



Association between prenatal exposure to perfluoroalkyl substances and asthma-related diseases in preschool children

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Abstract

Thus far, the few studies on the associations between perfluoroalkyl substances (PFASs) and asthma in children have yielded inconsistent results. In this study, we aimed to evaluate whether and to what extent prenatal PFASs exposure is associated with childhood asthmatic diseases. Eight PFASs were measured in cord blood drawn from 358 children in the Shanghai Allergy Birth Cohort, and a 5-year follow-up plan was completed. Asthma was diagnosed and reported by pediatric respiratory physicians via repeated symptoms (wheezing and coughing) and laboratory examination (Immunoglobulin E level test and skin prick test). A total of 26.6% and 17.4% subjects were diagnosed with wheezing and asthma, respectively. Multivariable logistic regression and piecewise linear regression were applied, and no association was found between PFASs and asthma or wheezing. However, cord serum PFOA, PFOS, and PFDA were positively correlated with serum total IgE in 5-year-old children as the level of the former beyond the turning point (4.37 ng/mL, 2.95 ng/mL, and 0.42 ng/mL, respectively), but negatively with IgE before it reach turning point.

Keywords Perfluoroalkyl substances · Prenatal exposure · Asthma · Immunoglobulin E · Birth cohort study

Introduction

Asthma is a common chronic disease whose prevalence, especially in children, has considerably increased around the world in recent years. The pathogenesis of asthma may be

associated with both environmental and immunological factors (Kim et al. 2010). Perfluoroalkyl substances (PFASs), a series of synthetic compounds, are widely used in a variety of consumer products and industrial applications, such as in furniture, clothing, and even food packaging (Fromme et al.

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2009). Since PFASs can cross the placental barrier to the fetus or enter a baby's system via breast milk (Cariou et al. 2015; Chen et al. 2017), it may have negative impacts on children's health. Previous cellular and animal studies have demonstrated the immunotoxic effects of PFASs (DeWitt et al. 2012), indicating that exposure to PFASs may cause decreased lymphoid organ weights and series of immunological responses. Asthma is an allergic disease that often coexists with rhinitis and eczema in children (Pinart et al. 2014). Previous studies on the associations between PFASs and asthma-related outcomes in children have yielded inconsistent results. A case-control study in adolescents with 231 asthma and 225 healthy controls found that blood perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), **perfluorobutane sulfonate** (PFBS), perfluorododecanoic acid (PFDoA), and perfluorohexane sulfonic acid (PFHxS) concentrations were significantly higher in children with asthma compared to those without asthma (Dong et al. 2013). A positive association was also detected between cord-blood IgE and prenatal PFOA exposure in Taiwan Birth Panel cohort, but no associations when the children were 2 years old (Wang et al. 2011). Odds ratios for the risk of wheezing was reduced with increasing maternal PFHxS levels in the Japanese birth cohort (Goudarzi et al. 2016), whereas other studies from the birth cohort found no association between prenatal PFASs exposure and asthma or wheezing (Granum et al. 2013; Impinen et al. 2018; Smit et al. 2015). Therefore, despite increasing evidence that PFASs lead to reduced vaccinations responses and an increased risk of infectious diseases, it is not well understood whether long-term exposure to PFASs causes allergy-related outcomes (Chang et al. 2016).

To our knowledge, in most of these studies, asthma was self-reported by patients (Humblet et al. 2014; Timmermann et al. 2017) or diagnosed via questionnaires (Goudarzi et al. 2016; Granum et al. 2013; Okada et al. 2012; Smit et al. 2015), and rarely performed lung function or IgE tests which may have contributed to the inaccuracies of asthmatic outcome definition and the inconsistencies in the results. In this study, with a team of pediatric experts and a 5-year follow-up plan, we analyzed data of the Shanghai Prenatal Cohort to comprehensively evaluate the association of cord-plasma PFASs concentrations and childhood asthma, as well as the extent of the associations.

Methods

Study population

The Shanghai Allergy Birth Cohort is an ongoing perspective birth cohort. Women in the third-trimester (29–41 gestational weeks) of pregnancy were recruited during June 2012–March

2015 from two tertiary-level hospitals in Shanghai, Xinhua Hospital and the International Peace Maternity and Child Health Hospital. At enrollment, a face-to-face questionnaire survey was administered by trained interviewers to collect information on maternal age, weight, parental education levels and types of occupation, and parental history of atopic diseases (i.e., atopic dermatitis, allergic rhinitis, hives, or asthma). At birth, trained nurses collected the information on the newborn's anthropometric measurements and umbilical cord blood specimen. Information was also extracted from the hospital medical records system with the patients' consent. The follow-up was conducted by a group of pediatric experts, particularly respiratory pediatricians, when the children were within 2 months of their birthday every year. In these sessions, information on allergy-related health outcomes and blood samples were collected. A total of 1143 mother-infant pairs were enrolled in our study as a baseline. Of these pairs, 743 pairs (65%) completed the 5-year follow-up visit (including 198 in telephone interview). Finally, 358 children for whom both measured cord serum PFASs concentrations and had asthma-related outcomes as reported by pediatricians were included in the present study. The study protocol was approved by the Ethics Committees of all the involved research institutions and hospitals. Written informed consent was obtained from all mothers.

Cord blood PFASs concentrations

A total of 10 mL of umbilical cord blood specimens were collected at delivery. The blood specimens were centrifuged at 4000 rpm for 10 min immediately after collection at the hospital. The plasma was then separated and stored at -80°C on dry ice until shipment to the central laboratory at Xinhua Hospital for analysis. The plasma samples were extracted using the protein precipitation extraction method developed by Lien et al (Lien et al. 2011). Ten PFASs, viz., PFOA, PFOS, PFNA, PFBS, PFDoA, PFHxS, perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnA), perfluorooctane sulfonamide (PFOSA), and perfluoroheptanoic acid (PFHpA), were measured by using liquid chromatography-mass spectrometry/mass spectrometry (LC/MS). The PFASs (95%) were purchased from Wellington Laboratories (Guelph, Ontario, Canada); $^{13}\text{C}_4$ -PFOS and $^{13}\text{C}_4$ -PFOA, supplied by Sigma-Aldrich (St. Louis, MO, USA), were used as the internal standard solution. Because of a detection rate of less than 30%, we excluded PFHpA and PFOSA prior to data analyses.

Detailed assay methods for cord serum PFASs have been described in our previously published article (Wang et al. 2016). Briefly, PFASs were separated and quantified on LC-MS (Agilent 1290-6490, Agilent Technologies Inc., USA). All operations were strictly in accordance with the operating instructions. The mass spectrometry was operated in the

electrospray ionization negative mode with multiple reaction monitoring. The limits of detection (LOD), defined as a signal-to-noise ratio of 3, ranged from 0.009 to 0.12 ng/mL for the selected PFASs, and for concentrations below LOD, a value of half the lower limit was assigned.

Asthma diagnosis

Airflow limitation, the main pathologic hallmark of asthma, was assessed by professional respiratory pediatricians (using Master Screen IOS, Jaeger, Germany) when the children reached the age of 5. Skin prick test (SPT) for 18 common inhalants and food allergens, including dust mites (*dermatophagoides pteronyssinus* and *dermatophagoides farinae*), cat/dog dander, *aspergillus niger*, ragweed/indus/birch tree/willow pollen, egg, cow's milk, mango, sea shrimp, sea crab, beef, mutton, cashew nut, and walnut, was performed by pediatricians according to the European standardization procedures for SPT, with a positive result defined as a wheal of diameter ≥ 3 mm (Heinzerling et al. 2013). We also tested the serum total IgE levels of children at 5 years of age using the Enzyme-linked Immunosorbent Assay (Roche Elecsys 2010 immunoassay analyzers, Roche, Basel, Switzerland). Asthma was thus diagnosed clinically by pediatricians according to the Global Initiative for Asthma (GINA) guidelines (Pedersen et al. 2011): repeated episodes of wheezing and coughing during the past 5 years or a positive SPT response to dust mites. Since the high false negative error of the diagnosis of asthma at 5-year-age, pediatric respiratory physician performed lung-function tests for every volunteer as compliment. A child would be classified as IgE-mediated asthma if he/she were diagnosed with asthma and had serum total IgE levels higher than 100 ng/mL.

Statistical analysis

Means (standard deviations: SD), medians (P_{25} , P_{75}), and frequency (percentage %) were calculated for sociodemographic characteristics, cord serum PFASs concentrations, and asthma-related health outcomes among boys and girls. The gender differences of baseline characteristics were tested by chi-squared tests or Student's *t* tests whenever appropriate. The serum total IgE levels in 5-year-old children and the cord serum PFASs concentrations were log₁₀-transformed in all analyze modals due to their initial skewed distribution. The associations between cord blood plasma PFASs concentrations and the risk of asthmatic diseases were analyzed using multivariate logistic regression. Potential confounders were selected based on a directed acyclic graph, and included data on childrens' gender, gestational age, weight at age 5, whether

or not they were breastfed during the first 6 months, and data on maternal on education, pre-pregnancy body mass index, and family annual household income (Supplementary Materials: Figure S1). Although a small number (0.3 to 10%) of mother-infant pairs were missing data on child weight at age 5, gestational age, breastfeeding during the first 6 months, maternal education, pre-pregnancy body mass index, and annual household income, they were also finally included into all models. We also conducted piecewise linear regression models to examine the threshold effects of PFASs concentrations on IgE concentrations according to the smoothing plot with the adjustment for the abovementioned potential confounders. The threshold level (i.e., turning point) was determined using a trial method. The turning point was moved along a pre-defined interval and detected the inflection point that gave the maximum model likelihood was detected (Liu et al. 2013). All analyses were performed using Empower R (www. [empowerstats.com](http://www.empowerstats.com), X&Y solutions, Inc., Boston MA, USA) and R software (<http://www.T-proje ct.org>). A *P* value of 0.05 or less for tails was considered statistically significant.

Furthermore, meta-analyses of PFASs-asthma epidemiologic studies were performed using the statistical software Stata 12.0 (Stata Corp, College Station, TX, USA). The [Supplementary Materials](#) include a brief explanation of how these meta-analyses were conducted.

Results

In total, 358 children were included in present research, about half of them were boys (52%) (Table 1). The maternal age ranged from 25 to 33 years. Over 90% of the mothers were nulliparous, and more than 80% had bachelor's degree. About a quarter of the mothers had a history of allergenic diseases. Only 2.70% of the boys and 3.49% of the girls were of pre-term birth. The baseline maternal characteristics for the girls and the boys were comparable (all *P* values > 0.05).

PFASs concentrations in cord serum

Of all the eight PFASs, PFOA was the most abundant in cord serum, with median concentrations of 7.13 ng/mL (P_{25} – P_{75} : 5.15–9.97) for boys and 6.51 ng/mL (P_{25} – P_{75} : 4.57–8.73) for girls. This was followed by PFOS, with median serum concentrations of 2.49 ng/mL for boys and 2.38 ng/mL for girls. The median concentrations of the remaining six compounds were very low, ranging from 0.09 to 0.64 ng/mL (Table 2). No statistically significant differences in PFASs were observed between boys and girls (*P* > 0.05), except for PFOA concentrations.

Table 1 Basic characteristics of mother-child pairs in the Shanghai Allergy Birth Cohort, 2012–2017 ($N = 358$)

Characteristics	Boys $n = 187$	Girls $n = 171$	P value ^a
Parental characteristics			
Maternal age, years ^b	28.8 ± 3.58	29.5 ± 4.20	0.12
Maternal pre-pregnancy body mass index, kg/m ² ^b	21.8 ± 4.14	21.5 ± 3.94	0.54
Maternal education, n (%)			0.54
< Bachelor	22 (12.0)	23 (13.4)	
Bachelor	147 (79.9)	131 (76.6)	
> Bachelor	15 (8.15)	17 (9.94)	
Positive maternal allergy, n (%)	38 (20.7)	28 (16.4)	0.52
Parity, n (%)			0.84
Nulliparous	171 (92.4)	159 (93.0)	
Gestational week at blood drawing, n (%)			0.87
Preterm birth (≤ 36 w)	5 (2.70)	6 (3.49)	
Full-term birth (37–41 w)	180 (97.3)	165 (96.5)	
Annual household income (USD), n (%)			0.86
< 15,000	16 (9.30)	10 (6.76)	
15,000–35,000	71 (41.0)	66 (44.6)	
35,000–70,000	57 (33.0)	44 (29.7)	
> 70,000	19 (11.0)	18 (12.2)	
Children characteristics			
Breastfeeding (6 months), n (%)	76 (42.7%)	79 (49.1%)	0.46
Age, years ^b	4.84 ± 0.15	4.84 ± 0.16	0.50
Weight, kg ^b	19.9 ± 3.33	18.9 ± 3.05	0.01
Height, cm ^b	111 ± 4.29	110 ± 4.46	0.00

^a P values were calculated by the chi-squared tests for the categorical variables and Student's t tests for the continuous variables

^b Data presented are median (P_{25} – P_{75}) or mean ± standard deviation

Association between cord serum PFASs concentration and risk of childhood asthma

Boys had significantly higher rates of asthma-related health outcomes compared to girls. With regard to serum total IgE levels, in 5-year-olds, it was found to be significantly higher in boys than in girls (median serum concentrations: 113 ng/mL for boys vs. 43.7 ng/mL for girls;

$P < 0.001$) (Table 3). There were no significant associations between cord serum PFASs and risk of childhood asthmatic diseases after adjustment for potential confounders (Table 4). The risk of SPT being sensitive to any allergen did not correlate with increasing PFASs levels, although several PFASs increased the risk of sensitivity to dog dander in preschool children (Table S1). Further, cord serum PFOA, PFOS, and PFDA were

Table 2 PFASs concentrations in cord blood for boys and girls ($N = 358$; 187 boys vs. 171 girls).

PFASs (ng/mL)	Boys median (P_{25} – P_{75})	Girls median (P_{25} – P_{75})	P value
PFOA	7.13 (5.15–9.97)	6.51 (4.57–8.73)	0.04
PFOS	2.49 (1.81–3.51)	2.38 (1.73–3.13)	0.31
PFBS	0.05 (0.04–0.06)	0.04 (0.04–0.06)	0.43
PFHxS	0.17 (0.13–0.21)	0.16 (0.13–0.20)	0.38
PFDoA	0.09 (0.07–0.12)	0.09 (0.07–0.12)	0.75
PFUnA	0.40 (0.29–0.52)	0.39 (0.27–0.53)	0.49
PFDA	0.36 (0.23–0.54)	0.35 (0.22–0.52)	0.40
PFNA	0.64 (0.51–0.83)	0.64 (0.48–0.84)	0.97

PFASs, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFBS, perfluorobutane sulfonate; PFHxS, perfluorohexane sulfonic acid; PFDoA, perfluorododecanoic acid, PFUnA, perfluoroundecanoic acid; PFDA, perfluorodecanoic acid; PFNA, perfluorononanoic acid

Table 3 Reported asthma-related disease outcomes during 0–5 years for boys and girls

Respiratory health outcomes	Boys <i>n</i> = 187	Girls <i>n</i> = 171	<i>P</i> value
Wheezing ever, <i>n</i> (%)	60 (32.3)	35 (20.5)	0.01
Asthma, <i>n</i> (%) ^a	41 (22.0)	21 (12.3)	0.02
IgE mediated asthma, <i>n</i> (%)	31 (19.6)	15 (9.6)	0.01
Positive skin prick test, <i>n</i> (%) ^b	86 (53.4)	65 (40.9)	0.04
Levels of IgE at 5 years old ^c	113 (37.0–313)	43.7 (17.9–111)	< 0.01

^a Asthma: eventual doctor-diagnosed asthma^b One or more positive skin prick test responses to 18 common inhalants and food allergens^c Data presented are median (P_{25} – P_{75}); Serum total IgE levels were evaluated by ELISA

nonlinearly correlated with serum total IgE levels in 5-year-old children (Table 5 and Fig. 1). Serum total IgE levels decreased with increasing PFOA before PFOA

reached 4.37 ng/mL, with a correlation coefficient of – 2.27 (– 3.79, – 0.76), but increased with increasing PFOA as the level of this indicator increased beyond the

Table 4 Adjusted associations between PFASs concentrations in cord blood and asthma-related health outcomes in 5-year-old boys and girls.

PFASs ^a	Boys		Girls		Total	
	OR ^b (95% CI)	<i>P</i> value	OR ^b (95% CI)	<i>P</i> value	OR ^b (95% CI)	<i>P</i> value
Wheezing ever						
PFOA	0.21 (0.04, 1.24)	0.09	1.19 (0.15, 9.74)	0.87	0.54 (0.16, 1.86)	0.33
PFOS	2.72 (0.43, 16.99)	0.29	0.28 (0.03, 2.51)	0.25	1.09 (0.29, 4.12)	0.90
PFBS	0.44 (0.04, 4.92)	0.50	0.29 (0.01, 5.87)	0.42	0.62 (0.11, 3.45)	0.58
PFHxS	0.90 (0.07, 11.23)	0.94	0.20 (0.01, 5.05)	0.33	0.63 (0.10, 3.80)	0.61
PFDaA	7.06 (0.85, 58.38)	0.07	0.31 (0.03, 3.25)	0.33	1.91 (0.46, 8.00)	0.37
PFUnA	2.20 (0.38, 12.61)	0.37	0.20 (0.02, 1.68)	0.14	0.94 (0.26, 3.36)	0.93
PFDA	1.28 (0.39, 4.17)	0.68	0.33 (0.08, 1.39)	0.13	0.80 (0.35, 1.88)	0.62
PFNA	0.64 (0.06, 6.48)	0.71	0.09 (0.01, 1.65)	0.11	0.43 (0.09, 2.20)	0.31
Asthma						
PFOA	0.32 (0.04, 2.36)	0.26	5.60 (0.22, 145.87)	0.30	0.98 (0.22, 4.49)	0.98
PFOS	4.69 (0.51, 42.77)	0.17	0.17 (0.01, 4.15)	0.27	1.49 (0.29, 7.54)	0.63
PFBS	0.36 (0.02, 6.69)	0.50	0.74 (0.01, 76.99)	0.90	0.38 (0.05, 3.23)	0.38
PFHxS	3.40 (0.18, 65.11)	0.42	0.48 (0.00, 85.33)	0.78	2.02 (0.24, 17.24)	0.52
PFDaA	9.40 (0.75, 117.95)	0.08	0.13 (0.01, 2.95)	0.20	1.98 (0.36, 10.80)	0.43
PFUnA	3.35 (0.41, 27.32)	0.25	0.10 (0.00, 1.90)	0.12	0.90 (0.20, 4.11)	0.89
PFDA	1.09 (0.26, 4.50)	0.90	0.21 (0.03, 1.47)	0.12	0.63 (0.23, 1.72)	0.37
PFNA	1.10 (0.07, 16.71)	0.95	0.67 (0.01, 36.13)	0.85	1.05 (0.15, 7.59)	0.96
IgE mediated asthma						
PFOA	1.86 (0.13, 25.68)	0.64	0.89 (0.03, 30.47)	0.95	0.94 (0.14, 6.13)	0.95
PFOS	13.82 (0.98, 194.99)	0.05	0.12 (0.00, 4.71)	0.25	1.68 (0.26, 10.76)	0.58
PFBS	0.21 (0.00, 9.20)	0.42	1.47 (0.01, 203.99)	0.88	0.53 (0.05, 6.11)	0.61
PFHxS	19.34 (0.51, 732.38)	0.11	0.01 (0.00, 6.28)	0.16	1.32 (0.11, 16.42)	0.83
PFDaA	22.19 (0.92, 534.47)	0.06	0.35 (0.01, 11.80)	0.56	2.10 (0.30, 14.52)	0.45
PFUnA	7.37 (0.60, 90.77)	0.12	0.18 (0.01, 5.50)	0.32	1.10 (0.19, 6.24)	0.91
PFDA	2.28 (0.39, 13.35)	0.36	0.15 (0.01, 1.48)	0.10	0.68 (0.22, 2.07)	0.50
PFNA	8.89 (0.29, 277.13)	0.21	0.10 (0.00, 11.41)	0.34	0.75 (0.07, 8.02)	0.82

^a PFASs concentrations were log10-transformed^b The logistic regression models are expressed as ORs and 95% CI adjusted for child weight at age 5, gestational age, breastfeeding during the first 6 months, maternal education, maternal pre-pregnancy BMI, and annual household income

Table 5 Threshold effect of PFOA, PFOS, PFNA, and PFDA on serum total Immunoglobulin E levels in boys and girls by using piecewise linear regression

PFASs ^a (ng/mL)	Turning point	Adjusted β ^b (95% CI)	P value
Log PFOA	<0.64	-2.27 (-3.79, -0.76)	0.00
	≥ 0.64	0.61 (0.12, 1.10)	0.02
Log PFOS	<0.47	-0.63 (-1.21, -0.05)	0.04
	≥ 0.47	1.47 (0.38, 2.56)	0.00
Log PFNA	<-0.18	-0.97 (-1.85, -0.09)	0.03
	≥ -0.18	0.96 (-0.02, 1.94)	0.06
Log PFDA	<-0.38	-0.47 (-0.88, -0.07)	0.02
	≥ -0.38	1.28 (0.45, 2.11)	0.00

^a PFAS concentrations were log10-transformed

^b The piecewise linear models are expressed as β and 95% CI adjusted for child gender, child weight at age 5, gestational age, breastfeeding during the first 6 months, maternal education, maternal pre-pregnancy BMI, and annual household income

turning point, with a correlation coefficient of 0.61 (0.12, 1.10). The association between PFOS and PFDA levels and IgE level, showing a dose-response relationship similar to PFOA, and the turning point of PFOS and PFOA was 2.95 ng/mL and 0.42 ng/mL, respectively.

Discussion

In our prospective birth cohort study, we did not find a significant association between cord serum PFASs concentrations and asthma in 5-year-olds. However, we found that the serum total IgE levels increased with increasing cord serum PFOA, PFOS, and PFDA concentrations beyond a certain range of concentrations, but inversely associated with them when lower than turning point. Our findings provide some evidence for the immunotoxicity effects of prenatal PFASs exposure for atopic response.

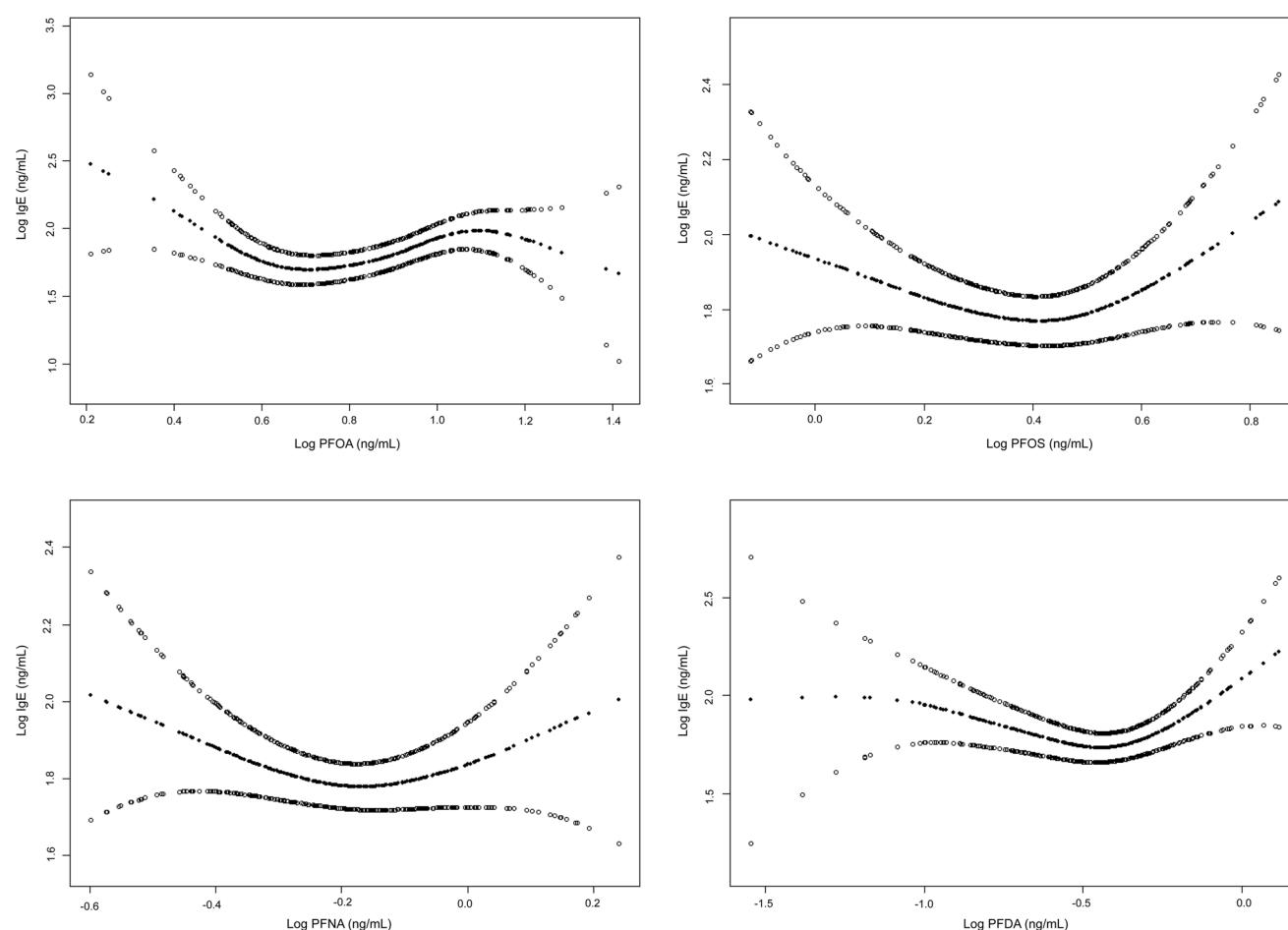


Fig. 1 The dose-response relationship between log-PFOA, log-PFOS, log-PFNA, and log-PFDA levels in cord blood and log-serum total IgE levels in 5-year-olds. The inflection point for PFOA, PFOS, PFNA, and PFDA were 4.37, 2.95, 0.66, and 0.42 ng/mL, respectively, adjusted for

child gender, child weight, gestational age, breastfeeding during the first 6 months, maternal education, maternal pre-pregnancy BMI, and annual household income.

To better understand the evidence for the association between PFASs and child asthmatic diseases, we retrieved the results of epidemiological studies from PubMed, including eight prospective studies, one case-control study, and two cross-sectional studies (Table 6). The study subjects were aged from 18 months to 18 years, and the final sample sizes varied from 56 to 1877 subjects. For asthma, our finding is in agreement with previous prospective studies in Faroese or Norwegian children where no associations were found between prenatal exposure to PFASs and asthma (Granum et al. 2013; Impinen et al. 2019; Impinen et al. 2018; Timmermann et al. 2017). Likewise, there were no associations between prenatal PFASs exposure and rhinitis and food allergy (Impinen et al. 2019; Impinen et al. 2018). Several other studies on allergy- and asthma-outcomes, however, have reported different findings. Cross-sectional studies from the USA and Norway have reported positive associations between juvenile asthma and concentrations of PFOS and PFOA (Averina et al. 2018; Humblet et al. 2014). With regard to risk of wheezing, a negative correlation between PFHxS and PFAS-PC5 (a component dominated by PFOA and PFHpA) was observed in children from Japan and Ukraine (Goudarzi et al. 2016; Smit et al. 2015), whereas other studies reported on no association (Impinen et al. 2018; Okada et al. 2012; Smit et al. 2015). Birth-cohort studies from Japan and Norway indicated that the risk of childhood eczema inverse associated with prenatal exposure to PFASs (Impinen et al. 2019; Okada et al. 2014). The results of the effects of PFASs exposure on childhood allergies are inconsistent; they may be attributed to several factors such as different timing of blood sampling, variation in the ages of the examined children, different PFASs exposure levels, and inconsistency in the definition of asthma. Nonetheless, the summary OR from further meta-analysis indicated that neither PFOS nor PFOA associate with asthma. There are some limitations in meta-analysis because the number of studies meeting the inclusion criteria is not large enough, and more research in this field are needed.

High serum IgE levels are a hallmark feature of allergic asthma and play a major role in allergic sensitization and chronic asthma (Johnson and Harker 2017). Studies on the effect of PFASs exposure on children's IgE level are rare and with controversial results (Chang et al. 2016). Our finding suggested that several PFASs positively associated with serum total IgE level when concentrations of the former higher than a certain range. Similarly, previous studies in Taiwan and the USA showed children with higher PFOA, PFOS, or PFNA had higher total IgE (Dong et al. 2013; Stein et al. 2016), whereas no association between PFASs and cord serum IgE were observed in children from Faroe Islands and Canada (Ashley-Martin et al. 2015; Timmermann et al. 2017).

The immunotoxic effects of prenatal PFASs have been demonstrated through *in vitro* and experimental animal studies (DeWitt et al. 2012). Although decreased splenic

and thymic weights, increased production of T-helper 2-type cytokines (Interleukin-4 (IL-4)), and IgE were reported in adult mice exposed to high doses of PFOS (Dong et al. 2011), the underlying mechanism of the immunotoxic effects of PFASs remains uncertain. Inhibition of nuclear factor kappa B (NF- κ B) and/or activation of the peroxisome proliferator-activated receptor (PPAR) signaling pathway could be a potential mechanism for this immunosuppression (Fang et al. 2008). The results of experimental animal study showed that production of IL-4 in high PFNA-treated groups was elevated compared with controls, as was expression of the PPAR (PPAR- α and PPAR- γ) (Fang et al. 2009). PFASs are known as agonists for PPARs, and PPAR- α agonists have been shown to promote IL-4 levels and negatively regulate NF- κ B signaling pathway (Fang et al. 2009; Lovett-Racke et al. 2004; Vanden Heuvel et al. 2006). Further, another experimental study by Fang et al. (2008) found that PFNA reduced production of IL-4 and upregulated expression of the PPAR (Fang et al. 2008). PFASs may effect the production of IL-4, a T-helper-type cytokine that induces IgE production, by activating the PPAR and/or inhibiting the NF- κ B signaling pathway, and thus indirectly regulate secretion of IgE in both directions. In addition, the results of a cohort study from Norway supported the immunotoxicity of PFAS and PPAR- and NF- κ B-mediated modes of action (Pennings et al. 2016). Our findings provide some evidence of immunotoxicity reported in these animal experiments. Nonetheless, this finding needs to be reconfirmed via further large-scale prospective cohort studies.

This study is a prospective cohort study involving the detailed characterization of children from birth to the age of five. A series of structured questionnaire surveys were administered by trained interviewers, and clinical examinations of children were conducted by a group of pediatricians from ten related specialties. There are some limitations to this study. First, the small size of this study gave it limited power to detect any associations, but it still provided some evidence for an association of prenatal PFASs exposure with serum total IgE levels due to sufficient subjects have IgE tested. Second, although asthma was diagnosed by an experienced pediatrician, making a diagnosis of asthma in 5-year-old children is difficult because wheezing and cough are very common in children who do not have asthma. About 40% of preschoolers worldwide have at least one episode of asthmatic symptoms (wheezing, coughing, or dyspnoea), but only 30% of them with recurrent wheezing are eventually diagnosed with asthma at age 6 (Ng and How 2014). Finally, airflow limitation, a standardized method for diagnosing respiratory diseases, cannot be applied routinely to children of this age group (Pedersen et al. 2011). Thus, the estimation of asthma may have slight errors (such as underestimations).

Table 6 Review of included or excluded studies meta-analysis of on PFASs and asthmatic diseases

Study	Study design	Location	Final sample size	Age of follow-up	Matrix	Gestational/week at blood draw	PFOA (ng/mL)	PFOS (ng/mL)	Major findings
Included									
Okada et al. (2012, 2014)	Prospective study	Japan	343	18 months	Maternal serum	After the second trimester	1.3 (0.8–1.7) ^a	5.2 (3.4–7.2) ^a	PFOAd and cord IgE (IU/ml) β (95% CI) = -1.0 (-1.9, -0.1)
Dong et al. (2013)	Case-control study	Taiwan	456	13 years	Child serum	Adolescence	With asthma: 1.2 (0.5, 2.2) ^a	With asthma: 33.9 (19.6, 61.1) ^a	PFOA and asthma Q ₄ vs Q ₁ OR (95% CI) = 2.6 (1.5, 4.7) PFOS and asthma Q ₄ vs Q ₁ OR (95% CI) = 4.0 (2.2, 7.4) PFOA ^a and Ever asthma OR (95% CI) = 1.18 (1.01, 1.39)
Humblet et al. (2014)	Cross-sectional study	USA	1877	12–19 years	Child serum	Adolescence	Current asthma: 4.2 (2.9, 5.6) ^a	Current asthma: 16.7 (10.3, 25.3) ^a	
Goudarzi et al. (2016)	Prospective study	Japan	1558	4 years	Maternal plasma	28–32 weeks	2.0 (1.3–3.3) ^a	4.9 (3.7–6.7) ^a	PFHxS and wheeze Q ₄ vs Q ₁ OR (95% CI) = 0.73 (0.497, 1.06) <i>P</i> trend = 0.038
Timmermann et al. (2017)	Prospective study	Farose	559	5 years/7 years/13 years	Maternal serum	At birth	3.3 (2.5; 4.0) ^a	27.4 (23.3; 33.3) ^a	Age 5 PFOAd and asthma OR (95% CI) = 10.37 (1.06; 101.93) Age 5 PFNAd and asthma OR (95% CI) = 12.52 (1.29; 121.67) NS ^c
Impinen et al. (2018)	Prospective study	Norway	641	2 years/10 years	Cord serum	At birth	1.6 (1.2–2.1) ^a	5.2 (4.1–6.6) ^a	
Averina et al. (2018)	Cross-sectional study	Norway	675	15 years/18 years	Child serum	Adolescence	Girls: 2.1 (1.2–3.7) ^c (0.7) ^c	Girls: 5.8 (2.7) ^c Boys: 6.8 (3.0) ^c	Σ PFOS and Current asthma Q ₃ vs Q ₁ OR (95% CI) = 2.23 (1.04, 4.76) NS ^d
Present study	Prospective study	Shanghai, China	357	5 years	Cord blood	At birth	6.70 (4.84–9.44) ^a	2.46 (1.77–3.32) ^a	PFOS and asthma OR (95% CI) = 1.24 (0.91, 1.69) PFOA and asthma OR (95% CI) = 1.34 (1.00, 1.79)
Overall*									
Excluded									
Wang et al. (2011)	Prospective study	Taiwan	244	2 years	Cord blood	At birth	1.7 (0.8–17.4) ^a	5.5 (0.1–48.46) ^a	PFOAd and cord IgE (KU/L) β (s.e.) = 0.13 (0.12) PFOSd and cord IgE (KU/L) β (s.e.) = 0.16 (0.15) NS
Granum et al. (2013)	Prospective study	Norway	56	3 years	Maternal serum	0–3 days after delivery	1.1 (0.8–1.4) ^a	5.5 (3.8–7.1) ^a	
Smit et al. (2015)	Prospective study	Greenland Ukraine	1024	5–9 years	Maternal serum	Mean: 25 weeks/24 weeks	Greenland: 1.8 (0.8–3.7) ^b Ukraine: 1.0 (0.5–2.3) ^b	Greenland: 20.6 (10.2–49.6) ^b Ukraine: 4.9 (2.3–9.9) ^b	PFAS-PC5 and wheeze Ukraine OR (95% CI) = 0.64 (0.41–0.99)

^aMedian (P25–P75)

^bGM (p5–p95)

^cGeometric mean with interquartile range (IQR)

^dPFAS concentrations were log10-transformed

^ePFAS concentrations were log 2-transformed

*Summary effect estimates calculated by random-effects models

Conclusions

Findings of this prospective birth cohort study indicated that no associations were found between prenatal exposure to PFASs and asthma in preschool children. However, several PFASs were positively correlated with serum total IgE in 5-year-old children as the level of the former higher than a certain range, but negatively with IgE before it reach turning point. A follow-up study of these same children at later ages and research on the mechanisms and potential immunotoxic effects of PFASs remain to be done.

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Ethics approval and consent to participate The ethics approval was obtained from the Xinhua Hospital and International Peace Maternity and Infant Health Hospital affiliated to the Shanghai Jiao Tong University School of Medicine. This study was conducted in accordance with the principles of the Helsinki Declaration.

Conflict of Interest The authors declare that they have no conflicts of interest.

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Supplemental Material

Table of Contents

Meta-analyses of PFAS–asthma epidemiologic studies

Figure S1. Direct Acyclic Graph (DAG) of the association between prenatal PFASs exposure and childhood asthmatic diseases.

Table S1. Adjusted associations between PFAS concentrations in cord blood and skin prick test (SPT) outcomes in preschool children.

References

Meta-analyses of PFAS–asthma epidemiologic studies

We retrieved human studies published in English up to December 2018 from the PubMed databases using the following search terms: ‘asthma’ and ‘perfluoralkyl substances’ or ‘PFASs’. This identified articles with the search terms in the title, abstract, or key words. Studies were eligible for inclusion in the analysis if they had results from an adjusted logistic regression model of asthma or wheezing as a function of Perfluorooctane sulfonate (PFOS) or Perfluorooctanoic Acid (PFOA) in concentrations of nanograms per milliliter in maternal blood from a prospective or cross-sectional study.

Five prospective studies (including the present study) and three cross-sectional studies were eventually included in the meta-analyses. In one prospective case (Goudarzi et al., 2016), Odd Ratio for the risk of wheezing were evaluated for PFASs concentrations in the second through fourth quartiles and compared. Three studies were excluded from the analysis for following reasons: the coefficients of interest could not be obtained (Granum et al., 2013); published results, atopic dermatitis and cord Immunoglobulin E were the outcome (Wang et al., 2011); and the analysis was performed using principal component analysis (Smit et al., 2015). We calculated summary effect estimates using random-effects models in the statistical software Stata 12.0 (Stata Corp, College Station, TX, USA).

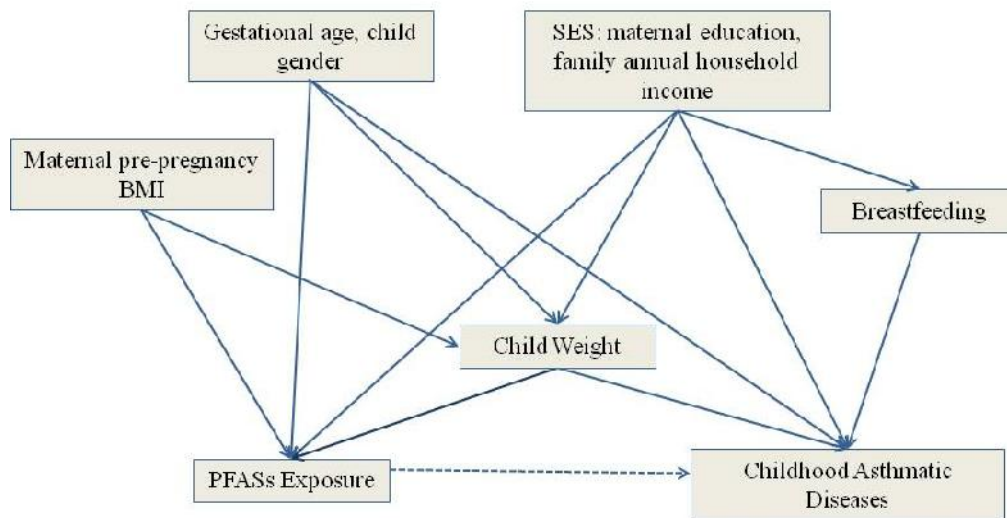


Figure S1. Direct Acyclic Graph (DAG) of the association between prenatal PFASs exposure and childhood asthmatic diseases.

Table S1. Adjusted associations between PFAS concentrations in cord blood and skin prick test (SPT) outcomes in preschool children.

PFAS ^a	SPT any positive ^c	D. pteronyssinus	D. farina	Dog dander	Cat dander
	OR ^b (95% CI)	OR ^b (95% CI)	OR ^b (95% CI)	OR ^b (95% CI)	OR ^b (95% CI)
PFOA	1.85 (0.58, 5.97)	1.46 (0.44, 4.86)	2.63 (0.75, 9.19)	11.61 (1.05, 129.04)	1.23 (0.13, 11.64)
PFOS	2.66 (0.75, 9.47)	2.33 (0.64, 8.49)	2.96 (0.80, 10.98)	6.86 (0.68, 69.18)	1.09 (0.10, 11.56)
PFBS	2.01 (0.41, 9.99)	2.09 (0.41, 10.62)	1.80 (0.35, 9.13)	6.08 (0.38, 98.21)	0.64 (0.04, 9.33)
PFHxS	1.51 (0.27, 8.48)	1.77 (0.30, 10.47)	2.31 (0.37, 14.39)	1.48 (0.07, 31.06)	0.52 (0.02, 12.51)
PFDoA	2.71 (0.68, 10.80)	2.34 (0.58, 9.49)	3.65 (0.86, 15.58)	6.56 (0.45, 95.84)	0.40 (0.04, 4.44)
PFUnA	1.95 (0.56, 6.76)	2.08 (0.58, 7.43)	3.18 (0.86, 11.78)	14.16 (1.11, 180.35)	0.54 (0.06, 4.86)
PFDA	1.67 (0.68, 4.08)	1.47 (0.59, 3.66)	2.13 (0.83, 5.46)	7.29 (1.15, 46.13)	1.10 (0.21, 5.82)
PFNA	1.78 (0.40, 7.95)	1.31 (0.28, 6.05)	2.26 (0.48, 10.64)	50.06 (2.77, 906.17)	1.97 (0.13, 29.36)

a, PFAS concentrations were log10-transformed;

b, The logistic regression models are expressed as ORs and 95%CI adjusted for child gender, child weight at 5 age, gestational age, breastfeeding during the first 6 months, maternal education, maternal pre-pregnancy BMI and annual household income;

c, SPT any positive: SPT that respond to at least one allergen.

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