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Unsupervised trajectories of respiratory/allergic symptoms throughout childhood in the PARIS cohort

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Abstract

Background: Natural course and co-occurrence of asthma, eczema, and allergic rhinitis through childhood are still not fully documented. We aim to identify and characterize profiles based on the time course, severity, and apparent triggers of respiratory/allergy symptoms in school-aged children.

Methods: Data on occurrence, severity, and triggers of asthma, rhinitis, and dermatitis symptoms were collected annually during the follow-up of the PARIS birth cohort. Children with similar symptom trajectories until 8-9 years were grouped into profiles using multidimensional (all symptoms considered simultaneously) cluster analysis. Associations between profiles and different health outcomes were analyzed using logistic or linear regression models.

Results: Six distinct symptomatic profiles were identified. A profile was defined by persistent dermatitis symptoms, associated with sensitization to food and aeroallergens. Two profiles were characterized by wheezing: one with early transient wheezing and the other with persistent wheezing related to doctor-diagnosed asthma, airway obstruction, and perennial aeroallergen sensitization. Three profiles were characterized by rhinitis symptoms: one non-allergic and two allergic, either with persistent rhinitis symptoms related to allergic multimorbidity and sensitization to perennial aeroallergens, or with late-onset symptoms, related to both pollen and perennial aeroallergens sensitization as well as low lung function.

Conclusion: This study brings further insights into the developmental profiles of respiratory/allergic outcomes from birth to school age. The identified profiles clearly

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differed regarding objective features such as diagnosed morbidity, sensitization, or lung function measurements, thus highlighting their biologic and clinical relevance. Allergic rhinitis profiles deserve particular attention, since they were likely to be involved in multimorbidity patterns.

KEYWORDS
allergy, birth cohort, cluster analysis, school-aged children, symptom trajectory

1 | INTRODUCTION

Respiratory and allergic diseases have become more common in childhood and may coexist in many children (multimorbidity) more often than expected by chance.[1] Natural history of these disorders has been documented by an increasing number of studies using phenotyping approaches to define groups of individuals that are homogenous in their clinical and biologic patterns. Recently, data-driven techniques dealing with longitudinal data were used to identify profiles based on trajectories of symptoms in an objective manner,[2] which might better reflect underlying biologic entities.[3]

However, few studies have investigated the co-occurrence of asthma, eczema, and allergic rhinitis over time using unsupervised approaches. In the PARIS (Pollution and Asthma Risk: an Infant Study) birth cohort, a previous work reported four profiles in preschoolers using K-means clustering: two transient profiles ("transient rhinitis" and "transient wheeze") potentially linked to irritation and infections, and two persistent profiles ("dermatitis" and "cough/rhinitis") associated with IgE sensitization at 18 months.[4] In two population-based British birth cohorts (ALSPAC and MAAS), Belgrave et al[5] used Bayesian learning machine methods and reported heterogeneous developmental profiles of eczema, wheeze, and rhinitis from birth to 11 years of age. Eight latent classes were identified, including four with multimorbidity that were the most associated with sensitization. Panico et al[6] identified four latent trajectories using longitudinal latent class analysis based on allergy symptoms at 3, 5, and 7 years of age, including one with co-existence of wheeze, eczema, and hay fever.

In this context, we aimed to identify profiles based upon time course, severity, and trigger of respiratory/allergy symptoms in school-aged children from the PARIS birth cohort and to evaluate their relevance by studying associations with doctor-diagnosed diseases, sensitization, lung function, and fractional exhaled nitric oxide (FeNO).

Key Message

Using an unsupervised and multidimensional technique, six distinct phenotypes of respiratory/allergic symptoms trajectories were identified based on the time course, severity and apparent triggers of respiratory/allergy symptoms in school-aged children from the PARIS birth cohort. These phenotypes clearly differed regarding objective features such as morbidity, sensitization and lung function measurements, thus highlighting their biological and clinical relevance. Special attention should be given to children with allergic rhinitis, as they were likely to be involved in multimorbidity patterns.

2 | METHODS

2.1 | Study design

The present study is part of the ongoing follow-up of the population-based PARIS birth cohort. Between February 2003 and June 2006, 3,840 healthy term singletons were enrolled from five public Paris maternity hospitals. Eligibility criteria have been previously described.[7] Children were followed up by repeated self-administered questionnaires and two medical examinations took place at 18 months and 8-9 years of age, in two tertiary referral hospitals in Paris. The French Ethics Committees approved the PARIS study, and written informed consent was obtained from all parents.

2.2 | Respiratory/allergic outcomes

Data on doctor-diagnosed diseases, medication, and respiratory/allergic outcomes (occurrence and severity), including wheezing (wheezing or whistling in the chest), dry night cough, rhinitis symptoms (sneezing or runny/blocked nose apart from a cold), and dermatitis symptoms (itchy rash coming and going), were yearly collected by standardized self-administered questionnaires derived from ISAAC (International Study of Asthma and Allergies in Childhood).[8] Asthma-related hospitalizations or emergency department visits were reported at 18 months and at 8-9 years. Current allergic diseases at 8-9 years were defined according to the MeDALL (Mechanisms of the Development of Allergy) consortium (see Supporting Information).[9] Briefly, current asthma was defined as the presence of any two of the following three items: doctor-diagnosed asthma, asthma medication in the last 12 months, and wheezing in the last 12 months. Current atopic eczema was defined as itchy rash in the last 12 months affecting specific places with sensitization at

8-9 years. Current allergic rhinitis was defined as rhinitis symptoms with itchy/watery eyes in the last 12 months and sensitization at 8-9 years.

2.3 | Sensitization

Skin prick tests to nine aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinea*, cat, dog, *Blatella germanica*, *Alternaria alternata*, birch, grass, and mugwort) were performed at 8-9 years of age. A wheal of ≥3 mm was considered as a positive response. Blood tests were performed at both 18 months and 8-9 years of age. Total IgE levels were measured by ImmunoCAP® Total IgE (Phadia, Uppsala, Sweden). At 8-9 years, twelve food allergens (egg white, cow's milk, peanut, mustard, fish, wheat, soy, hazelnut, sesame, shrimp, beef, and kiwi) and seven aeroallergens (*Dermatophagoides pteronyssinus*, cat, dog, *Blatella germanica*, *Alternaria alternata*, timothy-grass, and birch) were tested using ImmunoCAP® Phadiatop® and Trophatop® fx26, fx27, and fx28 (Phadia). IgE sensitization was determined by at least one allergen-specific IgE ≥0.35 kUA/L, and IgE polysensitization by at least two allergen-specific IgE ≥0.35 kUA/L.

2.4 | Lung function

Lung function tests were carried out at 8-9 years, as previously described.[10] Spirometry was performed at baseline and 20 minutes after the administration of 200 μg of salbutamol. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25%-75% of the FVC ($FEF_{25\%-75\%}$) were recorded. Before spirometry, FeNO was measured and expressed in parts per billion using NIOX MINO® (Circassia, Uppsala, Sweden). Predicted values of lung function were obtained from the Global Lung Function Initiative equations based on sex, age, height, and ethnicity.[11]

2.5 | Statistical methods

KmL3D, a version of K-means adapted to the analysis of joint trajectories,[12] was used to identify profiles according to the course of wheezing, severe wheezing (sleep disturbance, disturbance of daily activities, frequent attacks [≥4/y], or shortness of breath), dry night cough, rhinitis symptoms, rhinitis symptoms with itchy/watery eyes, rhinitis symptoms apparently triggered by dust mites, pets, or

TABLE 1 Baseline characteristics of the PARIS birth cohort children included in the cluster analysis and children not included in the cluster analysis but still followed up at 8-9 y of age

	Children included in the cluster analysis	Children not included in the cluster analysis			
		All		Still followed up at 8-9 y	
	n = 1820	n = 2020	*P*-value	n = 633	*P*-value
Boys [n (%)]	939 (51.6)	1031 (51.0)	0.732‡	321 (50.7)	0.702‡
Family socioeconomic status					
Low [n (%)]	109 (6.1)	250 (12.4)	<0.001‡	72 (11.5)	<0.001‡
Medium [n (%)]	474 (26.1)	589 (29.3)		198 (31.4)	
High [n (%)]	1,230 (67.8)	1,172 (58.3)		360 (57.1)	
Caucasian [n (%)]	1,483 (81.8)	1,527 (76.1)	<0.001‡	450 (71.8)	<0.001‡
Parental history of allergy [n (%)]	972 (53.6)	1,056 (52.4)	0.488‡	331 (52.5)	0.634‡
Parental history of asthma [n (%)]	348 (19.2)	416 (20.7)	0.239‡	131 (20.8)	0.377‡
Parental history of eczema [n (%)]	344 (19.0)	357 (17.8)	0.337‡	125 (19.9)	0.642‡
Parental history of hay fever [n (%)]	671 (37.0)	700 (34.8)	0.160‡	217 (34.4)	0.256‡
Older sibling(s)					
None [n (%)]	999 (54.9)	1,180 (58.4)	0.027‡	326 (51.5)	0.074‡
One [n (%)]	618 (34.0)	658 (32.6)		246 (38.9)	
Two or more [n (%)]	203 (11.2)	181 (9.0)		61 (9.6)	
Birthweight, kg (mean ± SD)	3.41 ± 0.39	3.39 ± 0.40	0.188†	3.41 ± 0.39	0.824†
Breastfeeding at birth [n (%)]	1,328 (73.3)	1,345 (71.2)	0.172‡	429 (72.5)	0.709‡
Maternal smoking during pregnancy [n (%)]	167 (9.2)	267 (13.2)	<0.001‡	76 (12.0)	0.040‡
Smokers at home at birth [n (%)]	357 (19.7)	456 (28.6)	0.004‡	134 (21.6)	0.300‡

SD, standard deviation.
†Student's *t* test.
‡Chi-squared test.

pollen according to parents, and dermatitis symptoms by considering 7 time periods (at age 1, 2, 3, 4, 5, 6, and 8-9 years). Children were partitioned into different clusters so that the Euclidean distance between children and the mean trajectory of their respective clusters was minimized. To choose the optimal number of clusters, the model was repeatedly fitted with 2-8 clusters. The optimal classification was determined using Bayesian information criterion (BIC) and considering the clinical relevance of clusters. The analysis was performed on children with data available for more than half of the time periods (≥4) for each symptom (n = 1820). Missing values were imputed by linear interpolation. Sensitivity analyses were conducted in the subgroups of children with complete data for all symptoms and with data available at ≥6 and ≥5 time periods.

Associations of profiles with ever doctor-diagnosed diseases at 8-9 years, current allergic diseases at 8-9 years, medication, and sensitization were studied using multinomial logistic regression. Associations of lung function and FeNO with profiles were tested using linear regression. Results were expressed as odds ratios (OR) or β coefficients with their 95% confidence intervals (95% CI).

Cluster analyses were conducted with R software (R Foundation for Statistical Computing, Vienna, Austria). Regression analyses were performed using Stata/SE 11.2 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Participants

Among the 2453 children still followed up at 8-9 years, 1820 children (74.2%) were included in the cluster analysis (Figure S1). Participants had a higher familial socioeconomic status (SES) and were more likely to be exposed to maternal smoking during pregnancy, compared to non-participants (Table 1). Prevalence and trajectories of symptoms among the participants are shown in Table S1 and Figure 1.

3.2 | Identification of respiratory/allergic profiles

Although the 8-cluster model had a slightly better BIC than the 7-cluster model (Table S2), the latter was selected regarding its clinical relevance. Indeed, the 8-cluster classification included two redundant groups with early transient wheezing (Figure S2). Thus, seven profiles were identified (Figure 2):

- The reference group [54.2% of children, 95% CI 51.9% to 56.5%] had low prevalence of symptoms throughout the study period.
- Children from the early transient wheeze (ETW) group [10.4%, 95% CI 9.0% to 11.8%] had severe wheezing during the first year of life, after which the great majority rapidly recovered.
- The persistent wheeze (PW) group [4.7%, 95% CI 3.7% to 5.6%] showed high prevalence of wheezing throughout childhood (most often severe) which gradually decreased between ages 3 and 8-9.
- Children from the persistent dermatitis symptoms (PD) group [7.6%, 95% CI 6.4% to 8.9%] had dermatitis symptoms with low probability of respiratory symptoms.
- Children from the cough/non-allergic rhinitis symptoms (CNAR) group [12.1%, 95% CI 10.6% to 13.6%] experienced both dry night cough and rhinitis symptoms not triggered by aeroallergens.
- The persistent allergic rhinitis symptoms (PAR) group [3.5%, 95% CI 2.6% to 4.3%] showed high prevalence of rhinitis symptoms (frequently triggered by allergens, with itchy/watery eyes and/or with dry night cough) with a peak at age 5. At each time point, about 40% of the children had dermatitis symptoms.
- All the children from the late-onset allergic rhinitis symptoms (LOAR) group [7.5%, 95% CI 6.3% to 8.7%] had rhinitis symptoms at 8-9 years, most often with itchy/watery eyes and/or apparently triggered by pollen.

The sensitivity analyses performed in children without any missing data (Figure S3) and with data available at ≥6 time periods and ≥5 time periods showed similar profiles.

3.3 | Profiles and diagnosed/current allergic diseases

In the CNAR and ETW groups, as well as in the reference group, about three-quarters of children did not have doctor-diagnosed allergic diseases (Figure S4). In the PD group, 77.6% of children had doctor-diagnosed eczema, whereas PW had the highest probability of current asthma at 8-9 years (49.2%) and doctor-diagnosed asthma

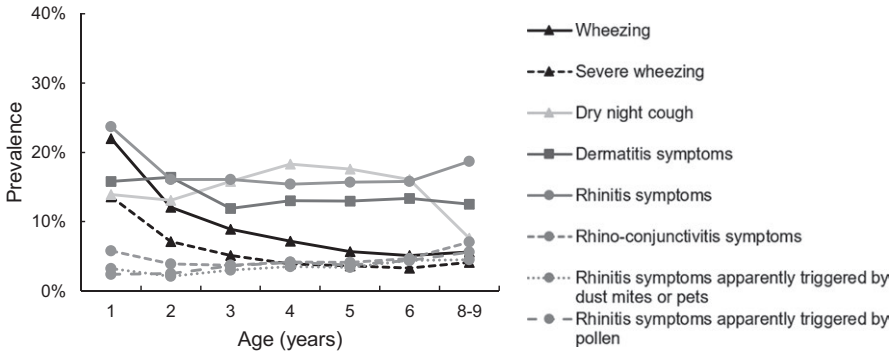

FIGURE 1 Symptom trajectories over the first 8-9 y of life in all the children from the PARIS birth cohort included in the cluster analysis

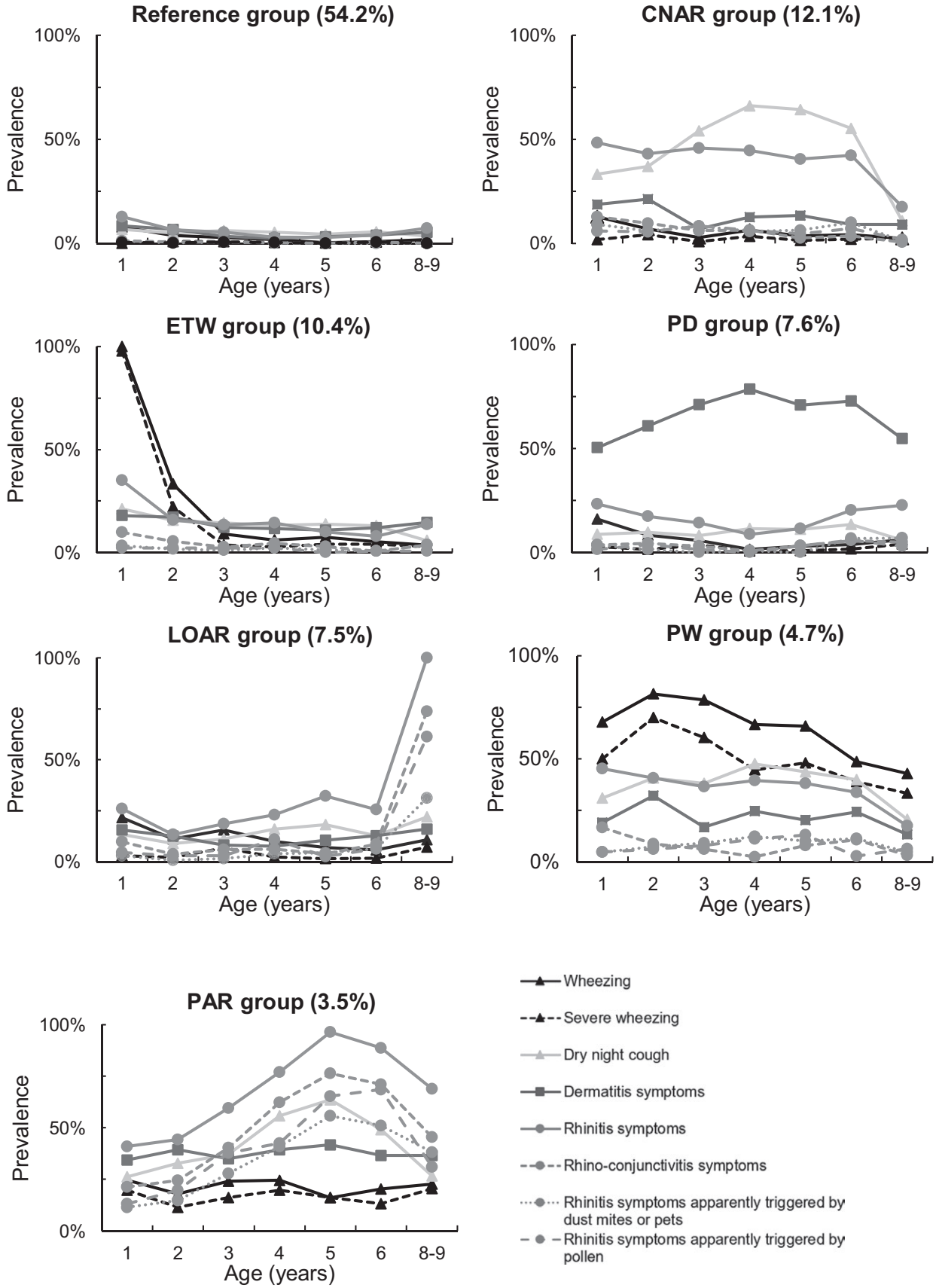

FIGURE 2 Symptom trajectories over the first 8-9 y of life for each respiratory/allergic profile identified in the cluster analysis in the PARIS birth cohort children. CNAR, cough/non-allergic rhinitis symptoms; ETW, early transient wheeze; PD, persistent dermatitis symptoms; LOAR, late-onset allergic rhinitis symptoms; PW, persistent wheeze; PAR, persistent allergic rhinitis symptoms

TABLE 2 Associations of respiratory/allergic profiles identified in the cluster analysis with IgE sensitization, in the PARIS birth cohort children

	IgE sensitization at 18 mo		IgE polysensitization at 18 mo		IgE sensitization at 8-9 y		IgE polysensitization at 8-9 y		IgE sensitization at 8-9 y					
									To any perennial aeroallergen		To any pollen aeroallergen		To any food allergen	
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Reference	8.1	1 (reference)	3.0	1 (reference)	25.6	1 (reference)	14.0	1 (reference)	17.9	1 (reference)	11.6	1 (reference)	10.6	1 (reference)
CNAR	14.0	1.8 (1.1-3.2)	5.2	1.8 (0.7-4.2)	27.5	1.1 (0.7-1.8)	13.7	1.0 (0.5-1.8)	16.7	0.9 (0.5-1.6)	15.7	1.4 (0.8-2.6)	15.7	1.6 (0.9-2.9)
ETW	9.1	1.1 (0.7-2.3)	4.6	1.5 (0.6-4.2)	29.9	1.2 (0.8-2.0)	14.9	1.1 (0.6-2.1)	21.6	1.3 (0.7-2.2)	10.2	0.9 (0.4-1.8)	10.3	1.0 (0.5-2.1)
PD	20.0	2.8 (1.6-5.1)	10.0	3.6 (1.6-8.2)	50.0	2.9 (1.8-4.8)	30.6	2.7 (1.5-4.7)	31.5	2.1 (1.2-3.6)	26.0	2.7 (1.5-4.9)	29.2	3.5 (1.9-6.2)
LOAR	21.3	3.1 (1.7-5.4)	11.7	4.3 (2.0-9.3)	64.7	5.3 (3.1-9.1)	51.5	6.5 (3.8-11.2)	49.3	4.4 (2.6-7.5)	42.0	5.6 (3.2-9.6)	32.4	4.0 (2.3-7.2)
PW	18.5	2.6 (1.3-5.1)	10.8	3.9 (1.6-9.6)	53.1	3.3 (1.8-6.0)	24.5	2.0 (0.9-4.0)	44.9	3.7 (2.0-6.8)	20.4	2.0 (0.9-4.1)	16.3	1.6 (0.7-3.7)
PAR	24.4	3.7 (1.8-7.7)	11.1	4.1 (1.4-11.4)	65.5	5.5 (2.5-12.2)	41.4	4.3 (2.0-9.5)	56.7	6.0 (2.8-12.8)	30.0	3.3 (1.4-7.5)	20.7	2.2 (0.9-5.7)
Total	11.9	-			33.8	-	19.6	-	24.3	-	16.4	-	14.9	-

CI, confidence interval; CNAR, cough/non-allergic rhinitis symptoms group; ETW, early transient wheeze group; LOAR, late-onset allergic rhinitis symptoms group; OR, odds ratio; PAR, persistent allergic rhinitis symptoms group; PD, persistent dermatitis symptoms group; PW, persistent wheeze group.

(57.7%). More than half of the children from the LOAR group (56.3%) had current allergic rhinitis at 8-9 years, and about one fifth (19.7%) had current asthma at 8-9 years. LOAR was mainly associated with doctor-diagnosed hay fever (OR 49.5, 95% CI 17.8 to 137.8; Table S3). PAR had intermediate-to-high probabilities of doctor-diagnosed eczema (50.0%), asthma (38.3%), and hay fever (29.4%). Furthermore, 27.0% had at least two current allergic diseases at 8-9 years. Associations of profiles with medication and asthma-related hospitalizations or emergency department visits are presented in the supplemental material.

3.4 | Profiles and sensitization

Compared to the reference group, all profiles, except ETW, were associated with IgE sensitization at 18 months (Table 2). At 8-9 years of age, CNAR and ETW were not significantly associated with IgE sensitization. PW and PAR were mainly associated with IgE sensitization to perennial aeroallergens. LOAR was strongly associated with IgE sensitization to pollen, to perennial aeroallergens, and to food allergens. PD was also significantly associated with food and aeroallergens, even if associations were a bit weaker. PAR and LOAR were the most likely groups to have IgE polysensitization at 8-9 years. Similar associations were reported for positive skin prick test responses (Table S4).

3.5 | Profiles, lung function, and FeNO

Compared to the reference group, PW was significantly associated with lower FEV_1, lower $FEF_{25\%-75\%}$, lower FEV_1/FVC ratio, and higher FEV_1 increase after bronchodilator (Table 3). ETW and LOAR were also associated with lower FEV_1 and lower $FEF_{25\%-75\%}$, but not with lower FEV_1/FVC ratio. The mean FeNO in children from the PAR group was twice as great as in children from the reference group. The mean FeNO was also significantly higher in children from LOAR and PW groups. Similar results were reported representing FEV_1 and FVC as percent predicted values (Table S5).

4 | DISCUSSION

Applying an unsupervised approach, we identified six symptomatic clusters of children with comparable temporal patterns (eg, early- or late-onset, transient, or persistent) and symptom picture (severity and triggers). These profiles clearly differed regarding morbidity, sensitization, and lung function measurements (as summarized in Figure 3), suggesting the existence of different disease entities. Two profiles were characterized by wheezing: one with early transient wheeze and the other one with early persistent wheeze, related to asthma and sensitization to perennial aeroallergens. Another profile was defined by persistent dermatitis symptoms and was associated with sensitization. Concerning rhinitis, we provide further insights since classifications have been historically built a priori without considering symptom trajectories throughout childhood.[13] We distinguished a non-allergic cluster, CNAR, probably triggered by

TABLE 3 Associations of respiratory/allergic profiles identified in the cluster analysis with lung function and FeNO at 8-9 y of age, in the PARIS birth cohort children

	FEV_1 (mL)		FVC (mL)		$FEF_{25\%-75\%}$ (mL/s)		FEV_1/FVC (%)		FEV_1 increase after bronchodilator (%)		FeNO (ppb)	
	Mean	β†	Mean	β†	Mean	β†	Mean	β†	Mean	β†	Mean	β
Reference	1735	Reference	1988	reference	2262	reference	87.6	reference	4.0	reference	14.4	reference
CNAR	1746	19.5 (−18.7; 57.8)	1989	13.0 (−32.8; 58.8)	2255	-0.8 (−99.5; 97.9)	88.6	0.4 (−0.7; 1.5)	3.7	-0.3 (−1.5; 0.9)	14.1	-0.2 (−2.6; 2.3)
ETW	1712	-56.2 (−98.8; −13.7)	1973	-57.5 (−108.4; −6.6)	2134	-159.5 (−269.1; −49.8)	87.5	-0.3 (−1.5; 1.0)	3.8	-0.3 (−1.6; 1.0)	14.6	-0.0 (−2.8; 2.8)
PD	1683	-14.2 (−58.9; 30.6)	1921	-19.1 (−72.7; 34.5)	2218	-13.9 (−129.9; 102.1)	87.5	0.1 (−1.3; 1.4)	3.0	-1.0 (−2.4; 0.5)	15.7	1.0 (−1.9; 3.9)
LOAR	1700	-47.8 (−94.6; −1.0)	1960	-45.4 (−101.4; 10.7)	2114	-160.9 (−281.6; −40.1)	86.7	-0.5 (−1.9; 0.9)	3.9	-0.2 (−1.6; 1.3)	21.7	7.0 (3.9; 10.1)
PW	1624	-83.0 (−138.5; −27.8)	1925	-33.2 (−99.4; 33.0)	1882	-339.9 (−482.3; −197.4)	84.8	-2.8 (−4.4; −1.1)	6.8	2.6 (0.9; 4.4)	21.3	6.7 (3.2; 10.1)
PAR	1877	92.1 (22.1; 162.1)	2123	68.4 (−15.5; 152.2)	2403	88.0 (−95.6; 271.6)	87.9	1.3 (−0.8; 3.4)	4.1	-0.0 (−2.3; 2.2)	32.1	17.5 (13.1; 21.8)
Total	1726	-	1980	-	2218	-	87.5	-	4.0	-	16.2	-

CNAR, cough/non-allergic rhinitis symptoms group; ETW, early transient wheeze group; $FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of the FVC; FeNO, fraction of nitric oxide in exhaled air; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LOAR, late-onset allergic rhinitis symptoms group; PAR, persistent allergic rhinitis symptoms group; PD, persistent dermatitis symptoms group; PW, persistent wheeze group.

†Adjusted for sex, age, height, and ethnicity

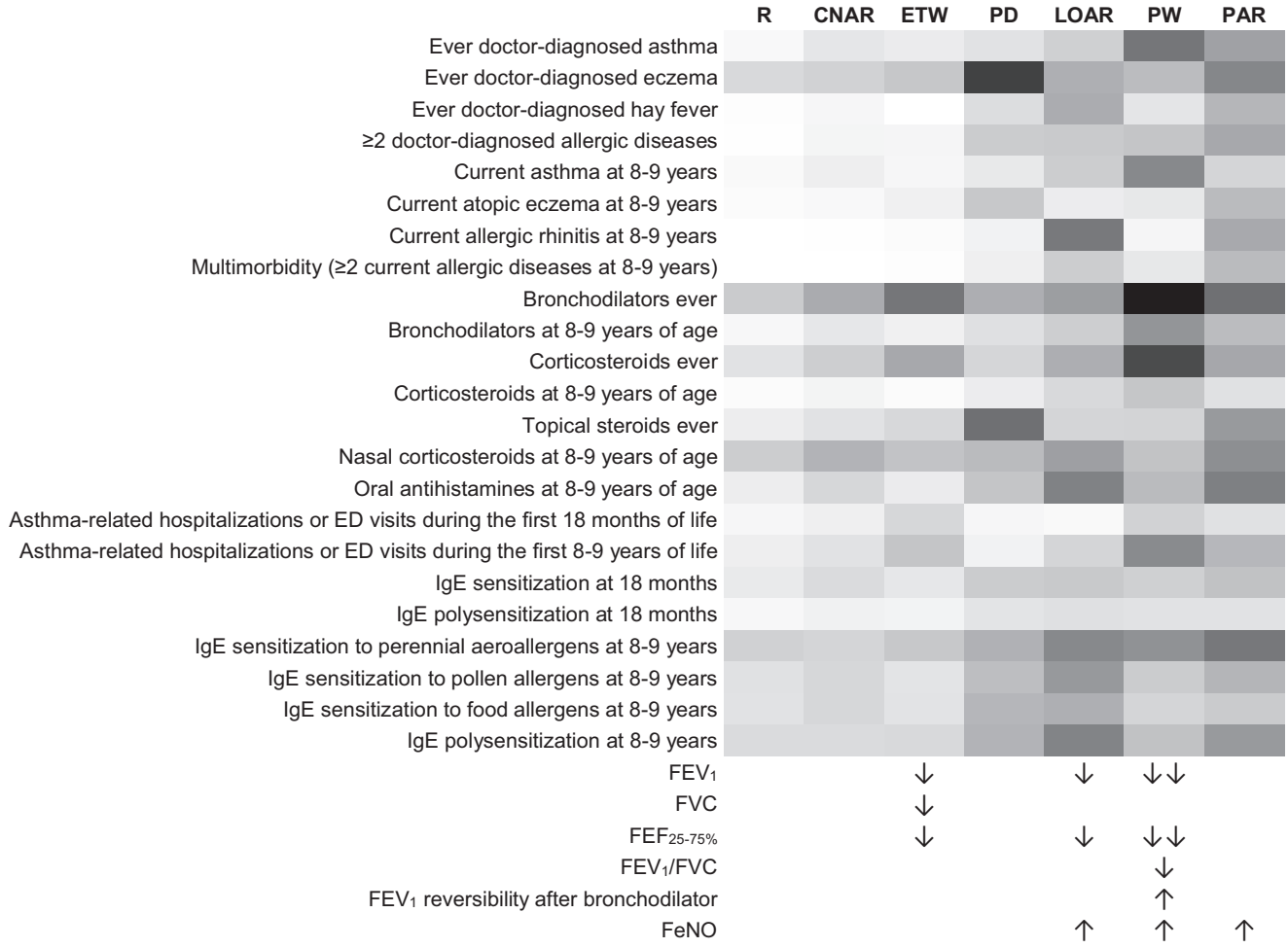

FIGURE 3 Summary of prevalence of clinical outcomes in each respiratory/allergic profile identified in the cluster analysis, and strength and direction of association of respiratory/allergic profiles with lung function and FeNO measurements, in the PARIS birth cohort children. Prevalence ranges: from 0% (white) to 100% (red). Strength and direction of associations of respiratory/allergic profiles with lung function and FeNO measurements are represented by the arrow signs (↓ and ↑). CNAR, cough/non-allergic rhinitis symptoms group; ED, Emergency department; ETW, early transient wheeze group; $FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of the FVC; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume during 1 second; FVC, forced vital capacity; LOAR, late-onset allergic rhinitis symptoms group; PAR, persistent allergic rhinitis symptoms group; PD, persistent dermatitis symptoms group; PW, persistent wheeze group; R, reference group

irritants, viruses, or bacteria, from two allergic clusters, PAR (mainly associated with perennial aeroallergens sensitization) and LOAR (related to both pollen and perennial aeroallergens sensitization). Among the allergy-like profiles, PAR and LOAR seemed the most allergic, with the highest probabilities of IgE polysensitization and allergic comorbidities.

This study refines our previous work[4] leading to four profiles during the first 4 years of life: two persistent ("cough/rhinitis" [11.3%] and "dermatitis" [12.2%]) and two transient ("transient rhinitis" [11.7%] and "transient wheeze" [15.8%]). In the present study, transient wheeze and dermatitis groups were also identified, while children with transient rhinitis were mainly considered as asymptomatic or were eventually assigned to the CNAR group. Children with persistent respiratory symptoms during the first 4 years of life, all of whom were assigned to the "cough/rhinitis" group, are now split into three distinct profiles (CNAR, PW, and PAR), which suggests that the predictive value of the "cough/rhinitis" group at 4 years may be limited, due to its heterogeneity.

Our findings reinforce the evidence for distinguishing early transient wheezing, that recovers spontaneously, from atopic persistent wheezing, as previously shown by Martinez et al[14] and confirmed by more recent studies[15] that also reported several persistent profiles.[16-20] We observed one profile of persistent wheezers that might gather all non-transient wheezers, as separation between these profiles is not so clear-cut, and overlay between related clinical features—including atopic status and lung function—has been reported.[21] PW was related to perennial aeroallergens and could represent the typical asthma phenotype, as PW was associated with lower FEV_1/FVC ratio, higher FEV_1 reversibility after bronchodilator, and higher FeNO, consistent with obstructive pattern and bronchial tree inflammation. Early transient wheezing commonly resolved by age 3 years, as airway diameters have grown enough to no longer

cause wheezing (especially in viral infections),[22] even if subnormal lung function can persist at school age,[16] which is consistent with our findings. Interestingly, we found that ETW was characterized by severe wheezing, challenging the paradigm that non-atopic wheezers experience mild-to-moderate symptoms.[23]

The PAR group had an intermediate-to-high probability of each doctor-diagnosed allergic disease, with a substantial prevalence of multiple doctor-diagnosed allergic diseases, but did not show symptom trajectories resembling the widely used atopic march, an archetype of development of allergy, in which early eczema is followed by asthma and rhinitis.[24] Belgrave et al[5] showed that a very small proportion of children with allergy symptoms followed a trajectory profile similar to atopic march. Another hypothesis involving disease-to-disease mechanisms is the united airways disease concept,[25] as allergic rhinitis has been shown to be followed by asthma in later childhood,[26,27] which suggests a close interaction between upper and lower airways. Interestingly, about one fifth of the children from the LOAR group had current asthma at 8-9 years. Moreover, we found that LOAR was associated with lower lung function and higher FeNO, which might potentially indicate future progression to asthma.

Our study has several strengths. We used a multidimensional and unsupervised technique which have the advantage of not being based on a priori assumptions even if choices about variables and number of clusters are subjective.[3] Few studies have used multidimensional approaches to characterize the co-evolution over childhood of a large set of respiratory/allergy symptoms[4-6]; most studies have been limited to one dimension, either longitudinal latent class analysis dealing with a single symptom[16-20,28] or cross-sectional cluster analysis dealing with several outcomes.[29,30] As new insights on multimorbidity are needed,[31] studying co-occurrence of allergic diseases is crucial.

Our study is the first to consider severity/triggers of multiple respiratory/allergy symptoms to build trajectories. We have distinguished whether rhinitis symptoms were triggered by aeroallergen (pollen, dust mites, or pets), with itchy/watery eyes or not, since rhinitis can be the result of diverse etiologies, including allergic or non-allergic causes such as infections or irritants.[13] We also have looked at the severity of wheezing, since mild and severe wheeze have been distinguished in previous studies.[3,29]

One limitation of our study was the substantial attrition rate during the follow-up, largely due to families who had moved out of the study area, consistent with high residential mobility rates observed in the Paris area. In common with numerous cohort studies, low SES and related features (maternal smoking during pregnancy, non-Caucasian) were more represented among non-participants. As low SES and maternal smoking are commonly linked to early wheeze, it is possible that proportion of children with early transient wheeze reported in this study was underestimated.[16] However, this should not affect etiologic analysis. Another limitation of our study, in common with most epidemiologic studies, was the lack of reliability of parental reporting of symptoms, especially wheezing,[32] even if symptoms were reported using ISAAC standardized questionnaires.[8] However, we reported clear associations of respiratory/allergic profiles with doctor-diagnosed allergic diseases, medication, and objective features such as allergy markers, lung function, and FeNO. In our opinion, such associations are essential for confirming the clinical relevance of profiles, as it is still unsure whether they are representations of discrete biologic entities or simply useful but artificial constructs.[3]

To conclude, this study brings further insights into the developmental profiles of respiratory/allergic outcomes from birth to school age, identifying profiles that clearly differed in terms of morbidity, sensitization, and lung function. Such distinctions are clinically relevant, and the follow-up of the PARIS cohort children through adolescence will be useful to determine their prognosis. Special attention should be given to children with allergic rhinitis symptoms, as they were likely to be involved in multimorbidity patterns.

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CONFLICT OF INTEREST

We declare no competing interests.

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SUPPORTING INFORMATION

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