Combined exposure to heavy metals in $PM_{2.5}$ and pediatric asthma

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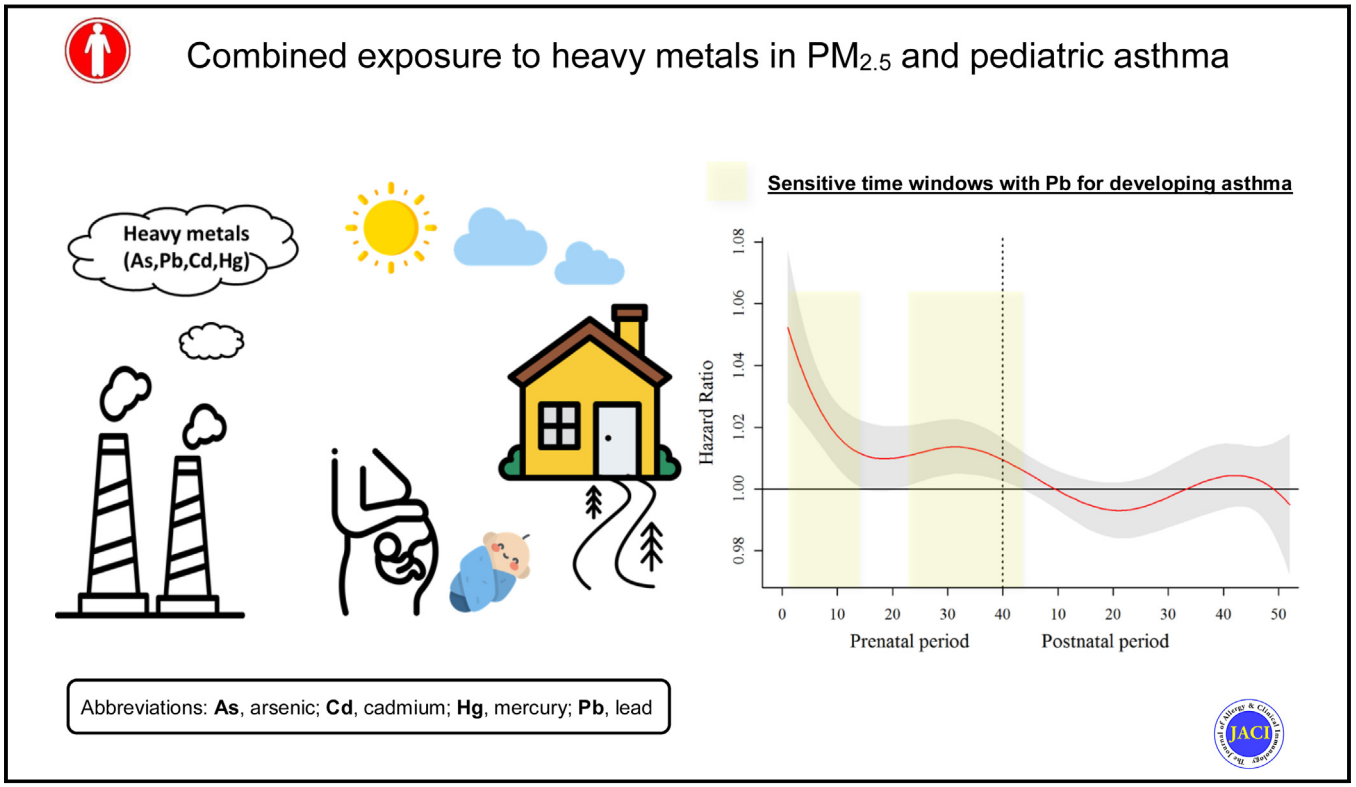
GRAPHICAL ABSTRACT



Background: Asthma is the most common chronic allergic disease in children; it affects more than 300 million people worldwide. Information on the association between exposure to ambient heavy metals and incidence of pediatric asthma is limited. Objective: We sought to evaluate the effects of heavy metals during pregnancy and infancy periods with asthma and identify a sensitive time window, clarifying the effect of ambient heavy metals on lung development.

Methods: A total of 171,281 children, who were born from 2004 to 2011 in Taichung City, were followed until 2014. Concentrations of ambient heavy metals such as arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb) were obtained from the Weather Research and Forecasting/Chem model, considering the top 75 emission sources in Taiwan. The distributed lag nonlinear model was used to investigate the relationship between combined exposure to heavy metals in

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2.5 μm particulate matter and asthma in pregnant women and 1-year-old infants.
Results: We identified 31,277 new asthma cases from the birth cohort. After adjustment for socioeconomic status, maternal age, maternal atopy, maternal anemia, and maternal kidney disease, distributed lag nonlinear model results revealed positive associations of asthma with exposure to Pb during gestational weeks 1 to 14 and 21 to 40, and 1 to 3 weeks after birth. Regarding the sensitivity analyses, coexposure to Pb and As, coexposure to Pb and Cd, and coexposure to Pb and Hg were positively associated with asthma onset as well.
Conclusions: Our study suggested that combined exposure to Pb with As, Cd, and Hg during early and late gestational weeks was associated with the incidence of pediatric asthma. (J Allergy Clin Immunol 2021;147:2171-80.)

Key words: *Heavy metals, asthma, birth cohort, vulnerable time windows, coexposure*

Abbreviations used
As: Arsenic
BLL: Blood Pb level
Cd: Cadmium
Hg: Mercury
HR: Hazard ratio
ICD-9-CM: *International Classification of Disease, Ninth Revision, Clinical Modification*
IQR: Interquartile range
Pb: Lead
PH: Proportional hazard
PM: Particulate matter
$PM_{2.5}$: PM with diameter less than 2.5 μm
SES: Socioeconomic status
TMCHD: Taiwan Maternal and Child Health Database
WRF/Chem: Weather Research and Forecasting/Chem

Globally, asthma is a common allergic respiratory disease in children, which also affects adults. More than 300 million people worldwide have asthma.[1] Both environmental and genetic factors play a crucial role in allergic diseases. The global prevalence rate of asthma in adults was estimated to be 4.3%.[2] Even though all chronic respiratory diseases impose burdens, the global burden of asthma is generally increasing.[3] The World Health Organization predicts that the number of patients with asthma will increase by 100 million by 2025.[4] Numerous recent studies have reported that long-term exposure to air pollution, such as NO_x and particulate matter (PM), is positively associated with asthma prevalence[5,6] and is often correlated with comorbidities such as allergic rhinitis and wheezing.[7]

Long-term exposure to heavy metals may damage the kidneys, heart, liver, and nervous system.[8] It may cause not only abnormalities of the immune system but also cardiovascular disease, respiratory disease, and neuropsychological diseases; all these dangers might affect child development.[9,10] A longitudinal study in Austria reported that long-term exposure to occupational heavy metal fumes significantly decreased lung function.[11] Studies on the effects of heavy metals in PM on the respiratory system have revealed that increased concentrations of heavy metals (lead [Pb]) directly or indirectly influence the morbidity of respiratory diseases.[12,13] According to a time-series study in Taiwan, a 10 $\mu g/m^3$ increase in PM with diameter less than 2.5 μm ($PM_{2.5}$) was associated with a 2% (95% CI, 1.5%-2.5%) increase in respiratory physician visits, and the association was stronger in winter than in summer; this association was also observed with arsenic (As), cadmium (Cd), stibium (Sb), and Pb.[14] Inflammatory disorders, allergic diseases, and asthma may arise from developmental immunotoxicity. Environmental Pb exposure and blood Pb levels (BLLs) are associated with increased levels of IgE.[15,16] An estimated 38% of the total effect of Pb exposure on asthma is mediated by IgE levels.[16] Current studies have mainly focused on occupational exposure to high levels of heavy metals.[17,18] However, few studies have evaluated the effects of low-level exposure to ambient heavy metals in the air on children with incident asthma. Lung development is a continuous multistage process from conception to adolescence. Therefore, the interference of environmental pollutants in any development stage of the lungs may change lung function and increase the risk of respiratory morbidities. We conducted a large population-based birth cohort study to evaluate the association between weekly average coexposure of Pb with As, Cd, and mercury (Hg) in $PM_{2.5}$ in pregnant women and 1-year-old infants with asthma. This study identified critical time windows for asthma onset.

METHODS

Study design and participants

Taichung City, located in central Taiwan, is Taiwan's second-largest metropolitan area, with a total population of approximately 2.81 million. It has an area of 2215 km^2 and consists of 29 districts. Taichung has had excellent development of various facilities and received resources for transportation, human activities, and economic activities. This city covers multiple types of topography and contains numerous emission sources such as major steel plants, a coal-fired power plant, and industrial and science parks. Taichung's road density is the highest in Taiwan.

Data were collected from 6 databases—Taiwan Maternal and Child Health Database (TMCHD),[19] Taiwan Birth Registry, ambulatory care expenditures by visits, inpatient expenditures by admissions, registry for beneficiaries of National Health Insurance Research Database, and Cause of Death Data. Using these nationwide databases, we considered a birth cohort for the 2004 to 2011 period. The registry for beneficiaries of National Health Insurance Research Database covered 99.9% of the population in Taiwan. The TMCHD contains health care outpatient and inpatient records and birth registration information for all live births in Taiwan, such as birth weight, gestational week, single/multiple births, history of visits to newborns, as well as children and their mothers. We considered each mother's residential address to be the child's location. Asthma was diagnosed using the *International Classification of Disease, Ninth Revision, Clinical Modification* (*ICD-9-CM*).

Our study was approved by the Institutional Review Board of China Medical University Hospital (CMUH104-REC3-003) and complied with the principles outlined in the Declaration of Helsinki.

A total of 191,330 infants were born in Taichung City as per the TMCHD from January 1, 2004, to December 31, 2011. We excluded multiple births (n = 5,852), birth defects (n = 867), stillbirths (n = 7), and preterm births (gestational age <37 weeks; n = 13,323) to eliminate possible confounding or effect modification in relation to asthma and ambient heavy metal exposure. Finally, 171,281 children conformed within the 2004 to 2011 birth cohort and were followed until December 31, 2014. During the follow-up period, 425

children were lost to follow-up because of withdrawal from insurance or death. The follow-up rate of the birth cohort was 99.75% (see Fig E1 in this article's Online Repository at www.jacionline.org).

Covariates

In this study, we obtained data on covariates such as child's sex (male/female), birth weight (>2500 g/≤2500 g), socioeconomic status (SES) derived from the insurance amount (≤25th, 25th-50th, 50th-75th, and >75th percentile), maternal age (>30/≤30 years), maternal atopy (asthma, allergic rhinitis, or atopic dermatitis), some diseases related to the mother including anemia, lung diseases, heart diseases, gestational diabetes mellitus, chronic hypertension, gestational hypertension, preeclampsia, and kidney diseases, and maternal status during pregnancy.

Exposure assessment for heavy metals

The Weather Research and Forecasting/Chem (WRF/Chem) model (version 3.6) was used to simulate weather parameters and the concentration of ambient heavy metals over central Taiwan. Heavy metal emissions values in the model were from Taiwan Environmental Protection Administration, which publishes a list of the top 75 emission sources that account for more than 90% of the total emissions in Taiwan. According to the emissions estimates of Taiwan Environmental Protection Administration, coal is one of the main sources of heavy metals in Taiwan. Coal emissions contributed approximately 70% of the As, 53% of the Cd, 36% of the Hg, and 64% of the Pb of all emissions.[20] Our study selected 4 major heavy metals (As, Cd, Hg, and Pb) in the models for simulation and investigated the effects of ambient heavy metals on different time and space-scale variations and meteorological conditions. Meteorological initial and boundary conditions for WRF/Chem were obtained from the National Center for Environmental Prediction Global Forecast System 0.5° × 0.5° analysis data sets at a 6-hour interval. Mellor-Yamada-Janjic turbulent kinetic energy (TKE) and Weather Research and Forecasting (WRF) single-moment 5-class schemes were selected for the planetary boundary layer and microphysics parameterizations, respectively. The horizontal resolution for heavy metal simulations was 5 km, and the grid box had 181 × 181 points in both east-west and north-south directions. The grid box had 45 vertical levels; the lowest level was approximately 20 m above the surface. To ensure that meteorological fields were accurately simulated, a 4-dimensional data assimilation scheme was activated according to the National Center for Environmental Prediction Global Forecast System analysis data.[21]

Pb in the air is mostly present in the particulate phase, especially fine particles. It can penetrate airway membranes and then enter the lungs and blood.[22] Because heavy metals were not monitored daily, we verified the concentration through measured values provided by Sinotech Engineering Consultants, Inc, in Taiwan. Atmospheric As, Cd, Pb, and Hg were measured at 21 stations throughout Taiwan in 2013. The atmospheric concentration ranges of As, Cd, Pb, and Hg were 0.53 to 3.35, 0.12 to 1.81, 5.57 to 454, and 1.89 to 17.15 ng/m^3, respectively. Hg usually exists in the atmosphere in a gaseous form. A field study reported that atmospheric Hg concentrations in metropolitan or industrial areas varied from 2.59 to 4.12 ng/m^3. In 2003, the Pb and Cd concentrations of $PM_{2.5\text{-}10}$ were 90.6 ng/m^3 and 3.8 ng/m^3, respectively, in Taichung.[23] For heavy metal concentration, the values obtained from WRF/Chem simulation model and air sampling showed a similar trend, but values obtained from the WRF/Chem simulation model were lower than those obtained through air sampling, which could be explained by adjustments to diffusion and chemical transport in our WRF/Chem simulation model.

The daily concentrations of ambient heavy metals corresponding to the residential address of each child's mother were estimated on the basis of residential postcodes. The weekly average exposure of each child to heavy metals was calculated on the basis of daily average exposure to evaluate the sensitive time windows of ambient heavy metals on pregnant women and 1-year-old infants with incident asthma.

Outcomes

We defined a patient with asthma as a child who received at least 2 consecutive diagnosis codes for asthma in either outpatient or inpatient visit claims (*ICD-9-CM* code 493) from birth to December 31, 2014. The date for incident asthma was defined as the date when the child was first diagnosed with asthma.

Statistical analysis

We first used the Cox proportional hazard (PH) models to assess the association of heavy metal (As, Cd, Pb, and Hg) exposure with asthma development from conception to 1 year. The children's survey time was tracked from pregnancy until December 31, 2014. The data of participants who were not diagnosed with asthma or were lost to follow-up were censored. Concentrations of heavy metals were calculated during the entire pregnancy period and for 1 year after birth for each child separately. We used the time-dependent coefficient ("tt" function) in the "coxph" package of R (survival) to consider the violation of PH assumption in the models. The Cox PH models were adjusted for SES and maternal age, atopy, anemia, and kidney diseases. Spearman correlation coefficient was used to explore the correlation between different heavy metals during the exposure period. The potential confounders were selected by using the Cox PH models (with $P < .05$), and some were selected on the basis of literature.[24] A directed acyclic graph was used to illustrate the relationships between the exposure and the outcome with the confounders (see Fig E2 in this article's Online Repository at www.jacionline.org). Sensitivity analyses were conducted to evaluate the robustness of the Cox PH models by adjusting for allergic rhinitis (*ICD-9-CM* code 477), allergic rhinitis due to pollen (*ICD-9-CM* code 477.0), allergic rhinitis due to food (*ICD-9-CM* code 477.1), allergic rhinitis due to animal hair and dander (*ICD-9-CM* code 477.2), allergic rhinitis due to other allergen (*ICD-9-CM* code 477.8), allergic rhinitis due to unspecific cause (*ICD-9-CM* code 477.9), and season of birth. Stratified analyses were performed to assess the effect modification by sex, low birth weight, maternal atopy, SES (>median and ≤median), and maternal age. An interaction term between a specific heavy metal and each characteristic (Heavy metal × Characteristic) was included in the model to test the statistical significance of effect modifications. In addition, given that asthma phenotypes depend on age of onset,[25,26] we restricted the analyses to children who received the first asthma diagnosis at age 3 years or less, 3 to 6 years, and more than 6 years.

Furthermore, we used a distributed lag nonlinear model to identify the association of incident asthma with weekly exposure to heavy metals in pregnant women and infants during their first year of birth. The model simultaneously estimated exposure-response and nonlinear effects by using lag-response associations. The lag effect was the weekly average exposure of each child to heavy metals, which was calculated on the basis of daily average exposure to evaluate the effects of ambient heavy metals on pregnant women and 1-year-old infants with incident asthma using the cross-basis function. The distributed lag nonlinear model equation is as follows:

$$h(t,\ X) = h_0(t)\exp\left[\beta_1 \mathrm{SES} + \beta_2 \mathrm{M}_{\mathrm{age}} + \beta_3 \mathrm{M}_{\mathrm{Atopy}} + \beta_4 \mathrm{M}_{\mathrm{Anemia}} + \beta_5 \mathrm{M}_{\mathrm{Kidney\ diseases}} + \delta 1 s(\mathrm{Heavy\ metal},\ t)\right]$$

$$X = \left[(\mathrm{SES},\ \mathrm{M}_{\mathrm{age}},\ \mathrm{M}_{\mathrm{Atopy}},\ \mathrm{M}_{\mathrm{Anemia}},\ \mathrm{M}_{\mathrm{Kidney\ diseases}},\ s(\mathrm{Heavy\ metal},\ t)\right]$$

where $h\,(t, X)$ is the hazard function for each child with a given specification of a set of explanatory variables; $h_0(t)$ is a baseline hazard function multiplied by an exponential function; X is the collection of explanatory variables (SES, maternal age, maternal anemia, maternal atopy, and maternal kidney diseases); and $s(Heavy\ metal,\ t)$ is a cross-basis function to model lag effect for exposure of each metal separately from conception to 1 year after birth. The result was presented as the hazard ratio (HR) and 95% CI for an interquartile range (IQR).

The lag effect and number of degrees of freedom were selected on the basis of Akaike information criterion, and an optimal curve was drawn.

TABLE I. Demographic characteristics of full-term children of the birth cohort in Taichung City, Taiwan (2004-2014)

Characteristic	Asthma (n = 31,277)	Total (N = 171,281)	Person-years at risk	Incidence rate	HR (95% CI)
Age at date of first diagnosis of asthma (y), mean ± SD					3.41 ± 1.78
Sex, n (%)					
Male	18,299 (58.51)	88,572	619,524.97	2.95	1.37 (1.34-1.40)*
Female	12,978 (41.49)	82,709	598,424.36	2.17	Reference
Birth weight (g), n (%)					
<2500	863 (2.76)	4,749	32,999.65	2.62	1.02 (0.95-1.09)
≥2500	30,414 (97.24)	166,532	1,184,949.68	2.57	Reference
SES, n (%)					
≥33,300	5,876 (18.79)	60,826	213,199.69	2.76	1.16 (1.12-1.20)*
20,100-33,300	7,740 (24.75)	399,555	288,097.41	2.69	1.11 (1.08-1.15)*
16,500-20,100	7,279 (23.27)	41,415	284,494.99	2.56	1.07 (1.04-1.11)*
<16,500	10,382 (33.19)	29,485	432,157.23	2.40	Reference
Maternal age (y), n (%)					
≤30	13,504 (43.18)	78,493	538,951.43	2.51	1.06 (1.04-1.09)*
>30	17,773 (56.82)	92,788	678,997.9	2.62	Reference
Maternal atopy, n (%)					
Yes	20,672 (66.09)	95,827	658,510.12	3.14	1.64 (1.61-1.68)*
No	10,605 (33.91)	75,454	559,439.21	1.90	Reference
Maternal anemia, n (%)					
Yes	97 (0.31)	746	4,605.26	2.11	1.30 (1.07-1.59)*
No	31,180 (99.94)	170,535	1,213,344.07	2.57	Reference
Maternal heart disease, n (%)					
Yes	19 (0.06)	87	584.63	3.25	1.26 (0.81-2.00)
No	31,258 (99.94)	171,194	1,217,364.7	2.57	Reference
Maternal lung disease, n (%)					
Yes	6 (0.02)	18	139.99	4.29	1.83 (0.83-4.04)
No	31,271(99.92)	171,263	1,217,809.34	2.57	Reference
Gestational diabetes, n (%)					
Yes	90 (0.29)	536	3,435.39	2.62	0.98 (0.80-1.20)
No	31,187 (99.71)	170,745	1,214,513.94	2.57	Reference
Maternal chronic hypertension, n (%)					
Yes	23 (0.07)	99	613.69	3.75	1.45 (0.96-2.18)
No	31,254 (99.93)	171,182	1,217,335.64	2.57	Reference
Gestational hypertension, n (%)					
Yes	199 (0.64)	1,274	8,181.52	2.43	1.10 (0.96-1.27)
No	31,078 (99.36)	170,007	1,209,767.81	2.57	Reference
Preeclampsia					
Yes	67 (0.21)	337	2,318.54	2.89	1.13 (0.89-1.43)
No	31,210 (99.73)	170,944	1,215,630.79	2.57	Reference
Maternal kidney disease, n (%)					
Yes	8 (0.03)	24	162.09	4.94	1.86 (0.93-3.72)
No	31,269 (99.97)	171,257	1217,787.24	2.57	Reference
Maternal smoking status, n (%)					
Yes	9 (0.03)	53	354.22	2.54	1.00 (0.52-1.91)
No	31 (99.97)	171,228	1,217,595.11	2.57	Reference

Incidence rate per 100 person-years.
HRs were derived by using univariate Cox PH models.
*$P < .05$.

We set the centering value at the 25th percentile concentration for each metal.

RESULTS

Characteristics of study population

A total of 191,330 infants were born in Taichung City as per the TMCHD; among the 171,281 full-term births, 31,277 had asthma (18.26%). Within the asthma cases, 14,020 (44.8%), 14,790 (47.3%), and 2,467 (7.9%) children received the first asthma diagnosis at age 3 years or less, 3 to 6 years, and more than 6 years, respectively. The average age at which asthma was diagnosed was 3.41 ± 1.78 years. The mean gestational week was 38.64 ± 1.08 weeks. Demographic characteristics of the birth cohort are presented in Table I. In our population, a high incidence of asthma was observed in male patients, patients with high SES, patients who had relatively young mothers, and patients whose mother had atopy and anemia.

TABLE II. Distribution of heavy metal concentrations during the period 2003-2012

Pollution (ng/m^3)	Mean ± SD	Min	Q1	Median	Q3	Max	IQR
Prenatal							
As	0.047 ± 0.023	0.021	0.033	0.042	0.052	0.182	0.019
Cd	0.039 ± 0.031	0.004	0.021	0.030	0.045	0.271	0.024
Pb	0.500 ± 0.339	0.034	0.263	0.400	0.652	2.448	0.388
Hg	0.037 ± 0.011	0.007	0.029	0.037	0.044	0.096	0.014
Postnatal							
As	0.047 ± 0.023	0.023	0.032	0.041	0.051	0.151	0.018
Cd	0.039 ± 0.032	0.004	0.020	0.029	0.046	0.212	0.026
Pb	0.507 ± 0.347	0.040	0.270	0.405	0.670	2.146	0.400
Hg	0.038 ± 0.010	0.009	0.032	0.038	0.043	0.075	0.011
All							
As	0.046 ± 0.023	0.021	0.033	0.041	0.050	0.157	0.018
Cd	0.038 ± 0.031	0.004	0.020	0.029	0.045	0.228	0.025
Pb	0.495 ± 0.337	0.038	0.263	0.399	0.656	2.231	0.393
Hg	0.037 ± 0.010	0.008	0.030	0.037	0.042	0.080	0.012

IQR, Interquartile range; *Max*, maximum; *Median*, 50th percentile; *min*, minimum; *Q1*, 25th percentile; *Q3*, 75th percentile.

Concentrations of heavy metals and correlations among heavy metals

Table II presents the distribution of 4 heavy metals during the prenatal and postnatal periods and from pregnancy to 1 year after birth. The concentrations of As, Cd, Pb, and Hg in these children from the prenatal period to age 1 year were 0.046 ± 0.023 (minimum-maximum, 0.021-0.157), 0.038 ± 0.031 (0.004-0.228), 0.495 ± 0.337 (0.038-2.231), and 0.037 ± 0.010 (0.008-0.080) ng/m^3, respectively. The distributions of heavy metals during the prenatal and postnatal periods in the 4 seasons of birth are shown in Fig E3 in this article's Online Repository at www.jacionline.org. For the prenatal period, the average Pb was highest in the summer, followed by fall, spring, and winter. The average As was highest in the summer, followed by spring, fall, and winter. The average Cd was highest in the fall, followed by summer, winter, and spring. The average Hg was highest in the summer, followed by spring, fall, and winter (Fig E3, *A*). For the postnatal period, the average Pb was highest in the fall, followed by summer, spring, and winter. The average As was highest in the winter, followed by fall, spring, and summer. The average Cd was highest in the fall, followed by winter, spring, and summer. The average Hg was highest in the fall, followed by summer, winter, and spring (Fig E3, *B*).

The patterns of correlations among heavy metals during prenatal and postnatal periods are similar (Fig 1). Significant associations were observed between heavy metals (all Spearman correlation coefficient, $r_s > 0.5$), especially between As and Cd ($r_s = 0.92$ and 0.93 for prenatal and postnatal periods, respectively) and between Pb and Cd ($r_s = 0.97$ and 0.96 for prenatal and postnatal periods, respectively). In addition, the correlations among heavy metals were consistent across seasons of birth (see Fig E4 in this article's Online Repository at www.jacionline.org).

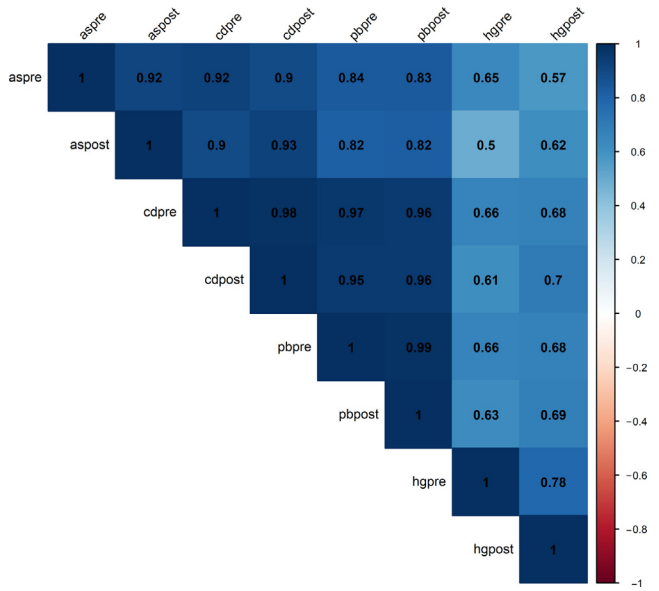

FIG 1. Spearman correlation coefficients of heavy metals during prenatal and postnatal periods. *Aspre*, Arsenic during the prenatal period; *aspost*, arsenic during the postnatal period; *cdpre*, cadmium during the prenatal period; *cdpost*, cadmium during the postnatal period; *hgpre*, mercury during the prenatal period; *hgpost*, mercury during the postnatal period; *pbpre*, lead during the prenatal period; *pbpost*, lead during the postnatal period.

Associations between ambient heavy metals and asthma

Associations between a single heavy metal and asthma within different exposure periods from 2004 to 2011 are presented in Table III. The mutually adjusted model for prenatal and postnatal periods revealed that asthma was positively associated with increased exposure to 0.39 ng/m^3 (IQR) increase in Pb during pregnancy (HR, 1.28; 95% CI, 1.07-1.53) but not to other heavy metals (As, Hg, and Cd). Moreover, we adjusted for As, Cd, and Hg individually in Pb exposure models to evaluate associations between coexposure and asthma (Table IV). We observed that coexposure of Pb with As (HR, 1.24; 95% CI, 1.01-1.53), coexposure of Pb with Cd (HR, 1.45; 95% CI, 1.13-1.87), and coexposure of Pb with Hg (HR, 1.29; 95% CI, 1.08-1.56) were significantly associated with asthma in the prenatal period. The sensitivity analyses showed that the associations between Pb

TABLE III. Adjusted HRs and 95% CIs for associations between single heavy metals and asthma within different exposure periods from 2004 to 2011

Heavy metal (ng/m^3)	Separate model, adjusted HR* (95% CI)	Mutually adjusted model, adjusted HR* (95% CI)
Prenatal		
As	1.07 (1.04-1.10)	0.99 (0.91-1.08)
Cd	1.03 (1.01-1.05)	1.02 (0.95-1.10)
Pb	1.04 (1.01-1.08)	1.28 (1.07-1.53)
Hg	1.01 (0.98-1.03)	0.99 (0.95-1.04)
Postnatal		
As	1.07 (1.05-1.10)	1.08 (1.00-1.18)
Cd	1.04 (1.01-1.07)	1.02 (0.91-1.13)
Pb	1.03 (1.00-1.07)	0.82 (0.68-0.97)
Hg	1.01 (0.98-1.04)	1.01 (0.96-1.07)

Adjusted HR of asthma with an IQR (ng/m^3) increase in heavy metals.
*The model adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases.

TABLE IV. Adjusted HRs and 95% CIs for associations between coexposure to heavy metals and asthma within different exposure periods from 2004 to 2011

Heavy metal (ng/m^3)	Separate model, adjusted HR* (95% CI)	Mutually adjusted model, adjusted HR* (95% CI)
Prenatal		
Pb		
+As	0.86 (0.79-0.93)	1.24 (1.01-1.53)
+Cd	0.97 (0.88-1.07)	1.45 (1.13-1.87)
+Hg	1.05 (1.00-1.09)	1.29 (1.08-1.56)
Postnatal		
Pb		
+As	0.82 (0.76-0.89)	0.67 (0.54-0.83)
+Cd	0.92 (0.83-1.01)	0.65 (0.51-0.83)
+Hg	1.03 (0.99-1.08)	0.81 (0.68-0.97)

Adjusted HR of asthma with an IQR (ng/m^3) increase in heavy metals.
*The model adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases.

and asthma did not change substantially after being adjusted for allergic rhinitis due to pollen, food, animal hair and dander, other allergen, unspecified cause, and season of birth (see Table E1 in this article's Online Repository at www.jacionline.org). In stratified analyses, we found significant effect modification by low birth weight, SES, and maternal age (all P values <.05), whereas there was no interaction with sex and maternal atopy (see Table E2 in this article's Online Repository at www.jacionline.org). The association of asthma with exposure to an IQR increase in Pb during the postnatal period among children born with low birth weight (HR, 1.00; 95% CI, 0.38-2.58) was higher than for those born with normal weight (HR, 0.81; 95% CI, 0.68-0.97) (Table E2). The association of asthma with exposure to an IQR increase in Pb during the prenatal period for children with high SES (HR, 1.38; 95% CI, 1.04-1.83) was higher than for children with low SES (HR, 1.22; 95% CI, 0.97-1.53), whereas the association with exposure to an IQR increase in Pb during the postnatal period for children with high SES (HR, 0.76; 95% CI, 0.57-1.00) was lower than for children with low SES (HR, 0.86; 95% CI, 0.68-1.08). Stratification by maternal ages showed that children born to mothers older than 30 years had a higher effect of exposure to Pb during the prenatal period on asthma, whereas they had a lower effect of exposure to Pb during the postnatal period (HR, 1.30, 95% CI, 0.98-1.73, and HR, 0.79, 95% CI, 0.60-1.06, for prenatal and postnatal periods, respectively) than children born to mothers 30 years or younger (HR, 1.26, 95% CI, 1.00-1.59, and HR, 0.84, 95% CI, 0.67-1.05, for prenatal and postnatal periods, respectively; Table E2). After restricting asthma cases by age of diagnosis, we found that asthma was significantly positively correlated with exposure to Pb during the prenatal period for children who received the first diagnosis at age 3 years or less and at age more than 6 years (HR, 1.45, 95% CI, 1.00-2.11, and HR, 17.15, 95% CI, 1.82-161.61, respectively). However, asthma was not significantly associated with exposure to Pb during the prenatal period (HR, 0.64; 95% CI, 0.36-1.12) and was significantly positively associated with exposure to Pb during the postnatal period (HR, 1.76; 95% CI, 1.02-3.05) when restricted to children who received the first asthma diagnosis at age 3 to 6 years (see Table E3 in this article's Online Repository at www.jacionline.org).

We further used distributed lag nonlinear models to examine the sensitive time window and exposure-response relationship focusing on association between exposure to As, Pb, Cd, and Hg and incident asthma and adjusted for SES, maternal age,

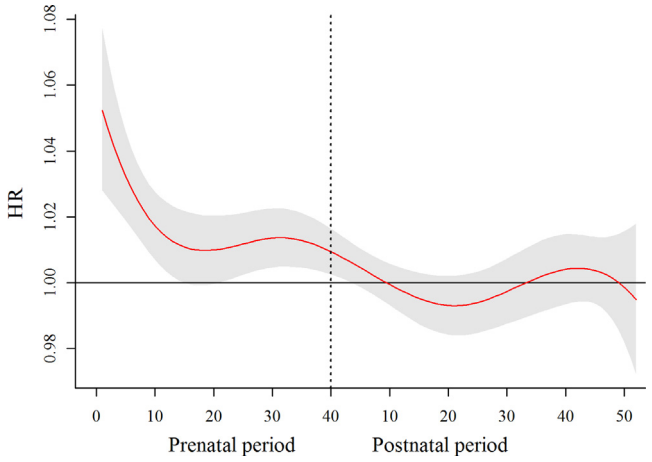

FIG 2. Adjusted HR (red line) with 95% CI (gray area) of asthma with an IQR increase in lead (Pb) during the prenatal (40 weeks) and postnatal (52 weeks) periods by using a distributed lag nonlinear model. The model was adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases. The dashed line indicates the HR of asthma with the weekly exposure during the gestational weeks 1 to 40 (*left part*) and the first 52 weeks of life (*right part*).

maternal atopy, maternal anemia, and maternal kidney diseases. Associations of asthma with weekly exposure to ambient Pb from conception to 1 year after birth are shown in Fig 2. We observed that exposure to an IQR increase in Pb during gestational weeks 1 to 14 and 21 to 40 and 1 to 3 weeks after birth was significantly associated with asthma (Fig 2). For the other metals, we found that exposure to an IQR increase in Cd during gestational weeks 1 to 6 and 32 to 52 weeks after birth and exposure to an IQR increase in Hg during gestational weeks 1 to 3 and 16 to 25 and 10 to 50 weeks after birth was significantly and positively correlated with asthma (see Figs E5 and E6 in this article's Online Repository at www.jacionline.org), whereas exposure to an IQR increase in As during gestational weeks 30 to 40 as well as 1 to 4 and 23 to 33 weeks after birth was significantly negatively associated with asthma (see Fig E7 in this article's Online Repository at www.jacionline.org). In the exposure-response relationship, we observed the effects of cumulative weekly exposure to metals on asthma. At gestational week 31, the HR of asthma increased with exposure to more than 0.26 ng/m^3 Pb, suggesting that the cumulative dose-response plateau had not been reached, yielding an increase in HR by 16% to 24% per 0.10 ng/m^3 of Pb (Fig 3). Furthermore, we observed an exposure-response relationship for coexposure to Pb and As, yielding an IQR increase in Pb during gestational weeks 1 to 6 and 24 to 40, and exposure to Pb 1 to 4 weeks after birth was associated with asthma (see Fig E8 in this article's Online Repository at www.jacionline.org). Coexposure to Pb and Cd was associated with asthma during gestational weeks 1 to 9 and 18 to 40 and 1 to 2 weeks after birth (see Fig E9 in this article's Online Repository at www.jacionline.org). Furthermore, coexposure to Pb and Hg was associated with asthma during gestational weeks 1 to 11 and 22 to 40 and 1 week after birth (see Fig E10 in this article's Online Repository at www.jacionline.org).

DISCUSSION

We observed that exposure to Pb during pregnancy (1-14 and 21-40 weeks) and infancy (1-3 weeks) was significantly associated with childhood asthma development (Fig 2). Although the ambient Pb exposure was relatively lower in the blood and urine from an occupational setting,[17] we observed that pregnant woman and infant cumulative exposure to a low level of ambient Pb may increase pediatric asthma risk.

Studies have indicated that oxidative stress plays an essential role in allergic inflammatory diseases.[27] The elevated BLLs enhance IgE, increasing the bronchial response.[28,29] Pregnancy is considered an extremely sensitive period, and children are susceptible to external environmental factors during this period, affecting their lung function. Human lung development is usually divided into 5 stages (embryonic, canalicular, pseudoglandular, saccular, and alveolar). In our study, we identified sensitive time windows to understand the lung development mechanism. Moreover, physical, hormonal, and genetic factors were considered crucial factors affecting lung development during the prenatal period.[30]

The biological mechanism of the association between Pb exposure and asthma is still not completely understood. Despite that, exposure to Pb enhances T_H2 immune responses and inhibits T_H1 responses, leading to an increase in the production of IgE through B-cell stimulation and type 1 hypersensitivity.[31] Exposure to Pb results in mitochondrial dysfunction, increased oxidative stress, increased apoptosis of T cells, and antioxidant defense inactivation. An imbalance between the production of free radicals and antioxidants can lead to increased oxidative stress. Increased oxidative stress and poor anti-inflammatory capacity reduce children's resistance to other contaminants, such as air pollution, and cause chronic inflammation of the airways, including asthma.[32]

In the past decades, Pb exposure was often observed if the workplace involved Pb manufacturing or leaded gasoline. Currently, because of the ban on leaded gasoline, Pb exposure mainly comes from occupational exposure or coal combustion. Only a few studies have assessed the relationship between exposure to ambient heavy metals Pb, As, Hg, and Cd and incident asthma; these studies have provided inconsistent results.[10,16,33,34] Some studies have reported that high serum Cd levels enhance oxidative stress and lung inflammation.[35]

Joseph et al[36] conducted a cohort study including 4634 children with a mean age of 1 to 2 years in Michigan to evaluate the relationship between BLLs and asthma risk and show a slightly elevated association between high BLLs (≥5 μg/dL) and asthma compared with low BLLs (<5 μg/dL) among whites (HR, 1.4; 95% CI, 0.7-2.9).

Wang et al[16] conducted a cross-sectional study in 930 Taiwanese children and indicated a positive association between BLLs (≥5 μg/dL) and asthma (adjusted odds ratio, 5.50; 95% CI, 1.69-17.94). Wu et al[37] conducted a population-based cross-sectional study of 5866 children to investigate the association between metal exposure and asthma or wheezing. They showed an elevated risk of childhood asthma at high BLLs (>1.12 μg/dL) (adjusted odds ratio, 1.18; 95% CI, 0.82-1.68) and continuous BLLs (adjusted odds ratio, 1.08; 95% CI, 1.00-1.16). To our knowledge, ours is the first study to demonstrate adverse effects of coexposure to ambient Pb with As, Cd, and Hg on incident asthma.

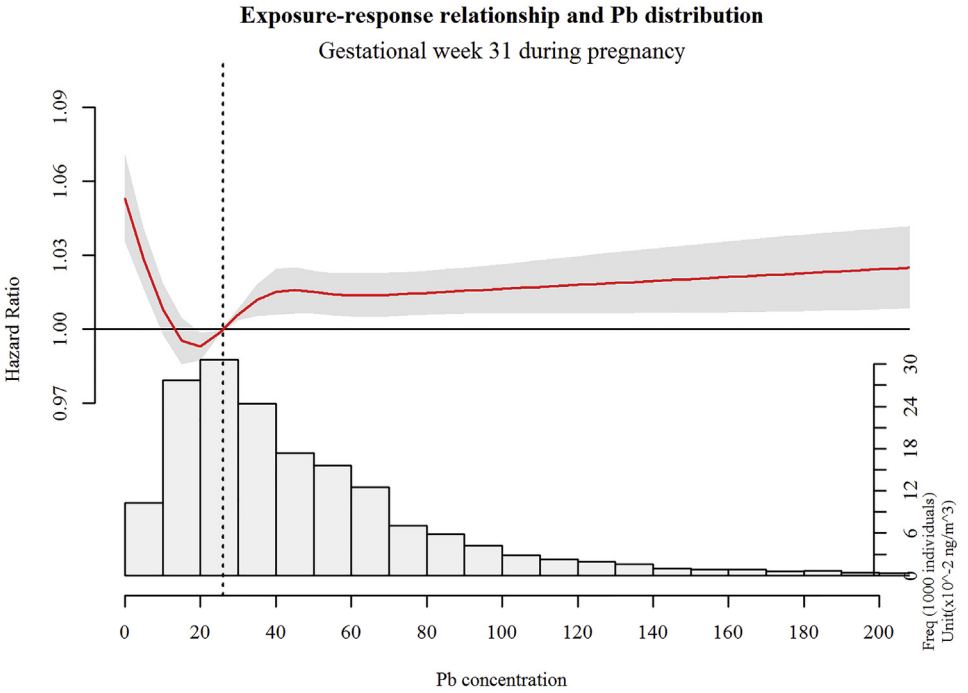

FIG 3. Exposure-response relationship between lead (Pb) exposure and asthma at gestational week 31. The red line shows predicted HR, and the gray area indicates 95% CI corresponding to Pb concentration distributions. The dashed line indicates the centering value of 26×10^{-2} ng/m^3 (Q1).

After restricting analyses to children who received the first asthma diagnosis at age 3 years or less, 3 to 6 years, and more than 6 years, we observed that the group of children that received asthma diagnosis at age 3 to 6 years has distinct patterns of associations with Pb (ie, a null association of asthma with prenatal Pb and a positive association with Pb during infancy) as compared with the other age groups. The inconsistent associations among age groups could be explained by the heterogeneity of asthma phenotypes. The Tucson Children's Respiratory Study was the first study that classified children into 4 categories: (1) no wheezing, (2) transient early wheezing (wheezing during the first 3 years but no wheezing at age 6 years), (3) late-onset wheezing (without wheezing during the first 3 years but had wheezing at age 6 years), and (4) persistent wheezing (with wheezing at the first 3 years and at age 6 years).[38] They observed that eczema, rhinitis apart from colds, and maternal atopy were risk factors for persistent wheezing but were not associated with transient early wheezing, and maternal smoking was the only risk factor for both age groups.[38] A cohort study that recruited 68,195 children by Sbihi et al[39] found that prenatal exposure to $PM_{2.5}$ was associated with transient asthma (adjusted rate ratio, 1.16, 95% CI, 1.00-1.32, in the second quartile level and 1.24, 95% CI, 1.08-1.42, in the third quartile as compared with the first quartile) and late-onset asthma (adjusted rate ratio, 1.24, 95% CI, 1.07-1.45, in the third quartile) but was not associated with early-onset (persistent) asthma. A study that included 339 children delivered by nonsmoking mothers in Poland found that the frequency of wheezing (the number of wheezing day) during the first 2 years of life was associated with prenatal exposure to $PM_{2.5}$ (incident rate ratio, 1.38; 95% CI, 1.25-1.51); however, the association between the frequency of wheezing and prenatal $PM_{2.5}$ became insignificant when analyses were carried out for children at age 3 to 4 years.[40] The different asthma phenotypes may have distinct responses to environmental factors, the associations between heavy metal exposures and different asthma phenotypes are required further investigation.

This study has several strengths. First, the study collected complete and detailed information on numerous mother-infant pairs; the database—TMCHD—followed up the participants from birth to death. We combined other large databases, such as Taiwan Birth Registry and registry for beneficiaries of National Health Insurance Research Database, constructing a nationwide population-based database to explore the effects of heavy metals on asthma. Second, we derived the heavy metal concentrations with a high temporal resolution (daily) from an advanced atmospheric model to identify vulnerable time windows. Obtaining heavy metal concentrations in the atmosphere was difficult because determining the source and measuring the daily production were difficult. By using the sophisticated atmospheric model, we can fill the knowledge gap in this field.

This study had some limitations. First, the ambient concentration of heavy metals was lower than their concentration in blood and urine. Few studies assessed the association of heavy metal in the air with asthma, and we were unable to compare this study with previous studies. In addition, we used the WRF/Chem model to estimate As, Cd, Pb, and Hg concentrations in the air; however, other hazardous heavy metals still exist in the atmosphere. All heavy metals in the air should be considered because the exposure model required huge computing resources and was complicated to operate. Second, because genetic

information and medication use data were unavailable in our current data sets, we are not able to consider the gene-environment interaction and the use of β-agonists and inhaled corticosteroids in the present study. Further investigations are required to evaluate the effect of interaction between gene and heavy metals on asthma as well as the associations between heavy metals and asthma in the subtypes of asthma (ie, mild, moderate, and severe asthma).

Conclusions

This study provided new evidence on the effects of ambient heavy metal (Pb) on the development of pediatric asthma. Our findings suggested that coexposure to ambient Pb with As, Cd, and Hg during early and late gestational weeks was associated with an increased incidence of pediatric asthma. Pregnant women and infants must avoid getting exposed to serious air pollution, environmental toxicity, and allergens. The novel findings of the present study warrant further study.

We appreciate the Health and Welfare Data Science Center, Taiwan Ministry of Health and Welfare, Taiwan for providing health data, and are grateful to Health Data Science Center, China Medical University Hospital, Taiwan for providing administrative, technical, and funding support.

Key messages

- **Prenatal exposure to Pb is associated with later development of asthma when considering postnatal exposure.**
- **Combined exposure to Pb with As, Cd, and Hg during early and late gestational weeks was associated with the incidence of pediatric asthma.**
- **An IQR increase in Pb during gestational weeks 1 to 14 and 21 to 40 and 1 to 3 weeks after birth was significantly associated with asthma.**

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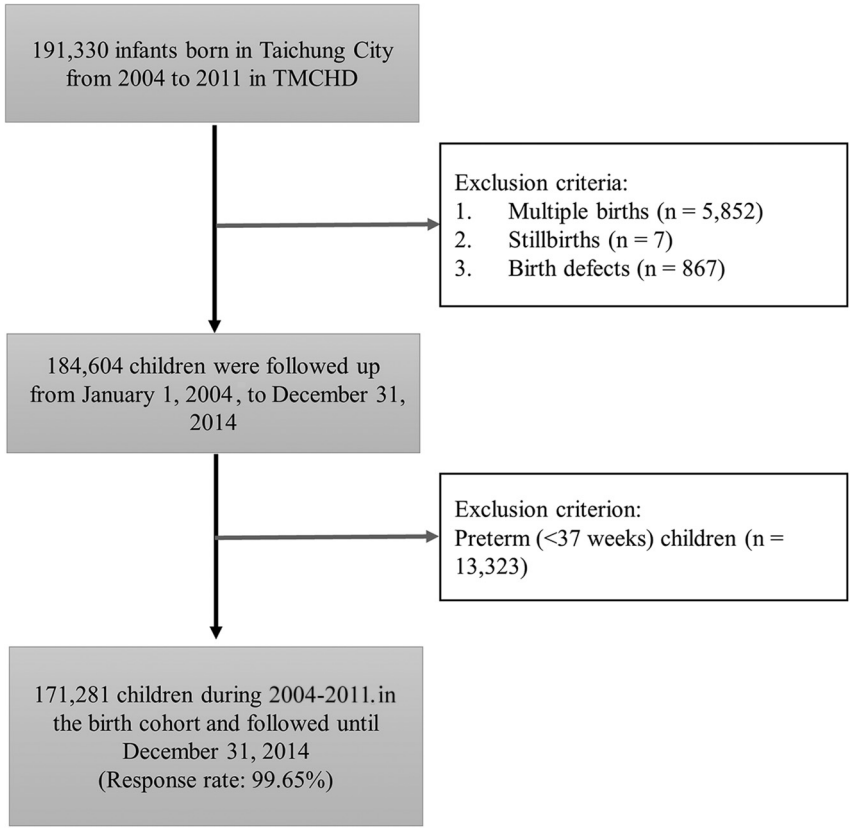

FIG E1. Flow diagram of birth cohort of the study.

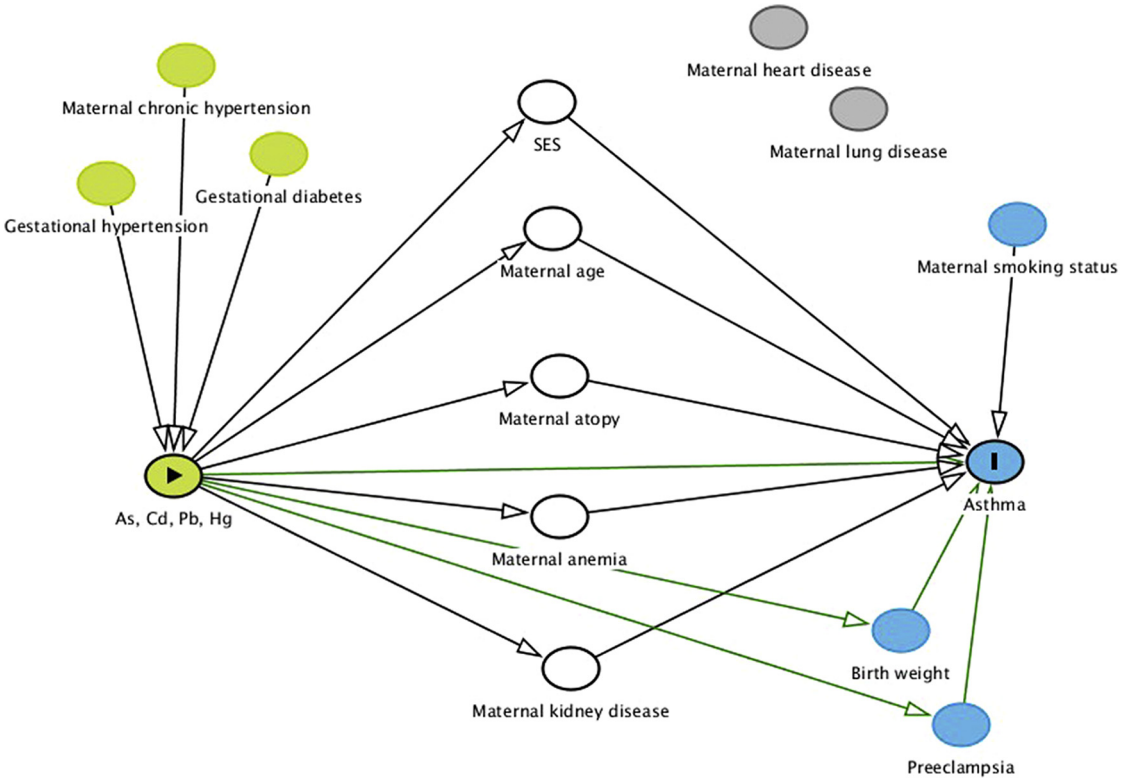

FIG E2. A directed acyclic graph showed the relationships between the exposure and the outcome with confounders in the study. The green node with an arrow indicates exposure, and the blue node with the *I* indicates the outcome of interest (asthma). The white nodes indicate adjusted confounders. The green node without an arrow is a covariate that is associated with heavy metal exposure but not associated with asthma. The blue node without an *I* and with a green edge connection line is an intermediate variable. The blue node without an *I* and with a black color connection line is a covariate that is associated with asthma but not with metals. The gray node is a variable that is neither associated with exposure nor with the outcome.

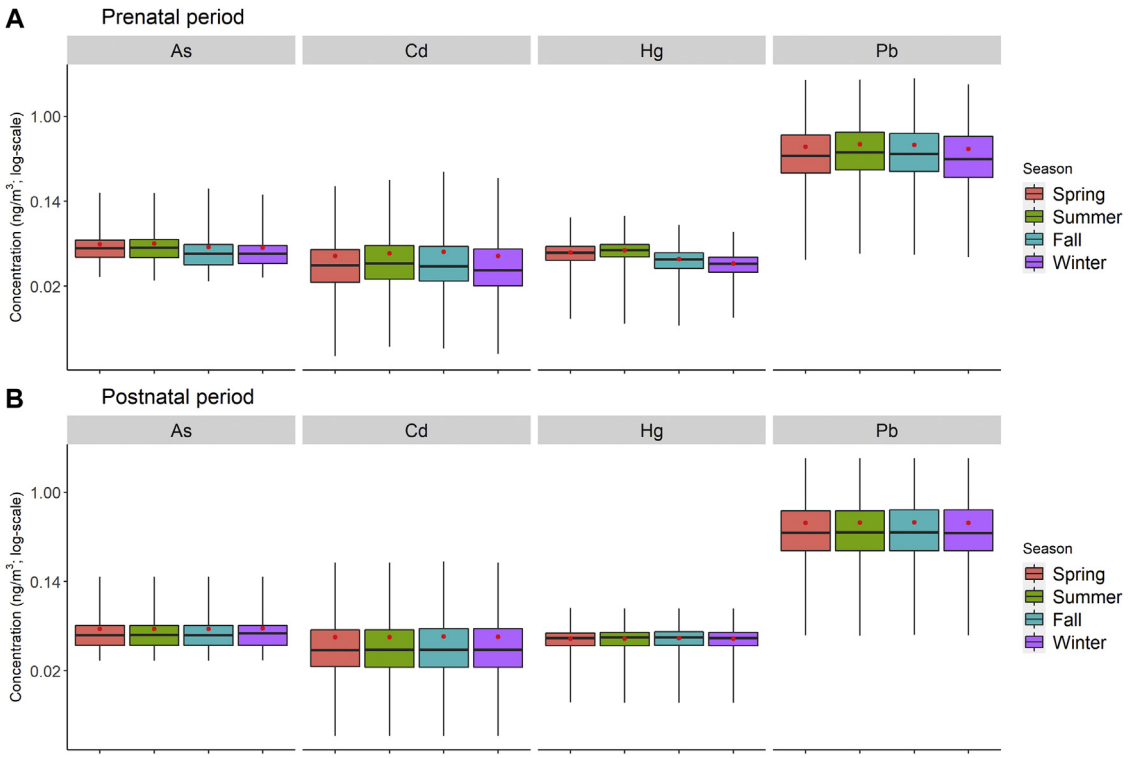

FIG E3. The distributions of heavy metals during (**A**) prenatal and (**B**) postnatal periods across seasons of birth. Red points indicate means of heavy metals. Spring, March-May; Summer, June-August; Fall, September-November; Winter, December-February.

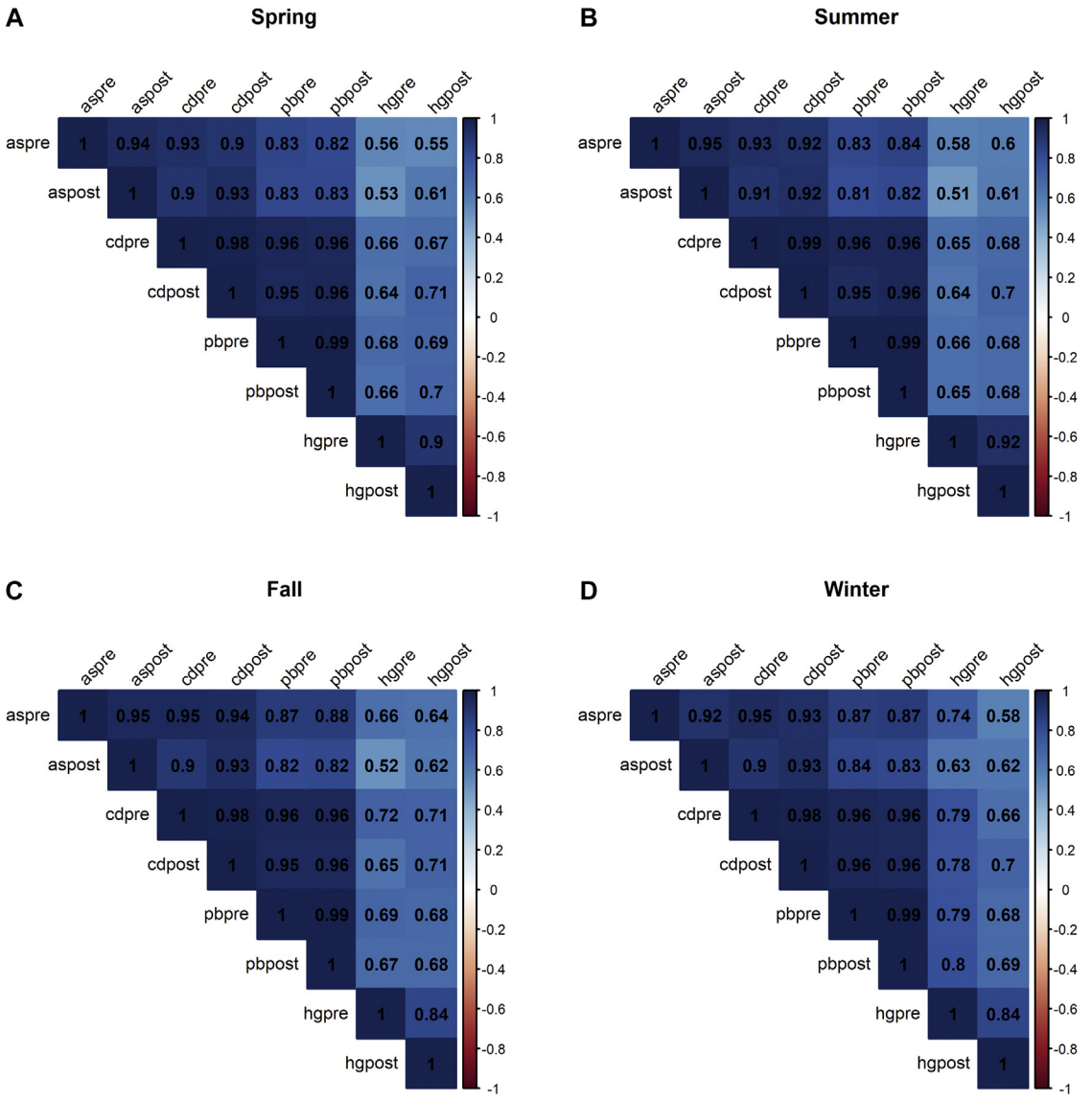

FIG E4. Spearman correlation coefficients of heavy metals during prenatal and postnatal periods across seasons of birth. Spring, March-May; Summer, June-August; Fall, September-November; Winter, December-February. *Aspre*, Arsenic during the prenatal period; *aspost*, arsenic during the postnatal period; *cdpre*, cadmium during the prenatal period; *cdpost*, cadmium during the postnatal period; *hgpre*, mercury during the prenatal period; *hgpost*, mercury during the postnatal period; *pbpre*, lead during the prenatal period; *pbpost*, lead during the postnatal period.

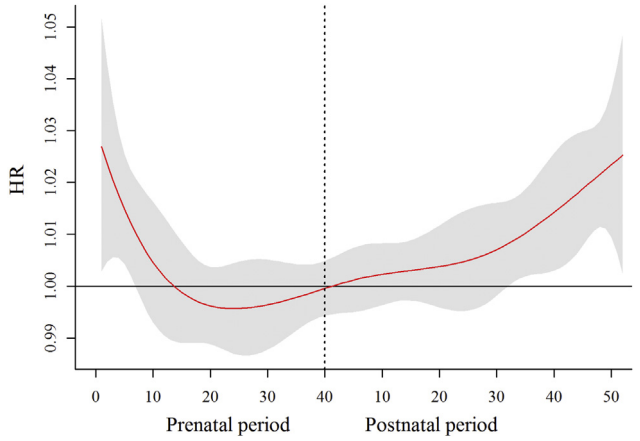

FIG E5. Adjusted HR (red line) with 95% CI (gray area) of asthma with an IQR increase in Cd during the prenatal (40 weeks) and postnatal (52 weeks) periods by using a distributed lag nonlinear model. The model was adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases. The dashed line indicates the HR of asthma with the weekly exposure during the gestational weeks 1 to 40 (*left part*) and the first 52 weeks of life (*right part*).

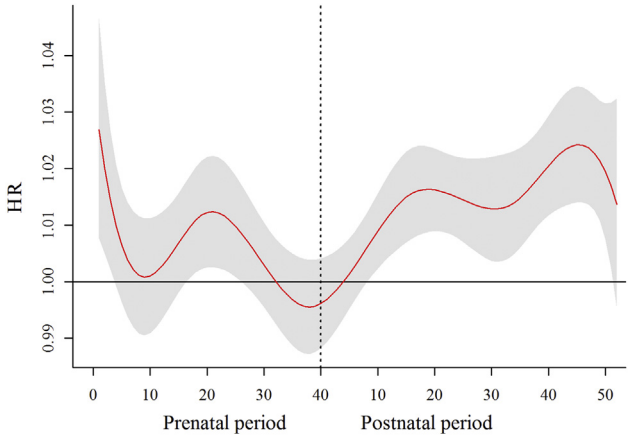

FIG E6. Adjusted HR (red line) with 95% CI (gray area) of asthma with an IQR increase in mercury (Hg) during the prenatal (40 weeks) and postnatal (52 weeks) periods by using a distributed lag nonlinear model. The model was adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases. The dashed line indicates the HR of asthma with the weekly exposure during the gestational weeks 1 to 40 (*left part*) and the first 52 weeks of life (*right part*).

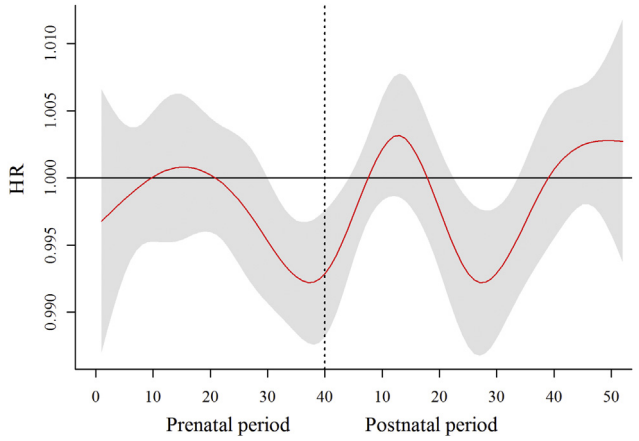

FIG E7. Adjusted HR (red line) with 95% CI (gray area) of asthma with an IQR increase in As during the prenatal (40 weeks) and postnatal (52 weeks) periods by using a distributed lag nonlinear model. The model was adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases. The dashed line indicates the HR of asthma with the weekly exposure during the gestational weeks 1 to 40 (*left part*) and the first 52 weeks of life (*right part*).

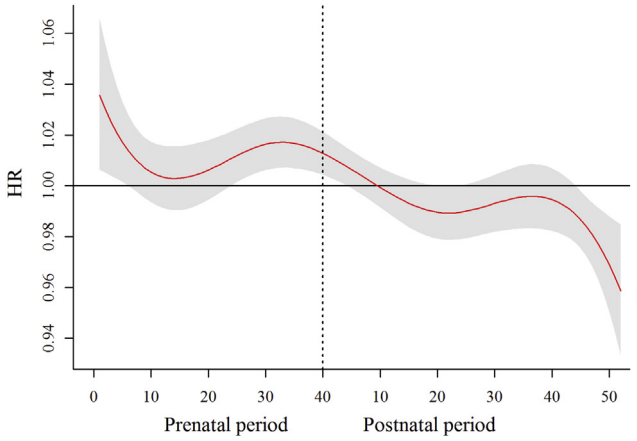

FIG E8. Adjusted HR (red line) with 95% CI (gray area) of asthma with an IQR increase in Pb and As coexposure during the prenatal (40 weeks) and postnatal (52 weeks) periods by using a distributed lag nonlinear model. The model adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases. The dashed line indicates the HR of asthma with the weekly exposure during the gestational weeks 1 to 40 (*left part*) and the first 52 weeks of life (*right part*).

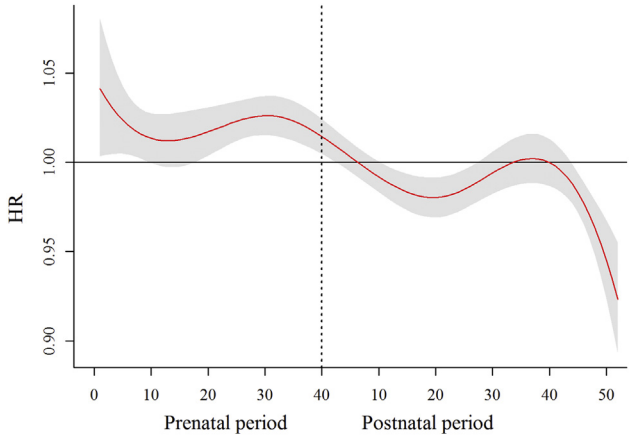

FIG E9. Adjusted HR (red line) with 95% CI (gray area) of asthma with an IQR increase in Pb and Cd coexposure during the prenatal (40 weeks) and postnatal (52 weeks) periods by using a distributed lag nonlinear model. The model adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases. The dashed line indicates the HR of asthma with the weekly exposure during the gestational weeks 1 to 40 (*left part*) and the first 52 weeks of life (*right part*).

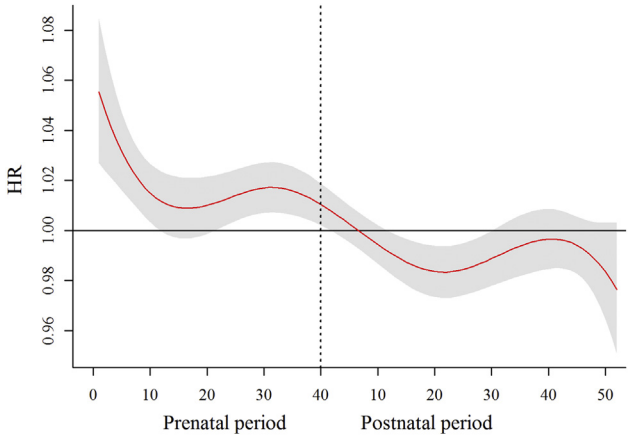

FIG E10. Adjusted HR (red line) with 95% CI (gray area) of asthma with an IQR increase in Pb and Hg coexposure during the prenatal (40 weeks) and postnatal (52 weeks) periods by using a distributed lag nonlinear model. The model adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases. The dashed line indicates the HR of asthma with the weekly exposure during the gestational weeks 1 to 40 (*left part*) and the first 52 weeks of life (*right part*).

TABLE E1. Adjusted HRs and 95% CIs for the associations between Pb and asthma during prenatal and postnatal periods with adjustment for allergic rhinitis and season of birth

Sensitivity analyses*	Separate model	Mutually adjusted model
Adjusted for allergic rhinitis (*ICD-9-CM* code 477)		
Prenatal	1.13 (1.10-1.15)	1.32 (1.20-1.46)
Postnatal	1.12 (1.10-1.15)	0.85 (0.77-0.93)
Adjusted for allergic rhinitis due to pollen (*ICD-9-CM* code 477.0)		
Prenatal	1.11 (1.09-1.13)	1.44 (1.30-1.58)
Postnatal	1.10 (1.08-1.12)	0.77 (0.70-0.84)
Adjusted for allergic rhinitis due to food (*ICD-9-CM* code 477.1)		
Prenatal	1.10 (1.08-1.12)	1.43 (1.30-1.57)
Postnatal	1.09 (1.07-1.11)	0.76 (0.70-0.84)
Adjusted for allergic rhinitis due to animal hair and dander (*ICD-9-CM* code 477.2)		
Prenatal	1.11 (1.09-1.13)	1.43 (1.30-1.58)
Postnatal	1.10 (1.08-1.12)	0.77 (0.70-0.84)
Adjusted for allergic rhinitis due to other allergen (*ICD-9-CM* code 477.8)		
Prenatal	1.11 (1.09-1.13)	1.43 (1.30-1.57)
Postnatal	1.10 (1.08-1.12)	0.77 (0.70-0.85)
Adjusted for allergic rhinitis due to unspecified cause (*ICD-9-CM* code 477.9)		
Prenatal	1.14 (1.12-1.16)	1.34 (1.21-1.47)
Postnatal	1.13 (1.11-1.16)	0.85 (0.77-0.93)
Adjusted for season of birth		
Prenatal	1.05 (1.01-1.09)	1.29 (1.08-1.54)
Postnatal	1.03 (1.00-1.07)	0.81 (0.68-0.97)

Adjusted HR of asthma with an IQR (ng/m^3) increase in Pb.

*The models were also adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases.

TABLE E2. Adjusted HRs and 95% CIs for the associations between Pb and asthma during prenatal and postnatal periods with stratification by selected characteristics

		Prenatal Pb		Postnatal Pb	
Characteristic	**N**	**HR (95% CI)**	***P* for interaction**	**HR (95% CI)**	***P* for interaction**
Low birth weight			.0811		.0282
Yes	4,749	1.07 (0.40-2.89)		1.00 (0.38-2.58)	
No	166,532	1.29 (1.07-1.54)		0.81 (0.68-0.97)	
Sex			.2293		.1461
Male	88,572	1.27 (1.01-1.60)		0.82 (0.65-1.03)	
Female	82,709	1.26 (0.95-1.67)		0.83 (0.63-1.10)	
Maternal atopy			.5932		.8504
Yes	95,827	1.28 (1.03-1.59)		0.84 (0.68-1.04)	
No	75,454	1.27 (0.93-1.73)		0.78 (0.57-1.06)	
SES			.0349		.031
High (>50%)	70,900	1.38 (1.04-1.83)		0.76 (0.57-1.00)	
Low (≤50%)	100,381	1.22 (0.97-1.53)		0.86 (0.68-1.08)	
Maternal age (y)			.0474		.0236
>30	78,493	1.30 (0.98-1.73)		0.79 (0.60-1.06)	
≤30	92,788	1.26 (1.00-1.59)		0.84 (0.67-1.05)	

TABLE E3. Adjusted HRs and 95% CIs for the associations between Pb and asthma during prenatal and postnatal periods after restricting to children who received asthma diagnosis at age ≤3 y, at 3-6 y, and >6 y

Group	Adjusted HR (95% CI)
Asthma diagnosis at age ≤3 y (14,020 asthma cases vs 140,004 no asthma children)	
Prenatal Pb	1.45 (1.00-2.11)
Postnatal Pb	0.60 (0.42-0.87)
Asthma diagnosis at age 3-6 y (14,790 asthma cases vs 140,004 no asthma children)	
Prenatal Pb	0.64 (0.36-1.12)
Postnatal Pb	1.76 (1.02-3.05)
Asthma diagnosis at age >6 y (2,467 asthma cases vs 140,004 no asthma children)	
Prenatal Pb	17.15 (1.82-161.61)
Postnatal Pb	0.05 (0.01-0.51)

The models were adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases.