Environment International 146 (2021) 106243

Contents lists available at ScienceDirect

Environment International

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

# Maternal and childhood exposure to inorganic arsenic and airway allergy – A 15-Year birth cohort follow-up study

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ARTICLE INFO

Handling Editor: Adrian Covaci

*Keywords:*
Birth cohort
Arsenic exposure
Asthma
Allergic rhinitis

ABSTRACT

*Background:* The prevalence of allergic diseases in children has increased globally. Early-life exposure to inorganic arsenic has been found to be associated with impaired immune function and decreased lung function in children; however, the results are inconsistent. We aimed to evaluate the effect of prenatal and childhood exposure to inorganic arsenic on allergic diseases in children, through a 15-year follow-up birth cohort study, conducted in central Taiwan.

*Methods:* Children born to women enrolled in the Taiwan Maternal and Infant Cohort Study (TMICS-pilot) from December 2000 to November 2001 were recruited and followed every 2–3 years until the age of 14 years. Urinary specimens were collected in the pregnant women during the 3rd trimester and the followed children. Diagnoses of allergic diseases were based on physician diagnoses using the International Study of Asthma and Allergies in Childhood questionnaire. Urinary arsenic speciation was performed using high-performance liquid chromatography and inductively coupled plasma dynamic reaction cell mass spectrophotometry.

*Results:* Of the 261 children from 358 mother-infant pairs for this study, those with asthma and allergic rhinitis reported a higher prevalence of maternal allergy (49.47%) than did non-allergic children (29.81%). In the fully adjusted model, levels of maternal urine (iAs + MMA + DMA) greater than the median were found to be significantly associated with an increased risk of asthma (OR = 4.28; 95% CI 1.32, 13.85). Levels of urinary (iAs + MMA + DMA) in children higher than the median were associated with an increased risk of allergic rhinitis (OR = 2.26; 95% CI 1.20, 4.26).

*Conclusion:* Prenatal and childhood exposure to inorganic arsenic were found to be significantly associated with the occurrence of asthma and allergic rhinitis in children, respectively. Further large cohort follow-up studies are important to validate the association between inorganic arsenic exposure and allergic diseases in children.

## 1. Introduction

The prevalence of childhood allergic diseases has increased worldwide (Asher et al., 2006; Wong et al., 2013). According to the National Health Insurance data collected from 2000 to 2007 in Taiwan, the prevalence of atopic dermatitis, asthma, and allergic rhinitis in children and adolescents less than 20 years of age was 9.6%, 15.7%, and 37.8%, respectively, far exceeding the prevalence reported (atopic dermatitis:

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https://doi.org/10.1016/j.envint.2020.106243
Received 30 January 2020; Received in revised form 20 October 2020; Accepted 22 October 2020
Available online 5 November 2020

1.1%–3.4%; asthma: 2.2%–7.0%; allergic rhinitis: 5.1%–27.6%) in previous studies (Hwang et al., 2010; Liao et al., 2009). The increasing prevalence and severity of allergic diseases and conditions are becoming important issues for the global burden of disease (James et al., 2018; Lai et al., 2009).

Atopic dermatitis is considered the first clinical characteristic and the beginning of the atopic march. This is followed by the onset of asthma and allergic rhinitis during the first several years of life; however, asthma can also occur after adolescence due to different pathogenesis (Fahy, 2015; Spergel, 2010). Asthma has three recurrent symptoms: bronchial hyperresponsiveness, reversible airflow obstruction, and airway inflammation; pathological changes in the airway are thought to be associated with exaggerated asthmatic responses (Fahy, 2015; National Asthma Education and Prevention Program, 2007). The gestational period plays an important role in the development of the immune system, due to the specialized regulatory T cell population that develops during this period in the human fetus, at the 12th or 13th week. Suppression of regulatory T cells is thought to be associated with allergic diseases (Dietert and Piepenbrink, 2006). Genetic factors, diet, infections, and exposure to indoor allergens and environmental chemicals have been reported to be associated with the development of allergic diseases from infancy to adulthood (Abreo et al., 2018; Lau et al., 2019). However, the notable increase in the prevalence of allergic diseases within a short period of time suggests that not only genetic factors but multiple environmental risk factors also play an important role in driving the upward trend in the occurrence of allergic diseases (Burke et al., 2003). For instance, environmental exposure to lead, phthalate, and house dust mite were found to associate with asthma-related airway inflammation in children and adolescents (Abreo et al., 2018; Franken et al., 2017; Wu et al., 2019), and prenatal exposure to *para*-dichlorobenzene and bisphenol A associated with increased allergy in boys (Buckley et al., 2018). Moreover, air pollutants (such as fine particulate matter or black carbon) and climate change (e.g. higher temperatures or extreme climate events) were reported to affect respiratory health and the occurrence of asthma and allergic rhinitis (Eguiluz-Gracia et al., 2020).

Exposure to arsenic in the environment is an important issue in various countries. Arsenic is a known carcinogen (IARC, 2012) and is associated with several non-cancer outcomes, including skin lesions, black-foot disease, peripheral neuropathy, cardiovascular diseases, hepatic cell damage, diabetes, and bone marrow depression (Abdul et al., 2015). The potential sources of exposure to arsenic include contaminated drinking water and food, air pollutants, industrial processes, cigarette smoking, cosmetics, etc., and individuals may contact or expose to arsenic through ingestion, inhalation, or dermal contact (Chung et al., 2014). Some studies reported that arsenic exposure might affect lung function or induce respiratory symptoms in children population (Ahmed et al., 2017; Khan et al., 2020; Smith et al., 2013). Recent studies have indicated that exposure to arsenic can disrupt innate immunity (Srivastava et al., 2013) and hinder lung function (Recio-Vega et al., 2015), and increase susceptibility to respiratory infections (Ramsey et al., 2013). Children exposed to high levels of arsenic were found to have a higher incidence of apoptosis in B cells and peripheral blood mononuclear cells (PBMC), as well as a greater inhibition of the proliferative response of T lymphocytes and secretion of interleukin 2 (IL-2) (de la Fuente et al., 2002; Soto-Pena et al., 2006), which may predispose this vulnerable population to microbial infections. Children exposed to higher levels of arsenic also showed increased granulocyte-macrophage colony-stimulating factor (GM-CSF) secretion that may be associated with chronic inflammation (Soto-Pena et al., 2006). Additionally, a previous study has shown that arsenicosis patients with respiratory and skin disorders had a higher serum IgE level (Islam et al., 2007). The studies on arsenic exposure and allergies in children are thus far lacking. Therefore, this study aims to evaluate the effect of prenatal and childhood exposure to inorganic arsenic on the development of allergic diseases in children in Taiwan from 2000 to 2015.

## 2. Methods

### 2.1. Study population

Pregnant women seeking care at a medical center from the general population in central Taiwan were invited to participate in the Taiwan Maternal and Infant Cohort Study (TMICS-pilot) from December 2000 to November 2001. Women who were enrolled in this study had their information collected via questionnaires, including their demographic and health history. They also provided urine and blood samples in the 3rd trimester (weeks 28–38 of pregnancy). Their newborns, who were enrolled at birth, had environmental and health assessments conducted via detailed personal interviews at follow-up visits (2, 5, 8, 11, and 14 years of age), which occurred at least once until the age of 14. Children who were followed up at least once and had a sufficient volume of blood and urine specimens available for laboratory analysis were analyzed in this study. This study was approved by the ethics committee of National Health Research Institutes in Taiwan and the cooperative hospital (EC0980405, EC1010505, CS12065, CS15069), and we received signed informed consent from the pregnant women and their children. We also obtained the written informed consent from the children when they were 6-year-old or above according to the institutional regulation for subject protections.

### 2.2. Data collection

At each follow-up visit, we collected information on the children's demographic details, lifestyle, dietary patterns, and residential environment via structural questionnaires administered by trained and certified interviewers. Physical examinations and the collection of blood and urine samples from the children were performed simultaneously. Besides, some participated children at 14 years of age were further evaluated by the physician and received the lung function testing by MicroLab™ Spirometer (Micro Medical Limited, England). The lung function test was carried out following the steps as follows: (1) The subject takes a standing posture. (2) Several normal breaths. (3) Inhalation with maximum force until the subject feels the lungs full. (4) After full inhalation then hold the breath. (5) Hold lips tightly around the mouthpiece and do not let the tongue to block the hole. (6) Blow in quickly and forcefully until the air in the lungs is completely expulsion (exhalation with maximum force). The urine samples were collected in polypropylene tubes and stored with the blood samples in a −70 °C freezer until the time for laboratory analysis.

### 2.3. Assessment of urinary arsenic level

Urinary arsenic speciation was performed by high-performance liquid chromatography using anion exchange columns (Hamilton PRP X-100, 10 mm particle size) to separate the arsenic species including arsenite [U-As(III)], arsenate [U-As(V)], monomethylarsonate (U-MMA), dimethylarsinate (U-DMA) and arsenobetaine (U-AsB). The mobile phase was 100 mmol/L $Na_2HPO_4/NaH_2PO_4$ (pH = 5.75) with a flow rate of 1 mL/min. Species-separated samples were quantified by inductively coupled plasma dynamic reaction cell mass spectrophotometry to determine the concentrations of each arsenic species. The calibration curve was based on a 5-point calibration model of standard solutions of urinary arsenic and was set to quantify 15 samples in each run. The samples were quantified when the correlation coefficients for the calibration curves and the outcomes were $> 0.999$.

The blanks were analyzed every 15 samples with the results of arsenic levels were $< 0.01$ μg/L; duplicate samples were also analyzed every 15 samples that relative percent difference (RPD) was between 0.1% and 30%. For all arsenic species, the recovery rate of the standard addition was between 81.9% and 119.3%. The results of the quality control procedure were monitored throughout the experiment. Additionally, interlaboratory comparisons were certified via the German

External Quality Assessment Scheme (G-EQUAS). Urinary creatinine levels were measured by the Beckman Synchron LX20 auto-system (Beckman Coulter, Brea, CA, USA) to adjust for the effect of urine dilution in the urine samples.

The limits of detection (LOD) of U-As(III), U-As(V), U-MMA, U-DMA, and U-AsB were 0.07, 0.28, 0.20, 0.26, and 0.17 μg/L respectively; when measurement of the arsenic level was under detection limits, the LOD divided by the square root of 2 was used. We calculated the sum of the inorganic and methylated arsenic species [U-As(III) + U-As(V) + U-MMA + U-DMA], which was used as an index for inorganic arsenic exposure [iAs + MMA + DMA; Σ(U-iAs)] (Navas-Acien et al., 2009); the concentrations were adjusted for urinary creatinine to account for urine dilution (μg/g cre).

### 2.4. Definition of allergic diseases

The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (Asher et al., 1995; Ellwood et al., 2005) was used to determine allergic disease status in the enrolled children at the ages of 8, 11, and 14 years. Subjects who answered "Yes" to the question items stating, "Have you ever had wheezing diagnosed by a physician?" or "Have you ever had asthma diagnosed by a physician?" were defined as asthma cases. Similarly, subjects who answered "Yes" to question item "Have you ever had allergic rhinitis diagnosed by a physician?" were defined as allergic rhinitis cases. Children with asthma were defined as those who "at least one time reported asthma/wheezing status at 8, 11, 14 years of age" and those who had "at least one time reported allergic rhinitis status at 8, 11, 14 years of age" were classified as having allergic rhinitis.

### 2.5. Statistical analysis

Continuous variables are presented as the mean value with the standard deviation, and *t*-test was used to compare values across groups. Categorical variables are presented as frequencies and percentages, and the chi-square test was used to compare across groups. The Σ(U-iAs) was used to represent the sum of the concentrations of arsenite, arsenate, MMA, and DMA. Prenatal exposure to arsenic was estimated by the levels of creatinine-adjusted maternal U-DMA and Σ(U-iAs) in the 3rd trimester. The children's postnatal exposure was estimated using the adjusted levels of U-DMA and Σ(U-iAs) obtained at each follow-up visit. The exposure status of each subject was classified as a low exposure or a high exposure based on the median of the urinary arsenic levels at each follow-up visit.

A generalized linear mixed model (GLMM) was used to estimate the effect of arsenic exposure at each follow-up visit on the allergic disease status in the children. It could fit data with correlations or nonconstant variability as well as the normal distribution of the dependent variable is not necessary. In statistical models, the Laplace approximation was used due to the estimations of Laplace approach have better asymptotic behavior and less small-sample bias than pseudo-likelihood estimators. A directed acyclic graph (DAG; Fig. S1) was used to determine the minimal sufficient adjustment factors for estimating the total effect of arsenic on allergic disease status (Howards, 2018). Furthermore, potential confounders and effect modifiers identified through a literature review were considered in the models; therefore, child's sex, maternal breastfeeding, maternal allergy status, paternal allergy status, child exposure to environmental tobacco smoke (ETS), and child's U-AsB and serum IgE were adjusted for in the statistical models. The rationale for adjustment of each variable was described as follows: (1) Child's sex: The sexual difference exists in the prevalence and incidence of allergic diseases; also, the metabolism of arsenic has a sexual difference (Ferrario et al., 2016; Hwang et al., 2010). (2) Maternal breastfeeding: Breastfeeding was considered to have a protective effect from allergy, but it also might be a source of arsenic exposure for children (Carignan et al., 2015; Fleischer et al., 2013). (3) Maternal allergy and paternal allergy: Family history of allergy is considered a risk factor for children's allergy model (Jackson et al., 2012; Tohidinik et al., 2019). (4) Child exposure to ETS: Tobacco smoke has been recognized as a risk factor for allergy (Abreo et al., 2018; Lau et al., 2019; Tohidinik et al., 2019). However, Skaaby et al. observed the negative association between ETS and hay fever (allergic rhinitis) (Skaaby et al., 2017). (5) Child's U-AsB: U-DMA and U-AsB are associated with seafood consumption, and AsB contributes partial DMA after the digestive process (Baek et al., 2017; Navas-Acien et al., 2011). Therefore, we adjusted U-AsB in the model to control the potential effect of seafood consumption. (6) serum IgE: In previous studies, IgE was adjusted as a potential confounder (Tohidinik et al., 2019).

We also predicted the effect of prenatal exposure to arsenic on allergic diseases in the children, and potential modifiers and factors were considered in the statistical models. Considering the potentiality of the genetic effect, maternal allergy status was stratified in a later analysis.

Semiparametric group-based trajectory modeling (GBTM) was used to characterize the trajectory patterns of urinary arsenic levels among children at the ages of 2, 5, 8, and 11 years. The GBTM is useful for approximating the distribution in a population with unknown trajectory shapes and unobserved individual differences (Nagin and Odgers, 2010). Participants following similar trajectories for arsenic exposure over time were clustered in the same trajectory group.

In this study, all analyses were performed by SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software version 4.0.0; p value $\leq 0.05$ was considered statistically significant.

## 3. Results

Of the 610 healthy pregnant women invited to participate in the Taiwan Maternal and Infant Cohort Study (TMICS-pilot) from December 2000 to November 2001. There were 180 pregnant women refused or did not plan to have their babies delivered in this collaborative hospital, and 430 pregnant women were enrolled (72 women without urinary specimens). Thus, 358 newborns were enrolled at birth. Two hundred sixty-one children were followed at least once in the follow-up period, and the response was 73% (261/358). The detailed response rate at each follow-up visit was 54% at age 2, 45% at age 5, 42% at age 8, 39% at age 11, and 40% at age 14 (Fig. 1).

Most maternal and child characteristics showed no difference between those who were followed, and those who refused or were lost to follow-up; however, the children who were followed had significantly higher levels of maternal education (Table S1). The main reason for lost to follow-up is the subjects might move away without leaving their contacts, and they could refuse due to schedule conflicts such as travel during the study period in summer vacations. Of the 261 children from 358 mother-infant pairs for this study, 96 allergic children had a significantly higher prevalence of maternal education > 16 years (67.42%) than 165 non-allergic children (52.83%), as well as a higher prevalence of maternal (49.47% vs. 29.81%) and paternal (46.32% vs. 30.68%) allergy statuses (Table 1). In this study, a high percentage of the concentrations of maternal U-As(III) + As(V), maternal U-MMA, and children's U-As(III) + As(V) were below the detection limits (Table 2). Non-allergic children appeared to have higher levels of maternal U-As (III) + As(V) and maternal U-MMA than allergic children did. However, 69% of U-As(III) + As(V) and 49% of U-MMA measurements are below the LOD in which case LOD divided by the square root of 2 was used. When DMA and Σ(U-iAs) were compared, there were no significant differences. Allergic children had higher serum IgE levels than non-allergic children at each follow-up visit; a significant difference in these levels was observed at 11 years of age (98.53 IU/mL vs. 47.45 IU/mL) (Table 2). In addition, maternal and childhood urinary arsenic levels did not have correlations (Fig. S2). The exposure status without adjustment of urinary creatinine also showed significantly higher urine arsenic levels than non-allergic ones (Table S2); the same conclusion

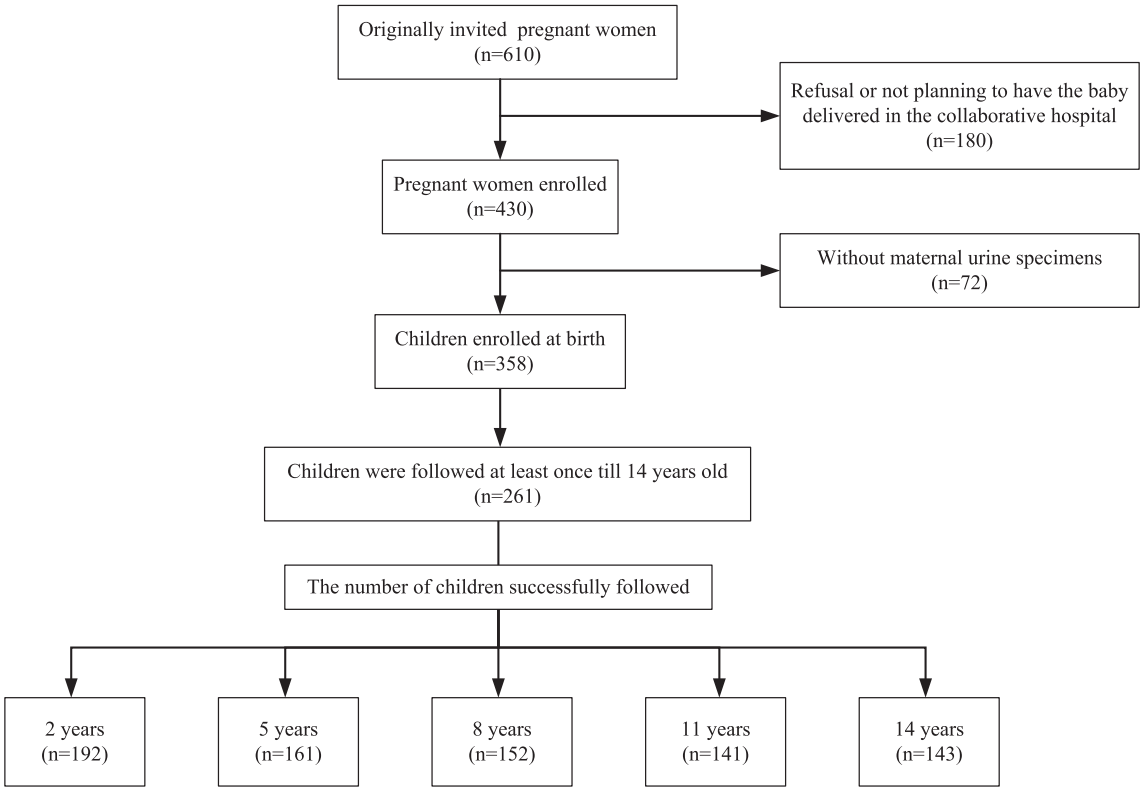


**Fig. 1.** The number of children in each follow-up of TMICS-pilot study.

**Table 1**
The demographic characteristics of children in TMICS-pilot 15-year follow-up cohort (n = 261).

| Baseline | *n* | | Allergy (n = 96) Mean ± SD / n (%) | Non-allergy (n = 165) Mean ± SD / n (%) | p value[b] | Total (n = 261) Mean ± SD / n (%) |
|---|---|---|---|---|---|---|
| *Maternal characteristics* | | | | | | |
| Age (years) | *248* | | 28.70 ± 3.83 | 28.29 ± 4.31 | 0.46 | 28.43 ± 4.14 |
| Pre-pregnancy BMI (kg/m$^2$) | *245* | | 20.53 ± 2.83 | 20.82 ± 3.09 | 0.48 | 20.72 ± 2.99 |
| Weight gain (kg) | *241* | | 11.65 ± 5.32 | 11.97 ± 5.71 | 0.68 | 11.85 ± 5.56 |
| Education (years) | *248* | < 12 yrs | 1 (1.12) | 7 (4.40) | **0.05** | 8 (3.23) |
| | | 12–16 yrs | 28 (31.46) | 68 (42.77) | | 96 (38.71) |
| | | > 16 yrs | 60 (67.42) | 84 (52.83) | | 144 (58.06) |
| Household income (USD) | *244* | < 19,460 | 35 (39.77) | 70 (44.87) | 0.74 | 105 (43.03) |
| | | 19460–32430 | 38 (43.18) | 62 (39.74) | | 100 (40.98) |
| | | > 32,430 | 15 (17.05) | 24 (15.38) | | 39 (15.98) |
| Parity | *188* | 1 | 44 (64.71) | 61 (50.83) | 0.13 | 105 (55.85) |
| | | 2 | 19 (27.94) | 41 (34.17) | | 60 (31.91) |
| | | ≥ 3 | 5 (7.35) | 18 (15.00) | | 23 (12.23) |
| Breastfeeding | *238* | Ever | 75 (78.13) | 112 (76.71) | 0.80 | 187 (77.27) |
| Perinatal cigarette smoking | *248* | Yes | — | 3 (1.90) | | 3 (1.21) |
| Serum IgE (IU/mL)[#] | *213* | | 32.30 (24.13, 43.23) | 32.16 (25.38, 40.74) | 0.98 | 32.21 (26.83, 38.66) |
| *Children's characteristics* | | | | | | |
| Sex | *182* | Boy | 37 (56.92) | 59 (50.43) | 0.40 | 96 (52.75) |
| Gestational age (weeks) | *179* | | 39.24 ± 1.23 | 39.02 ± 1.80 | 0.33 | 39.10 ± 1.62 |
| Birth weight (g) | *182* | | 3134 ± 471.1 | 3084 ± 376.1 | 0.46 | 3102 ± 412 |
| Parental allergy | *202* | Yes | 70 (72.92) | 45 (42.45) | **<0.01** | 115 (56.93) |
| Maternal allergy | *199* | Yes | 47 (49.47) | 31 (29.81) | **<0.01** | 78 (39.20) |
| Paternal allergy | *183* | Yes | 44 (46.32) | 27 (30.68) | **0.03** | 71 (38.80) |
| Disease positive at 8, 11, or 14 years | | | | | | |
| | | Asthma | 22 (22.92) | – | | 22 (8.43) |
| | | Allergic Rhinitis | 96 (100.0) | – | | 96 (36.78) |

[a]Disease status surveyed by ISSAC with positive answer either for each of the 3 times.
[b] Defined allergy vs. Control.
[#] Geometric mean (95% CI).

was observed for the unadjusted urine arsenic levels in relation to both airway allergies (data not shown).

The association between maternal or childhood urinary arsenic levels and allergic disease status in children was estimated using a GLMM. We analyzed the association between maternal or childhood urinary arsenic concentration with children's serum IgE. In both

**Table 2**
The exposure status of children in TMICS-pilot 15 years follow-up cohort.

| | Total (n = 261) | | Allergy (n = 96) | | Non-allergy (n = 165) | | | |
|---|---|---|---|---|---|---|---|---|
| | < LOD % | Median (IQR) | GM (95% CI) | Median (IQR) | GM (95% CI) | Median (IQR) | p value[a] | p value[b] |
| *Urinary As (μg/g creatinine)* | | | | | | | | |
| Maternal | | | | | | | | |
| AsB | 1.48 | 33.20 (63.47) | 28.78 (20.94, 39.56) | 32.89 (60.07) | 32.67 (26.40, 40.43) | 33.64 (72.12) | 0.50 | 0.90 |
| As(III) + As(V) | 69.31 | 0.72 (1.05) | 0.63 (0.50, 0.80) | 0.52 (0.99) | 0.87 (0.72, 1.05) | 0.81 (1.22) | **0.04** | **0.03** |
| MMA | 49.25 | 0.86 (2.01) | 0.75 (0.55, 0.99) | 0.66 (1.07) | 1.11 (0.89, 1.39) | 1.07 (2.35) | **0.03** | **0.02** |
| DMA | 3.03 | 20.19 (23.23) | 14.71 (11.14, 19.42) | 20.48 (24.23) | 17.08 (13.99, 20.85) | 20.19 (24.41) | 0.38 | 0.43 |
| Σ(U-iAs) | | 24.94 (26.19) | 18.53 (14.36, 23.92) | 24.79 (23.28) | 22.90 (19.25, 27.24) | 25.74 (29.20) | 0.16 | 0.23 |
| 2 yrs | | | | | | | | |
| AsB | 0.00 | 35.97 (60.93) | 45.15 (33.19, 61.42) | 40.52 (58.33) | 34.67 (26.33, 45.64) | 33.81 (59.76) | 0.21 | 0.28 |
| As(III) + As(V) | 54.55 | 1.89 (1.84) | 2.04 (1.70, 2.44) | 2.06 (2.23) | 1.72 (1.52, 1.96) | 1.86 (1.46) | 0.12 | 0.19 |
| MMA | 7.14 | 3.05 (3.60) | 3.33 (2.72, 4.07) | 3.50 (4.62) | 2.98 (2.58, 3.45) | 2.82 (3.43) | 0.38 | 0.29 |
| DMA | 0.00 | 31.88 (32.08) | 33.02 (27.61, 39.46) | 32.01 (32.89) | 33.38 (28.65, 38.89) | 31.22 (36.07) | 0.93 | 0.92 |
| Σ(U-iAs) | | 37.62 (36.22) | 39.09 (32.82, 46.55) | 39.99 (39.94) | 38.80 (33.51, 44.92) | 36.67 (36.07) | 0.95 | 0.79 |
| 5 yrs | | | | | | | | |
| AsB | 0.00 | 42.74 (63.96) | 47.16 (35.47, 62.68) | 45.69 (75.18) | 44.25 (34.80, 56.26) | 42.28 (54.59) | 0.73 | 0.74 |
| As(III) + As(V) | 43.29 | 2.20 (1.90) | 2.50 (2.14, 2.92) | 2.11 (2.09) | 2.32 (2.05, 2.63) | 2.21 (1.66) | 0.45 | 0.50 |
| MMA | 2.44 | 3.23 (2.25) | 3.42 (3.04, 3.85) | 3.74 (2.27) | 2.98 (2.67, 3.32) | 3.01 (2.27) | 0.09 | 0.11 |
| DMA | 0.00 | 34.85 (22.44) | 38.74 (33.92, 44.25) | 35.62 (31.15) | 34.45 (30.64, 38.73) | 33.62 (17.62) | 0.19 | 0.22 |
| Σ(U-iAs) | | 41.14 (26.27) | 45.51 (40.13, 51.61) | 42.47 (34.25) | 40.48 (36.26, 45.20) | 41.03 (21.23) | 0.16 | 0.19 |
| 8 yrs | | | | | | | | |
| AsB | 0.00 | 29.27 (49.47) | 29.73 (23.45, 37.68) | 30.75 (46.15) | 27.42 (20.72, 36.28) | 28.48 (52.05) | 0.65 | 0.65 |
| As(III) + As(V) | 50.61 | 2.07 (1.51) | 2.15 (1.92, 2.40) | 2.02 (1.51) | 2.07 (1.84, 2.34) | 2.12 (1.39) | 0.68 | 0.89 |
| MMA | 3.66 | 2.94 (1.76) | 3.06 (2.80, 3.35) | 2.99 (1.83) | 2.86 (2.58, 3.17) | 2.86 (1.53) | 0.31 | 0.44 |
| DMA | 0.00 | 27.38 (21.07) | 30.47 (26.94, 34.46) | 29.20 (21.64) | 27.17 (24.30, 30.37) | 25.96 (15.35) | 0.17 | 0.24 |
| Σ(U-iAs) | | 33.02 (20.85) | 36.44 (32.56, 40.79) | 35.00 (21.48) | 32.78 (29.62, 36.27) | 31.41 (17.17) | 0.17 | 0.21 |
| 11 yrs | | | | | | | | |
| AsB | 0.00 | 26.35 (33.00) | 22.70 (18.13, 28.42) | 21.02 (28.79) | 24.95 (19.22, 32.41) | 31.94 (34.36) | 0.58 | 0.28 |
| As(III) + As(V) | 56.29 | 1.77 (1.12) | 1.72 (1.58, 1.86) | 1.69 (0.98) | 1.88 (1.68, 2.11) | 1.81 (1.25) | 0.18 | 0.45 |
| MMA | 0.66 | 2.74 (1.95) | 2.60 (2.36, 2.86) | 2.71 (1.54) | 2.82 (2.50, 3.18) | 2.79 (2.08) | 0.29 | 0.33 |
| DMA | 0.00 | 23.76 (13.23) | 25.12 (22.78, 26.54) | 25.14 (12.98) | 23.0 (21.16, 26.54) | 23.45 (14.99) | 0.44 | 0.49 |
| Σ(U-iAs) | | 30.06 (15.20) | 29.86 (27.29, 32.67) | 30.44 (14.67) | 29.06 (26.21, 32.22) | 28.84 (15.95) | 0.69 | 0.82 |
| 14 yrs | | | | | | | | |
| AsB | 1.50 | 11.83 (17.36) | 13.72 (11.01, 17.11) | 12.93 (18.08) | 10.81 (8.08, 14.46) | 10.37 (16.88) | 0.19 | 0.27 |
| As(III) + As(V) | 62.41 | 1.44 (0.87) | 1.37 (1.24, 1.53) | 1.36 (0.75) | 1.54 (1.37, 1.75) | 1.57 (0.97) | 0.15 | 0.08 |
| MMA | 2.26 | 2.20 (1.40) | 2.22 (2.02, 2.44) | 2.19 (1.30) | 2.15 (1.86, 2.49) | 2.22 (1.55) | 0.74 | 0.94 |
| DMA | 0.00 | 13.33 (8.60) | 14.67 (12.79, 16.81) | 13.92 (8.17) | 13.15 (11.23, 15.41) | 12.15 (10.19) | 0.30 | 0.38 |
| Σ(U-iAs) | | 17.27 (10.26) | 18.56 (16.38, 21.05) | 17.54 (9.26) | 17.21 (14.88, 19.92) | 16.21 (13.27) | 0.43 | 0.47 |
| *Serum IgE (IU/mL)*[#] | | | | | | | | |
| Cord blood | | | 0.37 (0.25, 0.53) | 0.29 (0.79) | 0.54 (0.38, 0.79) | 0.32 (1.44) | 0.14 | 0.51 |
| 5 yrs | | | 58.84 (40.38, 85.75) | 51.80 (175.1) | 47.86 (36.43, 62.87) | 57.35 (75.45) | 0.37 | 0.47 |
| 8 yrs | | | 96.94 (67.77, 138.7) | 120.5 (313.1) | 62.16 (46.35, 83.36) | 61.90 (139.2) | 0.06 | **0.03** |
| 11 yrs | | | 98.53 (67.48, 143.8) | 145.8 (339.5) | 47.45 (33.53, 67.17) | 49.10 (144.5) | **0.01** | **0.01** |
| 14 yrs | | | 89.88 (59.66, 135.4) | 133.8 (338.3) | 69.08 (47.44, 100.6) | 69.90 (191.5) | 0.35 | 0.21 |

GM: geometric mean.
Σ(U-iAs) = As(III) + As(V) + MMA + DMA.
[a] t-test.
[b] Mann-Whitney *U* test.

unadjusted and full-adjusted models, maternal and childhood urinary arsenic levels did not show a significant association with serum IgE in children (Table S3). Table 3 described the association between maternal urine arsenic concentration and allergic diseases in children at the ages of 8, 11, and 14 years. After adjustment for minimal factors according to the DAG, maternal U-DMA [odds ratio (OR) = 1.96; 95% confidence interval (CI): 1.26, 3.05] and Σ(U-iAs) (OR = 2.03; 95% CI: 1.26, 3.26) had a significant positive association with asthma in children. On analyzing the data with the exposure status classified by the median of the concentration of the urinary arsenic species, levels of maternal U-DMA and Σ(U-iAs) higher than the median showed an increase in the odds ratios for asthma in children to 3.63 and 4.21, respectively (Table 3, Model 1). After the adjustment for maternal U-AsB levels and parental allergy in the statistical model, maternal U-DMA and Σ(U-iAs) remained positively associated with asthma in children at 8, 11, and 14 years of age. In the fully adjusted model, maternal urine concentration of iAs + MMA + DMA was found to be significantly associated with the consequent occurrence of asthma in children at 8, 11, and 14 years of age (Table 3, Model 3). No statistically significant association was observed for maternal urine arsenic concentration and allergic rhinitis in children.

The association between childhood urinary arsenic levels and the allergic disease status in children indicated that a child's level of U-DMA from the age of 2 to 11 years was significantly associated with a 67% increase in the risk of acquiring allergic rhinitis from the ages of 8, 11, and 14 years (Table 4, Model 1). The same effect was observed in the case of Σ(U-iAs) (OR = 1.73; 95% CI 1.12, 2.67). After classifying the exposure status by the median value, high U-DMA and high Σ(U-iAs) were found to be associated with an increased odds ratio for allergic rhinitis (Table 4, Model 1). After adjusting for U-AsB levels and parental allergy status in Model 2, U-MMA (OR = 1.65; 95% CI 1.03, 2.64), U-DMA (OR = 1.73; 95% CI 1.11, 2.69) and Σ(U-iAs) (OR = 1.82; 95% CI 1.13, 2.92) were found to be significantly associated with an increased odds for allergic rhinitis. Similar results were observed in the case of the

**Table 3**
Odds ratios for the association between prenatal arsenic exposure and child's allergy status from ages 8, 11, 14 years (n = 261) using generalized linear mixed model (GLMM).

| | Asthma OR (95% CI) | p value | Allergic Rhinitis OR (95% CI) | p value |
|---|---|---|---|---|
| *Unadjusted model* | | | | |
| Arsenic exposure as continuous scale ($log_2$-transformed) | | | | |
| U-DMA | **1.93 (1.28, 2.92)** | **<0.01** | 0.95 (0.78, 1.16) | 0.64 |
| Σ(U-iAs) | **1.92 (1.25, 2.98)** | **<0.01** | 0.87 (0.69, 1.11) | 0.26 |
| Arsenic exposure classified by median | | | | |
| High U-DMA | **2.83 (1.05, 7.62)** | **0.04** | 1.05 (0.58, 1.91) | 0.86 |
| High Σ(U-iAs) | **3.41 (1.26, 9.22)** | **0.02** | 1.11 (0.60, 2.06) | 0.74 |
| *Model 1 (n = 93)* | | | | |
| Arsenic exposure as continuous scale ($log_2$-transformed) | | | | |
| U-DMA | **1.96 (1.26, 3.05)** | **<0.01** | 0.92 (0.75, 1.13) | 0.44 |
| Σ(U-iAs) | **2.03 (1.26, 3.26)** | **<0.01** | 0.85 (0.67, 1.09) | 0.20 |
| Arsenic exposure classified by median | | | | |
| High U-DMA | **3.63 (1.23, 10.72)** | **0.02** | 0.91 (0.49, 1.69) | 0.76 |
| High Σ(U-iAs) | **4.21 (1.46, 12.13)** | **0.01** | 1.06 (0.57, 1.99) | 0.85 |
| *Model 2 (n = 91)* | | | | |
| Arsenic exposure as continuous scale ($log_2$-transformed) | | | | |
| U-DMA | **2.88 (1.60, 5.18)** | **<0.01** | 0.93 (0.74, 1.18) | 0.55 |
| Σ(U-iAs) | **3.00 (1.61, 5.59)** | **<0.01** | 0.87 (0.66, 1.14) | 0.30 |
| Arsenic exposure classified by median | | | | |
| High U-DMA | **4.00 (1.21, 13.26)** | **0.02** | 0.67 (0.30, 1.47) | 0.31 |
| High Σ(U-iAs) | **4.54 (1.44, 14.30)** | **0.01** | 0.87 (0.48, 1.78) | 0.71 |
| *Model 3 (n = 87)* | | | | |
| Arsenic exposure as continuous scale ($log_2$-transformed) | | | | |
| U-DMA | **2.69 (1.51, 4.80)** | **<0.01** | 0.97 (0.77, 1.24) | 0.82 |
| Σ(U-iAs) | **2.79 (1.52, 5.14)** | **<0.01** | 0.91 (0.69, 1.21) | 0.51 |
| Arsenic exposure classified by median | | | | |
| High U-DMA | **3.86 (1.13, 13.16)** | **0.03** | 0.81 (0.35, 1.85) | 0.62 |
| High Σ(U-iAs) | **4.28 (1.32, 13.85)** | **0.02** | 1.20 (0.56, 2.57) | 0.64 |

Model 1 adjusted for child's sex, breastfeeding, ETS exposure according to the DAG.
Model 2 adjusted for child's sex, breastfeeding, ETS exposure, prenatal AsB, parental allergy.
Model 3 adjusted for child's sex, breastfeeding, ETS exposure, prenatal AsB, maternal allergy, paternal allergy, child's serum IgE.
Σ(U-iAs) = U-As(III) + U-As(V) + U-MMA + U-DMA.

high levels of U-DMA and high Σ(U-iAs) after the classification of exposure status by the median (Table 4, Model 2). In the fully adjusted model, children's U-DMA and Σ(U-iAs) levels were associated with an increased risk of allergic rhinitis (Table 4, Model 3). No association was found between childhood urine arsenic levels and asthma in children. On further stratification of sex, urinary arsenic concentration in childhood was found to be significantly associated with an increased risk of allergic rhinitis in boys; a similar result was also observed in girls but the association was not statistically significant (Table S4).

Considering the possible modification by maternal allergy status on the occurrence of allergic diseases in children, the data were analyzed after stratifying maternal allergic status (Table S5). After adjusting for confounders according to the DAG, it was found that children's urine iAs + MMA + DMA levels from the ages of 2 to 11 years of age had a significant association with the increased occurrence of allergic rhinitis in children with allergic mothers (OR = 2.33; 95% CI 1.13, 4.80). After further adjusting for the child's U-AsB, paternal allergy status, and child's serum IgE level, similar results were observed (Table S5, Model 2 and Model 3).

We also performed a trajectory analysis to characterize the patterns of urinary arsenic levels at 2, 5, 8, and 11 years of age. The arsenic exposure status of children during the follow-up period was categorized as "relatively low", "relatively high" and "rising-high", according to the median of the Σ(U-iAs) levels (Fig. S3). After adjusting for sex,

**Table 4**
Odds ratios for the association between repeated measurements of urinary arsenic concentration from 2 yrs to 11 yrs old and child's allergy status from ages 8, 11, 14 years (n = 261) using generalized linear mixed model (GLMM).

| | Asthma OR (95% CI) | p value | Allergic Rhinitis OR (95% CI) | p value |
|---|---|---|---|---|
| *Unadjusted model* | | | | |
| Arsenic exposure as continuous scale ($log_2$-transformed) | | | | |
| U-MMA | 0.82 (0.43, 1.56) | 0.54 | 1.39 (0.90, 2.15) | 0.13 |
| U-DMA | 0.97 (0.56, 1.70) | 0.92 | **1.68 (1.13, 2.51)** | **0.01** |
| Σ(U-iAs) | 0.92 (0.50, 1.70) | 0.80 | **1.73 (1.12, 2.66)** | **0.01** |
| Arsenic exposure classified by median | | | | |
| High U-MMA | 1.02 (0.45, 2.30) | 0.96 | 1.41 (0.82, 2.43) | 0.21 |
| High U-DMA | 1.07 (0.47, 2.40) | 0.88 | **1.89 (1.10, 3.25)** | **0.02** |
| High Σ(U-iAs) | 1.19 (0.53, 2.67) | 0.68 | **2.14 (1.24, 3.71)** | **0.01** |
| *Model 1 (n = 123)* | | | | |
| Arsenic exposure as continuous scale ($log_2$-transformed) | | | | |
| U-MMA | 0.82 (0.40, 1.66) | 0.58 | 1.52 (0.97, 2.38) | 0.06 |
| U-DMA | 0.91 (0.50, 1.64) | 0.74 | **1.67 (1.12, 2.50)** | **0.01** |
| Σ(U-iAs) | 0.86 (0.45, 1.64) | 0.64 | **1.73 (1.12, 2.67)** | **0.01** |
| Arsenic exposure classified by median | | | | |
| High U-MMA | 1.07 (0.46, 2.49) | 0.87 | 1.49 (0.86, 2.58) | 0.15 |
| High U-DMA | 0.98 (0.42, 2.26) | 0.96 | **1.87 (1.08, 3.24)** | **0.03** |
| High Σ(U-iAs) | 1.15 (0.50, 2.65) | 0.75 | **2.13 (1.22, 3.70)** | **0.01** |
| *Model 2 (n = 120)* | | | | |
| Arsenic exposure as continuous scale ($log_2$-transformed) | | | | |
| U-MMA | 0.78 (0.37, 1.62) | 0.50 | **1.65 (1.03, 2.64)** | **0.03** |
| U-DMA | 0.97 (0.51, 1.83) | 0.93 | **1.73 (1.11, 2.69)** | **0.02** |
| Σ(U-iAs) | 0.92 (0.46, 1.83) | 0.81 | **1.82 (1.13, 2.92)** | **0.01** |
| Arsenic exposure classified by median | | | | |
| High U-MMA | 0.94 (0.39, 2.25) | 0.89 | 1.46 (0.82, 2.61) | 0.19 |
| High U-DMA | 1.05 (0.43, 2.55) | 0.91 | **1.92 (1.05, 3.51)** | **0.03** |
| High Σ(U-iAs) | 1.11 (0.46, 2.67) | 0.81 | **2.17 (1.19, 3.98)** | **0.01** |
| *Model 3 (n = 115)* | | | | |
| Arsenic exposure as continuous scale ($log_2$-transformed) | | | | |
| U-MMA | 0.76 (0.37, 1.60) | 0.47 | 1.61 (0.98, 2.65) | 0.06 |
| U-DMA | 0.98 (0.52, 1.86) | 0.95 | **1.75 (1.11, 2.74)** | **0.02** |
| Σ(U-iAs) | 0.92 (0.46, 1.84) | 0.82 | **1.81 (1.11, 2.93)** | **0.02** |
| Arsenic exposure classified by median | | | | |
| High U-MMA | 1.00 (0.41, 2.44) | 0.99 | 1.43 (0.78, 2.61) | 0.25 |
| High U-DMA | 1.03 (0.42, 2.53) | 0.94 | **1.96 (1.04, 3.69)** | **0.04** |
| High Σ(U-iAs) | 1.12 (0.46, 2.72) | 0.80 | **2.26 (1.20, 4.26)** | **0.01** |

Model 1 adjusted for child's sex, breastfeeding, ETS exposure according to the DAG.
Model 2 adjusted for child's sex, breastfeeding, ETS exposure, child's U-AsB, parental allergy.
Model 3 adjusted for child's sex, breastfeeding, ETS exposure, child's U-AsB, maternal allergy, paternal allergy, child's serum IgE.
Σ(U-iAs) = U-As(III) + U-As(V) + U-MMA + U-DMA.

breastfeeding, and ETS exposure, children with "relatively high" (OR = 1.93; 95% CI 1.05, 3.54) and "rising-high" arsenic exposure statuses (OR = 4.64; 95% CI 1.72, 12.47) had a significantly increased risk of allergic rhinitis (Table S6, Model 1). In Model 2 and Model 3 presented in Table S6, having a rising-high exposure remained significantly associated with having allergic rhinitis.

Fig. S4 showed the overlapped subjects of allergic asthma and rhinitis at each of follow-ups. Considering the concurrent airway allergy, we divided the allergic status as "no rhinitis and no asthma", "with rhinitis but no asthma", "with asthma but no rhinitis", and "with rhinitis and asthma", and calculated the OR associated with maternal and childhood urinary arsenic levels. After adjustment for the minimal sufficient factors according to the DAG, maternal U-DMA and Σ(U-iAs) both significantly associated with the elevated OR of "with rhinitis and asthma". Children's U-MMA, U-DMA, and Σ(U-iAs) were significantly and positively associated with the OR of "with rhinitis but no asthma" (Table S7). When urinary arsenic concentration was dichotomized below or above the median, the same conclusions were observed.

Though maternal urine Σ(U-iAs) levels showed negatively associated with "rhinitis but no asthma", this result was not significant when arsenic was classified by the median.

In the subgroup analysis, we estimated the association between the trajectory patterns of urinary arsenic levels from 2 to 14 years of age and the results of pulmonary function tests in children aged 14 years (Table S8, n = 84). After adjusting for child's sex and body mass index (BMI), we observed children with a "rising-high" exposure to arsenic had a significant decrease in forced expiratory flow (FEF) at 25%, 50%, and 25–75%, and decreased ratio of FEF 25–75% divided by forced vital capacity (FVC) (Table S8).

## 4. Discussion

To the best of our understanding, this is the first report on the association between arsenic exposure and airway allergy in children. In this birth cohort study, we observed that children's urinary concentration of iAs + MMA + DMA was associated with allergic rhinitis in children, while maternal urine iAs + MMA + DMA concentration was associated with the occurrence of asthma in children. Studies have previously depicted the association between prenatal and postnatal exposure to arsenic, and the elevated mortality due to lung diseases (Smith et al., 2006, 2011), but the epidemiologic evidence available for the association between arsenic exposure and allergic diseases is limited.

The toxicity of arsenic has a wide range depends on the speciation. In this study, five arsenic species were separated from urine. The inorganic forms of arsenic are generally more toxic to humans and other animals than organic forms, and As(III) is reported to be more toxic than As(V) (Sharma and Sohn, 2009). Nevertheless, urine As(III) and As(V) concentration in our study had high percentage below the detection limits, thus the statistical results from these species may not reasonable (data not shown). We observed higher maternal U-As(III) + As(V) and maternal U-MMA in children without allergy than allergic children. This result might be also due to the high percentage below the detection limits in these maternal urine arsenic species, particularly in allergic children.

After absorption in the human body, inorganic arsenic was metabolized into MMA and DMA, and further excreted with unchanged inorganic arsenic through urine (Navas-Acien et al., 2009). A high level of monomethylated arsenic metabolite is a susceptibility factor for arsenic-induced toxicity and carcinogenicity, and DMA was reported to cause genotoxicity, such as single-strand DNA breaks, oxidation of DNA bases, and chromosomal aberrations (Jomova et al., 2011). Therefore, the methylated-process of inorganic arsenic may cause toxic pathways that induce harmful biological effects. The AsB is a major organic species in marine animals and people may exposure through the consumption of seafood (Popowich et al., 2016). Although AsB is considered to be low or no toxicity, the methylated intermediates were reported to have higher toxicity (Popowich et al., 2016).

From an experimental study, increased arsenic concentration in pregnant mice's drinking water was associated with higher concentration of arsenic species in the brain or liver of newborn mice (Jin et al., 2006). Arsenic concentration in maternal blood in the last gestation was reported as high as that in cord blood in a previous study, and a significant correlation between arsenic concentration in cord and maternal blood was observed ($r^2 = 0.62$) (Concha et al., 1998). Thus, maternal arsenic may readily transfer across the placenta to the fetus after exposure, and the possible interaction between prenatal and postnatal arsenic exposure may occur and induce the health effects.

### 4.1. Pre-natal arsenic exposure and asthma

Exposure to high arsenic-contaminated well water was found to associate with respiratory symptoms (i.e. dyspnea, shortness of breath, or cough) (Pesola et al., 2012; von Ehrenstein et al., 2005). Even at low arsenic level, chronic exposure to the contaminated drinking water was also related to the increased prevalence of upper and lower respiratory symptoms in males (Das et al., 2014). Early-life exposure to arsenic was reported to elevated bronchiectasis mortality rates in adults (Smith et al., 2006). A prospective cohort study in Bangladesh showed a dose–response effect of low to moderate levels of As exposure (>7 μg/L) on respiratory symptoms (Parvez et al., 2010). More recent studies also demonstrated the increase in respiratory infections and airway inflammation in children due to prenatal exposure to arsenic in both high and low exposure (Ahmed et al., 2017; Farzan et al., 2016). Ahmed reported that increased maternal urine arsenic concentration associated with decreased FVC and forced expiratory volume in 1 s in children (Ahmed et al., 2017). In our study, we observed postnatal exposure to arsenic had a significantly negative association with some indexes of lung function in children at 14 years of age. Thus, prenatal or postnatal exposure to arsenic may associate with decreased lung function. In addition, early-life arsenic exposure may affect lung function with an observed effect similar to smoking throughout adulthood (Dauphine et al., 2011).

In our study, maternal urine concentration of iAs + MMA + DMA was observed to be associated with asthma in children. During lung development, the terminal saccular period is the most important step prior to ex utero life, due to the growth of lung parenchyma, thinning of connective tissue between the air spaces, and the maturation of the pulmonary surfactant system occurring in that period (Shojaie and Post, 2017). Therefore, prenatal arsenic exposure may affect the development of lung function. Prenatal exposure to arsenic was also reported to associate with increased total serum IgE in children at 9 years of age (Raqib et al., 2017). However, we analyzed the association between prenatal arsenic exposure with IgE in children, and we did not observe a similar result. The effect of arsenic exposure on multiple aspects of immune function has been reported (Andrew et al., 2008; Biswas et al., 2008). Thus, exposure to arsenic may alter the immune and lung functions to induce allergies through various mechanisms. Future investigations with sufficient sample size and exposure range are needed for the clarification of IgE pathway as mediation for the association between arsenic exposure and children asthma and/or lung function.

In a pregnancy cohort study in the United States, prenatal exposure to low-level arsenic was found to be associated with the presence of specific immunophenotypes of cord blood cells and impaired function of the T cell subsets (CD45RA+ CD69+ T cells and CD45RA+ CD69− CD294+ T cells). This effect leads to immune dysregulation and delays in normal T cell polarization from the fetal Th2 predominant toward the postnatal Th1 stage (Nadeau et al., 2014). Evidence has shown that newborns with a Th2-skewed immune system have enhanced responses to common environmental allergens, which contribute to exacerbated allergic conditions later in life (Martino and Prescott, 2010). In an experimental study on human bronchial epithelial cells, chronic low-dose arsenic exposure compromised airway epithelial wound repair, and altered intracellular signaling critical to normal airway innate immunity (Sherwood et al., 2013). Prenatal arsenic exposure has also been shown to have the potential to alter the fetal immune system probably through DNA methylation (Nadeau et al., 2014; Strickland and Richardson, 2008). In our study, postnatal arsenic exposure had no association with asthma. We speculated that arsenic exposure might associate with the development of immune function in utero, and consequent sensitization to asthma and impaired lung function in later life.

### 4.2. Post-natal arsenic exposure and allergic rhinitis

Our study observed an association between postnatal arsenic exposure and allergic rhinitis in childhood. Although ingestion is typically considered the main route of exposure to arsenic, the inhalation of arsenic through airborne particulate matter may also play an equally important role (Huang et al., 2014). Inhaled arsenic-bearing particles can deposit and trap in the nasal cavity, increasing the risk of toxicity to the local epithelium. A previous study has shown the correlation of

serum IgA levels with the urinary excretion of arsenic in human, which suggests a toxic effect on the mucosal immune response (Islam et al., 2007). In a recent study in rural Bangladesh, children urinary arsenic levels at 9 years of age associated with increased 110 IU/mL total IgE in children (Raqib et al., 2017).

The nasal-associated lymphoid tissue (NALT) is the defense in the respiratory mucosa; it activates the immune response when triggered by the inhalation of environmental antigens after birth (Debertin et al., 2003). Therefore, postnatal arsenic exposure may be a more important "trigger" for NALT than prenatal exposure. During allergic inflammation, Th2 release cytokines (including IL-4, IL-5, and IL-13) as the mediator which are associated with IgE-producing B cells, mast cells and eosinophils, and these cytokines may directly or indirectly explain the pathophysiological manifestations of patients with allergy (Romagnani, 2002). Although allergic rhinitis is a common type of IgE-mediated disease as an early phase response of allergen exposure, some human or *in vitro* studies have proven the role of proallergic cytokines in patients with allergic rhinitis (Pasha et al., 2019). After stimulation by allergen on the nasal epithelium, alarmins (such as IL-25, IL-33, and thymic stromal lymphopoietin) are released, and dendritic cells were directly activated by these mediators or indirectly through type 2 innate lymphoid cells (ILC2). The ILCs and these alarmins were reported to contribute to the pathogenesis of nasal inflammation in allergic rhinitis (Pasha et al., 2019).

The development of allergic rhinitis may occur due to genetic predisposition and exposure to environmental allergens, but could also be driven by the stimulation of environmental adjuvants (to favor the immune response) and immune response suppressors (including IL-10, transforming growth factor-b, programmed death-1, and cytotoxic T-lymphocyte antigen-4) (Sin and Togias, 2011). Nevertheless, more information is required to understand the function and regulation of ILCs in the context of nasal cavities chronically exposed to arsenic, as well as the signals activated during allergic rhinitis, other than the well-known IgE-mediated pathway.

### 4.3. Strengths and limitations

A major strength of this study is the prospective cohort study design and the collection of data in utero until early adolescence, which allowed the association between prenatal/postnatal exposure to arsenic and allergic disease status to be evaluated. The availability of data on urinary arsenic levels at each follow-up visit allowed for profiling of long-term exposure to arsenic. We performed high quality, rigorous methods for data collection, and the measurement of the levels of the urinary arsenic species in this study, from prenatal to early adolescent years. To make sure the observation is more robust, thus we additionally used pseudo-likelihood estimation in GLMM for verification and observed the consistent results (Table S9 and Table S10). Furthermore, the urinary level of inorganic arsenic (iAs + MMA + DMA) is a reliable biomarker that represents the total exposure from all sources and reflects the internal dose (Navas-Acien et al., 2009).

This study also had several limitations. The main limitation is the lack of complete clinical examination parallel with the questionnaire interview. Second, the allergic status only collected data at the ages of 8, 11, and 14 years. We could not estimate the association between exposure to arsenic and the complete profile of airway allergies throughout follow-up, such as the prognosis of asthma and allergic rhinitis from infancy to teenage, but the allergic status reported in the ISAAC questionnaire is based on a physician's diagnosis and it possibly reflects previous allergic statuses as well. The definition of asthma in this study is a combination of physician-diagnosed wheezing and asthma that may introduce the non-differential misclassification, and it may underestimate the effect of arsenic exposure on asthma. However, the analysis results of the asthma group without including wheezing children generated the same conclusion (data not shown). Third, we could not completely avoid the reverse causality in this study due to we did not have the accurate onset time of allergic rhinitis. Nevertheless, it is true that chronic rhinitis from the school age and wheezing from 10 to 11 years is mostly related to allergic rhinitis and allergic asthma in children, respectively. Fourth, the relatively small sample size resulted in insufficient statistical power; however, the subjects in this birth cohort have multiple observations recorded in the data over 15 years of follow-up, therefore the total observations from the subjects may be sufficient for accurate statistical estimation. Last, the potentially residual or unmeasured confounders (genetic factors and exposure to other environmental factors such as $PM_{2.5}$) could not be completely adjusted in this study. For example, a family history of allergies is considered one of the genetic factors associated with the offspring's allergic sensitization (Dold et al., 1992; Tohidinik et al., 2019). We adjusted for parental allergy status in the statistical model and stratified by maternal allergic status in a later analysis, to reduce the partial effect from genetic factors.

## 5. Conclusions

In this 15-year birth cohort observational study, prenatal exposure to arsenic is observed to be associated with asthma in children, and childhood exposure to arsenic is associated with allergic rhinitis. The occurrence of allergic diseases in childhood or adolescence has the potential to be an important event that can induce adult allergy or impaired lung function. Therefore, environmental improvement and identification of the susceptible population are important for primary prevention to reduce the risk of arsenic exposure. Future work is needed to clarify the association between arsenic toxicity and allergic diseases.

## Funding

This work was supported by grants from the Ministry of Science and Technology [MOST 106-2314-B-400-014-MY3; MOST 107-2811-B-400-527; MOST 108-2811-B-400-521], National Health Research Institutes [EM-107-PP-05; EM-108-PP-05], and Chung Shan Medical University Hospital [CSH-2017-C004], Taiwan.

## CRediT authorship contribution statement

**Tsung-Lin Tsai:** Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Wei-Te Lei:** Writing - original draft, Writing - review & editing. **Chin-Chi Kuo:** Writing - original draft, Writing - review & editing. **Hai-Lun Sun:** Resources, Investigation. **Pen-Hua Su:** Resources, Investigation. **Shu-Li Wang:** Conceptualization, Supervision, Funding acquisition, Writing - review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

The authors would like to acknowledge Mrs. Chien-Wen Sun at the National Institute of Environmental Health Sciences, National Health Research Institutes in Taiwan for the assistance with the data and specimen collection.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106243.

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