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EFFECT OF PRENATAL EXPOSURE TO FINE PARTICULATE MATTER ON VENTILATORY LUNG FUNCTION OF PRESCHOOL CHILDREN OF NONSMOKING MOTHERS. KRAKOW INNER CITY BIRTH COHORT PROSPECTIVE STUDY

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SUMMARY

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 “epigenetic 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} was performed over 48 hours in the second trimester of pregnancy. After delivery, infants were followed over five years and the interviewers visited participants at their homes to record children's respiratory symptoms every three months in the child's first two years of life and every 6 months later. In the fifth year of the follow-up, children were invited for standard lung function testing and quantified by FVC, FEV₁ and FEV₀₅ levels. Material consisted of 176 children of nonsmoking mothers, who performed at least two acceptable spirometry measurements. Multivariable linear regression model 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, birth weight, 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 FEV₀₅ was proportionally weaker (−72.7, P = 0.026) it was significant as well. 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 is 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 were 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 epidemiologic 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-birth weight, premature births, and intrauterine growth retardation was 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 repercussion in various fetal body organs and lead to their deficient function in postnatal life.

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 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 is associated with a number of adult chronic diseases.¹⁵⁻¹⁷ It is believed that these associations arise as a result of the phenomenon of "epigenetic 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 by specially designed personal samplers collecting air pollution particles over 48 hours 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 FVC, FEV₁ and FEV₀₅ 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 and HIV infection, free from chronic diseases such as diabetes or hypertension, and who had resided in Krakow for at least one year prior to pregnancy were eligible for the study. Prior to participation, women read and signed an informed consent. The Ethical Committee of the Jagiellonian University approved the research.

Upon enrollment, 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), three months in the first two years of the newborn's life, and every 6 months later, were submitted to a detailed standardized face-to-face interview on their infant's health and respiratory symptoms administered by a trained interviewer. The presence of wheezing was defined if the child reported two or more wheezing episodes over the follow-up. 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 was used to identify children with wheezing. Prenatal environmental tobacco smoke defined if the mother declared to be exposed to ETS in pregnancy period was validated by the cord blood cotinine levels. Postnatal ETS exposure was defined if the ETS exposure at home occurred in more than two years over the follow-up. The present analysis was based on data from one hundred seventy six 5-year-olds who were born after 36 weeks of gestation, completed the 5 year follow-up and performed two reliable and acceptable spirometry tests. The study sample in terms of important characteristics did not differ from the group of children not considered in the present analysis (Table 1).

Dosimetry of cord blood cotinine—The serum cotinine concentration was measured at CDC using the sensitive isotope-dilution high-performance liquid chromatographic/atmospheric pressure ionization tandem spectrometric (LC/MS/MS) procedure. The limit of detection (LOD) is below 0.050 ng/mL.^{19, 20}

Dosimetry of prenatal personal exposure to fine particles

A Personal Environmental Monitoring Sampler (PEMS), 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 $2.5 \mu\text{m}$ (Figure 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 LPM over the 48-hour period. Particles were collected on Teflon membrane filter (37 mm Teflo™, 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.

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 (Figure 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 staff-person 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 has been running continuously and that there have been no technical or

operating failures. A staff-member 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 computerized PC QRS Card 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 one-liter syringe. Each child made at least two good forced exhalation efforts and the primary indicators of lung function, i.e., FVC (Forced Vital Capacity), which is the total amount of air that can forcibly be blown out after full inspiration, FEV₁ (Forced Expiratory Volume in 1 second), which is the amount of air that you can forcibly be blown out in 1 second and FEV_{0.5} (Forced Expiratory Volume in 0.5 second) that is the amount of air that can be blown out in 0.5 second were recorded. Maneuvers were excluded if a sub-maximal expiratory effort was present in which a peak expiratory flow (PEF) was not clearly determined, a slow rise of PEF was apparent, an expiration time was less than 0.5 seconds, cough or an abrupt end of expiration effort appeared in the course of exhalation effort. In accordance with the ATS/ERS 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 recorded the spirometric index corrected to BTPS (body temperature, pressure saturated). 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 dummy variable and birthweight divided into ordinal scale by the quartiles of the distribution. As the distribution of PM_{2.5} was markedly skewed, the level of the exposure was divided into quartiles of the distribution. The preliminary analysis assessed associations between population characteristics and outcome variables in univariate statistical models, where Chi-square statistics (nominal variables), one way of analysis of variance (numerical variables), and nonparametric test for trend tested differences of outcome variables across subgroups with various air pollution level. In the multivariable regression analyses the associations between lung function and air pollution assessed by beta regression coefficients were adjusted for the covariates. All statistical analyses were carried out with STATA 11 version software for Windows.^{22, 23}

RESULTS

Median PM_{2.5} concentrations among the pregnant women enrolled in our study was 32.4 µg/m³ (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 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 FEV₀₅ by 36 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 FEV₀₅ values across the birthweight (in 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 declared having two or more episodes of wheezing over the follow-up. There was an inverse trend of unadjusted lung function indices with number of wheezing episodes and the corresponding z values for nonparametric trend of FVC, FEV₁ and FEV₀₅ were: -2.66 ($P = 0.008$), -2.16 ($P = 0.081$) and -1.89 ($P = 0.059$).

Multivariable linear regression model (Table 6) showed the very significant deficit of FVC at the highest quartile of PM_{2.5} exposure (regression coefficient = -91.9 , $P = 0.008$), which has been adjusted for covariates (age in months gender of child, birthweight, height, wheezing and prenatal/postnatal ETS). On average, girls had a 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 , $P = 0.038$). Positive effect of higher birthweight (highest quartile) was at border significance level (beta coefficient = 61.6 , $P = 0.094$). Neither prenatal nor postnatal ETS were significantly associated with FVC level.

Adjusted FEV₁ level in children 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 FEV₀₅ was proportionally weaker (-72.7 , $P = 0.026$) but significant as well (Table 8). The inverse association between FEV₀₅ and wheezing experienced by children over the follow-up was at the border significance level.

In order to estimate the individual effect of independent variables on the lung size of children the nested regression models 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, it is the first epidemiologic study to suggest that prenatal exposure to fine particulate matter may have a negative impact on the development of the fetal lung; and the effect of this exposure may be evidenced 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 they were not active smokers in pregnancy, the results point to the possibility that prenatal PM_{2.5} exposure on lung size might 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 PAHs (polycyclic aromatic hydrocarbons).²⁴ The biological mechanisms whereby PM_{2.5} might cause adverse effects on birth outcomes and development of the fetal lung are yet unclear. First, the formation of PAH-DNA adducts may induce the activation of the apoptosis or the binding to receptors of placental growth factors, resulting in the decreased exchange of oxygen and nutrients.²⁵ In this context we should refer to the findings published by Perera et al. who reported that higher PAH-DNA adducts levels measured in cord blood were inversely correlated with birthweight and other birth outcomes compared to 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 pollutant may affect lung 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-estrogenic effects which may also lead to a fetal toxicity.³²

Our results documenting the inverse association between wheezing and lung function is in a good agreement with findings in the literature documenting 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 NAC Manchester Asthma and Allergy Study Group in preschool children, which have shown that both transient and persistent wheezers have reduced lung function compared with nonwheezing children.³⁹ Interestingly, the latter study group was also able to show that diminished lung function in high risk infants at one month of age preceded the subsequent occurrence of wheezing and other respiratory symptoms.⁴¹

A strength of our study is the design which 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 of individual exposure incorporating outdoor and indoor exposures. Good agreement between the personal PM_{2.5} measurements across all trimesters of pregnancy carried out in the subsample of 85 subjects provided evidence that the measurements of fine particles done in the second trimester was a reflection of exposure level over other pregnancy periods.⁴² The validation of the questionnaire data on prenatal ETS by the cord blood cotinine measurements has shown a significantly higher cord blood cotinine concentrations in children with confirmed 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 residence 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 stations even 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 semiannually collected data on wheeze offered us a good opportunity to explore the importance of early wheeze on lung function.

On the other side, we are aware of the limitations of our study, which are mainly related to 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 the subject of 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 a 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 pollutant affects the development of lungs would be the 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 while setting air pollution guidelines.

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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

Table 1

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

	Total study sample		Children not attending	Total group of children recruited	P-value for difference between exposure groups
	N=176	N=305	N=481		
Gender: Boys	n (%)	158 (51.8)	245 (50.9)		
Girls	n (%)	89 (50.6)	147 (48.2)	236 (49.1)	0.6844
Gestational age (weeks):	mean	39.47	39.58	39.54	
> 36	SD	1.166	1.124	1.140	0.2894
Birth weight (g):	mean	3432.4	3452.3	3445.0	
	SD	422.7	444.2	436.1	0.6317
Length at birth (cm):	mean	54.9	54.7	54.8	
	SD	2.48	2.70	2.62	0.4080
Prenatal PM _{2.5} ($\mu\text{g}/\text{m}^3$) > 52.6	n (%)	45 (25.6)	77 (25.2)	122 (25.4)	1.0000

Table 2

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

		Total study sample	Lower PM _{2.5} 52.6 µg/m ³	Higher PM _{2.5} >52.6 µg/m ³	P-value for difference between exposure groups
Gender: Boys	n (%)	87 (49.4)	67 (51.1)	21 (44.4)	
Girls	n (%)	89 (50.6)	64 (48.9)	29 (55.6)	0.5466
Gestational age (weeks):					
> 36	mean	39.47	39.46	39.49	
	SD	1.166	1.152	1.218	0.8787
Birth weight (g):					
	mean	3432.4	3460.8	3349.8	
	SD	422.7	432.8	384.6	0.1288
Length at birth (cm):					
	mean	54.9	55.0	54.5	
	SD	2.48	2.49	2.42	0.1943
Age (in months)					
	mean	60.7	60.7	60.7	
	SD	0.92	0.97	0.75	0.9491
Weight (kg) at age of 5 years (kg):					
	mean	19.83	19.87	19.73	
	SD	2.885	2.840	3.041	0.7834
Height (cm) at age of 5 years:					
	mean	112.8	112.7	113.3	
	SD	4.539	4.650	4.218	0.4439
FVC (ml):					
	mean	1124.8	1141.0	1077.7	
	SD	194.1	200.9	165.9	0.0587
FEV ₁ (ml):					
	mean	1070.9	1084.7	1030.5	
	SD	183.8	187.9	166.6	0.0878
FEV _{0.5} (ml):					
	mean	843.1	852.1	816.8	
	SD	168.1	168.9	165.0	0.2250
Wheezing	n (%)	47 (26.7)	34 (26.0)	13 (28.9)	0.8504
ETS prenatal exposure	n (%)	44 (25.0)	30 (22.9)	14 (31.1)	0.3693
ETS postnatal exposure	n (%)	17 (9.7)	7 (5.3)	10 (22.2)	0.0026

Table 3

Correlation coefficients between lung function indices, birthweight, height and intrauterine exposure to PM_{2.5} (in brackets significance level)

	Birthweight	Height	FVC	FEV ₁	FEV ₀₅	PM _{2.5} (log)
Birthweight	1.0000					
Height	0.2678 (0.0003)	1.0000				
FVC	0.2249 (0.0024)	0.5475 (0.0000)	1.0000			
FEV ₁	0.1951 (0.0087)	0.5657 (0.0000)	0.9238 (0.0000)	1.0000		
FEV ₀₅	0.1728 (0.0203)	0.4779 (0.0000)	0.6537 (0.0000)	0.8344 (0.0000)	1.0000	
PM _{2.5} (log)	-0.1629 (0.0289)	-0.0195 (0.7945)	-0.1605 (0.0314)	-0.1405 (0.0600)	-0.1040 (0.1647)	1.0000

Table 4 Unadjusted values of respiratory efforts (FVC, FEV₁, FEV₀₅) and the quartiles of birthweight

FVC	n	mean	SD	P-level
Birthweight (quartiles)				
3165 g	43	1070.6	202.4	z for trend = 3.44 P = 0.0003
3166 – 3425 g	44	1098.0	170.4	
3426 – 3720 g	44	1110.6	192.0	
3720 g	45	1218.5	196.0	
Total	176	1124.8	194.1	
FEV₁				
Birthweight (quartiles)				
3165 g	43	1025.4	189.8	z for trend = 3.15 P = 0.0005
3166 – 3425 g	44	1040.9	179.3	
3426 – 3720 g	44	1054.5	176.8	
3720 g	45	1156.9	175.9	
Total	176	1070.9	183.8	
FEV₀₅				
Birthweight (quartiles)				
3165 g	43	861.0	158.1	z for trend = 3.35 P = 0.001
3166 – 3425 g	44	858.7	179.2	
3426 – 3720 g	44	836.8	168.0	
3720 g	45	816.8	157.0	
Total	176	843.1	168.1	

Table 5 Unadjusted values of respiratory efforts (FVC, FEV₁, FEV₀₅) and the quartiles of prenatal PM_{2.5} level

FVC	n	mean	SD	P-level
PM _{2.5} level (quartiles)				
< 20.95 µg/m ³	43	1133.9	177.0	z for trend = - 2.07 P = 0.039
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	
Total	176	1124.8	194.1	
FEV₁				
PM _{2.5} level (quartiles)				
< 20.95 µg/m ³	43	1084.0	172.5	z for trend = - 2.07 P = 0.039
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	
Total	176	1070.9	183.8	
FEV₀₅				
PM _{2.5} level (quartiles)				
< 20.95 µg/m ³	43	861.0	165.5	z for trend = - 1.72 P = 0.086
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	
Total	176	843.1	168.1	

Table 6

Prenatal PM_{2.5} exposure (in quartiles) and lung function (FVC) of 5-year-olds adjusted to potential confounders. Multivariable linear regression model

Predictors	Coef.	P>t	[95% Conf. Interval]
Age (in months)	29.14	0.038	[1.69, 56.59]
Height (cm)	18.89	0.000	[13.09, 24.69]
Gender of child (girls)	-49.61	0.047	[-98.60, -0.61]
Prenatal ETS	22.81	0.576	[-57.67, 103.28]
Postnatal ETS	43.40	0.443	[-68.01, 154.82]
Wheezing	-73.35	0.011	[-129.59, -17.11]
Birthweight g (quartiles)			
3165 g	Reference		
3166 – 3425 g	24.10	0.501	[-46.45, 94.65]
3426 – 3720 g	11.71	0.739	[-57.52, 80.94]
3720 g	61.60	0.094	[-10.62, 133.8]
Prenatal PM_{2.5} level (quartiles)			
< 20.95 µg/m ³	Reference		
20.95 – 32.42 µg/m ³	-10.97	0.755	[-80.37, 58.42]
32.43 – 52.6 µg/m ³	-42.04	0.234	[-111.58, 27.49]
> 52.6 µg/m ³	-91.92	0.008	[-159.60, -24.24]

Table 7

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

Predictors	Coef.	P>t	[95% Conf. Interval]
Age (in months)	28.97	0.029	[2.96, 54.99]
Height (cm)	18.44	0.000	[12.94, 23.93]
Gender of child (girls)	-35.42	0.134	[-81.86, 11.01]
Prenatal ETS	-17.15	0.657	[-93.41, 59.12]
Postnatal ETS	47.50	0.375	[-58.08, 153.09]
Wheezing	-54.65	0.045	[-107.95, -1.36]
Birthweight g (quartiles)			
3165 g	Reference		
3166 – 3425 g	12.99	0.702	[-53.87, 79.84]
3426 – 3720 g	-3.17	0.924	[-68.78, 62.43]
3720 g	54.28	0.119	[-14.16, 122.71]
Prenatal PM_{2.5} level (quartiles)			
< 20.95 µg/m ³	Reference		
20.95 – 32.42 µg/m ³	-32.84	0.325	[-98.61, 32.92]
32.43 – 52.6 µg/m ³	-39.79	0.235	[-105.68, 26.10]
> 52.6 µg/m ³	-87.71	0.008	[-151.85, -23.57]

Table 8

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

Predictors	Coef.	P>t	[95% Conf. Interval]
Age (in months)	2.13	0.871	[-23.84, 28.10]
Height (cm)	14.25	0.000	[8.76, 19.73]
Gender of child (girls)	-14.18	0.546	[-60.54, 32.19]
Prenatal ETS	-45.74	0.237	[-121.88, 30.41]
Postnatal ETS	38.54	0.471	[-66.88, 143.96]
Wheezing	-46.63	0.085	[-99.84, 6.58]
Birthweight in g (quartiles)			
3165 g	Reference		
3166 – 3425 g	19.50	0.565	[-47.26, 86.25]
3426 – 3720 g	1.72	0.959	[-63.79, 67.22]
3720 g	52.64	0.130	[-15.69, 120.97]
Prenatal PM_{2.5} level (quartiles)			
< 20.95 µg/m ³	Reference		
20.95 – 32.42 µg/m ³	-40.22	0.228	[-105.88, 25.43]
32.43 – 52.6 µg/m ³	-42.48	0.204	[-108.27, 23.31]
> 52.6 µg/m ³	-72.66	0.026	[-136.70, -8.62]

Table 9

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

Blocks	Beta standardized coefficients	R²	Change in R²	F test of the change in the R²
Birthweight (in quartiles)	0.079	0.072		0.0003
Age (months)	0.093	0.103	0.031	0.0149
Height (cm)	0.475	0.314	0.211	0.0000
Gender of child	−0.137	0.335	0.022	0.0185
Wheezing	−0.164	0.361	0.025	0.0103
PM _{2.5} (in quartiles)	−0.151	0.383	0.022	0.0143