

Perinatal risk factors for sensitization, atopic dermatitis and wheezing during the first year of life (PIPO study)

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Summary

Objective To evaluate the influence of perinatal environmental factors on early sensitization, atopic dermatitis and wheezing during the first year.

Methods Information on pregnancy-related factors, parental atopic history, environmental factors and the clinical course of the infant until age one was gathered by questionnaires, as part of a prospective birth cohort study (Prospective study on the Influence of Perinatal factors on the Occurrence of asthma and allergies [PIPO-study]). Quantification of total and specific IgE was performed in 810 children and their parents.

Results Early sensitization was found in 107/810 (13%) of the infants. Multiple regression analysis showed that specific IgE in fathers was a risk factor for early sensitization in their daughters (adjusted odds ratios (OR_{adj}) 2.21 (95% confidence interval (CI) 1.10–4.49); $P = 0.03$), whereas in boys, day care attendance was shown to be protective for early sensitization (OR_{adj} 0.38 (95% CI 0.20–0.71); $P = 0.001$). Atopic dermatitis occurred in 195/792 infants (25%). Specific IgE in the mother (OR_{adj} 1.52 (95% CI 1.06–2.19); $P = 0.02$) and in the infant (OR_{adj} 4.20 (95% CI 2.63–6.68); $P < 0.001$) were both risk factors for the occurrence of atopic dermatitis, whereas postnatal exposure to cats was negatively associated with atopic dermatitis (OR_{adj} 0.68 (0.47–0.97); $P = 0.03$).

Postnatal exposure to cigarette smoke (OR_{adj} 3.31 (95% CI 1.79–6.09); $P < 0.001$) and day care attendance (OR_{adj} 1.96 (95% CI 1.18–3.23); $P = 0.009$) were significantly associated with early wheezing, which occurred in 25% (197/795) of the infants.

Conclusion The effect of paternal sensitization and day care attendance on sensitization is gender dependent. Maternal sensitization predisposes for atopic dermatitis, whereas postnatal exposure to cats had a protective effect.

Keywords allergy, atopic dermatitis, infant, risk factor, sensitization

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Introduction

Atopic disorders, which include atopic dermatitis, allergic rhino-conjunctivitis and asthma, represent a major and increasing health problem in the western world, especially in children [1–3]. The mechanism behind this increase over the last 30 years is presumed to be multi-factorial. In particular, the interaction between genetic and environmental factors seems to play a crucial role [4–6].

Multiple epidemiological studies have associated the increase in atopic diseases with reduced and/or changed microbial burden through factors such as family size, day care attendance, vaccination and antibiotic use [7–10]. In addition, the development of atopic diseases has been related to allergen exposure, air pollution, cigarette smoking, nutri-

tional factors and socio-economic status [11–14]. The impact of environmental exposure on the development of atopic disorders seems most important during the first years of life [11, 13]. Furthermore, it is reasonable to believe that prenatal environmental factors and maternal influences during gestation may also contribute to the development of atopic diseases. Moreover, sensitization may even start *in utero* [15, 16]. Despite numerous publications on this subject, the main determinants of the sensitization process and subsequent development of atopic disorders remain to be disentangled. The theoretical dogma that allergen exposure induces sensitization and that continued exposure leads to clinical atopic diseases has recently been challenged. For example, exposure to cats has been found to increase as well as to decrease the risk for sensitization to inhalant allergens and development of atopic diseases in childhood [17–22].

Because identification of risk factors for the development of atopic disorders is a prerequisite for adequate prevention, additional research is warranted. Furthermore, the role of environmental factors needs to be addressed in well-defined

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populations, as the effect of certain environmental factors might differ according to, e.g., the atopic status of the parents and/or the time of exposure (prenatal, postnatal) [22].

In this report, we present the first results of our prospective birth cohort study followed up to 1 year. First, the influence of pre- and postnatal environmental factors on early sensitization to food and inhalant allergens is assessed. Then, we describe the relation between these environmental factors and the development of atopic and respiratory symptoms during the first year of life. Atopic dermatitis was considered as the initial clinical manifestation of an atopic constitution and the presence of wheezing is used as a marker for bronchial hyper-reactivity. In contrast to most other prospective studies, we performed measurements of specific IgE both in infants and parents, which enabled us to evaluate the contribution of a parental genetic predisposition for atopy on early sensitization, atopic dermatitis and wheeze and its possible interaction with the environmental factors.

Subjects and methods

Study subjects

The data of the present report were collected during the Prospective study on the Influence of Perinatal factors on the Occurrence of asthma and allergies (PIPO study), a prospective birth cohort study that is performed at the university of Antwerp, Belgium. Mothers were prenatally recruited for this study between June 1997 and December 2001 by gynaecologists. About 55% of the approached women were willing to participate in our study, leading to a total study population of 1128 mothers. The reasons for not participating in the study were mostly a lack of time (29%), no interest (28%) and failure to be contacted by phone (23%). Other reasons included language problems (6%), living outside the Antwerp region (7%) and miscarriages (2%). Participants were required to reside in the Antwerp region and to have sufficient knowledge of the Dutch language. Enrolment occurred at a median gestation duration of 20 weeks (range 13–40). The children were subsequently born between the summer of 1997 and the winter of 2001.

The ethics committee of the University of Antwerp approved this study. Written informed consent was obtained from all parents.

Questionnaires and definitions

Parents completed questionnaires at predefined time-points, i.e. during pregnancy and when the children were 12 months old. These questionnaires included data on pregnancy-related factors (duration of pregnancy, type of delivery, birth order, birth measurements), parental characteristics (atopic history, education level), environmental factors (breastfeeding, living and housing conditions, contact with pets, exposure to tobacco smoke, siblings, child care) and on the clinical course of the infant during the first year of life (respiratory and gastro-intestinal symptoms, presence of atopic dermatitis, fever episodes).

Parental atopic history was assessed by standardized questionnaires, adapted from International Study of Asthma

and Allergic disease in Childhood (ISAAC) and European Community Respiratory Health Survey (ECRHS), focusing on having ever experienced symptoms of allergic asthma, rhino-conjunctivitis and/or atopic dermatitis. Allergic asthma was defined by self-reported diagnosis of allergic asthma or by self-reported symptoms of cough, wheeze, dyspnoea or chest tightness after contact with cats and/or dogs, dust, pollen. Allergic rhinitis was defined as the occurrence of a runny, itchy or blocked nose because of allergen exposure (cats and/or dogs, dust, pollen). Atopic dermatitis was diagnosed upon a history of an itchy rash for at least 2 weeks with a typical distribution (such as in the neck, in the knee or elbow folds, at the front of the ankles), after excluding contact dermatitis. Parental sensitization was defined as the presence of at least one specific IgE antibody detected in the parents' sera (see 'Assessment of sensitization').

The duration of breastfeeding was recorded. Pre- and postnatal contact with cats or dogs was present when the pregnant woman or the infant kept a pet at home or was in regular contact (at least 4 days a week) with pets. Prenatal exposure to tobacco smoke was defined as active smoking during pregnancy or as passive smoking by the pregnant mother on a regular basis (at least 4 days a week). Postnatal tobacco smoke exposure meant that the infant was exposed to tobacco smoke after birth during at least 4 days a week. Carpeting included the presence of carpet in the child's bedroom. The level of education of the parents was divided into six categories, ranging from elementary school up to university. Parents in the highest two categories (college and university) were defined as having a 'high level of education', as opposed to those in the four lower categories of education, defined as a 'low level of education'. A child was defined to attend day care centres when the child regularly (at least 4 days a week) attended private day care services (where a small number of other children were present) or child care centres (usually 10 or more other children present).

Only children with a skin rash at typical localizations (around the eyes/ears, in the neck, in the knee or elbow folds, at the front of the ankles, at the cheeks and scalp) were defined as having atopic dermatitis. In the absence of internationally accepted criteria for the definition of atopic respiratory symptoms in early childhood, a symptom-based approach was used and the occurrence of wheezing (never vs. ever) during the first year of life was assessed. Early sensitization of the infant was defined as the presence of at least one specific IgE antibody detected at the age of 1 year (see next paragraph).

Assessment of sensitization

At the age of 1 year, the children were invited for clinical examination and, if the parents consented, a blood drawing for quantification of total and specific IgE was performed in children and their parents. In children, specific serum IgE to the following allergens were determined: *Dermatophagoides pteronyssinus*, cat, dog, egg's white and cow's milk (CAP FEIA systems, Pharmacia Diagnostics, Brussels, Belgium). In the parents, specific serum IgE to seven common inhalant allergens (*D. pteronyssinus*, cat, dog, birch pollen, timothy grass pollen, mugwort pollen and *Cladosporium herbarum*)

were quantified. Specific IgE below 0.35 kUa/mL was considered as negative. Atopic sensitization was defined as having at least one positive specific IgE.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 11.0; SPSS Inc., Chicago, IL, USA). Multiple logistic regression analysis was used to estimate the effect of various (environmental) factors on the occurrence of sensitization, atopic dermatitis and wheeze during the first year of life. The three research questions were addressed in three separate analyses, using identical methodology. Potential perinatal risk factors for early sensitization, atopic dermatitis and wheeze were selected according to data available in the literature and were used as covariates. In all analyses, the role of sex, mode of delivery, birth weight, breastfeeding (ever or at least 3 months), presence of siblings, day care attendance, pre- and postnatal contact with cats, dogs and cigarette smoke, educational level of the parents, presence of carpeting in the child's bedroom and parental atopy were assessed. For each research question, we started from a model including all potential risk factors and interaction terms for gender, educational level and atopic status of the parents. It was decided to perform a stratified analysis whenever one of these characteristics modified multiple exposure–outcome associations. Otherwise, significant interaction terms were kept in the model as well as their components. Other covariates were stepwise (manual) removed based on the maximum-likelihood statistics. Results are presented as adjusted odds ratios (OR_{adj}) and 95% confidence intervals (95% CI). A *P*-value of <0.05 was regarded as statistically significant.

Results

Study population

A total of 1128 children were recruited in the PIPO study. Of the 1084 (96%) participants that completed the follow-up until the postnatal age of 1 year, 821 families attended the hospital and blood sampling was performed in 810 children, 789 mothers and 605 fathers. This report focuses on the group of infants who had a blood sampling for determination of specific IgE at the age of 1 year. No differences in clinical outcome, parental atopy and environmental factors were noted between children tested for serum IgE antibodies and those not tested (data not shown). The general characteristics of the study population are shown in Table 1. Almost half the parents had a positive specific IgE result to at least one of the tested allergens. Fifty percent of the mothers and 25% of the fathers had a positive history for allergic disorders (allergic asthma, rhino-conjunctivitis and atopic dermatitis). However, the number of mothers and fathers with both atopic symptoms and specific IgE elevation was less frequent (30% and 16%, respectively). In contrast to the mothers, blood drawing for quantification of total and specific IgE was performed in only 75% of the fathers, mostly because of practical reasons. Nevertheless, the general characteristics of the 'sampled' and 'not-sampled' fathers were not significantly different (data not shown). Parental education in our study

Table 1. General characteristics of the study population

	N	%
Parental sensitization		
Mother	320/789	41
Father	277/605	46
Both	110/594	19
Parental atopic symptoms		
Mother	382/763	50
Father	187/763	25
Both	80/732	11
Higher parental education	593/711	83
Environmental exposure during pregnancy		
Cats	211/804	26
Dogs	172/803	21
Cigarette smoke	215/796	27
Birth characteristics		
Male gender	428/810	53
Birth by caesarean section	88/802	11
Environmental exposure during first year		
Cats	378/707	53
Dogs	242/693	35
Cigarette smoke	70/723	10
Carpeting in bedroom	98/718	14
Day care attendance	583/725	80
At least one older sibling	164/800	20
Breastfeeding		
Ever	648/809	80
At least 3 months	432/809	53
Clinical outcome during the first year		
Atopic dermatitis	195/792	25
Ever wheeze	197/795	25
Wheeze (≥3 episodes/year)	60/795	8
Sensitization during the first year	107/810	13
Sensitization to food allergens	87/810	11
Sensitization to inhalant allergens	30/810	4

Sensitization was defined as having at least one positive specific IgE. Descriptive statistics were carried out using all available data for each of the variables.

population was high, as 83% of the parents were higher educated (college or university). Eighty percent of the children were breastfed after birth and more than 50% were exclusively breastfed during the first 3 months of life.

In Fig. 1, a Venn diagram shows the overlap between the three different outcome variables studied: early sensitization, atopic dermatitis and wheezing during the first year. The areas of intersection between the three conditions are limited, especially between wheezing and early sensitization.

Risk factors for sensitization at the age of 1 year

Thirteen percent of the children were sensitized by the age of 1 year. The majority (81/810; 10%) was mono-sensitized, most frequently to food allergens (egg's white or cow's milk); however, 4% of the children (30/810) already showed sensitization to inhalant allergens, especially to house dust mite and cats.

Multiple logistic regression analysis showed that the majority of the exposure–outcome associations differed between boys and girls. Thus, gender was identified to be a

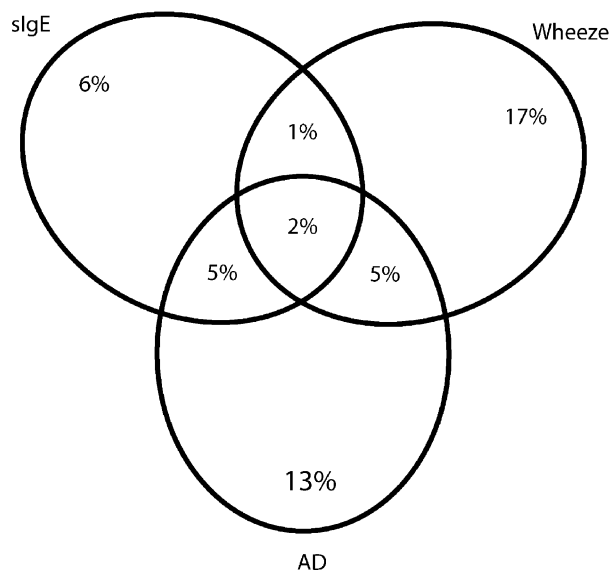


Fig. 1. Venn diagram showing the proportion of infants with early sensitization (slgE), atopic dermatitis (AD), wheeze or any combination of the three conditions during the first year of life. Subset areas are not proportional to the actual relative subset size.

significant effect modifier. No other effect modifications were noted. Therefore, we conducted analyses for girls and boys separately. The crude data on Figs 2 and 3 present the individual associations between the putative risk factors and early infant sensitization, respectively, for girls and boys. The multiple logistic regression analysis in girls showed that a positive specific IgE result in fathers was a risk factor for early sensitization in their daughters (OR_{adj} 2.21 (95% CI 1.10–4.49); $P = 0.03$) (Fig. 2). In boys, day care attendance was shown to be protective for early sensitization (OR_{adj} 0.38 (95% CI 0.20–0.71); $P = 0.001$) (Fig. 3).

Risk factors for atopic dermatitis during the first year of life

Atopic dermatitis, which is considered as the initial clinical manifestation of an atopic constitution, was very prevalent and occurred in 195/792 infants (25%), especially in boys ($n = 111$). The results of the crude and multiple logistic

regression analyses for atopic dermatitis in infants are presented in Fig. 4. The multiple regression analysis revealed that sensitization of the mother (OR_{adj} 1.52 (95% CI 1.06–2.19); $P = 0.02$) and sensitization of the infant (OR_{adj} 4.20 (95% CI 2.63–6.68); $P < 0.001$) were both risk factors for the presence of atopic dermatitis (Fig. 4). On the contrary, postnatal exposure to cats was negatively associated with atopic dermatitis (OR_{adj} 0.68 (95% CI 0.47–0.97); $P = 0.03$).

Risk factors for wheezing during the first year of life

One out of four infants presented at least one episode of wheezing during the first year of life. Only 60/795 (8%) had three or more episodes of wheezing and 58/782 (7%) infants suffered from both atopic dermatitis and wheezing during the first 12 months of life.

Figure 5 shows the results of the crude and multiple logistic regression analyses for early wheezing. Female gender protects against wheezing in infants (OR_{adj} 0.49 (95% CI 0.34–0.71); $P < 0.001$). Postnatal exposure to cigarette smoke (OR_{adj} 3.31 (95% CI 1.79–6.09); $P < 0.001$) and day care attendance (OR_{adj} 1.96 (95% CI 1.18–3.23); $P = 0.009$) was significantly associated with wheezing during the first year. On the contrary, prenatal exposure to cigarette smoke was negatively associated with wheezing (OR_{adj} 0.58 (95% CI 0.36–0.93); $P = 0.02$). This effect was more pronounced when the mother had allergic symptoms (interaction term: $P = 0.01$).

Discussion

Current literature on risk factors for the development of atopic disorders often shows contradictory results and conclusions. This can partly be because of differences in the epidemiological approach, such as study design, included subjects, specification of study variables and the type of statistical analysis [22]. Therefore, additional well-designed prospective studies with critical statistic assessment are needed. In this study, we present the first data of a prospective birth cohort, PIPO study, that evaluates the possible influence of a wide range of environmental factors during the prenatal

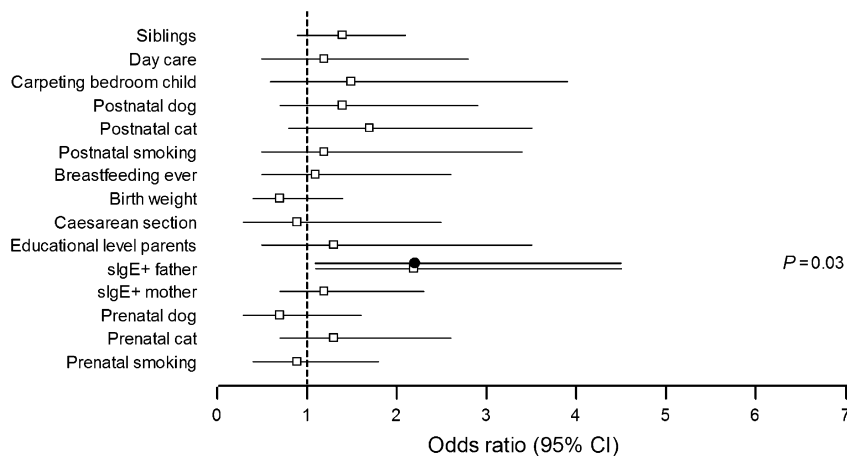


Fig. 2. Crude data and multiple logistic regression analysis for sensitization during the first year of life in girls (total number of subjects used in the final analysis: $n = 295$). □, unadjusted odds ratio; ●, adjusted odds ratio; horizontal bar denotes 95% confidence interval (CI).

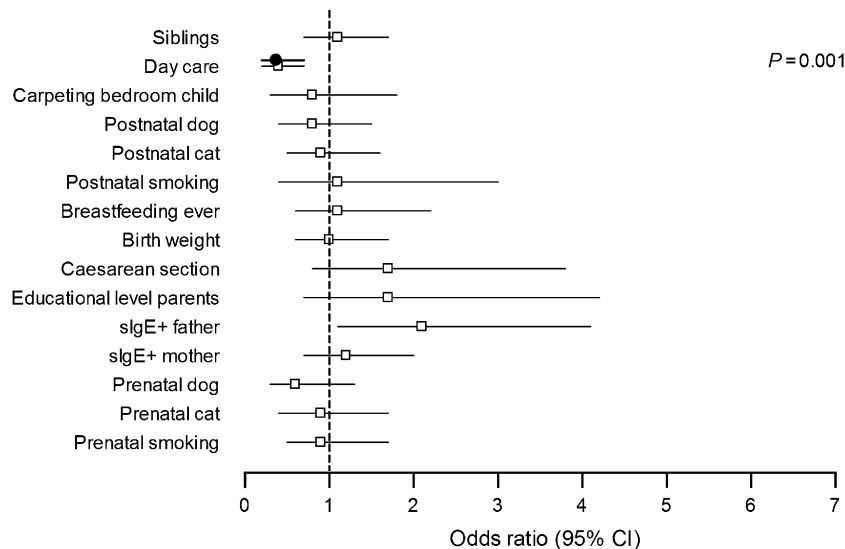


Fig. 3. Crude data and multiple logistic regression analysis for sensitization during the first year of life in boys (total number of subjects used in the final analysis: $n = 380$). □, unadjusted odds ratio; •, adjusted odds ratio; horizontal bar denotes 95% confidence interval (CI).

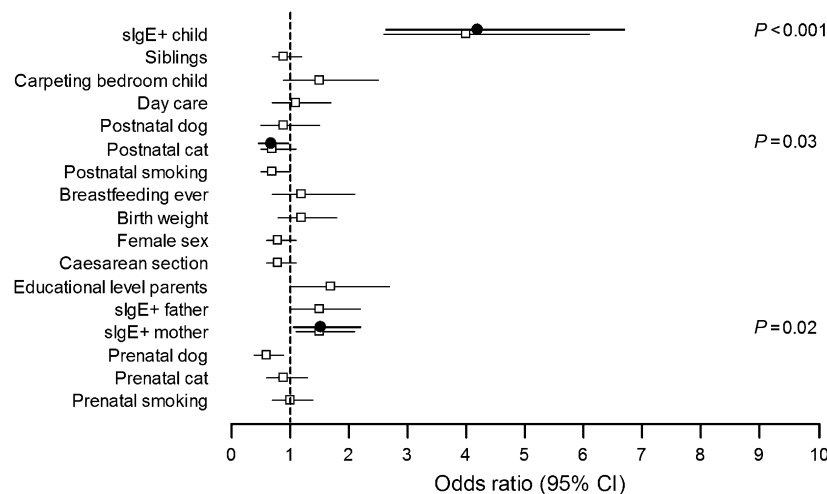


Fig. 4. Crude data and multiple logistic regression analysis for atopic dermatitis during the first year of life (total numbers of subjects used in the final analysis: $n = 669$). □, unadjusted odds ratio; •, adjusted odds ratio; horizontal bar denotes 95% confidence interval (CI).

and early postnatal period, including the presence of positive specific IgE results in both parents, on the occurrence of sensitization, atopic dermatitis and wheezing during the first year of life.

Early sensitization

The presence of specific IgE at the age of 1 year, which is known to be predictive for the development of atopic diseases in later childhood [23–25], was relatively frequent in our study population, although no requirements on atopic status were made at enrolment in our study. However, it should be acknowledged that parents with an atopic constitution are likely to be more interested in cooperating with epidemiological studies on allergy, a presumption that is confirmed by the high frequency of atopic symptoms and sensitization in parents included in our study. Logistic regression analysis for

sensitization at the age of 1 year emphasized the importance of evaluating interaction, as gender was demonstrated to be a significant effect modifier. Day care attendance might protect against atopic sensitization by facilitating the spread of infections through contact with other children in early life, which might skew the T-helper type 2 (Th2) response, present at birth, to a Th1 response [26]. However, this effect was restricted to boys, suggesting that environmental factors such as child care attendance might interact with unknown gender-specific genetic factors in their involvement in the sensitization process. The observation that sensitization in fathers is a risk factor for early sensitization in their daughters further supports this hypothesis of a gender-linked genetic relationship with atopic sensitization. In fact, it has been recently demonstrated that a polymorphism in cytotoxic T lymphocyte antigen 4 (CTLA4), which plays an important role in T cell activation and differentiation, is significantly associated

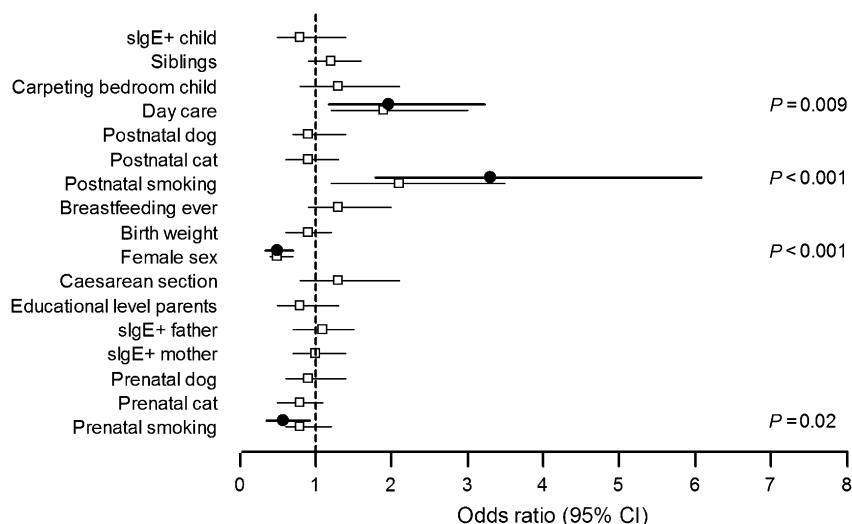


Fig. 5. Crude data and multiple logistic regression analysis for early wheezing during the first year of life (total numbers of subjects used in the final analysis: $n = 693$). □, unadjusted odds ratio; •, adjusted odds ratio; horizontal bar denotes 95% confidence interval (CI).

with elevation of total IgE and allergic rhinitis in females, but not in males [27]. Our data therefore indicate that a genetic basis for gender discrepancy of atopic sensitization might be present. Consequently, the influence of environmental factors might differ between sexes, as genetics and environment are in continuous interaction [4–6]. Recent epidemiological papers suggest an interaction between gender and environmental factors in childhood atopy, which could be explained by a possible effect of the endocrine system [28–30].

Atopic dermatitis

The high rate of sensitization in infants with atopic dermatitis confirms that this disorder can be considered as the first and most prevalent clinical symptom of an atopic constitution in early life [31–33]. The negative association between postnatal contact with cats and atopic dermatitis cannot be attributed to a selective avoidance of cats in allergic families, as we saw the same effect in atopic and non-atopic parents (i.e. no effect modification was present). Moreover, the protective effect of postnatal exposure on atopic dermatitis was less pronounced in highly educated parents (data not shown).

Therefore, other possible explanations must be considered, such as an effect through higher environmental concentrations of endotoxine (an intrinsic part of the outer membrane of Gram-negative bacteria), which has been described in association with cat keeping [34, 35]. However, our data demonstrated that this effect was restricted to postnatal exposure to cats and does not apply to prenatal cat exposure, neither to exposure to dogs, which indicates that apart from an endotoxine effect, additional cat allergen-specific characteristics are involved [36].

In analogy with the above-mentioned observation that paternal sensitization is associated with early sensitization in girls, maternal sensitization predisposes for atopic dermatitis in early life for both sexes. Although a possible role of many different environmental factors has been suggested in the development of allergy and was evaluated in the current report, our data emphasize that a genetic predisposition for atopy, assessed by the presence of specific IgE in parents, is an

important risk factor for early atopy in infants. The explanation why different genders provide a different influence will probably require additional genetic and endocrine research [28–30].

Early wheezing

No valid criteria for asthma are available for infants and preschoolchildren [37, 38]. Wheezing is considered as an important risk factor for asthma in later life [38, 39], but most children who wheeze in infancy will not develop asthma [40]. The identification of postnatal exposure to cigarette smoke and day care attendance as risk factors for wheezing in early life are in accordance with the assumption that wheezing in infancy is largely related to non-allergic triggers and irritants, causing a transient bronchial hyper-reactivity [40–42]. The male predisposition for early wheezing has been extensively demonstrated [43].

The observed protective effect of prenatal exposure to cigarette smoke on wheeze is a very paradoxical finding, as it has been extensively, and on several occasions, shown that prenatal smoking induces reduced lung growth and is an important risk factor for wheezing [44–46]. However, stratified analysis showed that exposure to cigarette smoke during pregnancy did not have any effect on wheezing in infants from mothers without allergic symptoms. The contradictory finding of a protective effect of prenatal contact with cigarette smoke on early wheeze in infants from mothers with atopic symptoms could be explained by the fact that mothers with severe atopic symptoms were more motivated to avoid exposure to cigarette smoke during pregnancy, as opposed to those with mild symptoms.

The assessment of risk factors for allergic asthma in our study population will possibly be revealed by a further clinical follow-up of our cohort, at this moment extending to 4 years.

Advantages and limitations of the study

The major strength of this study is the quantification of specific IgE in both parents and children. It allowed us

to investigate whether the presence of a genetic predisposition through the maternal and/or paternal line could modify the effect of environmental exposure on the process of sensitization and on the development of atopic dermatitis and wheezing during the first year of life. Another advantage of our study is the prospective design with inclusion of infants both with and without parental allergy. One might speculate that the over-representation of parents with an atopic constitution might have biased the outcome of our study. However, in our opinion this is not the case. It is unlikely that, at the moment of inclusion, the parents would be able to predict the studied outcome and behave accordingly. Moreover, by incorporating effect modification in our logistic regression analysis, we were able to assess the effect in atopic and non-atopic parents and the interpretation of the data was facilitated. A possible limitation of our study is that questionnaires were used for the assessment of exposure to allergens. However, for the time being, there is no 'golden standard' for measuring allergen exposure. Moreover, the overall very high educational level of the parents must be considered as a limitation as it restricts the assessment of the effect of the parental educational level on the different outcome parameters.

Conclusion

In conclusion, our results emphasize that the genetic predisposition for atopy, assessed by the presence of specific IgE in parents, is an important risk factor for early sensitization and atopic dermatitis in infants. Additionally, a protective effect of postnatal exposure to cats and day care attendance on the development of atopic dermatitis and sensitization, respectively, was demonstrated. We were not able to demonstrate an effect of other environmental factors, such as breastfeeding, exposure to dogs and cigarette smoke, on the development of early atopic manifestations. Moreover, our current data do not provide evidence for a role of prenatal exposure to pets or cigarette smoke. Further follow-up of the children, focusing on the development of sensitization and atopic disorders, is clearly needed to clarify the contribution of environmental factors.

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