Environmental Research 166 (2018) 150–157

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Lung function growth trajectories in non-asthmatic children aged 4–9 in relation to prenatal exposure to airborne particulate matter and polycyclic aromatic hydrocarbons – Krakow birth cohort study

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ARTICLE INFO

Keywords:
Krakow cohort
Spirometry parameters
PAH
$PM_{2.5}$
Trajectory

ABSTRACT

Background: Patterns of lung function development during childhood can be helpful in understanding the pathogenesis of respiratory diseases. A variety of environmental and lifestyle factors, present from the prenatal period to adulthood, may affect or modulate lung function growth. The aim of this study was to investigate, the associations between individual growth trajectories of children's lung function during childhood and prenatal exposure to airborne fine particulate matter ($PM_{2.5}$) and polycyclic aromatic hydrocarbons (PAH), which were hypothesized to adversely affect spirometry parameters.

Material and methods: The study group comprised 294 non-asthmatic, full term children from the Krakow birth cohort, who underwent annual spirometry testing at the ages of 4–9 years. Individual personal air monitoring of $PM_{2.5}$ and PAH were performed over 48 h in the second trimester of pregnancy. Possible confounders or modifiers such as child's gender, height, atopic status and exposure to environmental tobacco smoke (ETS) were considered. Polynomial multilevel mixed models were used to assess the growth rates of children's lung functions.

Results: Lung function trajectories differed significantly for boys and girls for FVC, FEV1 and FEF25–75. Girls had lower rates of increase than boys: − 20.5 (95%CI: − 32.4; − 8.6) ml/year (FVC); − 19.9 (95%CI: − 30.7; − 9.0) ml/year (FEV1); and − 32.5 (95%CI: − 56.9; − 8.2) ml/year (FEF25–75). Spirometry functions increased with age; however the growth rate decelerated over time. Significant lung function impairment (lower FVC and FEV1 levels) was observed from 4 to 9 years among subjects prenatally exposed to higher levels of $PM_{2.5}$ as well as PAH, but not in the case of FEF25-75. No significant differences were observed in the rates of increase over time in relation to prenatal $PM_{2.5}$ and PAH exposure.

Conclusion: Our results indicate that in non-asthmatic children high prenatal exposure to airborne $PM_{2.5}$ and PAH is associated with lower trajectories of FVC and FEV1, but not the rate of increase over time, suggesting that the initial effect is not diminishing in time.

1. Introduction

Research on lung function development indicates that pulmonary functions are growing up to 20–25 year of life, with the highest dynamics of lung growth observed in the pubertal period, and then are systematically decreasing (Stanojevic et al., 2009, 2010). Two large cohort studies in Tucson, USA (Stern et al., 2007) and Melbourne, Australia (Phelan et al., 2002) showed that spirometry at 4–6 years of age predicts the height of the maximum values of spirometry parameters achieved at age 20–25 years - the starting point for spirometry decline. A variety of factors associated with both the environment and life style, present from the prenatal period into adulthood, may affect or modulate lung function growth. Over the last 10 years there have been many publications indicating the adverse effect of tobacco smoking and exposure to environmental airborne pollutants such as particulate matter (PM), polycyclic aromatic hydrocarbons (PAH), sulfur dioxide(SO_2) or nitrogen dioxide (NO_2) on respiratory health and pulmonary functions parameters like forced vital capacity (FVC) and

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https://doi.org/10.1016/j.envres.2018.05.037
Received 9 January 2018; Received in revised form 29 May 2018; Accepted 30 May 2018

forced expiratory volume in 1 s (FEV1) not only in people with chronic respiratory diseases such as chronic obstructive pulmonary disease or asthma (Gan et al., 2013; Ierodiakonou et al., 2016; Mortimer et al., 2008) but also in healthy people (Forbes et al., 2009; Rosenlund et al., 2009; Tantisuwat and Thaveeratitham, 2014).

Children are more sensitive to air pollution than adults due to the rapid development of the respiratory system. Studies initiated at the beginning of this century on inhaled particles and complex mixtures provided new understanding of the multiple health impacts of prenatal air pollution exposure on children's health (Perera and Herbstman, 2011; Perera, 2014; Perera et al., 2003). Particulate matter represents a wide range of chemical compounds potentially hazardous for people's health, especially those with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), which pass through the filtration of nose hair, reach the periphery of the respiratory tract with the airflow and accumulate there by diffusion, damaging other parts of the body through transfer of toxic chemicals to the circulatory system. Airborne PAH are mainly emitted as gaseous pollutants, which in the non-industrial environment come mostly from diesel exhaust and incomplete coal combustion as well as indoor sources such as fumes from cooking, grilling, and frying, coal or wood stoves, fireplaces, kerosene heaters, unvented gas appliances and tobacco smoke (Jung et al., 2010; Junninen et al., 2009; Markiewicz et al., 2017). The gaseous pollutants can absorb onto the surface of small particles so that many PAH are found in the fine particulate fraction. PAH have received particular attention because of their potential of genetic damage in the form of DNA adducts or chromosomal abnormalities from *in utero* exposure (Bocskay et al., 2005; Perera et al., 2005) and their ability to cause oxidative stress and related cytotoxicity (Jeng et al., 2011). Exposure to PAH has been linked to several adverse outcomes in children, including lower birth weight, reduced birth head circumference, preterm birth, and small size for gestational age (Choi et al., 2006, 2008b; Jedrychowski et al., 2017; Perera et al., 2003), asthma symptoms (Gale et al., 2012; Miller et al., 2004) and respiratory illness (Hertz-Picciotto et al., 2007; Jedrychowski et al., 2005, 2014, 2015a). Prenatal exposure to $PM_{2.5}$ and PAH may have negative consequences for normal fetal development of various organs, such as the lungs, and the immunologic system. These, in turn, may lead to deficient function of the affected organs in postnatal life. Long term follow up studies in different populations have shown that changes in lung structure in early childhood resulting from prenatal exposure can persist and lead to an increased burden of respiratory illness in adult life (Dratva et al., 2016; Duijts, 2012; Duijts et al., 2014; Horak et al., 2003; Landau, 2006; Stern et al., 2008, 2007).

A number of publications have reported association between prenatal levels of PM and PAH during pregnancy and respiratory symptoms (Clark et al., 2010; Deng et al., 2016a, 2016b; Jedrychowski et al., 2008, 2014, 2010a, 2010b, 2013) as well as ventilatory lung function (Jedrychowski et al., 1999, 2015a, 2010a; Latzin et al., 2009; Mortimer et al., 2008) at different child ages, but none have described the pattern of lung function growth in childhood. To our knowledge, up to now, there have been only a few publications that were focused on trajectories of lung function growth among children (Belgrave et al., 2014; Turner et al., 2014), but they considered impact of wheezing, atopy phenotypes, and history of asthma, not prenatal exposure to $PM_{2.5}$ or PAH.

The aim of this study was to investigate the individual growth trajectories of children's lung function by prenatal exposure to airborne $PM_{2.5}$ and PAH, which were hypothesized to adversely affect these trajectories. In contrast to other air pollution studies, we assessed individual exposure to fine particulates ($PM_{2.5}$) and PAH in pregnant women using specially designed personal samplers collecting air pollution particles over a 48 h period during the second trimester of pregnancy. The cohort of children has been followed from birth through the age of 9.

2. Materials and methods

The analysis is based on an earlier established birth cohort of children living in Krakow, which is a result of a collaboration between the Jagiellonian University Medical College in Krakow, Poland and Columbia University in New York, USA. The design of the study and the detailed selection of the population have been described previously (Jedrychowski et al., 2003). Briefly, the enrollment included 505 women aged 18–35 recruited from Krakow ambulatory prenatal clinics in the first and second trimesters of pregnancy between November 2000 and March 2003. The exclusion criteria included non-singleton pregnancy, maternal active smoking, and a history of chronic diseases such as diabetes, hypertension or illicit drug use or HIV infection. Recruited women were given a description of the study and requirements for participation in the project. Upon enrollment, a detailed questionnaire was administered to each subject to obtain demographic data, information on diseases such as asthma and allergic diseases, household characteristics and exposure to environmental tobacco smoke (ETS). Prior to participation, women gave informed consent. The Bioethical Committee of Jagiellonian University approved the research.

After delivery, a detailed standardized face-to-face interview was given to mothers on their infant's health, household characteristics and environmental conditions, including postnatal ETS exposure in the home. The questionnaire was administered by a trained interviewer every 3 months during the first 2 years of the infants life, every 6 months up to 6th year of life, and annually thereafter.

The present analysis was restricted to 294 non-asthmatic and full term (> 36 weeks of gestation) children, who underwent spirometry testing at the ages 4 – 9 years, with at least two acceptable and reliable measurements.

2.1. Spirometry testing

Between ages 4–9, children were annually invited for standard lung function testing: FVC, FEV1 and maximal mid expiratory flow rate (FEF25-75) with a PC QRS Card Spirometer (QRS Diagnostic, Plymouth, MN, USA). The children were free of respiratory symptoms on the day of testing and the day prior to spirometric testing. Standing height and weight of each child was measured. Subsequently, children were trained to engage in maximal forced expiratory efforts in a standing position without nose clip. All spirometric measurements were carried out by the same staff member. The spirometer was calibrated each day with a syringe. Each child made at least two good forced exhalation efforts and the primary indicators of lung function were recorded, including FVC, FEV1 and FEF25-75.

Spirometric data were excluded (treated as unacceptable) 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 s, or a cough or an abrupt end of expiration effort appeared in the course of the exhalation effort. In the group of non-asthmatic and full term children 76% of 4 year-olds and 89% of 5 year-olds were able to make at least two acceptable efforts, and the percentage was increasing as children were getting older. In accordance with the American Thoracic Society and European Respiratory Society guidelines on pulmonary function testing in preschool children (Beydon et al., 2007), expiratory flows were reported from the attempt with the best flow (the greatest sum of FEV1 and FVC). Spirometric findings were accepted as reliable if the difference between two results of FVC and the difference between two results FEV1 of the two best curves were within the range of 20%. In the studied group of non-asthmatic and full term children with acceptable spirometric data, quality control based on repeatability was inadequate in case of 23% at the age of 4, in 17% at the age of 5 and in less than 10% at older ages.