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Intrauterine exposure to fine particulate matter as a risk factor for increased susceptibility to acute broncho-pulmonary infections in early childhood

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ABSTRACT

Over the last decades many epidemiologic studies considered the morbidity patterns for respiratory diseases and lung function of children in the context of ambient air pollution usually measured in the postnatal period. The main purpose of this study is to assess the impact of prenatal exposure to fine particulate matter ($PM_{2.5}$) on the recurrent broncho-pulmonary infections in early childhood.

The study included 214 children who had measurements of personal prenatal $PM_{2.5}$ exposure and regularly collected data on the occurrence of acute bronchitis and pneumonia diagnosed by a physician from birth over the seven-year follow-up. The effect of prenatal exposure to $PM_{2.5}$ was adjusted in the multivariable logistic models for potential confounders, such as prenatal and postnatal ETS (environmental tobacco smoke), city residence area as a proxy of postnatal urban exposure, children's sensitization to domestic aeroallergens, and asthma. In the subgroup of children with available $PM_{2.5}$ indoor levels, the effect of prenatal exposure was additionally adjusted for indoor exposure as well. The adjusted odds ratio (OR) for incidence of recurrent broncho-pulmonary infections (five or more spells of bronchitis and/or pneumonia) recorded in the follow-up significantly correlated in a dose-response manner with the prenatal $PM_{2.5}$ level (OR = 2.44, 95%CI: 1.12–5.36).

In conclusion, the study suggests that prenatal exposure to $PM_{2.5}$ increases susceptibility to respiratory infections and may program respiratory morbidity in early childhood. The study also provides evidence that the target value of 20 $\mu g/m^3$ for the 24-h mean level of $PM_{2.5}$ protects unborn babies better than earlier established EPA guidelines.

Introduction

The rising trends worldwide in respiratory diseases in children are of great public health concern since lower respiratory tract infections in early life can lead to decreased lung function, persistent lung damage and increased susceptibility to various lung diseases in later life (Shaheen et al., 1994; Tennant et al., 2012; Johnston et al., 1998; Barker et al., 1991) Many studies have analyzed the problem of respiratory health in terms of exposure to various outdoor air pollutants, such as particulate matter (PM) or polycyclic aromatic hydrocarbons (PAH), which are mostly generated by automobile traffic and power plants. Much smaller number of studies tried to explain the problem in the context of the effect of indoor air pollutants, which include emissions from the combustion of fuel for residential heating, unvented gas appliances, environmental tobacco smoke (ETS) and fumes from cooking (Zedeck, 1980; IARC Polynuclear Aromatic Compounds, 1983; Knize et al., 1999; Spengler et al., 2001).

Earlier epidemiologic studies considered the respiratory morbidity patterns in children in a wide range of context, but mainly for ambient air pollution measured in the postnatal period (Schwartz and Neas, 2000; Chauhan and Johnston, 2003; Peters et al., 1997; Gouveia and Fletcher, 2000; Barnett et al., 2005; Lewis et al., 2005). Moreover, the studies on postnatal exposure have usually quantified the concentrations of outdoor air pollutants in the residence area, and assigned approximate exposure levels to the study subjects. In some studies, residential proximity to industrial plants was also the proxy for exposure to industrial pollution. Estimating individual average exposures during specific study period by relying on the ambient air monitoring stations even close to the children's residence area may result in exposure misclassification. Networks of air pollution stations are usually located far away from the

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residences and may provide the inaccurate surrogate measures for personal exposure.

Reproductive epidemiology studies provide evidence that the fetus is likely to be significantly more sensitive to a variety of environmental toxicants than adults (Anderson et al., 2001; Perera et al., 2004a; Jedrychowski et al., 2005) This results from the fact that many environmental toxicants absorbed by the mother easily cross the placenta and accumulate in the fetus often at higher concentrations than in mothers (Perera et al., 2004b).

Although there is some epidemiologic evidence linking prenatal exposure to tobacco smoke and respiratory health in children (Stick et al., 1996; Tager et al., 1993; DiFranza et al., 2004; Miller et al., 2004), little research has been conducted on the effects of prenatal determinants of respiratory health in early childhood resulting from gestational exposure to fine particulate matter measured on an individual basis.

The main purpose of the study was to assess the impact of prenatal exposure to fine particulate matter, measured during the second trimester of pregnancy with personal monitors, on the incidence of recurrent broncho-pulmonary infections (physician diagnosed episodes of bronchitis and pneumonia) in the offspring over a seven-year postnatal period. The second trimester marks the halfway period of pregnancy, when the fetus starts to grow very quickly and the brain undergoes its most important period of growth. From now on, the fully developed placenta provides all the fetus' needs until birth and this may also create favorable conditions for toxicants absorbed by mother to cross placenta and eventually put fetus at risk. The effect of prenatal exposure to $PM_{2.5}$ on broncho-pulmonary infections was adjusted for a set of potential confounders, such as prenatal and postnatal ETS, city residence area as a proxy of postnatal outdoor exposure, children's sensitization to domestic aeroallergens, and asthma diagnosed by a physician. In the subgroup of children with available indoor pollution levels at the age 3, the effect of prenatal exposure was additionally adjusted for indoor exposure to $PM_{2.5}$. A secondary goal of the study was to assess the degree to which the present EPA 24-h air quality standards (35 $\mu g/m^3$) protect the developing fetus and young children (EPA, 2006).

Materials and methods

The study initially enrolled 502 newborns, 214 of whom have completed the seven-year follow-up and had skin prick testing for common domestic allergens. This is the part of an ongoing longitudinal investigation on the health impact of prenatal exposure to outdoor/indoor air pollution in infants and children from the Krakow city area. The detailed description of the study design has been presented elsewhere (Jedrychowski et al., 2003). In short, pregnant women were recruited from ambulatory prenatal clinics in the first or second trimester of pregnancy. The study included women between 18 and 35 years of age, who claimed to be non-smokers, with singleton pregnancies, without illicit drug use and HIV infection, free from chronic diseases such as diabetes or hypertension, and resident in Krakow for at least one year prior to pregnancy. All women participating in the study had read and signed an informed consent. The Jagiellonian University Bioethical Committee approved the research.

Upon enrollment, a detailed questionnaire was administered to each subject to elicit information on demographic data, house characteristics, medical history of mothers, and smoking practices of others present in the home. Over the seven-year follow-up, regular data on the occurrence of broncho-pulmonary infections (acute bronchitis and pneumonia) diagnosed by a physician were regularly collected by interviewers visiting homes of the children at intervals of three months in the first two years of life and six months later. Prenatal ETS was defined by the number of cigarettes smoked daily at home; and postnatal ETS by the number of years the child has lived in the house where at least one of the household members was an active smoker. Atopic status of children was defined as sensitization to at least one common domestic aeroallergen.

Dosimetry of prenatal and postnatal exposure to fine particles

Prenatal exposure was monitored during the second trimester of pregnancy in recruited mothers with a personal environmental monitoring sampler (PEMS) designed in Dr. Spengler's Lab. The PEMS is designed to achieve the particle mass target size of <2.5 μm at a flow rate of 4.0 liters per minute (LPM) with an array of 10 impactor nozzles. Flow rates are calibrated (with filters in place) using a bubble meter prior to the monitoring, and are checked again with a change of the battery pack on the second day and at the conclusion of the monitoring. Pumps operated continuously at 2 LPM over the 48-h period. To modify the sampler to achieve the 2.5 μm size cut at 2 LPM, 5 of the nozzles were blocked. Particles were collected on a Teflon membrane filter (37 mm Teflo^{TM}, Gelman Sciences). The combination of low pressure drop (permitting use of a low power sampling pump), low hygroscopicity (minimizing bound water interference in mass measurements), and low trace element background (improving analytical sensitivity) of these filters make them highly appropriate for personal particle sampling. Before the field study the validation was a series of QA/QC checks on flows, timing, filter integrity, and weighting protocols.

During the monitoring session, the woman was instructed to wear the PEMS monitor during the daytime hours for 2 consecutive days and to place the monitor near the bed at night. On the second day of the air monitoring, the technician and interviewer visited the woman's home to change the battery-pack and administer the full questionnaire. They also checked to see that the monitor had been running continuously and that there had been no technical or operating failures.

In the subset of 80 pregnant women, personal dosimetry was repeatedly taken once during each trimester to estimate how measurements of $PM_{2.5}$ in the second trimester may be representative for the whole pregnancy period. Additionally, in the subgroup of children ($n = 131$) for whom a consent was obtained, the indoor levels of $PM_{2.5}$ were measured using the same methodology.

Ascertainment of atopic status

All five-year olds were invited to undergo a skin prick test (SPT) for 4 common domestic aeroallergens (Dermatophagoides pteronyssinus, Dermatophagoides farinae, dog and cat hair). The results were read after 15 min by measuring the largest diameter of the wheal. Atopic status was ascertained as a wheal reaching diameter of 3 mm which is greater than the histamine control. The participants were defined as atopic if they had at least one positive skin prick test.

Statistical analysis

Statistical analyses were performed in order to assess a possible association between prenatal $PM_{2.5}$ levels with incidence of recurrent episodes of bronchitis and pneumonia occurring over the seven-year follow-up. As the distribution of $PM_{2.5}$ concentrations was skewed to the right, values were ln-transformed to normalize the distribution. $PM_{2.5}$ levels were provided as geometric mean values (average after ln-transformation, followed by back transformation) together with 95% confidence intervals. In the initial univariate analysis, the differences in continuous variables between groups were analyzed using a one-way analysis of variance; differences in the frequencies of categorical variables were

evaluated with the Chi-square test. After the descriptive univariate analysis we used the multivariable nested logistic regression models to explore the relationship between recurrent broncho-pulmonary infections and prenatal $PM_{2.5}$ exposure adjusted for a set of a priori selected covariates (prenatal and postnatal ETS, indoor $PM_{2.5}$, at the age 3, residence city area, children's atopy and asthma diagnosed by a medical doctor). The regression estimates are nested in the sense that the first regression is nested in the second since all the predictors in the first regression are included in the second. Similarly, the second regression is nested in the third regression and so on. Statistical analysis was performed by the statistical software STATA version 12.1 and two-sided $p < 0.05$ was considered statistically significant.

Results

Table 1 presents the characteristics of the total study sample grouped by values of prenatal exposure to $PM_{2.5}$ in the second trimester dichotomized by 35.0 $\mu g/m^3$ level, which was very close to the median value (35.9 $\mu g/m^3$, 95%CI: 23.3–50.4 $\mu g/m^3$). Characteristics of children who did not participate in the follow-up did not differ significantly from the participants except for prenatal level of $PM_{2.5}$ (Table 2).

Prenatal personal $PM_{2.5}$ values significantly correlated with the number of cigarettes smoked daily at home in pregnancy (nonparametric trend $z = 3.57$, $p < 0.001$) and the duration of ETS exposure in the postnatal period ($z = 3.93$, $p < 0.001$), and was significantly higher in subjects who lived in the city center compared with those from the outer city area (42.7 vs. 34.2 $\mu g/m^3$, $t = 2.26$, $p = 0.025$).

Personal dosimetry taken once during each trimester in the subset of 80 pregnant women showed a consistent trend between $PM_{2.5}$ levels over pregnancy trimesters. The nonparametric trend for $PM_{2.5}$ concentrations (in tertiles) measured in the second and third pregnancy trimester was highly significant ($z = 3.21$, $p = 0.001$); the corresponding level of statistical association between the measurements taken in the first and the second trimester was significant as well ($z = 2.42$, $p = 0.015$).

The mean number of acute bronchitis episodes recorded in the follow-up was about four times higher than the number of pneumonia episodes (2.02; 95%CI: 1.86–2.19 vs. 0.57; 95%CI: 0.48–0.66). Both physician-diagnosed bronchitis and pneumonia cases were lower in the younger age group than in older children (Table 3) and the frequency of bronchitis/pneumonia spells greatly depended on the asthma status. Children with asthma showed a two-fold higher number of bronchitis episodes and more than a three-fold higher number of pneumonia episodes. Importantly, the incidence of recurrent bronchitis (four or more spells) and pneumonia (two or more spells) significantly correlated with the level of prenatal $PM_{2.5}$ exposure level (Table 4).

In the next step of the statistical analysis, we used nested multivariable logistic regression models to assess the relationship between broncho-pulmonary infections (5 or more episodes of acute bronchitis and/or pneumonia) and prenatal $PM_{2.5}$ exposure. Table 5 shows the results of the hierarchical regression analysis for variables predicting odd ratios (ORs) of broncho-pulmonary infections for $PM_{2.5}$ ln-transformed values adjusted for covariates in participants of the seven-year follow-up. The variables added to each block are stepwise listed and the change in Wald Chi-square for a given block is reported with its significance level.

Table 1
Characteristics of the children who completed the follow-up grouped by prenatal exposure to P $PM_{2.5}$.

Variables	Low $PM_{2.5} \leq 35$ $\mu g/m^3$ ($N = 112$)	High $PM_{2.5} > 35$ $\mu g/m^3$ ($N = 102$)	Total ($N = 214$)	p for difference
Maternal age (yrs)				
Mean	27.73	27.85	27.79	0.7959
SD	3.12	3.70	3.40	
Maternal education (yrs)				
Mean	15.81	15.61	15.72	0.5837
SD	2.54	2.91	2.72	
Maternal allergy (+)				
n (%)	30 (26.8)	20 (19.6)	50 (23.4)	0.2812
Older siblings				
n (%)	39 (34.8)	39 (38.2)	78 (36.4)	0.7069
Gender, boys				
n (%)	58 (51.8)	45 (44.1)	103 (48.1)	0.3249
Gestational age (weeks)				
Mean	39.60	39.54	39.57	0.7040
SD	1.078	1.191	1.131	
Birth weight (g)				
Mean	3506.0	3383.6	3447.7	0.0424
SD	455.1	417.8	441.0	
Breastfeeding >6 months				
n (%)	31 (27.7)	30 (29.4)	61 (28.5)	0.8974
Prenatal ETS (+)				
n (%)	21 (18.8)	31 (30.4)	52 (24.3)	0.0682
Postnatal ETS:				
0 yrs, n (%)	90 (80.4)	69 (67.6)	159 (74.3)	
1–3 yrs, n (%)	17 (15.2)	11 (10.8)	28 (13.1)	
4–7 yrs, n (%)	5 (4.5)	22 (21.6)	27 (12.6)	0.0008
Residence area: city center				
n (%)	16 (14.3)	25 (24.5)	41 (19.2)	0.0847
Postnatal indoor $PM_{2.5}$ $\mu g/m^3$ measured at the age 3				
Mean	42.89	45.85	44.36	
SD	32.39	37.74	35.04	
Missing data	46	37	83	0.6312
Bronchitis (l–7 yrs) number of episodes				
Mean	1.8	2.1	1.9	0.2209
SD	1.8	2.4	2.1	
Pneumonia (l–7 yrs) number of episodes				
Mean	0.5	0.6	0.5	0.3622
SD	0.8	1.2	1.0	

Table 2
Characteristics of the children who completed and did not complete the seven-year follow-up.

Variables	Followed-up completed ($N=214$)	Followed-up not completed ($N=266$)	Total ($N=480$)	p for difference
Maternal age (yrs)				
Mean	27.79	27.38	27.57	
SD	3.40	3.73	3.59	0.2180
Maternal education (yrs)				
Mean	15.72	15.46	15.57	
SD	2.72	2.78	2.75	0.3040
Maternal allergy (+)				
n (%)	50 (23.4)	68 (25.6)	118 (24.6)	0.6530
Older siblings				
n (%)	78 (36.4)	97 (36.5)	175 (36.5)	1.0000
Gender, boys				
n (%)	103 (48.1)	142 (53.4)	245 (51.0)	0.2926
Gestational age (weeks)				
Mean	39.57	39.51	39.54	
SD	1.131	1.150	1.141	0.5750
Birth weight (g)				
Mean	3447.7	3442.2	3444.6	
SD	441.0	433.7	436.5	0.8914
Breastfeeding only >6 months				
n (%)	61 (28.5)	59 (23.1)	120 (25.6)	0.2222
Missing data	0	11	11	
Prenatal ETS (+)				
n (%)	52 (24.3)	77 (28.9)	129 (26.9)	0.2991
Residence area: city center				
n (%)	41 (19.2)	56 (21.1)	97 (20.2)	0.6897
Prenatal $PM_{2.5}$ ($\mu g/m^3$)				
Mean	42.37	45.27	43.98	
SD	27.55	41.79	36.14	0.3824
Postnatal indoor $PM_{2.5}$ ($\mu g/m^3$) at the age 3				
Mean	44.36	36.29	40.19	
SD	35.04	29.98	32.71	0.0422
Missing data	83	126	209	

Table 3
Cumulative incidence of respiratory infections diagnosed by a physician in the follow-up grouped by the age of children and medical diagnosis of asthma (in brackets 95% confidence intervals).

	Asthma (−)	Asthma (+)	Total
Bronchitis			
Age 1–3 yrs	0.75 (0.65–0.87)	1.60 (1.19–2.10)	0.85 (0.74–0.96)
Age 4–7 yrs	1.05 (0.92–1.19)	2.19 (1.71–2.76)	1.17 (1.04–1.30)
Age 1–7 yrs	1.80 (1.63–1.98)	3.79 (3.14–4.51)	2.02 (1.86–2.19)
Pneumonia			
Age 1–3 yrs	0.21 (0.15–0.27)	0.56 (0.33–0.89)	0.25 (1.19–0.31)
Age 4–7 yrs	0.25 (0.20–0.33)	0.90 (0.61–1.30)	0.32 (0.26–0.40)
Age 1–7 yrs	0.46 (0.38–0.55)	1.47 (1.08–1.92)	0.57 (0.48–0.66)

Prenatal $PM_{2.5}$ exposure entered in the first model was significant ($p=0.026$), however, neither prenatal or postnatal ETS separately added in subsequent models, nor atopy or the residence area were significant. The inclusion of asthma in the fifth model produced a substantial increment in the Wald Chi-square ($p=0.004$).

The same analysis performed for recurrent broncho-pulmonary infections in the subgroup of 131 children with available indoor $PM_{2.5}$ measurement confirmed a significant effect of prenatal $PM_{2.5}$ level (Table 6). The impact of indoor $PM_{2.5}$ measured at the age 3 showed a border significance level ($p=0.089$).

Fig. 1 presents the dose–effect relationship between the prenatal $PM_{2.5}$ exposure level and the probability of recurrent broncho-pulmonary infections in the total sample and in the subgroups of children with and without asthma. The probability of recurrent spells of respiratory infections increased linearly, but a little more steeply in asthmatic children than in those without asthma. Furthermore, the dose–effect relationship between recurrent infections and prenatal exposure showed that an increment of respiratory episodes even begins at $PM_{2.5}$ level below 35 $\mu g/m^3$.

Discussion

While most of the previous studies were mainly concerned with the effect of the postnatal ambient exposure to particulate matter on respiratory morbidity in children, this is the first study of its kind that has evaluated the association between the individual prenatal

Table 4
Frequency of recurrent cases of acute bronchitis and pneumonia reported in the follow-up grouped by the prenatal $PM_{2.5}$ level (in tertiles).

Variable	$PM_{2.5}$ concentrations in tertiles			p-Value
	11.1–26.6	26.7–45.9 $\mu g/m^3$	>45.9 $\mu g/m^3$	
Recurrent acute bronchitis	10 (14.3%)	8 (10.1%)	20 (30.8%)	Chi-square 11.263, $p=0.004$
Recurrent pneumonia	3 (4.3%)	7 (8.9%)	12 (18.5%)	Chi-square 7.617, $p=0.022$
Number of children	70	79	65	214

Table 5
Summary of hierarchical logistic regression analysis for variables predicting ORs for recurrent broncho-pulmonary infections (defined as five or more episodes) in the seven-year follow-up ($N = 214$).

Variables	OR	Pr > |z|	95% confidence intervals		Wald Chi-square	*df*	Pr > *F*
Model I							
Prenatal $PM_{2.5}$ exposure[a]	2.00	0.026	1.09	3.70	4.97	1	0.0257
Model II							
Prenatal $PM_{2.5}$ exposure[a]	2.17	0.018	1.14	4.12			
Prenatal ETS[b]	0.78	0.406	0.43	1.40	0.69	1	0.4063
Model III							
Prenatal $PM_{2.5}$ exposure[a]	2.22	0.015	1.17	4.23			
Prenatal ETS[b]	0.97	0.963	0.40	2.37			
Postnatal ETS[c]	0.76	0.511	0.33	1.73	0.43	1	0.5109
Model IV							
Prenatal $PM_{2.5}$ exposure [a]	2.20	0.017	1.15	4.19			
Prenatal ETS[b]	0.95	0.913	0.39	2.32			
Postnatal ETS[c]	0.78	0.559	0.34	1.79			
Atopy Y/N	1.26	0.640	0.48	3.26	0.22	1	0.6404
Model V							
Prenatal $PM_{2.5}$ exposure[a]	2.10	0.028	1.08	4.06			
Prenatal ETS[b]	0.92	0.885	0.36	2.39			
Postnatal ETS[c]	0.79	0.597	0.33	1.91			
Atopy Y/N	1.19	0.715	0.45	3.17			
Asthma Y/N	3.81	0.004	1.52	9.59	8.08	1	0.0045
Model VI							
Prenatal $PM_{2.5}$ exposure[a]	2.05	0.035	1.05	3.99			
Prenatal ETS[b]	0.93	0.885	0.36	2.39			
Postnatal ETS[c]	0.79	0.597	0.33	1.91			
Atopy Y/N	1.19	0.735	0.45	3.14			
Asthma Y/N	3.87	0.004	1.53	9.75			
Residence[d]	1.31	0.553	0.54	3.17	0.35	1	0.5525

[a] ln transformed concentrations.
[b] 0: no prenatal ETS exposure; 1: up to 5 cigarettes smoked daily; 2: more than 5 cigarettes smoked daily.
[c] 0: no postnatal ETS exposure; 1: short exposure (≤3 years); 2: long exposure (>3 years).
[d] 0: outer city area residents, 1: city center residents.

$PM_{2.5}$ and the recurrent broncho-pulmonary episodes as an indicator of children's susceptibility to respiratory tract infections. It is important to mention that the estimates of the effect remained significant after adjustment for a set of potential confounders. The impact of prenatal exposure to $PM_{2.5}$ on the risk of recurrent broncho-pulmonary infections during early childhood appeared to be independent of the effects of ETS, residence area and sensitization to common domestic aeroallergens, which were a proxy of quality of postnatal indoor/outdoor air quality. Prenatal exposure was also independent of indoor $PM_{2.5}$ levels measured in children's household at the age 3. The study supports a causal relationship between the prenatal $PM_{2.5}$ level and respiratory health and suggests that the prenatal exposure may program postnatal respiratory morbidity in childhood. Though the clear threshold level of $PM_{2.5}$ was not identified, the results of our study suggest that the $PM_{2.5}$ level of 20 $\mu g/m^3$ would better protect children against respiratory outcomes than higher values of 35 $\mu g/m^3$ established by EPA (EPA, 2006). However, our proposed standard value would be very close to the 24-h mean limit of 25 $\mu g/m^3$ recommended by the present WHO guidelines (Air quality guidelines for Europe, 2000).

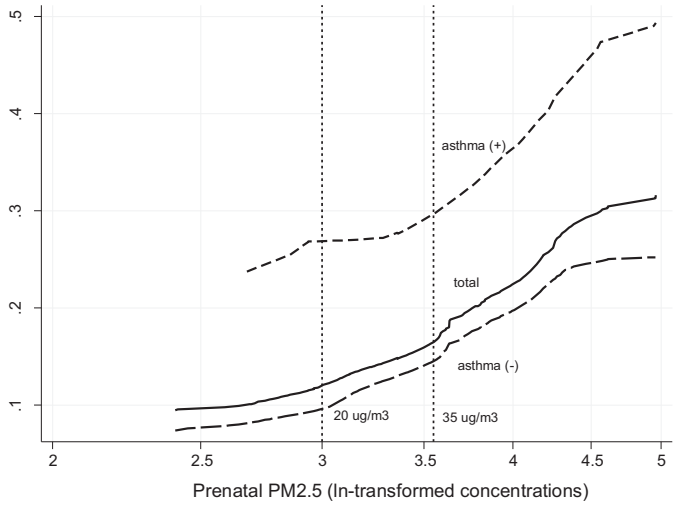

Fig. 1. Predicted probability of recurrent broncho-pulmonary infections (five or more episodes treated by physician in the follow-up) related to prenatal exposure (ln-transformed PM2.5 $\mu g/m^3$).

The biological mechanism whereby prenatal exposure to prenatal $PM_{2.5}$ may lead to the increased susceptibility is yet unclear. $PM_{2.5}$ is a proxy for a wide spectrum of environmental hazards, such as constituents of tobacco and wood smoke, organic compounds, sulfates, polycyclic aromatic hydrocarbons (PAHs), metals and many other chemicals, which may be implicated in generating oxidative stress (Spengler et al., 2001). Fine particles containing a very high proportion of organic carbon add to the biologic oxidative potency of these particles. While inhaled particles of 2.5 μm are linked to bronchial inflammatory effects, smaller particles (0.25 μm or less) are thought to move beyond the respiratory system and reach the bloodstream across placenta.

It is believed that the one of the key mechanism by which air pollutants is linked with the increased risk of respiratory infections is the inhibition of the production of immunocompetent cells contributing to immunosuppression. For example, exposure to absorbed airborne toxicants inhibits the differentiation of human monocytes, but mature differentiated immune cells also constitute their targets (Holgate, 2005; Lyte and Bick, 1986; Saxon and Diaz-Sanchez, 2000; Ward et al., 1984; Wojdani and Alfred, 1984). On the other hand, transplacental exposure of newborns to higher prenatal $PM_{2.5}$ and its compounds may result in the production of an "allergic response" typified by the proliferation of Th2 type T lymphocytes which secrete proinflammatory cytokines in the body tissues. As the Th2 cytokines promote allergen-specific IgE antibody and induce eosinophile-dominated inflammatory tissue responses,

Table 6
Summary of hierarchical logistic regression analysis for variables predicting ORs for recurrent broncho-pulmonary infections (defined as five or more episodes) in the seven-year follow-up ($N = 131$). The subgroup of children with indoor $PM_{2.5}$ measurements repeated at the age 3.

Variables	OR	Pr > |z|	95% confidence intervals		Wald Chi-square	*df*	Pr > *F*
Model I							
Prenatal $PM_{2.5}$ exposure[a]	2.44	0.025	1.12	5.36	5.00	1	0.0253
Model II							
Prenatal $PM_{2.5}$ exposure[a]	2.47	0.026	1.12	5.50			
Postnatal PM2.5[a]	1.53	0.177	0.83	2.83	1.82	1	0.1772
Model III							
Prenatal $PM_{2.5}$ exposure[a]	2.84	0.016	1.22	6.63			
Postnatal PM2.5 exposure[a]	1.76	0.102	0.89	3.48			
Prenatal ETS[b]	0.66	0.278	0.31	1.40	1.18	1	0.2784
Model IV							
Prenatal $PM_{2.5}$ exposure[a]	3.08	0.013	1.27	7.46			
Postnatal PM2.5 exposure[a]	1.84	0.086	0.92	3.67			
Prenatal ETS[b]	0.93	0.908	0.27	3.19			
Postnatal ETS[c]	0.67	0.499	0.21	2.12	0.46	1	0.4986
Model V							
Prenatal $PM_{2.5}$ exposure[a]	3.16	0.011	1.30	7.58			
Postnatal PM2.5 exposure[a]	1.83	0.089	0.91	3.66			
Prenatal ETS[b]	0.92	0.889	0.27	3.15			
Postnatal ETS[c]	0.69	0.402	0.22	2.16			
Atopy Y/N	1.47	0.558	0.41	5.28	0.34	1	0.5575
Model VI							
Prenatal $PM_{2.5}$ exposure[a]	2.79	0.026	1.13	6.88			
Postnatal PM2.5 exposure[a]	1.87	0.080	0.93	3.78			
Prenatal ETS[b]	0.81	0.745	0.23	2.90			
Postnatal ETS[c]	0.77	0.657	0.24	2.48			
Atopy	1.32	0.667	0.36	4.90			
Asthma	2.51	0.110	0.81	7.75	2.56	1	0.1096
Model VII							
Prenatal $PM_{2.5}$ exposure[a]	2.82	0.025	1.14	7.00			
Postnatal PM2.5 exposure[a]	1.85	0.089	0.91	3.75			
Prenatal ETS[b]	0.78	0.518	0.22	2.05			
Postnatal ETS[c]	0.78	0.674	0.24	2.52			
Atopy Y/N	1.32	0.885	0.35	4.91			
Asthma Y/N	2.53	0.107	0.82	7.83			
Residence area[d]	0.83	0.777	0.23	2.98	0.08	1	0.7769

[a] ln transformed concentrations.
[b] 0: no prenatal ETS exposure; 1: up to 5 cigarettes smoked daily; 2: more than 5 cigarettes smoked daily.
[c] 0: no postnatal ETS exposure; 1: short exposure (≤3 years); 2: long exposure (>3 years).
[d] 0: outer city area residents, 1: city center residents.

allergic reactions are enhanced within the bronchial tract and lead to an increased susceptibility of newborns and young infants to pulmonary infections (Kaan and Hegele, 2003; Davila et al., 1996; Nel et al., 1998; Devouassoux et al., 2002; Laupeze et al., 2002; Van Grevenynghe et al., 2003).

A strength of our study is the prospective birth cohort design that also enabled us to limit measurement error in estimating prenatal exposure to fine particles by assigning an individual prenatal personal exposure level to each child. The personal monitoring of ambient $PM_{2.5}$ exposure is a relevant measure incorporating outdoor and indoor exposures. Good agreement between the personal $PM_{2.5}$ measurements across all trimesters of pregnancy carried out in a subsample of 80 subjects provided evidence that the measurements of fine particles in the second trimester is also a good reflection of mean exposure level over pregnancy. Additional advantage of the study is the adjustment of prenatal $PM_{2.5}$ effect for repeated indoor measurement of $PM_{2.5}$ at the age 3 and constant monitoring of prenatal and postnatal ETS exposure over the follow-up. Another strong point of our study stems from the fact that we were able to monitor medical diagnoses of respiratory infections over regular time points in the course of face-to-face interviews with mothers of children. Since the mobility of the subjects under study was very moderate and mainly restricted to the same urban air pollution area, this gave us an additional confidence that the estimates of effects were unbiased. On the other hand, we are aware of the limitations of our study, which are mainly related to a relatively small sample size and the lack of data on time spent by children outdoors and their outdoor activity patterns.

In summary, the study suggests that prenatal exposure to $PM_{2.5}$ increases susceptibility to respiratory infections and may program respiratory morbidity in early childhood. The observed effect of the increased susceptibility to respiratory infections may result from cytokine deregulation and an "allergic response" phenotype possibly established in the fetal period as a result of transplacental exposure to fine particulate matter. The study also provides evidence that the daily exposure below 20 $\mu g/m^3$ may better protect unborn babies than that proposed by EPA.

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