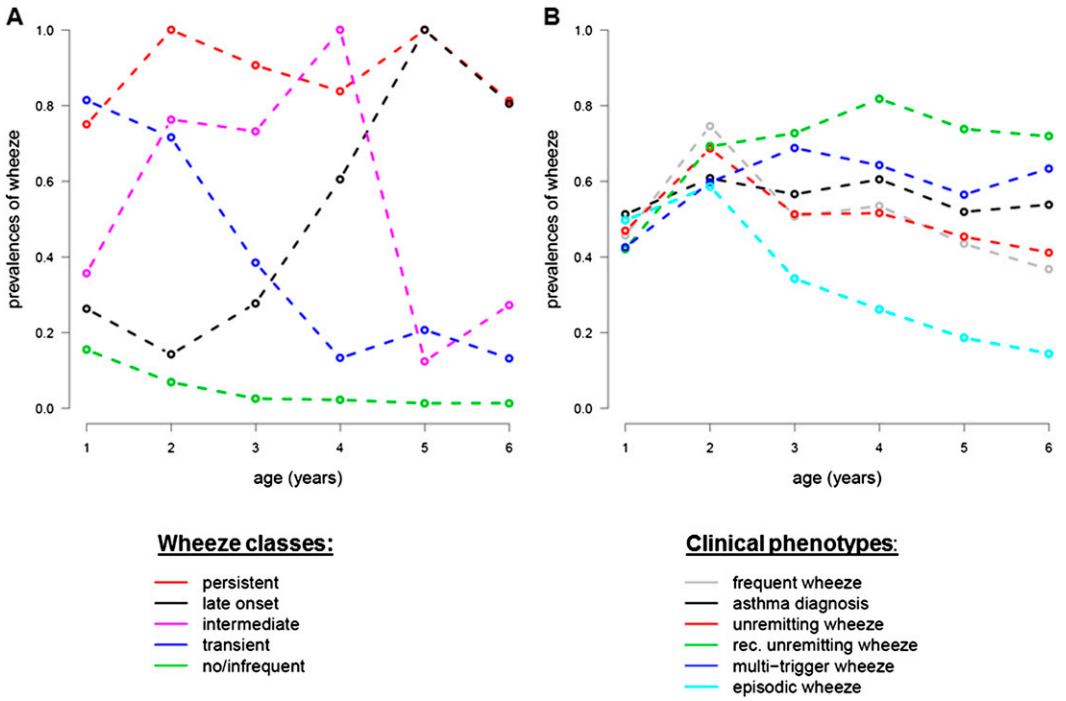

Figure 1. Course of wheeze prevalences in latent class analysis (LCA) and clinical phenotypes. (*A*) Prevalences of current wheeze (i.e., in the last 12 mo) in the first 6 years of life are shown for the five-class solution of the LCA. (*B*) Wheeze prevalences in the first 6 years of life stratified for the clinical phenotypes as defined in Table 1.

participants (92.2%) remained with acceptable FE_{NO} measurements according to guidelines (*see* online supplement).

Spirometry was performed as described previously (21). FEV_1 and maximum midexpiratory flow were determined as *z* scores (22) before and after application of a bronchodilator (400 μg of short-acting β-agonist [SABA]). A positive bronchodilator response was defined as a relative change of FEV_1 after versus before SABA of at least 12% (23). Measurements were acceptable in 648 children before (81.1%) and 595 children after bronchodilator test (74.5%), resulting in 578 complete sets of measurements.

Medication use during the last 12 months was classified into the following categories: oral or inhaled steroids, leukotriene receptor antagonists, long-acting β-agonists, and SABA.

Statistical Analyses

LCA was conducted in MPLUS Version 5 (Muthén and Muthén, 1998–2007) to determine subtypes of related cases from multivariable categorical data on wheezing over time. Individuals were assigned to the class for which they had the highest posterior probability of belonging. The resulting classes were then compared with clinical phenotypes by the polychoric correlation coefficient (rho) and with respect to true- and false-positive rates using receiver operating characteristics curves (24). To compare the respective area under the curve values, confidence intervals (CIs) were calculated according to DeLong and colleagues (25).

FE_{NO} values in parts per billion were log transformed, resulting in approximately normally distributed values. SNP data were analyzed in an additive model with respect to the increase of risk alleles. Associations of outcomes with potential determinants were calculated by linear or logistic regression using SAS 9.2 (The SAS Institute, Cary, NC) and R 2.14 (www.R-project.org). Effect estimates are given with 95% CIs as odds ratios (ORs) for dichotomous outcomes, β-estimates for linear continuous outcomes such as lung function parameters, and geometric mean ratios for log-transformed values. All regression analyses were adjusted for farming status and center because of the study design, and potential interactions with farming and center were explored.

Results

Study Population

Of the 1,133 enrolled children of the PASTURE birth cohort, 953 (84%) had complete data on wheeze during the last 12 months at no less than five of six yearly intervals under investigation and served as study population for the present LCA. Complete information on genetic risk was available for 896 children, and RAST tests were successfully performed in 745 children at the age of 6 years. Information about medication use, FE_{NO} measurements, and lung function testing was available in 799,

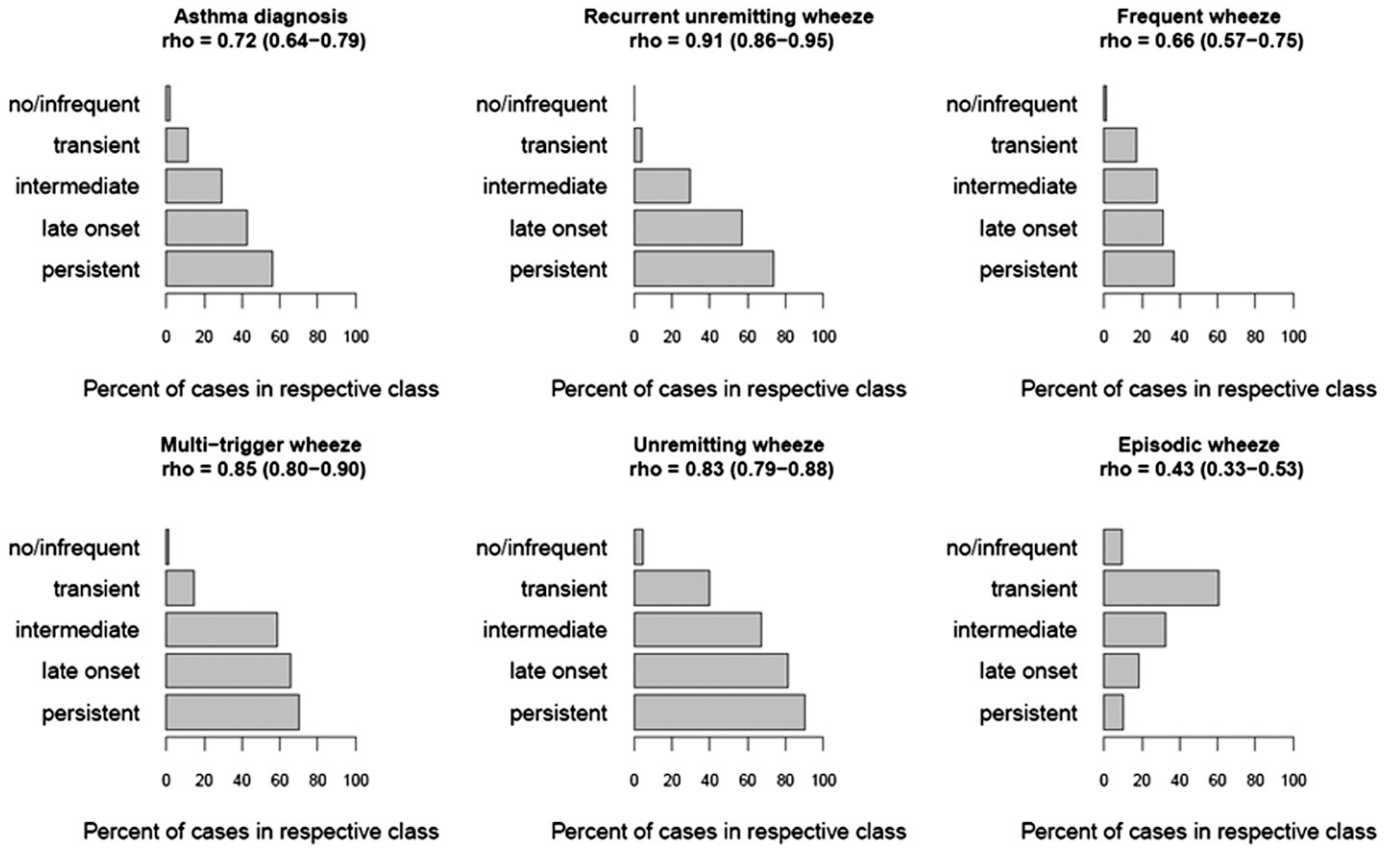

Figure 2. Proportions of children with clinical phenotypes within the five latent class analysis (LCA) classes. Prevalences of the respective clinical phenotypes are given, stratified for the five LCA classes. As a measure of concordance between clinical phenotypes and LCA, the polychoric correlation coefficient rho is given with 95% confidence intervals.

737, and 648 children, respectively (*see* Figure E1 in the online supplement). In these subsamples, children with low parental education and *in vitro* smoke exposure were somewhat underrepresented (Table E1).

Interrelations of LCA-defined and Clinical Phenotypes

Taking Akaike's information criterion, entropy, and interpretability into account, the LCA solution with five classes was superior to the four- and six-class solutions (Figure E2). Prevalences of LCA classes are shown in Table 2, and were rather consistent across the study centers (Table E2). The LCA classes followed individual trajectories of wheeze prevalences (Figure 1A) irrespective of the study group (Figure E3). Clinical phenotypes followed relatively parallel trajectories with little segregation before age 3 years (Figure 1B).

Except for episodic wheeze, the proportions of children with the respective clinical phenotypes increased consistently across the LCA classes (Figure 2).

LCA classes correlated very well with unremitting wheeze at least once, recurrent unremitting wheeze, and multitrigger wheeze as determined by a polychoric correlation coefficient rho greater than 0.8. In contrast, episodic wheeze correlated badly with the LCA classes and was thus not considered for further analyses. For internal validation we compared the correlation coefficients of clinical phenotypes and LCA classes across study centers and found a rather homogeneous pattern, with low coefficients of variation across countries (Table E3).

Identification and Prediction of Clinical Phenotypes by LCA Classes

Based on the clear increase of clinical phenotype prevalences across the LCA classes (Figure 2), we used the LCA classes also as an ordinal variable with five categories ranking the classes as in Figure 2. For the four different cut-offs of this ordered variable, true-positive rates were plotted against false-positive rates (Figure 3A). The resulting receiver operating characteristic curves revealed informative differences between the clinical phenotypes. Recurrent unremitting wheeze displayed the significantly highest area under the curve value, with the lower confidence limit being higher than the upper limits of all other phenotypes. Irrespective of any particular LCA classes, unremitting wheeze at least once displayed the highest positive predictive values and recurrent unremitting wheeze the highest negative predictive values (Figure 3B). In other words, when considering LCA classification as a reference, unremitting wheeze is the most sensitive and recurrent unremitting wheeze the most specific phenotype. The shaded area in Figure 3B reflects the difference in sensitivity between unremitting wheeze and asthma diagnosis.

Characteristics of LCA-defined and Clinical Phenotypes

Key characteristics are summarized in Figure 4. Details on environmental and genetic determinants are given in Table E4, on atopic sensitization in Table E5, and on lung function parameters and medication use in Table E6.

The particular LCA classes varied substantially with respect to major features. Persistent wheeze was strongly related to the asthma risk locus on chromosome 17 but unrelated to environmental determinants; compromised lung function resolved almost completely after bronchodilator administration. The hallmark of late-onset wheeze was an extremely strong association with Fe_{NO} and sensitization to inhalant allergens at 6 years (Figure 4) and at 4 years (adjusted OR [aOR] = 4.35; 95% CI, 1.89–10.02; $P < 0.001$); lung function was severely and irreversibly compromised, and medication use was as common as in an asthma diagnosis. In intermediate wheeze,

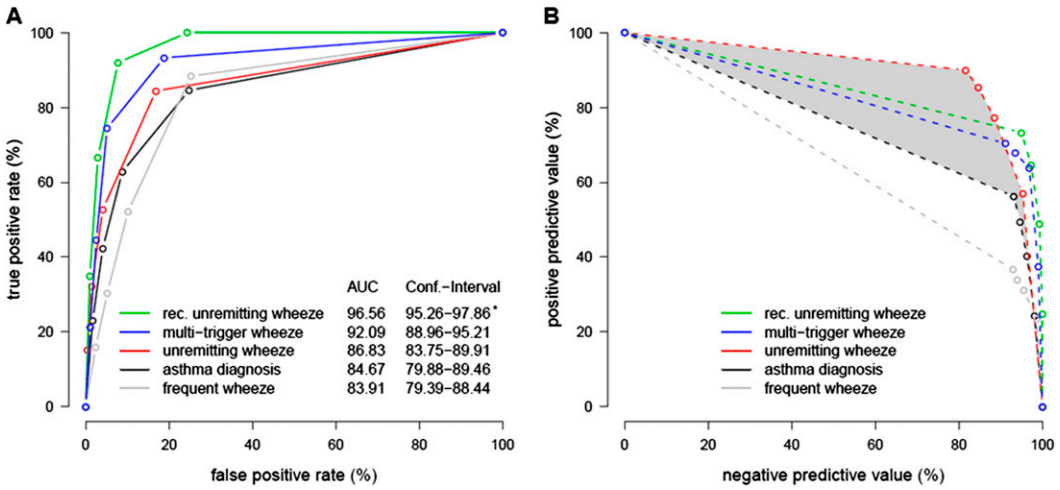

Figure 3. Correlation of clinical phenotypes and latent class analysis (LCA) asthma. (*A*) A receiver operating characteristics curve plotting true- against false-positive rate for all comparisons of clinical phenotypes with the respective LCA classes is shown. The *dots* refer to the following cut points between the LCA classes (from left to right): persistent versus late-onset/intermediate/transient/infrequent; persistent/late-onset versus intermediate/transient/infrequent; persistent/late-onset/intermediate versus transient/infrequent; persistent/late-onset/intermediate/transient versus infrequent wheeze. The area under the curve (AUC) is given as percentages with 95% confidence intervals (CI). *The CI of recurrent unremitting wheeze does not overlap with the CI of the other phenotypes, thereby demonstrating its significant advantage over all other phenotypes. (*B*) Positive predictive values are plotted against negative predictive values for all clinical phenotypes and all possible dichotomizations of LCA classes. The shaded area illustrates the difference between unremitting wheeze and asthma diagnosis (*see text*).

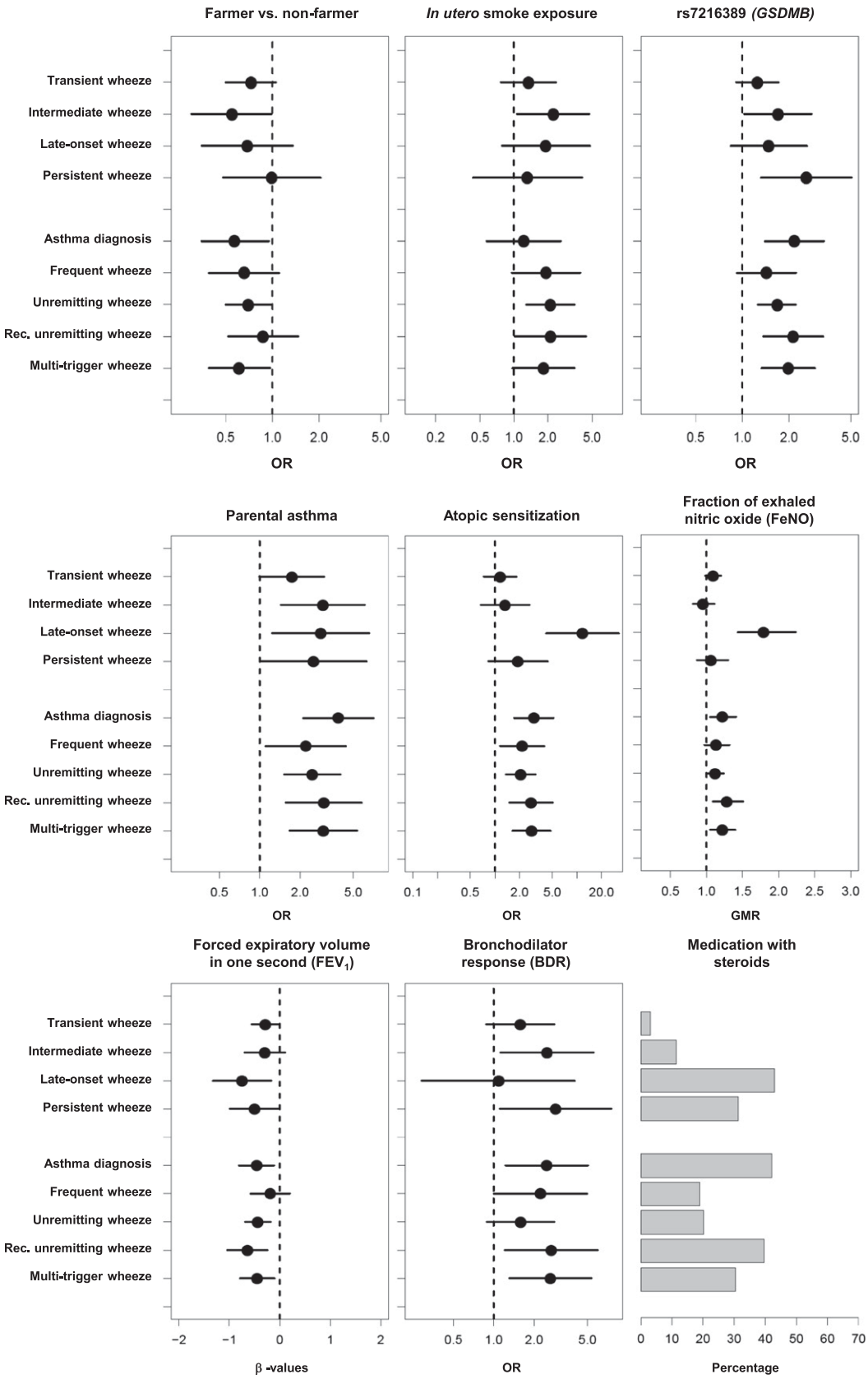

Figure 4. (See figure legend on following page)

associations with atopy were restricted to pollen sensitization; relevant associations were also found with environmental determinants and genetic risk. Transient wheeze was hardly related to atopy and genetic risk; lung functions were mildly impaired, and medication use was very uncommon.

The characteristics of multitrigger and unremitting wheeze were very similar. They were strongly associated with genetic risk, with atopic sensitization particularly to mites and pollen, and with elevated F_{ENO} levels. Lung function parameters were compromised but responded well to bronchodilators. Medication use was common. For the parameters given in Figure 4, the effect estimate of multitrigger wheeze ranged between unremitting wheeze and recurrent unremitting wheeze, with the latter showing the most pronounced effects.

Multitrigger and (recurrent) unremitting wheeze were positively associated with *in utero* smoke exposure and considerably with a family history of asthma and atopy. In contrast, an asthma diagnosis was not related to *in utero* smoke exposure but was related strongly to a family history. With respect to all other characteristics, however, asthma diagnosis resembled the above-mentioned clinical phenotypes.

The phenotype frequent wheeze was not related to genetic risk factors and hardly to atopic sensitization. Lung functions were only mildly impaired, and bronchodilator response was observable.

Relation of Asthma Diagnosis and Unremitting Wheeze

As demonstrated by the shaded area in Figure 3B, there was a considerable sensitivity gap between an asthma diagnosis and unremitting wheeze comprising 115 children. Hence, we stratified children with unremitting wheeze for the presence or absence of an established asthma diagnosis (Table 3). Children without a diagnosis were nevertheless affected by impaired lung function and inadequate response to bronchodilators. With few exceptions, they were not treated with asthma drugs. In contrast to children with an asthma diagnosis, they were significantly more exposed to smoke *in utero* than healthy control subjects. In turn, the 16 children with an asthma diagnosis but not covered by unremitting wheeze had strong associations with a family history of asthma (aOR = 2.84; 95% CI, 0.86–9.46; $P = 0.088$) and atopic sensitization (aOR = 4.29; 95% CI, 1.33–13.9; $P = 0.015$).

In children with unremitting wheeze but no asthma diagnosis, *in utero* smoke exposure was strongly related to a reduced FEV_1 at borderline significance ($\beta = -0.53$; 95% CI, −1.12 to 0.06; $P = 0.084$), whereas in the entire population FEV_1 was not related to *in utero* smoke exposure ($\beta = -0.03$; 95% CI, −0.31 to 0.25; $P = 0.824$).

Discussion

Asthma is not a single disease entity but rather a syndrome subsuming various wheezing-associated disorders. To disentangle these various phenotypes, seemingly incompatible approaches have been pursued. Here we intended to reconcile clinical and epidemiologic perspectives by exploring clinical definitions of wheeze and contrasting them with a data-driven classification by LCA.

The LCA revealed five classes similar to those seen in more urban cohorts (10, 11). The class transient wheeze was not associated with atopic predisposition and only weakly with lung function parameters, as published previously (11, 26). The hallmark of persistent wheeze was a strong association with the asthma locus on chromosome *17q21* (27). In contrast, late-onset wheeze showed weaker associations with genetic risk but was strongly related to atopic sensitization at 6 years and substantially higher F_{ENO} levels. The class intermediate wheeze is a genuine contribution of LCA (10, 11) to the four classes of never/infrequent, early transient, persistent, and late-onset wheeze, which have long been postulated based on epidemiologic observations (9). In contrast to the other LCA classes, intermediate wheeze comprises a rather heterogeneous group having only relatively strong environmental determinants in common.

Any LCA is never completely agnostic, because the choice of parameters entered into the model is usually based on prior knowledge. The present analysis was based only on temporal variations of wheeze symptoms inquired in yearly intervals; information on wheezing intensity, symptoms between episodes, or other concomitant features was ignored. Other LCA approaches integrating information on frequency of wheeze, relation to cough, and other characteristics revealed somewhat distinct categories but no completely novel wheeze phenotypes (28, 29).

Among the clinical phenotypes, we assessed an asthma diagnosis at age 6 years in all countries based on the German ISAAC definition (i.e., an established diagnosis of asthma *or* recurrent wheezy bronchitis). This was chosen because, particularly in the German language, the term asthma used to be avoided and replaced by spastic or obstructive bronchitis. Previously, this definition was validated against cold-air provocation in German schoolchildren (30). When ignoring wheezy bronchitis in a sensitivity analysis we missed half the cases of the German ISAAC definition (data not shown). Asked at school age, parents reported a lifetime prevalence of wheeze of 16.9%. However, the cumulative prevalence of yearly questions on wheeze was 56.8%. This discrepancy indicates that parents tend to forget early wheeze episodes; in other words, only wheeze episodes impressive enough to be recalled at school age might be relevant for an asthma diagnosis, thereby supporting the appropriateness of the German ISAAC definition.

The statistical association with family history was particularly strong for an asthma diagnosis consistently exceeding those for all other clinical and LCA phenotypes. To avoid labeling bias, clinicians should consider this issue cautiously when deliberating an asthma diagnosis.

Another major phenotype under investigation, frequent wheeze, has been proposed to quantify severity of symptoms. However, its correlation with LCA classes was substantially weaker as compared with (recurrent) unremitting/multitrigger

Figure 4. Associations of phenotypes with characteristics. Associations are given for the respective phenotypes versus control subjects (i.e., children without wheeze ever or asthma diagnosis). Effects are given in odds ratios (OR), geometric mean ratios (GMR), or β-values with 95% confidence intervals. All effects are adjusted for center and farming status. Percentage of intake is given for steroid medication in the last year before lung function testing.

Table 2: Prevalences of Latent Class Analysis Phenotypes and Clinical Phenotypes

Phenotype	Prevalence
LCA	
Persistent wheeze	3.3%
Late-onset wheeze	4.0%
Intermediate wheeze	5.9%
Transient wheeze	16.8%
No/infrequent wheeze	70.0%
Clinical	
Asthma diagnosis	8.4%
Multitrigger wheeze	11.4%
Unremitting wheeze	22.6%
Recurrent unremitting wheeze	8.1%
Frequent wheeze	8.5%
Episodic wheeze	19.5%

Definition of abbreviation: LCA = latent class analysis.
LCA phenotypes are mutually exclusive, whereas clinical phenotypes are correlated.

wheeze. Therefore, and because of the relatively weak associations with atopy, the mildly reduced lung function parameters, and the rare drug usage, we would rather not recommend frequent wheeze as a surrogate for disease severity.

Episodic wheeze was originally defined as wheeze in discrete episodes, with the child being well between episodes (4, 5). Episodes occur seasonally and are usually triggered by viral infections (4, 31). The condition of being well between episodes produces a rather mild phenotype, which is reflected by the comparably high proportion of children with transient or infrequent wheeze and the low correlation with LCA. Episodic wheeze is unlikely to describe a chronic condition with deteriorating lung function. Rather, it might reflect an initially disproportionate response to viral infections with altered airway mechanics, which resolves in the course of further growth (32).

In contrast to the above monotrigger phenotype, multitrigger wheeze has been introduced to collect children responding with airway obstruction readily to all sorts of environmental triggers, including viruses. Multitrigger and unremitting wheeze resembled each other most closely with respect to all other parameters under investigation. This is not surprising, because both are variants of the same phenotype. In our definition, unremitting wheeze was partially based on wheeze without a cold, which means any trigger in addition to the most common trigger of wheeze (i.e., a cold). The second component of unremitting wheeze was symptoms, mostly cough, between wheeze episodes. Similarly, this component reflects an increased vulnerability of the respiratory tract.

The most important findings of this analysis were the high correlations of (recurrent) unremitting wheeze and multitrigger wheeze with the LCA classes. Essentially, this is not self-evident because the clinical definitions focus on disease intensity and triggers of episodes, whereas the LCA was based on longitudinal patterns of wheeze ignoring disease intensity and trigger factors. Remarkably, two systematically different approaches yielded congruent results; thereby they support distinction of wheeze phenotypes as a genuine phenomenon. Clinical definitions hereby emerge as valid instruments for epidemiologic studies, and clinicians may benefit from phenotype classifications anchored in general populations.

The robust clinical phenotype of unremitting wheeze in its both flavors (i.e., the more sensitive at-least-once variant and the more specific recurrent variant) might be a promising outcome definition in epidemiologic studies. This applies particularly to cross-sectional studies, where exact information on the course of disease is difficult to collect retrospectively. For instance, the more restrictive variant of recurrent unremitting wheeze excluded transient wheezers almost completely.

The usefulness of the more inclusive variant of unremitting wheeze is exemplified by the inclusion of 115 children without a (reported) asthma diagnosis, which reflects 12% of the study population. The combination of impaired lung function, nonresponse to bronchodilators, association with *in utero* smoke exposure, and the prediction of

Table 3: Associations of Unremitting Wheeze with Various Characteristics Stratified for the Presence or Absence of an Asthma Diagnosis

	Stratum with Asthma Diagnosis (*n* = 60)			**Stratum without Asthma Diagnosis (*n* = 115)**		
	aOR	95% CI	*P* Value	aOR	95% CI	*P* Value
Girls vs. boys	**0.39**	**0.22 to 0.71**	**0.0019**	0.82	0.54 to 1.25	0.3628
Parental atopy	**3.18**	**1.63 to 6.20**	**0.0007**	**1.76**	**1.12 to 2.77**	**0.0138**
Parental asthma	**4.40**	**2.28 to 8.50**	**<0.0001**	**1.87**	**1.03 to 3.42**	**0.0407**
SNP rs7216389 of *GSDMB**	**2.28**	**1.40 to 3.72**	**0.0009**	**1.48**	**1.05 to 2.07**	**0.0238**
Sensitization against inhalant allergens†	**3.03**	**1.63 to 5.61**	**0.0004**	**1.72**	**1.04 to 2.84**	**0.0332**
Farmer vs. nonfarmer	0.60	0.34 to 1.06	0.0765	0.84	0.55 to 1.28	0.4177
In utero smoke exposure	1.54	0.69 to 3.46	0.2936	**2.03**	**1.12 to 3.68**	**0.0191**
F_{ENO}, aGMR	**1.23**	**1.04 to 1.45**	**0.0140**	1.07	0.96 to 1.21	0.2259
FEV_1, *z*-score before bronchodilation, β-coefficient	**−0.64**	**−1.03 to −0.26**	**0.0011**	**−0.33**	**−0.64 to −0.02**	**0.0382**
BDR	**3.36**	**1.60 to 7.04**	**0.0014**	0.74	0.32 to 1.71	0.4829
Steroids, %, n/N‡	50.0%	27/54		3.3%	3/91	

Definition of abbreviations: aGMR = adjusted geometric mean ratio; aOR = adjusted odds ratio; BDR = bronchodilator response; CI = confidence interval; F_{ENO} = fraction of exhaled nitric oxide; *GSDMB* = Gasdermin B; SNP = single-nucleotide polymorphism.
All analyses are adjusted for center and farming status and given with 95% CIs. Significant results ($P < 0.05$) are printed in bold.
*Effect given for an increase of the risk allele.
†Sensitization against inhalant allergens is based on RAST class 2 measured at age 6 yr.
‡No. of children with intake of steroid medication (n) of all children with information about medication (N).

reduced lung function by *in utero* smoke exposure restricted to this subgroup suggests a distinct disease entity with similarities to early stages of chronic obstructive pulmonary disease. Alternatively, this group might comprise children with an incomplete diagnostic work-up for asthma and accordingly inadequate treatment. In any case, clinicians should be made aware of the importance of *in utero* smoke exposure in children presenting with wheeze and intermittent symptoms.

Likewise, the dichotomy of the clinical phenotypes in episodic viral wheeze versus unremitting or multitrigger wheeze might be complemented by epidemiologic phenotypes defined by trajectories of wheezing or LCA classes. For instance, the time course of late-onset wheeze implicitly carries information on the likelihood of early sensitization and worsening lung function. The strong association of late-onset wheeze with sensitization to inhalant allergens already at 4 years suggests atopy as an antecedent element in this phenotype. Correspondingly, we detected the most strongly impaired lung function in late-onset wheezers, which is in line with the observation that atopic sensitization at 3 years predicts decreased lung function at school age (33).

Our analyses are limited by slight discrepancies from published phenotype definitions, because some questionnaire items were not asked consistently over time (Table 1). Nevertheless, the sensitivity analyses performed justified our approximations. Furthermore, clinical records were not available for the definition of the clinical phenotypes; however, we think that the extensive parent-reported questionnaire information on hand was sufficient for this comparison within the limits of an epidemiologic study.

A further drawback of this international study might be seen in country heterogeneity and linguistic inconsistencies; for example, the German language does not own a proper translation of wheeze. When comparing the correlation coefficients of LCA asthma with the clinical phenotypes across countries, we found a considerable homogeneity across languages and countries (Table E3). Whether the current phenotype definitions are useful throughout puberty and adolescence remains to be seen during subsequent follow-ups of the PASTURE birth cohort.

Taken together, we have replicated previously published LCA findings in an international multicenter birth cohort. Beyond that, we have corroborated existing clinical phenotypes by LCA. Furthermore, we have identified recurrent unremitting wheeze as a specific and unremitting wheeze at least once as a sensitive alternative to an asthma diagnosis as an outcome definition in epidemiologic studies. Finally, we spotted a group of children with *in utero* smoke exposure who merit greater awareness in asthma research and everyday medical care. ■

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