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In utero and childhood exposure to parental tobacco smoke, and allergies in schoolchildren

Chantal Raherison[a,*], Céline Pénard-Morand[b], David Moreau[b], Denis Caillaud[c], Denis Charpin[d], Christien Kopfersmitt[e], François Lavaud[f], André Taytard[a], Isabella Annesi-maesano[b]

[a]*Service des Maladies respiratoires, Hôpital du haut-Lévèque, avenue Magellan, 33604 Pessac, France*
[b]*EPAR-U707 INSERM, Villejuif, France*
[c]*Hôpital Montpied, Clermont-Ferrand, France*
[d]*Hôpital Nord, Marseille, France*
[e]*Hôpitaux Civils, Strasbourg, France*
[f]*Hôpital Maison Blanche, Reims, France*

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Summary Among early-life environmental factors, parental smoking (ETS) has been associated with adverse respiratory outcomes in children. The aim of the study was to evaluate whether parental smoking might lead to asthma and allergies taking into account family history of asthma, personal atopy, breast feeding as confounders and owing pets and day-care during the first 6 months of life as modifiers. About 9000 children of fourth and fifth grade were selected in six cities of France. About 7798 answered an epidemiological questionnaire, underwent a medical examination including skin prick test positivity to common allergens, skin examination for eczema, and run test to assess exercise-induced asthma (EIA). Prevalence of allergies was, respectively, 25.2% for eczema, 12.9% for rhinitis, 9.9% for asthma and 25% for atopy. About 8.3% had an EIA. About 21.6% of children were exposed to maternal tobacco smoking during pregnancy. Maternal smoking, in utero and later, was significantly related to lifetime wheezing (odds ratio (OR): 1.24[1.10–1.56]) and asthma (OR: 1.22[1.04–1.66]). There was no association between atopy, rhinitis, eczema and parental smoking, respectively. ETS remains a risk factor of wheezing in childhood. Counselling parents of children to quit smoking still remains a public health policy.

*Corresponding author. Tel.: +33 557571692; fax: +33 557571698.
E-mail address: chantal.raherison@chu-bordeaux.fr (C. Raherison).

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Introduction

Prevalence of asthma is nowadays a public health problem. Since few years, many publications high lined environmental factors specially air pollution. However, children's exposure to tobacco constituents during foetal development is perhaps the most ubiquitous and hazardous of children's environmental exposures.

Maternal smoking (during pregnancy and post-natal exposure), has been associated with adverse respiratory outcomes in children,[1,2] among which a diminished lung function and wheeze. Parental history of asthma and allergy was most strongly associated with early onset persistent asthma than late-onset asthma, suggesting that among genetically predisposed children,[3] environmental smoke exposure (ETS) in utero and later might favor the development of early-onset asthma.[4,5] However, no objective measure of atopy was available in that study. It is likely that in utero exposure to tobacco smoke, has a direct effect on lung and airway development.[6] ETS in utero has been related to a diminished body mass index.[7,8] Data also suggest that in utero exposure was associated with adverse effects on postnatal height growth.[9] Overall, it has been suggested that a delayed growth may have an effect on the development of the airways and the immune system.

Many debates have centred on whether the damage by exposure to tobacco smoke exposure occurs prenatal, post-natal or whether each has an independent effect.[10] Whether, environmental factors have been assumed to act after birth, maternal environmental risk factors for atopy, diet, and smoking seems to influence the development of the foetal immune system.[11] Genetically predisposed children (defined by presence of parental atopy), when exposed to ETS were at higher risk of developing a sensitization against house dust mites, which was related to persistence of wheezing in longitudinal studies.[12,13] However, for rhinitis, smoking exposure seems not to be a risk factor by contrast, whether there is an effect on atopic eczema is not clear.[14] Atopic sensitization seems to be associated with bronchial reactivity at 10 years of age, with maternal asthma.[13,15] However, the effect of environmental tobacco exposure on sensitization remains unclear.

The aim of our study was to determine if environmental tobacco exposure (in utero and post-natal exposure) was associated with allergies (i.e. asthma, rhinitis, eczema, atopy, exercise-induced asthma (EIA)) in a population-based study of children.

Methods

Population

Out of 9000 children of fourth and fifth grade (9–11 years old) selected in six cities of metropolitan France (Bordeaux, Clermont-Ferrand, Créteil, Marseille, Reims, Strasbourg, respectively), 7798 participated into the survey that included an epidemiological questionnaire addressed to the parents on health, potential risk factors and management of allergic and respiratory diseases, a medical examination including skin prick test positivity to common allergens, skin examination for eczema and urticaria, and run test to assess EIA, in 2000. Each centre randomly selected 16 schools according to ISAAC protocol.

Authorization by the ''National Commission of Informatics and Civil Liberties (CNIL)'' and by the Ethic 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 assent was requested.

Questionnaire

Parents filled out a self-administered standardized questionnaire at home. Main questions derived from the ISAAC questionnaire. Responses were used to assess the prevalence, severity and management of asthma and allied diseases, namely wheezing, allergic rhinitis, and eczema, respectively. Such questions had been previously validated and had been translated from English into French by a native French speaker, then back translated into English by a native English speaker. This process had been pursued until the initial English wording had been obtained. Final French wording was provided by consensus among the Allergy and Respiratory Medicine department heads of the participating centres.

The following health outcomes were considered in the analysis:

- *Lifetime wheezing*: A history of chest wheezing in the chest at some point in life according to the standardized question 'Has your child ever had wheezing and whistling?'
- *Current wheezing*: A history of 'chest wheezing or whistling in the chest over the previous 12 months';
- *Current asthma*: Chest wheezing or whistling over the previous 12 months with a history of asthma at some point in life;

- *Lifetime asthma*: A history of asthma at some point in life according to the standardized question 'Has your child ever had asthma?'
- *Allergic rhinitis*: A history of allergic rhinitis over the previous 12 months.
- *Lifetime hay fever*: A history of hay fever at least once in life ('Has your child ever had hay fever?');
- *Lifetime eczema*: A history of eczema or atopic dermatitis at least once in life ('Has your child ever had eczema?');
- We also studied gender, parental atopy, the number of siblings, the length of breast feeding, day care outside the home, pets ownership and SPT positivity (namely to house dust mite, cat) as potential modifiers.

Environmental tobacco exposure was defined on the basis of parental active smoking habits as follows:

(1) Non-exposure to smoking: children whose parents never smoked
(2) Parental tobacco smoking, respectively, by the mother and the father:
    - during pregnancy
    - during the first year of life of the baby
    - current exposure

To take into account the cumulative exposure of the children to parental tobacco smoking, three subtypes of active tobacco smoking were defined, respectively, for the father, for the mother and for both:

- exposure only during pregnancy;
- exposure during pregnancy and the first year of life;
- exposure during pregnancy, the first year of life and current exposure.

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, and family history of allergy, breast feeding, prematurity and birthweight obtained through the questionnaire and using the paediatric record.

Clinical tests

Consent of children was obtained before clinical examination in the classrooms. Then they underwent physical examination in the class by a physician with height, weight, respiratory symptoms, skin prick test, respiratory function with measure of peak-flow (three measures were obtained). According to Williams' protocol, atopic dermatitis was determined by questionnaire and physical examination. Fieldworkers were trained for respiratory function and physical examination. They run tests to assess EIA with a measure of peak flow after exercise. EIA was defined by diminution of 10% of PEF of the best values. An additional analysis was conducted for 15% for fall in PEF.

Skin prick tests (SPT) performed using Stallerpoints (Stallergens diagnostics). The allergens used for skin testing were cat, *Dermatophagoïdes pteronyssinus*, *Dermatophagoïdes farinae* (house dust mite), cat fur (*Feld I*), the outdoor mould genus *Alternaria tenuis*, *blatta germanica*, peanut, egg, fish, mixed grass and tree pollens; Histamine (1 mg/ml 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 the wheal size was recorded at 15 min as the largest diameter and the diameter at 90° to its midpoint, each to the nearest whole millimetre. Mean wheal diameter was calculated as the average of the two diameters. Skin prick test positivity to a specific allergen was regarded as positive if the corresponding mean wheal diameter was greater than that of the negative control.

EIA challenge

Baseline PEF was measured in all children who agreed. Before undergoing these lung function tests, subjects were advised to avoid β_2-agonist or anticholinergic inhaler for 4 h, and oral medications (β_2-agonists, theophylline or anti-muscarinic agents) for 8 h. When possible, children who reported a respiratory tract infection during the previous 3 weeks were rescheduled. Subjects were permitted five attempts to provide at least two technically acceptable manoeuvres. All those whose PEF attained at least 70% of the predicted value, were invited to undergo a exercise challenge test during 6 min unless they reported that they had heart disease or epilepsy, or were taking a β_2-blocker. Post-exercise PEF was recorded immediately after the challenge, 5, 10 and 15 min later. Subsequently, if a fall in PEF of 10% was determined or if the child presented any respiratory symptom, the physician examined him at first, and second, a β_2-agonist with inhalation chamber was administered in order to ensure the reversibility of the bronchospasm.

Statistical analysis

Conventional methods were used for comparing percentages. The logistic regression model was used to determine the risk (odds ratio), crude and adjusted, respectively, between asthma and each allergic disorder and parental smoking habit, after adjustment for other potential risk factors. The population taken into account for the present analysis is represented by the overall group of 9–11 years old surveyed in all centres. Based on previous knowledge, we also studied gender, parental atopy, siblings, the length of breast feeding, day care outside the home, pet's ownership and SPT positivity as potential modifiers both by adding exposure-modifier interaction terms in the logistic regression analysis and by stratifying the analysis of the data. Sex ratio was defined as, i.e. male/female ratio. The analyses were performed using STATA.[16]

Results

Response rate

The final sample included 7798 children who participated to the study and 7242 children with complete records (questionnaire, clinical examination, skin prick test, exercise challenge). The child's biological mother for 81% of questionnaires completed the questionnaire. Missing data were excluded from analysis, however for each variable (i.e. low birth weight, premature birth, and lifetime asthma) we compared non-respondents and respondents according to demographic data, smoking exposure, and atopic status. We did not find any significant difference in these comparisons. Children were excluded for the following reason such as missing information on exposure to parental smoking. 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 well balanced in all six centres. There was no significant difference in age in the centres. The children with missing information on ETS exposure for specific smoking questionnaire were compared with children with complete data. Children with missing information on exposure to parental smoking were not different from the other children with respect to atopic disease in father and siblings, parental age, sex, season of birth, number of siblings, day care attendance and pet ownership. However, children with missing information on exposure to parental smoking were more likely to be asthmatic (36.8% versus 11%, $P = 0.0001$), to have two parents with low level of education and with ethnic difference, not to belong to the European community. In particular, children with missing information on exposure to parental smoking were more frequent in the West Indies group (48%) than in the European group (15%, $P = 0.001$).

In Table 1, the general characteristics of the study population are summarized, 25% had no siblings and 95.4% had social security. One parent out of three had a high education. As expected, current prevalence of asthma and allergies were lower than lifetime prevalence. Half of the children were exposed to parental tobacco smoking at home at some times in their lives. Maternal smoking increased with children age whereas paternal smoking diminished.

Asthma and allied diseases

Eczema was the most frequent disorder among the studied children followed up by allergic rhinitis and asthma (Table 1). A history of asthma at some point in life and of current wheezing (current asthma) was reported by 7.9%. There were significantly more boys who had lifetime asthma and current wheezing and asthma, nasal allergic symptoms and lifetime and current eczema. Asthma and allied diseases were more frequent in the two southern French centres than in the two northern ones, with maximum prevalence in Marseille. 8.3% of children had an EIA according to the challenge performed in the school. 25% had skin prick test positivity. 21.5% of children had a mother with personal atopy (i.e. asthma or hay fever or eczema). 54.4% of mothers reported breast feeding for their child, however 46.7 of them (i.e. $n = 1286$) reported breast feeding for at least 3 months and 47.4% inferior to 1 month.

Exposure to parental smoking

About 32% of children were exposed to parental smoking during pregnancy. 43% were exposed to parental smoking during the first year of life, and 38.6% were currently exposed during the study. The prevalence of exposure to parental smoking rose during life with higher prevalence when children are older. The number of cigarettes smoked per day and declared by the parents, increased also with age of the children (Table 2), and was lower for the mother than for the father. Overall, father smokers consumed five cigarettes a day compared to 1.9 for mother smokers during pregnancy. Correlations

Table 1 General characteristics of the study population.

	Child	Mother	Father
Age	10±0.8	38.4±5.2	41.4±6.42
Male (%)	49.2		
Weight (kg) (M±SD)	36.5±12.6		
Height (m)(M±SD)	1.41±0.09		
BMI (M±SD)	18.38±12		
PEF (ml/mn) (M±SD)	330.46±49.41		
Ethnic group (%)			
White		68.13	62.7
West Indies		3	2.99
South Europe		4.67	4.9
North-Africa		11.52	12.6
Black Africa		3.45	3.3
Asia		3	3.2
Other		6.2	7.2
Parental education (%)			
Primary school		13.5	14.2
Secondary school		45.7	42.9
Vocational training certificate		3.3	3.9
Master degree standard		37.5	38.9
Siblings			
No	25		
1 sister or brother	34.6		
2 sisters or brothers	22.7		
3 sisters or brothers	8.5		
>4 sisters or brothers	6		
Insurance family social security (%)	96.8		
Complementary private insurance (%)	1.2		
Lifetime asthma, *n* (%)	695(9.9)		
Current asthma, *n* (%)	509(7.9)		
Lifetime wheezing, *n* (%)	1365(19.4)		
Current wheezing, *n* (%)	518(7.4)		
Lifetime hay fever, *n* (%)	866(12.9)		
Allergic rhinitis, *n* (%)	732(11.6)		
Lifetime eczema, *n* (%)	1715(25.22)		
Exercise-induced asthma, *n* (%)	610(8.3)		
Atopy, *n* (%)	1848(25)	1673(21.5)	1376(17.65)
Breast feeding		3710(54.4)	
Birthweight <2500 g	443(6.8)		
At least one sibling, *n* (%)	2705(34.6)		
Low birthweight birth (<37 weeks of gestation), *n* (%)	1879(27.9)		
Day care at least 6 months, out home, *n* (%)	1392(22.1)		
Exposure to pets during the first year of life, *n* (%)	504(6.9)		

between maternal and paternal smoking compared with never-smokers are presented in Table 3. About 786 children were exposed to other sources of smoking according to parents. The majority of exposed children were exposed to maternal smoking too.

Boys were more exposed to current paternal smoking than girls (sex ratio: 1.14[1.02–1.27], $P = 0.01$), and girls were more exposed to maternal smoking during the first year than boys (sex ratio: 0.88[0.79–0.99], $P = 0.04$). Taking into account exposure to both maternal and paternal smoking

during life, boys were significantly more exposed than girls (sex ratio: 1.35[1.06–1.73], $P = 0.01$). There was a significant association between passive exposure and a birthweight <2500 g (odds ratio (OR): 1.79[1.39–2.5]) with exposure-response pattern with the number of cigarettes smoked per day (>20 cig/d; OR: 2.91[1.11–7.62]). There was also a significant association between passive exposure during pregnancy and prematurity (OR: 1.2[1.04–1.38]). In utero exposure was significantly associated with low birth weight (9.4% vs. 5.4%; $P = 0.001$), however low birth weight was not associated with lifetime wheeze, but was associated with asthma (12.4% vs. 9.3%: $P = 0.001$).

We adjusted the model for low birth weight, in addition with others potential confounders, the association remains significant between smoking exposure and wheeze. Children with low birth weight were mostly premature (73.4%); however, not all premature children were of low birth weight.

Table 2 Prevalence of parental smoking and number of cigarettes smoked.

	N (%)	Number of cigarettes per day M(SD)
In utero (responders)		
Mother (5532)	1193(21.6)	1.9(5.4)
Father (4588)	1721(37.51)	5(8.9)
Other (2296)	111(4.6)	0.58(3.59)
Mother and father (4442)	540(12)	6.2(10.9)
First year of life		
Mother (5442)	1619(29.75)	3.5(7.44)
Father (4957)	2028(40.91)	5.54(9.77)
Other (2511)	178(7)	0.91(5.7)
Mother and father (4785)	977(20)	8.4(14)
Current		
Mother (6042)	2060(34.1)	3.9(7.5)
Father (5415)	1958(36.16)	4.6(9.2)
Other (2822)	345(12.2)	1.34(5.4)
Mother and father (5200)	1017(19.5)	7.5(13.1)

Asthma and allergies related to passive exposure

ETS during pregnancy was associated with both lifetime wheezing and asthma (Table 4). Smoking, both paternal and maternal, during pregnancy and during the first year of life of the child was associated with lifetime asthma. Maternal ETS was associated with both lifetime asthma and wheezing but there was no dose-effect cumulative exposure. Relations were stronger in girls. No relation was found between current wheezing and ETS exposure (Table 4), the same result was observed for allergic rhinitis. Surprisingly, an inverse relation was found between on one hand, current exposure and lifetime hay fever, and on the other hand, current exposure and lifetime eczema. EIA of children was associated with current paternal smoking exposure. No relationship was found between SPT positivity of the children and parental tobacco exposure.

Taking into account the number of cigarettes smoked by parents per day (Table 5), smoking at least 10 and more than 20 cigarettes per day during pregnancy was significantly associated with lifetime wheezing showing the existence of a trend. No relation was found between exposure to parental smoking, current exposure particularly, and current wheezing. Similarly, there was no association for lifetime asthma. EIA at the age of 10 was significantly associated with parental tobacco smoking more than 20 cig/d during the first year of life. We did not observe an exposure-response pattern for any outcome variables regarding the number of cigarettes smoked per day.

Modifier effects

We tested whether the effect of in utero exposure to smoking on asthma and wheeze could be mediated through prematurity.

The results of this analysis are now presented in Table 6.

Relations between ETS exposure during pregnancy and lifetime wheezing were stronger in children with atopic parents (OR: 1.8[1.33–2.4]).

Table 3 Correlations between paternal and maternal smoking, OR Ic95%.

	Never smoked	Maternal smoking only	Paternal smoking only	Both maternal and paternal smoking
In utero	1	2.4[2.1–2.7]	1.38[1.3–1.43]	5.8[4.9–6.9]
First year	1	3.08[2.7–3.4]	1.8[1.7–1.9]	8.9[7.7–10.4]
Current exposure	1	2.4[2.2–5.8]	1.9[1.8–2.1]	7.7[6.7–8.8]

Table 4 Odds ratios (and 95% confidence intervals) between asthma and allergic disorders and exposure to parental tobacco smoke, according to prior history of exposure.

	Lifetime wheezing ($N = 1365$)		Lifetime asthma ($N = 509$)		Exercise-induced asthma (fall of PEF 10%) ($N = 610$)		Positivity to SPT (all allergens*) ($N = 1848$)	
	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR
Mother, in utero	1.24[1.07–1.45]	1.28[1.1–1.5]	1.22[1.01–1.5]	1.3[1.01–1.67]	0.98[0.77–1.25]	1.08[0.85–1.39]	1.04[0.8–1.2]	0.94[0.81–1.1]
First year of life	1.16[1.01–1.34]	1.17[1.01–1.36]	1.20[0.99–1.4]	1.19[0.98–1.44]	1.05[0.8–1.3]	1.14[0.91–1.42]	1.03[0.9–1.2]	0.96[0.83–1.1]
Current	1.06[0.94–1.2]	1.02[0.8–1.3]	1.14[0.98–1.34]	1.23[1.02–1.47]	1.09[0.92–1.3]	1.11[0.90–1.36]	0.95[0.8–1.06]	0.97[0.86–1.1]
Father, in utero	1.18[1.01–1.36]	0.98[0.85–1.14]	1.01[0.83–1.2]	0.97[0.79–1.17]	1.18[0.94–1.47]	0.90[0.72–1.13]	0.9[0.7–1.03]	0.89[0.77–1.02]
First year of life	0.99[0.88–1.12]	1.02[0.87–1.19]	0.99[0.84–1.16]	1.10[0.89–1.36]	1.17[0.98–1.4]	0.87[0.69–1.1]	0.9[0.8–1.01]	0.9[0.78–1.04]
Current	1[0.89–1.13]	0.89[0.76–1.03]	1.06[0.91–1.24]	0.89[0.79–1.1]	1.25[1.05–1.48]	1.07[0.8–1.38]	0.95[0.8–1.06]	0.92[0.79–1.07]
Mother and father, in utero	1.35[1.09–1.66]	1.24[1.06–1.45]	1.02[0.76–1.37]	0.98[0.7–1.4]	1.13[0.8–1.55]	1.13[0.8–1.55]	0.93[0.76–1.15]	0.93[0.76–1.15]
First year of life	1.22[1.04–1.44]	1.2[0.98–1.4]	1.13[0.9–1.4]	1.13[0.9–1.4]	1.18[0.9–1.5]	1.18[0.9–1.5]	0.96[0.8–1.13]	0.96[0.8–1.13]
Current	1.14[0.97–1.35]	1.1[0.9–1.33]	1.07[0.85–1.3]	1.07[0.85–1.3]	1.03[0.8–1.3]	1.03[0.8–1.3]	0.96[0.82–1.12]	0.96[0.82–1.12]
Mother and father, all life	1.2[0.9–1.6]	1.2[0.78–1.5]	1.08[0.73–1.6]	1.08[0.73–1.6]	1.04[0.8–1.3]	1.04[0.8–1.3]	1.06[0.9–1.24]	1.06[0.9–1.24]

*$P < 0.05$, ***$P < 0.001$.

Adjusted on gender, siblings, exposure to pets during the first year of life, ethnic group, parental education, day care, breast feeding, geographic center, parental atopy, prematurity.

*$P < 0.005$ ref = 1 for no-exposed and no asthma or allergies.

Table 5 Odds-ratio between wheezing and asthma and the number of cigarettes smoked per a day.

	Lifetime wheezing (4386)	Wheezing during the past year (1854)	Lifetime asthma (5136)	Exercise-induced asthma (5124)
Cigarettes smoked per day (mother and father) during pregnancy				
0(2610)	1	1	1	1
1–9(939)	1.28[1.07–1.53]***	0.96[0.7–1.31]	1.08[0.84–1.38]	1.09[0.83–1.44]
10–19(544)	1.08[0.86–1.36]	0.84[0.56–1.28]	0.83[0.59–1.16]	0.95[0.66–1.36]
>20 (349)	1.35[1.04–1.77]*	1.28[0.83–1.98]	1.15[0.8–1.65]	1.42[0.97–2.06]
P for trend	0.02	0.52	0.45	$P = 0.30$
Cigarettes smoked per day (mother and father) during first year of life				
0(2583)	1	1	1	1
1–9(960)	1.28[1.07–1.53]***	0.95[0.70–1.29]	1.15[0.9–1.47]	1.14[0.86–1.5]
10–19(664)	1.05[0.85–1.3]	0.70[0.47–1.04]	0.82[0.6–1.12]	1.01[0.72–1.39]
>20(578)	1.14[0.91–1.42]	1.22[0.85–1.73]	1.25[0.94–1.67]	1.41[1.04–1.93]*
P for trend	0.05	0.14	0.10	0.16
Cigarettes smoked Currently per day (mother and father)				
0(2914)	1	1	1	1
1–9(1060)	1.07[0.9–1.28]	1.02[0.76–1.37]	1.15[0.91–1.45]	0.99[0.75–1.31]
10–19(660)	1.03[0.83–1.28]	0.97[0.67–1.39]	0.97[0.72–1.3]	1.22[0.89–1.67]
>20(566)	1.04[0.82–1.3]	0.89[0.61–1.30]	1.03[0.76–1.40]	1.30[0.94–1.8]
P for trend	0.87	0.93	0.66	0.28

Adjusted on gender, siblings, exposure to pets during the first year of life, ethnic group, parental education, day care, breast feeding, geographic center, parental atopy, prematurity.
The number given under each symptom indicates the number of subjects included in the analysis of that outcome variable, beside exposure, the number indicates the number of subjects with that exposure status.
*$P<0.05$.
***$P<0.001$.

Table 6 Associations between in utero exposure and asthma and wheeze by prematurity status.

	Prematurity ($n = 1879$)			Born at term ($n = 4866$)		
	Smoking exposure (%)	No-smoking exposure (%)	Adjusted OR Ic 95%	Smoking exposure (%)	No-smoking exposure (%)	Adjusted OR Ic 95%
Wheeze	29.3	25	1.24 [0.95–1.62]	23.8	18	1.23[1.01–1.49]
Asthma	15.7	11.4	1.44 [1.03–2.01]	9.9	9.1	1.01[0.84–1.4]

Adjusted on gender, siblings, exposure to pets during the first year of life, ethnic group, parental education, day care, breast feeding, geographic center, parental atopy.

Relations between ETS exposure and lifetime wheezing were significantly stronger in children with negative SPT to pollens or *Alternaria* (OR: 1.4[1.13–1.73]). Unlike with indoor allergens, the relations between ETS exposure and lifetime wheezing were stronger in children sensitized to house dust mites and cat (OR: 1.71[1.18–2.5]). Breast feeding did not modify the relations between exposure and the considered health outcomes. Owing pets during the first year of life had a modifier effect on the relation between smoking exposure and lifetime wheezing, with a stronger effect in children without pets (OR: 1.35[1.08–1.68]). In the same way, day care during the six first months of life had a stronger effect on the relations between exposure and considered outcomes (OR: 1.4[1.07–1.84]).

Children whose mothers smoked during the first year of life but did not smoke during pregnancy, had a reduced risk to have asthma (OR: 1.1[0.82–1.48]) and wheeze (OR: 1.08[0.86–1.35]) compared with others children, after adjustment on potential confounders.

Discussion

Statistically significant associations were observed between exposure to parental tobacco smoke and wheezing and asthma in this cross-sectional analysis of a large population-based sample of schoolchildren living in metropolitan France. The strongest and most consistent associations were observed for lifetime wheezing. The amount of smoking at home, as measured by self-report of parents, was more strongly associated with wheezing than was maternal smoking. There was no evidence of an association between current exposure to environmental tobacco smoke and current asthma or wheezing during the past year. By contrast, maternal tobacco smoke during pregnancy and first year of life were associated with lifetime asthma. There was no evidence of an association between atopy of the children and exposure to parental smoking. Our results yielded also after having taken potential confounders and modifiers of the relationship into account, which is original so far. Namely, early life factors that have been associated with either asthma and allied diseases or with parental smoking habits were considered in the study of the relationship in order to better disentangle it.

Previous studies of the relationship between childhood ETS exposure and the occurrence of asthma, wheezing and airway hyper responsiveness have produced conflicting results. Several studies have demonstrated a significant association between ETS exposure and diagnosed asthma. Other investigators, however have found ETS exposure associated with ''wheeze with colds'' or ''wheezy bronchitis'' rather than with other wheeze patterns.[17] Differences in symptoms ascertainment methods and subject characteristics may help to explain these apparently discrepant results. In our study, we chose to use the definition of wheezing and asthma according to the ISAAC protocol which has been[18] previously validated. However, we cannot formally exclude recall bias or information bias using questionnaire as usually reported in epidemiological studies.

The observed associations in the present study, between exposure to parental smoking and wheezing symptoms and asthma but not with current asthma (i.e. wheezing in the past year) had several explanations. These may be under diagnosis of asthma or underreporting of the diagnosis. This could occur if the families of smokers differed from those of non-smokers in their use of preventive health care services, or if smoking parents were less likely to bring a child's wheezing to a health practitioner' attention. Because of changes in the social acceptability of smoking and reports on the possible adverse consequences of ETS, parents of asthmatics may also have been more inclined to deny or underestimate their smoking. In our study, parents with asthmatic children answer less to the questions on their smoking habits whereas they answered correctly to other items, compared with parents with non-asthmatic children. Upon diagnosis of asthma in a child, parents may quit smoking or reduce their smoking at home, whereas the parents of children whose wheezing appears to be associated primarily with respiratory infections may continue their smoking habit. It is also possible that the children most likely to have asthma are also the least likely to have parents who tolerate smoking (i.e. both children and parents may have airway hyper responsiveness) that would again result in an underestimate of the true association. It has been suggested that a lack of awareness of asthma symptoms including diagnosis and management, among heavy smokers.[19] No information was collected on the smoking cessation by parents regarding the age of the symptoms in our as well as in the previous investigations.

The stronger associations of wheeze symptoms with total smoking than with maternal smoking may be related to the age of the children. Maternal smoking may be the most important aspect of ETS exposure when children are younger and spend more time with their mothers. We cannot exclude a selection bias concerning the self-reported smoking habits, particularly underestimation of the number of cigarettes smoked per day. We only have self-reported information on smoking habits on questionnaire and no objective measure as cotinine levels. A major concern of our investigation was the validity of the data on smoking habits, which were obtained through a questionnaire. Although no biological marker of smoking was assessed in our study, standardized questions on smoking habits have been largely used[20] and validated in the literature.[21] As in many previous studies, precision in the reporting of smoking onset and specially smoking cessation by the parents could not be evaluated in our study.

The number of cigarettes and the self-reported smoking habits provided equally useful information regarding the increased risk for all asthma and wheeze symptoms for children only exposed in utero. Non-response may have also affected the results of our study. The children in the present study were mostly middle-class white children and fewer asthmatics than children with missing data on tobacco exposure and the association reported here may underestimate the true relationship among asthmatic and minority children.

Although several potential confounders were controlled in the analyses, residual confounding or confounding by others factors is still a possibility. However, it appears difficult to adjust for the influence of avoidance behaviour (owning pets, breastfeeding) due to allergy status. The differences between crude and adjusted estimates were generally small, however, suggesting only weak confounding. One interesting finding of our study is the relationship between ETS exposure during pregnancy and wheezing which was stronger in children with atopic parents. Surprisingly, relations between ETS exposure and lifetime wheezing were significantly stronger in children with negative SPT to pollens or *Alternaria*. By contrast, the relations between ETS exposure and lifetime wheezing were stronger in children sensitized to house dust mites and cat, suggesting interaction between sensitization of the children and passive exposure. There was no evidence of an association between atopy of the children and exposure to parental smoking. Previous systematic review identified 12 studies relevant to ETS and including SPT. Studies of parental smoking during pregnancy or infancy were broadly consistent in showing no adverse effect on prick positivity (pooled OR: 0.87[0.62–1.24]).[22] Parental smoking either before or immediately after birth seems to be unlikely to increase the risk of allergic sensitization.

Surprisingly, we found a negative association between, on one hand current exposure to environmental tobacco smoke and hay fever, and on the other hand maternal current tobacco smoke and eczema. This could be due to selection bias as parents could avoid smoking in the presence of their allergic child. These reverse relations might be due to reverse causation, avoidance behaviour, or disease modification of exposure. The relationship of maternal smoking to clinical atopic disease has been reported in previous studies and is still debated.[23] Eczema was defined without reference to the SPT and was inversely related to maternal smoking during pregnancy and during previous year.[22] Hay fever, defined on the basis of symptoms of rhinitis was also less common if the mother smoked. The effects of maternal smoking were similar in children with and without a parental history of allergy disease. However, mechanism of such observation remains unknown.

Taking into account different patterns of asthma, these results add to the growing body of evidence regarding the associations between exposure to ETS and lifetime wheezing and asthma reporting in school-aged children. They support the hypothesis that the mechanism according to which ETS acts is not allergic. Prospective studies are needed to adequately address such issues as the long-term effects of early exposure, changes in level of smoking in the home as a consequence of respiratory symptoms in children. Policies need to be developed which reduce smoking among parents and protect infants and young children from exposure to environmental tobacco smoke. Counselling parents of children to quit smoking still remains a public health policy, especially by GP's and paediatricians.[24]

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