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Research Article

Cadmium body burden, hypertension, and changes in blood pressure over time: results from a prospective cohort study in American Indians

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Abstract

American Indian communities are at greater risk of hypertension and cardiovascular disease than the general US population and are exposed to greater cadmium levels. However, cadmium's effect on blood pressure is unclear. This study assesses the association between baseline urinary cadmium and longitudinal changes in blood pressure in American Indian communities. Cadmium was measured in 3047 baseline urine samples from Strong Heart Study participants from three geographic areas. Longitudinal changes in blood pressure across three study visits (1989–1999) were modeled using linear mixed models by baseline log urinary cadmium to creatinine ratio. Hypertension risk was evaluated using interval-censored survival analysis. Higher levels of urinary cadmium at baseline were associated with faster rates of increase in diastolic and systolic blood pressure (*P* [trend] = .001 and .02, respectively). The estimated change in diastolic and systolic blood pressures per year was 0.18 mm Hg (0.05–0.31) and 0.62 mm Hg (0.37–0.87) in the upper quintile of cadmium level compared with −0.11 mm Hg (−0.24 to 0.02) and 0.21 mm Hg (−0.04 to 0.46) in the lowest, respectively. A one-unit increase in log-transformed urinary cadmium was associated with 10% greater hypertension risk (95% confidence interval: 1.01–1.20). In conclusion, blood pressure of individuals with greater baseline levels of urinary cadmium increased at a faster rate relative to those with lower levels. J Am Soc Hypertens 2018;■(■):1–12. © 2018 Published by Elsevier Inc. on behalf of American Heart Association.

Keywords: Heavy metals; high blood pressure; indigenous population.

Introduction

Since 2000, approximately a quarter of the adult population worldwide had hypertension, defined as diastolic blood pressure (DBP) measurement of ≥90 mm Hg or systolic blood pressure (SBP) measurements of ≥140 mm Hg.[1] The prevalence of hypertension in the United States is higher at 29.1%.[2] Hypertension is a leading cause of cardiovascular disease (CVD)[3] and chronic kidney disease.[4] Although smoking, body mass index (BMI), diet, and physical inactivity are known to contribute to hypertension, an increasing body of evidence supports that metalloids and metals, such as arsenic, lead, and cadmium, may play a role.[5,6]

Cadmium is a heavy metal known to have a toxic effect on human kidneys and the skeletal and respiratory systems.[7] Sources of human exposure include active and passive smoking, diet, and occupational exposures, including

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iron and steel production and phosphate fertilizers.[8,9] Primarily, cadmium accumulates in the kidneys where it has a half-life of 10–35 years.[10] This accumulation can lead to renal tubular dysfunction.[11] Cadmium exposure is also associated with an increased CVD risk, including peripheral arterial disease,[12] heart failure,[13] stroke,[13] and myocardial infarction.[14]

American Indian communities are exposed to higher cadmium levels than the US population.[15] Furthermore, they are at greater risk of CVD[16] and other metabolic disorders including diabetes and obesity, than the general US population,[17,18] highlighting these individuals as an at-risk population.

Previous studies have identified an adverse effect of metals on blood pressure (BP) and hypertension risk, including cadmium.[19,20] However, findings have been inconsistent. A recent meta-analysis showed a positive association between blood cadmium and BP in women, but the study was limited by a small sample of population-based studies.[21] Some studies have not found evidence of a relationship between cadmium and subsequent BP levels,[22] whereas ours and other studies have identified an association, but lacked temporality due to a cross-sectional design.[23,24]

Within this context, we studied data collected from American Indian communities from the Northern and Southern plains and the Southwest and sought to address the nature of the relationship between urinary cadmium, an established biomarker of cadmium exposure,[25] and both longitudinal BP and hypertension risk.

Materials and Methods

Study Population

The Strong Heart Study (SHS) is a prospective cohort study of American Indian men and women. The study commenced from 1989 to 1991, recruiting men and women aged 45–75 years from American Indian communities based in Arizona, Oklahoma, and North and South Dakota. All eligible individuals in the communities in Arizona and Oklahoma were invited to participate, whereas a cluster sampling technique was used to invite participants from North and South Dakota communities.[26] Three thousand five hundred sixteen individuals (78% of those invited) consented to take part in the study and were included in this analysis, and 468 individuals were excluded as they lacked either a urinary cadmium or creatinine measurement. A further 200 individuals were excluded from the BP analysis, and 183 individuals were excluded from the hypertension analysis, due to missing covariate data and either BP measurements or hypertension data, respectively. This resulted in a cohort of 2853 in the BP analyses and 2865 in the hypertension analyses. All participants provided written and oral informed consent. The protocol for the SHS was approved by the Institutional Indian Health Service Review Boards, institutional review boards and by the participating communities.

Data Collection

Participants reported sociodemographic factors, smoking status, and medical history in a baseline questionnaire. A physical examination provided anthropometric measures, including height, weight, and BP, with a fasting blood test and spot urine collection. Participants were followed up between 1993 and 1995, and between 1998 and 1999. Deaths occurring during the follow-up were confirmed through the Indian Health Service or private hospital records and through direct contact by study personnel with participants' families or other informants, and included medical records, autopsy reports, and informant interviews; all materials were independently reviewed by physician members of the SHS study's morbidity and mortality committees.[27] Fatal coronary heart disease was defined by the occurrence of fatal myocardial infarction or sudden death. Other fatal events were classified as definitive or possible fatal stroke, or definitive or possible heart failure. Follow-up went from 1989 to 1991 through December 31, 2006.

Urinary Cadmium Measurement

The methodology has been described previously.[15] Briefly, spot urine samples were collected in polypropylene tubes in the morning of the baseline visit and frozen within 2 hours. After defrosting, dilution, and centrifugation, the cadmium concentration was measured using inductively coupled plasma mass spectrometry (Agilent 7700x ICP-MS; Agilent Technologies, Waldbronn, Germany). The ''Seronorm Trace Elements Urine Blank'' (SERO AS, Billingstad, Norway) was used for quality control. The limit of detection for urinary cadmium was 0.015 μg/L; three samples were below the limit of detection. The intra-assay and interassay coefficients of variation for cadmium in the SHS were 1.3% and 8.7%, respectively.

To account for kidney function differences, automated alkaline picrate methodology was used to assay urinary creatinine.[26] Creatinine-adjusted urinary cadmium levels were calculated from the ratio of urinary cadmium to creatinine. Quintiles of log-transformed creatinine-adjusted urinary cadmium were calculated, with the lowest quintile as the reference group, and when using continuous measures of cadmium exposure, the logarithm was taken to normalize the distribution.

BP Measurement and Hypertension Definition

During the physical examination at each visit, brachial artery BP (first and fifth Korotkoff sounds) was measured three consecutive times by a mercury sphygmomanometer (WA Baum Co). Participants were seated and rested for