



Prenatal perfluorooctanoic acid exposure is associated with early onset atopic dermatitis in 5-year-old children

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HIGHLIGHTS

- Prospective cohort study of 863 mother–infant pairs including AD children aged 0–5 years.
- Cord blood PFAS level was associated with significantly increased AD risk.
- Prenatal PFOA exposure is associated with earlier development of AD in children.

ARTICLE INFO

Article history:

Received 11 March 2019

Received in revised form

10 May 2019

Accepted 13 May 2019

Available online 16 May 2019

Handling Editor: A. Gies

Keywords:

Perfluorooctanoic acid

Atopic dermatitis

Birth cohort

Survival curve

ABSTRACT

Atopic dermatitis (AD) is the most common childhood skin disease and the first step of atopic march. Perfluoroalkyl substance (PFAS) exposure is associated with atopic diseases, including AD. However, whether PFAS exposure is related to earlier AD onset remains unclear. We aimed to investigate the association between prenatal PFAS exposure and earlier onset of AD in children in a 5-year follow-up study. From 2001 to 2005, 1264 mother–infant pairs were recruited from eight Taiwanese maternity hospitals. PFAS levels were analyzed from cord blood. Information on children's health status, including AD occurrence, was obtained via phone interviews at multiple time points. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) concentrations were measured by ultra-high performance liquid chromatography/tandem mass spectrometry. Cox proportional hazards models assessed associations between prenatal PFAS exposure and early onset AD. Overall, 863 mother–infant pairs with complete measurements were recruited. The prevalence of physician-diagnosed AD before 5 years of age was 7.1%. PFOA and PFOS concentrations were grouped based on whether they were above the 75th percentile. PFOA exposure was positively associated with earlier onset of AD (Kaplan–Meier estimate, $p = 0.014$). In the Cox model, after adjusting for sex, family income, parental atopy, breast feeding, and maternal age at childbirth, significance was observed in children above the upper quartile (≥ 75 th) of the PFOA group (hazard ratio: 1.89; 95% confidence interval, 1.10–3.16). Our findings suggested that children with higher prenatal PFOA exposure have a higher risk of earlier AD development. Minimizing early life PFAS exposure may help inhibit AD development.

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1. Introduction

Atopic dermatitis (AD) is a common skin disorder in children, is one of the first manifestations of the atopic march, and is a risk factor for respiratory allergic diseases, such as asthma and allergic rhinitis (Somanunt et al., 2017). The prevalence of AD is increasing

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worldwide (Nutten, 2015). In Taiwan, the prevalence of physician-diagnosed AD among school-age children increased from 1.6% in 1995–96 to 2.8% in 2001, and among preschool-age children was 8.7% in 2008 (Lee et al., 2005; Huang et al., 2018). Most AD symptoms appear early in life; about 50% of children with AD have symptoms before the age of 6 months and 85% of child patients develop symptoms in their first 5 years (Kay et al., 1994). The identification of risk factors of AD in early life may allow for potential prevention against AD development.

Perfluoroalkyl substances (PFASs) are widely used common synthetic chemicals in the environment (Fromme et al., 2009). In Taiwan, the concentration of PFASs in the downstream river of an industrial plant was 6930 ng/L for perfluorooctane sulfonate (PFOS) and 3298 ng/L for perfluorooctanoic acid (PFOA) (Lin et al., 2014). This concentration of PFOS exceeds the safe levels (43 ng/L) required for aquatic and avian life (Newsted et al., 2005). PFASs are composed of highly stable carbon-fluorine bonds with high chemical and thermal stability, durability, and strength (Buck et al., 2011). The health concerns for PFAS exposure are due to their persistence and bioaccumulation (Fernandez-Sanjuan et al., 2013).

The relationship between PFAS exposure and immune response/allergic disease has been reported previously. Decreased secretion of interferon- γ and interleukin (IL)-2 and increased secretion of IL-4, IL-10, and IgE antibody, the relevant immune response to atopic diseases, were found in PFOS exposed mice (Dong et al., 2011). In epidemiological studies, higher IgE concentrations were found in children with higher PFAS levels (Dong et al., 2013). Asthmatic children were also reported to have higher serum PFAS levels compared to children without (Dong et al., 2013). Furthermore, higher in utero PFOA exposure was associated with AD development in a 2-year follow-up birth cohort study (Chen et al., 2018).

Although PFAS exposure is associated with atopic diseases, the effect of PFAS exposure on earlier AD onset remains unclear. This study aimed to investigate the association between prenatal PFAS exposure and earlier onset of AD in children in a 5-year follow-up study.

2. Materials and methods

2.1. Study population

Pregnant women who had prenatal examinations at our eight cooperated maternity hospitals or medical centers were invited. They are from seven administration areas in Taiwan, including Taipei County, Yulin County, Jiayi City, Tainan County, Tainan City, Kaohsiung City, and Taitung City. Neonates born after July 2001 were consecutively recruited until July 2005 (Wen et al., 2011). Pregnant women provided written informed consent and were required to complete a structured questionnaire in their third trimester of pregnancy (range: 33.7–42.6 weeks). Peripheral venous blood samples were collected by well-trained nurses. After birth, neonatal umbilical cord blood was also obtained. A total of 1264 mother-neonate pairs were recruited. Our protocols were approved by the National Cheng Kung University Hospital Institutional Review Board and the National Taiwan University Hospital Institutional Review Board.

2.2. Data collection

Structured questionnaires were used to collect information regarding socioeconomic status, demographic data, indoor environmental exposure, and maternal/paternal history of allergic diseases. Data regarding birth outcomes, including birth weight and height, head circumference, and gestational age, were recorded by nurses after childbirth. Children were followed-up via phone

interview at the age of 3, 6, 12, 18, 24, and 60 months. Information on maternal breastfeeding status after delivery was also collected via phone interviews. The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was applied for informed allergic disease in children. Identification of children with or without AD in each follow-up was based on the response to the question “Did your child ever have physician-diagnosed atopic dermatitis?” and “Did your child ever have symptoms of itching and scratching of the skin and have a rash characteristic in arm folds and behind the knees?” Only children with the answer of “Yes” to both questions were considered as having AD. The age of AD onset was defined according to the first-time answer of “Yes” obtained from the six follow-up interviews.

2.3. Measurement of PFOA and PFOS

Cord plasma samples were sent to National Taiwan University for measurement of PFOA and PFOS as described previously. The detection of cord plasma PFOA and PFOS were performed on the Agilent-1200 high-performance liquid chromatography system (Agilent, Palo Alto, CA, USA) coupled with a triple-quadrupole mass spectrometer (Sciex API 4000, Applied Biosystems, Foster City, CA, USA). The limit of quantitation (LOQ) values for PFOA and PFOS were 0.45 ng/mL and 0.11 ng/mL, respectively. Neonatal cord plasma PFOA and PFOS levels below the LOQ were replaced by half-of-detection-limit values.

2.4. Statistical analyses

Student *t*-tests or non-parametric tests for continuous variables and chi-squared tests or Fisher's exact test for categorical variables were performed to assess the differences between study groups. Kaplan-Meier survival analysis was applied to evaluate the pattern of AD development, whereas the Log-rank test was used to compare the exposure groups. Cox proportional hazards models for evaluating hazard ratio (HR) was applied to assess the association between prenatal PFAS exposure and childhood AD. Sensitivity analysis for unmeasured confounding factors in the association between in-utero PFAS exposure and AD was assessed by E-value methodology (VanderWeele and Ding, 2017). $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed using JMP, version 13 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 863 out of 1264 mother-infant pairs who had at least one follow-up at 3, 6, 12, 18, 24 and 60 months were recruited in this study. Among excluded pairs, there was one pair with the outcome of infant death, one pair for infant adoption, 13 pairs exhibiting multiple births, 32 pairs without cord plasma PFAS concentrations, 91 pairs suspected of cord blood contamination via maternal blood, and 264 pairs lost during follow-up (Fig. 1).

The prevalence of AD was 7.1% ($n = 61$) in the followed-up children. Table 1 displays the characteristics of children and parents of children with ($n = 61$) and without ($n = 802$) AD. A higher prevalence of breastfeeding, paternal education >12 years, and parental atopy was found in children with AD than in children without AD.

The concentrations of PFOA and PFOS in the cord plasma are shown in Table 2. The detection rates of these two PFASs were above 50%. In preliminary analyses, we used exposure categories according to median and quartile of PFOA and PFOS concentrations. The increased risk of having AD in children was found when PFOA exposure levels reached the highest quartile. Therefore, we grouped the PFOA and PFOS exposure concentrations by the 75th

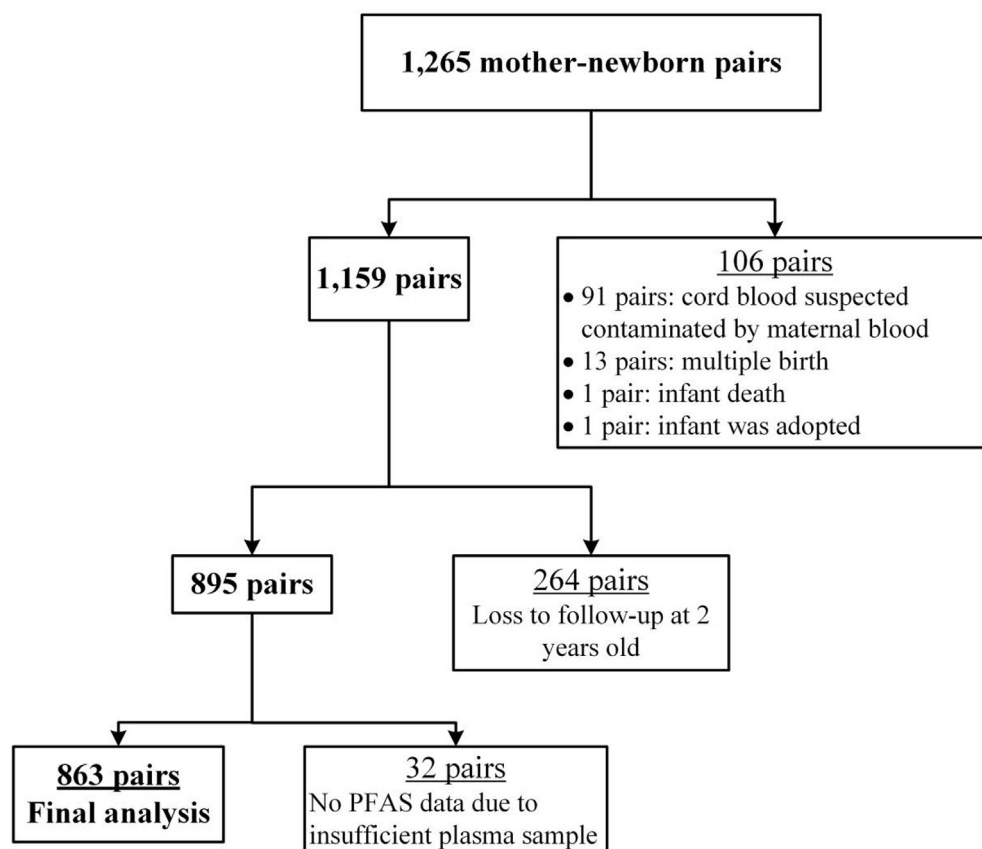


Fig. 1. Flow chart of mother–infant pair recruitment, including those lost during various times in the recruitment process.

percentile of cord plasma concentration (1.96 ng/mL for PFOA and 5.05 ng/mL for PFOS) to evaluate the relationship with AD development between the two groups for further analysis.

Fig. 2 indicates the Kaplan-Meier values estimating the distribution of the cumulative proportion on AD development for the PFOA and PFOS exposure groups. A higher proportion of AD development was found in the PFOA ≥ 1.96 ng/mL group when compared with the PFOA < 1.96 ng/mL group. The distributions of proportional curves on AD development were statistically different between the two PFOA exposure groups according to the Log-rank test ($p = 0.014$) (Fig. 2A). No significant differences were found between the two PFOS exposure groups (Fig. 2B). The median age of AD development was 6 months in children with in utero exposure to PFOA > 1.96 ng/mL and 9 months in children with in utero exposure to PFOA < 1.96 ng/mL (Table A1).

In the Cox proportional hazards model analysis, in utero exposure to PFOA ≥ 1.96 ng/mL was associated with an HR of 1.89 (95% CI, 1.10–3.16) for AD development in children before age 5 years after adjusting for sex, family income, parental atopy, breastfeeding, and maternal age at childbirth. No association was found between PFOS exposure and presence of childhood AD (Table 3). For the sensitivity analysis, the E-value as the relative risk of unmeasured confounders for the present model was 3.2 for the point estimate and 1.43 for the upper confidence bound. Therefore, it is unlikely that an unmeasured confounder with this large of a relationship with both in-utero PFOA exposure and earlier AD onset can overcome the observed effect of PFOA exposure on AD in children.

4. Discussions

The results of the present study indicate that in-utero PFOA exposure is associated with AD development in children younger than 5 years. Children with a cord plasma PFOA concentration > 1.96 ng/mL developed AD earlier than those with lower PFOA exposure. However, no significant association was found between in-utero PFOS exposure and AD. To our knowledge, this is the first study to investigate the effects of PFAS exposure on the age of AD development.

AD is a common skin disease in children and is a major risk factor for the progression of sensitization to allergens and respiratory allergic disease. Lowe et al. reported that children who developed eczema in their first 6 months exhibited increased risk of sensitization to food allergens at 1 year and sensitization to inhalant allergens at 2 years (Lowe et al., 2007). In a 7-year follow-up birth cohort study in Sweden, an increased risk of sensitization to airborne allergens at 3 years of age or later was observed in children with eczema before 4 months of age (Gustafsson et al., 2000). In Taiwan, children with AD before 6 months had a higher risk of developing asthma during the first 5 years of life in a nationally represented birth cohort study (Wen et al., 2015). Children with an early onset AD, particularly with a persistent phenotype, had an increased risk of developing asthma and allergic rhinitis. Moreover, such effects were more obvious among children with both AD and food allergies (Roduit et al., 2017). In the present study, we found that in utero PFOA exposure was affected the time of AD onset. Whether PFOA is related to the persistent symptoms of AD

Table 1

Characteristics of children and parents in children with and without atopic dermatitis (AD) during follow-up.

Characteristic	Mean (SD) or n (%)		p-value ^a
	With (n = 61)	Without (n = 802)	
Children			
Gestational length (weeks) ^b	38.92 (1.20)	38.92 (1.20)	0.785
Birth weight (g) ^b	3153.09 (407.60)	3087.92 (436.91)	0.515
Gender			
Boy	30 (49.2)	407 (50.8)	0.813
Girl	31 (50.8)	395 (49.3)	
Birth order			
1st	28 (46.7)	341 (46.1)	0.152
2nd	247 (45.0)	270 (36.5)	
≥3rd	5 (8.3)	128 (17.3)	
Breastfeeding ^c			
Yes	45 (73.8)	453 (59.7)	0.030
No	16 (26.2)	306 (40.3)	
Parents			
Maternal age at childbirth (year) ^b	27.81 (4.53)	27.82 (4.67)	0.930
Family income (10 ³ USD)			
<20	9 (16.1)	213 (28.1)	0.112
20–33.3	21 (37.5)	272 (35.9)	
≥33.3	26 (46.4)	272 (35.9)	
Maternal education			
<9 years	3 (4.9)	83 (10.4)	0.241
10–12 years	34 (55.7)	453 (57.0)	
>12 years	24 (39.3)	259 (32.6)	
Paternal education			
<9 years	5 (8.2)	112 (14.2)	0.026
10–12 years	26 (42.6)	421 (53.2)	
>12 years	30 (49.2)	258 (32.6)	
Maternal atopy ^c			
Yes	19 (31.2)	152 (19.1)	0.023
No	42 (68.8)	645 (80.9)	
Paternal atopy ^c			
Yes	20 (32.8)	151 (18.9)	0.009
No	41 (67.2)	646 (81.1)	

Some numbers do not add up to total n because of missing values.

Abbreviations: SD, standard deviation; USD, US dollars.

^a P value was calculated by Kruskal-Wallis tests for continues variables and χ^2 test for categorical variables as compared between children with and without AD.^b Mean (SD).^c Breastfeeding: “Yes” was defined as a mother ever feeding their baby breast-milk. Maternal or paternal atopy: “Yes” was defined if the mother or father ever had at least one allergic disease.**Table 2**

Concentration of PFOA and PFOS in cord plasma (ng/mL, N = 863).

PFAS	GM (95%CI)	Mean (SD)	Median	25th	75th	Detection rate (%)
PFOA	0.68 (0.63–0.73)	1.22 (1.38)	0.65	0.23	1.96	50.75
PFOS	2.50 (2.28–2.74)	4.27 (5.58)	3.49	2.18	5.05	89.57

Abbreviations: GM, geometrical mean; SD, standard deviation; PFAS, perfluoroalkyl substance; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

and consequently affects the development of other allergic diseases needs to be investigated in future studies.

Our result is consistent with a previous study regarding prenatal PFAS exposure and childhood allergic diseases in China (Chen et al., 2018). Chen et al. reported that prenatal exposure to PFOA significantly increased the risk of AD in girls aged <2 years (Chen et al., 2018). However, in another birth cohort study in Taiwan, Wang et al. indicated no association between cord plasma PFOA level and AD in children aged 2 years (Wang et al., 2011). Okada et al. also observed no association between maternal PFOA levels and presence of eczema during the first 2 years of life in a Japanese cohort study (Okada et al., 2014). In a follow-up birth cohort study in Norway, childhood AD was also not significantly associated with cord blood PFAS concentration. In contrast, they found that in utero PFAS exposure was related to an increased number of respiratory tract infections in the first 10 years of life (Impinen et al., 2018). However, the contrasting findings of these previous studied might

be due to different patient ages at follow-up or different methods to establish AD diagnosis. For other allergic diseases, PFOA was associated with asthma among children aged 12–19 years (Humblet et al., 2014). Asthmatic children also had higher serum PFAS levels than children without asthma in a case-control study (Dong et al., 2013). These studies indicated a potential effect of PFAS exposure on children health.

The biological mechanisms of PFAS exposure on AD development remain unclear. PFASs induce immunotoxicity and alter the immune response (DeWitt et al., 2012). In epidemiological studies, cord serum IgE concentration had a positive association with prenatal PFOA exposure (Wang et al., 2011). A dose-response effect of PFOA concentration on increasing IgE levels was also found in a case-control study of children (Dong et al., 2013). Furthermore, Fairley et al. reported that higher IgE levels were observed in mice that were co-administered ovalbumin (OVA) and PFOA, as compared to those only exposed to OVA and indicated that PFOA

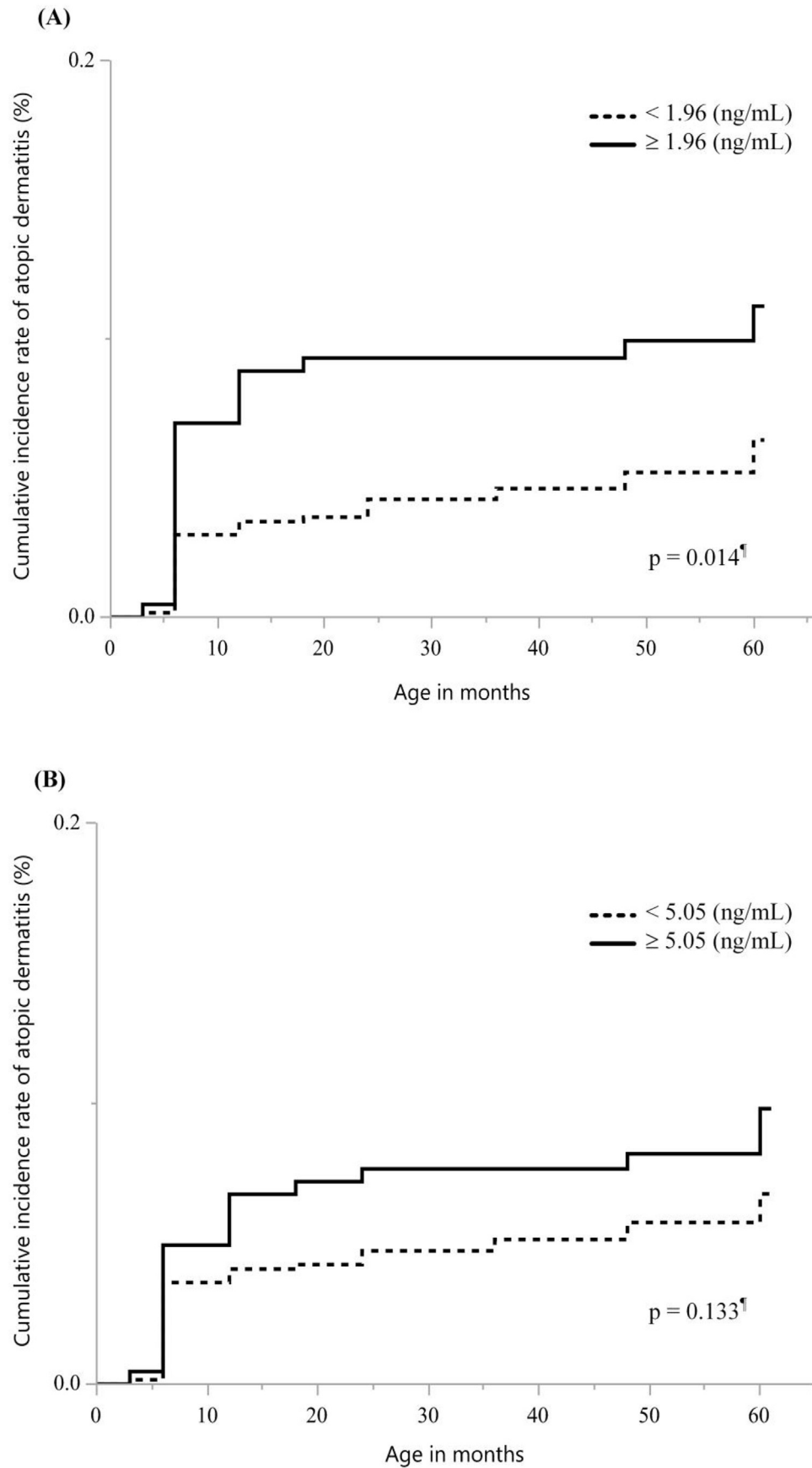


Fig. 2. Kaplan-Meier survival curve for childhood AD according to PFAS levels (ng/mL).

[†] P-values were calculated by Log-rank tests to evaluate comparisons among the exposure groups.

Abbreviations AD, atopic dermatitis; PFAS, perfluoroalkyl substance; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

Table 3

Estimated hazard ratio (HR) and 95% confidence interval (CI) of PFOA and PFOS levels (ng/mL) for childhood AD, obtained from cox proportional hazards regression model.

PFASs	n = 863	HR (95% CI)	AHR (95% CI) ^a
PFOA			
<1.96	644	Reference	Reference
≥1.96	219	1.88 (1.10–3.12) ^b	1.89 (1.10–3.16) ^b
PFOS			
<5.05	640	Reference	Reference
≥5.05	223	1.49 (0.87–2.50)	1.43 (0.82–2.43)

Abbreviations: AD, atopic dermatitis; PFAS, perfluoroalkyl substance; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

^a Adjusted HR (AHR) was adjusted by sex, paternal education, parental atopy, breast feeding, and maternal age at childbirth.

^b $p < 0.05$.

might augment the hypersensitive response to allergens (Fairley et al., 2007). PFOA triggered mast cell-derived allergic inflammatory reactions due to enhanced histamine secretion and the production of pro-inflammatory cytokines (Singh et al., 2012). Besides, PFOA is considered as a peroxisome proliferator and PPAR γ (peroxisome proliferator-activated receptor-gamma) is an important driver of the Th2 immune response in the lung, which is related to pulmonary allergic inflammation (Nobs et al., 2017).

The strengths of this study include recruiting a general population of pregnant women in their third trimester throughout Taiwan. With collection of biological specimens, we can evaluate internal exposure levels of environmental contaminants during the prenatal period. Second, we can clearly investigate the temporal sequence between environmental exposure and health impact due to a birth cohort study design, which reduces recall bias. Third, we have performed frequent follow-ups early in children's life to identify the period of AD occurrence.

Our study had some limitations. First, approximately one-third of participants were excluded from the final analysis due to unmeasured data, loss to follow-up, or other reasons, which might result in a selection bias. However, no significant differences in the characteristics of parents and children were found between included pairs ($n = 863$) and excluded pairs ($n = 402$), besides gestational week and parental education (Table A2). Although a slightly higher gestational week at birth was observed in included children compared to that in excluded ones, they were almost full-term babies with the gestational week in the normal range (37–40 weeks). Gestational week was not significantly associated with childhood AD in our study. Moreover, because the interviewers and participated mother–infant pairs were unaware of the research hypothesis, selection bias due to differential participation was less concerning. Second, we depend on maternal or main caretaker reports of physician-diagnosed AD to determine children with or without AD in each follow-up interview. A misclassification of childhood AD could be a cause of concern. However, we used the ISAAC questionnaire, an international standard questionnaire for allergic diseases, to identify specific symptoms of AD and combined the data of both physician-diagnosed AD and a rash in a specific position to identify children having AD, which might have decreased the probability of misclassification. Third, prenatal PFAS exposure was measured according to cord plasma concentrations of PFOA and PFOS, which might not be representative of PFAS exposure from the mother during her entire pregnancy. However, the estimated half-lives in humans are 3.8 and 5.4 years for PFOA and PFOS, respectively (Olsen et al., 2007). PFASs can also cross the placental barrier, consequently accumulating in the fetus, and can have a prolonged effect on the health of children owing to their bioaccumulation and persistence (Fromme et al., 2009; Fernandez-

Sanjuan et al., 2013). Cord plasma PFAS levels are therefore a good marker of fetus exposed to PFAS in utero. Finally, participating pairs were from eight hospitals located in seven areas of Taiwan. Therefore, our findings extended to all neonates in Taiwan are warranted.

5. Conclusions

In utero PFOA exposure was associated with childhood AD. Children with higher prenatal PFOA exposure exhibited an earlier occurrence of AD than those with lower exposure. AD is considered a major risk factor for the progression of respiratory allergic disease in later life, and knowing these risk factors for early onset AD is helpful for applying appropriate environmental preventive measures. Minimal PFAS exposure during pregnancy may be helpful towards protecting against allergic disease development in children.

Declarations and interest

All authors have no financial conflicts of interests to declare.

Acknowledgements

The authors thank all the pairs of mothers and their children who participated in this follow-up study. The authors thank the collaborating hospitals' medical personnel who helped with biological sample collection. The authors also thank the interviewers who supported the data collection and phone interview. This study was supported by the Ministry of Science and Technology, Taiwan [grant No. NSC101-2621-M-002-002-, MOST106-3114-B-400-002 -, MOST 107-2321-B-400-010 -].

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.chemosphere.2019.05.100>.

Authors' contributions

Conceptualization: Hui-Ju Wen, Yue Leon Guo.
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Formal analysis: Hui-Ju Wen.
Investigation: Hui-Ju Wen.
Methodology: Hui-Ju Wen, Yu-Chen Chuang, Pau-Chung Chen, Yue Leon Guo.
Project administration: Yue Leon Guo.
Resources: Hui-Ju Wen, Yue Leon Guo.
Supervision: Yue Leon Guo.
Validation: Hui-Ju Wen.
Visualization: Hui-Ju Wen.
Writing – original draft: Hui-Ju Wen.
Writing – review & editing: Hui-Ju Wen, Shu-Li Wang, Yue Leon Guo.

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