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SEPARATE AND JOINT EFFECTS OF TRANPLACENTAL AND POSTNATAL INHALATORY EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS. PROSPECTIVE BIRTH COHORT STUDY ON WHEEZING EVENTS

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Abstract

The goal of this epidemiologic investigation was to analyze the associations between prenatal and postnatal exposure to airborne polycyclic aromatic hydrocarbons (PAH) and severity of wheeze and recurrent wheeze. The 257 children included in this analysis had a complete set of prenatal and postnatal PAH measurements and attended regular health checkups over a four-year follow-up period since birth. Transplacental PAH exposure was measured by personal air monitoring of the mothers during the second trimester of pregnancy; postnatal exposure was estimated using the same instruments indoors at the children's residences at age 3. Chemical analysis tests were performed to determine airborne concentrations of nine PAH compounds.

The results show that both prenatal and postnatal exposure were associated positively with the severity of wheezing days and recurrent wheezing reported in the follow-up. While the IRR (incidence rate ratio) for severity of wheeze and prenatal PAH exposure was 1.53 (95%CI: 1.43 – 1.64) that for postnatal PAH exposure was 1.13 (95%CI: 1.08 – 1.19). However, recurrent wheezing was more strongly associated with airborne PAH levels measured at age 3 (OR= 2.31, 95%CI: 1.26 – 4.22) than transplacental PAH exposure (OR = 1.40, 95% CI: 0.85 – 2.09), but the difference was statistically insignificant.

In conclusion, it appears that prenatal PAH exposure may precipitate and intensify early onset of wheezing symptoms in childhood, resulting from the postnatal exposure and suggest that success in reducing the incidence of respiratory diseases in children would depend on reducing both fetal and childhood exposure to air pollution.

Keywords

birth cohort study; wheezing; prenatal and postnatal PAH exposure

Introduction

There has been a lengthy debate on the nature and meaning of early wheezing for respiratory health of children and in the course of adult life. Wheezing is a heterogeneous syndrome, which usually starts in early childhood and may occur in sporadic or recurrent forms. It originates in airways which may be narrowed by compression or by intrabronchial or intraluminal obstruction (inflammatory mucosal edema, secretions or spasm), which causes an increase in velocity of gas through them with resultant oscillation (1). Lower respiratory illnesses in infancy has been proposed as a cause of a chronic wheezing tendency (2 – 5) and it is presumed that frequent and recurrent episodes of chest wheezing in early life may lead to asthma, persistent lung damage and a long-standing susceptibility to all forms of lung disease in adulthood (6–7).

While wheezing may have a variety of causes of environmental origin, a number of recent epidemiologic studies focused on the occurrence of respiratory disorders in the context of traffic-related toxicants and provided evidence of the effect of diesel exhaust particles (DEP) as a critical factor for the onset of wheezing and airway allergic disease in children (8 – 12). DEP, which contain a wide spectrum of PAH are common atmospheric pollutants derived from diesel engine powered vehicles. Major indoor sources of PAH air compounds include 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 food (13 – 18).

The biological importance of PAH compounds in the context of respiratory health in children stems from the fact that they represent environmental immunotoxic contaminants, which have inflammatory effects and can promote the development of allergy (19). PAH compounds readily cross the placenta, and both experimental and epidemiologic observational studies have reported their harmful impact on fetal development (20 – 22). Although there is already a strong epidemiologic evidence linking prenatal exposure to PAH with respiratory health of children, little research has been conducted on the effects of prenatal determinants of respiratory health in early childhood resulting from transplacental exposure to PAH in comparison to the effect of exposure to airborne PAH compounds during the postnatal period.

Our previous studies showed that prenatal PAH exposure was associated with increased risk of wheezing episodes in infancy (23), but the important question remained as to the extent to which prenatal effects may be reversible and how they may be modified by the PAH exposure later in childhood. Therefore, the main purpose of the study was to compare the impacts of prenatal and postnatal airborne PAH compounds on wheezing events in 4-year old children, who have regularly been monitored since birth. The fetal individual PAH exposure was measured indirectly by personal air monitoring of mothers during the second trimester of pregnancy; postnatal exposure was assessed with the same instruments indoors

of the children's residences children at the age of 3. As the children spend most of their time indoors, indoor PAH level measured at the age of 3 was chosen an indicatory marker of postnatal exposure. The second trimester was preferred as it marks the halfway period of pregnancy and is characterized by a dramatic increase in the fetal growth rate. From then on, the fully developed placenta provides all the fetus' needs until birth; however, this may also create favorable conditions for toxicants absorbed by mother to cross the placenta and place the fetus at risk. In our analyses, the effects of prenatal and postnatal PAH exposure were adjusted for potential confounders, such as gender of child, season of birth, presence of older siblings, maternal education and maternal atopy, prenatal and postnatal ETS, and season of PAH indoor measurements.

Material and methods

This is the part of an ongoing longitudinal investigation on the health impact of prenatal exposure to outdoor/indoor air pollution in infants and children from the Krakow inner city area; the detailed description of the study design has been presented elsewhere (24). In short, pregnant women were recruited from ambulatory prenatal clinics in the first or second trimester of pregnancy. The study included women between 18 and 35 years of age, who claimed to be non-smokers, with singleton pregnancies, without illicit drug use and HIV infection, free from chronic diseases such as diabetes or hypertension, and resident in Krakow for at least one year prior to pregnancy. All women participating in the study had read and signed an informed consent. The Jagiellonian University Bioethical Committee approved the research.

Upon enrollment, a detailed questionnaire was administered to each subject to elicit information on demographic data, house characteristics, medical history of mothers, and smoking practices of others present in the home. 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.

After delivery, newborns were followed-up every three months over the first 2 years of life and in 6-month intervals later. Trained interviewers carried out detailed face-to-face standardized interviews on children's health at each home visits. All interviews were performed with the mothers of infants. Reported wheezing or whistling within the chest irrespective of respiratory infection was the main health outcome chosen for this analysis and its severity was defined by the overall number of wheezing days experienced by the child. Children were also assigned to recurrent wheezing phenotype defined by an excessive number of wheezing events (above 90th percentile, i.e. 20 or more wheezing days reported over the 4-year follow-up). Out of 505 newborns initially enrolled to the study, 257 have participated in all 12 health visits. The study sample did not differ in respect of important characteristics from the children not included (see Table 1).

Dosimetry of prenatal and postnatal exposure to PAH

The monitoring of pregnant women for personal exposure to airborne PAH and fine particles was carried out over a 48-hour period (working days) during the second trimester of pregnancy. The women were instructed by a trained staff member how to use a personal monitor and asked to wear the monitoring device during the daytime hours for two consecutive days and to place it near the bed at night. On the second day, the air monitoring staff assistant and interviewer visited the study participant's home to change the battery-pack and to complete the questionnaire on household characteristics.

For the indoor and outdoor residential air monitoring a Personal Environmental Monitoring Sampler (PEMS) was used to measure both PAH and particle mass collected on the PEMS Teflon membrane filter (37 mm Teflo, Gelman Sciences). The single pump/two impactors sampling method was developed at Harvard School of Public Health (Dr J. Spengler) and may be used to measure particles and gases. For the measurement of gaseous PAH compounds, the sampling pump draws air through a polyurethane (PUF) sampler. After sampling, the field samplers were frozen and shipped on dry ice to South-West Research Institute in Texas, where the chemical procedures in the analysis of the collected samples are described elsewhere (25). In the analysis concentrations of total PAH compounds were exposure variables.

Statistical analysis

The purpose of the statistical analysis was to assess the separate and combined effects of prenatal and postnatal PAH exposure on the cumulative number of wheezing days reported over the follow-up and the occurrence of recurrent wheezing phenotype (20 or more wheezing days in the follow-up). In the initial descriptive analysis, the differences in continuous variables between participants and non-participants groups under study were analyzed using a one-way analysis of variance; differences in the frequencies of categorical variables were evaluated with the Chi-square test. As the distribution of PAH concentrations were skewed to the right, values were natural log transformed to normalize the distribution. PAH levels are provided as geometric mean values (average after ln-transformation, followed by back transformation) together with 95% confidence intervals.

The association between the cumulative number of wheezing days and exposure variables was assessed by incidence rate ratios (a ratio based on the incidence of counts of wheezing events) estimated by the zero-inflated Poisson regression model (ZIP), which better fits the overdispersed count Poisson data with excess of observed zeros (null observations) than the traditional Poisson regression model. With the Vuong test the significant preference of the ZIP model over the standard Poisson model was assessed. The zero-inflated regression estimates two sets of parameters: one set for the "logistic portion" (the parameters of the regression models for the probability of extra zeros using the logistic function) and another set for the "Poisson portion" (the parameters of the Poisson regression model). For easy interpretation, the parameters of the first set are presented as odds ratio (OR) and those of the second set as incidence rate ratios (IRR); both come with 95% confidence intervals. The dependent variable was count of total number of wheezing days reported in the follow-up period (0, 1, 2, 3, 4, etc.). In the regression models, a set of potential confounders or

modifiers (gender of child, season of birth, parity, maternal education, maternal atopy, prenatal or postnatal exposure to PAH, ETS exposure) were taken into consideration. The association between recurrent wheezing and exposure was assessed by ORs estimated with the stepwise multivariable logistic model. All statistical analyses were performed using the statistical software STATA version 12.1.

Results

The median concentration of total airborne PAHs in personal maternal air samples (prenatal exposure) was 19.3 ng/m³. Air pollution survey carried out outdoors and in children's homes at age 3 showed that the median PAH concentrations outdoors were 25.2 ng/ m³ and 16.7 ng/ m³ indoors; the corresponding values for PM_{2.5} were 29.8 and 28.1 µg/ m³. There was a substantial seasonal variation of concentrations of air pollutants under study and their average levels were 5–7 times lower in the warm season. The PAH levels of indoor and outdoor levels were strongly correlated with each other in both heating and non-heating seasons (Figure 1). Concentrations of PM_{2.5} also significantly correlated with outdoor and indoor PAH levels. Major contribution for indoor PAH levels could be attributed to outdoor PAH concentrations and ETS (number of cigarettes smoked daily at home). Gas cooking had much lower impact on the PAH indoor concentrations (Table 1).

The characteristics of the newborns who participated in the four-year follow-up did not differ from the group who did not have all follow-up visits, except for a significantly higher prenatal PAH level in the group of non-participants (Table 2). On average, 40% of children reported wheezing events at some time in the follow-up period and 10% reported recurrent wheezing. Distribution of wheezing days in the study sample was presented in Figure 2. As a rule, the wheezing symptoms were reported more frequently in the first year of life and their prevalence decreased in the subsequent years. The number of wheezing days reported was higher in the groups of children with both high prenatal and postnatal PAH exposure compared with the rest (Table 3).

In order to assess the effects of prenatal and postnatal exposure on the occurrence of wheezing days we applied the ZIP multivariable regression model (Table 4). The Poisson portion of the analysis showed that the frequency of wheezing was significantly associated with both prenatal (IRR = 1.12, 95%CI: 1.07 – 1.18) and postnatal PAH exposure (IRR = 1.08, 95%CI: 1.02 – 1.14), but the difference between the effects was not significant (Chi-square = 1.26, P<0.263). Out of the covariates included in the model beside the gender of children, the birth season (IRR =11.48, 95%CI 1.27 – 1.59), gestational age (IRR =1.05, 95%CI: 1.03 – 1.08), and maternal atopy (IRR = 1.58; 95%CI: 1.14 – 1.39) increased the incidence risk ratio, however maternal education was related inversely with IRR. The interaction term between both exposure periods was insignificant (p<0.05). In the statistical analysis, ETS variables were dropped from the regression models since they failed to help explain the variation between health outcomes and exposure variables. The logistic portion of the model showed that the parity had a negative effect on the excessive number of zero outcomes, i.e., non-wheezers (OR = 0.61, 95%: 0.41 – 0.91). Figure 3 visualizes the predictive margins for wheezing days and joint effect of prenatal and postnatal PAH

exposure and shows that predicted adjusted means of wheezing events resulting from inhalation exposure in the follow-up depend on prior PAH exposure in the fetal period.

Table 5 summarizes the results of multivariable stepwise logistic regression model for recurrent wheezing phenotype related to prenatal and postnatal PAH exposures adjusted for a set of covariates. The latter analysis showed that the effect of prenatal PAH exposure was at the borderline significance level (OR = 1.40; 95%CI: 0.97 – 2.03) and confirmed a significant effect of postnatal exposure (OR= 1.61; 95%CI: 1.16 – 2.24). However, the difference between the effects was insignificant (Chi-square = 0.57, $p = 0.451$). Figure 4 illustrates changes in the dose-response pattern for PAH and recurrent wheezing at various levels of prenatal and postnatal total PAH exposure. It again indicates that the prenatal PAH level modifies the likelihood of recurrent wheezing in the postnatal period.

Discussion

To our knowledge, this is the first epidemiologic cohort investigation in which the associations between wheezing events and separate and joint effects of transplacental (prenatal) and postnatal PAH (indoor) exposure measured individually for each child were analyzed in the course of the prospective birth cohort study. We found that both exposures were associated positively with the frequency of wheezing days and recurrent wheezing in early childhood. Our results may suggest that the effect sizes of prenatal and postnatal PAH exposure on the wheezing events observed over 4 years was about the same, though airborne PAH compounds inhaled in the postnatal period have exerted their effect directly on the bronchial tract over a long period (four years). In contrast, the estimated dose of absorbed ambient toxicants by the fetus is about 10 times lower than that received by mother, and takes place for the relatively short period of gestation. Moreover, respiratory tract symptoms induced by prenatal exposure could have resulted only from the indirect biologic action of absorbed toxic compounds, most likely through immunotoxic effects. Observed different patterns for the dose-response curves for postnatal PAH exposure at various prenatal PAH levels suggest that the prenatal exposure may modify the likelihood of wheezing events resulting from inhalation exposure. This may mean that young children have an efficient defense capacity or a repair ability against bronchial damage up to a certain inhaled PAH dose, but this ability is limited to some extent if the child had previously been affected by higher prenatal PAH exposure.

Although the biological mechanisms whereby transplacental PAH might cause adverse respiratory health 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 DNA damage and forming PAH-DNA adducts (27, 28). Recent studies also provided evidence that prenatal PAH also cause epigenetic changes. For example, in NYC cohort study, it was found that global DNA methylation levels in cord blood white blood cells decreased with increasing prenatal PAH exposure and global DNA methylation levels in cord blood were positively correlated with levels of PAH-DNA adducts in cord blood (29, 30). In addition, a number of studies demonstrated that inhibited production of immunocompetent cells is likely to be one of the main mechanisms contributing to the immunosuppression caused by PAH, and documented that PAH inhibit the differentiation of human monocytes and

macrophages and induces apoptosis of both pre-T cells in the thymus and pre-B cells in the bone marrow (31–35). This may account for thymic atrophy and decreased cell recovery from the spleen, lymph nodes, and bone marrow in PAH- exposed experimental animals (36 – 39). Moreover, mature differentiated immune cells also constitute targets for PAH. Immunotoxic effect of PAH compounds impairing immune fetal function may explain the increased susceptibility of newborns and young children to viral respiratory infections and recurrent wheezing episodes.

Inhaled PAH compounds 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, (40 – 43) and enhance local mucosal IgE production and deviate cytokine production toward a Th2 profile (44). A well-established ability of PAH compounds to generate reactive oxygen species can initiate a oxidative stress cascade that leads to airway inflammation (45).

Prevalence of wheezing observed in our study amounted to 40% and it would be in the higher range of rates reported worldwide. The recently published review compared prevalence of wheezing symptoms in children, which included not only ISAAC but also all non-ISAAC studies (46). The highest prevalence rates of current wheezing were reported in the UK (32.2%), Australia (29.7%) and New Zealand (30.2%), and the lowest prevalence (less than 10%) was found in Albania, China, Ethiopia, Indonesia and Turkey. A nationwide survey in the USA between 1988–1994 showed that the current prevalence of wheezing amongst 2–3 year olds was 26.4% (47).

The observed differential effect of the separate and joint prenatal and postnatal PAH exposure may explain the development of an unequal respiratory health burden in various population groups and various time trends in different communities (48 – 51). As it is presumed that frequent and recurrent episodes of chest wheezing in early life may lead to asthma, persistent lung damage and a long-standing susceptibility to all forms of lung disease in adulthood, our study results may shed more light on the nature of the epidemic increase in asthma and respiratory infections worldwide. In this sense, the study would strongly support David Baker's hypothesis that the environmental factors "programme" particular body systems during critical periods of fetal growth, with long term consequences in later life (52, 53). The extent to which prenatal effects can be modified by later experience is a crucial question for public health policy. An alternative model hypothesizes that chronic disease reflects cumulative prenatal and postnatal exposure to damaging factors, but these two life course models are not mutually exclusive as they operate simultaneously and this must be considered in establishing public health policy guidelines.

The weakness of our study results from the relatively short follow-up period and a limited size of the subsample of children who fully participated in the four-year follow-up and took part in all 12 health check-ups and for whom postnatal PAH data were available. However, the subsample was representative of the parent study sample recruited initially to the study except for a higher prenatal PAH level in those who did not complete the follow-up. On the other hand, the study has a number of strengths including the measurement of individual

prenatal PAH exposure, which integrates various sources of exposure. Repeated measurements of indoor PAH level performed within each household also provide a measure of individual postnatal exposure. Previous studies have mostly quantified the concentration of air pollutants measured in the residence area, and assigned exposure values to the study subjects as approximate individual exposures. Another strong point of our study is the very careful monitoring of respiratory health outcomes in children performed by trained interviewers at all time points over the follow-up. Moreover, the important potential confounders of the relationship between exposure variables and respiratory health outcomes such as active tobacco smoking and chronic maternal diseases were removed through selection criteria. Other risk factors that are thought to affect the probability of recurrent wheezing in children (maternal atopy, older siblings, season of birth) and maternal care of children (maternal education) have been considered in the analysis.

Summing up, prenatal PAH exposure may be thought as a trigger for early wheezing symptoms, and postnatal PAH exposure appears to be a complementary factor for their exacerbations and recurrence in later life. However, due to difficulty of separating the prenatal effect size from that of postnatal PAH exposure, a cautious interpretation of results should be considered. Nevertheless, evidence from our study on the increased rate of recurrent wheezing in children exposed both prenatally and postnatally to PAH compounds suggests that success in reducing incidence of diseases in children and probably also in adults depends on how effectively we can protect children in the fetal period as well as the early years.

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Table 1

Results of multivariable linear regression for indoor PAH levels in-transformed and potential sources of exposure.

Predictors	Heating season ($R^2=0.87$)			Non-heating season ($R^2=0.80$)		
	B	Std. err.	p	B	Std. err.	p
In (Outdoor PAH level)	0.923	0.037	0.000	0.740	0.035	0.000
Outdoor temperature	0.120	0.052	0.022	0.001	0.055	0.973
Cigarette smoking at home						
None						
Less than 10 cigarettes	0.231	0.111	0.038	0.078	0.071	0.273
10 or more cigarettes	0.291	0.089	0.001	0.235	0.069	0.001
Residential block of flats	0.124	0.017	0.068	0.078	0.040	0.054
Cooking appliances used						
Electric cooker						
Gas cooker	0.096	0.055	0.084	0.059	0.045	0.194

Table 2

Characteristics of the children who had all full 4-yr follow-up (completed all 12 health check-ups) and children who did not complete the follow-up

Variables	Follow-up completed N=257	Follow-up uncompleted N=248	Total N= 505	P for difference
Maternal age(yrs):	mean SD	27.81 3.573	27.37 3.578	0.1682
Maternal education (yrs):	mean SD	15.60 2.743	15.55 2.773	0.8364
Maternal allergy (+):	n (%) Missing data	64 (24.9) 0	59 (23.9) 1	123 (24.4) 1
Older siblings (number):	0 1	163 (63.4) 94 (36.6)	154 (62.1) 94 (37.9)	317 (62.8) 188 (37.2)
Gender:	Boys Girls	126 (49.0) 131 (51.0)	132 (53.2) 116 (46.8)	258 (51.1) 247 (48.9)
Gestational age:	mean SD	39.35 1.725	39.31 1.395	39.33 1.570
Birth weight (g):	mean SD	3393.5 515.86	3409.3 454.76	3401.3 486.40
Prenatal ETS (+)	n (%)	69 (26.8)	66 (26.6)	135 (26.7)
Postnatal ETS (+)	n (%)	88 (34.2)	-	-
Residence area:	1- outer 2- center	207 (80.5) 50 (19.5)	194 (78.2) 54 (21.8)	401 (79.4) 104 (20.6)
Prenatal PAH (ng/m ³):	mean SD Missing data	44.60 54.28 0	62.42 78.74 50	52.35 66.56 50
Postnatal indoor PAH (ng/m ³): at the age 3	mean	41.23	51.41	43.26
				0.2105

Variables		Follow-up completed N=257	Follow-up uncompleted N=248	Total N= 505	P for difference
	SD	59.60	51.24	58.10	
	Missing data	0	184	184	

Table 3

Mean number of wheezing days reported in children over the follow-up (in wheezers) grouped by the level of prenatal (in tertiles) and postnatal indoor PAH exposure (by median)

	Number of non-wheezers	Number of wheezers	Mean number of wheezing days	Standard error
A. Low indoor PAH exposure (≤ 16.9 ng/m³)				
Prenatal PAH				
1. <12.0	19	13	13.8	4.0
2. 12.1 – 46.3	24	21	13.3	3.1
3. <46.3	42	22	24.0	6.0
B. High indoor PAH exposure (>16.9 ng/m³)				
Prenatal PAH				
1. <12.0	41	27	24.3	7.2
2. 12.1 – 46.3	20	13	21.2	7.9
3. >46.3	9	6	27.2	11.6

Table 4

Adjusted effects of prenatal and postnatal PAH exposure on the occurrence of wheezing reported in children over the 4-year follow-up. Zero-inflated Poisson multivariable model

Poisson portion	IRR	z	P>z	95% Conf.Interval	
Prenatal PAH (ln)	1.12	5.00	0.000	1.07	1.18
Postnatal PAH (ln)	1.08	2.48	0.013	1.02	1.14
Birth season *	1.42	6.24	0.000	1.27	1.59
Season of indoor PAH measurements *	1.20	1.93	0.054	1.00	1.44
Gestational age (weeks)	1.05	4.03	0.000	1.03	1.08
Sex (girls)	1.28	5.42	0.000	1.17	1.40
Maternal education (years of schooling)	0.94	-8.12	0.000	0.92	0.95
Maternal allergy (y/n)	1.58	9.63	0.000	1.44	1.73
Asthma (y/n)	1.11	1.19	0.236	0.93	1.33
Older siblings (number)	1.00	-0.04	0.968	0.94	1.06
Logistic portion	OR	z	P>z	95%Conf. interval	
Prenatal PAH (ln)	0.99	-0.05	0.958	0.71	1.28
Postnatal PAH (ln)	0.86	-0.73	0.465	0.58	1.28
Birth season *	1.82	1.89	0.059	0.98	3.35
Season of indoor PAH measurements *	1.04	0.07	0.943	0.36	3.00
Gestational age (weeks)	1.05	0.71	0.476	0.91	1.22
Sex (girls)	1.28	0.96	0.339	0.77	2.16
Maternal education (years of schooling)	0.96	-0.87	0.386	0.87	1.05
Maternal allergy (y/n)	0.97	-0.09	0.931	0.94	1.77
Older siblings (number)	0.61	-2.45	0.014	0.41	0.91

Vuong test of ZIP regression vs. standard Poisson method: z = 6.81 Pr>z = 0.0000

* / 0: non-heating; 1: heating season

Table 5

Effect of prenatal and postnatal indoor PAH exposure on recurrent wheezing reported in children over the 4yr-follow-up. Stepwise multivariable logistic regression (p for variable entry 0.1)

Predictors	Odds Ratio	Std. Err.	z	P>z	95% Conf.Interval	
Prenatal PAH (ln_transformed)	1.40	0.26	1.81	0.071	0.97	2.03
Postnatal PAH exposure (ln-transformed)	1.61	0.27	2.81	0.005	1.16	2.24
Asthma (y/n)	7.80	6.83	2.34	0.019	1.40	43.47
Older siblings (number)	2.16	0.55	3.04	0.002	1.31	3.56