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Association of perfluoroalkyl substances exposure with impaired lung function in children

Xiao-Di Qin[a], Zhengmin (Min) Qian[b], Shyamali C. Dharmage[c], Jennifer Perret[c], Sarah Dee Geiger[d], Steven E. Rigdon[e], Steven Howard[f], Xiao-Wen Zeng[a], Li-Wen Hu[a], Bo-Yi Yang[a], Yang Zhou[a], Meng Li[a], Shu-Li Xu[a], Wen-Wen Bao[a], Ya-Zhi Zhang[a], Ping Yuan[a], Jia Wang[a], Chuan Zhang[a], Yan-Peng Tian[a], Min Nian[a], Xiang Xiao[a], Wen Chen[a], Yungling Leo Lee[g,h,†], Guang-Hui Dong[a,†,*]

[a] Guangzhou Key Laboratory of Environmental Pollution and Health Risk Assessment, Department of Preventive Medicine, School of Public Health, Sun Yat-sen University, Guangzhou 510080, China
[b] Department of Epidemiology, College for Public Health and Social Justice, Saint Louis University, Saint Louis 63104, USA
[c] Allergy and Lung Health Unit, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Vic 3052, Australia
[d] School of Health Studies, Northern Illinois University, DeKalb, IL 60115, USA
[e] Department of Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis 63104, USA
[f] Department of Health Management & Policy, College for Public Health and Social Justice, Saint Louis University, Saint Louis 63104, USA
[g] Department of Environmental and Occupational Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[h] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei 100, Taiwan

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ABSTRACT

Previous studies have demonstrated associations between serum levels of perfluoroalkyl substances (PFASs) and asthma or asthma related-biomarkers. However, no studies have reported a possible relationship between PFASs exposure and lung function among children. The objective of the present study is to test the association between PFASs exposure and lung function in children from a high exposure area by using a cross-sectional case-control study, which included 132 asthmatic children and 168 non-asthmatic controls recruited from 2009 to 2010 in the Genetic and Biomarkers study for Childhood Asthma. Structured questionnaires were administered face-to-face. Lung function was measured by spirometry. Linear regression models were used to examine the influence of PFASs on lung function. The results showed that asthmatics in our study had significantly higher serum PFAS concentrations than healthy controls. Logistic regression models showed a positive association between PFASs and asthma, with adjusted odds ratios (ORs) ranging from 0.99 (95% confidence interval [CI]: 0.80–1.21) to 2.76 (95% CI: 1.82–4.17). Linear regression modeling showed serum PFASs levels were significantly negatively associated with three pulmonary function measurements (forced vital capacity: FVC; forced expiratory volume in 1 s: FEV_1; forced expiratory flow 25–75%: FEF_{25-75}) among children with asthma, the adjusted coefficients between lung function and PFASs exposure ranged from −0.055 (95%CI: −0.100 to −0.010) for FVC and perfluorooctane sulfonate (PFOS) to −0.223 (95%CI: −0.400 to −0.045) for FEF_{25-75} and perfluorooctanoic acid (PFOA). PFASs were not, however, significantly associated with pulmonary function among children without asthma. In conclusion, this study suggests that serum PFASs are associated with decreased lung function among children with asthma.

1. Introduction

Asthma is one of the most common chronic diseases throughout the world, especially among children (Lai et al., 2009). Although many asthma risk factors have been identified, reasons for its rising prevalence remain poorly understood (Beasley et al., 2015) and emerging environmental exposures may bear a portion of the attributable risk (Guarnieri and Balmes, 2014; Miller and Marty, 2010).

* Corresponding author at: Guangzhou Key Laboratory of Environmental Pollution and Health Risk Assessment, Department of Preventive Medicine, School of Public Health, Sun Yat-sen University, 74 Zhongshan 2nd Road, Yuexiu District, Guanghzou 510080, PR China. Phone: +86-20–87333409; Fax: +86-20-87330446.
† These authors contributed equally to this work.
E-mail addresses: donggh5@mail.sysu.edu.cn, donggh512@hotmail.com (G.-H. Dong).

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Perfluoroalkyl substances (PFASs) are a diverse class of chemicals with unique properties like extremely high thermal and chemical stability. They have long serum half-lives (in years) of 5.4 (perfluorooctane sulfonate, PFOS), 3.8 (perfluorononanoic acid, PFOA), and 8.3 (perfluorohexanesulfonate, PFHxS) years (Buck et al., 2011; Olsen et al., 2007). These properties are responsible for the accumulation of PFASs in the environment, wildlife, and humans (Fromme et al., 2007; Schecter et al., 2012; Zhou et al., 2014), but also make them ideal for applications such as firefighting foams, paints, semiconductors, photographic films, and pesticides, for which they have been widely used since the 1950s (Lindstrom et al., 2011). In addition, both human and animal studies have found that the lungs are likely a target organ of PFASs (Borg et al., 2010; Perez et al., 2013).

Animal evidence indicates that exposure to PFOA and PFOS cause a variety of asthma-related outcomes. Fairley et al. (2007) revealed that PFOA caused increased serum immunoglobulin E (IgE) and an exaggerated response to ovalbumin. The evidence suggests exposure to PFOA may intensify the IgE response to allergens in a murine model of asthma (Fairley et al., 2007). Furthermore, two animal studies show that prenatal PFOA and PFOS exposure may adversely affect lung development (Loewen et al., 2011; Ryu et al., 2014). One study noted that PFOS exposure lowered baseline airway resistance but significantly increased airway responsiveness in an allergic murine model of pups (Loewen et al., 2011). Another study did not identify maternal exposure to PFOA or PFOS as a risk factor for more severe asthma-like symptoms in pups, but found that PFOA induced airway inflammation and altered airway function (Ryu et al., 2014).

Epidemiologic evidence suggests that exposure to PFASs is positively associated with asthma, but results are inconsistent. Dong et al. (2013) reported a positive association between PFASs and asthma, asthma severity, and immune markers in Taiwanese children. Using 1999–2000 and 2003–2008 National Health and Nutrition Examination Survey (NHANES) data, Humblet et al. (2014) provided modest evidence for positive associations between exposure to PFASs and asthma-related outcomes among children. In the INUENDO birth cohort study from Greenland and Ukraine, however, Smit et al. (2015) did not find an association.

No study has examined whether PFAS exposure is associated with objective measures of lung function such as spirometry, which provides information on airway obstruction by measuring forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEF), and forced expiratory flow at 25–75% of FVC (FEF_{25-75}) (Pellegrino et al., 2005). These tools not only have utility for diagnosing and monitoring asthma (Gaffin et al., 2010; Pijnenburg et al., 2015), but also are the most commonly employed pulmonary function tests for assessing effects of environmental chemicals on lung function (Barraza-Villarreal et al., 2008; Miller and Marty, 2010). The objective of the present study was to test the association between PFAS exposure and lung function in a case-control study of asthmatic and non-asthmatic children, by using data from the Genetic and Biomarkers study for Childhood Asthma (GBCA).

2. Methods

2.1. Study participants

Study participants were from the Genetic and Biomarkers study for Childhood Asthma (GBCA) in Taiwan during 2009–2010. Study methods are available elsewhere (Dong et al., 2013). One hundred and thirty-two non-smoking children aged 10–15 with physician-diagnosed asthma were recruited from the cross-sectional component of GBCA from two hospitals in northern Taiwan. The 168 controls, without asthma and non-smokers, were randomly selected from seven public schools in northern Taiwan. The cases and controls were matched on sex and age with an average response rate of 72.0%. Demographics, asthma outcomes, and environmental exposures were collected via questionnaire; serum samples were collected by trained technicians for each child after 8 h of fasting. Height, weight, waist circumference and blood pressure were taken by individual physical examination. Parents and children provided written informed consent and the study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital Research Ethics Committee.

2.2. Lung function measurement

Lung function measurements were described earlier (Ma et al., 2013). Briefly, forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEF), and forced expiratory flow 25–75% (FEF_{25-75}) were measured with two portable electronic spirometers operated by experienced technicians (Spirolab, MIR, Italy) (Mehrparvar et al., 2014). Total lung capacity (TLC) and residual volume (RV) were also measured by asking children to stand comfortably and wear a nose clip to stop air from moving through the nose during the test. All measurements were corrected for body temperature and saturated pressure (BTPS). Spirometry was conducted according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) standards.

2.3. Serum PFAS measurement

The serum PFAS measurements were reported earlier (Dong et al., 2013). Briefly, Agilent high performance liquid chromatography (HPLC) in tandem with an Agilent 6410 Triple Quadrupole (QQQ) mass spectrometer (MS/MS) was used to quantify serum PFAS levels from 0.5 mL of serum (Agilent, Palo Alto and Santa Clara, CA). Methods regarding standards and reagents, sample preparation and extraction, instrumental analysis, quality assurance and control, and recovery experiments are included in the Supplementary material and described elsewhere (Hansen et al., 2001). We analyzed eight PFASs in serum samples: perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorotetradecanoic acid (PFTA), perfluorohexanoic acid (PFHxA), perfluorohexanesulfonate (PFHxS), and perfluorobutanesulfonate (PFBS). The limit of quantification (LOQ) was 0.03 ng/mL for PFOS, PFOA and PFNA, 0.07 ng/mL for PFBS and PFHxS, 0.1 ng/mL for PFDA, 0.05 ng/mL for PFHxA, and 0.02 ng/mL for PFTA. The average measurement was used as the sample concentration.

2.4. Statistical analysis

Statistical analyses were done in SAS (version 9.2, SAS Institute Inc., Cary, NC, USA). The lung capacity distributions were tested for normality (Shapiro–Wilks *W* test) and homogeneity (Bartlett's test for unequal variances). To correct skewed distributions, PFASs were natural log transformed. Continuous variables with normality and homogeneity were reported as the mean ± SD or median [Quartile 1(Q1)-Quartile 3(Q3)]. Due to skewed PFASs values, we used the Wilcoxon rank-sum test to compare PFASs between children with and without asthma. We conducted logistic regression models to calculate the odds ratios (OR) and 95% confidence intervals (CI) for the association between each PFASs exposure variable and asthma. Each pulmonary function measurement (FEV_1, FVC, PEF, and FEF_{25-75}) was treated as a continuous variable in a separate linear regression model with each single PFASs exposure variable. Covariates included age, sex (male, female), body mass index (BMI), regular exercise (at least 1 h per day outside of physical education class), parental education (less than or more than high school), environmental tobacco smoke exposure (ETS, amassed from current and past household smoking status of each participant's adult household members and regular household visitors) and month of survey. Statistical analyses were also stratified by sex because previous studies suggested sex