
Smoking exposure and allergic sensitization in children according to maternal allergies

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Background: Although the negative impact of environmental tobacco smoke (ETS) on airway diseases in children is well known, the effect of ETS on allergic sensitization is still debated.

Objective: To evaluate how maternal allergies modulate the effect of tobacco exposure on allergic sensitization in childhood.

Methods: Of 9,000 children in grades 4 and 5 selected in 6 cities in France, 7,798 participated in a survey that consisted of an epidemiologic questionnaire, skin prick testing to common allergens, and skin examination for eczema. Tobacco exposure was obtained from parent questionnaires.

Results: Twenty-five percent of the children had allergic sensitization, 25.2% had eczema, 11.6% had allergic rhinitis, 9.9% had asthma, and 8.3% had exercise-induced asthma. Twenty percent of the children were exposed to tobacco in utero. Maternal exposure had a greater impact than paternal exposure on children's allergic sensitization. Prenatal exposure was more associated with sensitization than postnatal exposure. Children with maternal allergies and exposure to maternal ETS during pregnancy were at higher risk for sensitization to house dust mite (25.7% vs 14.0%; odds ratio, 1.95; 95% confidence interval, 1.19–3.18; $P = .006$). In contrast, sensitization to food allergens was not associated with tobacco exposure.

Conclusions: Children exposed to maternal smoking had a higher risk of sensitization to house dust mite, especially when the mothers were allergic.

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INTRODUCTION

Studies of prenatal and postnatal tobacco smoke exposure in children have mainly examined the effect on the respiratory tract, including respiratory symptoms, asthma,¹ pulmonary function, and bronchial hyperreactivity.² Little is known about the effect of smoke exposure on immune system regulation.^{3,4} Tobacco hypersensitivity has been studied in 1 article.⁵ Some studies reported a positive association between tobacco smoke exposure and the occurrence of allergic sensitization,⁶ whereas others found no association, a controversy highlighted by the reviews by Halken et al⁷ and Strachan and Cook.⁸ Kulig et al⁹ reported that prenatal and postnatal exposure to environmental tobacco smoke (ETS) in children at the age of 3 years was associated with sensitization to food allergens. Although no association was found

with sensitization to inhalant allergens, sensitization to specific allergens was not analyzed.

Recent data showed that maternal environmental risk factors might affect the development of the fetal immune system.¹⁰ When exposed to ETS, genetically predisposed children (as defined by the presence of parental allergy) in a longitudinal study¹¹ were found to be at higher risk for sensitization against house dust mites (HDMs), which was, in turn, related to the persistence of wheezing. In children, allergic sensitization was associated with bronchial reactivity and maternal allergies (MAs).¹² Recently, the health effects of molds were most pronounced in infants whose mothers had asthma,¹³ but little is known about the possible role of ETS as a modifier. The aim of this study is to evaluate how MA modulates the effect of passive smoking and early ETS exposure on allergic sensitization as defined by skin prick test (SPT) positivity to common allergens in children.

METHODS

Population

The population comprised 7,798 of 9,000 schoolchildren in grades 4 and 5 selected in 6 cities in metropolitan France (Bordeaux, Clermont-Ferrand, Créteil, Marseille, Reims, and Strasbourg). Each center randomly selected 16 schools according to the International Study on Asthma and Allergies in Childhood protocol phase 2. The survey included a parental epidemiologic questionnaire, a medical examination including SPT positivity to common allergens, and skin examination for eczema. Authorization from the National Commis-

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sion of Informatics and Civil Liberties and the ethics committee was sought and obtained before conducting the survey. The parents of the children were informed by mail of the purposes and modalities of the survey, and their written consent was obtained.

Questionnaire

Parents completed a self-administered standardized questionnaire at home. The main questions were derived from the International Study on Asthma and Allergies in Childhood questionnaire. Responses were used to evaluate the prevalence, severity, and management of asthma and associated diseases, namely, wheezing, allergic rhinitis, and eczema. Such questions had been previously validated and translated from English into French by a native French speaker, then back-translated into English by a native English speaker. The process had been pursued until the initial English wording had been obtained. The final French wording was provided by consensus between the allergy and respiratory medicine department heads of the participating centers.

Clinical Tests

In addition to parents' consent, children's consent was obtained before clinical examination in the classrooms; the other pupils were not present at the time of examination. Physical examination by a physician included height, weight, respiratory symptoms, and SPT. According to Williams' protocol,¹⁴ atopic dermatitis was determined using a questionnaire and physical examination. Fieldworkers were trained for physical examination.

Skin Prick Tests

The SPTs were performed using Stallerpoints (Stallergens Diagnostics, Antony, France). The allergens used for skin testing were *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* (HDM), cat fur (Fel d 1), the outdoor mold *Alternaria tenuis*, cockroach (*Blatta germanica*), mixed grass, tree pollens (birch), and the trophallergens peanut, egg, and fish.

Histamine (1 mg/mL of histamine dihydrochloride) was used as a positive control and an uncoated lancet as the negative control. Tests were performed on the volar surface of the forearm using a standard template, and wheal size was recorded at 15 minutes as the largest diameter and the diameter at 90° to its midpoint, each to the nearest whole millimeter. Mean wheal diameter was calculated as the average of the 2 diameters. The SPT positivity to a specific allergen was defined as a wheal at least 3 mm and greater than the negative control.

Health Outcomes

The following health outcomes were considered in the analysis: (1) lifetime wheezing (a history of wheezing in the chest at some point in life according to the standardized question, "Have you ever had wheezing or whistling?"), (2) current wheezing (a history of "wheezing or whistling in the chest in the previous 12 months"), (3) current asthma (chest wheezing or whistling in the previous 12 months with a history of

asthma at some point in life), (4) lifetime asthma (a history of asthma at some point in life according to the standardized question, "Have you ever had asthma?"), (5) allergic rhinitis (a history of rhinoconjunctivitis in the previous 12 months), (6) lifetime hay fever (a history of hay fever at least once in life ["Have you ever had hay fever?"]), (7) lifetime eczema (a history of eczema or atopic dermatitis at least once in life ["Have you ever had eczema?"]), and (8) MAs (a history of asthma, atopic dermatitis, or hay fever for the mother).

ETS Exposure and Other Factors

Parents were asked about their smoking habits at home and at the birth and during the first year of life of the child. Additional data about the number of cigarettes smoked by parents were requested. Prenatal and postnatal tobacco smoke exposure was evaluated by means of a standard questionnaire collecting information on the mother and the father. A 4-class variable was defined:

- Control: no exposure during pregnancy or during the first year of life for mother and father
- Prenatal exposure: children with in utero exposure
- Postnatal exposure: children with ETS exposure only during the first year of life
- Prenatal and postnatal exposure: children with ETS exposure during pregnancy and the first year of life

The other factors taken into account as potential confounders or modifiers in the study of the relationship between smoking habits and allergic disorders were age, sex, geographic region (center), siblings, owning pets, parental education as a proxy of socioeconomic status, and breastfeeding obtained through the questionnaire and using the pediatric record.

Statistical Analysis

Conventional methods were used to compare percentages (χ^2 test). The population taken into account for the present analysis is represented by the overall group of 9- to 11-year-olds surveyed in all the centers. A logistic regression model was used to evaluate the association between ETS exposure and sensitization to allergens. The analyses were performed using a statistical software program (Stata 7.0; StataCorp, College Station, Texas).

RESULTS

Response Rate

The final sample included 7,798 children who participated in the study and 7,242 children with complete records (questionnaire, clinical examination, SPT, and exercise challenge). The mother completed 81% of the questionnaires. Most of the children were white, and most had well-educated, middle class parents. The response rate varied from 72% in Reims to 92% in Clermont-Ferrand. The sex ratio was equal (ratio = 1) in all 6 centers, and there were no significant differences in age. Children with missing information on exposure to ETS ($n = 1,710$) were not different from the others ($n = 5,532$) with respect to allergic disease in fathers and siblings, parental age, sex, season of birth, number of siblings, day care

attendance, and pet ownership. MA was less frequent in children missing information (11.4%) compared with others (25.5%). However, children with information missing on exposure to parental smoking were more frequent in the West Indian group (48%) than in the European group (15%; $P = .001$). The general characteristics of the study population are summarized in Table 1.

Sensitization to Allergens

Twenty-five percent of the children had SPT positivity; 15.5% were sensitized to *D pteronyssinus*, 11.8% to *D farinae*, 8.6% to Timothy grass, 3.46% to tree, 3.45% to cat Fel

d 1, 2.5% to *Alternaria*, and 1.5% to *B germanica*. Sensitization to food allergens was less frequent: 0.99% to peanut, 0.6% to fish, and 0.32% to egg. There was no difference according to sex (data not shown).

Asthma and Allergic Diseases

As expected, the current prevalence of asthma and allergies was lower than the lifetime prevalence. Eczema was the most frequent disorder in the children. A history of current wheezing (current asthma) was reported by 7.9%. There were significantly more boys than girls with lifetime asthma, current wheezing and asthma, nasal allergic symptoms, and

Table 1. General Characteristics of the Study Population

Characteristics	Child	Mother	Father
Age, mean $\pm$ SD, y	10 $\pm$ 0.8	38.4 $\pm$ 5.2	41.4 $\pm$ 6.42
Male sex, %	49.2	NA	NA
Weight, mean $\pm$ SD, kg	36.5 $\pm$ 12.6	NA	NA
Height, mean $\pm$ SD, m	1.41 $\pm$ 0.09	NA	NA
BMI, mean $\pm$ SD	18.38 $\pm$ 12	NA	NA
PEF, mean $\pm$ SD, mL/min	330.46 $\pm$ 49.41	NA	NA
Ethnic group, %			
White	NA	68.13	62.7
West Indies	NA	3	2.99
South Europe	NA	4.67	4.9
North Africa	NA	11.52	12.6
Black Africa	NA	3.45	3.3
Asia	NA	3	3.2
Other	NA	6.2	7.2
Parental education, %			
Primary school	NA	13.5	14.2
Secondary school	NA	45.7	42.9
Vocational training certificate	NA	3.3	3.9
Master degree standard	NA	37.5	38.9
Siblings, %			
0	25	NA	NA
1	34.6	NA	NA
2	22.7	NA	NA
3	8.5	NA	NA
>4	6	NA	NA
Insurance family social security, %	96.8	NA	NA
Complementary private insurance, %	1.2	NA	NA
Lifetime asthma, No. (%)	695 (9.9)	NA	NA
Current asthma, No. (%)	509 (7.9)	NA	NA
Lifetime wheezing, No. (%)	1,365 (19.4)	NA	NA
Current wheezing, No. (%)	518 (7.4)	NA	NA
Lifetime hay fever, No. (%)	866 (12.9)	NA	NA
Allergic rhinitis, No. (%)	732 (11.6)	NA	NA
Lifetime eczema, No. (%)	1,715 (25.2)	NA	NA
Exercise-induced asthma, No. (%)	610 (8.3)	NA	NA
Atopy, No. (%)	1,848 (25.0)	1,673 (21.5)	1,376 (17.65)
Breastfeeding	NA	3,71 (54.4)	NA
Birth weight <2,500 g	443 (6.8)	NA	NA
≥ 1 sibling, No. (%)	2,705 (34.6)	NA	NA
Premature birth (<37 wk of gestation), No. (%)	1,879 (27.9)	NA	NA
Day care at least 6 mo outside the home, No. (%)	1,392 (22.1)	NA	NA
Exposure to pets during the first year of life, No. (%)	504 (6.9)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); NA, not applicable; PEF, peak expiratory flow.

lifetime and current eczema; 8.3% of children had exercise-induced asthma according to the challenge performed at school.

Allergic Sensitization and Health Outcomes

Asthma was significantly associated with sensitization to *D pteronyssinus* (32.5% vs 12.4%), *D farinae* (28.3% vs 9.1%), cat (8.9% vs 2.6%), *Alternaria* (4.7% vs 2.1%), mixed grass (16.7% vs 7.1%), and tree pollens (6.9% vs 2.8%). In contrast, no association was found between asthma and sensitization to peanut, fish, cockroach, and egg. Allergic rhinitis was significantly associated with sensitization to *D pteronyssinus* (26.1% vs 12.7%), *D farinae* (20.4% vs 9.4%), cat (8.1% vs 2.4%), *Alternaria* (5.0% vs 2.0%), mixed grass (25.8% vs 5.5%), and tree pollens (10.1% vs 2.1%). No association was found between allergic rhinitis and sensitization to peanut, fish, cockroach, and egg. Eczema was associated with sensitization to mixed grass (13.4% vs 5.9%) and tree pollens (6.1% vs 3.1%) only.

Exposure to Parental Smoking (ETS) and Other Factors

Thirty-six percent of the children (n = 2,019) were not exposed to ETS during pregnancy or the first year of life. Sixty-four percent of the children (n = 3,513) were exposed to ETS at a moment during their life by the mother, the father, or both: 20.2% (n = 1,117) were exposed to ETS during pregnancy only, 10.7% (n = 591) were exposed only during the first year of life but not during pregnancy, and 32.6% (n = 1,805) were exposed to ETS during pregnancy and during the first year of life. Although 54.4% of the mothers reported breastfeeding their children, 46.7% of them (n = 1,286) reported breastfeeding for at least 3 months and 47.4% for less than 1 month.

Sensitization and Exposure to ETS

Sensitization to HDMs was higher in children exposed to maternal smoking during pregnancy than in the others (Table 2). There was no effect of paternal exposure on childhood sensitization or any additive effect on maternal exposure. Postnatal tobacco exposure had no effect on the sensitization

rate. Sensitization to allergens was not significantly different between children exposed only during the first year of life and those exposed during pregnancy and the first year of life. Only sensitization to cat was significantly associated with maternal tobacco exposure during the first year of life (4.5% vs 3.4%).

Twenty percent of the children with MAs and exposed to ETS during pregnancy and the first year of life were sensitized to HDM compared with 15.0% of children exposed to ETS without MAs, but the difference was not statistically significant. We did not find any significant differences in the 4 populations of children according to allergic status and tobacco exposure in terms of age, sex, and socioeconomic status. In terms of demographics, we did not find any significant difference between children exposed only to maternal smoking and the other children. Mothers from Europe had significantly less allergy (4.8% vs 6.9%; $P < .001$) and less smoking (16.5% vs 33.0%; $P < .001$), but no difference was found for sensitization of children (22.5% vs 23.4%) than for the others.

Sensitization and Exposure to ETS According to MAs

Children with MAs and exposure to prenatal ETS were at higher risk for sensitization to *D pteronyssinus* (25.7% vs 14.0%; odds ratio [OR], 1.95; 95% confidence interval [CI], 1.19–3.18; $P = .006$) and *D farinae* (24% vs 14%; OR, 1.58; 95% CI, 1.2–4.2) (Fig 1). Children with MAs and exposure to postnatal ETS during the first year of life had the same risk of sensitization to cat at the age of 9 years (OR, 1.24; 95% CI, 0.84–1.84) as children without MAs (OR, 1.07; 95% CI, 0.76–1.5). There was no effect of postnatal exposure on sensitization to food allergens, *Alternaria*, pollens, and cockroach. There was no modifying effect by sex. In the multivariate analysis, after adjustment for confounding factors, children with MAs and exposure to prenatal ETS were at higher risk for sensitization to HDM (*D pteronyssinus* and *D farinae*) and tree pollens (Table 3).

Table 2. Sensitization Rates According to Prenatal Tobacco Exposure

Sensitization to	Sensitization, %			
	No exposure (n = 2,019)	Maternal exposure only (n = 216)	Paternal exposure only (n = 820)	Maternal and paternal exposure (n = 46)
<i>Dermatophagoides pteronyssinus</i>	15.4	22.2 ^a	15.9	13.6
<i>Dermatophagoides farinae</i>	12.5	19.4 ^a	11.6	8.8
Cat	3.5	4.6	3.4	3.3
<i>Alternaria</i>	2.5	4.1	1.95	2.6
Timothy grass	9.5	10.2	9.3	8.25
Tree	4.3	5.6	3.2	3.9
Peanut	0.9	2.2	1.0	1.3
Fish	0.7	0.9	0.7	0.6
Cockroach	1.2	1.3	0.8	1.7
Egg	0.25	0	0.5	0

^a $P < .001$ by χ^2 test for differences in rates.

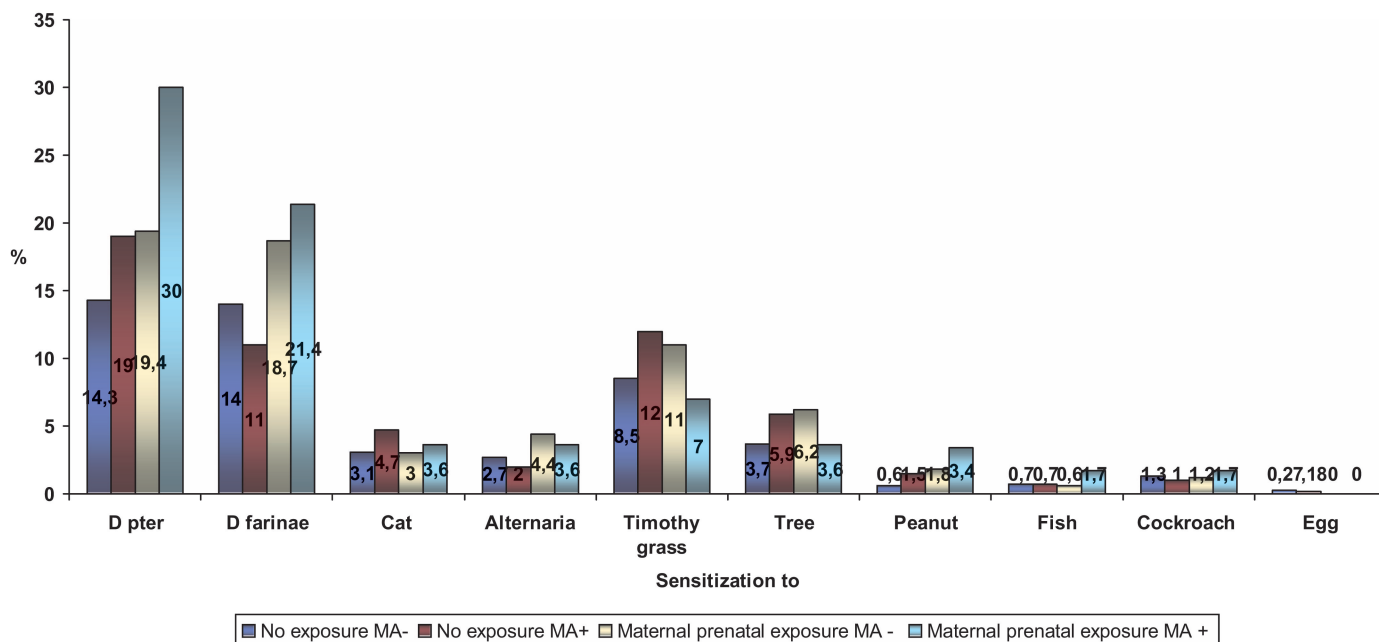


Figure 1. Sensitization of children according to prenatal exposure stratified by maternal allergies (MAs).

DISCUSSION

This cross-sectional analysis of a large population-based sample of schoolchildren living in metropolitan France shows the following: (1) maternal exposure had a greater impact than paternal exposure on children's allergic sensitization, (2) prenatal exposure was more associated with sensitization than postnatal exposure, and (3) children with MAs and exposure to maternal ETS during pregnancy were at higher risk for sensitization to HDM. Generally, maternal smoking might be the most important aspect of ETS exposure when children are younger and spend more time with their mothers, whereas paternal ETS exposure had no significant effect on the development of allergic sensitization.⁹

A previous systematic review¹⁵ identified 12 studies relevant to passive smoking and including SPTs. Studies of parental smoking during pregnancy or infancy were broadly consistent in showing no adverse effect on SPT positivity (pooled OR, 0.87; 95% CI, 0.62–1.24). Previous studies¹⁶ in adults showed that the association between smoking and sensitization to common environmental allergens varied according to different allergens. In particular, current smokers were at higher risk for sensitization to HDM allergen, with a decreased risk of sensitization to grass and cat allergens. A higher risk of current wheezing, current and lifetime asthma, or current eczema was observed in smokers exposed to passive smoking compared with those not exposed. Passive smoking was significantly associated only with current diseases. This suggests that the effect of passive smoking may exist later in life.¹⁵

The relationship of maternal smoking to clinical atopic disease has been reported in previous studies and is still

debated.⁷ In 1 study,⁸ eczema was defined without reference to SPTs and was inversely related to maternal smoking during pregnancy and during the previous year. Longitudinal studies¹⁷ have shown that a high proportion of children with eczema during the first year of life have a higher subsequent risk of being sensitized to inhalant agents, such as pollens.

Hay fever defined on the basis of symptoms of rhinitis was also less common if the mother smoked. Furthermore, the effects of maternal smoking were similar in children with and without a parental history of allergy disease, but the mechanism for this observation remains unknown.

Tobacco smoking has been described as a modifier of allergy markers (ie, total IgE level, SPT results, and eosinophilia).¹⁸ In adults, studies in the general population have shown higher IgE levels in smokers than in nonsmokers, perhaps due to a change in the mechanisms regulating IgE synthesis¹⁹ or an increase in specific IgE levels due to frequent airway infestation.²⁰ Furthermore, increased levels of cord IgE in newborns of mothers who smoke have been reported in some²¹ but not in all studies.²² Children from atopic families with 1 or more parents who smoke have higher IgE levels than those whose parents do not smoke.²³

Although some researchers observed no relationship between maternal smoking and sensitization,²⁴ others noted a relationship in boys only.²⁵ In individuals exposed to specific irritants in occupational settings, a higher prevalence of positive skin test results was reported in exposed smokers than in unexposed smokers.²⁶ This suggests that smoking may facilitate sensitization in exposed individuals, increasing bronchial mucosa permeability and facilitating the penetration of allergens throughout the respiratory mucosa. Ronchetti et al²³

Table 3. Odds Ratios Between Sensitization and Exposure to Parental Tobacco Smoke According to Maternal Allergies

Childhood SPT positivity	OR (95% CI) ^a			
	Maternal ETS during pregnancy		Maternal ETS during first year of life	
	MA+	MA–	MA +	MA–
House dust mite (<i>Dermatophagoides pteronyssinus</i>)				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.33 (1.01–1.72) ^b	0.94 (0.78–1.2)	1.15 (0.91–1.46)	0.95 (0.79–1.14)
House dust mite (<i>Dermatophagoides farinae</i>)				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.64 (1.25–2.2) ^b	0.90 (0.72–1.17)	1.02 (0.8–1.3)	0.98 (0.80–1.19)
Cat				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.07 (0.64–1.78)	1.04 (0.7–1.54)	1.24 (0.84–1.84)	1.07 (0.76–1.5)
<i>Alternaria</i>				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.67 (0.98–3.29)	1.39 (0.9–2.1)	1.45 (0.91–2.3)	1.39 (0.94–2.06)
Timothy grass				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.88 (0.57–1.34)	0.95 (0.72–1.25)	1.09 (0.83–1.42)	0.87 (0.69–1.09)
Tree pollens				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.65 (1.05–2.55) ^b	1.08 (0.73–1.62)	1.13 (0.75–1.71)	0.85 (0.59–1.24)
Cockroach				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.85 (0.54–1.33)	0.9 (0.73–1.34)	0.83 (0.58–1.17)	0.96 (0.73–1.25)
Peanut				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.86 (0.58–1.72)	1.21 (0.90–1.6)	0.98 (0.7–1.37)	1.05 (0.81–1.37)
Fish				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.7 (0.49–1.74)	1.07 (0.71–1.35)	0.94 (0.66–1.34)	1.03 (0.78–1.36)
Egg				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.8 (0.4–1.8)	1.01 (0.7–1.4)	0.94 (0.65–1.34)	0.98 (0.7–1.31)

Abbreviations: CI, confidence interval; ETS, environmental tobacco smoke; MA, maternal allergy; OR, odds ratio; SPT, skin prick test.

^a The OR was adjusted on age, sex, study center, number of siblings, pets, and parental education.

^b $P < .05$.

showed that children whose parents smoke have increased absolute counts and percentages ($\geq 4\%$) of eosinophils, but the effect was significant only in boys.

These results indicate an increased risk of sensitization to inhalant allergens in children who were prenatally exposed to tobacco smoke and have MAs. The effect seemed to be restricted to inhalant allergens, particularly HDM, whereas the risk of sensitization to food allergens²⁷ was not increased. The harmful effects on the respiratory tract that early exposure to tobacco smoke induces may interfere with the normal development of immunologic tolerance and facilitate sensitization to inhalant allergens.

A limitation of this study was the validity of the data on smoking habits, which were obtained via a questionnaire. A selection bias should not be ruled out. Because parents may have avoided smoking in the presence of their allergic child, they may have underreported active smoking, classifying themselves as nonsmokers rather than as smokers owing to

possible social stigmatization. Another limitation is the external validation of the results, because children with missing information were different from the group analyzed in terms of MA and ethnicity. In addition, although no biological marker of smoking was evaluated, standardized questionnaires on smoking habits have been widely used²⁸ and validated.²⁹ Another concern is that, as in many previous studies, precision in the reporting of smoking onset and especially cessation by parents could not be evaluated. Nonresponse may also have affected the findings. Although several potential confounders were adjusted for, residual confounding or confounding by other factors is still a possibility. Nevertheless, the differences between crude and adjusted estimates were relatively small, suggesting little confounding if any. Although 20% of mothers did not answer the questions directly concerning smoking, children with information missing on exposure to parental smoking were no different with respect to allergic status, number of siblings, parental age,

sex, pet ownership, and breastfeeding. In addition, because there were differences in the time lapse after exposure, a substantial recall bias in assessing prenatal and postnatal parental smoking habits may have occurred. For this reason, we preferred to investigate a large population-based sample of schoolchildren without selecting the most severe children and to adjust for clinical manifestations (ie, asthma, rhinitis, and eczema during the lifetime and during the past year) so as to minimize the selection bias.

These findings add to the growing body of evidence pointing to associations between exposure to ETS and sensitization to HDM. Prospective studies are now needed to adequately address issues such as the long-term effects of early exposure, changes in level of smoking in the home as a consequence of respiratory symptoms in children, and sensitization.

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