國立臺灣大學公共衛生學院職業醫學與工業衛生研究所

碩士論文

Institute of Occupational Medicine and Industrial Hygiene

Collage of Public Health

National Taiwan University

Master Thesis

產前全氟碳化物暴露可能改變八歲孩童時期肺功能

Intra-utero Exposure to Perfluoroalkyl Substances May Affect Lung Function Development at Eight Years of Age

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中華民國 105 年 7 月

July 2016

doi:10.6342/NTU201602459

國立臺灣大學碩士學位論文
口試委員會審定書

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本論文係龔晏平君（學號：R02841029）在國立臺灣大學職業醫學與工業衛生研究所完成之碩士學位論文，於 2016 年 7 月 29 日承下列考試委員審查通過及口試及格，特此證明

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doi:10.6342/NTU201602459

National Taiwan University

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We hereby recommend that thesis submitted by Yen-Ping Kung entitled be accepted as fulfilling the thesis requirement for the degree of Master of Science in the Institute of Occupational Medicine and Industrial Hygiene.

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Date July 29, 2016

doi:10.6342/NTU201602459

中文摘要

背景

全氟碳化物是環境中常見的環境中持續的有機汙染物，次分類包括有全氟辛酸(PFOA)、全氟辛烷磺酸鹽(PFOS)、全氟壬酸(PFNA)及全氟十一酸(PFUA)等。動物實驗證實全氟碳化物會影響改變肺部發展及發炎反應。然而，產前的暴露與孩童時期的暴露全氟碳化物對孩童肺部影響程度大小目前尚不清晰。

研究目的

本篇研究目的在於探討產前暴露和孩童時期暴露到不同的全氟碳化物，對於孩童肺部發展的影響。

研究方法

從台灣出生世代追蹤調查研究中，收案 165 位孩童，從出生時的臍帶血測量其全氟碳化物濃度，在孩童八歲時收取血清再測量其全氟碳化物濃度，方法是以極致液相層析/串聯式質譜儀作分析。並在孩童八歲時做肺功能檢查及兒童氣喘及過敏國際研究問卷調查。

結果

在 165 位收案孩童中，臍帶血中的 PFOA、PFOS、PFNA 和 PFUA 濃度分別為 2.4, 6.4, 6.0, 15.4 奈克每毫升。而八歲時的血清中 PFOA、PFOS、PFNA 和 PFUA 濃度則分別為 2.7, 5.9, 0.6, 0.3 奈克每毫升。八歲時期的肺功能平均第一秒用力呼氣量 (FEV1)、用力肺活量(FVC)、最大呼氣流率(PEF)及用力呼氣一秒率 (FEV1/FVC)分別為 1679 毫升、1835 毫升、3846 毫升每秒及 92.0%。本研究發現臍帶血中的 PFOA、PFOS、PFNA 和 PFUA 與肺功能的減少有關連性，對於減少肺功能的一致性最高者為臍帶血中 PFOS 濃度，對於次分類中的較輕出生體重孩童和過敏性鼻炎孩童的肺功能具有顯著的負向影響。

結論

doi:10.6342/NTU201602459

我們的世代研究發現 PFOA、PFOS、PFNA 和 PFUA 在臍帶血中濃度的幾何平均皆大於八歲孩童時期血清濃度。臍帶血中的 PFOS 濃度對孩童時期的第一秒用力呼氣量 (FEV1)、用力肺活量(FVC)、最大呼氣流率(PEF)有負向影響的趨勢，其中較輕出生體重和有過敏性鼻炎的孩童會有顯著影響。產前的全氟碳化物對於孩童未來的肺部發展可能扮演了重要的角色。

關鍵字

產前暴露、全氟碳化物、肺功能、肺部發展、過敏疾病

doi:10.6342/NTU201602459

Abstract

Background

The perfluoroalkyl substances (PFAS), such as perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA) and perfluoroundecanoic acid (PFUA), are common persistent organic pollutants in the environment. Animal studies had indicated PFAS would influence lung development and inflammatory responses. However, the effect of whether prenatal or childhood PFAS exposures affect more children's lung function is unclear.

Aim

The purpose of this study is to investigate the relationships between intra-utero exposure and childhood-exposure to PFAS and lung function development at children stage.

Methods

In total, 165 children were recruited from the Taiwan Birth Panel Study (TBPS). Cord blood plasma and children's serum while they're eight years old was collected. PFAS were analyzed by ultra-high-performance liquid chromatography/tandem mass spectrometry. Until reached eigth years of age, we enrolled these children to have lung function examinations and detailed questionnaire.

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Results

Among 165 study children, the mean concentrations of PFOA, PFOS, PFNA and PFUA in cord blood were 2.4, 6.4, 6.0, 15.4 ng/mL, respectively. The concentrations in eight-year-old serum were 2.7, 5.9, 0.6, 0.3ng/mL, respectively. At eight years of age, their mean values of FEV1 (forced expiratory volume in 1 second), FVC (forced vital capacity), PEF (peak expiratory flow) and FEV1/FVC were 1679 mL, 1835 mL, 3846 mL/sec and 92.0 percent, respectively. PFOA, PFOS, PFNA and PFUA levels in cord blood were inversely associated with FEV1, FVC and PEF values. PFOS in cord blood is the most consistently correlated to decreasing lung function even after adjusting confounding factors. PFOS significantly affects lung function in subgroup of lower birth weight and allergic rhinitis.

Conclusions

Our cohort study suggested that the concentrations of PFOA, PFOS, PFNA and PFUA were geometrically higher in cord blood than in eight-year-old serum. There are also trends noted between intrauterine PFOS and decreasing FEV1, FVC and PEF in children stage, especially in subgroups of lower birth weight and allergic rhinitis. Intrauterine PFAS may play an important role in children's lung development.

Key words: prenatal exposure, perfluoroalkyl substances, lung function, lung development, allergic disease

doi:10.6342/NTU201602459

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I. Introduction

Epidemiologic research have shown associations between common indoor materials in residences are related to adverse respiratory and allergic health effects, including increased risk of asthma, pulmonary infections, and allergy. (M. J. Mendell. 2007) These indoor risks includes These risk factors include indoor air concentrations, indoor materials, and use of chemical products for cleaning. For example, new furniture and new wall covering was reported to be associated with allergy increasing. New synthetic carpet was also reported to be associated with asthma, wheezing, and allergy. (Jaakkola et al. 2004) Perfluoroalkyl substances (PFAS) are exposed to human widely. The indoor household dusts were detected worldwide. (Eriksson U et al. 2015)

The perfluoroalkyl substances are widespread used organic pollutants with long half-life (Olsen et al. 2007). Lau et al. (2007) reported that PFOS and PFOA are commonly detected in the serum and tissues of humans and wildlife, and had been indicated to alter inflammatory responses (DeWitt et al. 2012). There are probability that pregnant women may contact subgroups of PFAS, such as perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA) and perfluoroundecanoic acid (PFUA).

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Animal studies have reported intra-utero PFAS exposure may cause adverse effects on lung development and immune system (Ryu et al. 2014). The potential mechanisms which PFAS may impairs immune system is through the activation of the peroxisome proliferator-activated receptor alpha (PPARα) (Abbott et al., 2007). Mice prenatally exposed to PFOA who express the PPARα gene compare to knockout mice had lower number of thymocytes and splenocytes (Yang et al., 2002).

Pollutants exposure in pregnant women is associated with development of lung growth and respiratory deficiencies after birth (Radhika 2007). Major known prenatal factors affecting lung development include placental insufficiency, preterm birth, intrauterine growth retardation, maternal tobacco smoking, and exposure to intrauterine infection (Gilbert et al. 2003, Richard et al. 2012). The possible mechanism may be the intrauterine stress disrupted development of interrelated systems and induced vulnerability to airway reactivity and inflammation (Rosalind 2010). Epidemiological studies have suggested a correlation between prenatal exposure to PFAS and levels of cord blood immunoglobulin (Ig) E (Okada et al. 2012; Wang et al. 2011). Serum IgE production may play a role in asthma pathogenesis (Manise et al. 2013). Chen et al. (2012) demonstrated that maternal exposure to 2.0 mg/kg d PFOS induced marked oxidative injuries and cell apoptosis in offspring

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lungs.

However, the effect of prenatal and postnatal PFAS exposures on lung development in childhood is unclear. The purpose of this study is to investigate the relationships between intra-utero exposure and postnatal exposure to PFAS and lung function at childhood to determine their influences.

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II. Methods

Study population

The prospective birth cohort study, Taiwan Birth Panel Study, enrolled pregnant women from one medical center, one local hospital, and two clinics in north Taiwan from April 2004 to January 2005. Details of study design were described in previous study (Hsieh et al. 2011). Briefly, cord blood plasma was collected at birth. A total of 439 mother-infant pairs had cord blood samples. After delivery, mothers who consented to join the study were interviewed by trained interviewers completing a structured questionnaire. The questionnaire included information related to maternal educational level, occupation, family income, smoking status, alcohol intake and medical information including pregnancy age, pre-pregnancy weight, height, gestational age, infant sex and birth weight.

Until 2013, when children reached eight years of age, we enrolled these children underwent lung function and physical examinations. Subjects were excluded because of withdrawal from the study and loss to follow-up. We also collected their blood to test the concentration of perfluoroalkyl substances in eight-year-old. There were 165 children recruited from the Taiwan Birth Panel Study (TBPS). All the specimens and data collection were approved by the Institutional Review Board (IRB) of National

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Taiwan University Hospital.

Exposure measurement

Cord blood concentrations of PFAS were analyzed by ultra-high performance liquid chromatography/tandem mass spectrometry. Details of analytical detection approach had been described in previous study (Lien et al. 2011). In brief, samples were primarily prepared using protein precipitation, and then mixed with stable isotope labeled standard, followed by sonication and centrifugation, finally were analyzed. Among 165 cord blood samples, the detection rates of PFOA, PFOS, PFNA and PFUA were 63.0, 99.4, 61.8 and 81.8%, and their limits of quantitation (LOQ) were 1.58, 0.22, 0.84, and 3.1 ng/mL, respectively. Due to PFOA, PFNA and PFUA were detected in blanks, their LOQ were calculated using the average background level 1.5, 0.75, and 3.0 ng/mL, respectively. If PFAS concentrations were less than quantitation limit, we distributed values equal to one-half of the LOQ. In those eight-year-old blood samples, the detection rates of PFOA, PFOS, PFNA and PFUA were 85.5, 92.7, 46.1 and 41.2%, and their limits of quantitation (LOQ) were 0.01, 0.05, 0.03, and 0.01 ng/mL, respectively. The undetected eight-year-old blood samples whose concentration less than quantitation limit; we also distributed values equal to one-half of the LOQ.

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Follow-up

When children were eight years old, participants were asked to complete another self-administered questionnaire for dietary preferences, history of environmental tobacco smoke exposure, living environment, pets and carpets at home. Diagnosis of allergic diseases was obtained from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires through following questions: “Has your child ever had asthma diagnosed by a doctor?”, “Has your child ever had allergic rhinitis (AR) diagnosed by a doctor?”, “Has your child ever had atopic dermatitis (AD) diagnosed by a doctor?” If the answer was yes, we estimated the subject having this allergic disease.

Lung function test

We used the Micro Medical MicroLab Spirometer (CareFusion 232 Ltd.) complying the American Thoracic Society spirometry standards (Miller et al. 2005) to conduct lung function tests for these eight-year-old children. After height and weight were measured, these children took lung function assessments by the same trained technician. Lung function values assessed were forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), and forced

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expiratory volume in 1 sec as a proportion of the forced vital capacity (FEV1/FVC).

Statistical Analysis

Due to the PFAS concentrations in cord blood and eight -year-old blood were not normally distributed, we used geometric mean with standard deviation to compare the PFAS levels in different demographic characteristics. Simple and multiple linear regression models were used to examine the association between lung function values (FEV1, FVC, PEF and FEV1/FVC) at eight years of age and PFAS levels, in the cord and eight -year-old blood serum. In statistical model, the cord blood PFAS concentrations were converted to log10-transformed data because of a right-skewed distribution. Considering potential confounders from literature review, including pregnancy age, infant sex, birth weight, gestational age, maternal nicotine concentration exposure, maternal education level, occupation, family income, parental history of allergic diseases, children height, weight, body mass index, prenatal smoke history, postnatal environment tobacco smoke exposure, children dietary preferences, whether using pesticide, incensing, pets and carpets at home. The variables with more than 10 percent change in point estimate were considering included in the adjusted model.

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To discuss the potential modification and lung development issues, we divided subjects into subgroups by infant birth weight (≤3200g or >3200g), family history of allergies (with or without), asthma (with or without) and allergic rhinitis (with or without). We used stratified analysis to identify the relationship between prenatal and postnatal PFAS exposure with lung function development. All of the analyses were two-sided and p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

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III. Results

The basic characteristics of the study population at birth and eight-year-old are described in Table 1. Compared with the subjects who lost to follow-up, the participant mothers had higher pregnancy age, educational level, family income, and prenatal environmental tobacco smoke exposure. Among 165 study children, the mean of birth weight was 3222.0 g and concentrations of PFOA, PFOS, PFNA and PFUA in cord blood were 2.4, 6.4, 6.0, and 15.4 ng/mL, respectively. And the concentrations of PFOA, PFOS, PFNA and PFUA in eight-year serum were 2.7, 5.9, 0.6, and 0.3ng/mL, respectively. At eight years of age, 27 (16%) developed asthma, 87 (53%) developed allergic rhinitis, and 30 (18%) developed atopic dermatitis. Their mean values of FEV1, FVC, PEF and FEV1/FVC were 1679 mL, 1835 mL, 3846 mL/sec and 92.0 percent, respectively.

Because of non-normal distribution of these concentrations, we used paired t test to compare the geographical means of the concentration in cord blood and eight-year-old serum. PFOA, PFOS, PFNA and PFUA were all higher in cord blood than in eight-year serum ($p= 0.0397$, $p<0.0001$, $p<0.0001$ and $p<0.0001$). The geometric mean concentrations of PFOA, PFOS, PFNA and PFUA in cord blood in relation to characteristics at birth and eight-year-old are shown in Table 2.

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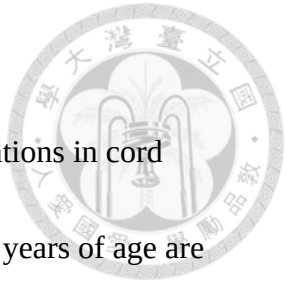

The results of linear regression model between PFAS concentrations in cord blood and in eight-year-old serum, and lung function values at eight years of age are shown in Table 3. There was an inverse correlation between log10 transformed PFOS concentration in cord blood and FEV1, FVC, PEF and FEV1/FVC values. However, these effects were failed to reach statistical significance. The other PFAS in cord blood had comparatively smaller correlation. The estimates of PFAS in eight-year-old blood were small in both crude and adjusted models.

Table 4 shows the results of stratified analysis by birth body weight, family history of allergy, asthma, and allergic rhinitis. For children whose birth weight no more than 3200 gram, PFOS levels in cord blood were negatively associated with FEV1 values [per log unit: β (95% confidence interval) = -64.7 (-115.5, -13.9) mL] after adjusted for children sex, height, body mass index, birth body weight, mother education, eating habit, prenatal smoke history, history of environmental tobacco smoke exposure, maternal nicotine concentration exposure, gestational age, family income, whether using pesticide and incensing at home. PFOS levels in cord blood also had a trend of inverse association with values of FVC and PEF [per log unit: β (95% confidence interval) = -49.1 (-112.6, 14.4) mL for FVC and -93.6 (-255.1, 67.9)

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mL/sec for PEF] after adjusted above mentioned confounding factors. However, there were no significant associations or consistent trend observed between PFAS level and lung function values among subgroup whose birth weight more than 3200 gram.

There were inverse correlation between log10PFOS concentration and PEF values in children who had allergic rhinitis [per log_{10} unit: β (95% CI) = -221.0 (-405.6,-36.5) mL/sec]. On the other hand, there were no consistent trends noted in the subgroup of children with allergic rhinitis.

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IV. Discussion

In this cohort study, we found the differences between participant and non-participant groups are small. Because of non-normal distribution of these concentrations, we used paired t test to compare the geographical means of the concentration in cord blood and eight-year-old serum. PFOA, PFOS, PFNA and PFUA were all higher in cord blood than in eight-year serum. We found that there was an inverse correlation between log10 transformed PFOS concentration in cord blood and FEV1, FVC, PEF and FEV1/FVC values. We further stratified analyzed the correlation between PFOS in cord serum and lung function. The lower birth weight group is significantly inversely correlated between their PFOS in cord blood and forced expiratory volume in 1 second. And the group of children with allergic rhinitis is significantly inversely correlated between their PFOS in cord blood and peak expiratory flow.

The demographic differences between participant and non-participant groups are small except the percentage of environmental tobacco smoking is higher in participant group. This condition could be explained by recall bias in participant group. On the part of property, the participant group has a lower percentage of property lower than 600 thousands New Taiwan Dollar (Namely, about less than 20 thousand US dollars)

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per family per year. This might be due to the accessibility is usually higher for high income families. Otherwise, the total TBPS, non-participants and participants, were generally similar in their demographic details.

In this cohort study, we found that PFAS were higher in cord blood than in eight-year-old blood. This might be related to the different mechanism which caused placental accumulation of PFAS or there were increased exposure to PFAS in pregnant women. A previous Spanish cohort study revealed the concentration of PFAS in cord samples and concentration in maternal plasma are correlated. There might be an active or passive transportation from mother plasma into crod plasma, which caused fetal intra-uterine exposure to PFAS. The transporting mechanism of PFAS need further survey (Manzano-Salgado et al. 2015).

We investigated the lung function in children with PFOA, PFOS, PFNA, and PFUA in cord blood and in eight-year-old blood. We found the concentration of PFOS in cord blood were inversely associated with FEV1 values at eight years of age among children whose birth weight no more than 3200 gram and with PEF values among children with allergic rhinitis. However, we did not find a convincing association between intra-utero exposure to PFOA, PFNA or PFUA and lung development at

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eight years of age. The explanations of why intra-uterine PFAS exposure influenced children's lung function might be the higher dose in prenatal stage or the timing of critical stage of lung development. A previous study showed that very low birth weight persons had more adulthood airways obstruction compared with controls (Gibson AM et al. 2015). Therefore, the low birth weight group might be a susceptible group in lung diseases development. There is a common pathophysiology in asthma and rhinitis shown in previous study (Chawes BL. 2011) . This explained our results that why the allergic rhinitis graoup is more susceptible.

Our study results found an increasing trend in cord blood PFOS levels with decreasing lung function values at eight years of age among children with lower birth weight (≤3200 gram). Human epidemiologic studies had reported that prenatal exposure to PFOS had an adversely associated with birth weight (Chen MH et al. 2012; Maisonet et al. 2012). There was an animal study demonstrated that rat intra-utero exposure to PFOS had the thicker alveolar walls, considering that PFOS may interfere with perinatal lung development (Grasty et al. 2005). On the other hand, Ye et al. (2012) suggested that PFOA and PFOS are the inhibitors of 11beta-hydroxysteroid dehydrogenase 1 (11βHSD1). The 11βHSD1 had been reported to regulate the levels of the glucocorticoid in the lung (Suzuki et al. 2003). The

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glucocorticoids are important hormones for pulmonary maturation and may affect the development of neonatal lung disease in preterm infants (Bolt et al. 2001). Hence, the inhibition of 11βHSD1 may be connected to the delay of fetal or neonatal lung development. According to our stratified result (Table 4) the influence of PFOS on lung function had been found only in children with lower birth weight (≤3200g). There was a possible modification effect of prenatal exposure to PFOS on lung development by birth weight.

Evidence from human studies suggested that prenatal exposures to PFAS may have deleterious effects on immune responses. Our previous TBPS researched the effects of intra-utero exposure to PFAS on atopic dermatitis at two years of age found that cord blood PFOA and PFOS levels is not correlated with the development of atopic dermatitis (Wang et al. 2011). Another Japanese birth cohort study indicated the similar result that there was no significant association between maternal PFOS and PFOA level and occurrence of infant wheezing and atopic dermatitis during the first 18 months of life (Okada et al. 2012). Furthermore, in a large-sized Danish National Birth Cohort demonstrated that there was not significant association between PFOS and PFOA levels in maternal blood and increased risk of infectious diseases hospitalization in early childhood (Fei et al. 2010). However, in a case-control study

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classified the PFAS levels into quartiles demonstrated that the levels of PFOA and PFOS in serum were positively correlated with IgE levels and asthma severity scores among children with asthma (Dong et al. 2013).

Our results also suggested an increasing trend in PFOS levels with decreasing lung function values among children with allergic rhinitis. Rhinitis had been reported having strongly associated with increased risk of asthma development (Tore´ n et al., 2002; Guerra et al. 2002). In view of this, the effects of prenatal PFAS exposures on allergic rhinitis in childhood warrants further investigation.

Potential limitations in this study should be concerned. First, the demographic characteristics of follow-up subjects were different from the original cohort, which may contribute the possibility of selection bias. The participation desire might be higher in those parents with higher income and education. And the higher ETS percentage might also related to their better self-awareness. Second, we only used cord blood and eight-year-old blood to represent prenatal and postnatal PFAS exposure concentration. However, the half-life of PFOA and PFOS in humans is 5.4 years and 3.8 years (Olsen et al. 2007). The concentrations though will remain fairly constant in short time and increase with age (Harada et al. 2007). More time points

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might be needed to reveal the tendency more clearly because breastfeeding might also increase PFAS concentration in early infant life. Third, the population size was relatively small. There were not sufficient cases to further clarify the correlation between intra-utero PFAS exposure and development of allergic diseases. There are some correlation tendency noted in some subgroups but failed to reach statistical power due to our smaller size of population. Finally, further long-term follow-up researches are needed to clarify the association between PFAS exposure, lung function and allergic disease due to long half-life of PFAS.

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V. Conclusions

Our cohort study suggested that the concentrations of PFOA, PFOS, PFNA and PFUA were geometrically higher in cord blood than in eight-year-old serum. We did not found the convincing evidences that PFAS significantly affect children's pulmonary functions. However, there were some trends noted between intrauterine PFOS and decreasing FEV1, FVC and PEF in children stage, especially in subgroups of lower birth weight and allergic rhinitis. The prenatal role of PFOS to children's lung development may need further investigation.

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Table 1 Basic characteristics of study population [mean ± standard deviation or n(%)].

Abbreviations: ETS, environmental tobacco smoke; PFOA, perfluorooctanoic acid; PFOS, perfluorooctyl sulfonate; PFNA, perfluorononanoic acid; PFUA, perfluoroundecanoic acid; FEV_1, forced expiratory

	Total	Non-participants	Participants
	n=439	n=274	n=165
Characteristics at birth			
PFOA in cord blood (ng/mL)[a]	2.6 ± 2.4	2.7 ± 2.5	2.4 ± 2.2
PFOS in cord blood (ng/mL)[a]	7.6 ± 7.3	8.4 ± 8.3	6.4 ± 5.1
PFNA in cord blood (ng/mL)[a]	6.3 ± 8.4	6.4 ± 7.9	6.0 ± 9.1
PFUA in cord blood (ng/mL)[a]	16.9 ± 15.9	17.7 ± 16.0	15.4 ± 15.6
Pregnancy age (years)[a]	30.8 ± 4.6	29.9 ± 4.7	32.3 ± 4.0
Gestational age (weeks)[a]	38.5 ± 1.7	38.3 ± 1.7	38.7 ± 1.7
Maternal education[b]			
high school or below	145 (33.3)	117 (43.3)	28 (17.0)
collage or above	294 (67.6)	157 (58.1)	137 (83.0)
Prenatal ETS exposure[b]			
no	317 (72.2)	227 (83.2)	89 (53.9)
yes	122 (27.9)	46 (16.9)	76 (46.1)
Family income per year[b]			
<600000 NT$	122 (28.0)	92 (34.1)	30 (18.2)
600000~1500000 NT$	248 (57.0)	141 (52.2)	107 (64.8)
> 1500000 NT$	65 (14.9)	37 (13.7)	28 (17.0)
Infant sex[b]			
boy	229 (52.2)	148 (53.8)	82 (49.7)
girl	210 (47.8)	127 (46.2)	83 (50.3)
Infant birth weight (g)[a]	3166.9 ± 471.8	3133.5 ± 461.7	3222.0 ± 484.2
Characteristics at 8-year-old			
PFOA in 8-year-old blood (ng/mL)[a]	—	—	2.7 ± 1.5
PFOS in 8-year-old blood (ng/mL)[a]	—	—	5.9 ± 20.4
PFNA in 8-year-old blood (ng/mL)[a]	—	—	0.6 ± 0.8
PFUA in 8-year-old blood (ng/mL)[a]	—	—	0.3 ± 0.4
Height (cm)[a]	—	—	135.1 ± 6.1
Weight (kg)[a]	—	—	31.9 ± 7.0
Body mass index (kg/m^2)[a]	—	—	17.4 ± 3.0
Asthma[b]	—	—	27 (16.4)
Allergic rhinitis[b]	—	—	87 (52.7)
Atopic dermatitis[b]	—	—	30 (18.2)
FEV_1 (mL)[c]	—	—	1679 ± 244
FVC (mL)[c]	—	—	1835 ± 295
PEF (mL/sec)[c]	—	—	3846 ± 608
FEV_1/FVC (%)[c]	—	—	92.0 ± 5.9

doi:10.6342/NTU201602459

volume in 1 sec; FVC, forced vital capacity; PEF, peak expiratory flow. For PFOA, PFOS, PFNA and PFUA concentration under limits of quantitation (LOQ) were set to be one-half of LOQ. [a]Values are mean ± standard deviation. [b]Values in parentheses are percent. [c]Values are range during spirometry.

doi:10.6342/NTU201602459

Table 2 Comparison of concentrations of perfluoroalkyl substances [geometric mean (geometric standard deviation) ng/mL] between in cord blood and in 8-year-old blood.

	PFOA	**PFOS**	**PFNA**	**PFUA**
in cord blood	1.7 ± 1.0*	5.2 ± 0.8**	2.2 ± 1.8**	9.1 ± 1.3**
8-year-old blood	1.1 ± 3.7*	2.8 ± 1.7**	0.1 ± 3.7**	0.0 ± 3.9**

Abbreviations: PFOA, perfluorooctanoic acid; PFOS, perfluorooctyl sulfonate; PFNA, perfluorononanoic acid; PFUA, perfluoroundecanoic acid.

For PFOA, PFOS, PFNA and PFUA concentration under limits of quantitation (LOQ) were set to be one-half of LOQ.

*P<0.05 **P<0.001

doi:10.6342/NTU201602459

Table 3 Regression coefficients (95% CI) between perfluoroalkyl substances concentrations (ng/mL) in cord blood and lung function values.

		FEV_1(mL)	FVC(mL)	PEF(mL/sec)	FEV_1/FVC (%)
		β coefficient (95% confidence interval)			
Cord blood					
log_{10}PFOA (ng/mL)	Crude	22.3 (-23.6, 68.2)	22.4 (-33.1, 78.0)	12.5 (-102.4, 127.4)	0.1 (-1.1, 1.2)
	Adjusted[a]	-4.6 (-39.3, 30.2)	-7.9 (-47.7, 31.8)	-44.8 (-148.7, 59.0)	0.1 (-1.0, 1.2)
log_{10}PFOS (ng/mL)	Crude	-47.2 (-104.9, 10.6)	-45.4 (-115.3, 24.6)	-109.2 (-253.5, 35.1)	-0.3 (-1.7, 0.3)
	Adjusted[a]	-33.2 (-77.5, 11.0)	-26.7 (-77.5, 24.1)	-83.7 (-216.4, 49.1)	-0.4 (-1.8, 1.1)
log_{10}PFNA (ng/mL)	Crude	5.6 (-18.6, 29.7)	9.1 (-20.1, 38.3)	-13.1 (-73.5, 47.2)	-0.3 (-0.9, 0.3)
	Adjusted[a]	-5.2 (-23.1, 12.7)	-3.1 (-23.6, 17.4)	-32.8 (-86.3, 20.6)	-0.3 (-0.8, 0.3)
log_{10}PFUA (ng/mL)	Crude	-0.5 (-33.8, 32.7)	-7.5 (-47.7, 32.7)	-23.6 (-106.6, 59.4)	0.3 (-0.5, 1.1)
	Adjusted[a]	3.2 (-21.6, 27.9)	-1.6 (-30.0, 26.7)	-15.1 (-89.2, 59.0)	0.2 (-0.6, 1.0)
8-year-old blood					
log_{10}PFOA (ng/mL)	Crude	11.1 (-27.5, 5.4)	-15.0 (-34.8, 4.9)	-20.5 (-61.7, 20.6)	0.1 (-0.3, 0.5)
	Adjusted[a]	-3.1 (-15.3, 9.2)	-5.8 (-19.8, 8.2)	1.0 (-35.8, 37.8)	0.1 (-0.3, 0.5)
log_{10}PFOS (ng/mL)	Crude	1.5 (-24.2, 27.3)	-2.7 (-33.8, 28.4)	3.0 (-61.2, 67.2)	0.2 (-0.4, 0.8)
	Adjusted[a]	2.8 (-16.3, 21.8)	-1.5 (-23.3, 20.3)	12.6 (-44.5, 69.6)	0.2 (-0.4, 0.8)
log_{10}PFNA (ng/mL)	Crude	-8.1 (-24.4, 8.3)	-15.9 (-35.6, 3.7)	-23.7 (-64.4, 17.1)	0.3 (-0.1, 0.7)
	Adjusted[a]	4.4 (-8.1, 16.9)	-0.4 (-14.7, 13.9)	1.7 (-35.8, 39.3)	0.2 (-0.2, 0.6)
log_{10}PFUA (ng/mL)	Crude	-1.2 (-17.3, 15.0)	-8.8 (-28.3, 10.7)	-14.4 (-54.7, 25.9)	0.3 (-0.1, 0.7)
	Adjusted[a]	1.4 (-10.7, 13.4)	-3.1 (-16.8, 10.7)	-7.2 (-43.2, 28.9)	0.2 (-0.2, 0.6)

Abbreviations: PFOA, perfluorooctanoic acid; PFOS, perfluorooctyl sulfonate; PFNA, perfluorononanoic acid; PFUA, perfluoroundecanoic acid.

For PFOA, PFOS, PFNA and PFUA concentration under limits of quantitation (LOQ) were set to be one-half of LOQ.

[a]Model adjusted for children sex, height, body mass index, birth body weight, mother education, eating habit, prenatal smoke history, history of environmental tobacco smoke exposure, maternal nicotine concentration exposure, gestational age, family income, whether using pesticide and incensing at home.

doi:10.6342/NTU201602459

Table 4 Regression coefficients (95% CI) between perfluorooctane sulfonate (PFOS) concentrations (ng/mL) in cord blood and lung function values stratified by birth weight and allergic diseases.

		FEV_1(mL)	FVC(mL)	PEF(mL/sec)	FEV_1/FVC (%)
		β coefficient (95% confidence interval)			
Birth body weight					
≦3200g(n=82)	Crude	-40.7 (-111.9, 30.6)	-29.9 (-116.7, 56.9)	-58.3 (-231.8, 115.1)	-0.7 (-2.2, 0.8)
	Adjusted[a]	**-64.7 (-115.5, -13.9)***	-49.1 (-112.6, 14.4)	-93.6 (-255.1, 67.9)	-1.1 (-2.8, 0.6)
>3200g (n=83)	Crude	-51.5 (-156.8, 53.8)	-66.0 (-192.2, 60.3)	-180.9 (-444.7, 82.9)	0.6 (-2.3, 3.5)
	Adjusted[a]	21.5 (-76.6, 119.6)	30.0 (-78.4, 138.5)	-181.5 (-449.6, 86.6)	0.2 (-2.9, 3.3)
Family history of allergy					
Without family history	Crude	-49.2 (-129.2, 30.8)	-34.2 (-141.1, 72.7)	-144.7 (-334.8, 45.5)	-0.7 (-2.9, 1.6)
(n=59)	Adjusted[a]	-34.3 (-98.3, 29.7)	-13.7 (-82.7, 55.4)	-60.9 (-255.5, 133.7)	-0.8 (-3.0, 1.5)
With family history	Crude	-45.2 (-130.5, 40.1)	-55.3 (-152.7, 42.1)	-73.2 (-291.3, 144.8)	0.1 (-1.8, 1.9)
(n=106)	Adjusted[a]	-41.2 (-112.1, 29.6)	-57.8 (-141.9, 26.2)	-34.9 (-238.3, 168.5)	0.4 (-1.7, 2.6)
Asthma					
Without asthma	Crude	-46.1 (-109.2, 16.9)	-38.4 (-113.3, 36.4)	-108.7 (-265.5, 48.2)	-0.4 (-1.9, 1.1)
(n=138)	Adjusted[a]	-27.6 (-74.0, 18.7)	-16.0 (-65.8, 33.8)	-62.9 (-205.1, 79.3)	-0.5 (-2.0, 1.1)
With asthma	Crude	-63.9 (-209.3, 81.5)	-96.0 (-306.7, 114.8)	-129.5 (-522.1, 263.1)	0.3 (-3.5, 4.2)
(n=27)	Adjusted[a]	-65.4 (-420.9, 290.1)	-148.6 (-640.3, 343.0)	-492.5 (-1359.9,374.9)	1.8 (-5.0, 8.6)
Allergic rhinitis					
Without allergic rhinitis	Crude	-61.2 (-149.7, 27.3)	-76.4 (-181.3, 28.5)	6.2 (-221.9, 234.2)	-0.5 (-1.9, 2.9)
(n=78)	Adjusted[a]	-23.7 (-94.5, 47.1)	-29.6 (-104.1, 44.9)	90.2 (-127.3, 307.8)	0.3 (-2.3, 2.9)
With allergic rhinitis	Crude	-38.7 (-116.6, 39.2)	-26.2 (-121.9, 69.5)	-182.9 (-371.3, 5.5)	-0.8 (-2.5, 0.9)
(n=87)	Adjusted[a]	-52.4 (-118.4, 13.5)	-37.2 (-116.8, 42.4)	**-221.0(-405.6,-36.5)***	-1.0 (-2.9, 1.0)

For PFOS concentration under limits of quantitation (LOQ) were set to be one-half of LOQ.

[a]Model adjusted for children sex, height, body mass index, birth body weight, mother education, eating habit, prenatal smoke history, history of environmental tobacco smoke exposure, maternal nicotine concentration exposure, gestational age, family income, whether using pesticide and incensing at home.

*P<0.05

doi:10.6342/NTU201602459