

## ORIGINAL ARTICLE

# Cough and dyspnoea may discriminate allergic and infectious respiratory phenotypes in infancy

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## Keywords

allergy; asthma; cluster analysis; phenotype; preschool children.

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## Abstract

Asthma symptoms are non-specific during infancy, making the identification of different subgroups among preschool children with early respiratory manifestations an important challenge. We previously used a clustering approach to identify bronchial obstructive phenotypes in 1-yr-old infants from the Pollution and Asthma Risk: an Infant Study (PARIS) birth cohort. In the present study, we examined whether these phenotypes were stable at 3 yr and studied their comorbidity and risk factors. Partitioning around medoids (PAM) method was applied at 1 and 3 yr of age to cluster children according to wheezing, dry night cough, dyspnoea with sleep disturbance and breathlessness. The resulting groups were used to derive phenotypes in 2084 children during their first 3 yr of life. Analysis of associated comorbidity and risk factors was conducted using multinomial logistic regression. PAM groups were similarly defined at both ages so that two respiratory phenotypes were identified between birth and 3 yr: cough phenotype (CP) and dyspnoea phenotype (DP) including 14.1% and 30.7% of children, respectively. CP infants experienced more often allergic features than DP, dominated by respiratory infections. Parental history of allergy, potential allergen exposure and psychosocial factors were associated with CP. Day care centre attendance was more frequent in DP as well as exposure to domestic chemical pollution, suggesting a greater vulnerability to pathogens. Finally, dry night cough and dyspnoea disturbing the sleep appear to be markers of two respiratory profiles potentially allergic and infectious before 3 yr old.

Asthma is a complex and heterogeneous condition often beginning in infancy. It is, however, difficult to diagnose asthma in young children, because lung function measurements such as spirometry are not suitable for this age group, and symptoms are variable and non-specific (1). Wheezing for instance is a quite frequent disorder during the first years of life because of viral respiratory infections, but not all early wheezers develop asthma later in life.

The Tucson Children's Respiratory Study investigated the wheezing occurrence from birth to 3 yr, then during the sixth year, so that never, early-transient, late-onset and persistent wheeze phenotypes were defined (2). Such a classification can only be applied retrospectively, as children need to have reached school age to be assigned to a group. Although these findings have gained widespread acceptance and provided very interesting new insights into the natural history of

respiratory allergic diseases, the identification of phenotypes based on respiratory symptoms at an earlier stage has become an important challenge.

In a previous study, we identified two bronchial obstructive phenotypes during the first year of life of 2632 infants from the Pollution and Asthma Risk: an Infant Study (PARIS) birth cohort using the partitioning around medoids (PAM) method (3). It is unclear whether such phenotypes are specific to only the first year of an infant's life, because the prevalence and coexistence of symptoms may change as children grow older.

The aim of the present study was therefore to replicate the PAM analysis when children were 3 yr old to discover whether they were clustered according to the same symptoms, and to identify respiratory phenotypes during their first 3 yr. We then studied the comorbidity and risk factors associated with these phenotypes.

## Methods

### Population and study design

The PARIS birth cohort enrolled 3840 full-term healthy new-born babies in five Paris maternity hospitals between February 2003 and June 2006. The study protocol is described elsewhere (4). Ethics approval was obtained from the French Ethical Committees and parents provided their written informed consent.

The present study deals with the first 3 yr of follow-up. Data about children's health and their environment/mode of life were gathered by self-administered parental questionnaires completed at 1, 3, 6, 9, 12, 18, 24 and 36 months.

### Health outcomes

Respiratory and allergic symptoms were mostly assessed by core questions from the International Study of Asthma and Allergies in Childhood (5) and the Asthma Multi-centre Infants Cohort Study (6).

Parents were asked whether the child experienced wheezing or whistling in the chest, dry night cough apart from a respiratory infection and attacks of breathlessness. Children were considered as suffering from dyspnoea disturbing the sleep if their parents reported awakenings because of breathing difficulties.

The total number of respiratory infections that occurred during the first 3 yr of life were assessed by questionnaires at all time points. We grouped bronchiolitis and bronchitis as lower respiratory infections (LRIs), whereas upper respiratory infections (URIs) included cold, rhinopharyngitis, laryngitis and tonsillitis.

Parents were also questioned about food reactions, the impact of wheezing on their child's daily life and whether a doctor had ever diagnosed an allergy in their child.

### Other factors

Co-variables that might be associated with the development of asthma and allergies were also recorded.

At maternity hospital, the mother was asked about parental history of asthma, eczema and allergic rhinitis, employment status of parents and maternal smoking during pregnancy. Familial socioeconomic status (SES) was assessed according to the highest parental occupation among the two parents and divided into three categories (low, medium, high).

The domestic environment of the child was first described by phone interview at 1 month of age. Number of cigarettes smoked per day at home, type of bedding, floor and wall coverings, signs of dampness, presence of pets and frequency of cleaning were documented. Breast-feeding, familial events (health problems, separation), day care attendance and any change in home characteristics or lifestyle habits were then assessed by mailed questionnaires at each time point.

## Statistics

In the present study a PAM analysis was first conducted at 1 yr of age on a larger sample than that used previously (3). This new sample comprised all children from the PARIS cohort with complete data at 1 yr. The analysis was then performed at 3 yr. At each time point, bronchial obstructive symptoms in the past 12 months were analyzed as: (i) wheezing, (ii) dry night cough, (iii) dyspnoea disturbing the sleep, (iv) breathlessness. On the basis of the reported frequency, wheezing symptoms were categorized into three classes: none, infrequent (1–3 episodes) and recurrent (>3 episodes). Before entering in the PAM analysis, this variable was standardized by dividing each entry by the range. The three other variables were treated as binary.

Partitioning around medoids is a clustering method used to partition a population into a set of  $k$  groups (7). The algorithm is based on the search for  $k$  representative subjects among the population, the medoids, which minimize the sum of the dissimilarities of the observations to their closest medoid. In our study, starting medoids were not *a priori* specified. Dissimilarities were calculated using the Euclidean distance metric. The number of clusters  $k$  was chosen comparing the silhouette plots for different values of  $k$ . Briefly, a silhouette width  $s(i)$  was defined for each child reflecting how well he/she has been assigned to a cluster. This value varied from  $-1$  (misclassified) to  $+1$  (well classified). A silhouette value around 0 indicated that the subject likely lied between two clusters. The silhouette plot consisted of a bar graph in which each child was represented by a bar of length  $s(i)$ , ranked in decreasing order and showing the children as visually grouped into clusters. The average of all  $s(i)$  indicated how good the overall clustering was. Above 0.70, the entire structure was considered as strong.

Once the PAM analyses were performed, we examined how clustering structures were defined at 1 and 3 yr. Then, the variation in children's classification between the first and the third years of life was studied.

Differences between phenotypes regarding comorbidity as well as lifestyle and environmental factors were investigated using multivariate multinomial logistic regression, compared to a reference group without symptoms. We included variables associated with a  $p$ -value < 0.20 in bivariate analyses or suggested in the literature. Results are shown with adjusted odds ratios (aOR) and their 95% confidence intervals (95% CI). PAM analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Regression analyses were fitted using Stata/SE 9.1 software (StataCorp, College Station, TX, USA). Significance level was 0.05.

## Results

### Population characteristics

Partitioning around medoids analyses were carried out on children without any missing information on bronchial obstructive symptoms: 3081 infants at 1 yr, 2142 at 3 yr. Loss to follow-up at 3 yr was because of moving from the

study area in nearly 30% of the cases. Table 1 shows the general characteristics of the initial population and the analyzed subjects at 1 and 3 yr. Children included in the analyses at both ages were characterized by a higher familial SES than children of the initial cohort not included in the analyses ( $p < 0.001$ ).

### Respiratory phenotypes over the first 3 yr of life

The full silhouette plots obtained with the PAM method at 1 and 3 yr are presented in Fig. 1. At both ages, we opted for a three-group solution which provided a strong clustering structure. Average silhouette widths of the models were, respectively, 0.73 and 0.84. As shown in Fig. 2, data were partitioned in the same way at 1 and 3 yr. Children in the G1 groups all suffered from dry night cough without dyspnoea, whereas all children with dyspnoea disturbing their sleep were allocated to the G2 groups. Dyspnoea was associated with other symptoms in half of the cases. Children assigned to the G0 groups were mainly asymptomatic, without dry night cough or dyspnoea. A few from this group experienced wheezing (14.9% at 1 yr, 4.8% at 3 yr), and G0 wheezers were mainly infrequent wheezers (86.4% at 1 yr and 95.9% at 3 yr).

However, although the clustering structure was stable, all children were not assigned to the same group at 1 and 3 yr. Figure 3 shows how children included in both analyses were redistributed at 3 yr. Sixty four per cent of children stayed in the same group, predominantly because 80% of children belonging to the G0<sub>1</sub> group remained in the G0<sub>3</sub> group. Regarding children of the G1<sub>1</sub> and G2<sub>1</sub> groups, most of them

were no longer symptomatic at 3 yr, and they were, respectively, 21% and 32% likely to remain in the same group at 3 yr.

Considering that the same symptoms partitioned the data set at 1 and 3 yr, children with complete data at both time points were divided into three groups according to the logic of the PAM classifications. Children were assigned to dyspnoea phenotype (DP) if their sleep had ever been disturbed by dyspnoea ( $n = 639$ ). Cough phenotype (CP) included children who had ever experienced dry night cough but never dyspnoea ( $n = 294$ ). The reference group ( $n = 1151$ ) consisted of children neither coughing nor dyspnoeic.

### Comorbidity

Comorbidity associated with CP and DP compared to 'non-symptomatic' children is shown in Table 2. Doctor-diagnosed asthma and nose disorders apart from a cold were significantly associated with both phenotypes. Conversely, doctor-diagnosed eczema and food reactions were only associated with CP. Children of DP showed the highest prevalence of respiratory infections during the first 3 yr of life. We showed that one more URI and LRI increased, respectively, by 7% and 14% the risk of belonging to DP.

When comparing DP and CP by logistic regression, diagnosed asthma tended to be more frequent in DP than in CP (aOR = 1.61,  $p = 0.08$ ), whereas nose disorders were significantly more reported in CP (aOR = 1.58,  $p = 0.005$ ). We found no difference in food reactions, whereas diagnosed eczema was significantly associated with CP (aOR = 1.38,  $p = 0.05$ ). Respiratory infections were statistically more

**Table 1** General characteristics of the study population (PARIS birth cohort)

| Characteristics             | Initial cohort<br>( $n = 3840$ ) | Children included<br>in the PAM analysis<br>at 1 yr ( $n = 3081$ ) | Children included<br>in the PAM analysis<br>at 3 yr ( $n = 2142$ ) | $p^*$  |
|-----------------------------|----------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|--------|
| Gender                      |                                  |                                                                    |                                                                    |        |
| Male                        | 1975 (51)                        | 1583 (51)                                                          | 1092 (51)                                                          | 0.5    |
| Female                      | 1865 (49)                        | 1498 (49)                                                          | 1050 (49)                                                          |        |
| Familial SES†               |                                  |                                                                    |                                                                    |        |
| Low                         | 366 (10)                         | 243 (8)                                                            | 139 (6)                                                            | <0.001 |
| Medium                      | 1080 (28)                        | 832 (27)                                                           | 551 (26)                                                           |        |
| High                        | 2394 (62)                        | 2006 (65)                                                          | 1452 (68)                                                          |        |
| Age of the mother           |                                  |                                                                    |                                                                    |        |
| ≤35 yr                      | 3128 (81)                        | 2529 (82)                                                          | 1729 (81)                                                          | 0.2    |
| >35 yr                      | 712 (19)                         | 552 (18)                                                           | 413 (19)                                                           |        |
| Older siblings              |                                  |                                                                    |                                                                    |        |
| No                          | 2179 (57)                        | 1779 (58)                                                          | 1214 (57)                                                          | 0.8    |
| ≥1                          | 1661 (43)                        | 1302 (42)                                                          | 928 (43)                                                           |        |
| Parental history of allergy |                                  |                                                                    |                                                                    |        |
| Asthma                      | 764 (20)                         | 614 (20)                                                           | 420 (20)                                                           | 0.5    |
| Eczema                      | 701 (18)                         | 561 (18)                                                           | 390 (18)                                                           | 0.6    |
| Hay fever                   | 1371 (36)                        | 1131 (37)                                                          | 803 (38)                                                           | 0.01   |

PAM, partitioning around medoids; SES, socio-economic status.

\*Comparison of children included in PAM analyses at 1 and 3 yr with those of the initial cohort not included in both analyses (Chi-square test); †The highest level among the two parents.

Data are presented as  $n$  (%).  $N$  total for each characteristic may vary due to missing information.

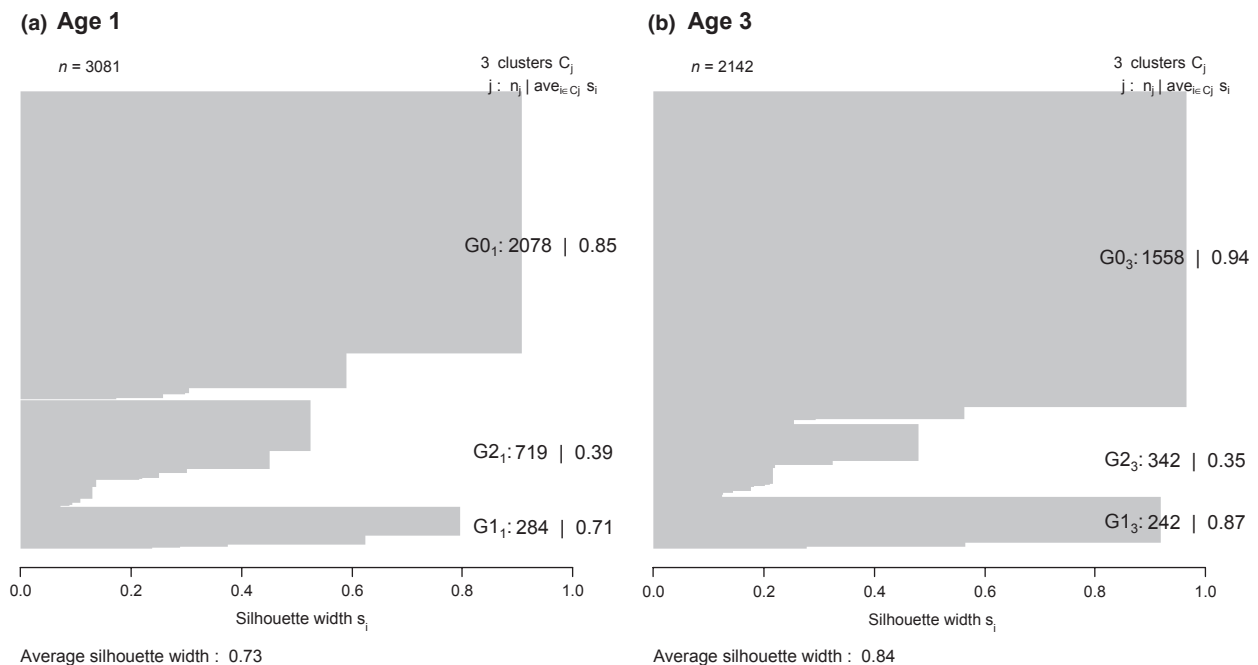


**Figure 1** Silhouette plots of the three-group solutions identified by the partitioning around medoids method at 1 and 3 yr. At both ages, the number of children and the average silhouette width within each cluster are displayed on the right side of the plot whereas the average silhouette width over the entire data set is provided under the graph. The height of the silhouettes is merely proportional to the number of children.

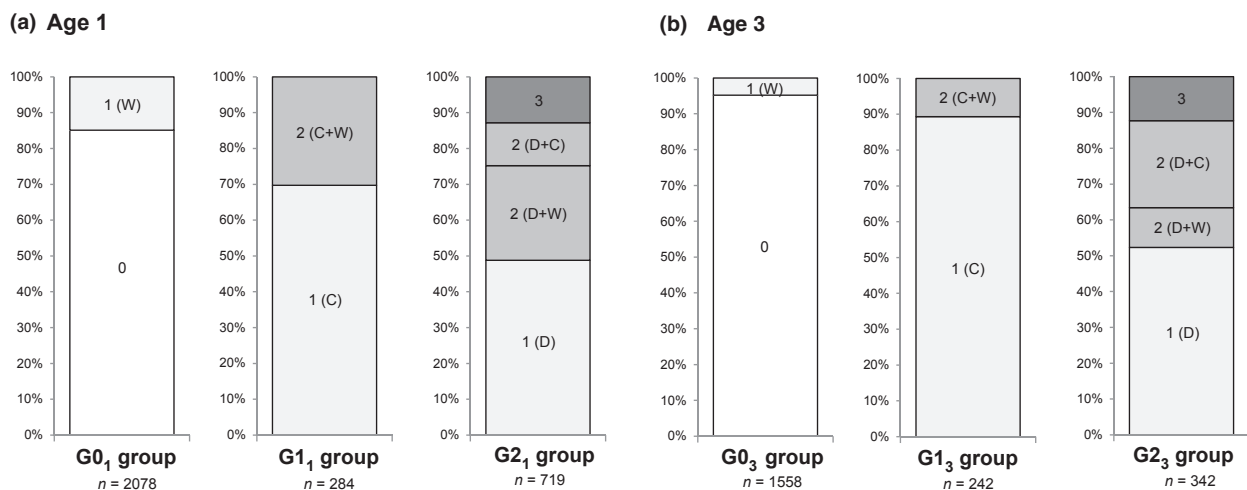


**Figure 2** Distribution of respiratory symptoms in the three groups identified by cluster analysis at ages 1 and 3 yr. The legend shows the number (0–3) and, in brackets, the type of experienced symptoms among wheezing (W), dry night cough (C) and dyspnoea with sleep disturbance (D).

prevalent in DP than in CP, both for URIs (aOR = 1.05,  $p = 0.001$ ) and LRIs (aOR = 1.21,  $p < 0.001$ ).

Nearly 50% of the DP children had ever had wheezing, vs. 30% in CP ( $p < 0.001$ ). Both phenotypes also differed with respect to recurrent wheezing (23.7% vs. 12.4%,  $p < 0.001$ )

and impact of wheezing on the children's life. DP wheezers were more affected than CP wheezers, their parents reporting more often nocturnal awakenings (65.4% vs. 35.3%,  $p < 0.001$ ) and disturbance of daily activities (51.5% vs. 34.1%,  $p = 0.003$ ).

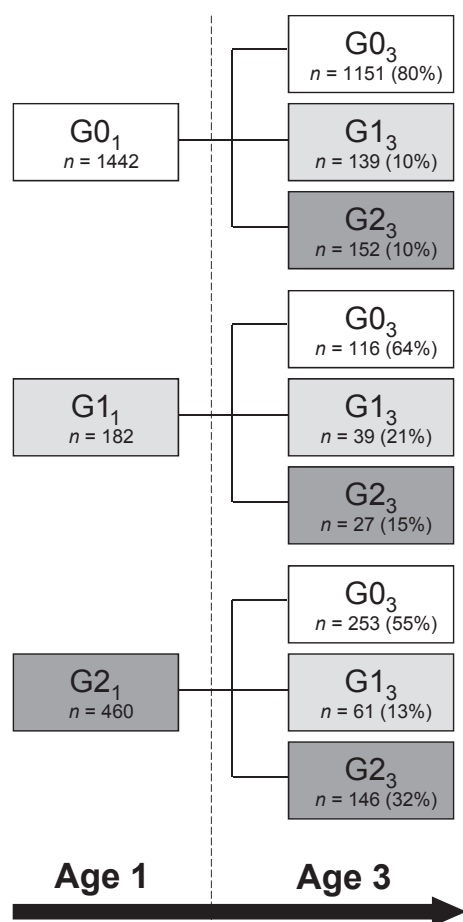


**Figure 3** Groups identified at age 1 (G0<sub>1</sub>/G1<sub>1</sub>/G2<sub>1</sub>) and age 3 (G0<sub>3</sub>/G1<sub>3</sub>/G2<sub>3</sub>) among PARIS children entered in both cluster analyses (n = 2084).

### Risk factors

Phenotypes associations with early-life sociodemographic, lifestyle and environmental factors are given in Table 3.

**Table 2** Comorbidity associated with cough and dyspnoea phenotypes during the first 3 yr of life compared with the reference group without cough or dyspnoea in the PARIS birth cohort (multivariate analysis)

| Comorbidity                                                              | Reference | Cough phenotype |                  |        | Dyspnoea phenotype |                  |        |
|--------------------------------------------------------------------------|-----------|-----------------|------------------|--------|--------------------|------------------|--------|
|                                                                          | % or m    | % or m          | aOR (95% CI)     | p      | % or m             | aOR (95% CI)     | p      |
| Asthma ever doctor diagnosed at 3 yr                                     | 3.3       | 9.7             | 2.17 (1.19–3.96) | 0.01   | 19.0               | 3.73 (2.35–5.91) | <0.001 |
| Eczema ever doctor diagnosed at 3 yr                                     | 31.6      | 41.5            | 1.36 (1.01–1.84) | 0.04   | 36.7               | 0.98 (0.77–1.26) | 0.9    |
| Any history of food reaction at 2 yr                                     | 3.2       | 7.8             | 1.97 (1.06–3.68) | 0.03   | 5.8                | 1.20 (0.67–2.16) | 0.5    |
| Any history of sneezing, runny or blocked nose apart from a cold at 3 yr | 25.9      | 60.1            | 4.08 (3.05–5.45) | <0.001 | 51.9               | 2.63 (2.08–3.33) | <0.001 |
| Number of URIs* during the first 3 yr (+1)                               | 8.8       | 9.5             | 1.02 (0.99–1.05) | 0.1    | 11.2               | 1.07 (1.05–1.10) | <0.001 |
| Number of LRIs† during the first 3 yr (+1)                               | 1.3       | 1.4             | 0.97 (0.89–1.06) | 0.5    | 2.4                | 1.14 (1.07–1.21) | <0.001 |

aOR, adjusted odds ratio; CI, confidence interval; m, mean.

\*URIs, upper respiratory infections included cold, rhinopharyngitis, laryngitis and tonsillitis; †LRIs, lower respiratory infections included bronchitis and bronchiolitis.

We found that CP was associated with parental history of allergy more strongly for both parents being allergic than for only one. Frequent vacuuming was negatively associated with CP, whereas visible mould in the home and familial events such as maternal health problems or separation of parents during the first year were significantly more frequent in this phenotype. CP children tended to have older siblings less often and to sleep more frequently on a used mattress.

Conversely, day care centre attendance during the first year, pre- and post-natal exposure to environmental tobacco smoke (ETS), refurbishment of the child's bedroom during the first year and frequent use of air fresheners were significantly associated to DP. Mopping the floor was also less frequent in DP.

### Discussion

We have identified two respiratory phenotypes in preschool children based upon dry night cough and dyspnoea disturbing the sleep. The study of the associated comorbidity and risk factors suggests that these symptoms are the markers of two distinct profiles, potentially allergic and infectious.

### Identification of respiratory phenotypes: strengths and limitations

Given that the heterogeneity of child respiratory disorders complicates asthma diagnosis, more and more studies resort to statistical techniques to disentangle phenotypes in a more objective way (8–12). These new approaches, generally carried out at school age, encompass a vast number of variables, related to symptoms, medication, skin-prick tests, lung function and/or biological parameters, not always available in infancy. Asthma often beginning early in life, the strength of our study is the identification of early respiratory phenotypes in general population, using a simple approach based only on clinical manifestations, readily identifiable by interviewing parents.

Many phenotypes previously described in the literature focused on wheezing. However, wheezing frequency did not discriminate toddlers in our cohort, suggesting that this

**Table 3** Early-life risk factors of belonging to both respiratory phenotypes compared with the reference group without cough or dyspnoea during the first 3 yr of life in the PARIS birth cohort

| Risk factors                                                       | Reference | Cough phenotype |                  |      | Dyspnoea phenotype |                  |        |
|--------------------------------------------------------------------|-----------|-----------------|------------------|------|--------------------|------------------|--------|
|                                                                    | % or m    | % or m          | aOR (95% CI)     | p    | % or m             | aOR (95% CI)     | p      |
| Parental history of allergy*                                       |           |                 |                  |      |                    |                  |        |
| No                                                                 | 48.4      | 40.1            | 1                |      | 43.1               | 1                |        |
| Yes, one parent                                                    | 41.2      | 44.6            | 1.34 (0.99–1.83) | 0.06 | 44.5               | 1.23 (0.97–1.55) | 0.08   |
| Yes, both parents                                                  | 10.4      | 15.3            | 1.78 (1.15–2.78) | 0.01 | 12.4               | 1.35 (0.94–1.94) | 0.1    |
| Sociodemographics                                                  |           |                 |                  |      |                    |                  |        |
| Number of older siblings (+1)                                      | 0.6       | 0.5             | 0.81 (0.65–1.02) | 0.07 | 0.6                | 0.99 (0.84–1.17) | 0.9    |
| Familial events during the first year of life†                     |           |                 |                  |      |                    |                  |        |
| No                                                                 | 94.6      | 91.2            | 1                |      | 94.3               | 1                |        |
| Yes                                                                | 5.4       | 8.8             | 1.73 (1.01–2.95) | 0.04 | 5.7                | 1.06 (0.66–1.71) | 0.8    |
| Lifestyle                                                          |           |                 |                  |      |                    |                  |        |
| Day care centre during the first year of life                      |           |                 |                  |      |                    |                  |        |
| No                                                                 | 62.2      | 56.6            | 1                |      | 51.3               | 1                |        |
| Yes                                                                | 37.8      | 43.4            | 1.25 (0.93–1.67) | 0.1  | 48.7               | 1.56 (1.25–1.94) | <0.001 |
| Environment                                                        |           |                 |                  |      |                    |                  |        |
| Exposure to chemical pollution                                     |           |                 |                  |      |                    |                  |        |
| Maternal smoking during pregnancy                                  |           |                 |                  |      |                    |                  |        |
| No                                                                 | 92.1      | 92.8            | 1                |      | 87.5               | 1                |        |
| Yes                                                                | 7.9       | 7.2             | 0.81 (0.46–1.43) | 0.5  | 12.5               | 1.52 (1.04–2.22) | 0.03   |
| Post-natal exposure to ETS‡ (+5 cigarettes)                        | 1.5       | 1.9             | 1.09 (0.95–1.26) | 0.2  | 2.4                | 1.13 (1.02–1.25) | 0.02   |
| Refurbishment of the child's bedroom during the first year of life |           |                 |                  |      |                    |                  |        |
| No                                                                 | 92.8      | 91.2            | 1                |      | 88.0               | 1                |        |
| Yes                                                                | 7.2       | 8.8             | 1.25 (0.75–2.09) | 0.4  | 12.0               | 1.82 (1.26–2.63) | 0.001  |
| Frequency of use of air fresheners                                 |           |                 |                  |      |                    |                  |        |
| Less than weekly                                                   | 86.6      | 89.6            | 1                |      | 82.9               | 1                |        |
| Weekly                                                             | 13.4      | 10.4            | 0.77 (0.49–1.21) | 0.3  | 17.1               | 1.37 (1.01–1.85) | 0.04   |
| Exposure to biological pollution                                   |           |                 |                  |      |                    |                  |        |
| Visible mould at home                                              |           |                 |                  |      |                    |                  |        |
| No                                                                 | 86.4      | 80.7            | 1                |      | 86.1               | 1                |        |
| Yes                                                                | 13.6      | 19.3            | 1.48 (1.02–2.15) | 0.04 | 13.9               | 1.00 (0.73–1.37) | 0.9    |
| Frequency of use of vacuum cleaner                                 |           |                 |                  |      |                    |                  |        |
| Less than daily                                                    | 75.3      | 83.1            | 1                |      | 75.5               | 1                |        |
| Daily                                                              | 24.7      | 16.9            | 0.64 (0.44–0.94) | 0.02 | 24.5               | 1.00 (0.77–1.31) | 0.9    |
| Age of the child's mattress                                        |           |                 |                  |      |                    |                  |        |
| Recent                                                             | 73.5      | 70.7            | 1                |      | 71.9               | 1                |        |
| Used                                                               | 26.5      | 29.3            | 1.29 (0.92–1.80) | 0.1  | 28.1               | 1.08 (0.84–1.40) | 0.5    |
| Frequency of mopping the floor                                     |           |                 |                  |      |                    |                  |        |
| Less than weekly                                                   | 14.4      | 20.1            | 1                |      | 20.3               | 1                |        |
| Weekly                                                             | 85.6      | 79.9            | 0.73 (0.50–1.06) | 0.1  | 79.7               | 0.64 (0.48–0.86) | 0.003  |

aOR, adjusted odds ratio; CI, confidence interval; m, mean; ETS, environmental tobacco smoke.

\*Parental history of allergy among asthma, eczema and allergic rhinitis; †Familial events among separation/divorce of parents and serious health problems of the mother; ‡Number of cigarettes smoked per day at home at 1 month of age.

The model was also adjusted for gender, maternal and paternal socioeconomic status (three classes: low, medium, high), breastfeeding between 0 and 6 months (yes/no), and keeping of cat or dog during the first year of life (yes/no).

symptom is not the only factor that should be taken into account when distinguishing respiratory phenotypes in the first 3 yr of life, as already underlined by Smith et al. (8) in an English birth cohort. These authors used the principal components analysis to highlight syndromes of coexisting respiratory symptoms in preschool children. The four-component model selected at 3 yr explained 53.2% of the variance in symptoms and was not only related to wheeze, but also to cough, colds and chronic symptoms. Contrary to our study,

dyspnoea disturbing the child's sleep was not considered in their analysis at age 3.

The replication of the PAM analysis at two different ages using comparative cross-sectional variables enabled us to underline the structural stability of these phenotypes suggesting that the symptomatology is quite homogeneous all along the first 3 yr of life. Likewise, the post-natal lung development is not achieved before 2–3 yr of age and structural changes can still occur (13). For these reasons, we defined

our phenotypes over the 0–3-yr period considering only one classification based upon those symptoms that similarly defined the clusters at both ages. Children could actually change groups between 1 and 3 yr but the age of 3 yr seems too young to explore temporal symptom patterns and was considered as a pivotal age in other birth cohorts. For instance, the wheezing phenotypes highlighted by the Tucson group defined the symptoms as 'early', 'late' or 'persistent' taking the age of 3 as threshold (2).

In spite of its innovative nature, our study has a few limitations that must be mentioned. The first one concerns the participation rate. Children included in the PAM analysis at 3 yr represent nearly 56% of the initial cohort but the comparison of children followed and not followed at age 3 did not reveal any major difference, except in familial SES as generally found in other studies. This high attrition rate could partly be explained by the location of the study. Paris area is the greatest urban centre in France. Its population moves a lot, especially young couples who often start their occupational life in Paris before moving or going back to the provinces later, notably when the family size increases. For instance, among the infants lost between 1 and 3 yr, about 30% stopped the follow-up because of moving away from the study area. Secondly, symptoms were based on parental report and were not objectivized with health examination and/or biological tests. Nevertheless, the use of standardized questionnaires and the longitudinal follow-up at regular intervals might limit the misclassification and the possibility of recall bias. Lastly, validation of phenotypes defined using statistical methods remains a critical and complex issue. Validation could be performed by comparing results in independent samples (12) or later by testing their predictive performance. Although it is too early to say whether our phenotypes will represent separate pathologic features, our profiles make sense. Indeed, our results indicate that these profiles are quite different regarding comorbidity and are significantly influenced by distinct lifestyle/environmental factors. Interestingly, risk factors did not overlap between both phenotypes.

### Cough phenotype

Our findings indicate that early dry night cough in the absence of dyspnoea could suggest allergy in infancy given the association we observed between CP and allergy-related disorders and the influence of genetics reflected by parental history of allergy. This result is consistent with a study in Swedish preschool children where night cough in the previous 12 months was associated with parental allergy (14).

The possible allergic orientation of CP is also strengthened by the associations we found with risk factors of sensitization described in the literature. We found a relation with potential exposure to indoor allergens, known to play an important role in the early development of atopic disease. The association we found with potential contact with fungal allergen exposure was consistent with other surveys reporting visible mould in the home as a risk factor for cough, hay fever and asthma (15). We also reported a protective effect of vacuum

cleaning. Indeed, frequent vacuuming may help to lower the amount of household dust and lead to a significant removal of allergens, notably of house dust mites (HDM) (16). In addition, intervention aiming to reduce HDM allergen exposure in early childhood by use of impermeable mattress covers has been associated with a lower prevalence of night cough without a cold, consistent with our results (17). Lastly, children sleeping on a used mattress tended to be more frequent in CP ( $p = 0.1$ ). This result may be explained because the age of the bedding is a rather crude indicator of exposure to HDM, whose levels were not measured in our large-scale epidemiological study.

Another important finding is the association we found between CP and separation of parents or the mother having a serious health problem during the first year of the child's life. This result appears consistent with that of another birth cohort: the LISA study has already linked divorce/separation of the parents during the first 2 yr with atopic eczema (18). There is increasing evidence that psychosocial factors, particularly early in life, could play a role in the development of atopic disorders in children (19). An increase in blood concentration of vasoactive intestinal peptide in children with separated/divorced parents has been suggested (20), this neuropeptide being involved in the regulation of the immune system by modulating the Th1/Th2 balance (21). Other mechanisms have been proposed regarding the impact of stress on allergy onset, such as an alteration of the hypothalamus–pituitary–adrenal axis function (22).

Lastly, living as an only child tended to be associated with CP, in agreement with many studies reporting an inverse relation between siblings and the development of allergic diseases such as eczema, hay fever, allergic sensitization and asthma (23).

### Dyspnoea phenotype

Dyspnoea phenotype seemed more severe than CP, regarding frequency, recurrence and coexistence of symptoms as well as the repercussion on the child's daily life. According to our findings, DP clearly appeared as a recurrent respiratory infection profile. Strong associations were also found between DP and known risk factors of infant viral infections, e.g., day care centre attendance which promotes contact with infectious agents and was associated with a greater occurrence of LRIs and recurrent wheezing (24). Even though contact with other children can also occur in the home, we did not find an association with the number of older siblings in our study where family units were in most cases small. The protective role of mopping the floor could reflect a decrease in the microbial burden. It is clear that this higher level of hygiene can be associated in the short term with fewer infectious illnesses, considering that children younger than 3 yr are more likely to be in contact with indoor surfaces and thus exposed to pathogens, through fomes-mouth or hand-mouth ingestion (25).

Our findings are also in accordance with the growing evidence that airborne chemical pollution helps to increase the incidence and severity of respiratory illnesses (26). In our

study, children exposed to factors reflecting domestic exposure to chemical pollution were more likely to belong to DP. These results are notably consistent with a recent meta-analysis in infants aged 2 yr and younger showing that both prenatal maternal smoking and any household member smoking are major risk factors for LRIs (27). In our cohort, we also found effects of intrauterine and early-life exposures to ETS. Indeed, such exposures occurring at two critical periods of life could enhance vulnerability to respiratory infections by distinct mechanisms. Exposure during gestation can impair lung growth, leading to narrow airways much more readily obstructed. Post-natal exposure may damage and thus increase the permeability of the airways epithelium, or reduce defence mechanisms such as mucociliary clearance. We also highlighted the role of potential exposure to volatile organic compounds (VOCs) reflected by the refurbishment of the child's bedroom and the use of air fresheners. Even if the role of VOC exposure in respiratory disorders in infancy has been less studied than ETS, epidemiological studies have associated indoor VOCs, or activities likely to release VOCs such as home renovation with lower respiratory disorders in children (28). Even if the underlying mechanisms are not fully understood, some of these pollutants are known to have irritant effects on the respiratory tract which could weaken the airways and thus promote susceptibility to pathogens.

### Potential implications

Given asthma begins in early life in most cases, the identification of children at risk of asthma in infancy remains an important issue. A few predictive scores have been recently developed to determine the risk of subsequent asthma in children. However, most of the clinicians consider they are complex and difficult to implement in practice (29). Several studies were interested in the identification of children at risk of asthma at an early stage studying the prognostic value of early respiratory symptoms for subsequent asthma. For instance, a prospective study in the USA (30) found a significant association between reported shortness of breath at 1–2 yr of age and the diagnosis of asthma at age 10. However,

in the same study, there was no association between frequent or chronic coughing in the first 2 yr of life and the development of asthma, but the nocturnal occurrence of cough was not taken into account in this work. Conversely, a Japanese study by Nishimura et al. (31) found that nearly half of the children with an early history of chronic dry cough without dyspnoea or wheezing were diagnosed with asthma after 10 yr of follow-up. Among the PARIS children, we highlighted that a simple classification based upon 0–3 yr bronchial obstructive symptomatology could isolate two rather distinct symptomatic groups. The issue which now arises concerns the long-term outcome of these children. Will infants suffering from dry night cough without dyspnoea develop allergic diseases? Will infants whose sleep has ever been disturbed by dyspnoea recover or will their symptoms persist beyond the age of 3? If our hypotheses are confirmed, this would justify looking carefully at these symptoms from the earliest age.

### Conclusion

We found evidence for distinct respiratory profiles before the age of 3 yr. Two phenotypes were identified with dry night cough and dyspnoea disturbing the child's sleep as key symptoms. These phenotypes appear oriented towards allergy and infections, respectively, and are strongly influenced by early-life environmental exposures. Further studies at a later stage of the follow-up are needed to assess whether these phenotypes represent real disease entities at school age.

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