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Associations of environmental exposure to metals with the risk of hypertension in China

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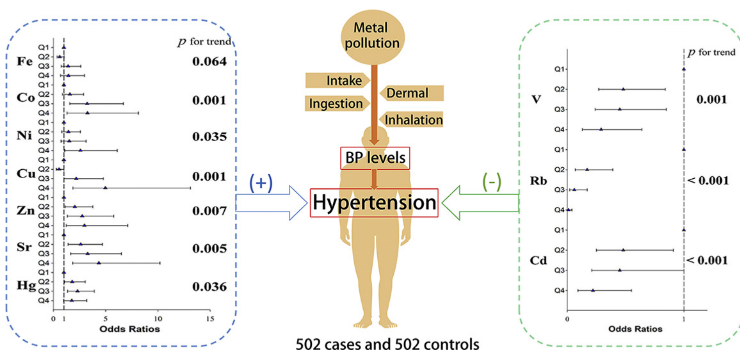
HIGHLIGHTS

- Multi-metal model was used to investigate the co-exposure to various metals.
- Urinary Fe, Co, Ni, Cu, Zn, Sr and Hg levels were related with hypertension risk.
- Urinary V, Rb and Cd levels were inversely associated with hypertension risk.
- Modification effects of gender, BMI, smoking status and income levels were found.

GRAPHICAL ABSTRACT



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ABSTRACT

Hypertension contributes largely to the global burden of disease and mortality. Environmental exposure to metals might be a causative factor for hypertension, but the association remains unclear. The present case-control study of 502 hypertension patients and 502 healthy participants aimed to evaluate the potential relationships between the concentrations of 20 metal in urine and the risk of hypertension in a Chinese population. Multivariate logistic analyses adjusted for potential confounders were performed separately considering the effects of single and multi-metal. We found the increasing trends of urinary Fe, Co, Ni, Cu, Zn and Sr quartiles and the decreasing trends of urinary V and Rb quartiles with the ORs for hypertension. These dose-response associations were confirmed in the RCS models and remained robust in the multi-metal model. Urinary Hg quartiles were positively associated with the risk of hypertension in the models of single-metal and multi-metal. Urinary Cd quartiles were inversely associated with the risk of hypertension in the multi-metal model. Besides, modification effects of gender, BMI and smoking status on the associations of the exposure to various metals with the risk of hypertension were also suggested in the subgroup analysis. Our findings suggest that environmental exposure to V, Fe, Co, Ni, Cu, Zn, Rb, Sr, Cd and Hg might be related with the prevalence of hypertension. Further studies with prospective design should be conducted to confirm these findings.

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1. Introduction

Hypertension affects nearly one billion people worldwide, and contributes largely to the global burden of disease and mortality (Kearney et al., 2005; Poulter et al., 2015). In China, increasing prevalence of hypertension has been reported in recent years (Wang et al., 2014). It was indicated that there were 18% Chinese adults with hypertension in 2002, and it increased to 33.6% in 2010 (Wu et al., 2008). Prevention and control of hypertension are thus urgently needed.

Environmental exposure is an important but underappreciated risk factor for hypertension (Cosselman et al., 2015). Recent studies have suggested the potential associations of environmental exposure to metals with the risk of hypertension (Abhyankar et al., 2012; Eum et al., 2008; Gambelunghe et al., 2016; Su et al., 2016). Metal pollution is a severe environmental issue in China. The general population is commonly exposed to various kinds of metals through air, water, soil, dust, and diet (Abuduwailil et al., 2015; Bian et al., 2015; Li et al., 2014). The cardiovascular effects of the metals without any known biological function, such as cadmium (Cd), lead (Pb), arsenic (As) and mercury (Hg), are well-documented (Cosselman et al., 2015). However, results from epidemiological studies are inconsistent. For example, several population-based studies had reported the positive association of hypertension with exposure to Cd, but null and even negative associations were both suggested (Eum et al., 2008; Kurihara et al., 2004; Mordukhovich et al., 2012; Telišman et al., 2001; Tellez-Plaza et al., 2008). Essential metals, including selenium (Se), vanadium (V), iron (Fe) and manganese (Mn), are suggested to be critical factors to normalize blood pressure (BP) levels and possess protective effects on hypertension (Coderre and Srivastava, 2004; Jiang and Zheng, 2005; Kuruppu et al., 2014). The deficiencies of these trace metals have been found to exacerbate the unfavorable effects of toxicants (Afridi et al., 2014). However, adverse effects in BP levels are reported when exposed to these metals at relatively high levels (Laclaustra et al., 2009; Lee and Kim, 2011).

In the present study, we explored the potential associations between the concentrations of 20 metal in urine and the risk of hypertension with a case-control study in China. We measured urine samples for the levels of environmental exposure to 20 metals, since urinary metals are easy-accessible and used more frequently in epidemiological studies with a large sample size. Multi-metal model was applied to investigate the simultaneous impacts of multiple metals on the risk of hypertension, which can reflect real scenarios in which humans are commonly exposed to multiple metals simultaneously. Subgroup analysis was conducted to further explore the associations in various stratified groups.

2. Material and methods

2.1. Study population

The study population consisted of 502 patients with hypertension and 502 healthy individuals was conducted from September 2015 to May 2017. The patients with hypertension were consecutively recruited during their first arrival to the department of cardiology, Union hospital, Wuhan, China. Concomitantly, we enrolled healthy individuals without hypertension who were frequency-matched by age (±5 years) and gender with patients from the physical examination center of the Union Hospital during the same period. Hypertension was defined as Systolic blood pressure (SBP) of ≥140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg, a physician diagnosis, or current use of antihypertensive medication. The inclusion criteria of hypertension and non-hypertension groups were age ≥ 30 years, and no history of diabetes, primary renal disease (e.g., renal failure, renal dysfunction), cerebrovascular disease (e.g., stroke, cerebral infarction), chronic obstructive pulmonary disease, thyroid disease (e.g., hyperthyroidism, hypothyroidism) and cancer. Thus, only primary hypertension was included in the present study. Besides, participants with potential occupational exposure were also excluded (n = 2). Most of the participants were from Chinese Han population (98.9%). Each included participant provided written informed consent at enrollment, and the study was approved by the Ethics Committee of Tongji Medical College.

2.2. Data collection

A face-to-face questionnaire by a skilled interviewer was applied to collect data. Information on demographic and socioeconomic factors, past medical history, medication use, status of smoking (e.g., non-smokers, current smokers, former smokers, and packs per year smoking) and drinking (e.g., non-drinkers, current drinkers, former drinkers), lifestyle habits, and living condition was gathered. All the included participants were asked to provide their urine samples at the morning after an overnight fast. Blood pressure (BP) determinations were taken for 3 times in a sitting position after 5 min rest using a mercury sphygmomanometer, with an appropriate size cuff placed on the bared right arm. SBP and DBP were assigned to be the average of the measurements, and pulse pressure (PP) was calculated as the difference between SBP and DBP.

2.3. Urine sample collection and analysis

First morning urine samples were collected from participants using containers confirmed to be uncontaminated by metals and then immediately packed into coolers with frozen ice packs. All the collected samples were sent to the laboratory within 4 h, and then stored at −20 °C within 6 months before further analysis. Urinary levels of 20 metals (aluminum, Al; vanadium, V; chromium, Cr; manganese, Mn; iron, Fe; nickel, Ni; cobalt, Co; copper, Cu; zinc, Zn; arsenic, As; selenium, Se; rubidium, Rb; strontium, Sr; cadmium, Cd; cesium, Cs; barium, Ba; thallium, Tl; lead, Pb; uranium, U; mercury, Hg) were measured using an inductively coupled plasma-mass spectrometer (NexION™ 300X, PerkinElmer Inc., USA) based on a previous method with minor modifications (Feng et al., 2015). Before analysis, frozen urine samples were thawed at room temperature (22.0 ± 7.0 °C) prior to the centrifugation. Five hundred microliter of the supernatant was then transferred to 10 mL polypropylene centrifuge tubes and acidified with 20 μL 67% (v/v) HNO3 (Optima™ grade, Fisher, Belgium) at 5 °C overnight. After the digestion, urine samples were brought to room temperature and diluted to 5 mL with 1% (v/v) HNO_3. The resulting samples were first under ultrasound for 30 min and then allowed to stand at room temperature for another 30 min before analysis. The status of hypertension and non-hypertension was masked throughout the analysis procedure. The concentrations of urinary creatinine (micrograms per liter, μg/L) were measured to account for urine dilution according to sarcosine oxidase method on a fully automated clinical chemistry analyzer (Mindray Medical International Ltd.).

2.4. Quality control/quality assurance

Standard reference materials (SRMs) 2670a (Toxic Elements in Urine) and 1640a (Trace Elements in Natural Water) purchased from NIST (National Institute of Standards and Technology, Gaithersburg, MD) were used as quality control samples in our analysis. SRM 2670a was applied to verify the accuracy of our method through the comparisons of the measurement results with the certified values and reference values according to the method by European Reference Material (Linsinger, 2005). The calculated values of U-Δm > 0 ensured the accuracy of the present method. For Fe, Rb and Sr, which were not given any value in SRM 2670a, spiked recovery method was applied at two concentration levels, with the spike recovery values of Fe, Rb and Sr ranging from 102.2% to 112.7%. Specially, considering the volatility of Hg, spiked recovery method was also applied for Hg, with the recovery values ranging from 76.4% to 83.6%. All the relative standard deviations (RSDs) ranged from 0.6% to 8.3%. We applied SRM 1640a to assess the