Ten-Year Follow-up of Cluster-based Asthma Phenotypes in Adults

A Pooled Analysis of Three Cohorts

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***Rationale*: The temporal stability of adult asthma phenotypes identified using clustering methods has never been addressed. Longitudinal cluster–based methods may provide novel insights in the study of the natural history of asthma.**

***Objectives*: To compare the stability of cluster-based asthma phenotype structures a decade apart in adults and to address the individuals' phenotypic transition across these asthma phenotypes.**

***Methods*: The latent transition analysis was applied on longitudinal data (twice, 10 yr apart) from 3,320 adults with asthma who took part in the European Community Respiratory Health Survey, the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults, or the Epidemiological Study on Genetics and Environment of Asthma. Nine variables covering personal and phenotypic characteristics measured twice, 10 years apart, were simultaneously considered.**

***Measurements and Main Results*: Latent transition analysis identifies seven asthma phenotypes (prevalence range, 8.4–20.8%), mainly characterized by the level of asthma symptoms (low, moderate, high), the allergic status, and pulmonary function. Phenotypes observed 10 years apart showed strong similarities. The probability of membership in the same asthma phenotype at both times varied across phenotypes from 54 to 88%. Different transition patterns were observed across phenotypes. Transitions toward increased asthma symptoms were more frequently observed among nonallergic phenotypes as compared with allergic phenotypes. Results showed a strong stability of the allergic status over time.**

***Conclusions*: Adult asthma phenotypes identified by a clustering approach, 10 years apart, were highly consistent. This study is the first to model the probabilities of transitioning over time between comprehensive asthma phenotypes.**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Clustering approaches have been used in the respiratory epidemiology field to disentangle the heterogeneity of asthma, but the temporal stability of such asthma phenotypes and the long-term phenotypic transition at the individual level have never been addressed.

What This Study Adds to the Field

Modeling shows strong similarities in cluster-based adult asthma phenotypes studied 10 years apart. Transition toward increased asthma symptoms is more common in nonallergic phenotypes than in allergic ones.

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Asthma is a complex disease characterized by a strong clinical heterogeneity and possible phenotypic variability over time (1–3). Accurate asthma phenotypes are needed for better asthma management and for better identification of phenotype-specific risk factors. Disentangling asthma phenotypes, or more generally

IgE-related phenotypes, is a current challenge (4, 5). Beside the "candidate" approach that identifies *a priori* phenotypes on the basis of one or few disease characteristics, unsupervised or data-driven approaches have been proposed to unravel the heterogeneity of asthma by means of a clustering approach integrating multiple disease features (6, 7).

To date, clustering analyses have been performed in a cross-sectional manner, by integrating several domains of the disease measured at one point in time (8–11), or longitudinally, by using a single disease characteristic assessed at several time points to define trajectories (12, 13). Latent class analysis (LCA), a model-based clustering method, has previously been conducted in two large epidemiological studies, and revealed four distinct asthma phenotypes in each sample (11). These phenotypes clearly discriminated populations in terms of quality of life and blood eosinophil and neutrophil counts. The validity of cluster-derived asthma phenotypes is supported by similarities in phenotypes across different populations and by discriminative properties and association with clinical prognosis or risk factors (8, 9, 11, 13–16). Although a previous study provided first results indicating a stability of cluster-based asthma phenotypes over 1 year (15), none applied such cluster analysis several years apart in the same population and compared the structure of the phenotypes obtained. Furthermore, the transitions between cluster-based asthma phenotypes at the individual level have never been addressed in large epidemiological studies (5). In addition, no studies have attempted to identify adult asthma phenotypes using a more comprehensive approach, simultaneously integrating several domains of the disease, repeatedly measured over time. Because asthma is a variable disease, such an approach may lead to the identification of more specific phenotypes, which could facilitate the identification of risk factors. Cohorts with long-term follow-up, such as the European Community Respiratory Health Survey (ECRHS) (17), the Epidemiological Study on Genetics and Environment of Asthma (EGEA) (18), and the Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults (SAPALDIA) (19), can provide this additional information.

Using a large sample of subjects with asthma, recruited in the frame of three 10-year follow-up epidemiological studies (ECRHS, EGEA, and SAPALDIA), the present study aimed to compare the stability of cluster-based adult asthma phenotype structures a decade apart and to address the individuals' phenotypic transition across these asthma phenotypes.

METHODS

Additional details on methods are provided in the online supplement.

Participants

We analyzed longitudinal data from three large epidemiological cohorts recruited in the early 1990s and followed 10–12 years later: ECRHS, an international population-based study of asthma (ECRHSI, 1991–1993; ECRHSII, 1999–2002) (17), SAPALDIA, a Swiss population-based study (SAPALDIA1, 1991; SAPALDIA2, 2001–2003) (19), and EGEA, a French case–control and family study of adults and children at baseline (Epidemiological Study on Genetics and Environment of Asthma [EGEA1] 1, 1991–1995; EGEA2, 2003–2007) (20).

Phenotypic Characteristics

In the three studies, all subjects were extensively characterized using standardized protocols and questionnaires. Examination procedures included a detailed respiratory questionnaire, with questions on asthma, respiratory symptoms frequency, and treatments for asthma problems and allergic rhinitis. Lung function and bronchial hyperresponsiveness (BHR) test results were measured according to standardized procedures. The questionnaires are available on the Web sites of the studies (http://www.ecrhs.org/, http://www.sapaldia.net, and http://egeanet.vjf.inserm.fr). Previous analysis combining these three epidemiological studies has already been conducted for other purposes (21).

"Ever asthma" was defined in ECRHS and SAPALDIA by a positive answer to: "Have you ever had asthma?" and in EGEA either by a positive answer to one of the two standardized questions: "Have you ever had attacks of breathlessness at rest with wheezing?" or "Have you ever had asthma attacks?" or being recruited as an asthma case. Current asthma was defined by subjects with ever asthma who reported asthma attacks or asthma treatment or at least one asthma symptom (Table 1) over the previous 12 months.

Biases

A standardized protocol and questionnaire were used in the three studies, allowing minimization of the risk for measurement biases. Analyses of follow-up bias have previously been addressed within each study, and showed that the follow-up participants did not strongly differ from the nonparticipants in regard to the main sociodemographic and clinical characteristics (18, 19, 22). A sensitivity analysis was conducted, which was restricted to the population-based cohorts (ECRHS and SAPALDIA) to address the role of potential selection bias introduced by the study design.

Strategy of Analysis

The main analysis was conducted on the pooled dataset. The latent transition analysis (LTA) is a cluster-based model developed for longitudinal data (23). Such models allow the integration of repeated data and the identification of discrete latent classes of individuals based on their shared characteristics across a set of observed categorical variables, and allow model change over time between classes. Parameters estimated in LTA include class membership probabilities, which represent the phenotype prevalence and the item response probabilities, which are used to characterize the phenotype structures. LTA also produces a transition probability matrix, estimating probabilities of membership in the same phenotype at each time point (entries along the diagonal) and probabilities of transitioning to a different phenotype over time (entries off the diagonal) (24, 25).

This longitudinal analysis was conducted based on the nine variables covering personal and phenotypic characteristics (Table 1). Variables included in our previous LCA analysis (11) that were constant/almost constant over time were not retained in the present analysis, because LTA is aimed at characterizing transition over time and requires variability in all variables. Interestingly, we replicated the four LCA-derived asthma phenotypes previously identified at follow-up (11) when applying the LCA model on this restricted number of variables (*see* Table E1 in the online supplement). Age, age at asthma onset, and sex were considered as covariates in the LTA model. The number of classes was statistically determined using the Bayesian information criterion (BIC). When different models showed BICs of similar magnitude, phenotype prevalences were also considered to avoid a solution leading to low prevalent phenotypes (<5%). To assess the stability of the structure of the asthma phenotypes 10 years apart, we tested the goodness of fit of the "constrained" LTA model in which identical item–response probabilities across time are estimated (meaning that the same cluster structure is forced in the two time points) as compared with the "unconstrained" LTA model in which item–response probabilities are estimated at each time point. Furthermore, to address sex differences in asthma phenotypes, models were also fitted by sex, and results observed in men and women were statistically compared.

We investigated how the LTA-derived asthma phenotypes defined at baseline were related to the subsequent risk for asthma exacerbation assessed at follow-up by the report of hospitalization for asthma or the use of oral steroids for breathing problems in the previous 12 months in ECRHS and EGEA (data not available in SAPALDIA).

RESULTS

Asthma Participants

The current study was based on 3,320 adults (2,031, 863, and 426 participants in ECRHS, SAPALDIA, and EGEA, respectively) reporting ever asthma at baseline or follow-up (mean [SD] follow-up time was 8.5 [±1.4], 11.0 [±0.3], and 11.7 [±1.1] yr

TABLE 1. DEFINITION OF THE VARIABLES SELECTED FOR THE ANALYSIS

Criteria	Definition Used in ECRHS	Definition Used in SAPALDIA	Definition Used in EGEA
Asthma symptom score, 12 mo	Sum of five symptoms: 1. "Have you had wheezing or whistling in your chest at any time in the last 12 months?" and "Have you been at all breathless when the wheezing noise was present?" 2. "Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?" 3. "Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?" 4. "Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months?" 5. "Have you been woken by an attack of shortness of breath at any time in the last 12 months?"	*Idem*	*Idem*
Woken up by attack of coughing, 12 mo	"Have you been woken by an attack of coughing at any time in the last 12 months?"	*Idem*	*Idem*
Chronic cough or phlegm	"Do you usually cough during the day, or at night, in the winter, on most days for as much as three months each year" or "Do you usually bring up any phlegm from your chest during the day, or at night, in the winter, on most days for as much as three months each year?"	*Idem*	*Idem*
Asthma attack, 12 mo	"Have you had an attacks of asthma in the past 12 months"	*Idem*	*Idem*
Asthma treatment*	"Are you currently taking any medicines including inhalers, aerosols or tablets for asthma?"	*Idem*	Did you take any medicines for your asthma attacks in the past 12 mo?
Allergic sensitization	Specific IgE to one allergen among cat, *Dermatophagoides pteronyssinus*, *Cladosporium*, and timothy grass at ECRHSI and ECRHSII	Positive Phadiatop test at SAPALDIA1 and SAPALDIA2	Skin-prick test to any of the 11 allergens (cat, *Dermatophagoides pteronyssinus*, *Blattela germanica,* olive, birch, *Parieteria judaica*, timothy grass, ragweed pollen, *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*) at EGEA1 and EGEA2
Total IgE	<100 IU/ml vs. ⩾100 IU/ml	*Idem*	*Idem*
FEV_1	Assessed using the best of five expiratory curves	Assessed using the best curve from spirometry with up to eight maneuvers (conforming to ATS/ERS quality criteria). Using Quanjer equations from 1993 for FEV_1 % predicted	Assessed using the best of five expiratory curves
	Two classes: <80% predicted vs. ⩾80%	Two classes: <80% predicted vs. ⩾80%	Two classes: <80% predicted vs. ⩾80%
Bronchial hyperresponsiveness	For subjects with $FEV_1 > 70\%$, $PD_{20} \leqslant 1$ mg methacholine	Idem	For subjects with $FEV_1 > 80\%$, $PD_{20} \leqslant 1$ mg methacholine

Definition of abbreviations: ATS = American Thoracic Society; ECRHS = European Community Respiratory Health Survey; EGEA = Epidemiological Study on Genetics and Environment of Asthma; ERS = European Respiratory Society; PD_{20} = provocative dose causing 20% decrease in FEV_1; SAPALDIA = Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults.

*The question "Are you currently taking any medicines, including inhalers, aerosols, or tablets for asthma?" was not available at EGEA1, so, for longitudinal consistency, we retained the following question "Did you take any medicines for your asthma attacks in the past 12 months?" in EGEA. Strong agreement was observed between answers to these two questions at EGEA2 (overall agreement was 81.5%; $\kappa = 0.63$).

for ECRHS, SAPALDIA, and EGEA respectively; Figure 1). A total of 2,072 subjects reported ever asthma at both points in time, 921 reported ever asthma at follow-up only, and 327 reported ever asthma at baseline only. The population includes 1,918 (58.5%) and 2,350 (72.5%) subjects with current asthma at baseline and follow-up, respectively.

Descriptive Data

Mean (±SD) age at baseline was 35.8 (±9.8) years, and 44.0% were men (Table 2). The prevalence of allergic characteristics (allergic sensitization, total IgE > 100 IU/ml) was stable over time. Low FEV_1 ($FEV_1 < 80\%$ predicted value) was observed in 12.0 and 14.0% of the subjects at baseline and follow-up, respectively. The prevalence of BHR was 44.8 and 40.6% at baseline and follow-up, respectively. About one-third of this population with asthma reported asthma attacks in the previous 12 months at both time points, and 54.7% reported adult-onset asthma. Because of the different study designs used, subjects with asthma recruited in EGEA had more asthma attacks, asthma symptoms, and asthma treatment at baseline, but these differences were lower at follow-up.

Phenotypes Using LTA

LTA analyses with seven, eight, and nine classes led to BIC of similar magnitude (Figure E1). The model with eight classes

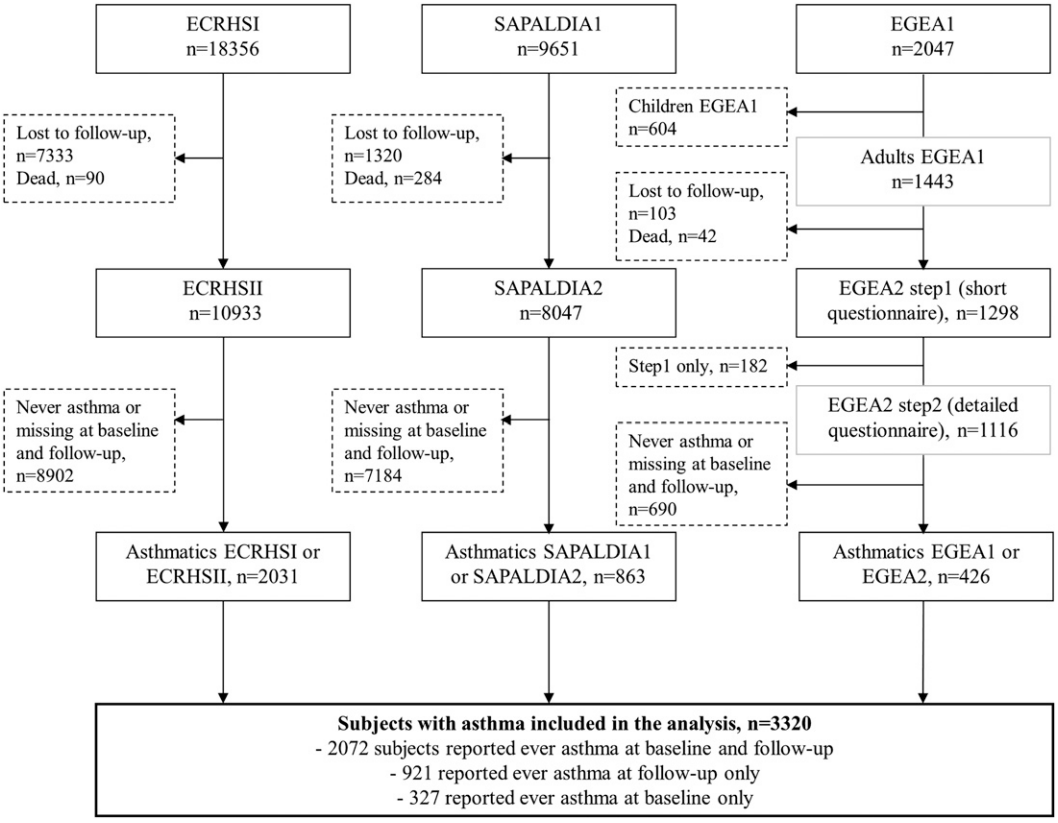

Figure 1. Flowchart of the population. ECRHS = European Community Respiratory Health Survey; EGEA = Epidemiological Study on Genetics and Environment of Asthma; SAPALDIA = Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults.

identified a low-prevalence phenotype (<5%); therefore, the seven-class model was retained. Strong similarities between asthma phenotypes identified at baseline and follow-up are evidenced by the "unconstrained" seven-class LTA analysis, in which specific asthma phenotype structures were freely estimated at each time point (Figure 2). Therefore, the "constrained" model in which asthma phenotypes are forced to be identical across time was retained as the main model to facilitate the interpretation of results. Phenotypes identified in the main model were largely characterized by the level of respiratory symptoms, the allergic status, and the pulmonary function (Figure 3 and Table 3):

- Phenotype A (prevalence: 21 and 19% at baseline and follow-up, respectively), labeled "allergic, few symptoms, no treatment," was predominantly composed of subjects with asthma with no or few respiratory symptoms (i.e., 1% had asthma attacks in the previous 12 mo) and with allergic sensitization.
- Phenotype B (prevalence: 17 and 16% at baseline and follow-up, respectively), labeled "nonallergic, few symptoms, no treatment" was also composed of subjects with asthma with no or few respiratory symptoms, but compared with phenotype A, subjects belonging to this group did not show allergic sensitization (4% were sensitized to aeroallergens).
- Phenotype C (prevalence: 8 and 12% at baseline and follow-up, respectively), labeled "nonallergic, high symptoms, treatment" was mainly composed of nonallergic subjects with high levels of respiratory symptoms.
- Phenotype D (prevalence: 18 and 14% at baseline and follow-up, respectively), labeled "allergic, high symptoms, treatment, BHR" showed similarities with phenotype C, but, compared with phenotype C, subjects belonging to this group were more frequently sensitized to aeroallergens.
- Subjects belonging to phenotypes E, F, and G (prevalence: between 9 and 16%) showed moderate levels of respiratory symptoms (between phenotypes A/B and C/D), but were distinguished by their allergic status, BHR status, and FEV_1 % predicted, and were therefore labeled "allergic, moderate symptoms, BHR," "allergic, moderate symptoms, normal lung function," and "nonallergic, moderate symptoms, no treatment," respectively.

Table 4 shows odds ratios corresponding to the association between covariates (sex, age, and age at asthma onset) and latent class membership. Compared with the phenotype B (nonallergic, few symptoms, no treatment; the group with the least at risk), men were more likely to belong to the allergic phenotypes (A, D, E, and F). Older subjects were more likely to belong to phenotypes C (nonallergic, high symptoms, treatment) and E (allergic, moderate symptoms, BHR) compared with phenotype B, and subjects with adult-onset asthma were more likely to belong to nonallergic phenotypes (C and G).

The sensitivity analysis restricted to population-based cohorts, ECRHS and SAPALDIA, showed similar patterns as those observed in the main analysis (Table E2). The LTA analyses conducted separately in men and women showed strong similarities in phenotype structures for the first four phenotypes (labeled A′′, B′′, C′′, and D′′ in these subpopulations) although nonallergic phenotypes (B′′ and C′′) were more prevalent in women than in men (Figure E2 and Table E3).

Phenotypic Transition over Time

The probabilities of membership in the same phenotype at each time point varied from 54 to 88% across phenotypes (Figure 3 and Table 3). For example, subjects belonging to phenotype G

TABLE 2. DESCRIPTION OF THE ASTHMA POPULATION IN ECRHS-SAPALDIA-EGEA

	Baseline				10-Year Follow-up			
	ECRHSI (*n* = 2,031)	SAPALDIA1 (*n* = 863)	EGEA1 (*n* = 426)	ESE1 (*n* = 3,320)	ECRHSII (*n* = 2,031)	SAPALDIA2 (*n* = 863)	EGEA2 (*n* = 426)	ESE2 (*n* = 3,320)
Age, %*	24.8	51.8	43.4	34.2	18.8	53.8	47.4	31.6
Sex, men, %	41.5	47.6	48.8	44.0	—	—	—	—
Age at asthma onset, >16 yr, %	54.2	57.8	51.1	54.7	—	—	—	—
Allergic sensitization, %†	63.0	59.2	70.8	63.1	65.4	59.1	71.1	64.4
Total IgE ⩾ 100 IU/ml, %	45.6	44.0	62.4	47.5	44.9	39.6	53.1	44.5
Woken by cough 12m, %	45.2	37.2	42.6	42.8	44.2	37.6	39.6	41.9
Chronic cough/phlegm, %	23.8	14.7	17.0	20.6	22.6	16.7	16.7	20.3
Asthma attack 12m, %	42.3	23.0	53.7	38.7	40.4	24.1	32.5	35.1
Asthma symptoms score 12m: 0, %	26.8	42.0	22.3	30.2	26.5	44.1	22.1	30.5
1 or 2, %	35.4	37.2	26.2	34.7	39.8	37.2	45.1	39.8
⩾3, %	37.8	20.8	51.5	35.1	33.6	18.6	32.8	29.6
FEV_1 < 80% predicted, %	10.9	10.8	18.7	12.0	12.6	14.1	19.7	14.0
Methacholine test, *n*	1,423	574	237	2,234	1,097	407	204	1,708
BHR (PD_{20} ⩽ 1 mg), %	49.6	31.2	48.5	44.8	45.9	24.1	45.1	40.6
Asthma treatment, %	35.0	16.1	73.7	33.7	43.5	25.9	53.5	39.7

Definition of abbreviations: BHR = bronchial hyperresponsiveness; ECRHS = European Community Respiratory Health Survey; EGEA = Epidemiological study on Genetics and Environment of Asthma; ESE = ECRHS-SAPALDIA-EGEA; PD_{20} = provocative dose causing 20% decrease in FEV_1; SAPALDIA = Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults.

* Older than 40 yr at baseline and >50 yr at follow-up.

† Skin-prick tests (11 allergens) in EGEA1 and EGEA2; specific IgE (four allergens) at ECRHSI and ECRHS II, positive Phadiatop test at SAPALDIA1 and SAPALDIA2.

(nonallergic, moderate symptoms, no treatment) at baseline had a 54% probability of being in the same phenotype at follow-up, whereas subjects belonging to phenotype E (allergic, moderate symptoms, BHR) at baseline had an 88% probability of being in that same phenotype at follow-up.

Many of the transitions between phenotypes occurred rarely, as shown by the transition probabilities matrix in which 65% of the probabilities had values lower than 5% (Figure 3 and Table 3). The transition probabilities between phenotypes varied from 0 to 38%. Although subjects belonging to nonallergic phenotypes (B, C, and G) do not show a stronger probability of changing phenotypes across time as compared with subjects belonging to the allergic phenotypes (A, D, E, and F), different pattern of transition across allergic phenotypes and across nonallergic phenotypes were observed. Among nonallergic phenotypes (B, C, and G), each probability of transitioning to any other nonallergic phenotype was greater than 8%. In contrast, among the allergic phenotypes (A, D, E, and F), only a few probabilities of transitioning were greater than 5%, indicating more specific transition patterns among the allergic phenotypes. Transitions toward increased asthma symptoms were more frequently observed in nonallergic phenotypes as compared with allergic phenotypes. In particular, among subjects with no or few respiratory symptoms at baseline, the chance of being in the asthma phenotypes characterized by high level of symptoms at follow-up was higher for the nonallergic phenotypes as compared with the allergic phenotypes (13 vs. <5%, respectively). Subjects belonging to the allergic phenotypes were generally more prone to move toward improvement than worsening as compared with the nonallergic phenotypes. All probabilities of transitioning from an allergic to a nonallergic phenotype, and *vice versa*, were below 2%.

Phenotypes A′′, B′′, C′′, and D′′ observed in men and women showed similar phenotypic structure as compared with phenotypes A, B, C, and D observed in the whole population. For these phenotypes, the probability of remaining in the same phenotype did not vary between sexes (Table E3).

Predictive Ability of the Clusters

The risk of subsequent asthma exacerbation significantly differed between the LTA-derived asthma phenotypes, phenotypes C and D showing the greater risks, phenotypes E, F, and G showing intermediate risks between phenotypes C/D and A/B (low risk; Table 5).

DISCUSSION

On a large sample of well characterized European adults with asthma (*n* = 3 320), a longitudinal cluster–based analysis (LTA) led to the identification of seven similar phenotypes over time (prevalence range, 8.4–20.8%), mainly characterized by level of respiratory symptoms, allergic status, and pulmonary function. These phenotypes defined at baseline were related to the subsequent risk for asthma exacerbation assessed at follow-up, which supports the predictive ability of the classification. The probability of remaining in the same phenotype at 10-year follow-up varied from 54 to 88% across phenotypes, indicating that some asthma phenotypes are more stable over time than others. Transition toward increased asthma symptoms were more frequently observed in nonallergic phenotypes as compared with allergic phenotypes.

One of the main strengths of our study relates to the populations under study. The study is based on a large sample of well characterized adults with asthma, examined in the context of three 10-year follow-up studies—ECRHS, SAPALDIA, and EGEA. The studies used standardized protocols and questionnaires. A further strength is in regard to the novelty of our approach to unraveling the asthma heterogeneity at the population level, resting on a longitudinal clustering approach, allowing us to simultaneously account for several domains of the disease repeatedly measured over time. We recognize that such an approach applied to a longitudinal dataset is exploratory and hypothesis generating. However, the phenotypes that we observed are clinically relevant. The different study designs, with two population-based studies and a case–control and family-based survey, may be seen as a limitation of the study. However, similar results were observed in the sensitivity analysis restricted to the population-based sample, suggesting that the study design does not strongly affect our findings. As a result of the study designs, the population includes both persistent and remittent asthma, and the prevalence of severe asthma in this population is low. By addressing the evolution of asthma at the population level, including subjects reporting "asthma ever,"

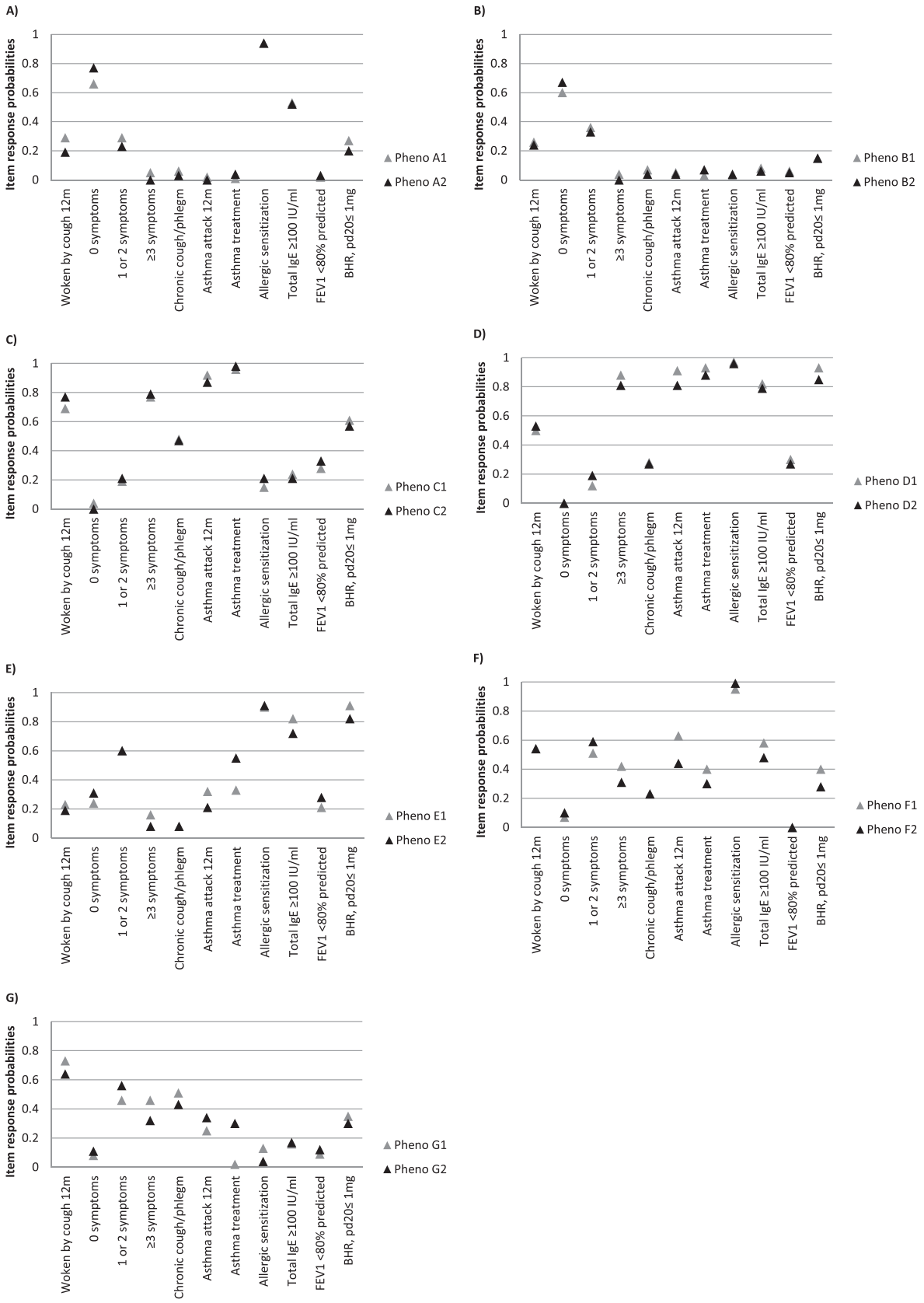

Figure 2. Profile figures show the item–response probabilities (identifying the main phenotypes' characteristics) estimated at each time point by the "unconstrained" seven-class latent transition analysis (LTA) model.

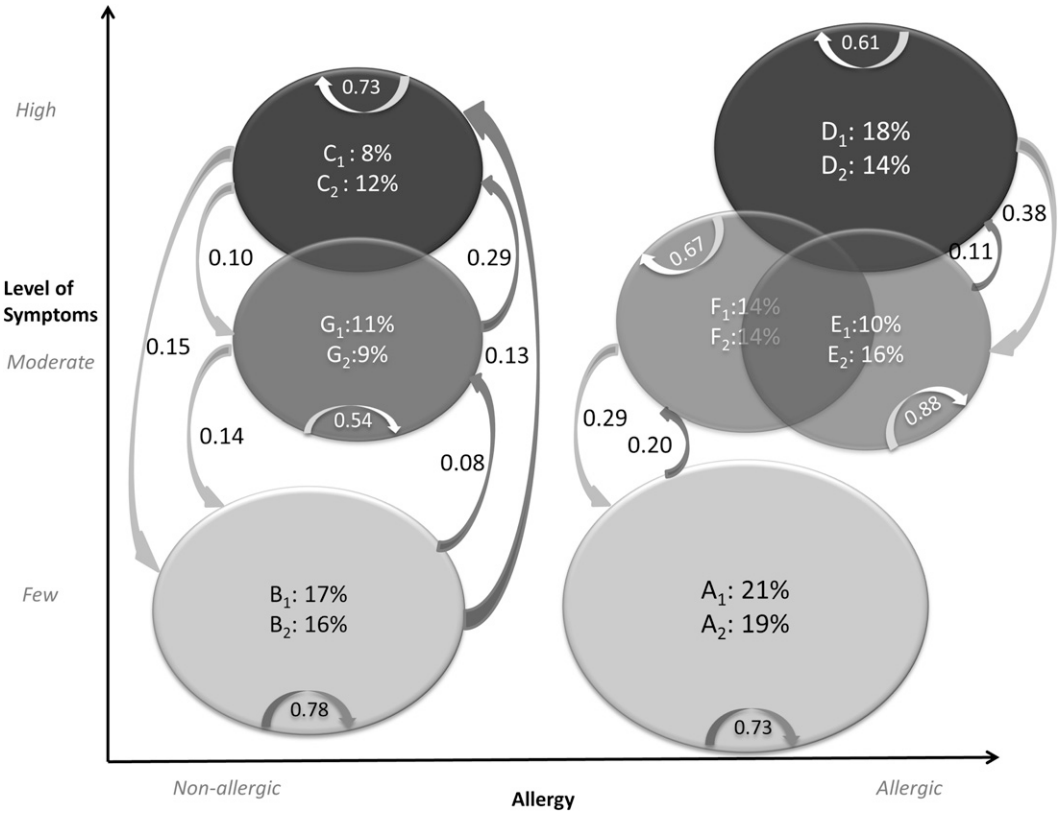

Figure 3. Schematic representation of the asthma phenotypes identified using the seven-class latent transition analysis (LTA) model. The phenotypes are plotted according to the characteristics playing a major role in the classification. Transition probabilities greater than 5% are represented by *arrows*. Change over time indicating remission or improvement of the asthma symptoms are indicated by *downward arrows* (i.e., subjects belonging to phenotype D have a 38% chance of being in phenotype E 10 yr later). Change over time indicating asthma incidence, worsening, or relapse are shown by *upward arrows* (i.e., subjects belonging to phenotype A have a 20% chance of being in phenotype F 10 yr later).

and not only current asthma, as in clinical settings, our study may provide complementary insights into the understanding of persistent versus remittent asthma. Our study, based on two observations in a 10-year period, is an important contribution to the understanding of the long-term variability, but does not account for the short-term variability of the disease. Other studies looking to the short-term variability and its integration with long-term patterns are needed. The identified asthma phenotypes can only account for the disease features represented by the variables included in the model, and therefore do not include, for example, the inflammatory components of the disease, as such information was not available in the three studies. We did not include environmental and genetic factors in the models, as our aim was to define asthma phenotypes on the basis of the clinical characteristics. Detailed information on asthma treatment was not available at baseline; therefore, we cannot provide information on the evolution of the treatment requirements. The selection of the number of classes is not straightforward in such models. LTA models with six to eight classes led to comparable BICs, and we retained the seven-class model where the prevalence of all classes was over 5%.

Our study is the first to compare asthma phenotypes obtained in an unsupervised manner by means of LTA in the same population over a long period of time. The asthma phenotypes obtained at both time points were qualitatively very similar. By showing the consistency of such cluster-derived phenotypes over time, our study provides additional evidence to support the validity of these phenotypes. Two previous studies, applying similar clustering methods on two different adult populations, were able to show strong similarities between the derived phenotypes across European and Korean populations (11, 15). Between-study comparability of the asthma phenotypes showed similarities in the phenotypes, although populations, methods, and disease features considered differed between studies (5). Recently, Patrawalla and colleagues (26) applied a simple algorithm to cluster asthma as defined in the Severe Asthma Research Program population (considering baseline FEV_1, maximal post-bronchodilator FEV_1, and age at asthma onset) in an urban population, and revealed five groups phenotypically similar to those identified in Severe Asthma Research Program subjects. Further evidence of validity of cluster-derived asthma phenotypes is provided by the assessment of the discriminative properties and effect of clinical prognosis of these phenotypes (8, 9, 11, 13, 14). Further studies on long-term follow-up cohorts are needed to replicate our findings.

The longitudinal LTA approach revealed seven phenotypes, four of which were highly comparable to the four LCA-derived asthma phenotypes previously reported in ECRHS and EGEA (11). We previously showed that these phenotypes clearly discriminated populations in terms of quality of life and blood eosinophil and neutrophil counts, better than classical phenotypes (11). The three novel phenotypes, mainly characterized by subjects with a moderate level of symptoms, differed with regard to the allergic status, BHR, and their evolution over time. As compared with LCA, LTA allows accounting for additional information from other points in time, and therefore leads to a refinement of asthma phenotypes by the identification of additional clusters. Further analyses are needed to address the relevance of such phenotypes in epidemiology and in asthma management.

Our findings show strong stability of the asthma phenotypes with regard to allergic status over time, indicating small changes in allergy in this adult population over a 10-year period. Prospective studies on the long-term evolution of allergy among adults are rare. Some adult population–based studies consistently found a low prevalence and a high remission of allergic sensitization at a 10-year (27) and a 25-year follow-up (28), whereas only a small change in specific IgE levels were observed over 10 years in ECRHS (29). Such data from cohorts of subjects with asthma is missing from the literature.

This study is the first to model the probabilities of transitioning over time between comprehensive asthma phenotypes defined by a clustering approach. Our findings clearly indicate different

TABLE 3. PARAMETER ESTIMATES BY THE "CONSTRAINED" SEVEN-CLASS LATENT TRANSITION ANALYSIS MODEL IN ECRHS-SAPALDIA-EGEA (N = 3,320)

	Phenotype A: "Allergic, Few Symptoms, No Treatment"	Phenotype B: "Nonallergic, Few Symptoms, No Treatment"	Phenotype C: "Nonallergic, High Symptoms, Treatment"	Phenotype D: "Allergic, High Symptoms, Treatment, BHR"	Phenotype E: "Allergic, Moderate Symptoms, BHR"	Phenotype F: "Allergic, Moderate Symptoms, Normal Lung Function"	Phenotype G: "Nonallergic, Moderate Symptoms, No Treatment"
Asthma phenotype prevalences (latent class membership probabilities)							
Baseline	0.21	0.17	0.08	0.18	0.10	0.14	0.11
Follow-up	0.19	0.16	0.12	0.14	0.16	0.14	0.09
Item–response probabilities							
Woken by cough 12 mo	0.25	0.25	0.71	0.53	0.21	0.54	0.72
Asthma symptom score: 0	0.71	0.61	0.05	0.00	0.27	0.07	0.08
1 or 2	0.27	0.36	0.29	0.14	0.60	0.55	0.49
⩾3	0.02	0.02	0.66	0.86	0.13	0.38	0.42
Chronic cough/phlegm	0.05	0.07	0.48	0.28	0.09	0.23	0.47
Asthma attack 12 mo	0.01	0.05	0.79	0.88	0.26	0.54	0.26
Asthma treatment	0.03	0.06	0.95	0.91	0.48	0.34	0.00
Allergic sensitization	0.95	0.04	0.13	0.95	0.91	0.97	0.12
Total IgE ⩾100 IU/ml	0.53	0.07	0.19	0.80	0.76	0.55	0.18
FEV_1 <80% predicted	0.02	0.06	0.26	0.29	0.25	0.00	0.09
BHR, PD_{20} ⩽1mg	0.25	0.15	0.52	0.90	0.84	0.35	0.32
Transition from baseline (rows) to follow-up (columns)							
Phenotype A	**0.73**	0.00	0.01	0.04	0.00	*0.20*	0.01
Phenotype B	0.00	**0.78**	*0.13*	0.00	0.00	0.01	*0.08*
Phenotype C	0.00	*0.15*	**0.73**	0.00	0.02	0.00	*0.10*
Phenotype D	0.00	0.00	0.00	**0.61**	*0.38*	0.01	0.00
Phenotype E	0.00	0.00	0.00	*0.11*	**0.88**	0.00	0.00
Phenotype F	*0.29*	0.00	0.00	0.03	0.00	**0.67**	0.00
Phenotype G	0.01	*0.14*	*0.29*	0.01	0.00	0.01	**0.54**

Definition of abbreviations: BHR = bronchial hyperresponsiveness; PD_{20} = provocative dose causing 20% decrease in FEV_1; ECRHS = European Community Respiratory Health Survey; EGEA = Epidemiological study on Genetics and Environment of Asthma; SAPALDIA = Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults.

Bold indicates the entries along the diagonal of the probability matrix and displays for each phenotype the estimated probabilities of membership in the same phenotype at each time point. Italics indicate a probability of ⩾5% of transitioning to a different phenotype over time.

patterns of transition over time across phenotypes, with some phenotypes showing higher stability than others and with transitions between phenotypes varying from implausible to very likely. Transitions toward increased asthma symptoms were more frequently observed in nonallergic phenotypes as compared with allergic phenotypes, indicating that allergic status may have an effect in the course of asthma activity in adulthood. Few studies have focused on the role of allergy in the natural history of asthma in adults. A recent Canadian study using health administrative databases did not suggest an effect of allergy in the course of asthma activity (30). Our results on the longitudinal analysis of phenotypic characteristics support the evidence derived from genetic investigations (31), that studies should be conducted to better understand the relationships of allergic characteristics with asthma expression.

Using this data-driven approach, strong similarities in phenotypic characteristics and evolution were observed between asthma phenotypes identified in men and women. Nevertheless, consistent with previous findings showing that women are at greater risk for nonallergic asthma (32), the prevalence of nonallergic asthma phenotypes was higher in women than in men.

From a methodological point of view, such a longitudinal approach may allow us to limit problems encountered in using incidence to analyze risk factors in follow-up studies (33). Indeed, as opposed to the analysis of incidence that assumes that asthma is a true dichotomous disease, which is unlikely to be true, LTA provides a novel modeling approach for longitudinal studies that does not make such an assumption. We therefore suggest that such modeling may help to discover the causes of asthma.

Although we emphasize the combined role of clinical characteristics routinely collected in the disease evaluation and provide novel insights into the natural history of asthma, it is too early to say to what extent this methodology will result in preventive and therapeutically relevant findings. However, our results provide

TABLE 4. ODDS RATIOS* FOR SEX, AGE, AND AGE AT ASTHMA ONSET ASSOCIATED WITH ASTHMA PHENOTYPES AT BASELINE

	Phenotype A: "Allergic, Few Symptoms, No Treatment"	Phenotype B: "Nonallergic, Few Symptoms, No Treatment"	Phenotype C: "Nonallergic, High Symptoms, Treatment"	Phenotype D: "Allergic, High Symptoms, Treatment, BHR"	Phenotype E: "Allergic, Moderate Symptoms, BHR"	Phenotype F: "Allergic, Moderate Symptoms, Normal Lung Function"	Phenotype G: "Nonallergic, Moderate Symptoms, No Treatment"	*P* Value
Sex (women vs. men)	0.44	1	1.18	0.60	0.22	0.51	1.15	<0.0001
Age (older vs. younger)	0.75	1	1.76	0.63	2.66	0.38	0.72	<0.0001
Age at asthma onset (adult vs. childhood onset asthma)	0.75	1	2.52	0.47	1.04	0.83	2.56	<0.0001

Definition of abbreviation: BHR = bronchial hyperresponsiveness.

*Example: Women are less likely (OR = 0.44) to belong to phenotype A as compared to phenotype B.

TABLE 5. ASSOCIATION BETWEEN ASTHMA PHENOTYPES IDENTIFIED AT BASELINE AND EXACERBATION REPORTED AT FOLLOW-UP IN ECRHS AND EGEA (N = 2,457)

	Asthma Phenotypes Identified at Baseline*						
	Phenotype A: "Allergic, Few Symptoms, No Treatment"	Phenotype B: "Nonallergic, Few Symptoms, No Treatment"	Phenotype C: "Nonallergic, High Symptoms, Treatment"	Phenotype D: "Allergic, High Symptoms, Treatment, BHR"	Phenotype E: "Allergic, Moderate Symptoms, BHR"	Phenotype F: "Allergic, Moderate Symptoms, Normal Lung Function"	Phenotype G: "Nonallergic, Moderate Symptoms, No Treatment"
Exacerbation reported at follow-up							
% (*n*)†	4.9 (20)	5.0 (16)	20.0 (40)	17.5 (85)	9.5 (21)	9.2 (28)	14.0 (37)
OR (95% CI)	0.98 (0.5–1.93)	1 (—)	4.75 (2.58–8.74)	4.02 (2.31–7.01)	2.04 (1.02–3.93)	1.93 (1.02–3.65)	3.10 (1.68–5.7)

Definition of abbreviations: BHR = bronchial hyperresponsiveness; CI = confidence interval; ECRHS = European Community Respiratory Health Survey; EGEA = Epidemiological study on Genetics and Environment of Asthma; OR = odds ratio.

*We assigned individuals to the latent classes that they had the highest probability of belonging to (based on the posterior probability provided by the model at baseline).

† Overall Chi-square test <0.0001.

the opportunity to investigate both the determinants and the outcomes of these phenotypes, which may eventually provide relevant, applicable findings.

In summary, this study adds new evidence to support the interest in cluster-derived asthma phenotypes for a better understanding of this complex disease and for asthma management. Although further studies with longer follow-up are warranted, clustering techniques applied to longitudinal data, allowing variability over time to be taken into account, may identify more accurate asthma phenotypes. This could facilitate the identification of risk factors, and may lead to the identification of specific phenotypes more prone to worsen over time.

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