Published in final edited form as:

Pediatr Pulmonol. 2015 May ; 50(5): 469–478. doi:10.1002/ppul.23104.

Antihistamine Medication May Alleviate Negative Effects of Prenatal Exposure to Polycyclic Aromatic Hydrocarbons (PAH) on Lung Function in Children. Birth Cohort Prospective Study

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Abstract

The main purpose of the present study was to test the hypothesis that the depressed lung growth attributable to prenatal exposure to polycyclic aromatic hydrocarbons (PAH) may be modified by the intake of antihistamine medications. Individual prenatal PAH exposure was assessed by personal air monitoring in 176 children who were followed over nine years, in the course of which outdoor residential air monitoring, allergic skin tests for indoor allergens, lung function tests (FVC, FEV₁, FEV₀₅ and FEF₂₅₋₇₅) were performed. The analysis with the General Estimated Equation (GEE) showed no association between prenatal PAH exposure and lung function in the group of children who were reported to be antihistamine users. However, in the group of antihistamine non-users all lung function tests except for FEF₂₅₋₇₅ were significantly and inversely associated with prenatal airborne PAH exposure.

Conclusion—The results of the study suggest that the intake of antihistamine medications in early childhood may inhibit the negative effect of fetal PAH exposure on lung growth and provides additional indirect evidence for the hypothesis that lung alterations in young children resulting from PAH exposure may be caused by the allergic inflammation within lung.

Keywords

prenatal PAH exposure; depressed lung function; preadolescent children; antihistamines; modification effect

Introduction

Over the last several decades there have been a number of cross-sectional and longitudinal studies on the impact of residential chronic exposure to airborne particulate matter (PM) or other airborne toxicants, such as NO₂, SO₂ and ozone, on lung growth of children¹. Although the results were not always consistent, they suggested that poor ambient air quality may be causally connected with impaired lung function. Recently published papers have revealed that exposure to diesel exhaust particles (DEP), which contain a wide spectrum of polycyclic aromatic hydrocarbons (PAH), may be one of the most important environmental causes of respiratory illness²⁻⁶. Although PAH compounds are common outdoor pollutants derived from diesel engine powered vehicles and coal burning, indoor sources produce PAH emissions from residential heating (e.g., coal or wood stoves, fireplaces, kerosene heaters), unvented gas appliances, environmental tobacco smoke (ETS), and fumes from cooking, grilling, and frying of food⁷⁻¹⁰. Animal and human exposure studies have already shown that PAH compounds, being immunotoxic¹¹⁻¹³, may induce an inflammatory response in human airways¹⁴⁻¹⁷.

The depressive effect of PAH exposure on lung growth is thought to be brought about by an inflammatory process within the respiratory tract resulting from the exposure. Although there have been numerous studies on the potential modifying effects of antihistamine medications on respiratory symptoms, no data exist on whether these can prevent depressed lung growth associated with air pollution exposure. Antihistamine medications are among the commonly prescribed medicines in pediatrics for the symptomatic treatment of various allergic disorders, such as seasonal and perennial allergic rhinitis, conjunctivitis, atopic dermatitis or chronic urticaria¹⁸⁻¹⁹. New recent studies investigating the mechanism underlying the effects of H1 antihistamines have shown that they exhibit anti-inflammatory activity as well as an antihistamine effect. Moreover, *in vitro* studies have demonstrated that the anti-inflammatory effects of these medications occurs at physiologically low concentrations^{18,19}.

The main purpose of the study was to test the hypothesis that depressed lung growth potentially caused by fetal PAH exposure may be modified by the intake of antihistamine drugs in childhood monitored between ages 5 and 9. Monitoring of individual fetal exposure to airborne PAH compounds was performed in the second trimester of pregnancy, which is an important period for the development of the airway system²⁰. As lung growth continues through postnatal life, each child's postnatal outdoor PAH exposure was also monitored at age 3. The presented analysis was performed in two groups of children i.e, users and non-users of antihistamine medications and the results adjusted for a wide set of potential confounders, such as gestational age, gender of child, children's body growth rate, postnatal ETS (environmental tobacco smoke), residential outdoor PAH exposure, the season of residential PAH survey, maternal allergy, atopy and asthma diagnosed or suspected in children by a physician.

Methods

This study is nested in a birth cohort study of Krakow children, a collaborative research project of the Jagiellonian University in Krakow and Columbia University in New York. The design of the study and the detailed selection of the population sample have been described previously²¹. 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 in Krakow and Columbia Presbyterian Medical Center approved the research.

Upon enrollment, a detailed questionnaire was administered to each woman to solicit information on demographic data, home 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, every three months in the first two years of the newborn's life and every 6 months thereafter mothers participated in a detailed face-to-face interview on their children's health and environmental conditions, including prenatal and postnatal ETS exposure in the home. Gestational age of children (in weeks) was obtained from the infant's medical record of birth date and the date of the last menstrual period. Maternal allergy was defined as the self-reported medical diagnosis of eczema, asthma or hay fever. Prenatal ETS was defined by the amount 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.

Estimated daily intake of oral antihistamines by children over the 5-year period (at ages 5 – 9) was based on regular face-to-face interviews of the mothers performed every 6 months by the trained field workers. Name(s) of the medication(s) reported by mothers were confirmed by the mother's showing the interviewer original packagings or containers of the medication(s) used in that period. If the intake of any antihistamine medications took place in a given period, the mothers were asked for how many days the medication(s) were taken. The classification of antihistamine medications was based on the medication names.

At the age of 3, residential monitoring was carried out to assess the indoor and outdoor levels of PAH compounds. At ages 5 - 8 allergic skin tests were performed for indoor allergens and between ages 5 to 9 children were annually invited for standard lung function testing (FVC, FEV₁, FEV₀₅ and FEF₂₅₋₇₅).

Measurement of prenatal and postnatal PAH airborne concentrations

Monitoring of individual prenatal exposure to airborne PAH over a consecutive 48-hour period was performed with Personal Environmental Monitoring Samplers (PEMS), designed by the Department of Environmental Health, School of Public Health at Harvard University (led by Dr J. Spengler). The battery operated sampling units collected fine particles on

quartz filters and gaseous PAH compounds on polyurethane foam (PUF). Participants were asked to wear the lightweight sampler installed in a backpack wherever they were during the daytime hours and to place it at the bedside at night. The flow rate of the sampling pump was calibrated using a bubble meter prior to the monitoring and was checked again with a change of the battery pack on the second day. For each child at the age of 3, residential airborne PAH outdoor monitoring was also conducted over 48 hours with the same samplers, which were attached to the external wall of the home at the level of the apartment.

The collected filters were sent to the Department of Analytical and Environmental Chemistry, Southwest Research Institute, San Antonio, TX, USA Texas (D. Camman) who performed PAH extraction and measured the PAH concentrations of pyrene and the eight carcinogenic PAH—benz[*a*]anthracene [B(*a*)A], chrysene/isochrysene, benzo[*b*]fluoranthene [B(*b*)F], benzo[*k*]fluoranthene [B(*k*)F], B(*a*)P, indeno[1,2,3-*c,d*]pyrene, dibenz[*a,h*]anthracene [D(*a,h*)A], and benzo[*g,h,i*]perylene [B(*g,h,i*)P] using gas chromatography/mass spectrometry as described elsewhere²²⁻²³. The detection limit for each target PAH was 1.0 ± 0.2 ng/sample. In the study we used the total sum of individual concentrations of all measured PAH compounds (in ng/m³).

Assessment of atopic status of children

Once at ages 5-8, children were invited to undergo skin prick testing (SPT) for four common domestic aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, dog and cat hair). The results were read after 15 minutes by measuring the largest diameter of the wheal. Atopic status was ascertained as a wheal reached diameter of 3 mm and greater than the histamine control. The participants were defined as atopic if they had at least one positive skin prick test.

Spirometric testing

Children were free of respiratory symptoms on the day of testing and instructed to exclude medication over one week preceding the spirometric testing. Prior to spirometric testing, standing height and weight of each child were measured. Subsequently, children were coached to engage in maximal forced expiratory efforts in a standing position without a nose clip. All spirometric measurements were carried out by the same staff member (E. Mroz), who was experienced in spirometric testing of children, using a computerized PC QRS Card Spirometer (QRS Diagnostic, Plymouth, MN, USA) with incentive display software. 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 were recorded including: FVC (the total amount of air that can forcibly be blown out after a full inspiration); FEV₁ (the amount of air that can be forcibly blown out in 1 second); and FEV₀₅ (the amount of air that can be blown out in 0.5 second). In addition, maximal mid expiratory flow over the middle 50% of the FVC (FEF₂₅₋₇₅) was recorded. Spirometric 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 1 second or a cough or an abrupt end of expiration 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 children²⁴, 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 recorded body temperature, pressure saturated (BTPS). Spirometric findings were accepted as reliable if the difference between FEV₁ of the two best curves were within the range of 5%.

Statistical data analysis

The descriptive analysis assessed the distribution of various parameters related to women and newborns under study. Chi-square statistics (nominal variables) and analysis of variance (numerical variables) tested differences between the participants and non-participants and subgroups (medication users vs. non-users). Initially, the interaction terms between PAH exposure and anti-histamine medication was estimated to ensure the significant difference between subgroups defined by medication status. As the interaction terms appeared to be statistically significant, the purpose of the subsequent part of the statistical analysis was to estimate the population average effect of the PAH exposure on lung function tests (measured at 5, 6, 7, 8 and 9 years of age) in two groups of children grouped by the medication status. The main aim of this part of the statistical analysis was to estimate the population-average interpretation of the data in the subgroups and not within-subject and between-subject variation. The assumption was also made that missing data are completely at random. For this purpose the generalized estimating equation (GEE) model was chosen, which accounts for the correlation between repeated health outcomes assessed in each child over the follow-up period²⁵⁻²⁶. The model utilizes data on all subjects, also including those with incomplete protocols, and permits simultaneous modeling of the relationship (regression) between specific risk factors and outcome variables (lung function tests) measured over the follow-up period. The described models computed regression coefficients of the outcome variable on the main predictor variables (prenatal PAH exposure) and accounted for potential confounders. The PAH concentrations were introduced in the GEE models as numeric variable after ln-transformation, which normalized their distributions. In all GEE models a dummy variable defining the season of the residential air pollution monitoring (0 = nonheating, 1 = heating season) was inserted as well. All statistical analyses were carried out with STATA 13.1 version software for Windows.

Results

The analysis presented was restricted to 176 children who took part in the prenatal and residential air pollution survey, performed reliable and acceptable spirometric tests over five annual visits and whose mothers completed the follow-up survey on the intake of antihistamine medications. The study sample did not differ in terms of basic characteristics from the group of children which was not included in the analysis, except that non participants were exposed to higher prenatal PAH exposure than those who participated in the study (Table 1).

In the sample studied, the geometric mean (gmean) of prenatal individual PAH concentrations was 20.3 ng/m³ (95%CI = 17.0 – 24.1 ng/m³) and the residential outdoor PAH concentrations showed a higher gmean and had a wider range of values (30.8 ng/m³,

95%CI: 24.7 – 38.3 ng/m³). Both the prenatal and residential PAH distributions were skewed. After (ln) transformation, the distribution of the PAH levels measured in all environmental compartments were bimodal, with a lower exposure range in the non-heating season (April–September) and a higher exposure range in the heating season (October–March).

Relevant characteristics of the children included in the study were not different across the antihistamine medication strata except for higher proportion of maternal allergy and asthma diagnosed or suspected by physician among children using antihistamines (Table 2). Standardized spirometric test on height and sex were not statistically different between medication users and not users. Users of antihistamines reported more days with cough and suffered more frequently from sore throat or angina than nonusers (Table 3).

The mean height of children attending spirometric testing was 112.0 (SD 4.8) cm at the age of 5 and 136.2 (SD 6.1) cm at the age of 9. On average, the annual increase in height was 6.7, 6.6, 5.5, and 5.2 cm between consecutive surveys, suggesting that children under study had not entered their prepubertal growth spurt. In the follow-up period mean FVC values standardized to height increased from the initial values 1080.8 mL (95%CI: 1026.2 – 1135.4) to 1846.3 mL (95%CI: 1801.6 – 1891.0) at the end of the follow-up. The average increase of FVC was 251.6, 209.7, 169.8, and 152.2 mL between consecutive annual surveys. Table 4 displays spirometric results in the study sample (N = 176) standardized to sex, height and age (means, 95% CI) with percent predicted values estimated from the total number of children who performed acceptable spirometry (N = 307). It shows that children under study did not differ in terms of lung function tests from the total group examined. Predicted values of spirometric parameters were estimated from the total number of children who performed acceptable spirometric tests, as there are no reliable standard equations for Polish population.

Eighty-three children reported intake of antihistamine medications over the follow-up. The first generation medications were used very rarely (mean number of days: 15.4, 95%CI 5.7 – 25.0) in contrast to the second generation histamines (mean number of days: 82.7, 95%CI 50.9 – 114.5) and the third generation medications (mean number of days: 17.2, 95%CI 4.1 – 30.2). Average medication (in term of days) reported over the follow-up by asthmatic children was 241 days (95%CI: 236 - 246), by atopic 167 days (95%CI: 163 - 170) and 32 days (95%CI: 31 - 33) in the rest of participants. In all groups the children took the medication most frequently at the age 5 and 6. Main reasons for the intake of antihistamines were atopy or asthma, allergic rhinitis, eczema and recurrent upper or lower respiratory infections.

In the initial stage of the multivariable analysis we examined the interaction terms between PAH exposure (prenatal and residential) and medication status (nominal variable), which have been estimated from the multivariable GEE models accounting for relevant confounders mentioned earlier. It turned out that all interaction terms were statistically significant except for FEF₂₅₇₅ (Table 5). The interaction term (residential PAH exposure × medication status) for FVC was at the border significance level (p = 0.055).

Subsequently, we explored the effect of prenatal PAH exposure on lung function tests recorded annually over the follow-up with the GEE models for each lung function test in medication users and non-users (Table 6). The effects of prenatal and residential PAH concentrations were introduced in the models as ln transformed variables and adjusted for the same set of covariates. In the group of non-users FEV₁ and FEV₀₅ levels were significantly and inversely associated with both prenatal and residential PAH exposure. However, FVC was significantly associated only with prenatal PAH exposure. In contrast, there was no association between prenatal or PAH residential exposure and lung function in the group of children who were reported to be antihistamine users

Figures 1 and 2 visualize the relationship between the prenatal and residential PAH concentrations (ln-transformed) and FEV₁ over the follow-up. Relationship between prenatal PAH exposure and FVC or FEV₀₅ were similar to that shown for FEV₁.

Discussion

To our knowledge this is the first prospective cohort study showing a modifying impact of the intake of antihistamines in early childhood on depressed lung growth associated with prenatal PAH exposure. The association between prenatal PAH exposure via mother's inhalation of the air pollutants during pregnancy and subsequent reduced lung function was seen only among the children who were reported to be non- antihistamine users. In that group of non-users, lung function tests (FVC, FEV₀₅ and FEV₁) were significantly and inversely associated with prenatal PAH exposure in a dose-dependent manner. It is noteworthy to add that the estimated effects were adjusted for a wide set of confounders including the residential PAH co-exposure measured in the postnatal period. The results suggest that the intake of antihistamine medications in early childhood may alleviate the impact of both prenatal and postnatal residential PAH exposure on lung function. It is all the more important, that the antihistamines were much more frequently administered in the age 5-6 at a plausible "window" of lung development. Furthermore, the study provides additional indirect evidence for the hypothesis that lung alterations in young children resulting from prenatal PAH exposure may be at least partly caused by the occurrence of allergic inflammation within lung. Our results in this respect is consistent with observations made by Peters et al.²⁷ that medication use modifies the health effects of particulate air pollution in children with asthma.

Although the biological mechanisms whereby prenatal PAH might cause adverse respiratory health effects in early childhood have not been yet clearly established, it is known that PAH compounds from maternal blood can easily reach the fetus leading to the formation of PAH-DNA adducts and DNA damage²⁸⁻³⁰. Fetal exposure to PAH may result in production of an "allergic response" typified by proliferation of Th2 type T lymphocytes that secrete proinflammatory cytokines such as interleukin IL-4, IL-5 and IL-13³¹. The Th2 cytokines promote allergen-specific IgE antibody and induce eosinophil-dominated inflammatory tissue responses³²⁻³⁷. Inhaled PAH compounds in postnatal life act directly on bronchial epithelial cells, which play a key role in the local synthesis of proinflammatory chemokines. *In vitro* and *in vivo* studies demonstrated that inhaled DEP particles have a capacity to up-regulate allergic or proinflammatory cytokines such as interleukin IL-4, IL-2, IL-8, and

enhance local mucosal IgE production and deviate cytokine production toward a Th2 profile^{11,16,32-37}.

The underlying mechanisms for the anti-inflammatory effects of antihistamines on the respiratory tract remain also yet unclear. Antihistamines presently available on the market have been classified as first, second or third generation medications and they differ in the chemical structures and, pharmacodynamics³⁸. Data from *in vitro* and *in vivo* studies suggest that most second-generation antihistamines have anti-allergic and anti-inflammatory properties but first-generation antihistamines have also anti-allergic, anti-inflammatory properties³⁸⁻⁴⁰. Children in our study who reported intake of antihistamine medications over the follow-up period used the second generation histamines most frequently. It is thought that the mechanism of anti-inflammatory activity of antihistamine medications is not related to the H1 receptor-antagonist blockade, but rather from blocking the release of histamine from mast cells and other proinflammatory cytokines such as IL-5, IL-6, IL-8, TNF- α and GM-CSF from activating human lymphocytes⁴¹. Recent investigations also indicate that H1-antihistamines may modulate airway inflammation by down-regulating the activity of airway epithelial cells, which have an important role in allergic airway inflammation. The modulation of adhesion molecules and of inflammatory cell infiltration by H1-antihistamines may be beneficial in chronic subclinical inflammation of respiratory tract⁴¹⁻⁴³.

A limitation of this nine-year birth cohort study is the relatively small study sample, which covers 35% of the subjects enrolled at the entry and the fact that subjects not included in the follow-up did differ from participants in higher prenatal PAH exposure. This may eventually weaken the power and external validity of the study. The users of anti-histamine medication more often reported asthma and maternal allergy than those from the group of non-users and this could have had an impact on the internal validity, but neither maternal allergy nor child's asthma were related to lung function levels and these variables were inserted in the statistical models as potential confounders. Another weakness of the study is the fact that SPT were carried only once at ages 5 – 8. Although the medication data could not be compared with medical records, however, it should be emphasized that reported drugs were validated by visual examination of the medications. Strong points of our study include the prospective study design, which was based on precise individual objective measurements of prenatal and residential PAH exposure, annual measurements of lung function over the follow-up period, assessment of individual usage of antihistamine medications, and the ability to control important confounding variables in the analysis. In addition, a set of relevant confounders of the relationship between the intake of antihistamines and respiratory diseases were considered. Other potential confounders, such as maternal active tobacco smoking in pregnancy, using illicit drugs or chronic diseases of mothers, have been removed through entry criteria to the study.

In conclusion, the results of this analysis suggest that the intake of antihistamine medications in early childhood might mitigate the negative effect of fetal and postnatal PAH exposure on lung function and provides additional indirect evidence for the hypothesis that lung alterations in young children resulting from PAH exposure may be caused by the allergic inflammation within lung. While the reduction of ambient PAH levels should be the

first goal in prevention, antihistamine medications may have potential in treatment of children exposed to high concentrations of PAH.

Acknowledgments

This is part of an ongoing comparative longitudinal investigation on the health impact of prenatal exposure to outdoor/indoor air pollution in infants and children being conducted in New York City and Krakow. The study received funding from an RO1 grant entitled, "Vulnerability of the Fetus/Infant to PAH, PM_{2.5} and ETS" (5 RO1 ES10165 NIEHS; 02/01/00 - 01/31/04) and from the NIEHS (RO1 ES010165-0451). Principal investigator: Prof. FP Perera, Co-investigator: Prof. WA Jedrychowski. The study was also partly supported by the grant from the International Center for Research in Biommedicine, Luxembourg

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List of Abbreviations

DEP	diesel exhaust particles
ETS	environmental tobacco smoke
FEF₂₅₋₇₅	maximal mid expiratory flow over the middle 50% of the FVC
FEV₁	the amount of air that can be forcibly blown out in 1 second
FEV₀₅	the amount of air that can be blown out in 0.5 second
FVC	the total amount of air that can forcibly be blown out after a full inspiration
GEE	Generalized Estimation Equations
PAH	polycyclic aromatic hydrocarbons
PM	particulate matter

Figure 1. Mean predicted FEV₁ levels presented for the levels of the prenatal PAH exposure and the intake status of antihistamines in early childhood (linear fitting)

Figure 2. Mean predicted FEV₁ levels presented for the levels of the residential outdoor PAH exposure and the intake status of antihistamines in early childhood (linear fitting)

Table 1
Characteristics of the study sample compared with children not included in the analysis

Variables		Included in the study N =176	Not included N = 329	P for difference between groups
Maternal age:	mean	27.68	27.54	0.674
	SD	3.57	3.59	
Maternal education: (years of schooling)	mean	15.62	15.56	0.807
	SD	2.78	2.74	
Maternal allergy	n (%)	38 (21.59)	85 (25.91)	0.281
Parity: 1	n (%)	117 (66.48)	200 (60.79)	0.208
	2	59 (33.52)	129 (39.21)	
Gender: Boys	n (%)	85 (48.30)	173 (52.58)	0.358
	Girls	91 (51.70)	156 (47.42)	
Gestational age in weeks:	mean	39.29	39.35	0.699
	SD	1.73	1.48	
Term births (>36 weeks)	n (%)	168 (95.45)	316 (96.05)	0.816
Birth weight (g):	mean	3367.2	3419.5	0.249
	SD	508.41	473.98	
Prenatal PAH level in ng/m ³	gmean	20.25	27.70	0.005
	95% CI	17.03-24.09	24.33-31.53	
	missing	-	3	
Postnatal outdoor PAH level in ng/m ³	gmean	30.76	30.01	0.882
	95% CI	24.71-38.28	23.58-38.20	
	missing	-	187	
Season of postnatal PAH measurement (heating one):	n(%)	89 (50.57)	80 (53.69)	0.574
Prenatal ETS	n (%)	43 (24.43)	92 (27.96)	0.393
Postnatal ETS: n (%)	none	136(77.27)	61 (81.33)	0.540
	1-3years	29 (16.48)	12(16.0)	
	>3years	11 (6.25)	2 (2.67)	
	missing	-	254	
Children's atopy		37 (21.02)	23(14.02)	0.091
Asthma diagnosed or suspected by physician	n (%)	28(15.91)	23(13.45)	0.518

General characteristics of the study sample grouped by the use of antihistamine medication reported during the follow-up period

Table 2

Variables	Total N=176	Non-users of medication N=93	Users of medication N=83	P for difference between subgroups
Maternal age:				
mean	27.68	27.64	27.72	
SD	3.57	3.64	3.51	0.887
Maternal education: (years of schooling)				
mean	15.62	15.61	15.63	
SD	2.78	2.88	2.70	0.968
Maternal allergy (+)	38 (21.59)	14 (15.05)	24 (28.92)	0.026
Gender: Boys	85 (48.30)	44 (47.31)	41 (49.40)	0.782
Parity: 1	117 (66.48)	61 (65.59)	56 (67.47)	
2	59 (33.52)	32 (34.41)	27 (32.53)	0.792
Gestational age (weeks):				
mean	39.29	39.53	39.03	
SD	1.73	1.40	2.00	0.056
Term births (>36 weeks)	168 (95.45%)	91 (97.85%)	77 (92.77%)	0.151
Prenatal PAH(ng/m ³):				
gmean	20.25	19.55	21.01	
95% CI	17.03-24.09	15.26-25.05	16.41-26.90	0.683
Postnatal outdoor PAH (ng/m ³):				
gmean	30.76	36.82	25.48	
95% CI	24.72-38.28	27.64-49.05	18.26-35.57	0.097
Prenatal ETS:	43 (24.43%)	25 (26.88%)	18 (21.69%)	0.423
Reported postnatal ETS: n (%)				
none	136(77.27)	71 (76.34)	65 (78.31)	
1-3years	29 (16.48)	14(15.05)	15 (16.48)	
>3years	11 (6.25)	8 (8.60)	3 (3.61)	0.385
Children's atopy	37(21.02)	15 (16.13%)	22 (26.51%)	0.092
Asthma diagnosed or suspected by physician	28(15.91%)	9 (9.68%)	19 (22.89%)	0.015

Table 3
Disease and infection characteristics of the 5 - 9-year-old children under study, grouped by report of antihistamine medication use during the follow-up period

	Total N=176	Non-users of antihistamines N=93	Users of antihistamines N=83	P for difference between subgroups
Cough				
n (%)	174 (98.86)	88 (97.78)	86 (100.0)	0.497
Mean (SD) number of days with cough in 5-year period	117.4 (90.91)	92.4 (56.80)	143.1 (110.48)	0.0002
Wheezing				
n (%)	46 (26.14)	21 (23.33)	25 (29.07)	0.387
Mean (SD) number of days with wheezing in 5-year period	20.4 (46.05)	18.33 (20.21)	22.1 (46.05)	0.731
Difficult breathing				
n (%)	39 (22.16)	15 (16.67)	24 (27.91)	0.073
Mean (SD) number of days with difficult breathing in 5-year period	28.7 (62.82)	17.3 (23.08)	35.9 (77.83)	0.375
Laryngitis				
n (%)	74 (42.05)	33 (36.67)	41 (47.67)	0.139
Mean (SD) number of laryngitis episodes in 5-year period	2.3 (2.44)	2.8 (3.23)	1.9 (1.50)	0.326
Bronchitis				
n (%)	80 (45.45)	38 (42.22)	42 (48.84)	0.378
Mean (SD) number of bronchitis episodes in 5-year period	2.5 (1.67)	2.5 (1.72)	2.4 (1.64)	0.801
Pneumonia				
n (%)	28 (15.91)	14 (15.56)	14 (16.28)	0.896
Mean (SD) number of pneumonia in episodes 5-year period	1.5 (0.92)	1.6 (1.15)	1.4 (0.65)	0.548
Sore throat/angina				
n (%)	146 (82.95)	70 (77.78)	76 (88.37)	0.062
Mean (SD) number of sore throat /angina episodes in 5-year period	4.5 (3.69)	3.5 (2.55)	5.4 (4.30)	0.001

Table 4

Comparison of spirometric results standardized to sex, height and age (means, 95% CI) obtained in the study sample (N = 176) with percent predicted values estimated from the total number of children who performed acceptable lung function tests (N = 307).

	FVC		FEV ₁		FEV _{0.5}		FEF ₂₅₋₇₅	
	Observed [ml]	percent predicted	Observed [ml]	percent predicted	Observed [ml]	percent predicted	Observed [ml/s]	percent predicted
Age 5	1080.8 (1026.2-1135.4)	96.2 (92.0-100.4)	1045.0 (995.8-1094.3)	97.5 (93.7-101.3)	852.4 (810.6-894.3)	100.8 (96.9-104.8)	1668.4 (1558.3-1778.6)	105.4 (99.2-111.5)
Age 6	1380.4 (1331.7-1429.2)	104.4 (101.3-107.5)	1301.6 (1256.3-1346.9)	103.6 (100.8-106.5)	1008.7 (967.6-1049.8)	103.9 (100.5-107.3)	1805.1 (1698.6-1911.5)	101.6 (96.3-107.0)
Age 7	1541.3 (1499.8-1582.7)	100.7 (98.4-103.0)	1457.5 (1416.9-1498.1)	100.7 (98.4-103.0)	1097.5 (1060.7-1134.4)	99.6 (96.7-102.4)	1954.1 (1864.8-2043.4)	99.0 (94.9-103.1)
Age 8	1723.7 (1674.6-1772.8)	100.6 (98.5-102.6)	1629.0 (1584.6-1673.5)	101.0 (99.0-103.0)	1226.5 (1188.9-1264.1)	101.1 (98.5-103.7)	2161.1 (2077.8-2244.5)	101.3 (97.7-104.9)
Age 9	1846.3 (1801.6-1891.0)	99.1 (97.3-100.9)	1734.1 (1689.6-1778.7)	99.1 (97.4-100.9)	1301.9 (1263.3-1340.6)	99.7 (97.5-101.9)	2256.4 (2161.1 2351.8)	99.4 (95.8-103.0)
Total	1574.5 (1543.7-1605.2)	100.3 (99.2-101.4)	1488.1 (1459.6-1516.6)	100.4 (99.4-101.5)	1132.8 (1110.8-1154.8)	100.8 (99.6-102.1)	2017.5 (1971.2 2063.7)	100.9 (99.0-102.8)

Table 5

Interaction terms between PAH exposure (prenatal and residential) as continuous variable and using anti-histamine drugs (A-h) as nominal variable (Yes/No) estimated from the multivariable GEE models adjusted for potential confounders (gestational age, sex, postnatal ETS, parity, maternal allergy, season of the residential pollution survey, child's asthma, and atopy) in the total study sample (N = 176)

		Coef.	Std. Err.	z	P>z	[95% Conf. Interval]
FVC						
Prenatal PAH (ln-transformed) x A-h treatment		49.83	22.75	2.19	0.028	5.25
Residential PAH (ln-transformed) x A-h treatment		35.06	18.28	1.92	0.055	-0.76
FEV ₀₅						
Prenatal PAH (ln-transformed) x A-h treatment		38.63	18.84	2.05	0.040	1.70
Residential PAH level in ug/m3 (ln-transformed) x A-h treatment		35.29	15.14	2.33	0.020	5.62
FEV ₁						
Prenatal PAH (ln-transformed) x A-h treatment		49.52	20.61	2.40	0.016	9.12
Residential PAH (ln-transformed) x A-h treatment		36.39	16.57	2.20	0.028	3.92
FEF ₂₅₇₅						
Prenatal PAH (ln-transformed) x A-h treatment		43.27	54.39	0.80	0.426	-63.33
Residential PAH (ln-transformed) x A-h treatment		67.33	43.77	1.54	0.124	-18.46
						153.13

Table 6

Modifying effects of antihistamine medication on lung function associated with prenatal and residential outdoor PAH exposure level (ln-transformed), adjusted for gestational age, gender, height, postnatal ETS exposure, maternal allergy, atopy and asthma in child and season of residential air pollution survey

Non-users of anti-histamines (N = 93)						
FVC	Coef.	Std. Err.	z	P>z	95% Conf. Interval	
Prenatal PAH (ln)	-38.57	16.58	-2.33	0.020	-71.08	-6.07
Residential PAH (ln)	-22.01	21.27	-1.03	0.301	-63.69	19.68
FEV₀₅						
Prenatal PAH (ln)	-27.59	13.09	-2.11	0.035	-53.25	-1.93
Residential PAH (ln)	-37.74	16.79	-2.25	0.025	-70.64	-4.84
FEV₁						
Prenatal PAH (ln)	-36.14	14.94	-2.42	0.016	-65.41	-6.86
Residential PAH (ln)	-39.93	19.16	-2.08	0.037	-77.48	-2.38
FEF₂₅₋₇₅						
Prenatal PAH (ln)	-39.927	38.799	-0.85	0.394	-108.972	43.117
Residential PAH (ln)	-88.810	49.814	-1.78	0.075	-186.444	8.824
Users of anti-histamines (N=83)						
FVC	Coef.	Std. Err.	z	P>z	95% Conf. Interval	
Prenatal PAH (ln)	12.89	15.04	0.86	0.391	-16.59	42.38
Residential PAH (ln)	23.06	21.70	1.06	0.288	-19.47	65.60
FEV₀₅						
Prenatal PAH (ln)	10.02	13.79	0.73	0.468	-17.01	37.04
Residential PAH (ln)	17.68	19.93	0.89	0.375	-21.39	56.75
FEV₁						
Prenatal PAH (ln)	11.88	14.14	0.84	0.401	-15.84	39.60
Residential PAH (ln)	20.71	20.43	1.01	0.311	-19.33	60.75
FEF₂₅₋₇₅						
Prenatal PAH (ln)	0.606	39.726	0.02	0.988	-77.257	78.468

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Non-users of anti-histamines (N = 93)					
Residential PAH (ln)	39.027	57.617	0.68	0.498	-73.900
					151.954