



Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh



Allergic sensitisation in early childhood: Patterns and related factors in PARIS birth cohort

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ARTICLE INFO

Article history:

Received 10 May 2016

Received in revised form 30 August 2016

Accepted 1 September 2016

Keywords:

Allergen-specific IgE

Allergic sensitization

Dietary diversification

Early life

Population-based birth cohort

Risk factors

ABSTRACT

Background: Allergic sensitisation is poorly documented in infants. This study aims to provide new insights into allergic sensitisation patterns and related factors in infancy.

Methods: This study concerns 1860 infants involved in the *Pollution and Asthma Risk: an Infant Study (PARIS)* population-based birth cohort who had a standardised health examination when 18 months old, from 2004 to 2008. Sensitisation was assessed by measurements of serum specific IgE to 12 food and 4 inhalant allergens and defined by IgE ≥ 0.35 kU_A/L. Information regarding lifestyle and environment were obtained from questionnaires prospectively administered.

Results: Prevalence of allergic sensitisation to any allergen, to food allergens, and to aeroallergens was 13.8%, 12.3%, and 2.3%, respectively. Multiple sensitisation (to at least two allergens) concerned 6.2% of toddlers. Intrinsic factors such as male gender, family history of allergy, and high birth weight increased the risk of food allergen sensitisation and multiple sensitisation. Caesarean section was also positively associated with multiple sensitisation. Day-care attendance was negatively related to food allergen, aeroallergen, and multiple sensitisation. A cat entering the baby's room in early life was strongly associated with aeroallergen sensitisation (ORa 3.21, 95%CI: 1.29–8.01). An introduction of meat in infant's diet after 6 months of age was negatively related to food allergen sensitisation (ORa 0.46, 95%CI: 0.24–0.91). **Conclusion:** Our results suggest that intrinsic factors and indicators of exposure to microorganisms such as caesarean section and day-care attendance may be associated with inhalant as well as food allergen sensitisation in infancy. For example, male gender, family history of allergy, high birth weight, and caesarean section could be positively related whereas day-care attendance could be negatively related to both aeroallergen and food allergen sensitisation. Conversely, early life exposure to inhalant allergens or food allergens may be specifically linked to either aeroallergen sensitisation or food allergen sensitisation, respectively.

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1. Introduction

The prevalence of allergic diseases, namely asthma, allergic rhinitis, atopic dermatitis, and food allergies has increased critically in industrialised countries over the last thirty years, although prevalence curves for respiratory forms tend to stabilise or even to decline in countries with high-prevalence (Asher et al., 2006;

Sicherer, 2011). Allergic sensitisation has been shown to be predictive of these diseases in longitudinal epidemiological studies (Arbes et al., 2007; Pinart et al., 2014). Allergic sensitisation prevalence ranges from about a third of children below 6 years of age to nearly half of older children (Gruzdeva et al., 2014; Salo et al., 2014). But this prevalence is poorly documented in infancy, when allergic sensitisation is likely to develop (Nissen et al., 2013). Moreover, allergic sensitisation is complex, and evolves over time: children naturally become sensitised and unsensitised (Kalevayas et al., 2002; Kulig et al., 1999; p. 199), with sensitisation peaks to specific allergens being age-dependant (Sun et al., 2014).

Besides, although factors such as male gender and parental history of allergy are known to be associated with allergic sensitisation

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(Kerkhof et al., 2005; Salo et al., 2014), the potential role of many factors related to lifestyle and environment (for instance: age at introduction of solid foods (Nwaru et al., 2013; Zutavern et al., 2006), exposure to pets (Chen et al., 2008, 2007; Mandhane et al., 2009), to microorganisms (Bager et al., 2008; Krämer et al., 1999; Sozańska et al., 2015)) is still discussed in the literature, and therefore needs to be clarified. This knowledge is absolutely essential for prevention, early diagnosis and management of allergic sensitisation, in order to reduce the development of consecutive allergic diseases.

This paper therefore aims to assess the prevalence and patterns of allergic sensitisation and related factors at 18 months of age in the *Pollution and Asthma Risk: an Infant Study* (PARIS), a population-based prospective birth cohort designed to explore the development of respiratory and allergic diseases in relation to lifestyle and environment (Clarisse et al., 2007).

2. Material and methods

2.1. Population

The present allergic sensitisation study was conducted in the population-based PARIS birth cohort, consisting as previously described (Clarisse et al., 2007) of 3860 full-term and healthy singletons, born from parents living in Paris or close suburbs and from a mother with a good understanding of French. They were recruited between February 2003 and June 2006 from five public Parisian maternity hospitals. Every day, eligible infant's mothers were solicited at the hospital within 24–72 h after delivery and 59.4% accepted to participate. During this interview, PARIS study objectives and framework were presented to the families.

Our study deals with the children whose parents opted to participate in a free health examination offered to children when they were 18 months old, from 2004 to 2008.

2.2. Data collection and ethics

During the medical examination at 18 months, parents were given a standardised questionnaire by the paediatrician. A blood sample was also taken from each child and analysed for immunoglobulin E (IgE) measurement. The National Ethics Committee approved the research protocol (permissions no. 031153 and 051289) and written informed consent was obtained from the parents.

Parents documented the environment of each new-born one month after birth via a phone interview. New information and changes in the infants' environment, health, and lifestyle habits were then documented by quarterly self-administered questionnaires (Clarisse et al., 2007).

2.3. Studied factors

Family history of allergy was determined according to whether the mother, father and/or one of the older siblings had ever experienced allergic diseases such as asthma, allergic rhinitis, or eczema. Delivery (vaginal birth or caesarean section) was recorded and birth weight was measured by trained nurses. Breastfeeding duration and habits (exclusive or not), age at introduction of solid foods, and day-care attendance were prospectively recorded at each follow-up point. Parents were also asked about prenatal (active maternal) and postnatal (anybody at home, one month after birth) smoking. Finally, the presence of furred pets (cat and/or dog) and moulds and/or dampness in the dwelling (four items in total: moisture stains on the walls, mould stains on surfaces, infiltration or water

stagnation, and musty odour) were also documented by questionnaire at 1 month of age.

2.4. Allergic sensitisation

Firstly, IgE were analysed in sera with ImmunoCAP® Phadiatop® and Trophatop® fx26, fx27, and fx28 (Phadia, Thermo Fisher Scientific, Uppsala, Sweden). Phadiatop® comprises a mixture of several inhalant allergens including house dust mite, cat, dog, moulds and a range of pollens. Trophatop® include the following 12 food items: egg white, cow's milk, peanut, and mustard (fx26), fish, wheat, soya, and hazelnut (fx27), and sesame, shrimp, beef, and kiwi (fx28). A positive result using Phadiatop® led to the measurement of specific IgE towards 4 aeroallergens: dust mite (*Dermatophagoides pteronyssinus*), cat, moulds (*Alternaria tenuis*) and cocksfoot (*Dactylis glomerata*). Similarly, a positive result of Trophatop® led to the measurement of specific IgE towards all the respective food items.

Allergic sensitisation was defined by at least one allergen-specific IgE ≥ 0.35 kU_A/L and multiple sensitisation by at least two allergen-specific IgE above this threshold.

2.5. Statistical analyses

Prevalence of sensitisation to any allergen, food allergens, and aeroallergens and of multi-sensitisation were estimated.

The age when each type of food was first introduced was categorised into two classes – before or after 6 months – with regard to current guidelines concerning infants' dietary diversification (Agostoni et al., 2008; Muraro et al., 2014). Socio-economic status was assessed according to the highest occupation of the two parents, and categorised as either low, medium, or high. Day-care attendance was categorised according to whether the child attended day-care or was looked after in child-minder's home, or whether the infant was always minded at home. The presence of moulds in dwellings was determined by the presence of at least two of the criteria among the four recorded. Three variables concerning pet allergen exposure in early life were tested: furred pets (cat and/or dog) at home, cat at home, and cat entering the baby's room.

Risk factors of food allergen, aeroallergen and multiple sensitisation were assessed by logistic multivariate regressions after adjusting for relevant potential confounders. Known and suspected risk factors according to the literature as well as variables associated with sensitisation in univariate analyses with a p -value ≤ 0.25 were introduced in multivariate models. In order to study potential modifying effects of gender and family history of allergy on associations between allergic sensitisation and the studied variables (parity, delivery, birth weight, exclusive breastfeeding, age of introduction of food categories, day-care attendance, dwelling dampness, and pet ownership), each OR were compared between strata using Mantel-Haenszel χ^2 tests. Besides, potential reverse causality was also taken into account for all studied variables: OR were adjusted for family history of allergy in multivariate analyses, potential associations between the studied variables and family history of allergy were assessed by χ^2 tests, and separate analyses were performed in infants with family history of allergy. All statistical analyses were performed using Stata® software version 11.2.

3. Results

3.1. Study sample characteristics

The present study dealt with the 1860 toddlers who participated in the health examination at 18 months and for whom

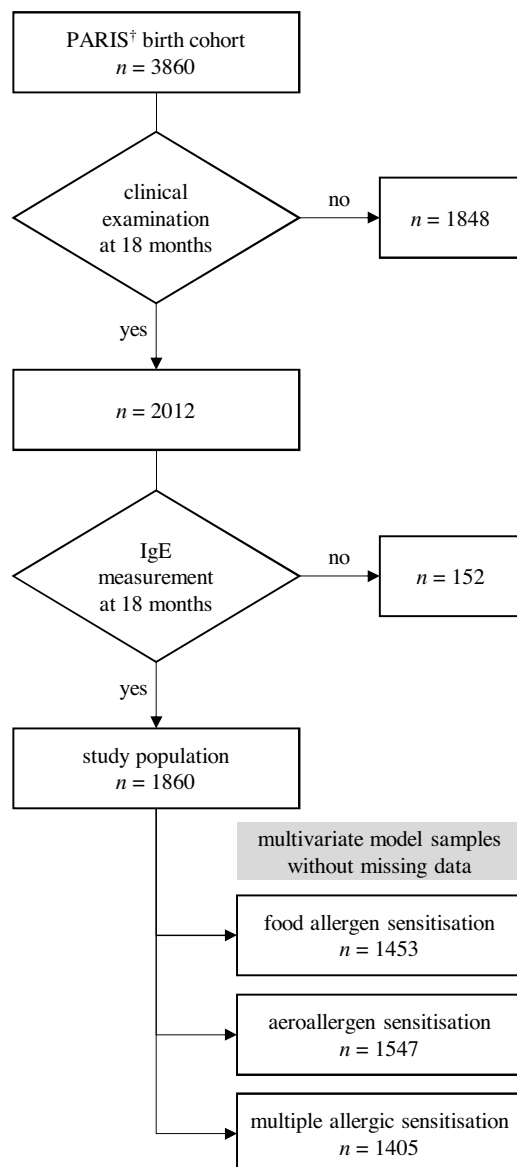


Fig. 1. Flow chart of PARIS birth cohort infants participating in the allergic sensitisation study.

† PARIS: Pollution and Asthma Risk: an Infant Study.

allergen-specific IgE data were available (Fig. 1). Their mean age was 19.1 ± 1.7 months.

Table 1 compares participants and non-participants: participants were more likely to have parents with a high socio-economic status, and to have been breastfed for longer. There was however no significant difference between the two groups with regard to gender, siblings, family history of allergy, birth weight, or prenatal and postnatal smoking.

3.2. Prevalence of allergic sensitisation

Sensitisation to at least one allergen was found in 13.8% (95%CI: 12.2–15.3, $n=249$) infants. Sensitisation to food allergens concerned 12.3% (10.8–13.9, $n=225$) of infants (Fig. 2a) and to inhalant allergens 2.3% (1.6–3.0, $n=43$) (Fig. 2b). Furthermore, 6.2% (5.0–7.3, $n=111$) toddlers were multi-sensitised either to several food allergens (81.3%) or to both food and inhalant allergens (18.7%).

The main concerned foods (Fig. 2a) were cow's milk (7.6%, $n=139$), egg white (6.6%, $n=121$), hazelnut (2.3%, $n=42$), and

peanut (1.9%, $n=34$), accounting for 93.3% of food sensitisation cases. Furthermore, almost half of the infants with food allergen sensitisation were sensitised to at least two different items (46.7%, $n=105/225$). Besides, aeroallergen sensitisation (Fig. 2b) was mostly due to dust mites and cat in equal shares: 1.1% ($n=21$ and $n=20$, respectively).

3.3. Risk factor analyses

Tables 2–4 describe statistical associations between potential risk factors and food allergen (multivariate regression on $N=1453/1860$ infants, due to missing values), aeroallergen ($N=1547/1860$), and multiple sensitisation ($N=1405/1860$), respectively. Table 2 shows that boys, infants with family history of allergy, and those belonging to the highest birth weight quartile have a higher risk of food allergen sensitisation at 18 months. Caesarean delivery also tended to be associated with an increased risk. Conversely, day-care attendance and the introduction of meat after 6 months led to a reduced risk of food sensitisation. Aeroallergen sensitisation at 18 months (Table 3) is associated negatively with day-care attendance and positively with the presence of a cat only when it enters the baby's room (ORa 1.50, 0.65–3.47 for “furred pets at home”, ORa 1.74, 0.71–4.22 for “cat at home”, and ORa 3.21, 1.29–8.01 for “cat entering the baby's room”). Finally, multiple sensitisation risk factors (Table 4) are male gender, family history of allergy, high birth weight, and caesarean section. Conversely, a strong negative association was observed between day-care attendance and multi-sensitisation (ORa 0.43, 0.26–0.71), the latter also tending to be less frequent in toddlers with older siblings. The age at the beginning of day-care attendance did not have any effect.

Lastly, there was no modifying effect of gender or family history of allergy (Mantel-Haenszel χ^2 all not significant, *data not shown*). Besides, no evidence of reverse causality was found, whatever the studied variable (*data not shown*): family history of allergy was not associated with any studied variable, and associations between risk factors and allergic sensitisation remain similar among the subgroup of children with family history of allergy, in comparison with the whole study population.

4. Discussion

This study on infants from a population-based birth cohort emphasises that allergic sensitisation prevalence is already high as soon as eighteen months of age. Intrinsic factors such as gender, family history of allergy, and birth weight and indicators of exposure to microorganisms like day-care attendance and caesarean section seem associated with inhalant as well as food allergen sensitisation in infancy. Aeroallergen sensitisation is positively and strongly associated with cat ownership only when it enters the baby's room. An introduction of meat above the recommended age of six months appears to be protective against food allergen sensitisation.

4.1. Strengths and limitations

The present study draws its strength from dealing with nearly two thousands infants from a prospective population-based birth cohort. This design, combined with the parents' interview by a paediatrician during the health examination, reduces the reporting bias of the clinical history. Furthermore, the definition of sensitisation is based upon blood measurements from a large panel of allergens. As far as the reported family history of allergy is concerned, we restricted the definition by only considering asthma, allergic rhinitis and eczema. Food allergies were omitted in order to avoid misclassification: results of oral food challenges were not available

Table 1

Characteristics of PARIS birth cohort infants participating or not in the allergic sensitisation study at 18 months.

	n (%) sensitisation study		p-value
	Participating infants N = 1860 ^a	Not participating infants N = 2000 ^{a,b}	
gender			0.070
boy	926 (49.8)	1054 (52.7)	
girl	934 (50.2)	946 (47.3)	
older siblings			0.43
no	1074 (59.2)	1136 (57.9)	
yes	741 (40.8)	826 (42.1)	
socio-economic status			<0.001
low	141 (7.6)	222 (11.1)	
intermediate	481 (26.0)	589 (29.6)	
high	1229 (66.4)	1182 (59.3)	
family history of allergy			0.58
no	759 (41.4)	837 (42.3)	
yes	1075 (58.6)	1143 (57.7)	
birth weight (Kg, mean $\pm$ SD)	3.396 $\pm$ 0.403	3.408 $\pm$ 0.387	0.32
exclusive breastfeeding			0.002
< 3 months	1263 (70.1)	1395 (74.7)	
$\geq$ 3 months	539 (29.9)	473 (25.3)	
prenatal smoking			0.79
no	1652 (88.9)	1771 (88.6)	
yes	207 (11.1)	228 (11.4)	
postnatal smoking			0.74
no	1365 (74.3)	1419 (73.8)	
yes	472 (25.7)	503 (26.2)	

Socio-economic status: the highest parental occupation among the two parents, at birth. Family history of allergy: mother's, father's and/or older siblings' history of asthma, allergic rhinitis or eczema, at birth. Prenatal smoking: active maternal smoking. Postnatal smoking: anybody smoking at home, one month after birth.

^a Number of children may vary because of missing information.

^b 1848/3860 infants did not performed the health examination at 18 months of age, and sensitisation data were not available for 152/2012 who performed it.

and reported food allergies were not considered due to a common confusion with food intolerance.

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 prone to enrol in longitudinal studies, and to perform clinical examinations (Lau et al., 2000; Moore et al., 2004). And, further, they live nearer to the city centre where the health examination took place (p -value < 0.001). It is also possible that parents from the low socio-economic category have less job flexibility to attend the health examination, even though it was free-of-charge. Besides, PARIS toddlers are more likely to be still exclusively breastfed at age 3 months with socio-economic status increase (p -trend = 0.005). Breastfeeding duration and socio-economic status are generally related (Amir and Donath, 2008; Logan et al., 2016): parents from a higher socio-economic 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. Furthermore, there is not any other significant difference between participants and non-participants, especially with regard to the variables of interest. Consequently, the afore-mentioned differences should not greatly affect our results.

4.2. Prevalence and patterns of allergic sensitisation

Allergic sensitisation has been well described in childhood, and its prevalence varies from 24.1% to 40.4% before the age of 6 years and between 34.8% and 47.9% above this age in cohorts, according to the studied population (Gruzdeva et al., 2014). However, few studies have assessed the prevalence of allergic sensitisation in early life. In infants aged 2 years or less involved in European population-based birth cohorts, published prevalence statistics based on specific IgE measurements (≥ 0.35 kU_A/L) towards common food and inhalant allergens vary between 8.0% and 26.1% (Nickel et al., 1997; Nissen et al., 2013; Zutavern et al., 2006). These differences may be due to

the diversity of the tested allergens, or to the features of the studied populations.

Nissen et al. (2013), for instance, rated sensitisation at 8% among 276 eighteen month old Danish children. They measured specific IgE towards egg, cow's milk and a brand of inhalant allergens, only. According to Zutavern et al. (2006), 12% and 9% of 2094 children from *Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood* (LISA) birth cohort were sensitised at 2 years of age to any allergen and to food allergens (egg, cow's milk, wheat, peanut, soybean, and cod fish), respectively. The higher prevalence we found at the same age (13.8% to any allergen and 12.4% to food allergens) may be explained by the larger panel of food allergens tested in our study, especially hazelnut against which 2.3% of PARIS toddlers were sensitised. Apart from this, Nickel et al. (1997) evaluated sensitisation in 1314 infants involved in *Multicentre Allergy Study* (MAS) birth cohort at 12 and 24 months of age: 16.4% and 26.1%, respectively, with regard to both food and inhalant allergens and 14.1% and 17.9%, respectively, regarding food allergens only. These higher values may result from the fact that the MAS population was enriched with children at high risk for allergic diseases (Bergmann et al., 1994).

Overall, the prevalence of sensitisation to at least one allergen (13.8%) assessed in PARIS birth cohort – on a large number of infants – appears already high at 18 months of age. Considering the tested allergen panel, food allergen sensitisation prevails over inhalant allergen sensitisation, which is consistent with the literature (Baatenburg de Jong et al., 2011; Salo et al., 2014). Nevertheless, hazelnut-specific sensitisation ranks as the third highest prevalence rate which has not yet been reported (Arshad et al., 2001; Nickel et al., 1997; Zutavern et al., 2006), especially in the French general population (Rancé et al., 1999).

4.3. Risk factors of allergic sensitisation

The identified factors belong to two categories: firstly intrinsic factors such as gender, family history of allergy, and birth weight

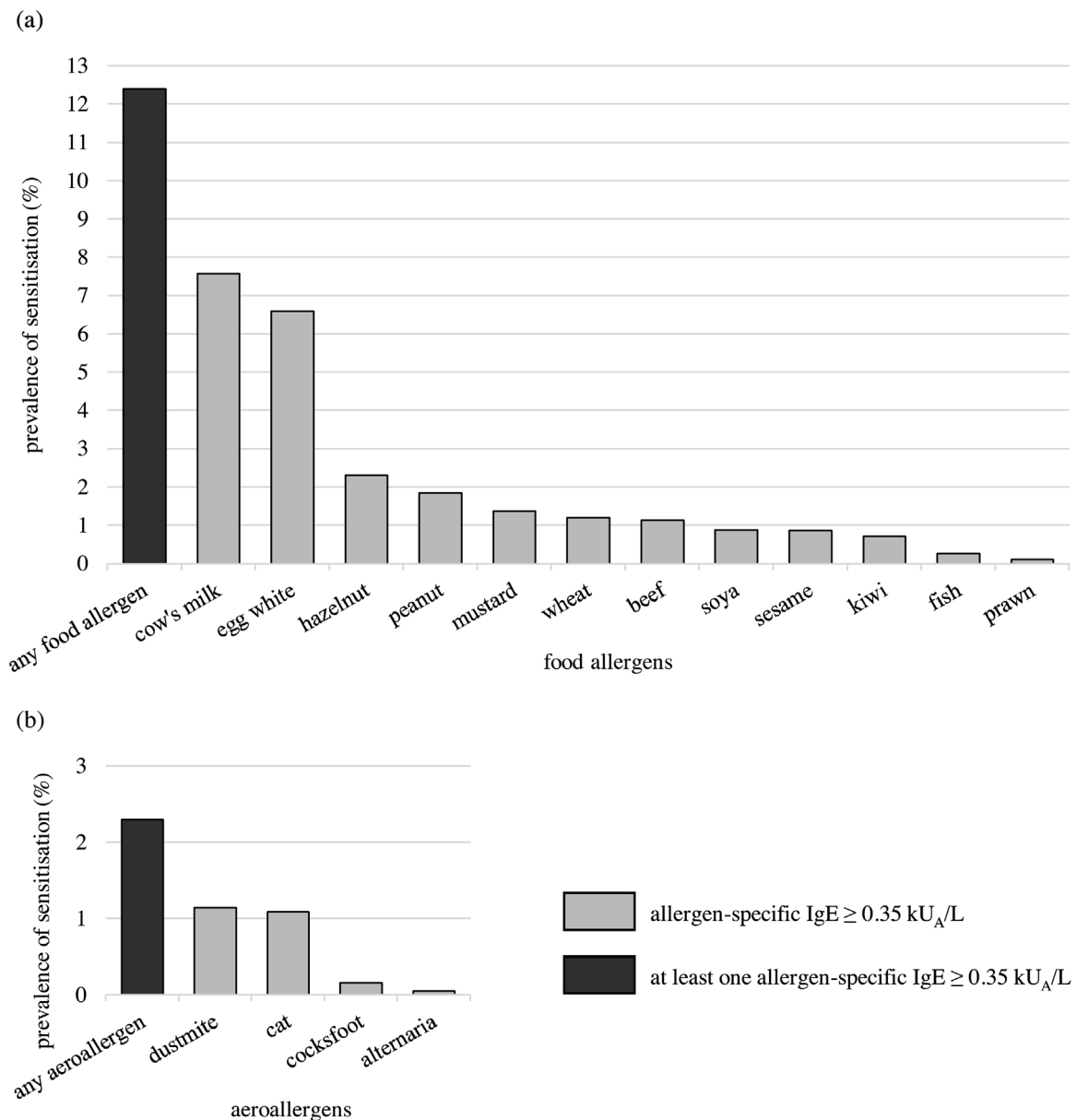


Fig. 2. Sensitisation to (a) food allergens and (b) aeroallergens at 18 months of age in PARIS birth cohort infants (N = 1860).

and then extrinsic factors related to various exposures either to microorganisms, aeroallergens, or foods.

In this study, boys appeared to be more sensitised than girls concerning food allergen sensitisation and multi-sensitisation at 18 months. These results confirm – in early childhood – some data previously reported in older children (Baatenburg de Jong et al., 2011; Kerkhof et al., 2005; Nissen et al., 2013; Salo et al., 2014). Several works focusing on inhalant allergens (Kuehr et al., 1992; Leadbitter et al., 1999) also reported an increase in sensitisation risk in boys and some authors (Govaere et al., 2007) even highlighted the younger the children the stronger the association. We did not observe such association at 18 months of age probably due to a lack of power, the number of infants sensitised to inhalant allergens being low at this age.

The absence of association between family history of allergy and inhalant allergen sensitisation in offspring could be explained by this lack of power. The atopic march might also be the main reason of the discrepancy between our results and those from previous studies conducted in older children (Arshad et al., 2012; Kerkhof

et al., 2005; Kuehr et al., 1992) which generally report positive associations whatever the type of sensitisation.

Lastly, new-borns belonging to the highest birth weight quartile were more likely to be sensitised to food allergens. The relation between weight status and allergic sensitisation is unclear in the literature, especially because of methodological differences between studies as pointed out in a recent review (Wandalsen et al., 2014). Nevertheless, our result is in accordance with some studies (Remes et al., 2008; Tedner et al., 2012) and the hypothesis of Hersoug and Linneberg (2007) that an increase in adipose tissue leads to reduced production of IL-10, which is an anti-inflammatory cytokine maintaining immunological tolerance.

Besides these intrinsic factors, we identified several factors negatively associated to sensitisation that are indicators of early exposure to infectious microorganisms, in line with the hygiene hypothesis. Day-care attendance appeared negatively and strongly associated to sensitisation at 18 months in all models. PARIS data showed that infants' minding began massively soon after age 3 months (57.3% of infants), which matches with the end of the

Table 2Risk factor analysis for food allergen sensitisation^a in PARIS birth cohort infants at 18 months of age (N = 1453).

Potential factors	Crude OR (95%CI)	Adjusted OR ^b (95%CI)	p-value ^c
intrinsic factors			
gender			
girl	1	1	
boy	1.48 (1.12–1.97)	1.62 (1.16–2.25)	0.005
family history of allergy			
no	1	1	
yes	1.34 (1.00–1.80)	1.40 (1.00–1.97)	0.048
birth weight			
≤3th quartile	1	1	
>3th quartile	1.60 (1.18–2.16)	1.74 (1.19–2.54)	0.004
indicators of exposure to microorganisms			
older siblings			
no	1	1	
yes	0.78 (0.58–1.04)	0.79 (0.56–1.13)	0.20
delivery			
vaginal birth	1	1	
caesarean section	1.32 (0.94–1.86)	1.45 (0.97–2.19)	0.073
day-care attendance			
no	1	1	
yes	0.62 (0.43–0.87)	0.62 (0.43–0.91)	0.014
infant's diet			
exclusive breastfeeding			
< 3 months	1	1	
≥ 3 months	0.97 (0.71–1.32)	0.92 (0.64–1.32)	0.65
age at introduction of fruit			
<6 months	1	1	
>6 months	1.01 (0.76–1.35)	1.16 (0.78–1.74)	0.46
age at introduction of vegetables			
<6 months	1	1	
>6 months	0.90 (0.68–1.21)	0.99 (0.65–1.52)	0.97
age at introduction of egg			
<6 months	1	1	
>6 months	0.54 (0.18–1.63)	1.09 (0.26–4.62)	0.91
age at introduction of fish			
<6 months	1	1	
>6 months	0.58 (0.31–1.08)	0.90 (0.35–2.29)	0.82
age at introduction of meat			
<6 months	1	1	
>6 months	0.55 (0.35–0.87)	0.46 (0.24–0.91)	0.026

Family history of allergy: mother's, father's and/or older siblings' history of asthma, allergic rhinitis or eczema. Day-care attendance: infants attending day-care or child-minder's home *versus* infants minded at home.

^a Defined by at least one food allergen-specific IgE ≥ 0.35 kU_A/L.

^b OR were adjusted for socio-economic status, prenatal and postnatal smoking, presence of furred pets at birth, gestational age, mother's geographic origin, mother's age at birth, infant's age at the health examination, body mass index z-score at the health examination and all the other variables of interest listed in this table.

^c p-value associated with the adjusted Odds Ratio.

French legal maternal leave time. However, some children were minded lately (11.7% after age 12 months): latency period could be reduced for these children because day-care attendance was regarded until age 18 months. In addition, later-born children tended to be less frequently multi-sensitised. These results confirm several published works showing sometimes protective associations in older children with parity (Sozańska et al., 2015) and day-care attendance (Krämer et al., 1999), although these relations were not always observed (Caudri et al., 2009; Kerkhof et al., 2005; Leadbitter et al., 1999; Nicolaou et al., 2008; Perzanowski et al., 2008). Furthermore, diet habits could also explain these results for food allergen sensitisation. Indeed, introduction of solid foods could happen earlier, and diet could be more diversified in infants attending day-care or having older siblings. This early diversification is generally regarded as protective towards allergic sensitisation (Kull et al., 2006; Nwaru et al., 2013; Roduit et al., 2014; Zutavern et al., 2008).

In the PARIS study sample, sensitisation also tended to be more frequent in children born by caesarean section. Several teams related caesarean section to sensitisation to food (van Nimwegen et al., 2011) or inhalant (Pistiner et al., 2008) allergens, whereas some other authors did not (Kerkhof et al., 2005; Maitra et al., 2004). Through a meta-analysis, Bager et al. (2008) underlined a

possible risk increase for food allergen sensitisation, and no effect on aeroallergen sensitisation. The lower food tolerance observed in infants born by caesarean section might be due to a gut microbial flora proven modification, especially to a less frequent colonisation with enterococci and bifidobacteria and to an increase in clostridia counts (Björkstén et al., 2001).

As expected, the associations observed with risk factors of food allergen sensitisation also appear and even strongly for simultaneous sensitisation to several allergens, mainly food allergens at this age.

We clearly report an increased risk of aeroallergen sensitisation when infants have been in close contact with a cat as soon as birth. The role of cat allergen exposure in infancy remains unclear in the literature (Chen et al., 2008), results being conflicting: sometimes protective (Kerkhof et al., 2005; Mandhane et al., 2009), sometimes deleterious (Al-Mousawi et al., 2004; p.; Chen et al., 2007; Kuehr et al., 1992), and sometimes without any significant relation (Campo et al., 2006; Van Gysel et al., 2009). These equivocal results may be explained in part by differences in age at the sensitisation assessment (Chen et al., 2007; Kerkhof et al., 2005), age of exposure (Al-Mousawi et al., 2004, p.; Kuehr et al., 1992), presence of other pets (Mandhane et al., 2009), and by the modifying effect of parental socio-economic status (Apfelbacher et al., 2010). A poten-

Table 3Risk factor analysis for aeroallergen sensitisation^a in PARIS birth cohort infants at 18 months of age (N = 1547).

Potential factors	Crude OR (95%CI)	Adjusted OR ^b (95%CI)	p-value ^c
intrinsic factors			
gender			
girl	1	1	
boy	1.40 (0.76–2.59)	1.18 (0.58–2.41)	0.64
family history of allergy			
no	1	1	
yes	0.81 (0.44–1.48)	0.96 (0.48–1.92)	0.90
birth weight			
≤3th quartile	1	1	
>3th quartile	0.95 (0.46–1.94)	1.30 (0.56–3.04)	0.54
indicators of exposure to microorganisms			
older siblings			
no	1	1	
yes	0.69 (0.36–1.32)	0.61 (0.28–1.32)	0.21
delivery			
vaginal birth	1	1	
caesarean section	1.86 (0.94–3.65)	1.77 (0.79–3.96)	0.17
day-care attendance			
no	1	1	
yes	0.39 (0.20–0.79)	0.40 (0.19–0.83)	0.014
environmental factors			
cat entering the baby's room			
no	1	1	
yes	2.38 (1.04–5.46)	3.21 (1.29–8.01)	0.012
dampness and/or moulds at home			
no	1	1	
yes	1.35 (0.64–2.85)	1.67 (0.74–3.74)	0.22

Family history of allergy: mother's, father's and/or older siblings' history of asthma, allergic rhinitis or eczema. Day-care attendance: infants attending day-care or child-minder's home *versus* infants minded at home. Cat entering the baby's room: one month after birth. Dampness and/or moulds at home: one month after birth, and at least two criteria among the four recorded.

^a Defined by at least one inhalant allergen-specific IgE ≥ 0.35 kU_A/L.

^b OR were adjusted for socio-economic status, prenatal and postnatal smoking, gestational age, mother's age at birth, season of birth, exclusive breastfeeding, infant's age at the health examination, body mass index z-score at the health examination and all the other variables of interest listed in this table.

^c p-value associated with the adjusted Odds Ratio.

Table 4Risk factor analysis for multiple sensitisation^a in PARIS birth cohort infants at 18 months of age (N = 1405).

Potential factors	Crude OR (95%CI)	Adjusted OR ^b (95%CI)	p-value ^c
intrinsic factors			
gender			
girl	1	1	
boy	1.97 (1.31–2.94)	1.88 (1.18–3.00)	0.008
family history of allergy			
no	1	1	
yes	1.78 (1.16–2.72)	2.58 (1.54–4.31)	<0.001
birth weight			
≤3th quartile	1	1	
>3th quartile	1.73 (1.15–2.61)	1.92 (1.15–3.21)	0.013
indicators of exposure to microorganisms			
older siblings			
no	1	1	
yes	0.60 (0.39–0.91)	0.65 (0.39–1.06)	0.083
delivery			
vaginal birth	1	1	
caesarean section	1.36 (0.85–2.17)	1.75 (1.02–2.99)	0.041
day-care attendance			
no	1	1	
yes	0.47 (0.30–0.76)	0.43 (0.26–0.71)	0.001
environmental factors			
cat entering the baby's room			
no	1	1	
yes	1.46 (0.78–2.73)	1.58 (0.79–3.17)	0.20

Family history of allergy: mother's, father's and/or older siblings' history of asthma, allergic rhinitis or eczema. Day-care attendance: infants attending day-care or child-minder's home *versus* infants minded at home. Cat entering the baby's room: one month after birth.

^a Defined by at least two allergen-specific IgE ≥ 0.35 kU_A/L.

^b OR were adjusted for socio-economic status, prenatal and postnatal smoking, gestational age, mother's age at birth, exclusive breastfeeding, infant's age at the health examination, body mass index z-score at the health examination and all the other variables of interest listed in this table.

^c p-value associated with the adjusted Odds Ratio.

tial classification bias concerning cat allergen exposure assessment could also be in cause. Although cat allergens have been shown volatile and stable (Antens et al., 2006), crude variables “furred pets

at home” and “cat at home” may not be fully accurate for the assessment of the true exposure to cat allergens. The association with aeroallergen sensitisation is indeed only observed with the vari-

able “cat entering the baby’s room”. It is in accordance with Chen et al. (2007) who showed the higher the cat allergen level in house dust, the more the cat allergen sensitisation risk increases.

Regarding dietary diversification, current guidelines recommend the introduction of food before 6 months of age (Agostoni et al., 2008; Muraro et al., 2014), the evidence of a protective effect against allergic diseases of a delayed introduction could not be highlighted (Zutavern et al., 2006). Conversely, a delayed (Zutavern et al., 2008) and undiversified (Kull et al., 2006; Nwaru et al., 2013; Roduit et al., 2014) introduction of solid food seems to be harmful regarding sensitisation in childhood. Our work, without contradicting previous results (no associations were found here for fruit, vegetables, egg and fish) (Nwaru et al., 2013; Roduit et al., 2014), questions these recommendations as far as meat is concerned. Indeed, for the first time we clearly show that an introduction of meat beyond the age of 6 months is associated with a decreased risk of food allergen sensitisation at 18 months. This relation does not result from a reverse causality, the age of introduction of solids did not differ in infants with or without heredity of allergic diseases. Kull et al. (2006) posited the benefits of fish intake regarding allergic sensitisation, possibly due to the anti-inflammatory effect of omega-3 polyunsaturated fatty acid (Devereux and Seaton, 2005). Consequently, it can be speculated that the delayed introduction of meat, low in omega-3 fatty acids in favour of pro-inflammatory omega-6 fatty acids (Devereux and Seaton, 2005), could protect against allergic sensitisation.

5. Conclusion

This study provides new insights into the prevalence and patterns of allergic sensitisation in early childhood. It suggests – in very young children as early as 18 months of age – that intrinsic factors such as gender, family history of allergy, and birth weight and indicators of exposure to microorganisms like day-care attendance and caesarean section are associated with inhalant as well as food allergen sensitisation in infancy. For example, intrinsic factors and caesarean section could be positively related whereas day-care attendance could be negatively related to both aeroallergen and food allergen sensitisation. Conversely, exposure in early life to inhalant allergens or food allergens may be specifically linked to either aeroallergen sensitisation or food allergen sensitisation, respectively.

Conflicts of interest

The authors have no conflicts of interest to declare.

Authors' contributions

SG was in charge, under the supervision of IM and NS, of data management, statistical analyses, results interpretation and manuscript writing. RC was in charge of IgE measurements. JJ and NS contributed to results interpretation providing allergy and paediatric expertise for JJ and biological expertise for NS. JJ, NS and IM reviewed the manuscript and revised it critically for content.

Funding

All phases of this study were supported by the Social, Childhood and Health Direction (DASES) of the Paris Municipality, the Paris Descartes University – Sorbonne Paris Cité, the French Agency for Food, Environmental and Occupational Health and Safety (Anses), the Paris Health Centre of the National French Health Insurance System, and the Paris Municipality Saint Marcel's Centre.

Acknowledgments

This survey is supported by the Social, Childhood and Health Direction (DASES) of the Paris Municipality. We are thankful to the Paris Health Centre of the National French Health Insurance System and the Paris Council Saint Marcel's Centre that received the infants for the health examination. We also thank the physicians, the nurses and the administrative staff members for their collaboration in ensuring that the health examination went smoothly. Finally, we are grateful to all the parents and children who participated in this study and for their continuous involvement in the PARIS cohort over the years.

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