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## Title

Early polysensitisation is associated to allergic multimorbidity in PARIS birth cohort infants

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## Running title

Early polysensitisation & multimorbidity

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## Abstract

### Background

Profiles of allergic sensitisation are poorly documented in infancy. Relations between early sensitisation and allergic morbidity need to be clarified.

### Methods

This study dealt with children involved in the *Pollution and Asthma Risk: an Infant Study* (PARIS), a population-based prospective birth cohort. Allergic sensitisation to 12 food and 4 inhalant allergens was assessed at 18 months and defined by a specific IgE level  $\geq 0.35$  kU<sub>A</sub>/L. Health data were collected by standardised questionnaires at 2 and 6 years. Early allergic profiles were identified by an unsupervised cluster analysis based on health data at 2 years and IgE measurements. Profiles were compared with regard to allergic morbidity and multimorbidity at 6 years.

### Results

Sensitisation to any allergen concerned 13.6% of infants. By cluster analysis, 1525 infants were grouped in 3 profiles: 89.2% not or rarely sensitised (only 3.7% of sensitised), 9.2% mainly sensitised to one or few allergens (45.2% of *monosensitised* and 45.9% of *paucisensitised*), and 1.6% all *polysensitised*. The prevalence of doctor-diagnosed asthma, rhinitis, eczema, food allergy, and multimorbidity at 2 years increased from profile 1 to profile 3 ( $p$ -trend  $< 0.001$ ). At 6 years, symptoms of current asthma, rhinitis, eczema, and multimorbidity were significantly more frequent in the last two profiles.

### Conclusions

This study highlights, as early as 18 months of age, 3 profiles of increasing severity with regard to allergic sensitisation and diseases. These profiles also differ in terms of allergic morbidity at 6 years. Early sensitisation can predict allergic multimorbidity in childhood, and in the case of early polysensitisation, multimorbidity is more frequent as soon as infancy.

### Keywords

allergic morbidity; birth cohort; cluster analysis; early allergic profiles; IgE; polysensitisation.

## Introduction

The prevalence of asthma, allergic rhinitis, eczema, and food allergy has increased critically in childhood in all countries over the past decades (1–3), although prevalence curves of respiratory forms tend to stabilise or even to decline in industrialised countries (3,4). In cohorts, allergic sensitisation is predictive of these diseases (5,6). Allergic sensitisation prevalence ranges from about a third of children below 6 years of age to nearly half of older children (7,8). But this prevalence is poorly documented in infancy, when allergic sensitisation is most likely to develop (9), particularly to food allergens (8–10).

Several cohorts have highlighted allergic profiles in childhood using *hypothesis driven* (10–12) or *data driven* (13–18) methods, models being based on sensitisation data (11–14,18), or both sensitisation and clinical data (15–17). These studies have shown that sensitisation to several allergens (*multisensitisation*) in infancy can be considered as a risk factor for later asthma (12–15) or rhinitis (12). Multimorbidity is another important aspect of allergic diseases in children (6). In *Mechanisms of the Development of ALLergy* (MeDALL), allergic multimorbidities and IgE polysensitisation in preschool children were often

associated with the persistence or severity of asthma (19,20). However, associations between polysensitisation and allergic multimorbidity need to be clarified in infants (19).

This paper examines prevalence and profiles of allergic sensitisation and morbidity in infancy, and aims to determine whether identified profiles are related to allergic morbidity in childhood. This study was conducted in *Pollution and Asthma Risk: an Infant Study* (PARIS), a birth cohort especially designed to explore the development of respiratory and allergic diseases (21).

## Methods

### Design

The present study was conducted in PARIS, a French on-going population-based prospective birth cohort.

### Population and data collection

The PARIS birth cohort consists of 3860 full-term and healthy singletons recruited from five Paris maternity hospitals between 2003 and 2006, as previously described (21). Parents documented the environment of each new-born one month after birth via a phone interview. New information and changes in the infants' environment, lifestyle habits, and health were then documented by quarterly self-administered questionnaires in the first year of life, half-yearly in the second one, and yearly until age 6 (21). When children were 18 month old, all parents were offered a medical examination during which a blood sample was taken from each child and analysed for immunoglobulin E (IgE) measurements (total and allergen-specific IgE). The National Ethics Committee approved the research protocol (permissions no. 031153 and 051289) and written informed consent was obtained from the parents.

The present study concerns the PARIS infants for whom serum IgE measurements and health data at 24 months were available.

### Health data

Health data were prospectively collected by parental reporting.

Doctor-diagnosed allergic diseases were assessed at 24 months by four standardised questions, taken up by MeDALL (22): *Has your child ever been diagnosed by a doctor with having...*

1. *asthma?*
2. *eczema?*
3. *allergic rhinitis?*
4. *food allergy?*

Asthma and allergic rhinitis were categorised as *respiratory allergy*.

Furthermore, current symptoms (in the past 12 months) of asthma, allergic rhinitis (confirmed by allergic tests and/or doctor-diagnosis), and eczema were documented at 6 years using standardised questions from the ISAAC protocol (23).

### Allergic sensitisation

Allergic sensitisation to 4 inhalant (dust mite, cat, moulds and cocksfoot) and 12 food allergens (egg white, cow's milk, peanut, mustard, fish, wheat, soya, hazelnut, sesame, shrimp, beef, and kiwi) was assessed at age 18 months with ImmunoCAP® (Phadia, Thermo Fisher Scientific, Uppsala, Sweden) as previously described (24). Total serum IgE level was measured by ImmunoCAP® Total-IgE (Phadia, Thermo Fisher Scientific, Uppsala, Sweden). Sensitisation was defined by an allergen-specific IgE  $\geq 0.35$  kU<sub>A</sub>/L and a total serum IgE

level  $\geq 45$  kU<sub>A</sub>/L was considered high (25). According to the number of allergen-specific sensitisations, toddlers were named *monosensitised* (sensitised to one allergen), *paucisensitised* (to few allergens), or *polysensitised* (to many allergens).

### Statistical analyses

Prevalence of allergic diseases and sensitisation to any allergen, food allergens, and aeroallergens were estimated.

A hierarchical clustering on principal components using the "FactoMineR" R software package (26) was performed to identify allergic profiles. Infants were grouped into clusters with regard to total serum IgE levels ( $\geq 45$  kU<sub>A</sub>/L or not), specific sensitisation to nine allergens (cow's milk, egg white, hazelnut, peanut, mustard, wheat, beef, house dust mite, and cat), and reported doctor-diagnosed eczema, respiratory allergy, and food allergy at age 2 years. The method imputed the median value when sensitisation data were missing. Then, clusters were compared with regard to prevalence of allergic sensitisation, morbidity, and multimorbidity (co-occurrence of at least two morbidities). Mann-Whitney (for continuous variables) and  $\chi^2$  or Fisher exact tests (for dichotomous variables) with Bonferroni correction were applied to compare clusters two by two, and Cochran-Armitage test was used to study trends.

All statistical analyses were performed using R software version 3.2.2 and Stata® version 11.2.

## Results

### Study population

The present study dealt with the 1525 infants for whom allergen-specific IgE at 18 months and health data at 24 months were available (Figure 1). At the health examination, their mean age was  $19.0 \pm 1.7$  months.

Study participants were more likely to have parents with a high socio-economic status, and to have been breastfed for longer than non-participants ( $p$ -value  $< 0.001$  and  $p$ -value = 0.002, respectively; *see* Table S1). There was however no significant difference between the two groups with regard to gender, siblings, family history of allergy, or prenatal and postnatal smoking.

### Prevalence of allergy and sensitisation in infancy

Figure 2 shows that 25.5% ( $n = 389$ ) of 24 month-old toddlers were ever diagnosed by a doctor with having eczema, 7.3% ( $n = 111$ ) with having asthma, rhinitis, or both, and 6.0% ( $n = 92$ ) with having food allergy.

Sensitisation to at least one allergen was found in 13.6%, ( $n = 201$ ) of infants. Sensitisation to food allergens was more common than to inhalant allergens (*see* Figure S1): 12.1% ( $n = 180$ ) *versus* 2.5% ( $n = 38$ ), respectively ( $p$ -value  $< 0.001$ ). The main foods (*see* Figure S1a) were cow's milk (7.4%,  $n = 112$ ), egg white (6.4%,  $n = 97$ ), hazelnut (2.1%,  $n = 32$ ), and peanut (1.9%,  $n = 28$ ), accounting for 92.2% of food sensitisation cases. Aeroallergen sensitisation (*see* Figure S1b) was mostly due to house dust mite and cat: 1.3% ( $n = 19$ ) and 1.2% ( $n = 18$ ).

### Allergic profiles in infancy

Cluster analysis identified 3 profiles in infants (Table 1 and Figure 3). The first profile included 89.2% of children. They had the lowest total serum IgE levels, and were not or rarely sensitised (only 3.7% of allergic sensitisation, percentiles 10<sup>th</sup>–90<sup>th</sup> of allergen-specific sensitisation count: 0–0). The intermediate profile involved 9.2% of children, mainly sensitised to one or few allergens (45.2% of *monosensitised* and 45.9% of *paucisensitised*,

perc. 10<sup>th</sup>–90<sup>th</sup>: 1–3). Finally, the third profile concerned 1.6% of infants, all *polysensitised* (perc. 10<sup>th</sup>–90<sup>th</sup>: 4–8) and showing the highest total serum IgE levels. Furthermore, boys and infants with family history of allergy were more frequent in the later profile ( $p$ -trend < 0.001 and < 0.01).

Figure 4a highlights an increasing allergy prevalence gradient: more doctor-diagnosed eczema, respiratory allergy, and food allergy were reported from the first to the last profile ( $p$ -trend < 0.001). Infants in the third profile – those *polysensitised* – were more likely to be affected by several allergies ( $p$ -trend < 0.001): 54.2% of them with multimorbidity, compared to 26.9% and 4.0% of children in the second and first profiles, respectively (Figure 4b).

Table 2 shows that current symptoms of asthma, allergic rhinitis, and eczema at 6 years were more frequent in the second and third profiles (trend statistically significant for all studied symptoms). Similarly, symptoms of at least two different allergic diseases were also more frequently reported in childhood in these two profiles.

## Discussion

This study, in infants from a population-based birth cohort, shows that allergic sensitisation prevalence, poorly documented in infancy, is high as early as 18 months of age. Furthermore, an unsupervised approach brought new insights into early allergic profiles: 3 profiles were highlighted, with distinct allergic severity, and with different morbidity at 6 years of age.

### Prevalence of allergic sensitisation

Allergic sensitisation has been well described in childhood, its prevalence varying from 24.1% to 40.4% before the age of 6 years, and between 34.8% and 47.9% above this age in European birth cohorts, according to the studied population (7). However, few studies have assessed the prevalence of allergic sensitisation in early life. Published prevalence from studies with a design close to ours, i.e. based on specific IgE measurements towards common food and inhalant allergens ( $\geq 0.35$  kU<sub>A</sub>/L) in infants aged 24 months or less involving in population-based cohorts, vary between 8.0% and 26.1% (9,27,28). These differences may be due to the diversity of the tested allergens (9,27,28), or to the features of the studied populations (29).

### Allergic profiles in infancy

The 3 profiles we identified differed in terms of allergic severity: the prevalence and the number of both allergen-specific sensitisations and allergic doctor-diagnosed diseases in early life increased from the first to the third profile. Thus, the link between sensitisation – more particularly polysensitisation – and allergic morbidity and multimorbidity (based on doctor-diagnosed disease reporting) in the PARIS birth cohort is clearly shown as soon as 18 months of age. This result confirms in early life the MeDALL hypothesis that allergic multimorbidity is closely related to polysensitisation (19). Garcia-Aymerich *et al.* (2015) (16) previously identified 2 groups in older children (at age 4 and 8 years) enrolled in 7 European longitudinal studies: a symptomatic and a reference group, respectively characterised by high and low prevalence of allergic sensitisation, morbidity, and multimorbidity. Similarly, Ballardini *et al.* (2016) (30) showed that "sensitisation ever" (defined as sensitisation at 4, 8, or 16 years of age) among children involved in the *Stockholm Children Allergy and Environmental Prospective Birth Cohort Study* (BAMSE) was associated with an increase in allergic multimorbidity at each follow-up point (1, 2, 4, 8, 12, and 16 years of age).

Moreover, early allergic profile severity was also related to current allergic symptoms at 6 years in PARIS. These symptoms were statistically more frequent in profile 2 and 3 children: those with the highest prevalence of allergic sensitisation, morbidity, and multimorbidity in infancy. This is in accordance with Pinart *et al.* (2014) (6) who related multimorbidity of asthma, allergic rhinitis, and/or eczema at age 8 years to prior sensitisation or multimorbidity at age 4 years in children involved in 12 European birth cohort studies.

Some other teams have assessed allergic profiles based on either sensitisation data (10–14,18) or both sensitisation and clinical data (15–17) collected throughout childhood, and studied relations between sensitisation and allergic morbidity. Simpson *et al.* (2010) (13) highlighted through a latent class analysis 5 sensitisation profiles in children from the *Manchester Asthma and Allergy Study* (MAAS) birth cohort, followed-up from 1 to 8 years. Among these sensitisation profiles, only the "multiple early" profile could predict asthma at age 8 years. These results were confirmed by Lazic *et al.* (2013) (14) in the population-based *Isle of Wight* (IoW) birth cohort. Garden *et al.* (2013) (18) identified 4 sensitisation profiles thanks to a latent class analysis, which was based on skin prick tests at 1.5, 3, 5, and 8 years in children at risk of asthma belonging to the *Childhood Asthma Prevention Study* (CAPS) birth cohort. All 3 "sensitised" classes were linked to asthma, eczema, and rhinitis at 8 years. A few authors have shown that multiple sensitisation increases the allergic disease risk in non-population-based children's cohorts. Amat *et al.* (2015) (15) for instance found 3 allergic profiles in infants with early onset of eczema participating in the *Observatory of Respiratory risks linked with Cutaneous Atopy* (ORCA) study. Prevalence of asthma at 6 years was higher in the "multiple sensitisation" profile. Besides, aeroallergen sensitisation patterns in 1, 3, 6 year-old children at risk of allergy enrolled into the *Childhood Origins of ASThma* (COAST) study were established by Stoltz *et al.* (2013) (12). They showed that risks at 6 years of asthma and allergic rhinitis were higher in polysensitised children at 3 and 6 years and at all ages, respectively. Finally, Brockrow *et al.* (2009) (11) observed increased prevalence of asthma, allergic rhinitis, and eczema at 6 years in sensitised 12 month-old infants with positive family history of allergy included in the prospective *multicenter German Infant Nutritional Intervention* (GINIplus) study. The risk of subsequent allergic diseases was greatest in aeroallergen sensitised children, and as far as eczema was concerned the risk was higher in polysensitised infants.

### Strengths and limitations

One of the strengths of the present study is that it deals with more than 1500 infants from a population-based birth cohort. Another strength is that sensitisation has been defined according to blood measurements from a large panel of allergens. Also, our study is innovative in the way allergic profiles were identified: we used an unsupervised method where data were collected exclusively in early life, and not later in childhood as usually reported in the literature. These early profiles can be used to test their prediction with regard to later allergic morbidity and multimorbidity.

Classification of subjects by an unsupervised method has the advantage of not being related to an *a priori* opinion. Nevertheless, hierarchical clustering on principal components remains conditional on analytical decisions such as dimension number settings and hierarchical tree cutting (26), which could be a limit. Therefore, we used a range of models to make sure our results were stable, and not related to the later methodological specificities. Furthermore, cluster analysis was based on 9 allergen-specific IgE of the 16 available in our database. We did not consider 7 allergens for which the prevalence of sensitisation was lower than 1% to

prevent variables with infrequent categories from being over-represented (26). In order to overcome this data loss, we strengthened the model by including total serum IgE levels which are relevant for atopy assessment in infants (25).

Infants included in the analysis were from families with a higher socio-economic status than non-participants. They were also breastfed for longer. Several teams have similarly shown that parents with a higher socio-economic status might be more likely to enrol in longitudinal studies, and to participate in clinical examinations (31,32). Also, participants live nearer to the city centre where the health examinations took place ( $p$ -value < 0.001). As observed in our population ( $p$ -value = 0.017), breastfeeding duration is generally related to socio-economic status (33,34): parents from a higher socio-economic status may be more aware of the benefits of breastfeeding. In any case, socio-economic status and exclusive breastfeeding were not related to allergic sensitisation in our study (*data not shown*).

The location of the study could explain the substantial attrition rate at 6 years of age ( $n = 1056/1525$ ). Paris is the largest French urban area, where young couples often start their career before moving away as family size increases: around 55% of PARIS were not followed-up due to an exit from the study area. Having said that, the fact that 6 year-old children did not statistically differ from non-participants with regard to family history of allergy and reporting of doctor-diagnosed allergy at 24 months should limit this selection bias.

Whilst parental reporting of health information could be another limitation, in common with most large epidemiological studies, the prospective framework of the PARIS birth cohort should reduce the reporting bias. As far as current symptoms of allergic rhinitis at 6 years are concerned, we only considered those with reporting of positive allergic tests and/or doctor-diagnosis confirmation, in order to reduce misclassification.

The aforementioned differences should therefore not greatly affect our results.

In conclusion, this study provides new insights into the prevalence and patterns of allergic sensitisation in early childhood. Three profiles have been identified using an unsupervised method, allergic severity differing in terms of sensitisation, morbidity, and multimorbidity. We show that early sensitisation can predict allergic multimorbidity in childhood, and in the case of early polysensitisation, multimorbidity is more frequent as soon as infancy. These results suggest it is important to assess early allergic sensitisation, in order to foresee the development of consecutive allergic diseases.

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## Supporting information

Additional supporting information:

**Table S1.** Characteristics of PARIS birth cohort infants participating or not in the allergic profile study.

**Figure S1.** Sensitisation to (a) food allergens and (b) aeroallergens at 18 months of age in PARIS infants participating in the allergic profile study ( $N = 1525$ ).

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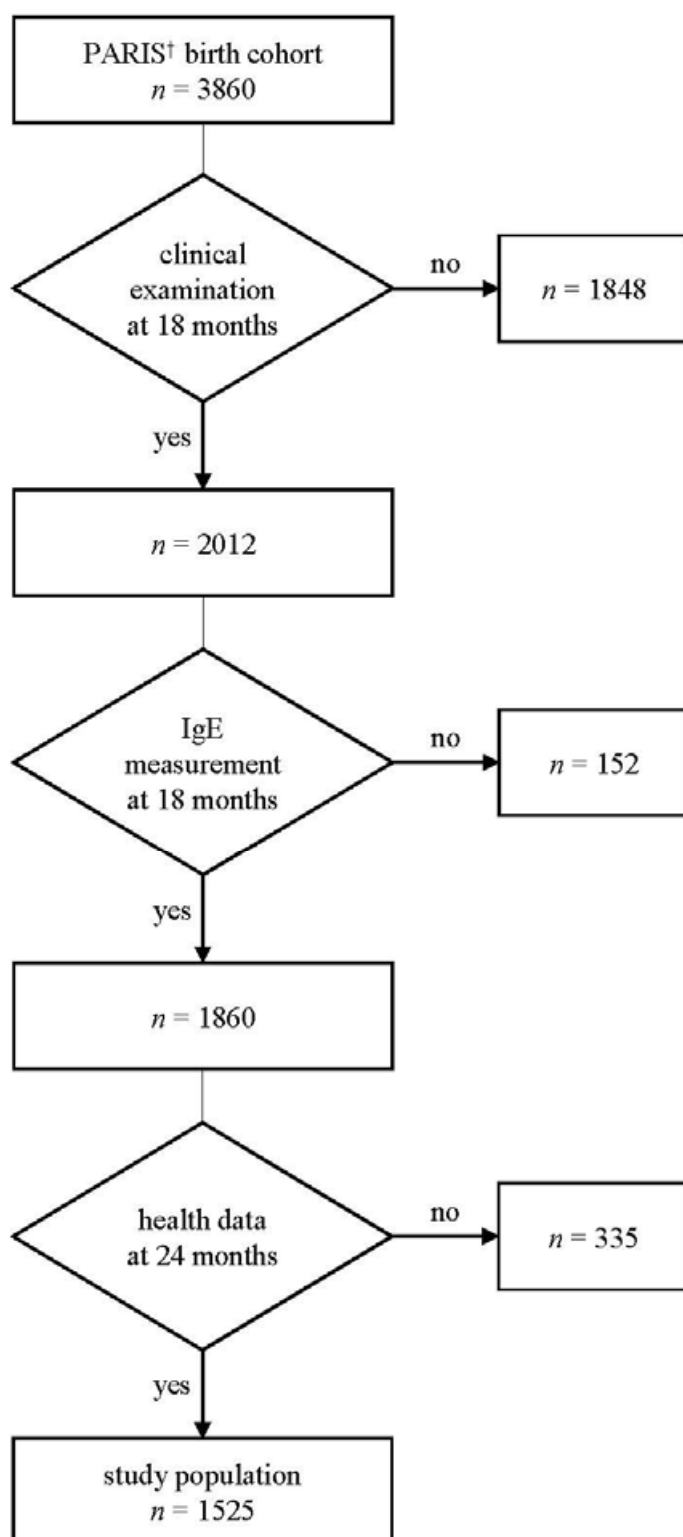


**Figure 1.** Flow chart of PARIS birth cohort infants participating in the allergic profile study  
PARIS: *Pollution and Asthma Risk: an Infant Study*

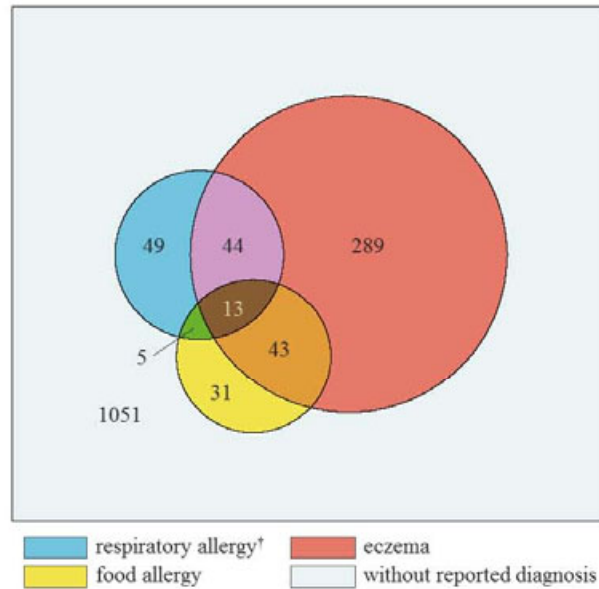


**Figure 2.** Reporting of doctor-diagnosed allergy at 24 months of age in PARIS infants participating in the allergic profile study ( $N = 1525$ )

<sup>†</sup> Respiratory allergy: asthma and/or allergic rhinitis.

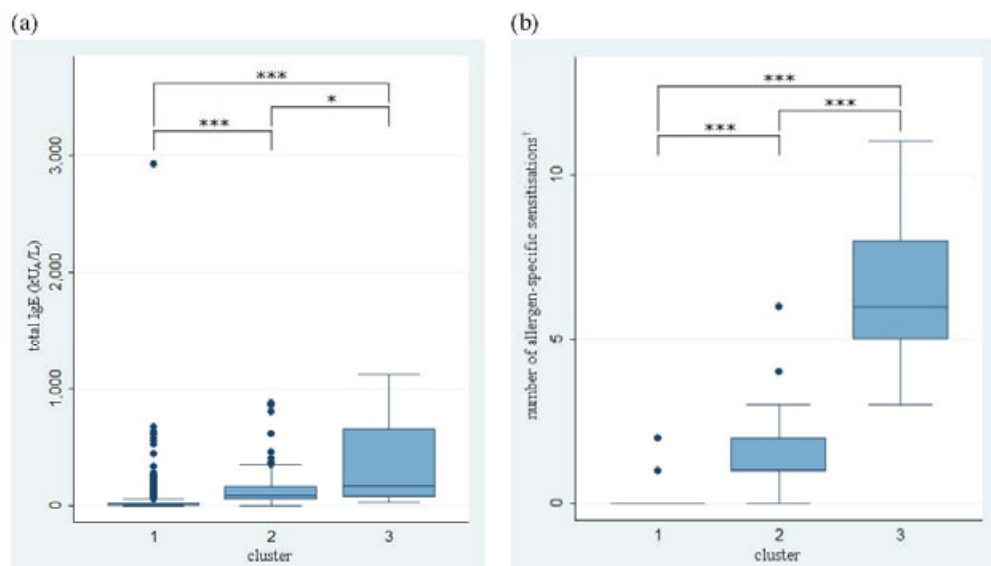


**Figure 3.** Comparison of the allergic clusters in PARIS infants participating in the allergic profile study with regard to (a) total IgE level and (b) number of allergen-specific sensitisations<sup>†</sup> ( $N = 1525$ )

<sup>†</sup> Defined by an IgE  $\geq 0.35 \text{ kU}_A/\text{L}$ .

After Bonferroni correction: \*  $p$ -value  $< 0.05$ , \*\*\*  $p$ -value  $< 0.001$ .

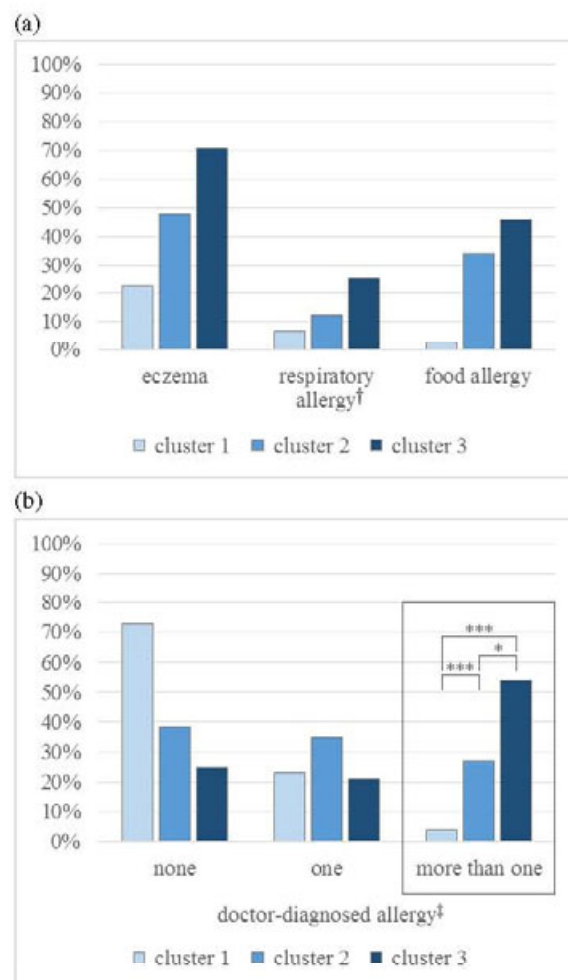


**Figure 4.** Comparison of the allergic clusters in PARIS infants participating in the allergic profile study with regard to prevalence of (a) morbidity¶ and (b) multimorbidity¶ (N = 1525)

¶ Reported at 24 months of age.

† Respiratory allergy: asthma and/or allergic rhinitis.

‡ Among eczema, respiratory allergy, and food allergy.

After adjusting for gender and family history of allergy, and Bonferroni correction: \*  $p$ -value < 0.05, \*\*\*  $p$ -value < 0.001.

**Table 1.** Description of the allergic clusters<sup>¶</sup> in PARIS infants participating in the allergic profile study (*N* = 1525)

|                                              | cluster     |           |          |
|----------------------------------------------|-------------|-----------|----------|
|                                              | 1           | 2         | 3        |
| % ( <i>n</i> )                               | 89.2 (1360) | 9.2 (141) | 1.6 (24) |
| infants' characteristics (%)                 |             |           |          |
| male gender                                  | 47.8        | 61.0      | 79.2     |
| family history of allergy <sup>§</sup>       | 57.5        | 66.7      | 75.0     |
| prevalence of sensitisation <sup>†</sup> (%) |             |           |          |
| monosensitised (= 1 allergen)                | 3.5         | 45.2      | 0        |
| multisensitised ( $\geq 2$ allergens)        | 0.2         | 45.9      | 100      |
| to any food allergen <sup>‡</sup>            | 2.9         | 85.4      | 100      |
| cow's milk                                   | 1.0         | 57.7      | 79.2     |
| egg white                                    | 0.7         | 47.1      | 100      |
| hazelnut                                     | 0.2         | 9.1       | 77.3     |
| peanut                                       | 0.2         | 6.6       | 70.8     |
| mustard                                      | 0.2         | 8.7       | 50.0     |
| wheat                                        | 0.1         | 0         | 79.2     |
| beef                                         | 0           | 3.6       | 57.9     |
| soya                                         | 0.1         | 3.0       | 37.5     |
| sesame                                       | 0.2         | 0.7       | 54.6     |
| kiwi                                         | 0.3         | 4.3       | 5.0      |
| fish                                         | 0.1         | 1.5       | 8.7      |
| prawn                                        | 0.1         | 0         | 5.0      |
| to any aeroallergen <sup>‡</sup>             | 0.8         | 15.9      | 22.7     |
| dustmite                                     | 0.3         | 9.5       | 9.1      |
| cat                                          | 0.5         | 5.1       | 17.4     |
| cocksfoot                                    | 0           | 2.2       | 0        |
| <i>Alternaria</i>                            | 0           | 0         | 4.6      |

<sup>¶</sup> Identified by hierarchical clustering on principal components.<sup>§</sup> Mother's, father's and/or older siblings' history of asthma, allergic rhinitis or eczema, recorded at birth.<sup>†</sup> Defined by an allergen-specific IgE  $\geq 0.35$  kU<sub>A</sub>/L.<sup>‡</sup> At least one allergen-specific IgE  $\geq 0.35$  kU<sub>A</sub>/L.

**Table 2.** Comparison of the allergic clusters in PARIS infants participating in the allergic profile study with regard to symptoms at 6 years of age ( $N = 1056$ )

|                                             | cluster             |                    |                    | <i>p</i> -trend   |
|---------------------------------------------|---------------------|--------------------|--------------------|-------------------|
|                                             | 1<br><i>n</i> = 944 | 2<br><i>n</i> = 98 | 3<br><i>n</i> = 14 |                   |
| current symptoms of asthma (%)              |                     |                    |                    |                   |
| wheezing                                    | 4.4                 | 11.2               | 14.3               | <b>0.001</b>      |
| wheezing during or after exercise           | 1.7                 | 7.1                | 13.3               | <b>&lt; 0.001</b> |
| shortness of breath                         | 2.7                 | 11.2               | 20.0               | <b>&lt; 0.001</b> |
| dry cough at night <sup>¶</sup>             | 15.9                | 30.6               | 20.0               | <b>0.002</b>      |
| current symptoms of allergic rhinitis (%)   |                     |                    |                    |                   |
| any nose problem <sup>†</sup>               | 4.7                 | 15.6               | 33.3               | <b>&lt; 0.001</b> |
| accompanied by itchy-watery eyes            | 4.2                 | 9.4                | 13.3               | <b>0.007</b>      |
| current symptoms of eczema (%) <sup>‡</sup> | 10.5                | 23.2               | 33.3               | <b>&lt; 0.001</b> |
| current multimorbidity <sup>§</sup>         | 6.3                 | 20.2               | 21.4               | <b>&lt; 0.001</b> |

<sup>¶</sup> When the child did not have a cold, the flu, or a chest infection.

<sup>†</sup> Sneezing, or a runny, or blocked nose when the child did not have a cold, the flu, or a chest infection, only if confirmed by allergic tests and/or doctor-diagnosis.

<sup>‡</sup> An itchy rash which was intermittently coming and going for at least 6 months, and affected the folds of the elbows, behind the knees, in front of the ankles, the buttocks, or around the neck, ears, or eyes.

<sup>§</sup> Symptoms of at least two allergic diseases among asthma, allergic rhinitis, and eczema.