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EPIDEMIOLOGY AND GENETICS

Onset and persistence of respiratory/allergic symptoms in preschoolers: new insights from the PARIS birth cohort

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Abstract

Background: The natural course of childhood asthma and allergy is complex and not fully understood. We aimed to identify phenotypes based upon the time course of respiratory/allergic symptoms throughout preschool years.

Methods: As part of the PARIS cohort, symptoms of wheezing, dry night cough, rhinitis and dermatitis were collected annually from birth to age 4 years. K-means clustering was used to group into phenotypes children with similar symptoms trajectories over the study period. Associations of phenotypes with IgE sensitization and risk factors were studied using multinomial logistic regression.

Results: Besides a group with low prevalence of symptoms considered as reference ($n = 1236$, 49.0%), four distinct respiratory/allergic phenotypes were identified: two transient [transient rhinitis phenotype ($n = 295$, 11.7%), transient wheeze phenotype ($n = 399$, 15.8%)], without any relation with IgE sensitization, and two persistent [cough/rhinitis phenotype ($n = 284$, 11.3%), dermatitis phenotype ($n = 308$, 12.2%)], associated with IgE sensitization. Transient rhinitis phenotype was only associated with tobacco smoke exposure, which could irritate the airways. Transient wheeze phenotype was related to male sex and contact with other children (older siblings, day care attendance). Lastly, risk factors for both IgE-associated phenotypes encompassed parental history of allergy, potential exposure to allergens and stress, known to be associated with the development of allergic diseases.

Conclusion: This study provides evidence for the existence of different respiratory/allergic phenotypes before school age. The fact that they differ in terms of sensitization and risk factors reinforces the plausibility of distinct phenotypes, potentially linked to irritation and infections for the transient phenotypes and to allergy for the persistent phenotypes.

Respiratory and allergic disorders in early childhood are a complex issue due to the heterogeneity of symptoms that can vary in terms of localization, co-occurrence, time of onset and prognosis. In this age group, transient and persistent wheezing phenotypes have been identified (1) but their association with allergic sensitization is not clear-cut. Overlap in phenotypes and instability over time increase the complexity to define discrete groups of children with specific outcomes (2). Consequently, more studies are needed in preschoolers.

Many recent studies have demonstrated the relevance of unsupervised statistical methods to determine phenotypes of asthma/allergy in children (3). Most of these studies were cross-sectional. However, symptoms suggestive of asthma/

allergy are heterogeneous, correlated and can vary over time. Longitudinal approaches seem therefore more appropriate to reflect clinical reality and further understand the development of allergic diseases in early childhood. A few studies have dealt with the time course of one single feature, wheeze (4–6) or sensitization (7), during the first years of life but, to our knowledge, no study has examined trajectories of several respiratory/allergic symptoms jointly considered.

Thus, as part of the PARIS (Pollution and Asthma Risk: an Infant Study) birth cohort, the specific objectives of the study were (i) to identify phenotypes based upon the time course of respiratory/allergic symptoms throughout preschool years and (ii) to explore the associations of these phenotypes

with IgE-mediated sensitization and lifestyle/environmental risk factors.

Methods

Study design and setting

Data were collected from birth to age 4 years and included a face-to-face interview with the mother at the maternity hospital, a phone interview at age 1 month, regular self-administered questionnaires from 1 month to 4 years and a clinical examination including a blood sample at age 18 months (Fig. S1).

Participants

PARIS is a population-based birth cohort study that enrolled 3840 full-term healthy babies born between 2003 and 2006 in five Paris maternity hospitals. Information about medical and sociodemographic eligibility criteria and methods of selection was previously published (8). The French Ethical Committee approved the study protocol, and written informed consent was obtained from the parents.

Variables

Respiratory/allergic outcomes

Health outcomes were assessed by standardized questions (9) used in the MeDALL consortium (3). At ages 1, 2, 3 and 4 years, parents were questioned about the occurrence in the previous year of wheezing, dry night cough without respiratory infection, rhinitis symptoms (sneezing or runny/nasal discharge apart from a cold) and dermatitis symptoms (itchy rash coming and going). Parents also reported at each birthday whether a doctor had ever diagnosed their child with asthma, eczema, hay fever, food allergy and the occurrence of respiratory infections.

Biological data

At age 18 months, 2012 infants attended a health examination including a blood sample offered to all PARIS children. Total immunoglobulin E (IgE), specific IgE and eosinophils were measured. Elevated total IgE level was defined as a concentration of ≥ 45 IU/ml and eosinophilia as ≥ 470 eosinophils/ μ l (10) or $\geq 4\%$ of total white blood cells (11). Sensitization against a mixture of inhalant/food allergens was assessed with a multi-allergen-specific IgE screen (Phadia, Uppsala, Sweden): inhalant allergens using ImmunoCAP[®] Phadiatop[®] (house dust mite, pet, pollen, mould allergens), food allergens using ImmunoCAP[®] Trophatop[®] fx26 (egg white, cow's milk, peanut, mustard), fx27 (codfish, nut, soya bean, wheat) and fx28 (shrimp, kiwi, beef, sesame). If one of the tests was positive, measurement of specific IgE directed towards the respective food allergens was taken. The detection limit was 0.35 IU/ml.

Lifestyle/environment characteristics

At the maternity hospital, the mother was questioned about family characteristics such as parental history of allergy,

older siblings, parental occupation, smoking habits and medication use during pregnancy. Familial socio-economic status (SES) was based upon parental occupation, according to the French nomenclature of the National Institute of Statistics and Economic Studies (INSEE) by taking into account the highest position among the two parents, and divided into three categories (low/medium/high).

At age 1 month, a trained interviewer administered a phone questionnaire to one of the parents about housing characteristics and living habits, notably related to type/age of wall/floor coverings, furniture and bedding, presence of pets, visible moulds and tobacco smoking.

Between 3 months and 4 years of age, regular self-administered questionnaires were mailed to the families to update previously collected data and document duration of breastfeeding, type of day care setting and occurrence of familial events including serious health problem in the mother such as chronic diseases, cancer, depression, surgery and hospitalization.

Statistical methods

Identification of phenotypes

Clustering was used to identify, among the study population, phenotypes based upon the time course of four respiratory/allergic symptoms during preschool years, with a k-means algorithm especially designed for longitudinal data (12). Children were partitioned into different clusters according to their trajectories of wheeze, dry night cough, rhinitis and dermatitis symptoms, by considering 4 time periods (1st, 2nd, 3rd and 4th years of life), so that children in the same cluster had the closest Euclidean distance from one another, while children in different clusters were as far as possible.

The optimal number of clusters cannot be known *a priori*. We therefore performed different models, and the classification with the best data separation according to the cluster validity index of Davies–Bouldin (13) was finally selected. As the method used is able to deal with missing values, the analysis was carried out on children with data available at ≥ 2 time periods for each symptom, and we conducted a sensitivity analysis on children with complete reports for all symptoms at all time periods.

Morbidity and risk factors associated with phenotypes

Once the phenotypes were identified, their relations with IgE-mediated sensitization, blood eosinophilia and doctor-diagnosed diseases were studied using logistic regression. The risk factors for belonging to the phenotypes were investigated using multinomial logistic regression. Variables associated with phenotypes in bivariate analyses, as well as known or suspected risk factors for asthma/allergy, were introduced into the final model.

Cluster analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria) and the package kml3d. Regression analyses were fitted using Stata/SE 9.1 software (StataCorp, College Station, TX, USA), and results were expressed as odds ratios (OR) and their 95% confidence intervals (95% CI). The level of significance was 0.05.

Results

Participants

Of the 3840 children initially enrolled in the cohort, 2522 (65.7%) were included in the cluster analysis (Fig. 1). Nearly, 27% of the children not included had to stop the follow-up before their 4th birthday due to moving outside the study area, a withdrawal criterion specified in the protocol (8).

When comparing the baseline characteristics of children included and not included in the analysis, no significant difference was found except for familial SES and maternal age: children included were more likely to have a higher familial SES and an older mother than children from the initial cohort not included. In the same way, among children included in the analysis, it appeared that children without missing data were more likely to have a higher familial SES and an older mother than those with missing data (Table 1).

Identification of respiratory/allergic phenotypes

The statistical analysis revealed that the five-cluster solution best fitted the data set, and four phenotypes and one reference group were identified (Fig. 2).

The group considered as reference included about half of the sample and showed low annual prevalence for each symptom (between 0% and 10%). The transient phenotypes (rhinitis and wheeze) were similar in that all children from these two clusters experienced during the first year rhinitis or wheeze symptoms, after which the great majority rapidly recovered. The cough/rhinitis phenotype showed high prevalence of both dry night cough and rhinitis symptoms, which gradually increased during the first 4 years. Half of children

from this phenotype also suffered from wheezing and dermatitis symptoms during the study period. Lastly, all children included in the dermatitis phenotype experienced itchy rash symptoms between birth and 4 years, and only very few of them had respiratory symptoms during the same period.

The sensitivity analysis conducted in children with complete data showed that phenotypes were similarly structured (Fig. S2).

Doctor-diagnosed diseases associated with phenotypes

Early lower respiratory infections (LRI) were far more prevalent among the transient wheeze phenotype where 87.3% of children had experienced bronchitis and/or bronchiolitis during their first year of life vs 30.6% in the reference group, 26.6% in the transient rhinitis phenotype, 51.6% in the cough/rhinitis phenotype and 43.1% in the dermatitis phenotype ($P < 0.001$).

The prevalence of diseases that had ever been doctor diagnosed at 4 years within each phenotype is shown in Table 2. The transient rhinitis phenotype never statistically differed from the reference group nor did the transient wheeze phenotype except for diagnosed asthma. The dermatitis phenotype had the highest prevalence of diagnosed eczema and food allergy. It did not differ, however, from the cough/rhinitis phenotype with regard to the prevalence of diagnosed food allergy. Lastly, the cough/rhinitis phenotype showed the highest prevalence of diagnosed asthma and hay fever, which statistically differed from all the other phenotypes.

Biomarkers associated with phenotypes

Compared with the reference, significant differences were only shown for the cough/rhinitis and dermatitis phenotypes.

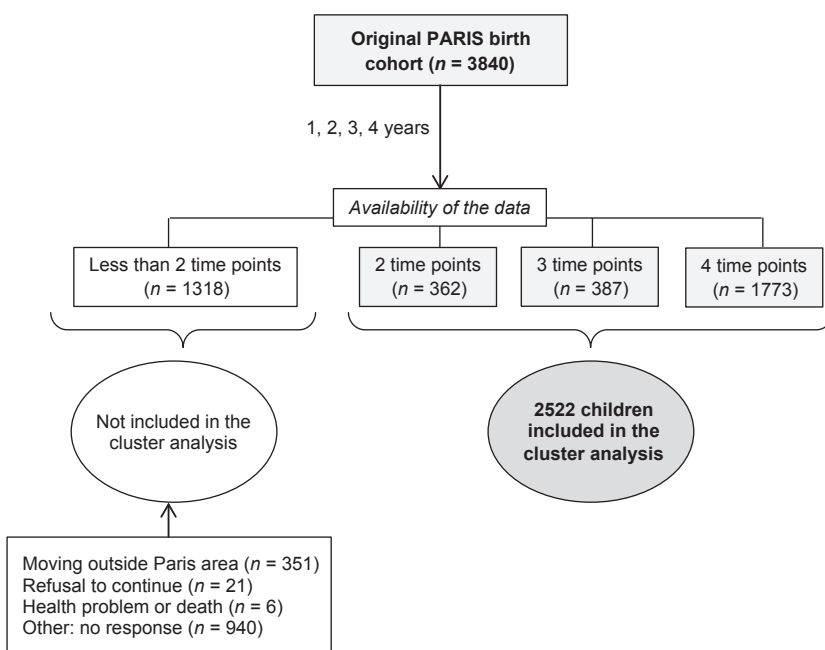


Figure 1 Flow chart of study participants from the PARIS birth cohort.

Table 1 Characteristics of PARIS children included in the cluster analysis over the first 4 years of life, according to the presence of or not of missing data

	Analysed subcohort (<i>n</i> = 2522)	
	Children with complete data (<i>n</i> = 1773) <i>n</i> /Total (%)	Children with missing data (<i>n</i> = 749) <i>n</i> /Total (%)
Male gender	893/1773 (50.4)	393/749 (52.5)
High socio-economic status	1211/1773 (68.3)	494/749 (66.0)
Maternal age at birth ≥ 35 years	479/1773 (27.0)	160/749 (21.4)
Parental history of allergy*	948/1766 (53.7)	407/747 (54.5)
Prevalence of wheezing		
0–1 year	386/1773 (21.8)	164/728 (22.5)
1–2 years	212/1773 (12.0)	77/630 (12.2)
2–3 years	146/1773 (8.2)	42/441 (9.5)
3–4 years	109/1773 (6.1)	29/238 (12.2)
Prevalence of dry night cough		
0–1 year	249/1773 (14.0)	111/728 (15.2)
1–2 years	254/1773 (14.3)	89/626 (14.2)
2–3 years	294/1773 (16.6)	84/427 (19.7)
3–4 years	341/1773 (19.2)	38/211 (18.0)
Prevalence of rhinitis symptoms		
0–1 year	419/1773 (23.6)	199/728 (27.3)
1–2 years	306/1773 (17.3)	115/627 (18.3)
2–3 years	289/1773 (16.3)	86/419 (20.5)
3–4 years	269/1773 (15.2)	33/189 (17.5)
Prevalence of dermatitis symptoms		
0–1 year	292/1773 (16.5)	116/728 (15.9)
1–2 years	288/1773 (16.2)	121/629 (19.2)
2–3 years	302/1773 (17.0)	75/420 (17.9)
3–4 years	314/1773 (17.7)	38/211 (18.0)

*Asthma, eczema and/or allergic rhinitis.

Children from the cough/rhinitis phenotype were more likely to have elevated total IgE level and IgE sensitization to both inhalant and food allergens and eosinophilia, whereas the dermatitis phenotype was positively associated with IgE sensitization to food allergens and eosinophilia (Table 3). The use of different cut-offs showed similar results.

Risk factors associated with phenotypes

Lifestyle/environment factors included in the multivariate multinomial regression analysis are presented in Table 4.

The only factor associated with the transient rhinitis phenotype was postnatal exposure to environmental tobacco smoke (ETS) in the home. Regarding the transient wheeze phenotype, the strongest association was found for early day care centre attendance, but it was also associated with male sex, older siblings, prenatal exposure to maternal smoking and exposure to new particle board furniture and coverings in the home.

Children from the cough/rhinitis and dermatitis phenotypes shared associations with parental history of allergic

diseases (this association being all stronger when both parents had already been affected) and maternal serious health problem during the first 4 years of her child's life. These two phenotypes also had distinct risk factors: the cough/rhinitis phenotype was positively associated with maternal antibiotics use during pregnancy and early exposure to moulds in the home, whereas it was negatively associated with prolonged breastfeeding and cat allowed in the child's bedroom. Lastly, concerning children from the dermatitis phenotype, they were also more likely to attend a day care centre, to have a used mattress and to be highly exposed to ETS in the home.

Discussion

Key results

In the general population, the present study identified four distinct phenotypes based upon the time course of respiratory/allergic symptoms in the first 4 years of life. Children from these phenotypes differed in terms of IgE sensitization and risk factors, suggesting that different aetiologies such as irritation, respiratory infections and allergy might be involved.

Strengths and limitations

Novel approaches have recently emerged to identify respiratory/allergic phenotypes using statistical techniques to overcome the investigators' subjectivity (4–7, 14–18), even if the choice of variables and number of clusters are not without bias. Because there are no specific symptoms that can reliably identify which infants will develop asthma or allergy, it is relevant to explore a set of symptoms that may frequently affect children and that may suggest an underlying allergic disease. Up to now, only cross-sectional studies (14–18) have looked at more than one asthma/allergy-like symptom. In our opinion, cross-sectional approaches are not fully satisfactory and research should focus on multidimensional trajectories, more likely to reflect clinical reality, because symptoms suggestive of asthma/allergy are heterogeneous, correlated and are expected to evolve quickly. To date, the few authors who identified phenotypes based upon longitudinal data only considered the evolution of one single outcome, wheezing (4–6) or allergic sensitization (7) over the first years of life. The novelty of our study is that it is the first one, to the best of our knowledge, to investigate joint trajectories of several respiratory/allergic symptoms. The previous work of Clarisse et al. (16) in the PARIS birth cohort targeted bronchial obstructive symptoms and underlined the importance of dry night cough, isolating a group of children more likely to be associated with allergic features. Thus, in the present study, we studied both wheeze and cough. We also dealt with a broader approach by considering now allergy and its different manifestations. We therefore focused not only on lower respiratory symptoms but also expanded our research to upper respiratory and skin symptoms. Interestingly, both persistent phenotypes were not defined according to wheezing

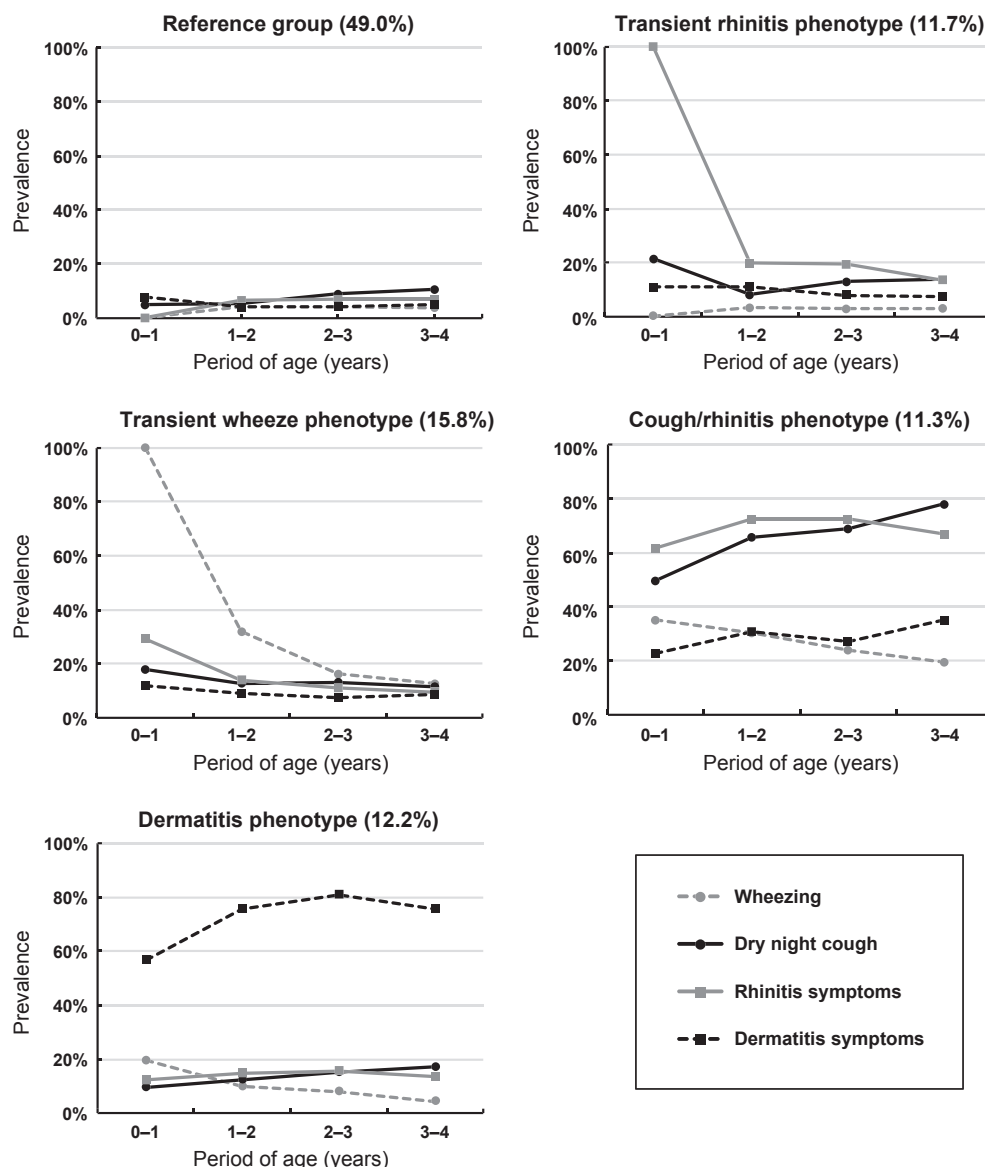


Figure 2 Respiratory/allergic phenotypes based upon symptom trajectories identified over the first 4 years of life in children from the PARIS cohort ($n = 2522$).

symptoms. The short period of time we have considered for the identification of phenotypes could be seen as a weakness compared with other studies that dealt with the evolution of wheezing from birth to school age (4–6). The time course of symptoms during preschool years was rarely studied, and the age of 3 years has often been considered as a pivotal age, for example, used as threshold in the Tucson cohort to define early-transient, late-onset and persistent wheezing phenotypes (1). Another innovative aspect of our study is to show that it is possible to identify distinct respiratory/allergic phenotypes at an early stage of life, before children have reached school age, which could result in earlier management. The follow-up of the PARIS cohort will allow the study of how our new

phenotypes fit in with the existing knowledge, especially with the traditional classification of wheezing symptoms described by Martinez et al. (1) in the Tucson cohort.

One limitation of our study is participation. In the PARIS cohort, we observed a substantial attrition rate during follow-up, as previously mentioned (19). Briefly, this is partly due to families moving outside the study area. Paris and suburbs have one of the highest residential mobility rates in France, and it is common that young couples move after starting a family. This decrease in participation was, however, partly offset using a method dealing with missing values, so we did not have to exclude from the cluster analysis all children for whom some data were missing. Another

Table 2 Association of respiratory/allergic phenotypes identified over the first 4 years of life in children from the PARIS cohort with doctor-diagnosed diseases

		Phenotypes							
Reference		Transient rhinitis		Transient wheeze		Cough/rhinitis		Dermatitis	
%		%	aOR (95% CI)*	%	aOR (95% CI)*	%	aOR (95% CI)*	%	aOR (95% CI)*
Asthma	5.4	4.8	0.87 (0.45–1.70)	24.0	5.45 (3.72–7.98)	35.8	7.50 (4.95–11.35)	11.0	1.42 (0.83–2.42)
Eczema	28.3	28.1	0.98 (0.71–1.35)	35.5	1.29 (0.98–1.71)	53.9	2.24 (1.60–3.12)	88.6	17.53 (11.44–26.89)
Food allergy	6.2	6.1	0.98 (0.54–1.80)	7.0	0.89 (0.53–1.51)	19.6	2.04 (1.25–3.31)	22.9	2.56 (1.65–3.97)
Hay fever	1.9	3.5	1.88 (0.81–4.36)	2.2	0.87 (0.35–2.15)	13.7	4.66 (2.40–9.02)	5.1	1.46 (0.66–3.24)

aOR, adjusted odds ratio; CI, confidence interval.

*Multinomial logistic regression model (outcome: reference [children with no or very few symptoms], transient rhinitis, transient wheeze, cough/rhinitis, dermatitis). The odds ratios in bold differ significantly from the reference ($P < 0.05$).

Table 3 Association of respiratory/allergic phenotypes identified over the first 4 years of life in children from the PARIS cohort with total IgE, IgE sensitization and blood eosinophilia

	Phenotypes								
	Reference %	Transient rhinitis		Transient wheeze		Cough/rhinitis		Dermatitis	
		%	OR (95% CI)*	%	OR (95% CI)*	%	OR (95% CI)*	%	OR (95% CI)*
Elevated total IgE ≥45 IU/ml	19.1	21.1	1.13 (0.75–1.70)	21.5	1.16 (0.81–1.66)	28.8	1.71 (1.18–2.50)	20.8	1.11 (0.74–1.67)
IgE sensitization To inhalant and/or food allergens	13.3	14.3	1.09 (0.67–1.78)	14.9	1.15 (0.75–1.75)	25.0	2.28 (1.52–3.42)	23.7	2.03 (1.34–3.06)
To inhalant allergens	2.3	1.8	0.81 (0.23–2.79)	2.2	0.95 (0.35–2.61)	4.7	2.41 (1.05–5.49)	4.7	2.12 (0.90–5.01)
To food allergens	12.6	11.9	0.94 (0.56–1.58)	13.2	1.06 (0.68–1.64)	22.0	2.08 (1.37–3.16)	22.8	2.06 (1.36–3.13)
Cow’s milk	5.9	5.8	1.00 (0.49–2.02)	8.3	1.45 (0.83–2.54)	11.9	2.17 (1.24–3.78)	11.0	1.99 (1.13–3.50)
Egg white	5.3	5.3	0.99 (0.47–2.07)	5.7	1.07 (0.56–2.03)	7.2	1.37 (0.70–2.68)	11.6	2.34 (1.33–4.11)
Nut	1.1	1.2	1.11 (0.23–5.28)	2.2	2.08 (0.67–6.42)	6.0	5.88 (2.28–15.13)	4.2	4.06 (1.45–11.36)
Peanut	0.9	1.2	1.25 (0.26–6.09)	0.9	0.93 (0.19–4.53)	4.2	4.61 (1.59–13.32)	5.3	5.89 (2.16–16.04)
Blood eosinophilia ≥470 eosinophils/μl	10.3	8.4	0.83 (0.47–1.48)	12.8	1.29 (0.82–2.02)	16.3	1.63 (1.02–2.62)	21.7	2.31 (1.02–2.62)
≥4% of total white blood cells	19.4	20.5	1.07 (0.71–1.61)	19.9	1.03 (0.71–1.49)	27.6	1.59 (1.08–2.32)	31.1	1.87 (1.30–2.69)

OR, odds ratio; CI, confidence interval.

*Multinomial logistic regression model (outcome: reference [children with no or very few symptoms], transient rhinitis, transient wheeze, cough/rhinitis, dermatitis). The odds ratios in bold differ significantly from the reference ($P < 0.05$).

limitation is parental-reported symptoms, in common with most of large epidemiological studies; thus, we also included biomarkers of atopy. Biological data at age 18 months were used to investigate whether differences between phenotypes could be highlighted because IgE-mediated sensitization in early life is a risk factor for later development of asthma and allergy. They are not intended to reflect the atopic status of children at age 4 years. Interestingly, our analyses revealed differences between phenotypes, even at this early age, when IgE sensitization is less prevalent than later in life. Blood samples will be collected later in the PARIS cohort, at age 7–8 years. Lastly, it is essential to validate phenotypes identified using data-driven approaches before considering practical

implications. This validation could be achieved by replicating the method in another cohort or later in the follow-up of the PARIS cohort, by testing the predictive value of these phenotypes for long-term prognosis of children.

Interpretation

Overall, showing differences in sensitization and risk factors reinforced the plausibility of these phenotypes, contributed to further understand these entities and led to hypotheses about underlying aetiologies, which could be viewed as a first step of validation. Interestingly, the proportion of children included in the cough/rhinitis phenotype (11.3%) approximates

Table 4 Risk factors for belonging to respiratory/allergic phenotypes identified over the first 4 years of life in children from the PARIS cohort

Phenotypes									
Reference % or m	Transient rhinitis		Transient wheeze		Cough/rhinitis		Dermatitis		
	% or m	aOR (95% CI)*	% or m	aOR (95% CI)*	% or m	aOR (95% CI)*	% or m	aOR (95% CI)*	
47.7	50.0	1.12 (0.81–1.54)	59.2	1.64 (1.22–2.22)	51.2	1.19 (0.85–1.68)	54.1	1.34 (0.97–1.84)	
Child and family factors									
Sex, male (vs female)									
Parental history of asthma, eczema and/or allergic rhinitis									
38.6	44.2	1.24 (0.88–1.74)	45.7	1.32 (0.97–1.81)	45.3	1.58 (1.09–2.30)	44.3	1.61 (1.13–2.28)	
10.3	9.0	0.94 (0.53–1.67)	8.6	0.95 (0.55–1.62)	18.2	2.35 (1.41–3.92)	18.0	2.36 (1.46–3.80)	
0.54	0.45	0.82 (0.64–1.07)	0.69	1.42 (1.15–1.76)	0.50	0.93 (0.71–1.21)	0.62	1.08 (0.85–1.36)	
11.5	14.2	1.24 (0.77–1.97)	7.3	0.59 (0.34–1.01)	25.9	2.42 (1.59–3.68)	18.6	1.71 (1.11–2.64)	
(vs no)									
Living habits									
29.6	28.9	1.00 (0.69–1.43)	226.1	0.97 (0.69–1.36)	21.2	0.64 (0.42–0.98)	27.8	0.97 (0.67–1.39)	
Breastfeeding during the first 6 months, yes (vs no)									
Day care attendance during the first 6 months									
25.4	22.6	0.85 (0.57–1.27)	20.8	1.19 (0.81–1.76)	19.4	0.74 (0.47–1.16)	23.7	1.06 (0.71–1.60)	
16.0	15.3	0.88 (0.56–1.40)	34.7	3.13 (2.19–4.47)	24.1	1.49 (0.96–2.30)	23.7	1.74 (1.15–2.63)	
(vs no)									
Day care centre (vs no)									
Prenatal exposure to chemicals									
7.6	10.0	0.98 (0.54–1.78)	12.7	1.88 (1.13–3.14)	12.9	1.54 (0.85–2.80)	10.3	1.16 (0.64–2.08)	
3.0	2.6	0.85 (0.31–2.27)	3.7	1.49 (0.66–3.33)	6.5	2.23 (1.04–4.80)	3.1	1.08 (0.43–2.73)	
Maternal active smoking during pregnancy, yes (vs no)									
Maternal antibiotics use during the first trimester of pregnancy, yes (vs no)									
Postnatal exposure to biological pollution									
25.9	20.5	0.85 (0.56–1.27)	28.2	0.96 (0.67–1.36)	25.9	1.10 (0.73–1.66)	36.6	1.65 (1.15–2.37)	
Child sleeping on a used (>3 years old) mattress at birth, yes (vs no)									
12.4	14.2	1.12 (0.70–1.78)	15.5	1.24 (0.82–1.89)	21.2	1.76 (1.13–2.73)	13.9	1.04 (0.65–1.66)	
9.1	6.8	0.62 (0.33–1.16)	7.8	0.81 (0.46–1.42)	2.9	0.28 (0.11–0.71)	6.2	0.59 (0.30–1.13)	
5.5	7.9	1.48 (0.79–2.77)	4.1	0.74 (0.36–1.55)	7.1	1.42 (0.70–2.86)	8.8	1.72 (0.93–3.17)	
Acquisition of a cat in the first 4 years, yes (vs no)									
Postnatal exposure to chemical pollution									
5.5	5.3	0.88 (0.43–1.79)	9.8	1.87 (1.09–3.22)	7.6	1.30 (0.67–2.51)	5.7	0.96 (0.48–1.93)	
New particle board furniture in the living room at birth, ≥2 (vs <2)									
31.2	30.5	0.99 (0.70–1.40)	35.9	1.38 (1.01–1.89)	38.2	1.40 (0.98–2.00)	34.5	1.18 (0.84–1.66)	
New varnished parquet floor or wall painting in the child's bedroom in the first 4 years, yes (vs no)									
6.3	13.2	2.08 (1.19–3.62)	10.2	1.38 (0.79–2.42)	12.4	1.68 (0.91–3.11)	11.3	1.85 (1.04–3.30)	
≥10 cigarettes smoked per day in the dwelling during at least 1 year in the first 4 years, yes (vs no)									

aOR, adjusted odds ratio; CI, confidence interval.

*Multinomial logistic regression model [outcome: reference (children with no or very few symptoms), transient rhinitis, transient wheeze, cough/rhinitis, dermatitis]. The odds ratios in bold differ significantly from the reference ($P < 0.05$). The model was also adjusted for place of residence in the first year (2 classes: Paris city, Paris suburb), familial socio-economic status (3 classes: low, medium, high) and maternal level of education (2 classes: primary/secondary, postsecondary).

the prevalence of asthma expected in our French population at school age.

The transient phenotypes were not associated with IgE sensitization. The only risk factor found for the transient rhinitis phenotype suggested an irritant effect of ETS on the nasal mucosa at the origin of congested and runny nose (20). Symptoms of children from the transient wheeze phenotype appeared related to LRI given the associations found with factors reflecting close physical contact with other children in the home or in day care centre, which can promote the transmission of pathogens (21). We also found risk factors for having narrow airways, more easily obstructed. Indeed, boys are known to have smaller airways than girls in relation to lung size in early childhood (22), and intrauterine exposure to maternal smoking can slow down lung growth (23). Lastly, exposure to chemicals emitted by new particle board furniture and coverings such as formaldehyde was previously associated with an increased incidence of LRI in infants from the PARIS cohort (24) and could enhance the susceptibility of children to infectious agents.

The development of allergy is often described as the concept of 'atopic march', a representation of how allergic manifestations succeed in childhood from atopic dermatitis to allergic asthma. The reality in clinical practice, however, is not as simple, the likelihood being that there would be more than one single temporal pattern of allergic diseases in childhood. Our findings revealed two allergy-like phenotypes, one implicating mainly the respiratory tract and the other the skin. In a consistent way, only the cough/rhinitis phenotype was associated with early IgE sensitization to inhalant allergens, whereas both phenotypes were associated with sensitization to food allergens. They shared common risk factors known to play a role in the development of allergy such as genetic predisposition, potential exposure to allergens and serious maternal health problems as a possible source of family stress, in accordance with the growing body of literature supporting the importance of psychosocial factors in childhood atopic diseases (25).

Regarding other risk factors for cough/rhinitis phenotype, our results were in keeping with a large-scale British epidemiological study showing positive association between maternal antibiotics consumption during pregnancy and symptoms of asthma, eczema and hay fever in offsprings (26). This association could be explained by a decreased microbial exposure during foetal life. Children from this phenotype were also more likely to be exposed early to moulds, in agreement with a European meta-analysis concluding that such exposure increased the risk of allergic rhinitis symptoms at school age (27). Lastly, two factors appeared protective against the cough/rhinitis phenotype. First, cat allowed in the child's bedroom could reflect an early and intensive exposure to endotoxins, consistent with the hygiene hypothesis and has already been shown to protect against the development of atopic asthma in German school children (28). Second, our results are consistent with studies showing a decreased risk of asthma and allergy associated with prolonged breastfeeding (29, 30). Indeed, immunomodulatory and anti-inflammatory

components present in maternal milk could be beneficial to infants whose immune system is still immature (31).

The dermatitis phenotype was associated with risk factors for persistence and severity of atopic dermatitis in children already prone to the disease. Patients with atopic dermatitis have a genetically impaired skin barrier function (32), making their skin more permeable to the penetration of environmental contaminants, which can induce or enhance inflammatory reactions. Sleeping on a used mattress could reflect skin contact with house dust mite and mould allergens, and there is evidence that exposure to ETS has an adjuvant effect on atopic dermatitis (33). Finally, our findings are in agreement with those of Kerkhof et al. (34) who found an increased risk of atopic dermatitis in children attending day care centre. One explanation could be related to exposure to infectious agents in day care centres because *Staphylococcus aureus* is believed to play a significant role in the pathogenesis of atopic dermatitis by maintaining skin inflammation (35).

To conclude, this study helps to clarify the complex issue of respiratory and allergic disorders in young children and provides evidence for distinct respiratory and allergic patterns in early life. The follow-up of the PARIS cohort will allow testing the predictive value of these phenotypes for allergic asthma at school age.

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Author contributions

LN and IM were involved in the implementation of the PARIS birth cohort. FR and IM analysed the data. JB

contributed to interpretation of data. FR drafted the first version of the manuscript. All authors revised it for important intellectual content and approved the final version of the article as submitted.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Design of the PARIS cohort study from birth to 4 years of age.

Figure S2. Respiratory/allergic phenotypes based upon symptom trajectories identified over the first 4 years of life in children from the PARIS cohort with complete data [4 observations for each symptom ($n = 1773$)].

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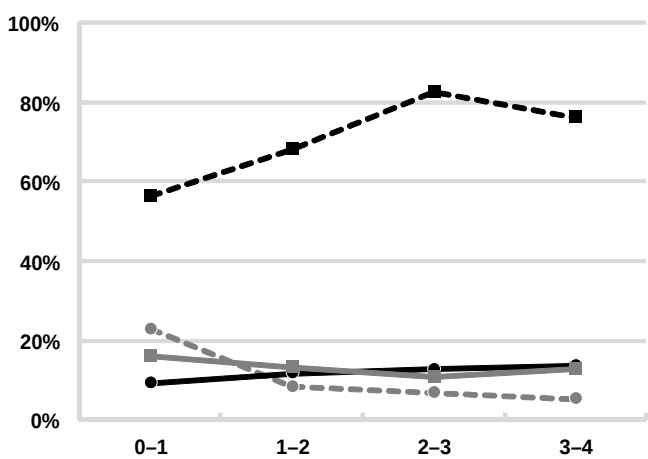
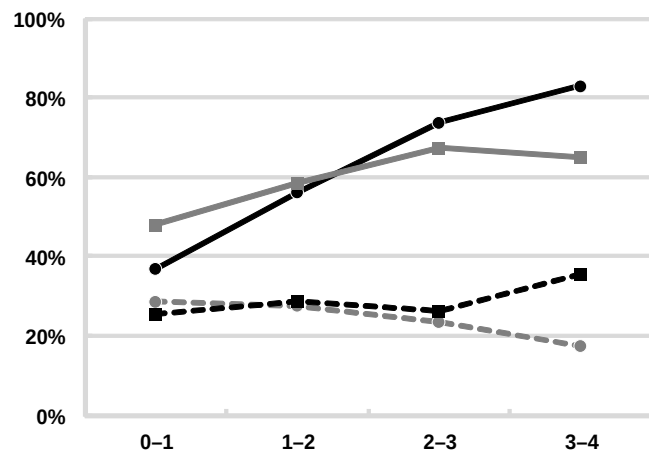
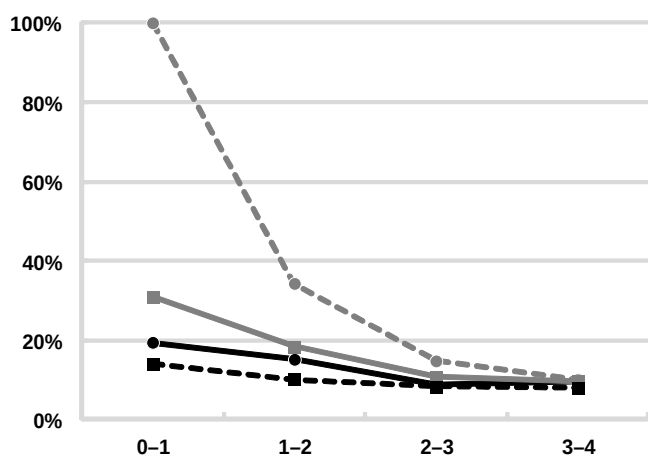
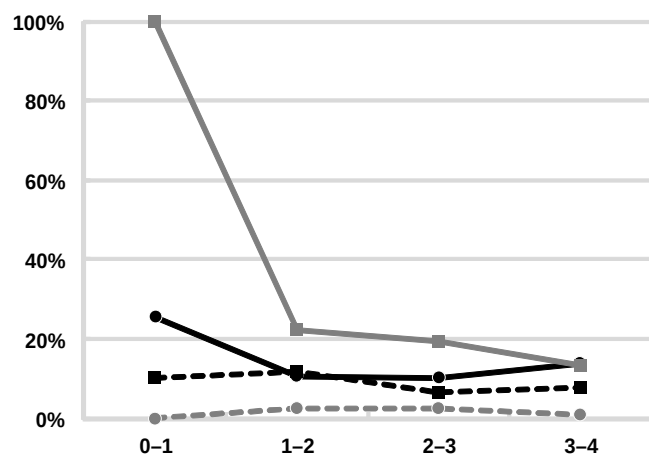
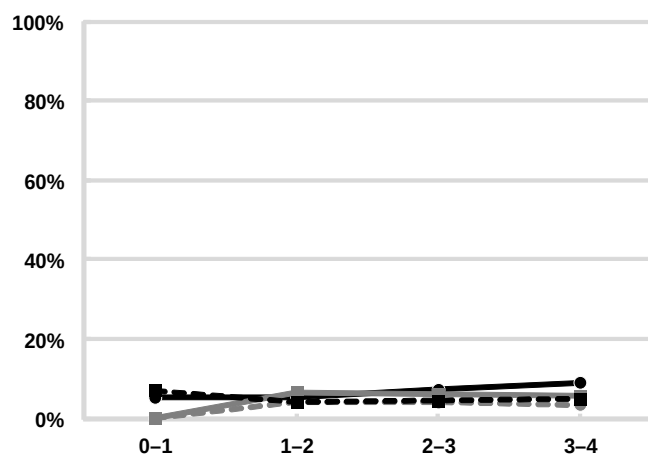
Supporting information

Figure S1 Design of the PARIS cohort study from birth to 4 years of age.

Figure S2 Respiratory/allergic phenotypes based upon symptom trajectories identified over the first 4 years of life in children from the PARIS cohort with complete data [4 observations for each symptom (n=1773)].

Figure S1

Figure S2



- Wheezing
- Dry night cough
- Rhinitis symptoms
- Dermatitis symptoms