

Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren

C. Pénard-Morand*, D. Charpin†, C. Raheison‡§, C. Kopferschmitt¶, D. Caillaud||, F. Lavaud** and I. Annesi-Maesano*

*INSERM U472, Epidemiology of Allergic and Respiratory Diseases, Villejuif, France, †Hôpital Nord, Marseille, France, ‡Hôpital du Haut-Lévêque, Bordeaux, France, §ISPED Université, Bordeaux, France, ¶Hôpitaux Civils, Strasbourg, France, ||Hôpital Montpied, Clermont-Ferrand, France and **Hôpital Maison Blanche, Reims, France

Summary

Background The impact of air pollution on asthma and allergies still remains a debate.

Objective Our cross-sectional study was intended to analyse the associations between long-term exposure to background air pollution and atopic and respiratory outcomes in a large population-based sample of schoolchildren.

Methods Six thousand six hundred and seventy-two children aged 9–11 years recruited from 108 randomly schools in six French cities underwent a clinical examination including a skin prick test (SPT) to common allergens, exercise-induced bronchial reactivity (EIB) and skin examination for flexural dermatitis. The prevalence of asthma, allergic rhinitis (AR) and atopic dermatitis was assessed by a standardized health questionnaire completed by the parents. Three-year-averaged concentrations of air pollutants (NO₂, SO₂, PM₁₀ and O₃) were calculated at children's schools using measurements of background monitoring stations.

Results After adjusting for confounders, EIB, lifetime asthma and lifetime AR were found to be positively related to an increase in the exposure to SO₂, PM₁₀ and O₃. The adjusted odds ratios (aOR) per increase of 5 µg/m³ of SO₂ was 1.39 (95% confidence interval (CI) = 1.15–1.66) for EIB and 1.19 (1.00–1.41) for lifetime asthma. The aOR for lifetime AR per increase of 10 µg/m³ of PM₁₀ was 1.32 (CI = 1.04–1.68). Moreover, SPT positivity was associated with O₃ (aOR = 1.34; CI = 1.24–1.46). Associations with past year symptoms were consistent, even if not always statistically significant. Results persisted in long-term resident (current address for at least 8 years) children. However, no consistent positive association was found with NO₂.

Conclusions A moderate increase in long-term exposure to background ambient air pollution was associated with an increased prevalence of respiratory and atopic indicators in children.

Keywords air pollution, allergic rhinitis, asthma, atopy, background monitoring stations, children, eczema, exercise-induced bronchial reactivity, skin prick test positivity

Submitted 7 December 2004; revised 24 June 2005; accepted 26 July 2005

Introduction

Several epidemiological studies have investigated the association between exposure to urban air pollutants [1–8] and respiratory and allergic diseases. While positive relationships between background concentrations of nitrogen dioxide (NO₂) [2–4, 7], sulphur dioxide (SO₂) [2–4], particles matter (PM) [2, 3, 7] and ozone (O₃) [8] and chronic respiratory symptoms (cough, bronchitis, wheezing) [2–4] and lung function [7] were reported, no association was found with asthma [1–3] and allergic sensitization and diseases [2–5], except in two studies, in which O₃ was correlated to asthma [6] or to bronchial hyper-responsiveness [4]. Epidemiological

studies that focused on the effects of traffic-related air pollutants [9–16] or road traffic [17–22] also found positive associations with respiratory tract illnesses [12, 16, 17, 19], lung function [13, 17] and even allergic rhinitis (AR) [20, 21], while results on asthma [10–12, 16, 17, 22] and atopy [9, 11, 12] were still contradictory.

However, there is substantial evidence from experimental studies that urban air pollutants, and especially diesel exhaust particulate (DEP), one of the major contributors to PM in urban areas, has an effect on allergic sensitization and morbidity. A series of *in vivo* animal studies have shown that DEP, in association with allergen exposure, enhance immunoglobulin E (IgE) synthesis [23] and increase the inflammatory response in target organ tissues [24, 25]. Human exposure studies [26–30] suggest that DEP, NO₂ and SO₂ increase symptoms in allergic subjects [27, 30] and even have a direct inflammatory effect [26, 28, 29]. *In vitro* culture studies have shown that DEP induce IgE production [31].

Correspondence: Céline Pénard-Morand, INSERM U472, EPAR (Epidemiology of Allergic and Respiratory Diseases) Department, 16 avenue Paul Vaillant Couturier F94807, Villejuif, France.

E-mail: celine.morand@polytechnique.org

A limitation of the epidemiological studies having studied health effects of urban air pollution has been the lack of objective indicators of exposure. Most studies took into account traffic frequency but not other potential sources of inner city air pollution like heating or industry [4, 32]. Studies having used concentrations recorded by monitoring stations were often based on very few stations [33]. Moreover, background and proximity levels of air pollution were often mixed up, while the latter vary over very short distances [34].

The present study was intended to analyse the relationship between long-term exposure to background concentrations of air pollutants [NO₂, SO₂, particles with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM₁₀) and O₃] based on objective assessments and atopic and respiratory outcomes in a large population-based sample of French children.

Methods

Study subjects

Between March 1999 and October 2000, 9615 children aged 9–11 years recruited in six French communities (Bordeaux, Clermont-Ferrand, Créteil, Marseille, Strasbourg and Reims) chosen for differences in the quality of air were studied using the phase II modules of the International Study of Asthma and Allergies in Childhood (ISAAC) [35]. All children in the 401 relevant classes were included from the 108 schools randomly selected in the six communities.

Study design

The parents completed a standardized questionnaire containing the ISAAC core questions on respiratory and allergic disorders [36, 37], how these were managed and their potential risk factors. Children were invited to undergo clinical examination including skin prick test (SPT) to assess allergic sensitization, objective evidence of visible flexural dermatitis [38] and a measure of exercise-induced bronchial reactivity (EIB). Physicians especially trained for the survey performed the tests. Data collection was avoided at the end of spring and during summer to limit seasonal exacerbation of allergic symptoms because of pollens. Children were tested with the following aeroallergens: mixed grass pollen, mixed tree pollen (birch), *Alternaria tenuis*, *Blatta germanica*, *Dermatophagoides Pteronyssinus*, *Dermatophagoides Farinae* and cat (Stallergènes laboratories, France). Histamine was used as a positive control and glycerine was used as a negative control. The weal size after 15 min was calculated as the mean of the longest diameter and its perpendicular diameter. SPT positivity was defined as a weal ≥ 3 mm and greater than the negative control. EIB was assessed according to the standardized protocol of the run test [39, 40]. Peak expiratory flow (PEF) rate was measured immediately before and 5 min after a 6 min period of running with a Mini-Wright Peak Flow meter[®].

Written informed consent was obtained from the parents. The study protocol obtained approval from the National Ethics Board (C.C.P.P.R.B.).

Health outcomes classification

We classified health outcomes according to the time of their occurrence as follows:

During the clinical examination: EIB, flexural dermatitis Children were classified as having EIB if the decrease in PEF after exercise exceeded 10%. Children were considered to have flexural dermatitis if the physician had observed itchy rash that had affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles or around the neck or eyes.

Past year: wheeze, asthma, rhinoconjunctivitis, atopic dermatitis These four outcomes, which referred to symptoms in the last 12 months, were assessed using the replies to the following ISAAC questions: 'Has your child had wheezing or whistling in the chest in the last 12 months?' for past year wheeze, and 'In the last 12 months, has your child ever had an itchy rash which was coming and going for at least six months at any time?' for past year atopic dermatitis. Past year rhinoconjunctivitis was defined as having affirmative answers to the following two questions: 'In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?' and 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?'. Past year asthma was derived using the combination of the question on 'wheezing or whistling in the chest in the last 12 months' and the following question: 'Has your child ever had asthma?'.

Lifetime: asthma, allergic rhinitis, atopic dermatitis, atopy Using ISAAC core questions, lifetime asthma was assessed from the question 'Has your child ever had asthma?', lifetime AR from at least one affirmative answer to the following questions 'Has your child ever had hayfever?' or 'Has your child ever had other types of AR?' and lifetime atopic dermatitis from the question 'Has your child ever had eczema?'.

Atopy was defined as at least one positive SPT to one of the seven tested aeroallergens. Aeroallergens were grouped into pollen (mixed grass and tree pollen), indoor allergens (house dust mites, cat and *Blatta germanica*) and moulds (*Alternaria tenuis*).

Potential confounders included age, sex, family history of allergy, passive smoking and parental education. A child had a family history of allergy if his/her father or his/her mother had ever suffered from asthma, AR or eczema. Passive smoking was defined as any current exposure to cigarettes, pipes or cigars in the home. Parental education was defined as highest parental school education.

Exposure to air pollution assessment

Children' long-term exposure to background air pollution was estimated at the 108 school addresses in collaboration with the Air Quality Monitoring Networks of the six cities (AIRAQ in Bordeaux, AIRPARIF in Créteil, ATMO Auvergne in Clermont-Ferrand, AIRMARAIX in Marseille, ATMO Champagne-Ardenne in Reims and ASPA in Strasbourg). These six networks, which belong to the same

national agency, used the same measurement methods and site selection criteria. We calculated the mean concentrations between January 1, 1998 and December 31, 2000 of NO₂, SO₂, PM₁₀ and O₃, respectively, measured at background monitoring stations in the six cities. Data for the preceding periods were not used because they were not available for a sufficient number of stations in the cities. To determine the distance between the schools and the stations, the addresses of the 108 schools and the 29 background monitoring stations were geo-coded with a geographic information system (GIS) or were located on the IGN (Institut Géographique National) town plan. Successively, a modelization expert in each Air Quality Monitoring Network identified the nearest and most representative background monitoring stations for each school. The 3-year-averaged concentrations measured at the relevant background monitoring stations were averaged, to estimate the 3-year-averaged concentrations of air pollutants at each school.

Statistical analyses

In order to limit exposure misclassification, the analyses were restricted to children who had spent at least the last 3 years in their house at the time of the clinical examination. A sensitivity analysis was repeated in the 2834 children for whom exposure to air quality was likely to have been relatively stable most of their lives as they had spent the last 8 years at the same address (long-term resident children).

To assess the associations between exposure to each air pollutants and health outcomes, two variables were used: (1) the two-category variable of exposure classifying 'low' vs. 'high' exposure, which was defined with respect to the median value of the distribution of the evaluated concentrations at schools for each pollutant (categorical variable) and (2) the concentration value of the pollutant in µg/m³ (continuous variable). The prevalence of health outcomes was calculated in each category of exposure, and unadjusted odds ratios (OR) with 95% confidence intervals (95% CI) were estimated using χ^2 analyses. Successively, multiple logistic regression analysis was performed to estimate the OR with 95% CI for the influence of pollutant exposure on the respiratory and atopic outcomes adjusted for potential confounders using both the categorical and the continuous variable. A marginal model [41] was also applied in order to take into account the potential non-independence of data between children attending the same city, because of the fact that they share the same environment, climate, pollens, social factors and probably food products and diet. The parameters of the marginal model were estimated by the generalized estimating equation (GEE) approach applying the SAS PROC GENMOD with an independent working correlation structure using the city as a stratum. In the case of the continuous variable, the ORs were calculated for concentration differences usually common in inner cities. Version 8.2 of SAS System for Windows was used for statistical analysis.

Results

Participation rate

Eighty-one percent of the children (7781/9615) accepted to participate in the study. Completed valid data on both clinical

examination and questionnaire were available for 6672 children (69%). Protocol completion rate among the children having accepted to participate ranged from 79% (Créteil) to 98% (Strasbourg). Four thousand nine hundred and one children of the 6672 (73%) had lived a minimum of 3 years at their address. The characteristics of these 4901 children are given in Table 1. No significant differences were found between children included in the analyses ($N = 4901$) and the others ($N = 1771$) in terms of individual characteristics and potential confounders but in family history of allergy, which was more prevalent in the former group (44.3 vs. 40.4%). Similarly, when comparing children included in the analyses with the others, no significant differences were found for all the health outcomes listed in Table 2.

Table 1. Characteristics of the study population ($N = 4901$ who had lived a minimum of 3 years at their address)

Factors	Child	Mother	Father
Age (years) (m $\pm$ SD)*	10.4 $\pm$ 0.7	38.7 $\pm$ 5.1	41.7 $\pm$ 6.2
Sex (male) (%)	49.9		
Weight (kg) (m $\pm$ SD)	36.1 $\pm$ 8.1		
Height (m) (m $\pm$ SD)	1.42 $\pm$ 0.08		
BMI [†] (m/kg ²) (m $\pm$ SD)	17.8 $\pm$ 2.9		
Passive Smoking (%)	43.6		
Family history of allergy (%)	44.3		
Education (%)			
Primary		11.4	12.2
Secondary		45.1	42.9
High school and university		38.2	39.6
Other		5.3	5.3

*Mean $\pm$ standard deviation. [†]BMI (Body mass index) = weight/height².

Table 2. Prevalence of respiratory and atopic outcomes in the population study ($N = 4901$)

Health outcome	All ($N = 4901$)	Boys [‡] ($N = 2446$)	Girls ($N = 2455$)	OR (95% CI)
During the clinical examination				
EIB	8.8 [‡]	9.1	8.5	0.92 (0.76–1.14)
Flexural dermatitis	10.4	8.6	12.3	1.50 (1.24–1.81)***
Past year				
Wheeze	8.0	9.8	6.3	0.61 (0.49–0.77)***
Asthma	5.3	6.9	3.8	0.53 (0.40–0.71)***
Rhinoconjunctivitis	12.1	13.6	10.7	0.76 (0.63–0.92)**
Atopic dermatitis	12.8	10.7	14.9	1.46 (1.23–1.74)***
Lifetime				
Asthma	9.8	12.5	7.1	0.54 (0.44–0.65)***
Allergic rhinitis	20.1	22.7	17.6	0.73 (0.63–0.84)***
Atopic dermatitis	26.1	24.7	27.4	1.15 (1.01–1.32)*
Atopy [§]	27.4	32.2	22.7	0.62 (0.54–0.70)***
Pollen	12.3	14.7	9.9	0.64 (0.54–0.77)***
Indoor	20.9	24.5	17.4	0.65 (0.56–0.75)***
Moulds	2.4	3.3	1.5	0.45 (0.30–0.68)***

[‡]Reference category. [‡]Prevalence rate (%). [§]Skin prick test positivity ≥ 3 mm to at least one aeroallergen. * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

EIB, exercise-induced bronchial reactivity; OR, odds ratio; CI, confidence interval.

Prevalence of respiratory and atopic outcomes

Atopic dermatitis had the highest prevalence (26.1% lifetime, 12.8% past year), followed by AR (20.1% lifetime, 12.1% past year) and asthma (9.8% lifetime, 5.3% past year). During the clinical examination, 8.8% of the children had EIB and 10.4% suffered from flexural dermatitis. 27.4% of the children were sensitized to at least one aeroallergen (Table 2).

Health outcomes, except EIB, were related to sex (Table 2) and were, as expected, more prevalent in children with a family history of allergy than in children without family history. Passive smoking was associated with a higher prevalence of past year atopic dermatitis. A higher parental education was related to a higher prevalence of flexural dermatitis, past year atopic dermatitis, and lifetime atopic dermatitis.

Distribution of air pollutants

The distributions of 3-year-averaged concentrations of air pollutants estimated at the 108 schools are shown in Fig. 1. 54.9% of the children attended schools with high exposure to NO₂, 59.5% to SO₂, 63.5% to PM₁₀ and 57.6% to O₃ (Table 3).

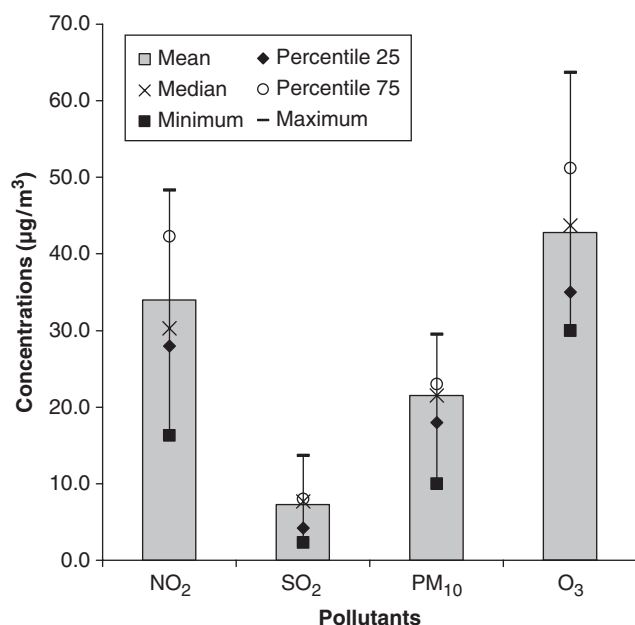


Fig. 1. Distributions of 3-year-averaged concentrations of air pollutants estimated at the 108 schools in the ISAAC II-France study ($N = 4901$).

A higher parental education was associated with higher concentrations of O₃ and lower concentrations of NO₂. No other statistical relationships were observed between potential confounders and air pollution.

Associations between air pollution and health outcomes

Children attending schools in areas with high exposure to O₃ had significantly more EIB, allergic diseases and atopy than others (Table 4). Children attending schools in settings with high exposure to PM₁₀ had significantly more EIB and allergic diseases than others. Children attending schools in zones with high exposure to SO₂ had significantly more EIB but less flexural dermatitis and less atopy than others. No positive association was found between categories of exposure to NO₂ and health outcomes. Moreover, children attending schools in areas with high exposure to NO₂ had significantly less EIB, less flexural dermatitis and less atopy than others.

When the effect of air pollutants concentrations on health outcomes was stratified for sex, no effect of modification was seen. There was also no effect modification for family history of allergy, passive smoking, parental education and atopy.

After adjusting for potential confounders in a logistic regression model, EIB showed the most consistent positive associations with concentrations of SO₂, PM₁₀ and O₃ (Table 5). In contrast, EIB was negatively associated with NO₂. Past year wheeze and asthma were significantly positively associated with SO₂ and almost significantly with O₃. There was a trend towards positive associations between past year rhinoconjunctivitis and past year atopic dermatitis and the four air pollutants. Lifetime AR was consistently positively related to SO₂, PM₁₀ and O₃. A borderline significance was observed between lifetime asthma and these three pollutants. Atopy was significantly positively associated with O₃, but negatively with NO₂. Sensitization to pollen was strongly positively associated with O₃ and almost significantly with PM₁₀, but negatively with NO₂.

To take into account the co-linearity of the gases (NO₂–SO₂: $r = 0.35$; NO₂–PM₁₀: $r = 0.46$; NO₂–O₃: $r = -0.76$; SO₂–PM₁₀: $r = 0.76$; SO₂–O₃: $r = -0.02$; PM₁₀–O₃: $r = -0.02$), we introduced into the logistic regression model the two sets of pollutants that were highly correlated (NO₂ and O₃; SO₂ and PM₁₀). Negative associations with NO₂ disappeared, except for indoor allergens (Table 6). Moreover, significant positive associations between NO₂ and allergic outcomes appeared. The association of EIB with PM₁₀ and O₃ lost statistical significance, while the association of AR and atopic dermatitis (past year and lifetime) with NO₂, PM₁₀ and O₃ became more consistent.

Table 3. Estimated 3-year-averaged concentrations of air pollutants at the 108 schools in the ISAAC II-France study ($N = 4901$)

Pollutant (µg/m ³)	N Monitoring stations	Low concentrations		High concentrations*		Children in schools with high exposure (%)
		Range	Mean	Range	Mean	
NO ₂	29	[16.3–30.0]	26.9	[30.3–48.3]	40.6	54.9
SO ₂	25	[1.3–7.4]	4.6	[7.7–13.7]	9.6	59.5
PM ₁₀	16	[10.0–20.0]	18.0	[21.5–29.5]	23.8	63.5
O ₃	22	[30.0–39.3]	34.1	[43.7–63.7]	50.9	57.6

*The two categories of exposure 'low' vs. 'high' were defined with respect to the median value of the distribution of the evaluated concentrations at schools. NO₂, nitrogen dioxide; SO₂, sulphur dioxide; PM, particles matter; O₃, ozone.

Table 4. Prevalence of respiratory and atopic outcomes by categories of exposure to air pollutants at school address in the ISAAC II-France study ($N = 4901$)

Health outcome	NO ₂		SO ₂	
	Low exposure† $N = 2208$	High exposure $N = 2693$	Low exposure $N = 1984$	High exposure $N = 2917$
During the clinical examination				
EIB	10.1	7.7**	7.2	9.9***
Flexural dermatitis	15.3	6.3***	11.8	9.5**
Past year				
Wheeze	8.5	7.5	7.5	8.3
Asthma	6.0	4.7	5.4	5.2
Rhinoconjunctivitis	12.5	11.8	11.8	12.4
Atopic dermatitis	11.8	13.6 [‡]	12.2	13.2
Lifetime				
Asthma	10.6	9.1 [‡]	9.6	9.8
Allergic rhinitis	21.0	19.4	19.6	20.5
Atopic dermatitis	26.3	26.6	26.6	25.7
Atopy‡	32.2	23.5***	29.9	25.8**
Pollen	13.2	11.5 [‡]	13.5	11.4*
Indoor	25.9	16.8***	22.4	19.9*
Moulds	3.1	1.8**	3.4	1.7***

	PM ₁₀		O ₃	
	Low exposure $N = 1791$	High exposure $N = 3110$	Low exposure $N = 2079$	High exposure $N = 2822$
During the clinical examination				
EIB	6.1	10.3***	7.2	10.0***
Flexural dermatitis	5.6	13.2***	5.4	14.1***
Past year				
Wheeze	7.0	8.6 [‡]	7.1	8.7 [‡]
Asthma	4.3	5.9*	4.7	5.8
Rhinoconjunctivitis	11.4	12.6	11.7	12.4
Atopic dermatitis	10.6	14.0***	12.2	13.2
Lifetime				
Asthma	8.7	10.3 [‡]	9.0	10.3
Allergic rhinitis	18.6	21.1*	17.9	21.8**
Atopic dermatitis	24.3	27.0*	25.6	26.4
Atopy‡	26.4	28.0	21.5	31.6***
Pollen	11.4	12.8	8.3	15.1***
Indoor	20.4	21.2	16.6	24.0***
Moulds	2.0	2.6	1.5	3.0***

†The two categories of exposure 'low' vs. 'high' were defined with respect to the median value of the distribution of the evaluated concentrations at schools. OR: odds-ratios; 95% CI: 95% confidence interval.

‡Skin prick test positivity ≥ 3 mm to at least one aeroallergen.

* $P < 0.10$. ** $P < 0.05$. *** $P < 0.01$. **** $P < 0.001$.

EIB, exercise-induced bronchial reactivity; OR, odds ratio; CI, confidence interval; PM, particles matter; O₃, ozone; ISAAC, International Study of Asthma and Allergies in Childhood; NO₂, nitrogen dioxide; SO₂, sulphur dioxide; EIB, exercise-induced bronchial reactivity.

Results were globally unaffected when the non-independence of data was taken into account using the marginal model. Positive associations of past year wheeze and asthma with SO₂ and O₃ became statistically significant. Moreover, lifetime asthma was more consistently related to SO₂, PM₁₀ and O₃. However, associations of these three pollutants to lifetime AR and EIB partly lost significance.

When including children who had spent less than 3 years at their address, the general pattern of the associations remained unchanged. However, this procedure slightly reduced the point estimates of the OR. Restricting the analyses to the 2834 long-term resident children (current address for at least 8 years) yielded similar or even higher OR for the health outcomes, in spite of the reduction of the sample size.

Discussion

In this large population-based sample of children, elevated concentrations of SO₂, PM₁₀ and O₃ were significantly associated with an increased risk of suffering from EIB, lifetime asthma and lifetime AR. Results concerning past year symptoms were consistent, even if not always statistically significant. Moreover, atopy was significantly positively associated with concentrations of O₃. No consistent positive association was found between NO₂ and respiratory and atopic indicators, except when taking into account the co-linearity with O₃.

Experimental and human studies corroborate our results. Exposure to O₃ is known to increase inflammatory response in epithelial cells [42], to enhance allergic sensitization [43] and to decrease lung function in asthmatic subjects [44]. SO₂ has been clearly shown to enhance allergic sensitization [45] and to exacerbate symptoms of asthma [46]. DEP have been shown to enhance immunologic responses to allergens [23, 26, 30].

Moreover, our results were consistent with previous epidemiological studies [6, 14]. The American AHSMOG study of cohort suggests that long-term exposure to ambient ozone is associated with development of asthma in adult males [6]. In a Dutch birth cohort study with about 4000 children, long-term exposure to urban air pollutants (NO₂, PM_{2.5} and soot) was positively associated with wheezing, asthma and respiratory infections at 2 years of age [14]. Other studies reported positive associations between allergic sensitization or diseases and traffic density which considerably influences background concentrations of air pollutants in urban areas [9–11, 16, 18]. A Dutch study showed that children attending schools close to motorways with high truck traffic counts experienced more rhinoconjunctivitis, eczema and allergic sensitization to pollen than did children attending schools near motorways with low truck traffic counts [11]. In studies including separate counts for trucks and for cars, associations with atopy remained consistent only with truck density [13, 18], which is relatively strongly correlated with proximity levels of NO₂ and even more highly correlated with proximity and even background levels of PM [13, 32]. Thus, these results are consistent with our findings between background concentrations of PM₁₀ and respiratory and atopic outcomes.

In addition, 5-day measurements of PM_{2.5} were performed in schoolyards during the week of medical examination in our sample of children. After adjustment for potential confounders, the odds of suffering from EIB and flexural dermatitis during the clinical examination, past year atopic asthma, lifetime AR and SPT positivity were significantly higher in settings with elevated PM_{2.5} concentrations (Annesi-Maesano I et al., 2005).

Table 5. Association of respiratory and atopic outcomes with exposure to air pollutants at school address after adjustment for potential confounders in the ISAAC II-France study ($N = 4,901$)

Health outcomes	NO ₂ OR (95% CI) for +10 µg/m ³	SO ₂ OR (95% CI) for +5 µg/m ³	PM ₁₀ OR (95% CI) for +10 µg/m ³	O ₃ OR (95% CI) for +10 µg/m ³
During the clinical examination				
EIB	0.87 (0.76–0.99)*	1.39 (1.15–1.66)***	1.43 (1.02–2.01)*	1.17 (1.03–1.31)*
Flexural dermatitis	0.51 (0.44–0.59)***	0.86 (0.73–1.02) [†]	0.79 (0.59–1.07)	1.60 (1.43–1.80)***
Past year				
Wheeze	0.87 (0.75–1.01) [†]	1.23 (1.00–1.51)*	1.05 (0.72–1.54)	1.12 (0.98–1.28)
Asthma	0.92 (0.77–1.10)	1.28 (1.00–1.65)**	1.23 (0.77–1.95)	1.11 (0.94–1.30)
Rhinoconjunctivitis	1.08 (0.96–1.22)	1.05 (0.89–1.24)	1.17 (0.86–1.59)	1.00 (0.89–1.11)
Atopic dermatitis	1.06 (0.95–1.18)	1.01 (0.86–1.18)	1.28 (0.96–1.71) [†]	1.02 (0.92–1.13)
Lifetime				
Asthma	0.94 (0.83–1.07)	1.19 (1.00–1.41) [†]	1.32 (0.96–1.81) [†]	1.09 (0.97–1.22)
Allergic rhinitis	1.00 (0.90–1.10)	1.16 (1.01–1.32)*	1.32 (1.04–1.68)*	1.09 (1.00–1.19)*
Atopic dermatitis	1.01 (0.93–1.10)	0.93 (0.82–1.05)	1.09 (0.88–1.36)	1.04 (0.96–1.12)
Atopy [‡]	0.73 (0.67–0.80)***	1.02 (0.90–1.14)	0.98 (0.80–1.22)	1.34 (1.24–1.46)***
Pollen	0.78 (0.69–0.88)***	1.00 (0.85–1.18)	1.14 (0.85–1.53)	1.40 (1.25–1.56)***
Indoor	0.71 (0.64–0.78)***	1.05 (0.92–1.20)	0.91 (0.72–1.15)	1.30 (1.19–1.41)***
Moulds	0.59 (0.45–0.79)**	0.83 (0.58–1.19)	1.00 (0.53–1.88)	1.64 (1.28–2.10)***

EIB, exercise-induced bronchial reactivity; OR, odds ratio; CI, confidence interval.

[†]Skin prick test positivity ≥ 3 mm to at least one aeroallergen.

* $P < 0.10$. ** $P < 0.05$. *** $P < 0.001$.

Values are odds ratios (OR) and 95% confidence interval (95% CI) obtained with the logistic regression model adjusted for age, sex, family history of allergy, passive smoking and parental education. Pollutant exposure was treated as a continuous linear variable.

Table 6. Association of respiratory and atopic outcomes with exposure to air pollutants at school address after adjustment for potential confounders and the highest correlated air pollutant in the ISAAC II-France study ($N = 4901$)

Health outcomes	NO ₂ OR (95% CI) for +10 µg/m ³	O ₃ OR (95% CI) for +10 µg/m ³	SO ₂ OR (95% CI) for +5 µg/m ³	PM ₁₀ OR (95% CI) for +10 µg/m ³
During the clinical examination				
EIB	0.98 (0.78–1.22)	1.14 (0.93–1.40)	1.46 (1.12–1.90)**	1.16 (0.72–1.85)
Flexural dermatitis	0.86 (0.63–1.12)	1.04 (0.86–1.25)	0.86 (0.68–1.10)	0.93 (0.60–1.43)
Past year				
Wheeze	0.90 (0.70–1.15)	1.04 (0.83–1.30)	1.45 (1.09–1.93)*	1.31 (0.71–2.36)
Asthma	1.02 (0.76–1.38)	1.12 (0.86–1.48)	1.40 (0.99–1.99) [†]	1.25 (0.66–2.37)
Rhinoconjunctivitis	1.24 (1.01–1.52)*	1.16 (0.97–1.40) [†]	0.97 (0.76–1.23)	1.22 (0.98–1.68) [†]
Atopic dermatitis	1.22 (1.00–1.47)*	1.17 (0.98–1.40) [†]	0.82 (0.66–1.03)	1.63 (1.07–2.49)*
Lifetime				
Asthma	1.06 (0.86–1.31)	1.14 (0.95–1.35) [†]	1.15 (0.90–1.47)	1.11 (0.70–1.74)
Allergic rhinitis	1.23 (1.04–1.44)*	1.27 (1.10–1.47)**	1.08 (0.96–1.23) [†]	1.19 (0.94–1.59) [†]
Atopic dermatitis	1.15 (0.99–1.33) [†]	1.15 (1.01–1.31)*	0.89 (0.77–1.04)	1.47 (1.07–2.00)*
Atopy [‡]	0.88 (0.71–1.09)	1.22 (1.07–1.39)**	1.04 (0.88–1.24)	0.93 (0.69–1.26)
Pollen	1.14 (0.93–1.40)	1.54 (1.28–1.84)***	0.90 (0.72–1.13)	1.30 (0.98–1.57) [†]
Indoor	0.73 (0.62–0.85)***	1.03 (0.89–1.19)	1.19 (0.99–1.43) [†]	0.83 (0.63–1.12)
Moulds	0.81 (0.52–1.26)	1.42 (0.97–2.10) [†]	0.69 (0.42–1.14)	1.62 (0.64–4.09)

ISAAC, International Study of Asthma and Allergies in Childhood; NO₂, nitrogen dioxide; SO₂, sulphur dioxide; PM, particles matter; O₃, ozone; EIB, exercise-induced bronchial reactivity; OR, odds ratio; CI, confidence interval.

[†]Skin prick test positivity ≥ 3 mm to at least one aeroallergen.

* $P < 0.10$. ** $P < 0.05$. *** $P < 0.001$.

Values are odds-ratios (OR) and 95% confidence interval (95% CI) obtained with the logistic regression model adjusted for age, sex, family history of allergy, passive smoking, parental education and the highest correlated air pollutant. The 2-pollutants models included NO₂ and O₃ for one and SO₂ and PM₁₀ for the other. Pollutant exposure was treated as a continuous linear variable.

Whereas we found positive associations between SO₂, PM₁₀ and O₃ and health indicators, so confirming previous studies, concentrations of NO₂ were inversely associated with EIB, flexural dermatitis and atopy. However, these negative associations disappeared in the model on including NO₂

and O₃ simultaneously, probably because of the strong negative correlation between NO₂ and O₃. The most likely explanation for not finding a similar relationship for all pollutants is that their production and fate differ considerably [32]. Moreover, misclassification of exposure status to air

pollutants may have been greater for NO₂ than for other pollutants. Indeed, in urban areas, proximity levels of NO₂, which vary at a very small scale, can be locally much higher than background levels of NO₂ [47], while differences between proximity and background levels are lower for PM₁₀, and very small for SO₂ and O₃. To take into account small-scale spatial variations in proximity levels of air pollution, we have modelled annual mean ambient concentrations of traffic-related air pollutants using a 3D dispersion model (Pénard-Morand et al., 2005). We will assess the impact of these proximity levels on health. Moreover, background concentrations of outdoor NO₂ do not take into account high peak of outdoor exposure with NO₂, which occurs mostly during the morning rush hours when children are on their way to school. In addition, the absence of a positive association between NO₂ and health outcomes can be because of the fact that background concentrations of NO₂ are lower than those for which experimental effects have been seen [27, 28]. Similar to our results, a Dutch study found consistent positive relations of lung function to black smoke concentrations measured in children's classrooms, highly associated with truck traffic, but not to NO₂ concentrations, associated with total traffic density [13].

Assessment of air pollution exposure remains difficult in epidemiological studies because of potential misclassification of exposure. Even if we used detailed measurements of air pollutants concentrations and were advised by Air Quality Monitoring Networks, we estimate concentrations only at the child's school. Actually, most children live within 500 m of their elementary school in urban areas in France, so that children's exposure at school may serve as a reasonable proxy measure of children's total exposure to background outdoor air pollution. In our study, the distance between each school and the nearest station was less than 1500 m except for five schools, whereas exposure to air pollution was often assessed through one monitoring station supposed to represent air pollution levels over a large area. To limit exposure misclassification, as children may have experienced different levels of air pollution in their life if they have moved, we excluded from the analysis children who had spent less than 3 years at their home. The associations between air pollutants concentrations and health outcomes persisted in long-term resident children, which argues in favour of a real effect of air pollution on respiratory health and atopy. Our assessment of background air pollution exposure might also have led to misclassification insofar as children spend a fraction of their time at their home, or in transit. However, not considering transit or indoor exposure to pollution may have attenuation of the effect estimates, but in no way to a bias. Concerning respiratory and atopic outcomes, we use internationally validated indicators and objective tests to determine allergic sensitization [35–40]. Clinical examination and SPT were assessed blindly with respect to exposure status. Moreover, the protocols used were standardized and the technicians were certified in their ability to obtain comparable results. Thus, significant misclassification is unlikely. Lastly, confounders were taken into account either directly (age, sex, family history of allergy, passive smoking and parental education) or through the marginal model (climate, pollens, social factors, food products and diet), which enables us to control the potential city effect [48].

In conclusion, our study shows positive relationships between long-term background concentrations of SO₂, PM₁₀ or O₃ and an increased prevalence of respiratory and atopic outcomes in schoolchildren. These results support the hypothesis that not only high peaks of air pollutants concentrations but even a moderate increase in background air pollution might have an influence on childhood respiratory and allergic health.

Acknowledgments

We are particularly indebted to the pupils and parents without whom the study would not have been possible. We wish to thank the Education Nationale, the schools doctors, school principals, the teachers in the 6 cities and Ginette Debotte, who participated in data collection. We thank the modelling specialists of Air Monitoring Networks who helped us to assess air pollution exposure, and particularly Charles Schillinger from ASPA, Laurent Letinois from ATMO Champagne-Ardenne, Serge Pellier and Lionel Rosset from ATMO Auvergne, Alexandre Armengaud and Yann Channac-Montgredien from AIRMARAIX, Rafaël Bunales from AIRAQ and Frédéric Mahé from AIRPARIF. We thank Prof. Pauli from the Hôpital Lyautet in Strasbourg, Prof. Tunon de Lara and Prof. Taytard from the Hôpital du Haut-Lévêque in Bordeaux, who contributed to the conception and design of the study. We are grateful to Prof. Mercier from Comité Contre la Tuberculose et les Maladies Respiratoires, on the aegis of whom the survey was conducted. Allergen extracts were kindly provided by Stallergènes Laboratoires (France).

The ISAAC-II France study was supported by the National Institut for Health and Medical Research (INSERM) (Programme Déterminants de la Santé), the Ministry of Health (DGS), the Environmental Programme PRIMEQUAL-PREDIT of the Ministry of Environment, the Agency for Environment and Energy Management ADEME, the ANTADIR association and the Mutuelle Générale de l'Education Nationale (MGEN).

References

- 1 Baldi I, Tessier JF, Kauffmann F, Jacqmin-Gadda H, Nejjar C, Salamon R. Prevalence of asthma and mean levels of air pollution: results from the French PAARC survey. *Pollution Atmosphérique et Affections Respiratoires Chroniques*. *Eur Respir J* 1999; 14: 132–8.
- 2 Braun-Fahrlander C, Vuille JC, Sennhauser FH et al. Respiratory health and long-term exposure to air pollutants in Swiss schoolchildren. SCARPOL Team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen. *Am J Respir Crit Care Med* 1997; 155:1042–9.
- 3 Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, Ferris BG Jr. Effects of inhalable particles on respiratory health of children. *Am Rev Respir Dis* 1989; 139:587–94.
- 4 Hirsch T, Weiland SK, von Mutius E et al. Inner city air pollution and respiratory health and atopy in children. *Eur Respir J* 1999; 14:669–77.
- 5 Charpin D, Pascal L, Birnbaum J et al. Gaseous air pollution and atopy. *Clin Exp Allergy* 1999; 29:1474–80.

- 6 McDonnell WF, Abbey DE, Nishino N, Lebowitz MD. Long-term ambient ozone concentration and the incidence of asthma in non-smoking adults: the AHSMOG Study. *Environ Res* 1999; 80: 110–21.
- 7 Gauderman WJ, Avol E, Gilliland F et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004; 351:1057–67.
- 8 Schmitzberger R, Rhomberg K, Buchele H et al. Effects of air pollution on the respiratory tract of children. *Pediatr Pulmonol* 1993; 15:68–74.
- 9 Kramer U, Koch T, Ranft U, Ring J, Behrendt H. Traffic-related air pollution is associated with atopy in children living in urban areas. *Epidemiology* 2000; 11:64–70.
- 10 Kim JJ, Smorodinsky S, Lipsett M, Singer BC, Hodgson AT, Ostro B. Traffic-related air pollution near busy roads: the East Bay Children's Respiratory Health Study. *Am J Respir Crit Care Med* 2004; 170:520–6.
- 11 Janssen NA, Brunekreef B, van Vliet P et al. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. *Environ Health Perspect* 2003; 111: 1512–8.
- 12 van Vliet P, Knape M, de Hartog J, Janssen N, Harssema H, Brunekreef B. Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways. *Environ Res* 1997; 74:122–32.
- 13 Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knape M, van Vliet P. Air pollution from truck traffic and lung function in children living near motorways. *Epidemiology* 1997; 8: 298–303.
- 14 Brauer M, Hoek G, Van Vliet P et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Respir Crit Care Med* 2002; 166:1092–8.
- 15 Zmirou D, Gauvin S, Pin I et al. Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study. *J Epidemiol Community Health* 2004; 58:18–23.
- 16 Nicolai T, Carr D, Weiland SK et al. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. *Eur Respir J* 2003; 21:956–63.
- 17 Wjst M, Reitmeir P, Dold S et al. Road traffic and adverse effects on respiratory health in children. *BMJ* 1993; 307:596–600.
- 18 Wyler C, Braun-Fahrlander C, Kunzli N et al. Exposure to motor vehicle traffic and allergic sensitization. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *Epidemiology* 2000; 11:450–6.
- 19 Ciccone G, Forastiere F, Agabiti N et al. Road traffic and adverse respiratory effects in children. SIDRIA Collaborative Group. *Occup Environ Med* 1998; 55:771–8.
- 20 Weiland SK, Mundt KA, Ruckmann A, Keil U. Self-reported wheezing and allergic rhinitis in children and traffic density on street of residence. *Ann Epidemiol* 1994; 4:243–7.
- 21 Duhme H, Weiland SK, Keil U et al. The association between self-reported symptoms of asthma and allergic rhinitis and self-reported traffic density on street of residence in adolescents. *Epidemiology* 1996; 7:578–82.
- 22 Edwards J, Walters S, Griffiths RK. Hospital admissions for asthma in preschool children: relationship to major roads in Birmingham, United Kingdom. *Arch Environ Health* 1994; 49:223–7.
- 23 Muranaka M, Suzuki S, Koizumi K et al. Adjuvant activity of diesel-exhaust particulates for the production of IgE antibody in mice. *J Allergy Clin Immunol* 1986; 77:616–23.
- 24 Takano H, Yoshikawa T, Ichinose T, Miyabara Y, Imaoka K, Sagai M. Diesel exhaust particles enhance antigen-induced airway inflammation and local cytokine expression in mice. *Am J Respir Crit Care Med* 1997; 156:36–42.
- 25 Kobayashi T. Exposure to diesel exhaust aggravates nasal allergic reaction in guinea pigs. *Am J Respir Crit Care Med* 2000; 162: 352–6.
- 26 Nordenhall C, Pourazar J, Blomberg A, Levin JO, Sandstrom T, Adelroth E. Airway inflammation following exposure to diesel exhaust: a study of time kinetics using induced sputum. *Eur Respir J* 2000; 15:1046–51.
- 27 Devalia JL, Rusznak C, Herdman MJ, Trigg CJ, Tarraf H, Davies RJ. Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. *Lancet* 1994; 344:1668–71.
- 28 Blomberg A, Krishna MT, Bocchino V et al. The inflammatory effects of 2 ppm NO₂ on the airways of healthy subjects. *Am J Respir Crit Care Med* 1997; 156:418–24.
- 29 Diaz-Sanchez D, Tsien A, Casillas A, Dotson AR, Saxon A. Enhanced nasal cytokine production in human beings after in vivo challenge with diesel exhaust particles. *J Allergy Clin Immunol* 1996; 98:114–23.
- 30 Diaz-Sanchez D, Penichet-Garcia M, Saxon A. Diesel exhaust particles directly induce activated mast cells to degranulate and increase histamine levels and symptom severity. *J Allergy Clin Immunol* 2000; 106:1140–6.
- 31 Takenaka H, Zhang K, Diaz-Sanchez D, Tsien A, Saxon A. Enhanced human IgE production results from exposure to the aromatic hydrocarbons from diesel exhaust: direct effects on B-cell IgE production. *J Allergy Clin Immunol* 1995; 95:103–15.
- 32 Pénard-Morand C, Annesi-Maesano I. Air pollution: from sources of emissions to health effects. *Breathe* 2004; 1:28–39.
- 33 Jerrett M, Arain A, Kanaroglou P et al. A review and evaluation of intraurban air pollution exposure models. *J Expo Anal Environ Epidemiol* 2005; 15:185–204.
- 34 Nerriere E, Zmirou-Navier D, Blanchard O et al. Can we use fixed ambient air monitors to estimate population long-term exposure to air pollutants? The case of spatial variability in the Genotox ER study. *Environ Res* 2005; 97:32–42.
- 35 Weiland SK, Bjorksten B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J* 2004; 24:406–12.
- 36 Asher MI, Keil U, Anderson HR et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8:483–91.
- 37 The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; 351:1225–32.
- 38 Williams HC, Forsdyke H, Boodoo G, Hay RJ, Burney PG. A protocol for recording the sign of flexural dermatitis in children. *Br J Dermatol* 1995; 133:941–9.
- 39 Priftanji A, Strachan D, Burr M et al. Asthma and allergy in Albania and the UK. *Lancet* 2001; 358:1426–7.
- 40 Debrock C, Menetrey C, Bonavent M et al. Prevalence of exercise-induced asthma in school children. *Rev Epidemiol Sante Publique* 2002; 50:519–29.
- 41 Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; 73:13–22.
- 42 Devlin RB, McDonnell WF, Mann R et al. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. *Am J Respir Cell Mol Biol* 1991; 4:72–81.
- 43 Osebold JW, Zee YC, Gershwin LJ. Enhancement of allergic lung sensitization in mice by ozone inhalation. *Proc Soc Exp Biol Med* 1988; 188:259–64.
- 44 Kehrl HR, Peden DB, Ball B, Folinsbee LJ, Horstman D. Increased specific airway reactivity of persons with mild allergic asthma after 7.6 hours of exposure to 0.16 ppm ozone. *J Allergy Clin Immunol* 1999; 104:1198–204.

- 45 Riedel F, Kramer M, Scheibenbogen C, Rieger CH. Effects of SO₂ exposure on allergic sensitization in the guinea pig. *J Allergy Clin Immunol* 1988; 82:527–34.
- 46 Balmes JR, Fine JM, Sheppard D. Symptomatic bronchoconstriction after short-term inhalation of sulfur dioxide. *Am Rev Respir Dis* 1987; 136:1117–21.
- 47 Monn C, Carabias V, Junker M, Waeber R, Karrer M, Wanner HU. Small-scale spatial variability of particulate matter <10 µm (PM₁₀) and nitrogen dioxide. *Atmosp Environ* 1997; 31:2243–7.
- 48 Chavance M. Modeling correlated data in epidemiology: mixed or marginal model? *Rev Epidemiol Sante Publique* 1999; 47: 535–44.