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Wheezing and lung function measured in subjects exposed to various levels of fine particles and polycyclic aromatic hydrocarbons

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Abstract: The main purpose of the study was to assess the occurrence of wheezing and lung function in non-smoking women exposed to various levels of fine particulate matter(FP) and polycyclic aromatic hydrocarbons (PAH). Out of the total study group, 152 women were included in the lower exposed group ($PM_{2.5}$ $\leq$34.3μg/m^{3}or PAHs $\leq$ 22.9ng/ m^3) and 96 persons in higher concentrations of both air pollutants ($PM_{2.5}$>34.3μg/m^{3}and PAHs > 22.9ng/ m^3). Except for FVC and FEV1, all lung forced ventilatory flows (PEFR, $FEF_{25\%}$ $FEF_{50\%}$, $FEF_{75\%}$, $FEF_{25-75\%}$) were significantly lower in the higher exposed group. The findings suggest bronchoconstriction within the respiratory tract, which may be related to the exposure under study. This was consistent with a higher prevalence of wheezing in more exposed subjects. It was shown that higher levels of both pollutants increased the risk of wheezing by factor 5.6 (95% CI: 1.77-17.8) after accounting for potential confounders such as allergic diseases and exposure to ETS. This study suggests that pollutants in question may have the capacity to promote broncho-constriction and asthmatic symptoms, possibly by bronchial inflammation resulting from the exposure.

Keywords: Personal exposure, fine particles, polycyclic aromatic hydrocarbons, lung function, wheezing

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1 Introduction

There is a large body of evidence that air pollution, even at low levels, could have various adverse health effects. In fact, many epidemiological studies demonstrated that air pollutants, like particulate matter, sulphur dioxide, and nitrogen oxides are related to acute and chronic respiratory effects [1–11], a decrease in pulmonary function [12–15], an increase in mortality from cardiovascular diseases and from lung cancer [16–26]. An excellent reanalysis of time-series studies on air pollution and health was recently published by the Health Effects Institute [27].

Most previous epidemiological respiratory studies have focused on health effects of coarse particulate matter or black smoke, however epidemiologic data on the effect of fine particles on the respiratory tract are limited. However, fine particles with diameters less than about 2.5 μm are more likely than large particles to be inhaled and to penetrate deep into lungs. Moreover, most organic aromatic compounds in ambient air are usually absorbed onto fine particulate matter and the correlation is often so high that it may be extremely difficult to disentangle separate effects. Specific classes of organic compounds identified with airborne particular matter include polycyclic aromatic hydrocarbons (PAH) and aliphatic hydrocarbons. Of all the airborne organic compounds, the polycyclic organic matter compounds - particularly polycyclic hydrocarbons – have received the most attention because many of these compounds are potent carcinogens. However, experimental evidence indicates that airborne PAH may also have proinflammatory effects on airways, however, literature offers insufficient supporting evidence of their effects on asthma or lung function [28].

In air pollution epidemiology, exposure assessment is traditionally based on fixed site measurements in ambient air. However, in our study, the total integrated personal exposure of subjects was assessed and this is considered a more accurate estimate of the subject's exposure. Air pollution concentrations measured at outdoor fixed sites may correlate poorly with personal exposure because pollutants are also generated indoors by routine household activities, including cooking, cleaning and laundry, and smoking. If the variation in outdoor concentrations is weakly linked to personal exposures, use of outdoor concentrations as a surrogate for personal exposure would tend to misclassify personal exposures and exposure-response relationships would be attenuated.

The main purpose of the study was to describe the occurrence of wheezing and assess lung function in subjects exposed to various levels of fine particulate matter and PAHs. in the cohort of non-smokers. Unlike other studies, the current assessment of environmental hazards was based on the total personal exposure to air pollutants.

2 Statistical methods and Experimental Procedures

2.1 Patients

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 design and detailed population selection of this study have been described previously [29]. The Ethical Committee of Jagiellonian University approved this study. The cohort in the present analysis consisted of 248 women who gave birth to babies at 34-43 weeks of gestation between January 2001 and March 2003 and were requested to undergo spirometric testing and interviewing six months after delivery. Women attending ambulatory prenatal clinics in the first and second trimesters of pregnancy were eligible for the study. Enrollment included only non-smoking women free from chronic diseases such as diabetes and hypertension with singleton pregnancies ages 18-35 years. Recruited women were interviewed and given a description of the study and requirements for participation in the project. A detailed questionnaire was administered to each subject upon the entry to the study and in the third trimester to solicit information on demographic data, house characteristics, date of the last menstrual period (LMP), medical and reproductive history, occupational hazards, alcohol consumption, and smoking practices of other individuals present in the home. Data about respiratory health were collected by personal interviewing carried out before spirometric testing. Information about wheezing symptoms was derived from the question "in the last six months have you ever had wheezing ?". If "yes", "how many episodes and over how many days did the symptoms occur?" Questions about allergy symptoms were "in the last six months have you ever had hay fever?", and "in the last six months have you ever had eczema? ".

Spirometric measurements of forced lung volumes such as FVC (Forced Expiratory Capacity) and FEV_1(Forced Expiratory Volume in one second)were measured. In addition, forced ventilatory flows such as PEFR, $FEF_{25\%}$ $FEF_{50\%}$, $FEF_{75\%}$, $FEF_{75\%}$, and $FEF_{25-75\%}$ were calculated from the spirograms [30]. All spirometric measurements were carried out in women 6 months after delivery with a computerized PC QRS Card Spirometer. The spirometer program chose the best flow out of three blows executed by each subject and recorded the spirometric indices corrected to BTPS. The spirometric measurements were carried out according to the guidelines of the British Thoracic Society [31]. Each day, prior to the lung function examination, the spirometer was calibrated with a one-liter syringe. A single trained technician performed all spirometer testing.

2.2 Dosimetry of personal exposure to $PM_{2.5}$ and PAH

Once a woman was enrolled, a member of the air monitoring staff instructed the woman in the use of the personal monitor, which is lightweight, quiet and worn in a backpack. The woman was asked to wear the monitor during daytime hours for 2 consecutive days and to place the monitor near her 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 administered the full questionnaire. They also checked to see that the monitor had been running continuously and that there were 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.

Personal monitors draw air at a constant flow rate of 4 liters per minute (LPM). The inlet of the pump is attached to a two-way flow splitter, consisting of tubing with different amounts of flow restriction for each of the paths. One path (with a flow rate of 2 LPM) is for the PAH sampler and the other path (with a flow rate of 2 LPM) is for $PM_{2.5}$ sampler. Flow rates are calibrated (with filters in place) using the Bios flow meter prior to monitoring and are checked again with a change of the battery pack on the second day and at the conclusion of monitoring. The Personal Environmental Monitoring Sampler (PEMS) was used to measure particle mass. The PEMS is designed to achieve the particle target size of ≤ 2.5 μm at a flow rate of 4.0 LPM with an array of 10 impactor nozzles. To modify the sampler to achieve the 2.5 μm size cut at 2 LPM, 5 of the nozzles were blocked. Particles were collected on the same type of Teflon membrane filter (37 mm Teflo^{TM}, Gelman Sciences). The combination of low pressure drop (permitting use of a low power sampling pump), low hygroscopicity (minimizing bound water interference in mass measurements), and a low trace element background (improving analytical sensitivity) of these filters make them highly appropriate for personal particle sampling. The PUF sample cartridge is preceded by an impactor inlet with a 2.5 μm cut at 2 LPM. Vapors and particles of ≤ 2.5 μm in diameter pass through the impactor inlet and collect on a precleaned quartz microfiber filter (Palliflex Tissuquartz 2500 QAS, 25 mm diameter) and a precleaned polyurethane (PUF) cylinder. After sampling is completed, the field samplers are frozen and are shipped to the South-West Research Institute,Texas, packed in dry ice. Determination of target PAH (B[a]A, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(ghi)perylene, BaP, chrysene/isochrysene, dibenz(a,h)anthracene, indeno(1,2,3cd)pyrene, and pyrene) in extracts was performed using GC/MS. From the monitoring data, we are able to derive each woman's measured personal inhalation exposure to PAH (ng/m^3) and $PM_{2.5}$ (μg/m^3) during the 2nd trimester as a continuous variable. The PAH exposure variable was defined by the sum of all individual measured compounds.

2.3 Statistical methods

The effect of $PM_{2.5}$ and PAHs exposure in terms of lung function was assessed in multiple linear regression models, including potential confounders (age, height and weight of women and presence of asthma and season of lung function measurement). In the multiple regression models more than one explanatory (independent) variable may be included in the prediction equation. To identify potential confounders, associations between population characteristics and outcome variables were investigated using 2x2 tables. Chi-square statistics and analysis of variance tested differences between subgroups with low and high exposure. Initially, the multiple regression analysis of the effects related to air pollutants

as continuous variables were performed separately for PAH and $PM_{2.5}$and the interaction terms assessed in the regression models. Subsequently, in the main analysis, the combined effects of both pollutants were evaluated using a dichotomised classification of exposure to low and high levels of both pollutants, which was based on the median values of given distributions. A low level of $PM_{2.5}$ exposure was defined as concentration equal or below the median value (34.3 $\mu g/m^{3)}$ and a high exposure was defined as exceeding the median; the corresponding cut- point for PAH was 22.9 ng/m^3. In addition, multiple logistic regression models were used to measure the risk in the occurrence of wheezing associated with exposure during pregnancy.. In the logistic regression technique wheezing symptoms were used as dichotomous outcome health variable. Statistical analyses were performed with BMDP and NCSS software for Windows.

3 Results

Average total personal exposure among the 248 women enrolled in our study showed that $PM_{2.5}$ averaged 40.8 $\mu g/m^3$ (range: 11.5-147.3) and the mean value for PAH was 49.6 ng/m^3 (range: 3.3-316.4). Both air pollutants were strongly correlated with each other, however, with a tendency to higher PAHs values at the extreme range of PM2.5 values (Figure 1). $PM_{2.5}$ was found to be two times lower in the non-heating season, while PAHs levels were about 10 times lower in this season (Table 1).

Table 1 Levels of air pollutants by heating (October-March) and non-heating season (April – September) in the total study sample.

Variables	SEASON		Total group
	Heating N=131	Non- heating N=117	N=248
PM $_{2.5}$ ($\mu g/m^3$)			
Median	46.690	24.600	34.345
$(Q_3\text{-}Q_1)/2$	18.425	8.437	15.177
Mean	51.131	29.273	40.819
SD	28.089	14.537	25.181
PAHs (ng/m^3)			
Median	65.580	7.590	22.895
$(Q_3\text{-}Q_1)/2$	40.510	3.695	30.957
Mean	83.336	11.727	49.553
SD	65.853	10.027	60.106

Table 2 presents the exposure subgroups defined by the level of both pollutants. Out of the total study group, 152 women were included in the lower exposed group ($PM_{2.5} \leq 34.3 \mu g/m^3$or PAHs $\leq$ 22.9ng/ m^3) and 96 persons were exposed to higher concentration of both air pollutants ($PM_{2.5} > 34.3 \mu g/m^3$ and PAHs > 22.9ng/ m^3). Most of the subjects with the higher exposure level had their spirometric measurements during the heating season (84.4%), while 46.7% of subjects in the low exposure group had their

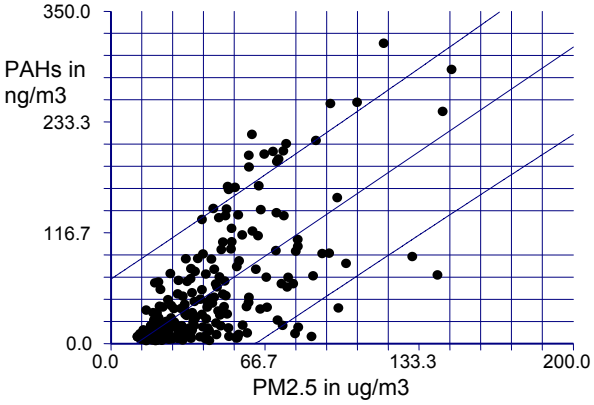

Fig. 1 Scatterplot of exposure to PM25 vs. PAHs.

Table 2 Characteristics of study subjects and the respiratory symptoms by level of exposure to $PM_{2.5}$ and PAHs.

Variables	Total group N=248 n, (%)	$PM_{2.5}$ ≤34.3 $\mu g/m^3$ or PAHs≤22.9 ng/m^3 N=152 n, (%)	$PM_{2.5}$>34.3 $\mu g/m^3$ and PAHs>22.9 ng/m^3 N=96 n, (%)	P*
Education:				
Primary School	6 (2.4)	1 (0.7)	5 (5.2)	
Vocational School	19 (7.7)	8 (5.3)	11 (11.5)	
Technical College	28 (11.3)	21 (13.8)	7 (7.3)	
High School	39 (15.7)	21 (13.8)	18 (18.8)	0.0225
College	27 (10.9)	20 (13.2)	7 (7.3)	
University	129 (52.0)	81 (53.3)	48 (50.0)	
Smoking status:				
Never smoker	176 (71.0)	110 (72.4)	66 (68.7)	
Ex- smoker	60 (24.2)	38 (25.0)	22 (22.9)	0.1245
Current smoker	12 (4.8))	4 (2.6)	8 (8.3)	
Exposure to ETS at home:	42 (16.9)	23 (15.1)	19 (19.8)	0.3406
Cough whenever	28 (11.3)	14 (9.2)	14 (14.6)	0.1928
Cough persistent -3m	12 (4.8)	7 (4.6)	5 (5.2)	0.8293
Phlegm whenever	28 (11.3)	16 (10.5)	12 (12.5)	0.6324
Phlegm persistent -3m	14 (5.6)	8 (5.3)	6 (6.2)	0.7429
Wheezing whenever	23 (9.3)	9 (5.9)	14 (14.6)	0.0220
Dyspnea on exertion	6 (2.4)	2 (1.3)	4 (4.2)	0.1547
Asthma diagnosed by medical doctor	7 (2.8)	2 (1.3)	5 (5.2)	0.0714
Season of spirometric measurement (October-March)	152 (61.3)	71 (46.7)	81 (84.4)	0.0000

*p: p-level of statistical difference based on Chi^2 statistics

measurements taken during the heating season. Both study subgroups were not different in respect to parity, number of pregnancies, exposure to active and passive smoking, coughing symptoms or phlegm, dyspnea on exertion and asthma diagnosed by physician. However, the less exposed subgroup was better educated and reported significantly less wheezing than the women from the more exposed subgroups.

Table 3 reports mean and standard deviations of spirometric indices in both exposure groups together with their anthropometrical characteristics. The higher exposure subgroup displayed significant lower mean uncorrected values of lung expiratory flows - PEFR, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, $FEF_{75\%}$, and $FEF_{25-75\%}$ - however, values of FVC and FEV_1 did not differ significantly across the exposure.

Table 3 Characteristics of the study sample and lung function (non-adjusted) by level of exposure to $PM_{2.5}$and PAHs (means and SD in brackets).

Variables	Total group N=248 n, (%)	$PM_{2.5}$ $\leq$34.3μg/m^3 or PAHs $\leq$ 22.9ng/ m^3 N=152 n, (%)	$PM_{2.5}$>34.3μg/m^3 and PAHs > 22.9ng/ m^3 N=96 n, (%)	AVA* p
Age (yrs)	28.46 (3.67)	28.42 (3.50)	28.51 (3.95)	0.8522
Height (cm)	164.76 (5.61)	165.03 (5.38)	164.32 (5.95)	0.3327
Weight (kg)	60.29 (9.25)	60.41 (9.63)	60.10 (8.65)	0.7975
BMI	22.21 (3.27)	22.19 (3.49)	22.24 (2.90)	0.9026
FVC (L)	3.673 (0.673)	3.696 (0.744)	3.638 (0.544)	0.5124
FEV_1 (L)	3.343 (0.572)	3.395 (0.646)	3.260 (0.421)	0.0687
PEFR (L/sec)	6.504 (1.468)	6.681 (1.622)	6.223 (1.136)	0.0163
$FEF_{25\%}$ (L/sec)	6.127 (1.431)	6.305 (1.572)	5.844 (1.125)	0.0132
$FEF_{50\%}$ (L/sec)	4.659 (1.152)	4.781 (1.264)	4.465 (0.921)	0.0348
$FEF_{75\%}$ (L/sec)	2.497 (0.816)	2.623 (0.878)	2.296 (0.663)	0.0020
$FEF_{25-75\%}$ (L/sec)	4.208 (1.032)	4.342 (1.129)	3.996 (0.819)	0.0098

*AVA: analysis of variance

The multiple regression analysis performed for FVC and FEV1 on two categories of exposure (higher vs. lower) after accounting for age, height, weight, asthma diagnosed by physician and the season of spirometric measurement showed no effect of exposure (Table 4). The statistical association between the exposure level and lung ventilatory flows were statistically significant for PEFR (p=0.04), $FEF_{25\%}$ (p=0.04), and $FEF_{75\%}$ (p=0.05) or were at borderline significance level ($FEF_{25-75\%}$, p = 0.08).

In the final part of the statistical analysis the multiple logistic regression was performed to assess relative risk for wheezing symptoms related to exposure variables, accounting for confounders such as hay fever, eczema and exposure to passive smoking at home. This latter analysis showed that relative risk of wheezing (estimated by OR) due to high exposure level was 5.61 (95% CI: 1.77-17.8). Both hay fever (OR=4.97; 95%

Table 4 Pulmonary function due to exposure levels of $PM_{2.5}$ (>34.3μg/m^3) and PAHs (>22.9ng/m^3), and asthma adjusted in multiple regression models to confounders and risk factors (age, height, weight, season spirometric).

	Beta coefficient	SE	p-level	Significance of regression models
FVC (L)				R = 0.35
Asthma	-0.5640	0.2480	0.02	F ratio = 5.59
Higher exposure to $PM_{2.5}$ and PAHs	0.0255	0.0907	0.78	p = 0.000
FEV_1 (L)				R = 0.38
Asthma	-0.5332	0.2085	0.01	F ratio = 6.58
Higher exposure to $PM_{2.5}$ and PAHs	-0.0596	0.0762	0.44	p = 0.000
PEFR (L/sec)				R = 0.32
Asthma	-0.4556	0.5460	0.40	F ratio = 4.74
Higher exposure to $PM_{2.5}$ and PAHs	-0.4173	0.1996	0.04	p = 0.000
$FEF_{25\%}$ (L/sec)				R = 0.30
Asthma	-0.4608	0.5373	0.39	F ratio = 3.90
Higher exposure to $PM_{2.5}$ and PAHs	-0.4012	0.1964	0.04	p = 0.001
$FEF_{50\%}$ (L/sec)				R = 0.27
Asthma	-0.8548	0.4362	0.05	F ratio = 3.16
Exposure to $PM_{2.5}$ and PAHs	-0.2217	0.1595	0.17	p = 0.005
$FEF_{75\%}$ (L/sec)				R = 0.36
Asthma	-0.5328	0.2996	0.08	F ratio = 5.90
Higher exposure to $PM_{2.5}$ and PAHs	-0.2135	0.1095	0.05	p = 0.000
PEFR (L/sec)				R = 0.32
Asthma	-0.4556	0.5460	0.40	F ratio = 4.74
Higher exposure to $PM_{2.5}$ and PAHs	-0.4173	0.1996	0.04	p = 0.000
$FEF_{25-75\%}$ (L/sec)				R = 0.30
Asthma	-0.7491	0.3870	0.05	F ratio = 4.04
Higher exposure to $PM_{2.5}$ and PAHs	-0.2453	0.1415	0.08	p = 0.001

CI: 1.55-15.9) and eczema (OR=3.19; 95% CI: 1.02-9.92) were also found to have had a significant impact on the occurrence of symptoms.

4 Discussion

Analysis of personal air samples from the study subjects enrolled in the Krakow study showed that $PM_{2.5}$ exposures averaged 40.8 μg/m^3 with a range of 11.5 – 147.3 μg/m^3. The mean concentration of PAHs was 49.6 ng/m^3 with a wide range of exposure (3.3-316.4 ng/m^3). As expected, both pollutants were strongly correlated with each other.

Table 5 Odds ratio for wheezing whenever and category of personal exposure to fine particles and PAHs accounted for hay fever, eczema and ETS exposure. Estimated from logistic regression (without subjects with confirmed asthma by medical doctor).

Predictors	Odds ratio	95% Confidence Interval
Hay fever	4.97	1.55 - 15.9
Eczema	3.19	1.02 - 9.92
Exposure to higher $PM_{2.5}$ and PAHs	5.61	1.77 - 17.8
Exposure to ETS at home	1.47	0.41 - 5.28

Our results showed that despite the fact that the individuals under study were not exposed to dusty occupational jobs, they experienced very high doses of fine particles and PAHs. If we compared PAH exposure in Krakow with the results of a similar study carried out in New York City - where the same sampling design and the same chemical analysis techniques for environmental monitoring were used – personal exposure in New York was much lower (mean PAH 4.0 ng/m^3, range of 0.36-44.81 ng/m^{3}than in Krakow [32].

Both air pollutants, treated separately as continuous variables, were inversely associated with indices of ventilatory expiratory flow and their beta regression coefficients accounted for potential confounders of similar magnitude. When the combined exposure to both pollutants was divided into two categories (high vs. low), the harmful effect of a high exposure level on lung function was more pronounced. The effect measured in terms of decreased ventilatory flows may suggest bronchoconstriction within the lower respiratory tract, which may be related to the exposure under study. Our study could not disentangle the effects of fine particles from that of PAH as they were very strongly correlated with each other. If one considers the two day personal exposure monitoring an acceptable medium-term or long-term exposure assessment, then this study is comparable with other papers dealing with the subject [33].

The study has also shown that the higher level of both pollutants increased the risk of wheezing by a factor of 5.6 (95% CI: 1.77-17.8) after accounting for potential confounders such as presence of allergic diseases and exposure to ETS. The latter result strengthens the hypothesis that combined pollutants under study may have the capacity to promote bronchial constriction, possibly by allergic responses through direct immunological influence or by facilitating allergen processing. There is convincing evidence that the deposition of air pollutants within the respiratory tract gives raise to lung inflammation [34] and these pollutants may modify epithelial integrity and mucosa permeability, facilitating the penetration and access of allergens to the immune system.

However, the results of our study must be treated with caution, as we did not make measurements of lung function at the time of the air pollution survey and before the exposure measurements took place. As a number of physiologic changes important for lung function measurements occur in the second trimester of pregnancy, we assumed, that lung function measurements performed 6 months after delivery should be a reliable estimate

of lung function free from the physiologic effects of pregnancy. The extent to which the findings resulted from the interaction between susceptibility of women during pregnancy to environmental hazards is debatable. The lack of a corresponding control group of non-pregnant women makes it impossible to have insight into this matter. Nevertheless, the environmental monitoring and the eventual reversibility of the findings will be further investigated over the two-year follow-up period. Another potential limitation of our study comes from the fact that personal monitoring of exposure among pregnant women was performed over a short period of 48 hours in the second trimester of pregnancy. However, to evaluate the correlation between the level of $PM_{2.5}$ measured over 48 hours in the second trimester of pregnancy with those in the second and the third trimesters, a series of repeated measurements in each trimester was carried out in a subsample of 51 pregnant women who were recruited in the first trimester. The mean concentration of $PM_{2.5}$ in the second trimester was 44.4 ug/m3 (SD: 46.5), not significantly different from the mean concentration in the first (46.2 (μg/m^3, SD: 34.0) and in the third trimester (35.9 (μg/m^3, SD: 35.3). The latter results may indicate that the mean levels of fine particles were rather stable over the whole pregnancy. This provides some confidence that the measurements of total personal level of exposure to fine particles and to PAHs taken in the second trimester may be representative for other pregnancy periods

In conclusion, our study demonstrated that among women during pregnancy the combined exposure to higher levels of communal air pollutants such as fine particles and PAHs give rise to lung function damage with some evidence of bronchoconstriction. This relationship with exposure was strengthened by the higher prevalence of wheezing among those exposed to higher levels of air pollutants.

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