

Effect of prenatal exposure to fine particulate matter on ventilatory lung function of preschool children of non-smoking mothers

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Summary

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Impaired fetal development is associated with a number of adult chronic diseases and it is believed that these associations arise as a result of the phenomenon of prenatal programming, which involves persisting changes in structure and function of various body organs caused by ambient factors during critical and vulnerable periods of early development. The main goal of the study was to assess the association between lung function in early childhood and prenatal exposure to fine particulate matter (PM_{2.5}), which represents a wide range of chemical compounds potentially hazardous for fetal development. Among pregnant women recruited prenatally to the study, personal measurements of PM_{2.5} were performed over 48 h in the second trimester of pregnancy. After delivery, infants were followed for 5 years; the interviewers visited participants in their homes to record children's respiratory symptoms every 3 months in the child's first 2 years of life and every 6 months thereafter. In the fifth year of the follow-up, children were invited for standard lung function testing of levels of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁) and forced expiratory volume in 0.5 s (FEV_{0.5}).

There were 176 children of non-smoking mothers, who performed at least two acceptable spirometry measurements. Multivariable linear regression showed a significant deficit of FVC at the highest quartile of PM_{2.5} exposure (beta coefficient = -91.9, *P* = 0.008), after adjustment for covariates (age, gender, birthweight, height and wheezing). Also FEV₁ level in children was inversely correlated with prenatal exposure to PM_{2.5}, and the average FEV₁ deficit amounted to 87.7 mL (*P* = 0.008) at the higher level of exposure. Although the effect of PM_{2.5} exposure on FEV_{0.5} was proportionally weaker (-72.7, *P* = 0.026), it was also statistically significant. The lung function level was inversely and significantly associated with the wheezing recorded over the follow-up. The findings showed that significant lung function deficits in early childhood are associated with prenatal exposure to fine particulate matter, which may affect fetal lung growth.

Keywords: prenatal exposure, air pollution, birth cohort, lung function, preschool children.

Introduction

Although over the last few decades there have been many studies on children's health related to air pollution, they were concerned mainly with morbidity from respiratory diseases in schoolchildren associated with postnatal ambient hazards. There have also been environmental epidemiological studies investigating prenatal hazards on children's respiratory health but they were limited to the effects of maternal smoking in pregnancy or postnatal environmental tobacco smoke (ETS).

To date, however, there is a shortage of data on the effect of prenatal ambient air pollution on respiratory health in early childhood, though in the last decade the effect of air pollution on adverse birth outcomes, including low birthweight, preterm delivery and intrauterine growth retardation has been confirmed by many publications.^{1–14} It is reasonable to assume that the prenatal exposure to ambient air hazards is not only associated with adverse birth outcomes but also may have repercussions on various fetal body organs, leading to their deficient function postnatally.

Development of the fetus proceeds in a sequence of carefully timed events that progress from the cellular level to the formation of tissues and morphologic structures such as the lung. Prenatal hazards may permanently change these developmental processes. The issue is of great importance since impaired fetal development and its consequences in postnatal life are associated with a number of adult chronic diseases.^{15–17} It is believed that these associations arise as a result of the phenomenon of prenatal programming, which involves persistent changes in structure and function of various body organs caused by environmental factors during critical and vulnerable periods of early development.

To our knowledge, up to now there have been no studies on lung function in early childhood and prenatal exposure to ambient fine particulates. The main goal of this study was to test the hypothesis that prenatal exposure to fine particulate matter, which represents a wide range of chemical compounds potentially hazardous for fetal development, may be associated with impaired lung function of children. In contrast to other air pollution studies, we assessed individual exposure to fine particulates (PM_{2.5}) in pregnant women using specially designed personal samplers collecting air pollution particles over 48 h in the second trimester of pregnancy. The cohort of children is being followed

from birth through childhood. This analysis concerns those children whose expiratory lung volumes were assessed at 5 years of age by standard spirometry and quantified by forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁) and forced expiratory volume in 0.5 s (FEV_{0.5}) levels. Beside the main exposure variable (PM_{2.5}), the statistical analysis considered a set of covariates including age in months, gender, birthweight, height of children and their wheezing experience as reported by mothers over the follow-up.

Methods

Subjects

This study uses data from an earlier established birth cohort of children in Krakow, which is the result of a collaboration between the Jagiellonian University in Krakow and Columbia University in New York. The design of the study and the detailed selection of the population have been described previously.¹⁸ In short, pregnant women were recruited from ambulatory prenatal clinics in their first or second trimesters of pregnancy. Only women 18–35 years of age, who claimed to be non-smokers, with singleton pregnancies, with no history of illicit drug use or HIV infection, free from chronic diseases such as diabetes or hypertension, and who had resided in Krakow for at least 1 year prior to pregnancy were eligible for the study. Prior to participation, women gave informed consent. The Ethical Committee of Jagiellonian University approved the research.

Upon enrolment, a detailed questionnaire was administered to each woman to solicit information on demographic data, house characteristics, medical and reproductive history, occupational hazards and smoking practices of others present at home. A total of 505 enrolled pregnant women gave birth between January 2001 and February 2004. After delivery, mothers of term babies (>36 weeks of gestation) participated in a detailed standardised face-to-face interview on their infant's health and respiratory symptoms administered by a trained interviewer, every 3 months in the first 2 years of the newborn's life, and every 6 months thereafter. During the interviews, mothers were asked whether their children experienced wheezing or whistling in the chest, irrespective of respiratory infection, since the previous interview. The data collected over the course of the 14 follow-up time points were used to identify children with at least two epi-

Table 1. Characteristics of the study sample in comparison with the total group of children recruited to the study (gestation age >36)

	Study sample <i>n</i> = 176	Children not attending <i>n</i> = 305	<i>P</i>
Gender			
Boys <i>n</i> (%)	87 (49.4)	158 (51.8)	0.684
Girls <i>n</i> (%)	89 (50.6)	147 (48.2)	
Gestational age (weeks):			
>36			
Mean	39.47	39.58	0.289
SD	1.166	1.124	
Birthweight (g)			
Mean	3432.4	3452.3	0.632
SD	422.7	444.2	
Length at birth (cm)			
Mean	54.9	54.7	0.408
SD	2.48	2.70	
Prenatal PM _{2.5} ($\mu\text{g}/\text{m}^3$) > 52.6 <i>n</i> (%)	45 (25.6)	77 (25.2)	1.000

sodes of wheezing. Prenatal ETS was defined if the mother declared that she was exposed to ETS in pregnancy and validated by the cord blood cotinine levels. Postnatal ETS exposure was defined if the ETS exposure at home occurred in more than 2 years over the follow-up. The present analysis was based on data from 176 children born after 36 weeks of gestation, who completed the 5 year follow-up and had performed two reliable and acceptable spirometry tests. The study sample did not differ from the group of children not considered in the present analysis in important characteristics (Table 1).

Dosimetry of cord blood cotinine

The serum cotinine concentration was measured at the Centers for Disease Control using the sensitive isotope-dilution high-performance liquid chromatographic/atmospheric pressure ionisation tandem spectrometric procedure. The limit of detection is below 0.050 ng/mL.^{19,20}

Dosimetry of prenatal personal exposure to fine particles

A Personal Environmental Monitoring Sampler, designed by the Department of Environmental Health,

School of Public Health at Harvard University, was used to measure mass of the particles with size of $\leq 2.5 \mu\text{m}$ (Fig. 1). Flow rates were calibrated (with filters in place) using a bubble meter prior to the monitoring, and were 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 L/min over the 48-h period. Particles were collected on Teflon membrane filter (37 mm Tefl, Gelman Sciences, Ann Arbor, Michigan, USA). The combination of low pressure drop (permitting use of a low power sampling pump), low hygroscopicity (minimising 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.

During the second trimester, a member of the air monitoring staff instructed the woman in the use of the personal monitor, which was lightweight, quiet and was worn in a backpack (Fig. 2). The woman was asked to wear the monitor during the daytime hours for 2 consecutive days and to place the monitor near the bed at night. During the morning of the second day, the air monitoring researcher and interviewer visited the woman's home to change the battery pack and administer the full questionnaire. They also checked to see

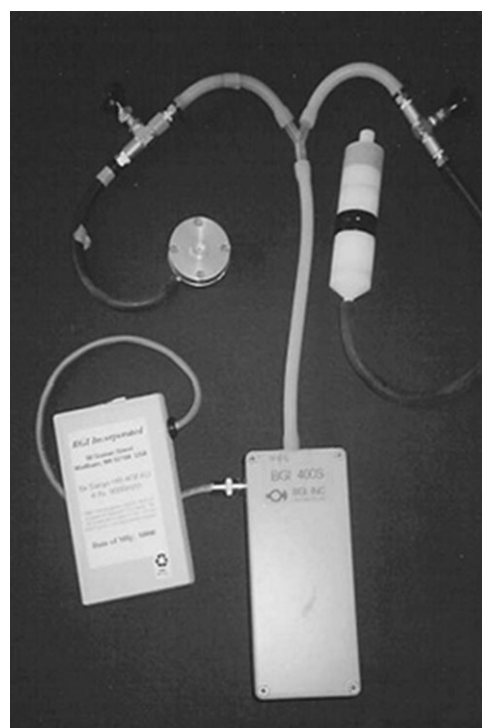
**Figure 1.** Sampling instruments placed in the backpack.



Figure 2. One of the study participants wearing the backpack with personal monitoring sampler for collection of fine particulate matter (photograph reproduced with participant's permission).

that the monitor has been running continuously and that there have been no technical or operating failures. The researcher returned to the woman's home on the morning of the third day to pick up the equipment.

Spirometry testing

Children were free of respiratory symptoms on the day of testing and none of the children had any previous experience performing spirometry. Prior to spirometric testing standing height and weight of each child was measured and the children were coached to engage in maximal forced expiratory efforts in a standing position without nose clip. All spirometric measurements were carried out with a computerised PC QRS Card (QRS Diagnostic, Plymouth, MN, USA) Spirometer with incentive display software by only one staff member (E. Mroz) who was highly experienced in spirometric testing of children. Each day, prior to the lung function examination, the spirometer was calibrated with a 1-L syringe. Each child made at least two good forced exhalation efforts and the primary indicators of lung function, that is, FVC, which is the total amount of air that can forcibly be blown out after full

inspiration, FEV₁, which is the amount of air that can be forcibly blown out in 1 s and FEV_{0.5}, which is the amount of air that can be blown out in 0.5 s, were recorded. Data were excluded if a submaximal expiratory effort was present in which a peak expiratory flow was not clearly determined, a slow rise of peak expiratory flow was apparent, an expiration time was less than 0.5 s or a cough or an abrupt end of expiration

Table 2. Characteristics of children with acceptable spirometry grouped by prenatal exposure to fine particulate matter (PM_{2.5})

	Total study sample <i>n</i> = 176	Lower PM _{2.5} ≤52.6 µg/m ³ <i>n</i> = 131	Higher PM _{2.5} >52.6 µg/m ³ <i>n</i> = 45	<i>P</i>
Gender				
Boys <i>n</i> (%)	87 (49.4)	67 (51.1)	21 (44.4)	0.547
Girls <i>n</i> (%)	89 (50.6)	64 (48.9)	29 (55.6)	
Gestational age (weeks): >36				
Mean	39.47	39.46	39.49	0.879
SD	1.166	1.152	1.218	
Birthweight (g)				
Mean	3432.4	3460.8	3349.8	0.129
SD	422.7	432.8	384.6	
Length at birth (cm)				
Mean	54.9	55.0	54.5	0.194
SD	2.48	2.49	2.42	
Age (in months)				
Mean	60.7	60.7	60.7	0.949
SD	0.92	0.97	0.75	
Weight (kg) at age of 5 years (kg)				
Mean	19.83	19.87	19.73	0.783
SD	2.885	2.840	3.041	
Height (cm) at age of 5 years				
Mean	112.8	112.7	113.3	0.444
SD	4.539	4.650	4.218	
FVC (mL)				
Mean	1124.8	1141.0	1077.7	0.059
SD	194.1	200.9	165.9	
FEV ₁ (mL)				
Mean	1070.9	1084.7	1030.5	0.088
SD	183.8	187.9	166.6	
FEV _{0.5} (mL)				
Mean	843.1	852.1	816.8	0.225
SD	168.1	168.9	165.0	
Wheezing				
<i>n</i> (%)	47 (26.7)	34 (26.0)	13 (28.9)	0.850
ETS prenatal exposure				
<i>n</i> (%)	44 (25.0)	30 (22.9)	14 (31.1)	0.369
ETS postnatal exposure				
<i>n</i> (%)	17 (9.7)	7 (5.3)	10 (22.2)	0.003

ETS, environmental tobacco smoke; FEV_{0.5}, forced expiratory volume in 0.5 s; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

effort appeared in the course of the exhalation effort. In accordance with the American Thoracic Society and European Respiratory Society guidelines on pulmonary function testing in preschool children,²¹ expiratory flows were reported from the attempt with the best flow (the greatest sum of FEV₁ and FVC) executed by each subject and the spirometric index corrected to BTPS (body temperature, pressure saturated) recorded. Spirometry findings were accepted as reliable if the absolute difference between FVCs and the absolute difference between FEV₁ of the two best curves were within the range of 100 mL.

Statistical analysis

The main purpose of the statistical analysis was to assess the relationship between lung function indices (outcome variables) and exposure to fine particulate matter over pregnancy (independent variable) after accounting for covariates (gender, age, height and wheezing). While in all statistical analyses lung function indices, age of children (in months) and height (cm) were treated as continuous variables, the wheezing was treated as a dummy variable and birthweight was divided into the quartiles of the distribution. As the distribution of PM_{2.5} was markedly skewed, the level of the exposure was also divided into quartiles of the distribution. The preliminary analysis assessed associations between population characteristics and outcome variables in univariable statistical models, where χ^2 statistics (nominal variables), one way of analysis of variance (numerical variables) and non-parametric test for trend tested differences between the outcome variables across subgroups with various air

pollution levels. In the multivariable regression analyses, the associations between lung function and air pollution assessed by regression coefficients were adjusted for the covariates. All statistical analyses were carried out with STATA version 11 software for Windows (Stata Corp., College Station, TX, USA).^{22,23}

Results

Median PM_{2.5} concentrations among the pregnant women enrolled in our study was 32.4 $\mu\text{g}/\text{m}^3$ (interquartile range: 30.1). Basic characteristics of the children grouped by the level of prenatal exposure to fine particulates (highest quartile of exposure vs. the rest) only differed in terms of spirometric indices (Table 2). Children from the higher exposed group were more likely to be exposed to postnatal ETS. On average, those exposed had lower FVC by 63 mL ($P = 0.059$), FEV₁ by 54 mL ($P = 0.088$) and FEV_{0.5} by 35 mL ($P = 0.225$).

Pearson correlation coefficients between lung function indices, PM_{2.5} and potential confounders (birthweight, height of children) indicate that birthweight, but not height of children at the testing time was inversely associated with PM_{2.5} exposure ($r = -0.163$, $P = 0.029$) (Table 3). The positive trend for unadjusted FVC, FEV₁ and FEV_{0.5} values across the birthweight quartiles was statistically significant (Table 4). The inverse trend for unadjusted FVC, FEV₁ values across the levels of PM_{2.5} appeared to be statistically significant (Table 5).

In the study sample there was 26.7% of wheezers who reported having had two or more episodes of wheezing over the follow-up. There was an inverse trend of unadjusted lung function indices with number

Table 3. Correlation coefficients between lung function indices, birthweight, height and intrauterine exposure to PM_{2.5} (P value in brackets)

	Birthweight	Height	FVC	FEV ₁	FEV _{0.5}	PM _{2.5} (log)
Birthweight	1.0000					
Height	0.2678 (0.0003)	1.0000				
FVC	0.2249 (0.002)	0.5475 (<0.0001)	1.0000			
FEV ₁	0.1951 (0.009)	0.5657 (<0.0001)	0.9238 (<0.0001)	1.0000		
FEV _{0.5}	0.1728 (0.020)	0.4779 (<0.0001)	0.6537 (<0.0001)	0.8344 (<0.0001)	1.0000	
PM _{2.5} (log)	-0.1629 (0.029)	-0.0195 (0.795)	-0.1605 (0.031)	-0.1405 (0.060)	-0.1040 (0.165)	1.0000

FEV_{0.5}, forced expiratory volume in 0.5 s; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 4. Unadjusted values of respiratory efforts (FVC, FEV₁, FEV_{0.5}) and the quartiles of birthweight

Birthweight (quartiles)	<i>n</i>	Mean	SD
FVC			
≤3165 g	43	1070.6	202.4
3166–3425 g	44	1098.0	170.4
3426–3719 g	44	1110.6	192.0
≥3720 g	45	1218.5	196.0
<i>z</i> for trend = 3.44; <i>P</i> = 0.0003			
FEV ₁			
≤3165 g	43	1025.4	189.8
3166–3425 g	44	1040.9	179.3
3426–3719 g	44	1054.5	176.8
≥3720 g	45	1156.9	175.9
<i>z</i> for trend = 3.15; <i>P</i> = 0.0005			
FEV _{0.5}			
≤3165 g	43	861.0	158.1
3166–3425 g	44	858.7	179.2
3426–3719 g	44	836.8	168.0
≥3720 g	45	816.8	157.0
<i>z</i> for trend = 3.35; <i>P</i> = 0.0001			

FEV_{0.5}, forced expiratory volume in 0.5 s; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

of wheezing episodes and the corresponding *z*-values for non-parametric trend of FVC, FEV₁ and FEV_{0.5} were: −2.66 (*P* = 0.008), −2.16 (*P* = 0.081) and −1.89 (*P* = 0.059).

Table 5. Unadjusted values of respiratory efforts (FVC, FEV₁, FEV_{0.5}) and the quartiles of prenatal PM_{2.5} level

PM _{2.5} level (quartiles)	<i>n</i>	Mean	SD
FVC			
<20.95 µg/m ³	43	1133.9	177.0
20.95–32.42 µg/m ³	44	1182.6	213.9
32.43–52.6 µg/m ³	44	1106.5	206.6
>52.6 µg/m ³	45	1077.7	165.9
<i>z</i> for trend = −2.07; <i>P</i> = 0.039			
FEV ₁			
<20.95 µg/m ³	43	1084.0	172.5
20.95–32.42 µg/m ³	44	1108.2	189.1
32.43–52.6 µg/m ³	44	1062.0	202.1
>52.6 µg/m ³	45	1030.5	166.6
<i>z</i> for trend = −2.07; <i>P</i> = 0.039			
FEV _{0.5}			
< 20.95 µg/m ³	43	861.0	165.5
20.95–32.42 µg/m ³	44	858.7	156.6
32.43–52.6 µg/m ³	44	836.8	186.0
>52.6 µg/m ³	45	816.8	165.0
<i>z</i> for trend = −1.72; <i>P</i> = 0.086			

FEV_{0.5}, forced expiratory volume in 0.5 s; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 6. Prenatal PM_{2.5} exposure (in quartiles) and lung function (FVC) of 5-year-olds adjusted for potential confounders

Predictors	Coefficient	[95% CI]	<i>P</i>
Age (in months)	29.1	[1.69, 56.6]	0.038
Height (cm)	18.9	[13.1, 24.7]	0.000
Gender of child (girls)	−49.6	[−98.6, −0.61]	0.047
Prenatal ETS	22.8	[−57.7, 103]	0.576
Postnatal ETS	43.4	[−68.0, 155]	0.443
Wheezing	−73.4	[−129, −17.1]	0.011
Birthweight g (quartiles)			
≤3165 g	0.00	Reference	0.146
3166–3425 g	24.1	[−46.5, 94.6]	
3426–3719 g	11.7	[−57.5, 80.9]	
≥3720 g	61.6	[−10.6, 133]	
Prenatal PM _{2.5} level (quartiles)			
<20.95 µg/m ³	0.00	Reference	0.003
20.95–32.42 µg/m ³	−11.0	[−80.4, 58.4]	
32.43–52.6 µg/m ³	−42.0	[−111, 27.5]	
>52.6 µg/m ³	−91.9	[−159, −24.2]	

Multivariable linear regression model.

ETS, environmental tobacco smoke.

Multivariable linear regression (Table 6) showed the very significant deficit of FVC at the highest quartile of PM_{2.5} exposure (regression coefficient = −91.9, *P* = 0.008), adjusted for covariates (age in months, gender of child, birthweight, height, wheezing and prenatal/postnatal ETS). On average, girls had a

Table 7. Prenatal PM_{2.5} exposure (in quartiles) on lung function (FEV₁) of 5-year-olds adjusted to potential confounders

Predictors	Coefficient	[95% CI]	<i>P</i>
Age (in months)	29.0	[2.96, 55.0]	0.029
Height (cm)	18.4	[12.9, 23.9]	<0.001
Gender of child (girls)	−35.4	[−81.9, 11.0]	0.134
Prenatal ETS	−17.2	[−93.4, 59.1]	0.657
Postnatal ETS	47.5	[−58.1, 153.1]	0.375
Wheezing	−54.6	[−107, −1.36]	0.045
Birthweight g (quartiles)			
≤3165 g	0.00	Reference	0.238
3166–3425 g	13.0	[−53.9, 79.8]	
3426–3719 g	−3.17	[−68.8, 62.4]	
≥3720 g	54.3	[−14.2, 122.7]	
Prenatal PM _{2.5} level (quartiles)			
<20.95 µg/m ³	0.00	Reference	0.008
20.95–32.42 µg/m ³	−32.8	[−98.6, 32.9]	
32.43–52.6 µg/m ³	−39.8	[−105, 26.1]	
>52.6 µg/m ³	−87.7	[−151, −23.6]	

Multivariable linear regression model.

ETS, environmental tobacco smoke.

Table 8. Prenatal PM_{2.5} exposure (in quartiles) and lung function (FEV_{0.5}) of 5-year-olds adjusted to potential confounders

Predictors	Coefficient	[95% CI]	P
Age (in months)	2.13	[-23.8, 28.1]	0.871
Height (cm)	14.3	[8.76, 19.7]	<0.001
Gender of child (girls)	-14.2	[-60.5, 32.2]	0.546
Prenatal ETS	-45.7	[-121, 30.4]	0.237
Postnatal ETS	38.5	[-66.9, 143]	0.471
Wheezing	-46.6	[-99.8, 6.58]	0.085
Birthweight in g (quartiles)			
≤3165 g	0.00	Reference	0.199
3166–3425 g	19.5	[-47.3, 86.3]	
3426–3719 g	1.72	[-63.8, 67.2]	
≥3720 g	52.6	[-15.7, 121]	
Prenatal PM _{2.5} level (quartiles)			
<20.95 µg/m ³	0.00	Reference	0.060
20.95–32.42 µg/m ³	-40.2	[-105, 25.4]	
32.43–52.6 µg/m ³	-42.5	[-108, 23.3]	
>52.6 µg/m ³	-72.7	[-136, -8.62]	

Multivariable linear regression model.
ETS, environmental tobacco smoke.

slightly lower FVC (regression coefficient = -49.6, $P = 0.047$) and wheezing was inversely associated with FVC values (beta coefficient = -73.4, $P = 0.011$). FVC level was positively associated with height (beta coefficient = 18.9, $P < 0.0001$) and age of children ((beta coefficient = 29.1, $P = 0.038$). Neither prenatal nor postnatal ETS were significantly associated with FVC level.

Adjusted FEV₁ level was also inversely correlated with PM_{2.5} prenatal exposure and the average deficit amounted to 87.7 mL ($P = 0.008$) at the higher level of exposure (Table 7). The estimate of the effect of PM_{2.5} exposure on FEV_{0.5} was proportionally weaker (-72.7, $P = 0.026$) but significant as well (Table 8). The inverse association between FEV_{0.5} and wheezing experienced by children over the follow-up was at the border significance level.

Table 9. Nested regression model to establish the effect of various independent variables (blocks) on FVC level in 5-year-olds

Blocks	R ²	Change in R ²	P for change in R ²
Birthweight (in quartiles)	0.072		0.0003
Age (months)	0.103	0.031	0.0149
Height (cm)	0.314	0.211	<0.0001
Gender of child	0.335	0.022	0.0185
Wheezing	0.361	0.025	0.0103
PM _{2.5} (in quartiles)	0.383	0.022	0.0143

In order to estimate the individual effect of independent variables on the lung size of children a nested regression model has been used (Table 9), where the variables (in blocks) were successively introduced in the regression procedures. While the birthweight explained 7.2% ($P = 0.0003$) of the FVC variability (measured by R^2), adding height of children increased R^2 by 21.1% ($P < 0.00001$); other added variables to a lesser degree increased R^2 – age (3.1%, $P = 0.015$), wheezing (2.5%, $P = 0.010$), gender (2.2%, $P = 0.019$) and PM_{2.5} (2.2%, $P = 0.014$).

Discussion

To our knowledge, this is the first epidemiological study to suggest that prenatal exposure to fine particulate matter may have a negative impact on the development of the fetal lung, with effects apparent in 5-year-olds. The estimates of effect were adjusted for covariates such as birthweight, height, age in months, prenatal/postnatal ETS exposure and wheezing. As the study has been performed only in children whose mothers stated that they were not active smokers in pregnancy, the results point to the possibility that prenatal PM_{2.5} exposure on lung size does not reflect maternal tobacco smoking. In addition, the findings show a negative impact of wheezing on lung function indices.

Fine particles are always present in particle-generating processes, especially combustion processes that generate many toxic agents and PM_{2.5} may be treated as a proxy measure of a whole complex of toxic agents present in the environment including polycyclic aromatic hydrocarbons (PAHs).²⁴ The biological mechanisms whereby PM_{2.5} might cause adverse effects on birth outcomes and development of the fetal lung are unclear. First, the formation of PAH-DNA adducts may induce the activation of apoptosis or the binding to receptors of placental growth factors, resulting in a decreased exchange of oxygen and nutrients.²⁵ In this context, Perera *et al.* reported that higher PAH-DNA adducts levels measured in cord blood were inversely correlated with birthweight and other birth outcomes compared with infants with lower PAH-DNA adducts.^{26,27} Since children's height, being the strongest determinants of the lung size, is associated with birthweight, which inversely correlates with prenatal PM_{2.5} exposure, then the main potential pathway through which the intrauterine exposure to this pollutant may affect the lungs of children would be the fetal

growth restriction resulting from this exposure. Second, other toxic components absorbed in the maternal circulation can cross the placenta and directly affect the fetus,^{28–30} producing cytotoxic reactive oxygen species that ultimately induce inflammatory and oxidant stress responses.³¹ Third, high exposure near to the end of gestation may cause disturbances of the pituitary-adrenocortico-placental system with possible anti-oestrogenic effects, which may also lead to fetal toxicity.³²

Our result documenting the inverse association between wheezing and lung function is in good agreement with findings in the literature showing that persistent wheezing or asthma, which begin in early life, are often associated with increased airway responsiveness and reduced infant lung function.^{33–41} The study is particularly consistent with the recent results of the Manchester Asthma and Allergy Study Group in preschool children, which have shown that both transient and persistent wheezers have reduced lung function compared with non-wheezing children.³⁹ Interestingly, the latter study group was also able to show that diminished lung function in high risk infants at 1 month of age preceded the subsequent occurrence of wheezing and other respiratory symptoms.⁴¹

A strength of our study is the design that enabled us to limit measurement error in estimating prenatal exposure to fine particles by assigning an individual personal exposure level to each child. The personal monitoring of ambient PM_{2.5} exposure is a highly 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 85 subjects provided evidence that the measurements of fine particles in the second trimester was a reflection of exposure level over other pregnancy periods.⁴² The validation of the questionnaire data on prenatal ETS using the cord blood cotinine measurements has shown significantly higher cord blood cotinine concentrations in children with prenatal ETS exposure than in those without it (7.68 vs. 0.86 ng/mL, $P = 0.005$). Moreover, there was a significant correlation between the average number of cigarettes smoked daily at home and cord blood cotinine level ($r = 0.510$, $P < 0.0001$). Previous studies have attempted to quantify the concentration of air pollutants measured in the residential area and assign these exposure values to the study subjects. Estimating individual average exposures during specific gestational months by relying on the ambient air-monitoring sta-

tions close to the maternal residence may result in exposure misclassification. Furthermore, in our study important potential confounders of the relationship between prenatal ambient risk factors and the fetal development of infants, such as chronic diseases of mothers or maternal active tobacco smoking have been removed through entry criteria.

Another strong point of our study on prenatal PM_{2.5} and lung function in preschool children stems from the fact that we were able to show the effect of wheezing episodes, which in our study were carefully monitored over many regular time points in the course of face-to-face interviews with mothers of children. Other studies usually considered current wheeze (over the last 12 months) and very often used self-administered questionnaires. We believe that quarterly and semi-annually collected data on wheeze offered us a good opportunity to explore the importance of early wheeze on lung function.

In contrast, we are aware of the limitations of our study, which are mainly related to a relatively small sample size and the lack of repeated comparable measurements of PM_{2.5} in the postnatal period. It is obvious that the household level of fine particulate matter is subject to variation over time, which depends to some extent on the number of cigarettes smoked daily at home. Since the mobility of the subjects under study was very moderate and mainly restricted to the same communal air pollution area, this gave us confidence that the estimates of effects were not biased.

Conclusions

The findings link prenatal PM_{2.5} exposure to lung function deficits in childhood, which were not mediated by intrauterine tobacco smoke. Although the main potential pathway through which the intrauterine exposure to pollutants affects the development of lungs would be fetal growth restriction, the prenatal PM_{2.5} exposure may lead to additional decrement of fetal lung growth through other pathways. The data presented should help clinicians better understand respiratory health problems in early childhood, and persuade policy makers to consider the effect of prenatal airborne PM_{2.5} exposure on lung function of young children when setting air pollution guidelines.

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