

Risk factors and characteristics of respiratory and allergic phenotypes in early childhood

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Background: Unsupervised approaches can be used to analyze complex respiratory and allergic disorders.

Objective: We investigated the respiratory and allergic phenotypes of children followed in the Pollution and Asthma Risk: An Infant Study (PARIS) birth cohort.

Methods: Information on respiratory and allergic disorders, medical visits, and medications was collected during medical examinations of children at 18 months of age; biomarker data were also collected (total and allergen-specific IgE levels and eosinophilia). Phenotypes were determined by using latent class analysis. Associated risk factors were determined based on answers to questionnaires about environmental exposures.

Results: Apart from a reference group, which had a low prevalence of respiratory symptoms or allergies ($n = 1271$ [69.4%]), 3 phenotypes were identified. On the basis of clinical signs of severity and use of health care resources, we identified a mild phenotype ($n = 306$ [16.7%]) characterized by occasional mild wheeze and 2 severe phenotypes separated by atopic status. The atopic severe phenotype ($n = 59$ [3.2%]) included 49 (83%) children with wheezing and was characterized by a high prevalence of atopy (61% with allergenic sensitization) and atopic dermatitis (78%). In contrast, atopy was rare among children with the nonatopic severe phenotype ($n = 195$ [11%]); this group included 88% of the children with recurrent wheezing. Risk factors for respiratory disease included parental history of asthma, male sex, siblings, day care attendance, exposure to tobacco smoke or molds, indoor renovations, and being overweight, although these factors did not have similar effects on risk for all phenotypes.

Conclusion: Atopy should be taken into account when assessing the risk of severe exacerbations (that require hospital-based care) in wheezing infants; precautions should be taken against respiratory irritants and molds and to prevent children from becoming overweight. (*J Allergy Clin Immunol* 2012;130:389-96.)

Key words: Atopy, phenotype, infancy, severity, wheeze, risk factors, cluster analysis

Respiratory and allergic disorders are highly prevalent in children.¹ The different manifestations of allergic diseases involve the upper (allergic rhinitis) and lower (asthma) respiratory airways, as well as the skin (atopic dermatitis). Identification of phenotypes of respiratory and allergic symptoms can be used to look at the heterogeneity of the disease in children and improve our understanding of disease progression and management.² The Tucson study identified 3 wheezing phenotypes, which differed in chronology of wheeze during preschool years, respiratory function, and atopic background.³ On the basis of these findings, researchers developed the Asthma Predictive Index, a screening tool to identify preschool-aged children with wheezing who are at risk for persistent asthma. According to the Asthma Predictive Index, children with recurrent wheezing who have 1 major risk factor (parental history of asthma or personal history of atopic dermatitis) or 2 minor risk factors (wheeze apart from a respiratory tract infection, eosinophilia, or allergic rhinitis) are at risk for asthma.^{4,5}

Current classifications of phenotypes rely mainly on only 1 variable. For instance, the European Respiratory Society Task Force⁶ defined wheezing phenotypes in preschool-aged children according to factors that induced wheeze, and therefore “virus-associated wheeze” was distinguished from “multiple-trigger wheeze.” According to the Global Initiative for Asthma,⁷ asthma phenotypes could be assessed based on the severity or control of symptoms. Nevertheless, cluster analyses performed in epidemiologic studies identified distinct phenotypes of asthma that did not correspond to definitions of asthma proposed by current guidelines.⁸⁻¹¹ In particular, Fitzpatrick et al¹² recently increased our understanding of the heterogeneity of severe asthma in children, reporting the importance of atopy in defining pediatric asthma.

Few studies have focused on respiratory and allergic phenotypes in infants; the first months of life represent an important period for the development of the respiratory and immune systems, and therefore measures to reduce exposure to risk factors should be considered.¹³ We aimed to identify phenotypic clusters in a population-based sample of infants based on clinical manifestations, evidence of severity, and atopy. We also investigated risk factors for respiratory disorders in infants. This work is part of the Pollution and Asthma Risk: An Infant Study (PARIS), a longitudinal study of a birth cohort to investigate respiratory and allergic disorders in early childhood.

METHODS

Study design and ethics

The PARIS birth cohort comprises healthy newborn babies recruited at birth between 2003 and 2006 from 5 Paris maternity hospitals according to

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Abbreviation used

PARIS: Pollution and Asthma Risk: An Infant Study

medical and sociodemographic criteria.¹⁴ The study included single-birth, full-term newborns with a birth weight of 2500 g or greater, without malformation, and with an uncomplicated birth and neonatal period. Exclusion criteria included infants with mothers who were less than 18 years old or did not receive medical care during pregnancy, infants who were part of a multiple pregnancy, infants whose mothers had alcohol or drug addiction, and infants whose mothers had difficulty speaking French. Among eligible newborns, 63% were included in the study. Parents provided written informed consent, and the research protocol was approved by the National Ethics Committee. The PARIS birth cohort was followed by telephone interviews, questionnaires were given to parents, and participants were evaluated in 2 health examinations. The first health examination took place in the Paris Health Centre of the National French Health Insurance System when children were 18 months old and included a standardized questionnaire (administered by a pediatrician) and measurements of anthropometric parameters and blood markers of atopy. We present data collected during this health examination and from questionnaire-based follow-up.

Clinical outcomes

Respiratory and allergic outcomes were defined according to parents' answers to the questionnaire administered at the 18-month health examination. Wheeze during the previous 12 months was identified by using the following question: "In the past 12 months, did your child experience whistling in the chest?" Additional information was collected on recurrence of wheezing episodes in the past 12 months (>3 episodes), limitations to daily activities, and sleep disturbances. In addition to these clinical variables, the use of health care resources for wheezing disorders was used to determine the severity of wheeze. Data were collected on antiasthma medications taken and medical visits (particularly emergency department visits and hospitalizations for bronchiolitis, wheezy bronchitis, or asthma crisis during the previous 12 months). Pediatricians examined prescriptions issued in the first 18 months and also showed parents a list of inhaled medications so they could identify any that had been used to assess the use of antiasthma medications. We also collected information on the presence or absence of nocturnal dry cough (apart from a cold), allergic rhinitis-like symptoms (sneezing, runny, or blocked nose during the past 12 months when the child did not have a cold or the flu), and atopic dermatitis (red and itchy skin rash that appeared and disappeared for at least 6 months). On the basis of anthropometric measures performed during the medical examination, overweight was defined as a weight-for-length value of greater than the 95th percentile¹⁵ by using international age- and sex-specific tables as references.¹⁶ Information about upper and lower respiratory tract infections during the first 18 months of life was also collected from questionnaires given to parents.

Biomarkers

Biological markers measured at age 18 months were eosinophilia, total IgE levels, and allergen-specific IgE levels. Total and allergen-specific IgE levels are markers of atopy, and eosinophilia is commonly found in conjunction with atopic manifestations. Full blood count was determined, and blood eosinophilia was measured by using flow cytometry (Beckmann Coulter, Miami, Fla), whereas total IgE levels were measured with ImmunoCAP (Phadia, Uppsala, Sweden). Blood eosinophilia was defined as a concentration of 470 eosinophils/mm³ or greater, and an increased total IgE level was defined as a concentration of 45 U/mL or greater.¹⁷ These thresholds were selected based on previous determinations for patients of comparable age (toddlers <30 months old)¹⁷ and consistency with thresholds used in other studies, ranging from 30 to 51 U/mL for total IgE levels¹⁸⁻²⁰ and 400 to 600 eosinophils/mm³ for eosinophilia.^{21,22} Sensitization to inhalant allergens (house dust mites, pets, grass pollens, weed pollens, tree pollens, and mold) and food

allergens (egg white, cow's milk, peanut, mustard, fish, wheat, soy, hazelnut, sesame, shrimp, beef, and kiwi) was analyzed by using ImmunoCAP Phadia-top and Trophatop fx26, fx27, and fx28 (Phadia), with a detection limit set at 0.35 U/mL. Sensitized infants were tested to identify specific allergens. Different markers of allergenic sensitization were considered: sensitization to any allergen, to food allergens, and to inhalant allergens, each defined by the presence of a specific IgE concentration of 0.35 U/mL or greater.²³ We also considered the multiplicity and strength of sensitization. Multiple sensitizations were defined as at least 2 sensitizations. A specific IgE concentration of greater than 0.70 U/mL for at least 1 allergen was used to define the strength of the sensitization; a threshold of 0.70 U/mL was used to distinguish low from high levels of sensitization.^{24,25}

Potential risk factors

Information about parental history of disease and sociodemographic factors was collected at study enrollment. Parents were asked about their history of asthma, allergic rhinitis, and eczema. Sociodemographic factors included sex, siblings, and socioeconomic status. Socioeconomic status was determined based on the highest level of occupation of the parents. Occupations were categorized as low (low-level white-collar workers, blue-collar workers, and the unemployed), intermediate (intermediate white-collar workers, craftsmen, and shopkeepers), and high (high-level, white-collar workers). Information about behavioral and environmental factors was collected from telephone interviews of parents when children were 1 month old; this information was regularly updated by questionnaires mailed when children were 3, 6, 9, 12, and 18 months old. Behavioral factors assessed included duration of exclusive maternal breast-feeding, prenatal and postnatal exposure to tobacco smoke, day care attendance, and stressful events. Children who were overweight (considered a behavioral factor) were identified at the examination at 18 months. Environmental factors included potential sources of chemical pollution in the household environment^{26,27}: gas for cooking, heating, or both; cleaning sprays; odorous compounds used in home repairs; newly painted walls or replaced floor covers; particle-board furniture; or parquet floors varnished within 12 months. Potential sources of biological pollution were also examined^{28,29}: presence of molds (reported visible molds, moldy smell, or both), pets, or cockroaches in the home and factors related to house dust mite exposure, such as cleaning habits (frequency of mopping and vacuum cleaning), carpet-covered floor, age of the bedding, and use of an anti-dust mite cover on the mattress. Additional information about environmental variables is presented in the **Methods** section in this article's Online Repository at www.jacionline.org.

Statistical analysis

Respiratory and allergic phenotypes were determined from data collected at the 18-month examination; data were analyzed by using multiple correspondence and latent class analyses. Multiple correspondence analysis was used to identify the most relevant variables for cluster analysis among clinical outcomes (frequency of wheezing episodes, limitation of daily activities, sleep disturbance because of wheeze, nocturnal dry cough, allergic rhinitis-like symptoms, and atopic dermatitis), use of health care resources (use of inhaled bronchodilators and inhaled corticosteroids, medical visits, emergency department visits, and hospitalizations for respiratory disorders), and biomarkers of atopy (total IgE level ≥ 45 U/mL, blood eosinophilia ≥ 470 eosinophils/mm³, allergenic sensitization ≥ 0.35 U/mL, allergenic sensitization ≥ 0.70 U/mL, and multiple sensitizations). Latent class analysis was then performed based on the selected variables. The optimal number of clusters was determined by comparing models with 3, 4, 5, and 6 clusters with regard to statistical information criteria,³⁰ notably the Bezdek partition coefficient,³¹ which is based on latent class membership probabilities (the closer to 1, the better the partition). Each model was estimated 10 times to select the one model of the 10 corresponding to the greatest likelihood.³²

We tested the reproducibility of the resulting classification by repeating the analysis with data from 10 random samples of 80% of the initial population. Risk factors associated with each phenotype were investigated by using a

TABLE I. Characteristics of the study cohort compared with the entire PARIS cohort

	Analyzed subcohort (n = 1831)	Children of the original birth cohort not included in the analysis (n = 2346)	P value
Sex			.119
Male	910 (49.7)	1223 (52.1)	
Female	921 (50.3)	1123 (47.9)	
Gestational age (d), mean $\pm$ SD	278 $\pm$ 8	279 $\pm$ 8	.409
Birth weight (kg), mean $\pm$ SD	3.39 $\pm$ 0.40	3.41 $\pm$ 0.39	.360
Siblings			.192
No	1050 (57.4)	1298 (55.3)	
Yes	781 (42.7)	1048 (44.7)	
Parental history			
Asthma	339 (18.5)	444 (18.9)	.735
Allergic rhinitis	656 (35.8)	774 (33.0)	.055
Eczema	311 (17.0)	415 (17.7)	.551
Socioeconomic status			<.001
High	1202 (66.0)	1322 (56.4)	
Intermediate	479 (26.2)	703 (30.0)	
Low	144 (7.9)	321 (13.7)	
Geographic origin of the parents			<.001
France	1357 (74.1)	1564 (66.7)	
≥ 1 Parent of another origin	474 (25.9)	782 (33.3)	
Prenatal exposure to active maternal smoking	202 (11.0)	279 (11.9)	.391
Parental smoking at home	375 (20.7)	492 (23.4)	.046

Except for birth weight and gestational age, all values shown are numbers (percentages). Values in boldface are significant.

polytomous regression model. Factors associated with a *P* value of less than .20, as well as risk factors described in the literature,⁷ were introduced into the model. The final model was obtained by eliminating variables associated with phenotypes with a *P* value of greater than .10. Results are shown with adjusted odds ratios and 95% CIs. Respiratory and allergic phenotypes were defined by using R software version 2.11.1; risk analysis was performed with Stata software, version 9.1 (StataCorp, College Station, Tex). Additional information about statistical analyses is available in the [Methods](#) section in this article's Online Repository.

RESULTS

Study population

A total of 2012 children were examined when they were 18 months old; data from 1831 with available information on health outcomes and atopy were used in the final analysis. The mean age of the children was 19 ± 2 months, and there were equal numbers of girls and boys. Parents of the children included in the analysis were more likely to have high socioeconomic status and to be nonsmokers compared with those not included and to originate from France ([Table I](#)). Having at least 1 parent who originated from another European country (7.1% of the families in the original cohort) or from Sub-Saharan Africa (4.0%) did not influence study inclusion; infants with 1 parent from northern Africa (11.0%) were less likely to be included in the analysis (32.5% vs 45.2%, *P* < .001). Moreover, there was a trend toward a greater inclusion of children whose parents had a history of allergic rhinitis. Children included in the analysis did not differ from others in the PARIS cohort with regard to sex, gestational age, birth

weight, siblings, exposure to parents' tobacco smoke, or parental history of asthma and eczema.

Selection of variables

Respiratory and allergic variables considered in this analysis are presented in [Table II](#). Wheeze was the most reported symptom, with a prevalence of 28.0%, followed by atopic dermatitis (15.5%), allergic rhinitis–like symptoms (9.2%), and nocturnal dry cough (6.7%). Allergenic sensitization was reported in 301 (16.4%) infants, and sensitization to food allergens was more common (*n* = 276) than sensitization to inhalant allergens (*n* = 53). The main food allergens involved were cow's milk (*n* = 139), egg whites (*n* = 123), hazelnuts (*n* = 43), and peanuts (*n* = 34); the main inhalant allergens were house dust mite (*n* = 22) and cat (*n* = 20) allergens. Multiple correspondence analysis identified 2 dimensions that accounted for 38% of the variability of the data: the first was related to the severity of respiratory outcomes and the second to variables related to the atopic status of the child (see [Table E1](#) in this article's Online Repository at www.jacionline.org). Eight relevant variables were selected for use in the latent class model: frequency of wheezing episodes, nocturnal dry cough, allergic rhinitis–like symptoms, atopic dermatitis, hospital-based care, use of inhaled corticosteroids, use of inhaled bronchodilators, and sensitization of greater than 0.70 U/mL.

Characteristics of phenotypic clusters

Classifications into 3, 4, 5, and 6 groups were compared to identify a classification system that met meaning and statistical requirements. Classification into 3 groups was not informative because it reflected only 1 dimension, the severity of respiratory outcomes. Classification into 6 groups was discarded because the subgroups were too small in size. Finally, statistics guided the choice between models of 4 and 5 latent classes. The model of 4 latent classes had a better partition than that of 5 latent classes; corresponding values of the Bezdek coefficient were 0.90 and 0.73, respectively.

Characteristics of the phenotypic clusters are presented in [Table II](#). We created a reference group, and the 3 respiratory and allergic phenotypes were named “atopic severe,” “nonatopic severe,” and “mild.” The reference group included 69.4% of the population and was characterized by a low prevalence of respiratory and allergic outcomes. The other 3 clusters largely comprised children with wheezing (83% to 93%, depending on the cluster). The mild phenotype comprised children with occasional mild wheezing, whereas children assigned to the other 2 clusters had signs of severity.

Disturbance in daily activities or sleep because of wheeze was reported for 34% of the children with the nonatopic severe phenotype, and hospital-based care was required for 29% of the children with the atopic severe phenotype. Although children with the atopic severe phenotype had a high prevalence of atopy (61.0% with allergenic sensitization), children with the nonatopic severe phenotype had a high prevalence of recurrent respiratory tract infections (48.6%) and nocturnal dry cough (19.8%).

In agreement with results from the entire study sample, the main food allergens involved in sensitization of infants with the atopic severe phenotype were cow's milk, egg white, and hazelnut, and the main inhalant allergens were cat and house dust mites

TABLE II. Characteristics of the respiratory and allergic phenotypes of infants participating in the 18-month health examination of the PARIS birth cohort

	Total	Phenotypes			
		Reference group*	Atopic severe phenotype	Nonatopic severe phenotype	Mild phenotype
Health outcomes during the past 12 mo	1831	1271 (69.4)	59 (3.2)	195 (10.7)	306 (16.7)
Wheeze†					
Occasional	463 (25.4)	0	44 (77.2)	134 (69.1)	285 (94.7)
Recurrent	48 (2.6)	1 (0.1)	5 (8.8)	42 (21.7)	0
Limitation of daily activities	99 (5.4)	0	14 (23.7)	52 (26.7)	33 (10.8)
Sleep disorders	98 (5.4)	0	13 (22.0)	47 (24.1)	38 (12.4)
Nocturnal dry cough apart from a cold	121 (6.7)	61 (4.8)	0	38 (19.8)	22 (7.2)
Allergic rhinitis-like symptoms	166 (9.2)	104 (8.3)	7 (12.3)	23 (12.2)	32 (10.6)
Atopic dermatitis	283 (15.5)	193 (15.3)	46 (78.0)	1 (0.1)	43 (14.1)
Upper respiratory tract infections (apart from colds)					
1-3	827 (47.2)	557 (45.8)	30 (50.9)	92 (49.7)	148 (51.0)
≥4	311 (17.8)	197 (16.2)	11 (18.6)	49 (26.5)	54 (18.6)
Lower respiratory tract infections					
1-3	678 (37.1)	325 (25.6)	36 (61.0)	110 (56.4)	207 (67.9)
≥4	110 (6.0)	27 (2.1)	9 (15.3)	55 (28.2)	19 (6.2)
Use of health care resources during the past 12 mo					
Antiasthma medications		4 (0.3)	59 (100)	195 (100)	137 (44.9)
Inhaled bronchodilators	384 (21.0)	0	56 (94.9)	195 (100)	133 (43.6)
Inhaled corticosteroids	244 (13.3)	4 (0.3)	47 (79.7)	190 (97.4)	3 (1.0)
Hospital-based care because of respiratory disorders‡		6 (0.5)	17 (28.8)	37 (19.0)	15 (4.9)
Emergency department visit	64 (3.5)	4 (0.3)	14 (23.7)	34 (17.5)	12 (4.0)
Admission to hospital	35 (1.9)	2 (0.2)	11 (18.6)	18 (9.3)	4 (1.4)
Biological markers of atopy at 18 mo of age					
Total IgE (U/mL), geometric mean (95% CI)	15 (14-16)	14 (13-15)	48 (31-75)	14 (12-18)	16 (14-19)
Total IgE ≥45 U/mL	402 (22.0)	258 (20.3)	33 (57.9)	40 (20.5)	71 (23.2)
Blood eosinophilia (eosinophils/mm ³), geometric mean (95% CI)	214 (206-222)	213 (204-222)	299 (253-354)	196 (169-227)	215 (196-237)
Eosinophilia ≥470 eosinophils/mm ³	231 (12.9)	141 (11.3)	16 (28.1)	28 (14.7)	46 (15.4)
Allergic sensitization	301 (16.4)	192 (15.1)	36 (61.0)	17 (8.7)	56 (18.3)
Food allergens	276 (15.1)	177 (14.0)	33 (55.9)	15 (7.8)	51 (16.7)
Inhalant allergens	53 (2.9)	35 (2.8)	8 (13.6)	2 (1.0)	8 (2.6)
Allergic sensitization ≥0.70 U/mL	177 (9.7)	119 (9.4)	29 (49.2)	0	29 (9.5)
Sensitization to ≥2 allergens	113 (6.2)	70 (5.5)	22 (37.3)	3 (1.5)	18 (5.9)

Except for concentrations of total IgE and eosinophil numbers, all values shown are numbers (percentages). Variables in boldface are those introduced in the latent class model.

*The reference group is the less symptomatic group.

†Wheeze was defined according to parental report: occasional wheeze is defined as 1 to 3 episodes during the past 12 months, and recurrent wheeze is defined as greater than 3 episodes during the past 12 months.

‡Hospital-based care because of a bronchiolitis, wheezy bronchitis, or asthma crisis during the previous 12 months.

(further details are shown in Table E2 in this article's Online Repository at www.jacionline.org). Fig 1 represents the clusters identified based on scores of atopy and severity.

Validation of the classification

The mean probabilities for children in the reference, atopic severe, nonatopic severe, and mild phenotype groups to be classified to another cluster were 1.5%, 15.3%, 10.4%, and 21.7%, respectively (see Fig E1 in this article's Online Repository at www.jacionline.org). The analysis was repeated with 10 randomly selected subsamples. In half of the cases, the results were similar to those for the entire study sample. In the other 5 subsamples the 2 severe phenotype groups were combined into a single group, and there was a new group that was characterized by cutaneous symptoms rather than respiratory disorders. Sensitivity analyses showed that sensitization to allergen concentrations of greater than 0.70 U/mL and multiple sensitizations

were interchangeable in the model and that including infants with some missing data (3.8%) in the analysis did not affect results.

Risk factors associated with different phenotypes

Lifestyle and household features of the children included in the analysis are described in Table III. In our study sample most families lived in an apartment (91.9%), and there were low rates of parental smoking and pets in the home; 8.1% of the children in the study sample were overweight.

The different phenotypes had common risk factors, such as male sex and day care attendance, but they also had specific risk factors (Table IV). Parental history of asthma and/or allergic rhinitis and/or eczema were associated with the atopic severe phenotype; a parental history of asthma was strongly associated with this phenotype, with an odds ratio of 1.95 (95% CI, 1.06-3.58). Considering environmental factors, postnatal exposure to parents'

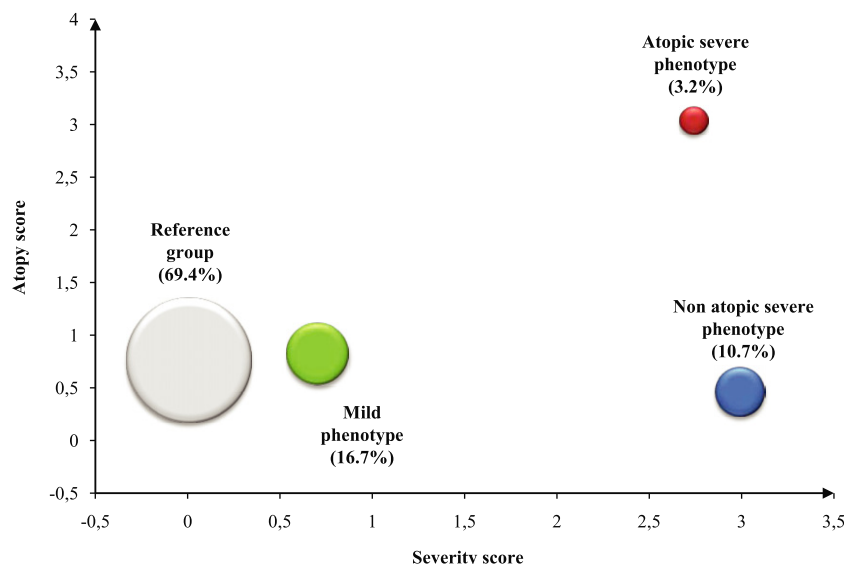


FIG 1. Respiratory and allergic phenotypes at 18 months based on severity and atopy in the PARIS birth cohort. Percentages represent the percentage of the total study sample. The disk area is proportional to the prevalence of the phenotype. The reference group refers to the less symptomatic phenotype, including 69.4% of the study population. The *severity score* is defined as the sum of the variables "recurrent wheeze," "limitation of daily activities," "sleep disturbance," "visit to the emergency department of the hospital," "admission to the hospital," "use of inhaled bronchodilators," and "use of inhaled corticosteroids." The *atopy score* is defined as the sum of the variables "atopic dermatitis," "eosinophilia ≥ 470 eosinophils/mm³," "total IgE level ≥ 45 U/mL," "allergenic sensitization," "allergenic sensitization ≥ 0.70 U/mL," and "multiple sensitizations."

tobacco smoke and the presence of molds in the home more than doubled the risk for severe atopic disorders. The nonatopic severe phenotype was most strongly associated with day care attendance, although it was also associated with the presence of siblings. Overweight children were most likely to have the mild phenotype. Children exposed to indoor renovations were most likely to have the mild phenotype, which also tended to be associated with post-natal exposure to tobacco smoke.

DISCUSSION

Our study identified 4 phenotypes of respiratory disease in children at 18 months of age; these differ in atopic features, severity, and risk factors. The strengths of the study include its large sample size and the unique nature of the sample (a birth cohort of nearly 2000 children). The medical examination provided a reliable assessment of different health outcomes, especially atopy and anthropometric parameters. The data were collected consistently and accurately because trained pediatricians administered the questionnaires. Responses to questions about symptoms that occurred during the past 12 months could have been affected by recall bias. Although parents are likely to remember health outcomes in the past year because of the young age of their child, they might not remember all medications. We therefore asked parents to bring all prescriptions issued in the first 18 months of their children's lives.

Regrettably, only 45% of the original birth cohort participated in the health examination, and compared with nonparticipants, participating parents were of higher socioeconomic status, a difference also observed in the overall PARIS cohort.¹⁴ Participation of subjects of higher economic status is commonly observed in many studies and could cause classification bias because

socioeconomic status is related to many lifestyle and household environment characteristics.³³ In our study infants from the lower socioeconomic class were more likely to be exposed to parental smoking, furred pets, cockroaches, and daily use of cleaning sprays, whereas children from the higher socioeconomic class were breast-fed longer. Higher rates of participation were expected from parents who had personal history of asthma, allergic rhinitis, or eczema because of increased awareness of the disease. Except for the trend toward greater participation by parents with personal history of allergic rhinitis, there was no significant difference between participating and nonparticipating parents, indicating minor selection bias.

To gain a comprehensive overview of the phenotypes of respiratory diseases, we considered different signs of bronchial obstruction and allergic disorders (eg, atopic dermatitis and allergen-specific sensitization). We also investigated use of health care resources to assess the severity of respiratory disorders. Latent class analysis was used because it is particularly suitable for heterogeneous diseases, such as asthma.^{8,10,34,35} The consistency of the classifications is supported by the good separation between clusters (shown by the high degree of membership in each cluster) and the differences in risk factors among clusters.

We focused our analysis on sensitization to allergens at concentrations of greater than 0.70 U/mL, which was the variable most strongly linked to the atopy dimension in the preliminary multiple correspondence analysis.²⁴ We excluded weak sensitizations in our study because results from longitudinal follow-up analysis of the Multicentre Allergy Study demonstrated that weak sensitizations at age 2 years were likely to disappear in childhood.³⁶ We considered multiple sensitizations in another analysis because Simpson et al¹¹ showed that multiple early

TABLE III. Lifestyle and household features of infants participating in the 18-month health examination of the PARIS birth cohort

Lifestyle characteristics	
Maternal breast-feeding	
No	310 (17.0)
<3 mo	1001 (54.7)
≥3 mo	518 (28.3)
Exposure to parental smoking at home	
No	1433 (79.3)
1-10 cigarettes/d	88 (10.4)
≥10 cigarettes/d	187 (10.3)
Day care attendance	664 (63.4)
Stressful event during the first 18 mo of life	553 (30.5)
Parents' rupture	30 (1.7)
Discharge of one of the parents	88 (4.9)
Disease or death of a close relative	477 (26.3)
Overweight*	146 (8.1)
Household characteristics related to chemical pollution	
Use of gas for cooking and/or eating	1088 (60.1)
Indoor renovation activities	1066 (58.5)
During the year before birth	773 (42.7)
During the first 18 mo of life	433 (23.8)
Particle-board furniture at less than 1 y	
In the home	873 (48.3)
In the child's bedroom	576 (31.8)
Varnished parquet floor at less than 1 y	
In the home	349 (19.3)
In the child's bedroom	289 (16.0)
Use of cleaning sprays	
Rarely	1535 (85.0)
Once a week	174 (9.6)
Almost daily	97 (5.4)
Do-it-yourself activities with odorous compounds	400 (22.0)
Household characteristics related to biological pollution	
Presence of molds	337 (18.6)
Presence of pets	348 (19.1)
Cat	232 (12.7)
Dog	75 (4.1)
Rodent	36 (2.0)
Presence of cockroaches	154 (8.5)
Anti-dust mite-covered mattress	1297 (71.2)
New bedding	794 (43.6)
Carpet covered floor in the child's bedroom	490 (27.1)
Vacuum cleaning	
Rarely	139 (7.7)
Once a week	1228 (68.0)
Almost every day	440 (24.3)
Wet mopping	
Rarely	295 (16.3)
Once a week	1209 (67.0)
Almost every day	301 (16.7)

All values shown are numbers (percentages). Information about lifestyle and household characteristics comes from the prospective questionnaire-based follow-up.

*Body weight/body length ratio of the 95th percentile or greater according to World Health Organization standards.

sensitizations are a marker of severity, especially of the risk for hospitalization caused by a crisis.

One strength of our study is that we collected detailed and regularly updated information on early environmental exposures. We also performed telephone interviews with parents of infants at 1 month of age to reduce classification bias. Although environmental and behavioral data were self-reported, previous studies²⁶⁻²⁹ have determined the effects of different lifestyle and household environment features on levels of chemical and

biological pollutants, as measured in a random subsample of 196 children of the PARIS birth cohort.

Respiratory and allergic phenotypes

Unsupervised methods have been used mostly in epidemiologic studies to analyze the time course of asthma symptoms and sensitization during childhood and to identify prognostic factors.^{8,10,11,35} We used these methods to explore the heterogeneity of respiratory and allergic outcomes in children, especially with regard to atopy. In addition to a reference group, we identified 3 groups of children with wheezing discriminated by severity and atopy. The predominance of wheezing among all phenotypes results, in part, from the use of antiasthma medications in the analysis; wheezing is the main symptom considered in asthma management guidelines.^{6,7,37}

We identified a severe phenotype group, in which were included almost 90% of the children with recurrent wheezing, confirming this as a marker of asthma severity.⁷ We also identified a severe phenotype that is characterized by atopy, but only 9% of the children in this group have recurrent wheezing. These findings confirm, by using an unsupervised approach, the relationship between atopy and severe wheeze (which requires inhaled corticosteroids or hospital-based care) at 18 months of age, as previously indicated by data from the PARIS cohort.³⁸ Our findings indicate that more attention should be given to the risk of severe respiratory outcomes in infants with atopic dermatitis, sensitization to allergens at concentrations of greater than 0.70 U/mL, or multiple sensitizations. Unlike the prevalence of atopic dermatitis, the prevalence of allergic rhinitis-like symptoms did not differ among phenotypes, probably because this disorder is a challenge to diagnosis in infants.³⁹

Risk factors associated with the identified phenotypes

Differences in patterns of risk for each phenotype helped us to solve 2 challenges to clustering methods.⁴⁰ First, these differences supported the validity of the classification, and second, they made it possible to formulate hypotheses about the cause of phenotypes. Respiratory tract infections are the main cause of wheezing in early life.⁴¹ Their role in the development of the nonatopic severe phenotype is clear based on the prevalence of respiratory tract infections in this group and by the association between this phenotype and siblings and day care attendance, factors that reflect exposure to viruses.

Genetic factors are likely to contribute to the atopic severe phenotype, which is associated with parents' history of asthma, allergic rhinitis, and/or eczema. Environmental factors are also involved in this phenotype, particularly exposure to parents' tobacco smoke and the presence of molds in the home. Epidemiologic data support the ability of mold exposure to increase the severity of asthma in infants,⁴² older children,⁴³ and adults.⁴⁴

The mild phenotype was associated with exposure to inflammatory factors, such as chemical pollutants (released by materials used for indoor renovations) and being overweight. The risk of respiratory disease in overweight subjects is thought to result from the release of inflammatory mediators from visceral adipose tissue.⁴⁵ The lack of association of these factors with the other phenotypes was unexpected because inflammatory

TABLE IV. Risk factors associated with different respiratory and allergic phenotypes

	Reference group (n = 1271)		Atopic severe phenotype (n = 59)		Nonatopic severe phenotype (n = 195)			Mild phenotype (n = 306)		
	No. (%)	No. (%)	Adjusted OR* (95% CI)	P value†	No. (%)	Adjusted OR* (95% CI)	P value†	No. (%)	Adjusted OR* (95% CI)	P value†
Sex										
Female	677 (53.3)	19 (32.2)	1		80 (41.0)	1		145 (47.4)	1	
Male	594 (46.7)	40 (67.8)	2.60 (1.46-4.62)	.001	115 (59.0)	1.74 (1.27-2.40)	.001	161 (52.6)	1.45 (1.12-1.90)	.006
Parental history of asthma, allergic rhinitis, and/or eczema										
No	601 (47.3)	17 (28.8)	1		82 (42.1)	1		138 (45.1)	1	
Yes	670 (52.7)	42 (71.2)	2.31 (1.28-4.16)	.005	113 (58.0)	1.21 (0.88-1.66)	.247	168 (54.9)	1.08 (0.83-1.40)	.569
Overweight at age 18 mo‡										
No	1167 (93.1)	53 (89.8)	1		176 (91.2)	1		264 (87.7)	1	
Yes	86 (6.9)	6 (10.2)	1.51 (0.61-3.73)	.376	17 (8.8)	1.22 (0.69-2.14)	.490	37 (12.3)	1.83 (1.19-2.80)	.006
Siblings										
No	743 (58.5)	36 (61.0)	1		99 (50.8)	1		172 (56.2)	1	
Yes	528 (41.5)	23 (39.0)	0.87 (0.50-1.52)	.635	96 (49.2)	1.43 (1.04-1.96)	.028	134 (43.8)	1.09 (0.83-1.42)	.528
Presence of molds										
No	1034 (82.5)	41 (69.5)	1		152 (78.4)	1		245 (80.9)	1	
Yes	219 (17.5)	18 (30.5)	2.01 (1.11-3.62)	.021	42 (21.7)	1.34 (0.91-1.97)	.138	58 (19.1)	1.11 (0.79-1.55)	.556
Day care attendance										
No	884 (69.9)	30 (50.9)	1		93 (47.7)	1		151 (49.8)	1	
Yes	381 (30.1)	29 (49.2)	2.20 (1.28-3.76)	.004	102 (52.3)	2.63 (1.92-3.60)	<.001	152 (50.2)	2.41 (1.85-3.13)	<.001
Exposure to parental smoking at home										
No	1003 (80.1)	44 (74.6)	1		151 (77.8)	1		235 (77.6)	1	
1-10 cigarettes/d	137 (10.9)	5 (8.5)	0.86 (0.33-2.26)	.759	18 (9.3)	0.80 (0.47-1.37)	.414	28 (9.2)	0.85 (0.55-1.34)	.493
≥10 cigarettes/d	112 (9.0)	10 (17.0)	2.43 (1.12-5.25)	.024	25 (12.9)	1.44 (0.86-2.40)	.168	40 (13.2)	1.50 (0.98-2.29)	.064
Indoor renovation activities since birth										
No	977 (77.2)	43 (72.9)	1		160 (82.1)	1		209 (69.0)	1	
Yes	288 (22.8)	16 (27.1)	1.42 (0.77-2.60)	.264	35 (18.0)	0.74 (0.49-1.11)	.143	94 (31.0)	1.55 (1.16-2.07)	.003

Phenotypes identified in infants participating in the 18-month health examination of the PARIS birth cohort determined based on data collected during the health examination at 18 months of age. Information about risk factors came from the prospective questionnaire-based follow-up.

OR, Odds ratio.

*Odds ratio adjusted for duration of exclusive maternal breast-feeding; birth weight; prenatal exposure to active maternal smoking; parents' socioeconomic status; presence of a cat in the home; use of gas for cooking, heating or both; and presence of cockroaches in the home.

†P value in the multivariate model.

‡Body weight/body length ratio of the 95th percentile or greater according to World Health Organization standards.

processes are not specific, contrary to allergic mechanisms. Strong risk factors identified for severe phenotypes might explain this absence of effect. Most of the children with the atopic severe phenotype were boys or had a parental history of asthma, whereas factors related to respiratory tract infections were the strongest risk factors for the nonatopic severe phenotype. Other studies reported that environmental pollution was a greater risk factor for nonatopic asthma than atopic asthma in schoolchildren.^{46,47}

Our results regarding severity and overweight status are similar to those of Halder et al,⁴⁸ who performed a cluster analysis of adults with asthma. In addition to a phenotype of benign asthma, they identified 3 phenotypes of asthma with more symptoms and specific features of eosinophilic inflammation and obesity. Consistently with our findings, they associated obesity with a mild noneosinophilic phenotype, whereas the other 2 phenotypes differ with regard to their atopic status. These phenotypes require detailed mechanistic assessment in endotyping studies.⁴⁹

The respiratory and allergic phenotypes identified in this study indicate a risk for severe exacerbation in children with atopy or recurrent respiratory tract infections. Infants with wheezing should therefore be tested for atopy and protected against exposure to respiratory irritants and molds and becoming overweight. The clinical relevance of these findings requires validation in other epidemiologic settings and through long-term follow-up analyses.

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Clinical implications: Atopy should be taken into account when assessing the risk of severe exacerbations (those that require hospital-based care) in wheezing infants. Precautions should be taken to prevent exposures to respiratory irritants and molds and to keep children from becoming overweight.

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METHODS

Details about environmental variables

Day care attendance means that the child attended collective day care at least once before the age of 18 months. The presence of molds was established on the basis of parental report of visible molds, a moldy smell, or both. Indoor renovation activities refers to changes of walls coating, floor coating, or both in the home. The renovated room or rooms was or were specified. In the first environmental questionnaire parents were asked whether they undertook such renovations in the past 12 months. This question defined the variable "indoor renovations before the birth of the child." Then parents were asked regularly (at 3, 6, 9, 12, and 18 months) whether they undertook new renovation activities in the home. Parental report of renovation activities at least once during this follow-up defined the variable "indoor renovation activities during the first 18 months of the child."

Details about statistical analysis

The determination of respiratory and allergic phenotypes was based on the data collected during the health examination at age 18 months and used multiple correspondence analysis and latent class analysis.

Multiple correspondence analysis. The principle and its implementation are as follows:

Principle. Multiple correspondence analysis enables a general view of the relationships between variables in large databases. It is the counterpart to principal component analysis for categorical data. The basic dataset for multiple correspondence analysis is an individuals $\times$ variables table, in which each variable has a finite number of categories. Multiple correspondence analysis provides a multidimensional representation of the dependence between the rows and columns of the table as a cloud of points. The cloud is projected on axes that cross at the barycenter of the cloud. The eigenvalue corresponding to each axis is the variance of the projected cloud on the axis.^{E1}

Implementation. Here multiple correspondence analysis was first used to identify the most relevant variables to select as input for cluster analysis between clinical outcomes, use of health care resources, and biomarkers. Multiple correspondence analysis was performed by using the R FactoMineR package. Axes accounting for at least 10% of the variance were analyzed, and variables that contributed the most to each axis were selected as input for cluster analysis.

Latent class analysis. The principle and its implementation are as follows:

Principle. The central idea of latent class analysis is to fit a model for measuring latent (unobserved) categorical variables by means of a set of observed categorical variables; these observed variables are considered to be indicators of the underlying concepts, in this case the phenotypes.^{E2} Latent class analysis is based on the expectation-maximization algorithm, which proceeds iteratively to maximize the overall log likelihood. A number of clustering methods result in crisp clusters (ie, nonoverlapping clusters). An important difference of latent class analysis is that cases are not absolutely assigned to classes but have a probability of membership for each class. Although the model does not automatically determine the number of latent classes in a given dataset, it does offer a variety of statistics that can be used to make a theoretically and empirically sound assessment. In addition, the iterative nature of the expectation-maximization algorithm makes it possible to estimate the latent

class model, even when some of the observations on the manifest variables are missing.

Implementation. A latent class analysis was performed after the data selection by using multiple correspondence analysis to identify and characterize clusters of similar cases. The R poLCA package was used. Observations with missing data were retained in the algorithm. Every subject was assigned to the latent class in which he or she had the highest membership probability. The optimal number of clusters was determined by comparing models with 3, 4, 5, and 6 clusters with regard to statistical information criteria, such as the Bayesian information criterion, the Akaike information criterion,^{E2} and the Bezdek partition coefficient.^{E3} This latter criterion is based on latent class membership probabilities. Its values range between 1 and $1/nc$, where nc is the number of clusters. The closer the coefficient is to 1, the better the partition. On the contrary, a value close to $1/nc$ indicates that there is no clustering tendency in the considered dataset or that the clustering algorithm failed to reveal it.^{E4} Each model was estimated 10 times to select the one model of the 10 corresponding to the greatest likelihood.^{E5}

Validation of the classification. Different aspects of the reliability and validity of the classification were assessed in this study:

- First, we analyzed posterior membership probabilities to ensure the high degree of membership in each cluster.
- Then we tested the reproducibility of the resulting classification by repeating the analysis in 10 random samples of 80% of the initial population.
- Sensitivity analyses were conducted by changing parameters introduced into the model. For instance, we compared the classifications obtained with and without taking into account missing data. The variable representative of atopy was also changed in the model.
- Finally, demonstration of differences in risk factors between groups is a way to support the existence of different groups in the population considered. Here risk factors associated with the identified phenotypes were investigated by using a polytomous regression model. Factors associated with a P value of less than .20, as well as risk factors described in the literature,^{E6} were introduced into the model. The final model was obtained by eliminating variables associated with phenotypes with a P value of greater than .10. Results are shown with adjusted odds ratios and their 95% CIs. Risk analysis used Stata software, version 9.1 (StataCorp).

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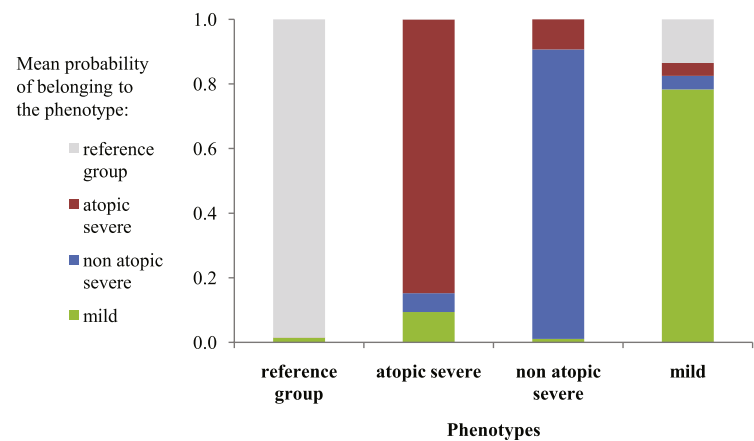


FIG E1. Mean membership probabilities in each cluster. Clusters were determined by using latent class analysis. An important specificity of latent class analysis is that cases are not absolutely assigned to classes but have a probability of membership for each class. We estimated, for each cluster, the mean probability of belonging to the other clusters. The figure shows that the mean probabilities of being classified in another cluster were low, ranging from 1.5% to 21.7%. This result reflects the high degree of membership for each cluster.

TABLE E1. Description of the dimensions in multiple correspondence analysis

Variable_category	Dimension 1	Dimension 2
Atopic dermatitis_No	0,007376	0,306440
Atopic dermatitis_Yes	0,040867	1,697748
Nocturnal dry cough_No	0,046952	0,005920
Nocturnal dry cough_Yes	0,668651	0,084312
Wheezing_No	4,238897	0,028793
Wheezing_Occasional	6,895262	0,011391
Wheezing_Recurrent	7,387277	0,320482
Nocturnal awakening because of wheeze_No	0,667617	0,019468
Nocturnal awakening because of wheeze_Yes	11,994843	0,349773
Limitation of daily activities because of wheeze_No	0,691102	0,024588
Limitation of daily activities because of wheeze_Yes	13,026469	0,463455
Allergic rhinitis-like symptoms_No	0,026873	0,002463
Allergic rhinitis-like symptoms_Yes	0,272944	0,025017
Inhaled bronchodilators_No	3,700642	0,034365
Inhaled bronchodilators_Yes	14,662718	0,136160
Inhaled corticosteroids_No	2,170542	0,017020
Inhaled corticosteroids_Yes	14,519164	0,113853
Emergency department visit_No	0,362428	0,010166
Emergency department visit_Yes	9,616033	0,269732
Admission to hospital_No	0,143834	0,034700
Admission to hospital_Yes	7,077474	0,017075
Eosinophilia ≥ 470 eosinophils/mm ³ _No	0,053025	0,325338
Eosinophilia ≥ 470 eosinophils/mm ³ _Yes	0,352868	2,165028
Total IgE ≥ 45 U/mL_No	0,099160	3,193123
Total IgE ≥ 45 U/mL_Yes	0,354639	11,419991
Allergenic sensitization_No	0,063698	4,311928
Allergenic sensitization_Yes	0,334591	22,649470
Sensitization to ≥ 2 allergens_No	0,017596	1,399952
Sensitization to ≥ 2 allergens_Yes	0,282760	22,497230
Allergenic sensitization ≥ 0.70 U/mL_No	0,020968	2,633811
Allergenic sensitization ≥ 0.70 U/mL_Yes	0,202731	25,465660

Dimensions 1 and 2 accounted for 21% and 17%, respectively, of the variance in multiple correspondence analysis. Values shown in the table represent the contribution of the different variables, with details about their categories, to the variance of the dimensions. Variables contributing the most to each dimension were selected as input for cluster analysis. Dimension 1 was characterized by variables related to the severity of respiratory disorders, and the most contributive were the frequency of wheezing episodes and variables related to the use of health care resources ahead of variables related to clinical signs of severity, such as limitation in daily activities and nocturnal awakening related to wheeze. Dimension 2 was characterized by variables related to atopy, and allergenic sensitization of greater than 0.70 U/mL was the most contributive variable.

TABLE E2. Specific allergen sensitization by phenotype

	Phenotype				
	Total (n = 1831)	Reference group* (n = 1271)	Atopic severe phenotype (n = 59)	Non atopic severe phenotype (n = 195)	Mild phenotype (n = 306)
Food allergens	276 (15.1)	177 (14.0)	33 (55.9)	15 (7.8)	51 (16.7)
Cow's milk	139 (7.7)	85 (6.8)	23 (39.7)	5 (2.6)	26 (8.6)
Egg white	123 (6.8)	75 (6.0)	20 (35.1)	4 (2.1)	24 (7.9)
Hazelnut	43 (2.4)	23 (1.9)	9 (47.0)	1 (0.5)	10 (3.3)
Peanut	34 (1.9)	25 (2.0)	5 (8.6)	0	4 (1.3)
Mustard	25 (1.4)	15 (1.2)	6 (10.9)	1 (0.5)	3 (1.0)
Wheat	23 (1.3)	10 (0.8)	7 (12.5)	0	6 (2.0)
Beef	20 (1.1)	11 (0.9)	5 (8.8)	0	4 (1.3)
Sesame	17 (0.9)	8 (0.6)	4 (7.0)	0	5 (1.7)
Soy	16 (0.9)	10 (0.8)	3 (5.4)	0	3 (1.0)
Kiwi	13 (0.7)	8 (0.6)	4 (7.0)	0	1 (0.3)
Fish	5 (0.3)	3 (0.2)	2 (3.6)	0	0
Shrimp	3 (0.2)	2 (0.2)	1 (1.8)	0	0
Inhalant allergens	53 (2.9)	35 (2.8)	8 (13.6)	2 (1.0)	8 (2.6)
<i>Dermatophagoides pteronyssinus</i>	22 (1.2)	17 (1.4)	3 (5.2)	0	2 (0.7)
Cat	20 (1.1)	12 (1.0)	4 (6.9)	0	4 (1.3)
Orchard grass	3 (0.2)	3 (0.2)	0	0	0
<i>Alternaria tenuis</i>	1 (0.1)	0	1 (1.7)	0	0

All values shown are numbers (percentages).

*The reference group is the less symptomatic group.