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Association between prenatal exposure to metal mixtures and early childhood allergic diseases

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ABSTRACT

The association between prenatal exposure to the metal mixture and allergic diseases is poorly understood. We aimed to explore the individual effect and the combined effect of prenatal exposure to vanadium (V), chromium (Cr), nickel (Ni), arsenic (As), cadmium (Cd), thallium (Tl), and lead (Pb) on early childhood allergic diseases based on a birth cohort study that included 628 mother-infant pairs. Metals were measured in maternal urine samples collected in the first, second, and third trimesters. Children were prospectively followed up at age 4 years to collect information on allergic rhinitis, wheeze, and eczema status. By applying logistic regression models, weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR), the different statistical analyses revealed urinary metals were only associated with early childhood allergic rhinitis. The averaged prenatal As exposure was significantly associated with an increased OR for allergic rhinitis in both single-metal (OR = 2.04, 95% CI: 1.35, 3.07) and multiple-metal logistic regression models (OR = 1.78, 95% CI: 1.15, 2.78). The WQS index of mixed metal exposure was positively associated with allergic rhinitis (OR = 1.66, 95% CI: 1.26, 2.19), and As and Tl had the largest weights in the WQS index (weighted 0.51 and 0.29, respectively). The BKMR analysis also showed the overall effect of the metal mixture was significantly associated with allergic rhinitis when all the metals were at their 55th percentile or above, compared to their 50th percentile. The effect of As and Tl on the risk of allergic rhinitis was significant when all of the other metals were fixed at the specific percentiles. Our findings suggest that prenatal co-exposure to higher levels of the seven metals increases the risk of allergic rhinitis in children, and As and Tl may contribute most to the combined risk.

1. Introduction

The prevalence of allergic diseases has risen dramatically over the past few decades, which have become the most common chronic childhood disease in many countries, including China (Asher et al., 2006; Wong et al., 2018). Multiple risk factors such as genetics, diet, and infection have been reported to influence the incidence of allergic diseases (Halken, 2004). However, the rapid increase in the prevalence of allergic diseases within a short period suggests that environmental factors, rather than genetic factors, are the main driving forces behind the increasing prevalence (Alkotob et al., 2020). Therefore, recent studies have focused on the role of environmental chemical exposure, such as metals, in promoting the development of allergic diseases (Joseph et al., 2005; Kim et al., 2013; Stelmach et al., 2014).

In daily life, people are exposed to a variety of metals through ambient air, drinking water and food, industrial processes, and consumer products (Hillyer et al., 2014; Hoover et al., 2019). Previous studies have shown that metals, such as vanadium (V) (Edel and Sabbioni, 1989), chromium (Cr) (Ziaee et al., 2007), nickel (Ni) (Hou et al., 2011), arsenic (As) (Hall, 2007), cadmium (Cd) (Li et al., 2019), thallium (Tl) (Wu et al., 2019) and lead (Pb) (Li et al., 2019), can cross the placental barrier and accumulate in fetal tissues. Studies have reported that allergic diseases can be caused by inhalation sensitization as airway hyper-responsiveness in children is often associated with allergic sensitization (Halken, 2004). In addition to the possible link between inhaled environmental allergens and allergic diseases, maternal exposures during pregnancy can affect the programming of the immune system and may also play a role in atopy development (Hui and Leung,

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2020). For instance, studies have shown that prenatal exposure to metals, such as As, was reported to be associated with the number of specific $CD4^+$ T cell populations present in cord blood, which may alter the fetus's immune system and lead to immune dysregulation (Nadeau et al., 2014). Some epidemiological studies have also reported an increased risk of childhood allergic diseases associated with prenatal exposure to metals, such as Cr (Kim et al., 2019), As (Tsai et al., 2021b), Cd (Pesce et al., 2021), and Pb (Kim et al., 2019; Lee et al., 2021). Several other metals, including V, Ni, and Tl, have also been suggested to have embryotoxicity and fetotoxicity (Bell et al., 2010; Hu et al., 2017; Xia et al., 2016). However, limited information is available about the relationships between prenatal exposure to these metals and the risk of allergic diseases in children (Tsai et al., 2021a).

In addition, previous studies that evaluated the effect of prenatal metal exposure on allergic rhinitis in children either focused on a single metal or only attempted to analyze multiple-metal exposure using traditional regression models that forced all metals into the model, which may ignore the possible multicollinearity and complex interactions between metals. Besides, the traditional regression models cannot estimate the combined effect of exposure to the metal mixture which is closer to the real exposure situation (Braun et al., 2016). In recent years, weighted quantile sum (WQS) regression and Bayesian kernel machine regression (BKMR) have emerged as new statistical approaches that can be used to estimate the combined effect of mixture exposure on health outcomes and identify the important individual components that contribute most to the health effects of the mixture (Bobb et al., 2015; Carrico et al., 2015).

Previous studies have reported that maternal exposure levels of metals may change along with pregnancy (Hopenhayn et al., 2003), which underlines the importance of measuring metal levels in different pregnancy periods to investigate the effect of prenatal metal exposure. However, none of the previous studies have measured metals in three urine samples throughout pregnancy to assess the effect of maternal metal exposure on childhood allergic diseases. Therefore, in the present study, we measured seven metals, including V, Cr, Ni, As, Cd, Tl, and Pb in maternal urine samples collected in the first, second, and third trimesters. Our objective was to apply the WQS regression and the BKMR method to investigate the associations of prenatal exposure to the seven metals individually and in mixture with the subsequent risk of allergic diseases among children and identify important metals that are responsible for the risk. We hypothesized that higher prenatal levels of the metal mixture would be associated with an increased risk of allergic diseases among children.

2. Methods

2.1. Study population

This study was conducted between 2013 and 2016 at the Wuhan Medical & Healthcare Center for Women and Children in Wuhan, China. Wuhan, is one of the industrial, transportation, and regional economic center of China, with a thriving steel industry in its urban areas. Pregnant women with a singleton gestation, residing in Wuhan city and coming for their first prenatal care visit (before 16 weeks) were invited to participate in the study, with the willingness to provide urine samples during pregnancy and complete a face-to-face interview questionnaire. Newborns were enrolled at birth and continued to be followed up at age 4 years with standardized parental-administered questionnaires after entering kindergarten. The follow-up survey was conducted on kindergarten children in main urban districts of Wuhan. Information on children's allergic disease status was collected through structured questionnaires issued to parents through health-care teachers in each kindergarten. In the study period, 3,981 pregnant women came to the study hospital to give birth. Then, 1,973 children completed the follow-up for the allergic diseases status survey. Based on the availability of urine samples, 628 pregnant women had three complete urine samples in the first (median = 13 weeks' gestation), second (median = 24 weeks' gestation), and third (median = 35 weeks' gestation) trimester of gestation, and had urinary metal data. Most important characteristics, except the breastfed status, were not statistically different between the original population (n = 1973) and the analysis population (n = 628). The study was approved by the ethics committees of the Tongji Medical College, Huazhong University of Science and Technology, and Wuhan Medical & Child Healthcare Center for Women and Children, and informed consents were received from the pregnant women and the guardians of their children.

2.2. Data collection

Individual socioeconomic characteristics (e.g., income, education) and lifestyle habits (e.g., active and passive smoking, alcohol consumption) were obtained from pregnant woman through face-to-face interviews conducted by trained interviewers within three days before or following parturition. Information on parity, gestational age at birth, and fetal sex was extracted from medical records. Passive smoking was defined as non-smoking women exposed to tobacco smoke during pregnancy at home or at work. Pre-pregnancy body mass index (BMI) was calculated using self-reported pre-pregnancy weight and height. In addition, no one reported active smoking or drinking alcohol during pregnancy in the present study, so the two variables were not included in further analyses. During follow-up, we collected information on child demographics (child's age), and child-dwelling environment factors (pet ownership) via structural questionnaires. The health-care teachers of the kindergartens distributed the questionnaire together with the consent form to the parents.

2.3. Definition of allergic diseases

The questions used to obtain information on allergic rhinitis, wheezing, and eczema were partly derived from the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al., 1995; Chan et al., 2001). Since the ISAAC questionnaire only targeted at symptoms of allergic diseases, to increase the reliability of determination of allergic disease cases and reduce false positives, we also set the question of whether the child was diagnosed with allergic diseases by the pediatric doctor in the questionnaire. According to the parents' responses in the follow-up questionnaire, subjects who answered "Yes" to the following both question items stating, "Has your child ever had physician-diagnosed allergic rhinitis?" and "Has your child ever had a problem with sneezing, or a runny, or a blocked nose when he/she DID NOT have a cold or the flu?" were defined as having allergic rhinitis. Similarly, subjects who answered "Yes" to the following both question items stating, "Has your child ever had physician-diagnosed wheezing?" and "Has your child ever had wheezing or whistling in the chest at any time in the past?" were defined as having wheeze. Subjects who answered "Yes" to the following both question items stating, "Has your child ever had physician-diagnosed eczema?" and "Has your child ever had an itchy rash which was coming and going for at least 6 months and this itchy rash affected any of the following places: the fold of elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?" were identified as having eczema. Of the 628 total analysis subjects, 609 had information on the outcome of allergic rhinitis, 614 had information on the outcome of wheezing, and 611 had information on the outcome of eczema.

2.4. Maternal urinary metals and creatinine measurements

The present study measured metal levels in urine samples because urine is a noninvasive sample and easier to collect. In addition, most of the urinary metals analyzed in our study (e.g., V, As, Cd, and Ni) have been extensively used as exposure biomarkers (Chandra et al., 2007; Liu et al., 2016, 2018; Vacchi-Suzzi et al., 2016). Prenatal metal exposure

was assessed in maternal urine samples, which were collected from the pregnant women in the first (median = 13 weeks' gestation), second (median = 24 weeks' gestation), and third (median = 35 weeks' gestation) trimester of gestation. The samples were stored at −20 °C until further analysis. Urinary concentrations of seven different metals (V, Cr, Ni, As, Cd, Tl, and Pb) were measured by an inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7700, Agilent Technologies, Santa Clara, CA, USA). Briefly, the urine samples were thawed at room temperature, nitrated overnight with 3% nitric acid, and sonicated at 40 °C for 1 h before ICP-MS analysis. A standard human urine reference sample (SRM2670a; National Institute of Standards and Technology, Gaithersburg, MD) was measured in each batch as an external quality control measure. The spike recovery of urine metals ranged from 98.81% to 105.75%. The intra-assay and inter-assay coefficient of variations (CVs) for all urine metals were <5%. More details about the analytical methods and the limit of detections (LODs) of the seven metals were shown in the Supplemental materials (Table S1).

To adjust for variations in urine dilution, urinary concentrations of metals were corrected by urinary creatinine, which was measured using an automatic biochemical analyzer (Mindray Medical International Ltd.). The creatinine-adjusted urinary concentrations of metals were expressed as μg/g creatinine.

2.5. Statistical analysis

Urinary concentrations of metals below the LOD were imputed with LOD divided by the square root of 2. To provide better reliability of estimation of individual metal exposure levels across pregnancy, we used the average value of the creatinine-adjusted metal concentrations measured at the first, second, and third trimester of pregnancy due to the moderate to high variability of metals during pregnancy (Table S2) and the potential misclassification in exposure measurement using single spot urine samples. Metal concentrations were then natural log (ln) transformed to satisfy the requirements of normally distributed residuals. Pearson correlation coefficients (*r*-values) were calculated to measure pairwise correlations between all the ln-transformed urinary concentrations of the seven different metals.

A multivariate logistic regression model was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the averaged ln-transformed creatinine-adjusted metals exposure during the whole pregnancy with each of the three allergic outcomes (allergic rhinitis, wheeze, and eczema). Additionally, generalized estimating equation (GEE) model was used to estimate the associations of trimester-specific metal exposure with each of the three allergic outcomes. Confounders were included in the models if they were associated ($p < 0.1$) with allergic diseases in bivariate analyses in this study, or had been associated with metal exposures and allergic diseases risk in previous studies. We also conducted a directed acyclic graph (DAG) to illustrate the relations between exposure and outcome with these confounders (Fig. S1). Maternal (i.e., education, pre-pregnancy BMI, parity, and passive smoking during pregnancy) and child (i.e., child's sex and pet ownership) variables were included in the adjusted model. Although gestational age may affect the status of childhood allergic diseases, we did not adjust for this variable since it may be a mediator in the association. All the above covariates were introduced into single-metal models. Multiple-metal models were used to evaluate the simultaneous exposure to the seven metals by mutually adjusting for all metals and the above covariates.

WQS regression (Carrico et al., 2015) model was used to evaluate the effect of metal mixtures during the whole pregnancy on each of the three allergic outcomes (allergic rhinitis, wheeze, and eczema). For each metal, the average concentration was divided into ordinal concentration ranges as quartiles. A total of 1000 bootstrap samples were generated from the full data set and used to estimate the unknown weights for each metal. The weighted average of the weights across the bootstrap samples were then used to construct the WQS index, which was used to estimate the combined effect of the metal mixture on the risk of each allergy outcome. To identify the important components within a set of related multiple metals, the corresponding average weight of each metal was estimated. Since the WQS method constrains the association between mixture exposure and the outcome in the same direction (all negative or all positive), the model was run twice to test for association in either direction. In the main analyses, we conducted training and validation on the same full dataset. We further performed a sensitivity analysis by applying repeated holdout validation, a method that combines cross-validation and bootstrap resampling to evaluate the robustness of the results (Tanner et al., 2019, 2020). Specifically, the full dataset was randomly split into 40–60% training-test sets and the WQS regression was repeated 100 times to simulate a distribution of validated results from the underlying population.

Considering the possible nonlinear and non-additive associations between metal mixtures and each allergy outcome, Bayesian kernel machine regression (BKMR) (Bobb et al., 2015, 2018) analysis with a probit link function was used to flexibly model the adjusted association of the metal mixture during the whole pregnancy on the risk of developing each of the allergic outcomes. We conducted a component-wise variable selection method with 10,000 iterations by a Markov chain Monte Carlo (MCMC) algorithm. The conditional posterior inclusion probability (conditional-PIP) was calculated to describe the relative importance of each metal exposure for each study outcome. A PIP threshold of 0.5 was used to determine whether the metal was important for each allergy outcome (Coker et al., 2018). The covariates adjusted for in the WQS and BKMR models were similar as in the multivariate logistic regression analysis.

SAS (version 9.4; SAS Institute Inc.), and R (version 3.6.3; R Foundation for Statistical Computing) software were used for statistical analyses. WQS and BKMR models were implemented with the "gWQS" (version 3.0.3) and "bkmr" (version 0.2.0) R packages, respectively. A two-sided p-value < 0.05 was considered to be statistically significant in all tests.

3. Results

3.1. Study population characteristics and prenatal metal exposure

The general characteristics of the study population are presented in Table 1. The average maternal age at delivery was 29.18 ± 3.52 years. Most of the pregnant women were nulliparous (79.46%), had normal pre-pregnancy BMI (67.20%), and had a college degree or above (83.28%). Among the children, 53.82% were boys and 38.54% were breastfed for over 6 months during infancy. The average gestational age was 39.32 ± 1.10 weeks. The mean children's age upon follow-up was 3.96 ± 0.47 years. The percentage of pet ownership in the dwelling was 10.03%. The prevalence of allergic rhinitis, wheeze, and eczema was 20.23%, 6.19%, and 5.56%, respectively.

All urinary metals had a detection rate higher than 90% (Table S1). The concentration distributions of the trimester-specific and average urinary metal are shown in Table S2. The ICCs of the metal concentrations throughout the pregnancy were low for As and Tl (0.27, 0.38, respectively), and were moderate for the other metals (ICC range = 0.41–0.52). Pearson *r*-values revealed significant positive correlations ranging from 0.14 to 0.68 between the concentrations of urinary metals (Fig. 1).

3.2. Logistic regression results

The results of the averaged prenatal metal exposure on the allergic disease status of children are shown in Table 2. After adjusting for the covariates, only childhood allergic rhinitis was statistically associated with maternal urinary metal concentrations. The single-metal models showed that both As (OR = 2.04, 95% CI: 1.35, 3.07) and Tl (OR = 1.91, 95% CI: 1.18, 3.09) were significantly associated with childhood allergic

Table 1
Characteristics of the study population (N = 628).

Characteristic	Mean ± SD or n (%)
Maternal age (years)	29.18 ± 3.52
Maternal education level	
High school and below	105 (16.72)
More than high school	523 (83.28)
Family annual income	
<100,000 yuan	319 (50.80)
≥100,000 yuan	308 (49.04)
Missing	1 (0.16)
Pre-pregnancy BMI (kg/m2)	
<18.5	99 (15.76)
18.5–24	422 (67.20)
≥24	107 (17.04)
Passive smoking during pregnancy	
Yes	183 (29.14)
No	443 (70.54)
Missing	2 (0.32)
Parity	
Nulliparous	499 (79.46)
Multiparous	129 (20.54)
Gestational age (weeks)	39.32 ± 1.10
Child's age (years)	3.96 ± 0.47
Child's sex	
Male	338 (53.82)
Female	290 (46.18)
Breastfeeding for 6 months	
Yes	242 (38.54)
No	310 (49.36)
Missing	76 (12.10)
Pet ownership	
Yes	63 (10.03)
No	553 (88.06)
Missing	12 (1.91)
Disease positive	
Allergic rhinitis	123 (20.23)
Wheeze	38 (6.19)
Eczema	34 (5.56)

Abbreviation: BMI, body mass index.
Notes: Of the 628 children, 609 had information on the outcome of allergic rhinitis, 614 had information on the outcome of wheezing, and 611 had information on the outcome of eczema.

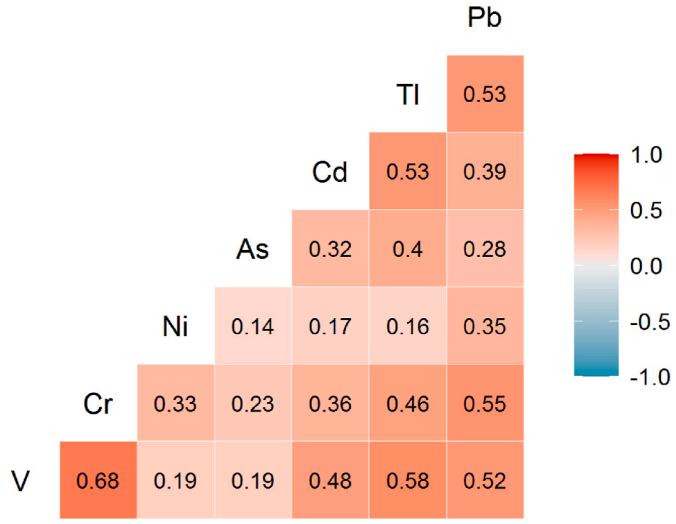

Fig. 1. Pearson correlations between urinary concentrations of seven metals during the whole pregnancy. All the correlations were statistically significant (p-value < 0.001).

rhinitis. In multiple-metal models, only As (OR = 1.78, 95% CI: 1.15, 2.78) showed a significant positive association with childhood allergic rhinitis. Tl was marginally positively associated with childhood allergic rhinitis (p = 0.053). In the further trimester-specific analysis (Table S3), an increased OR for allergic rhinitis was found to be associated with maternal As concentrations in the second and third trimester (2nd trimester: OR = 1.52, 95% CI: 1.06, 2.18; 3rd trimester: OR = 1.73, 95% CI: 1.23, 2.42), maternal Tl concentrations in the first trimester (OR = 1.59, 95% CI: 1.01, 2.49), and maternal Cr concentrations in the third trimester (3rd trimester: OR = 1.41, 95% CI: 1.02, 1.95). However, V in the third trimester was associated with a decreased OR for allergic rhinitis (OR = 0.57, 95% CI: 0.37, 0.89). In addition, V in the second trimester was also associated with decreased ORs for wheeze and eczema (OR = 0.48, 95% CI: 0.23, 0.98; and OR = 0.44, 95% CI: 0.21, 0.90, respectively).

Table 2
Associations of ln-transformed average creatinine adjusted maternal urinary metals with the odds ratio (OR) of allergic rhinitis, wheeze, and eczema in children.

Metals	Allergic Rhinitis		Wheeze		Eczema	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Single-metal models[a]						
V	1.11 (0.80, 1.54)	0.533	0.89 (0.53, 1.48)	0.649	0.69 (0.40, 1.19)	0.186
Cr	1.25 (0.96, 1.61)	0.096	1.16 (0.78, 1.71)	0.459	1.05 (0.70, 1.56)	0.830
Ni	1.16 (0.93, 1.44)	0.178	1.24 (0.87, 1.75)	0.237	0.93 (0.69, 1.27)	0.654
As	**2.04 (1.35, 3.07)**	**0.001**	1.00 (0.53, 1.90)	0.997	1.27 (0.65, 2.46)	0.485
Cd	1.20 (0.78, 1.84)	0.417	0.91 (0.47, 1.79)	0.789	1.03 (0.51, 2.07)	0.943
Tl	**1.91 (1.18, 3.09)**	**0.009**	1.15 (0.55, 2.40)	0.707	0.84 (0.38, 1.83)	0.658
Pb	1.28 (0.96, 1.71)	0.098	1.22 (0.78, 1.91)	0.379	0.93 (0.57, 1.52)	0.776
Multiple-metal models[b]						
V	0.74 (0.44, 1.26)	0.269	0.55 (0.24, 1.25)	0.154	0.45 (0.20, 1.01)	0.054
Cr	1.19 (0.80, 1.78)	0.391	1.30 (0.72, 2.35)	0.387	1.53 (0.86, 2.73)	0.145
Ni	1.08 (0.85, 1.38)	0.539	1.17 (0.79, 1.73)	0.440	0.88 (0.63, 1.23)	0.454
As	**1.78 (1.15, 2.78)**	**0.010**	0.87 (0.42, 1.80)	0.700	1.31 (0.62, 2.75)	0.477
Cd	0.77 (0.44, 1.33)	0.345	0.81 (0.34, 1.93)	0.635	1.28 (0.54, 3.04)	0.581
Tl	1.93 (0.99, 3.75)	0.053	1.50 (0.52, 4.33)	0.449	0.89 (0.29, 2.69)	0.836
Pb	1.06 (0.70, 1.60)	0.780	1.24 (0.69, 2.25)	0.472	1.03 (0.52, 2.05)	0.927

Abbreviations: V, Vanadium; Cr, Chromium; Ni, Nickel; As, Arsenic; Cd, Cadmium; Tl, Thallium; Pb, Lead; OR, odds ratios; CI, confidence interval.
Notes: Of the 628 children, 609 had information on the outcome of allergic rhinitis, 614 had information on the outcome of wheezing, and 611 had information on the outcome of eczema.
[a] Model 1 was adjusted for maternal education, pre-pregnancy BMI, parity, passive smoking during pregnancy, child's sex, breastfeeding for 6 months, and pet ownership.
[b] Model 2 was additionally adjusted for urinary levels of the other six metals except for covariates in model 1.

3.3. WQS regression results

In the WQS results (Fig. 2), the WQS index was positively associated with allergic rhinitis in children (OR = 1.66, 95% CI: 1.26, 2.19), and the highest weighted metal was As (0.51), followed by Tl (0.29). The WQS index of the metal mixture during the whole pregnancy was not significantly associated with wheeze or eczema after adjustment for potential covariates (Table S4). We also analyzed whether there was a negative association between the metal mixture during the whole pregnancy and allergic diseases, and found no significant association (Table S4). In the

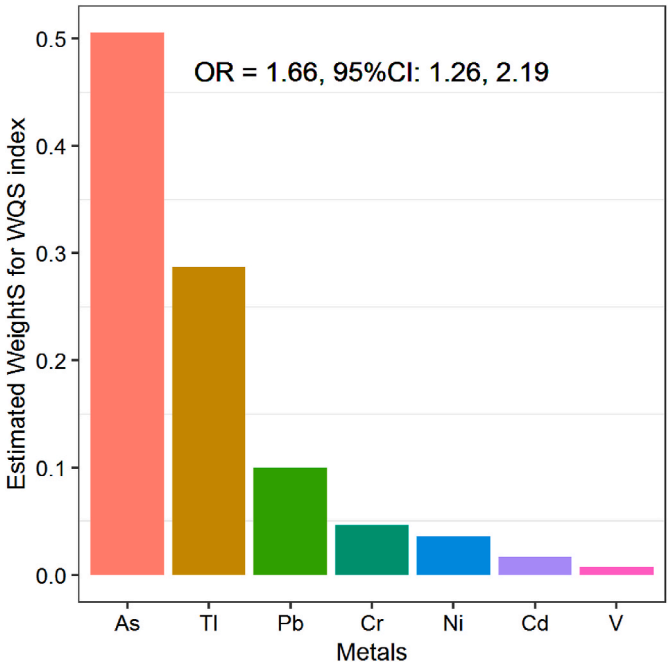

Fig. 2. Weighted quantile sum (WQS) regression index weights for allergic rhinitis estimated in the study population. WQS regression model was constrained the association between metal mixture exposure and the outcome in the positive direction. WQS model was adjusted for maternal education, pre-pregnancy BMI, parity, passive smoking during pregnancy, child's sex, breastfeeding for 6 months, and pet ownership.

sensitivity analysis that applied the repeated holdout validation for WQS regression, although the observed association was attenuated (Tables S4–S5), the WQS index was still positively associated with allergic rhinitis and the highest weighted metal was still As, followed by Tl.

3.4. BKMR results

The results of BKMR model for allergic rhinitis revealed the condPIP of As (0.78) was the highest, followed by Tl (0.65) (Table 3). The metal mixture during the whole pregnancy was significantly associated with a higher risk of allergic rhinitis when all metals were at the 55th percentile or above compared to their 50th percentile (Fig. 3A). To characterize the contribution of individual metal exposure to the overall effect, we further estimated the association of an inter-quartile range (IQR) increase of each metal exposure on allergic rhinitis when the other metals were set at different percentile levels (25th, 50th, or 75th percentile).

Table 3
Posterior inclusion probabilities (PIPs) for conditional inclusion into allergic rhinitis models, using Bayesian kernel machine regression (BKMR) model.

Metals	condPIP
V	0.300
Cr	0.200
Ni	0.112
As	0.775
Cd	0.268
Tl	0.647
Pb	0.284

Model was adjusted for maternal education, pre-pregnancy BMI, parity, passive smoking during pregnancy, child's sex, breastfeeding for 6 months, and pet ownership.

The effect of As and Tl on the risk of allergic rhinitis was significant when all of the other six metals were fixed at the 25th, 50th, and 75th percentiles (Fig. 3B). Exposure to single metal showed a linear relationship with allergic rhinitis when other metals were fixed at the median (Fig. S2). Cr, Ni, As, Tl, and Pb showed a positive association with allergic rhinitis, whereas V and Cd showed an inverse relationship. No interaction effect was found among the seven metals in the bivariate exposure-response analysis, since the slopes of the exposure-response function of a certain metal were similar at the different percentiles of other metals, with others fixed at median levels (Fig. S3).

The condPIPs were less than 0.5 for wheeze and eczema (Tables S6–S7), and the overall association analyses performed for the relationships between the metal mixture and the latent continuous outcomes of wheeze or eczema were not statistically significant (Fig. S4). The trends of exposure-response functions of the single metals on wheeze and eczema are shown in Fig. S5. Cr showed a positive association with wheeze and eczema, whereas V showed an inverse relationship with wheeze and eczema when all the other metals were at their median levels.

4. Discussion

Increasing evidence suggests that prenatal metal exposures adversely affect the subsequent development of allergic diseases in children (Kim et al., 2019; Lee et al., 2021; Pesce et al., 2021; Tsai et al., 2021b), but few studies have considered the mixture effect. Since the synergistic or antagonistic effects may exist when multiple metals are co-exposed, studying one element at a time could overlook these effects (Howe et al., 2020; Zheng et al., 2020). In the present study, by applying the mixture modeling method i.e., WQS regression and BKMR, we explored the combined effect of the metal mixture exposure during the whole pregnancy on early childhood allergic diseases. Consistent with our study hypothesis, higher levels of the metal mixture were associated with an increased risk of childhood allergic rhinitis, and the combined effect of the mixed metals were dominated by As and Tl. In the trimester-specific analysis, we also found that higher levels of urinary As and Tl were associated with an increased OR of childhood allergic rhinitis, whereas higher urinary V levels were associated with decreased ORs of allergic rhinitis, wheeze, and eczema.

As is a non-essential toxic heavy metal that is widely distributed in the environment. People are chronically exposed to As, primarily through ingestion of contaminated drinking water or foods (Palma-Lara et al., 2020). In our study, all of the study population were residents of Wuhan, an inland Chinese city with a flourishing steel industry. In our study, maternal urinary concentrations of As was higher than that of the pregnant women from the USA (Gilbert-Diamond et al., 2016), Canada (Thomas et al., 2015), and Australia (Callan et al., 2013), but lower than the pregnant women from regions with arsenic contamination of groundwater like Bangladesh (Gao et al., 2019) and Vietnam (Navasumrit et al., 2019), and were also lower than those from Japan (Shirai et al., 2010) and Spain (Fort et al., 2014). Urinary As levels are generally regarded as the most reliable exposure biomarker for recent low-level arsenic exposure (Liu et al., 2018). The variety of As concentrations across studies may be due to differences in population characteristics, sampling time, and particular locations.

In addition to its identification as a human carcinogen (Straif et al., 2009), As has a wide range of effects on human health. Recent studies have shown that As may have immunotoxicity, affecting immunomodulatory function and altering the immune response (Dangleben et al., 2013). Several *in vivo* and *in vitro* studies have provided evidence that As exposure could be implicated in the immune dysfunctions with the imbalanced differentiation of Th1/Th2 cells (Liu et al., 2020a; Morzadec et al., 2012; Zhao et al., 2019). In addition, a US pregnancy cohort study reported that maternal urinary As (median = 4.23 μg/L) was associated with unbalanced T lymphocyte subpopulations in umbilical cord blood (Nadeau et al., 2014), which may lead to immune dysregulation and an

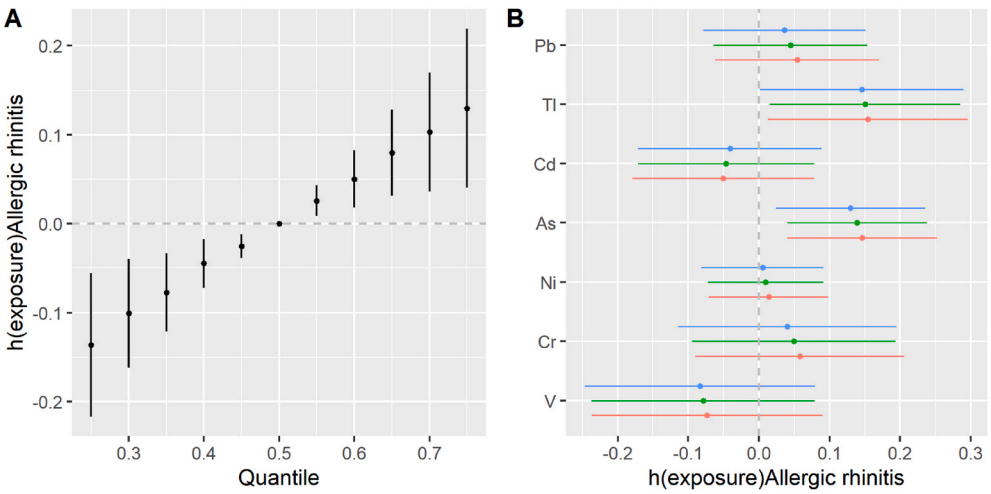

Fig. 3. Joint effect of the metal mixture on allergic rhinitis by using Bayesian kernel machine regression (BKMR) model. The results were adjusted for maternal education, pre-pregnancy BMI, parity, passive smoking during pregnancy, child's sex, breastfeeding for 6 months, and pet ownership. (A) Overall effect of the metal mixture (estimates and 95% confidence intervals). The figure plots the estimated change in a latent continuous outcome (a continuous marker of the binary allergic rhinitis) when all the metals at particular percentiles (x-axis) were compared to all the metals at their 50th percentile. (B) Single metal association (estimates and 95% confidence intervals, gray dashed line at the null) for a change in each metal from its 25th to its 75th percentile with allergic rhinitis, when all of the other metals are set at their 25th (red), 50th (green), or 75th (blue) percentile. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

increased response to common environmental allergens and exacerbate allergies later in life (Belderbos et al., 2009; Martino and Prescott, 2010). In the present study, prenatal As exposure (the averaged median concentration in urine = 25.27 μg/g creatinine) was found to be associated with later allergic rhinitis in children. The above findings suggest that prenatal exposure to As may affect the development of immune function in utero, leading to sensitization of allergic rhinitis. To date, only one previous study from Taiwan estimated the association of prenatal As exposure with childhood allergic rhinitis, which analyzed inorganic As, and found no significant association between maternal urinary inorganic As concentration and childhood allergic rhinitis (Tsai et al., 2021b). The contrasting findings with our study might be due to the differences in the extent of As exposure, sample size, children's ages at follow-up, and general characteristics.

To our knowledge, the present study is the first to report a positive association between prenatal Tl exposure and the risk of allergic rhinitis in children. Tl is generally at low levels in the environment, but it is a highly toxic element, and the general population is mainly exposed to it through ingestion of food contaminated by Tl (Peter and Viraraghavan, 2005). There are rich Tl-bearing mineral resources in China, which have been widely exploited and utilized, resulting in the release of a large amount of Tl into the environment (Liu et al., 2020b). Urinary levels of Tl in our population were slightly higher than those reported for pregnant women in Israel (Karakis et al., 2021) and Spain (Lozano et al., 2021). Tl is involved in the production of reactive oxygen species, decreasing mitochondrial function (Eskandari et al., 2015; Hanzel and Verstraeten, 2006). However, the biological mechanisms of Tl exposure on the development of allergic diseases remain unclear, and more epidemiological and mechanism studies are needed to elucidate the relationship of Tl exposure on allergic diseases.

V is a transition metal which is ubiquitously distributed in the environment (Barceloux, 1999). Compared with the general population, urinary V levels in our study population (the averaged median concentration in urine = 1.40 μg/g creatinine) were lower than in the UK (median = 2.33 μg/g creatinine in women) (Morton et al., 2014), but higher than in Belgium (median = 0.22 μg/g creatinine) (Hoet et al., 2013). Previous epidemiological studies have reported that prenatal exposure to V has adverse effects on fetal growth and early-childhood growth, which may suggest the potential developmental toxicity of prenatal V exposure (Hu et al., 2017, 2018; Jiang et al., 2016; Li et al., 2021; Zhou et al., 2019). However, V is also reported to have important biological roles, including insulinotropic ability, growth-promoting effect, anti-tumor effect, and antioxidant defense (Tripathi et al., 2018). In addition, V compounds are involved in immune regulation and could be used as a promising metallodrugs for immunotherapy in the future (Tsave et al., 2016). In the trimester-specific analysis, we found that higher urinary V levels were negatively associated with allergic rhinitis, wheeze, and eczema. Meanwhile, in the BKMR analysis, V showed an inverse association with allergic rhinitis, wheeze, and eczema, when all the other metals were at their median levels. As far as we know, this is the first study examining prenatal V exposure in associations with the incident of allergic diseases in children. However, the underlying mechanism between V and allergic diseases remains unclear and the potential role of V in programming immune function development needs to be elucidated by future functional studies.

Previous studies regarding prenatal metal exposure and allergic diseases mostly focused on the effects of Pb and Cd exposure. Our study found no significant association of prenatal exposure to Pb and Cd with any allergic disease outcomes. Similar to our results, one previous study from the UK found that cord blood Pb or Cd concentration was not significantly associated with later onset wheeze at 30–42 months or eczema at 18–30 months (Shaheen et al., 2004). A study from Korea also reported that maternal blood Cd level during pregnancy was not significantly associated with atopic dermatitis in 6-month-old infants (Lee et al., 2021). A previous study conducted in France also reported that maternal blood Pb level was not significantly associated with the incident rates of childhood eczema, while they found that cord blood Cd level was associated with a greater risk of eczema (Pesce et al., 2021). The differences in children's ages at follow-up, sample size, biological sample, and the timing of metal exposure assessment may contribute to the heterogeneity of the results. Future studies are needed to clarify the influence of Pb and Cd on allergic diseases in children.

To analyze the combined effect of the metal mixture on allergic diseases in children, we used the WQS and BKMR models. The results of the two models consistently indicated that co-exposure of the seven metals had a significant combined effect on allergic rhinitis in children. As and Tl were identified as the most critical contributors to the increased risk of allergic rhinitis in the metal mixture, while other metals had a low contribution. In the BKMR analysis, Cr, Ni, As, Tl, and Pb showed a positive relationship with allergic rhinitis, whereas V and Cd showed an inverse relationship. Different from the BKMR model, the WQS regression model could not simultaneously evaluate the joint effect of metals in different directions, which is a limitation of WQS regression (Czarnota et al., 2015). V and Cd, which showed an inverse relationship

with allergic rhinitis in the BKMR analyses, were estimated to have negligible weight in the WQS index when exploring the positive effect of the metal mixture on allergic rhinitis. Besides, it is noticeable that the association between Tl and allergic rhinitis was weakened as the concentrations of other metals increased to their 75th percentile in the BKMR model. This suggests that the association between Tl and allergic rhinitis is affected by other metal concentrations, and the toxicity of Tl is more apparent when other metals are at lower levels. In the present study, there was a relatively stronger correlation between metal Tl and V, and these two metals showed opposite trends in the incidence of allergic rhinitis. Thus, the negative exposure-response relationship of V may partially neutralize the positive association between Tl and allergic rhinitis. Nevertheless, our findings need to be confirmed in more studies. These findings also underline the importance of considering metals in the context of a mixture.

One strength of the study was that maternal metal exposure was repeatedly measured in the first, second, and third trimesters. By calculating the subject-specific average of these repeated measurements, we were able to better estimate individual metal exposure levels throughout pregnancy. Secondly, we collected detailed demographic and lifestyle data from a prospective cohort study to adjust for potential confounding factors.

However, several potential limitations also need to be noted when interpreting these findings. Firstly, in this study, metal exposure levels were only assessed in the urine of pregnant women. We did not assess metal exposure levels in umbilical cord blood or urine samples from children. Secondly, we depended on parental reports in the follow-up questionnaire to determine children with or without allergic rhinitis, wheeze, and eczema, which might misclassify the status of allergic diseases in children. However, to identify cases of allergic diseases, we adopted the ISAAC questionnaire, an international standard questionnaire for allergic diseases, which may reduce the potential for misclassification. Thirdly, this study did not include the outcome of food allergy, because the diagnosis of food allergy is complicated that requires a careful medical history, laboratory studies, and an oral food challenge to confirm a diagnosis (Sicherer and Sampson, 2010). However, these data were not available to us. Fourthly, we used urinary metals as the indicators of body exposure which might not be representative of some metals exposure, such as Pb. The biological material commonly used in research to measure Pb exposure levels is blood (Saoudi et al., 2018; Skroder et al., 2016; Weitzman, 2019). We did not observe a significant association between Pb and allergic diseases in our study, which may be due to the potential misclassification of metal exposure levels of Pb using urine samples rather than blood samples. The potential misclassification may lead to an underestimate of the true association. Finally, we did not evaluate the effect of urinary As speciation as we only measured the total As concentrations. In general, the toxicity of inorganic As forms is much higher than that of naturally occurring organic As forms (Gundert-Remy et al., 2015). Therefore, in our study, we used the total As concentrations as an indicator of As exposure, which would result in indistinguishable toxic contributions from organic and inorganic As and may lead to the overestimation of inorganic As exposure.

5. Conclusions

In summary, our findings suggest that the joint exposure of the seven metals during pregnancy may increase the risk of childhood allergic rhinitis. As and Tl displayed the most significant effect in the mixed metals. Future research is needed to confirm these associations and recognize the importance of assessing the health impacts of chemical mixtures.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.112615.

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