Hypertension

HEAVY METALS EXPOSURE AND BLOOD PRESSURE

Urinary Heavy Metals and Longitudinal Changes in Blood Pressure in Midlife Women: The Study of Women's Health Across the Nation

Xin Wang, Carrie A. Karvonen-Gutierrez, William H. Herman, Bhramar Mukherjee, Sioban D. Harlow, Sung Kyun Park

ABSTRACT: Environmental exposure to heavy metals may contribute to increased blood pressure; however, evidence from midlife women who are at greater risk of cardio-metabolic disease is limited. We evaluated the associations of urinary concentrations of arsenic, cadmium, mercury, and lead with longitudinal changes in blood pressure in the Study of Women's Health Across the Nation Multi-Pollutant Study. The sample included 1317 White, Black, Chinese, and Japanese women, aged 45 to 56 years at baseline (1999–2000), whose systolic blood pressure (SBP) and diastolic blood pressure were measured annually or biannually through 2017. Urinary metal concentrations were determined at baseline. Longitudinal changes in SBP and diastolic blood pressure were modeled using linear mixed-effects models by tertiles of metal concentrations. After multivariable adjustment, estimated annualized increases (95% CI) in SBP in the highest and lowest tertiles were 0.93 (0.85–1.01) mm Hg and 0.74 (0.66–0.82) mm Hg for arsenic, 0.82 (0.75–0.90) mm Hg and 0.72 (0.65–0.80) mm Hg for mercury, and 0.86 (0.78–0.93) mm Hg and 0.72 (0.64–0.79) mm Hg for lead, respectively. Similar results were observed for associations of arsenic, mercury, lead with diastolic blood pressure. Urinary cadmium was associated with a greater rate of increase in SBP only among never smokers. Women with higher concentrations of all four metals had greater annualized increases in SBP and diastolic blood pressure than those with lower concentrations. Our findings suggest that exposure to heavy metals may accelerate the increase in blood pressure in midlife women, supporting the need for continued efforts to reduce these environmental exposures. **(*Hypertension*. 2021;78:543–551. DOI: 10.1161/HYPERTENSIONAHA.121.17295.)** • **Data Supplement**

Key Words: arsenic ■ cadmium ■ blood pressure ■ lead ■ mercury ■ women

High blood pressure remains a significant public health concern in the United States.[1] People with high blood pressure are at a higher risk of developing cardiovascular disease, chronic kidney disease, and mortality.[2,3] Although obesity, smoking, unhealthy diet, and physical inactivity are important contributors to high blood pressure, growing evidence suggests that exposure to environmental toxicants may also play a role.[4]

Heavy metals, including arsenic, cadmium, mercury, and lead are well-known environmental toxicants that may exert adverse effects on blood pressure through the generation of reactive oxygen species and induction of oxidative stress.[5] Animal studies have demonstrated that exposure to these metals is associated with an increase in blood pressure.[6] Epidemiological studies have reported a consistent positive association between lead and blood pressure,[7,8] whereas results have been mixed for other metals. Both arsenic and mercury concentrations have been associated with elevated blood pressure,[9,10] but these associations are largely based on studies in populations exposed to moderate-to-high levels of these metals. The few studies that have examined low-level exposure, for example, in the United States, have been inconclusive.[9,10] Similarly, findings for cadmium and blood pressure have been inconsistent.[11] Additionally, these previous

Correspondence to: Sung Kyun Park, Department of Epidemiology, University of Michigan, M5541 SPH II, 1415 Washington Heights, Ann Arbor, MI 48109-2029. Email sungkyun@umich.edu.

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Novelty and Significance

What Is New?

- This is the first prospective cohort study of associations of heavy metal exposures with trajectories of blood pressure in midlife women.

What Is Relevant?

- Women become more susceptible to cardio-metabolic diseases. Exposure to heavy metals including arsenic, cadmium, mercury, and lead may accelerate the increase in blood pressure during midlife for women.

Summary

In the SWAN (Study of Women's Health Across the Nation), higher urinary concentrations of arsenic, mercury, and lead accelerated the elevation of blood pressure in midlife women. Urinary cadmium was associated with accelerated elevation of systolic blood pressure among never smokers. Thus, this analysis of SWAN suggests that heavy metal exposure may exacerbate blood pressure profiles in midlife women.

Nonstandard Abbreviations and Acronyms

DBP	diastolic blood pressure
SBP	systolic blood pressure
SWAN	Study of Women's Health Across the Nation
SWAN-MPS	SWAN Multi-Pollutant Substudy

studies have been predominantly cross-sectional, suggesting a need to investigate the association between heavy metals and blood pressure, especially in a well-characterized prospective cohort study.

Women become more susceptible to cardio-metabolic diseases, including high blood pressure, in their midlife because women at this stage experience the menopausal transition marked by a dramatic shift in women's sex hormone profile owing to permanent changes in the ovarian functions, which are further linked with increased risks of cardio-metabolic diseases in postmenopause.[12] Menopause is also considered a risk factor for oxidative stress attributed to the estrogen depletion over the menopausal transition.[13] Due to this increased sensitivity, as a key environmental source of oxidative stress, heavy metals may be an important risk factor for high blood pressure, particularly for women during this life stage. However, the evidence of the associations between heavy metals and blood pressure in midlife women is extremely limited.

Thus, to inform the hypothesis that exposure to heavy metals may increase blood pressure prospectively, we investigated the associations of urinary concentrations of heavy metals including arsenic, cadmium, mercury, and lead with longitudinal changes in blood pressure over 17 years of follow-up in the SWAN (Study of Women's Health Across the Nation).

METHODS

SWAN provides access to public-use datasets that include data from SWAN screening, the baseline visit, and follow-up visits (https://agingresearchbiobank.nia.nih.gov/). To preserve participant confidentiality, some, but not all, of the data used for this article are contained in the public-use datasets. A link to the public-use datasets is also located on the SWAN website: http://www.swanstudy.org/swan-research/data-access/. Investigators who require assistance accessing the public-use dataset may contact the SWAN Coordinating Center at the following email address: swanaccess@edc.pitt.edu.

Study Population

SWAN is an ongoing, multisite, multiethnic, community-based prospective study of midlife women. The study goal is to assess psychosocial changes that occur during the menopausal transition and their effects on subsequent health end points. In 1996 and 1997, 3302 women were enrolled from seven study sites: Boston, MA; Chicago, IL; Southeast Michigan; Los Angeles, CA; Newark, NJ; Oakland, CA; and Pittsburgh, PA. Each site enrolled White women and women from one minority group (Black women from Boston, Chicago, Southeast Michigan, and Pittsburgh; Chinese women from Oakland; Japanese women from Los Angeles; and Hispanic women from Newark). Eligibility criteria for enrollment into the SWAN cohort included the following: age 42 to 52 years, intact uterus and at least one ovary, no use of exogenous hormones affecting ovarian function in the past 3 months, at least one menstrual period in the previous 3 months, and self-identification with a site's designated racial/ethnic groups. These women returned for regular approximate examinations annually with ≈75% of still-living participants completed the 15th SWAN follow-up visit (2015–2017). Institutional review board approval was obtained at each study site, and all participants provided signed informed consent at each study visit.

Participants in the current analysis were from the women enrolled in the SWAN-MPS (SWAN Multi-Pollutant Substudy),[14–16] which provided urine samples from the SWAN Repository collected at the third SWAN follow-up visit (visit 3, 1999–2000). Of 2694 women enrolled at visit 3, we excluded women from Chicago (n=368) and Newark (n=278) because urine samples were not available in these two sites. We additionally excluded 648 women with insufficient urine samples at visit 3, yielding the 1400 women with urinary metal concentrations measured in the SWAN-MPS. For this analysis, we further excluded 65 participants who had no information on key covariates, and 18 participants with missing information on

blood pressure throughout the follow-up, yielding a final analytic sample of 1317 women with 12637 observations from 1999 to 2017.

Blood Pressure

This analysis considers two outcomes, systolic blood pressure (SBP) and diastolic blood pressure (DBP). At each in-person clinic visit, SBP and DBP were measured in the morning once the participants visited the study clinic after a 12-hour fast by trained and certified technicians according to a standardized protocol. The participant was asked to refrain from smoking or consuming any caffeinated beverage within 30 minutes of blood pressure measurement. Readings were taken on the right arm, with the participant seated and feet flat on the floor for at least 5 minutes before measurement. Appropriate cuff size was determined based on arm circumference. A standard mercury sphygmomanometer was used to record readings at the first and fifth phase Korotkoff sounds. Two sequential measurements were taken with a minimum 2-minute rest period between measurements. The average of the two SPB and DBP measures was used in this analysis.

Heavy Metals

At the follow-up visit in 1999 to 2000, SWAN participants provided a morning spontaneously voided urine sample. These samples were sent to the Applied Research Center of NSF International (Ann Arbor, MI) for metal assessments. Urinary concentrations of arsenic, cadmium, mercury, and lead were measured using high-resolution inductively coupled plasma-mass spectrometry (Thermo Scientific iCAP RQ, Waltham, MA). The laboratory methods and quality control procedures have been described previously.[14] The detection rate was 100% for arsenic, 94.3% for cadmium, 99.8% for mercury, and 97.8% for lead. For participants with metal concentrations below the limit of detection, a value equal to the limit of detection divided by the square root of 2 was assigned.

Covariates

Information on age, self-defined race/ethnicity (White, Black, Chinese, and Japanese), study site (southeast Michigan, Boston, Oakland, Los Angeles, and Pittsburgh), education (high school or less, some college, and college degree or higher), smoking status (never smoked, former smoker, and current smoker), alcohol drinking (<1 drink/mo, >1 drink/mo and ≤1/wk, and >1 drink/wk), physical activity, and menopausal status (premenopausal, postmenopausal, and unknown due to hormone therapy use) were obtained from standardized interviews. Physical activity was assessed based on a modified version of the Kaiser Physical Activity Survey and summarized into a score ranging from 3 to 15 with 15 indicating the highest level of activity.[17] Body mass index was calculated as measured weight in kilograms divided by the square of measured height in meters. Dietary seafood and rice intake was collected using a detailed semi-quantitative food frequency questionnaire adapted from the Block food frequency questionnaire.[14] Urinary specific gravity was determined using a handheld digital refractometer (ATAGO model PAL-10S, Tokyo, Japan) as a marker of urine dilution.

Statistical Analysis

We used linear mixed-effects models with random intercepts to estimate longitudinal changes in SBP and DBP in relation to each tertile of urinary metal concentration. We added a constant of 10 mm Hg and 5 mm Hg to participants' SBP and DBP, respectively, at time points when they reported current use of antihypertensive medications, according to an established method to adjust for medication use.[18] Urinary metal concentrations were categorized into tertiles. To test whether metals affected the rate of change in blood pressure over time, multiplicative interaction terms between time elapsed from the SWAN-MPS baseline and tertiles of metal concentrations were included in each model. Time was modeled using a linear term of year. We decided not to add a quadratic term of time into the model or use linear splines of time due to the worse model fitting performance based on the Bayesian information criterion. The model is shown as

$$BP_{ij} = \beta_0 + \beta_1 Metal_{Tertile2_i} + \beta_2 Metal_{Tertile3_i} + \beta_3 Time_{ij} + \beta_4 Time_{ij} \times Metal_{Tertile2_i} + \beta_5 Time_{ij} \times Metal_{Tertile3_i} + b_{0j} + \beta Covariates_{ij}$$

where BP_{ij} represents SBP or DBP for the i[th] participant with the j[th] observation; $Metal_{Tertile2_i}$ and $Metal_{Tertile3_i}$ represents the second and third tertiles of metal concentrations, respectively, comparing with the first tertile (reference group). $Time_{ij}$ indicates for follow-up time (time-on-study, in years). b_{0j} is the random intercept. The annualized rate of changes in blood pressure equals β_3, $\beta_3 + \beta_4$, and $\beta_3 + \beta_5$ in the first, second, and third tertile of the metal concentration, respectively. We adjusted *P* values for multiple comparisons at a false discovery rate of 0.05 using the Benjamini-Hochberg Method.[19]

Potential confounders were adjusted progressively. The base model included age (baseline), race/ethnicity (baseline), study site (baseline), and specific gravity (log-transformed; baseline). The same terms were included in the fully adjusted model along with education level (baseline), body mass index (baseline), smoking (time-varying), alcohol drinking (time-varying), physical activity (time-varying), and menopausal status (time-varying). We also adjusted for seafood and rice intake at baseline in the full model as we have identified these dietary components to be important determinants of heavy metal concentrations in a previous study.[14] Multiplicative interaction terms between race/ethnicity and follow-up time were also included in the full model for accounting for its potential impact on longitudinal changes in blood pressures.[20] Body mass index was not included as a time-varying covariate in our analysis because of its role as a risk factor for high blood pressure and the fact that it could be affected by metal exposures at baseline.[21] As smoking is considered a primary source of cadmium for the general population and as the association between cadmium and blood pressure could be complicated by smoking status,[22] we further evaluated the association of cadmium with blood pressure stratified by smoking status (never smoker versus former or current smoker) at baseline. To quantify differences in longitudinal changes in blood pressure associated with exposure to metal mixtures, we also included tertiles of all four metals and their interaction terms with follow-up time simultaneously in a final adjusted model.

Several sensitivity analyses were conducted to evaluate the robustness of our findings. First, because adjustment for seafood intake may not sufficiently control for the less toxic organic arsenic in evaluation of the association between arsenic and

blood pressure,[23] we evaluated the association in a subpopulation with seafood intake less than 1.5 times/wk (median level). Second, menopause has been suggested to play an important role in the mobilization of lead from bone into the circulation due to an increased bone turnover rate.[24] Participants who were approaching menopause at the time when metal exposure was assessed may have elevated urinary lead concentrations due to the mobilization of lead from bone,[25] thus the observed associations could be confounded by increased bone resorption. As a sensitivity analysis, we used urinary N-telopeptide adjusted urinary lead concentration. Finally, we used raw values of SBP and DBP and adjusted for use of antihypertensive medications in regression analyses. All analyses were conducted using R, version 4.0.2 (www.R-project.org).

RESULTS

The median age of the 1317 women included in the current analysis was 49.4 years with an interquartile range of 47.4 to 51.5 years at baseline (Table S1 in the Data Supplement). Of those, 50.2% were White, 21.5% were Black, 12.9% were Chinese, and 15.4% were Japanese. Most women had never smoked (63.2%) and were premenopausal (70.5%) at SWAN-MPS baseline. The medians (interquartile ranges) of blood pressure at baseline were 112 (103–125) mm Hg for SBP and 73 (67–81) mm Hg for DBP. The distributions of urinary metal concentrations are shown in Table S2.

Baseline SBP did not differ by tertiles of metals, except for mercury, where SBP levels were higher for participants in the lowest tertile (Table S3). As shown in Table 1, SBP consistently increased with time, as was observed with a positive annualized change estimate in each tertile for each metal examined. Statistically, significantly higher rates of increase in SBP were observed in higher tertiles of arsenic (P for interaction=0.0003), mercury (P for interaction=0.01), and lead (P for interaction=0.007). To adjust for multiple comparisons, a significance level of α=0.01 was used, which corresponded to a false discovery rate of 5% using the Benjamini-Hochberg method. The estimated annualized increase in SBP was 0.93 (95% CI, 0.85–1.01) mm Hg/y in the highest and 0.74 (95% CI, 0.66–0.82) mm Hg/y in the lowest tertile of arsenic; 0.82 (95% CI, 0.75–0.90) mm Hg/y in the highest and 0.72 (95% CI, 0.65–0.80) mm Hg/y in the lowest tertile of mercury; and 0.86 (95% CI, 0.78–0.93) mm Hg/y in the highest and 0.72 (95% CI, 0.64–0.79) mm Hg/y in the lowest tertile of lead. At the end of the follow-up period when participants had reached ages between 62 and 73 years, the mean SBP was estimated to be 126.2 (95% CI, 124.2–128.1) mm Hg in the highest and 124.3 (95% CI, 122.4–126.2) mm Hg in the lowest tertile of arsenic; 123.6 (95% CI, 121.7–125.6) mm Hg in the highest and 125.3 (95% CI, 123.3–127.2) mm Hg in the lowest tertile of mercury; and 125.7 (95% CI, 123.6–127.7) mm Hg in the highest and 123.1 (95% CI, 121.2–125.0) mm Hg in the lowest tertile of lead.

DBP at baseline did not differ across tertiles of metals (Table S4). Similar to SBP, a positive annualized change estimate in each tertile for each metal examined was observed for DBP (Table 2), with the rates of increase greater in the higher tertiles of arsenic (P for interaction=0.004), mercury (P for interaction=0.0004), and lead (P for interaction=0.004). A significance level of α=0.004 was used, corresponding to a false discovery rate of 5%. In the fully adjusted model, the estimated annualized increase in DBP was 0.20 (95% CI, 0.15–0.25) mm Hg/y in the highest and 0.09 (95% CI, 0.04–0.14) mm Hg/y in the lowest tertile of arsenic; 0.17

Table 1. Estimated Annualized Changes in Systolic Blood Pressure (mm Hg) by Tertiles of Urinary Heavy Metal Concentrations

Tertiles of metal concentration	Annual change (95% CI) in systolic blood pressure, mm Hg			P for interaction
	Tertile 1	Tertile 2	Tertile 3	
Arsenic				
Base model*	0.68 (0.61–0.75)	0.70 (0.63–0.77)	0.87 (0.80–0.94)	0.0004
Full model†	0.74 (0.66–0.82)	0.76 (0.68–0.83)	0.93 (0.85–1.01)	0.0003
Cadmium				
Base model*	0.70 (0.63–0.77)	0.75 (0.69–0.82)	0.80 (0.73–0.87)	0.13
Full model†	0.75 (0.68–0.83)	0.81 (0.73–0.89)	0.85 (0.78–0.93)	0.12
Mercury				
Base model*	0.67 (0.60–0.74)	0.81 (0.75–0.88)	0.77 (0.70–0.84)	0.01
Full model†	0.72 (0.65–0.80)	0.87 (0.79–0.94)	0.82 (0.75–0.90)	0.01
Lead				
Base model*	0.66 (0.59–0.73)	0.79 (0.72–0.85)	0.80 (0.74–0.87)	0.006
Full model†	0.72 (0.64–0.79)	0.84 (0.77–0.92)	0.86 (0.78–0.93)	0.007

*Adjusted for age at baseline, race/ethnicity, study site, specific gravity (log-transformed).

†Adjusted for age at baseline, race/ethnicity, study site, specific gravity (log-transformed), education, smoking status, alcohol drinking, physical activity, body mass index at baseline, menopausal status, seafood and rice intake at baseline, and interaction term between race/ethnicity and follow-up time.

Table 2. Estimated Annualized Changes in Diastolic Blood Pressure (mm Hg) by Tertiles of Urinary Heavy Metal Concentrations

Tertiles of metal concentration	Annualized change (95% CI) in diastolic blood pressure, mm Hg			*P* for interaction
	Tertile 1	Tertile 2	Tertile 3	
Arsenic				
Base model*	0.08 (0.04–0.13)	0.10 (0.05–0.14)	0.19 (0.14–0.23)	0.004
Full model†	0.09 (0.04–0.14)	0.11 (0.06–0.16)	0.20 (0.15–0.25)	0.004
Cadmium				
Base model*	0.11 (0.07–0.16)	0.12 (0.08–0.17)	0.13 (0.09–0.18)	0.80
Full model†	0.12 (0.07–0.17)	0.13 (0.08–0.18)	0.14 (0.09–0.19)	0.78
Mercury				
Base model*	0.05 (0–0.09)	0.15 (0.11–0.20)	0.17 (0.12–0.21)	0.0003
Full model†	0.05 (0.01–0.11)	0.16 (0.11–0.21)	0.17 (0.13–0.22)	0.0004
Lead				
Base model*	0.07 (0.02–0.11)	0.13 (0.08–0.17)	0.17 (0.13–0.22)	0.004
Full model†	0.07 (0.03–0.12)	0.14 (0.09–0.18)	0.18 (0.13–0.23)	0.004

*Adjusted for age at baseline, race/ethnicity, study site, specific gravity (log-transformed).

†Adjusted for age at baseline, race/ethnicity, study site, specific gravity (log-transformed), education, smoking status, alcohol drinking, physical activity, body mass index at baseline, menopausal status, seafood and rice intake at baseline, and interaction term between race/ethnicity and follow-up time.

(95% CI, 0.13–0.22) mm Hg/y in the highest and 0.05 (95% CI, 0.01–0.11) mm Hg/y in the lowest tertile of mercury; and 0.18 (95% CI, 0.13–0.23) mm Hg/y in the highest and 0.07 (95% CI, 0.03–0.12) mm Hg/y in the lowest tertile of lead. At the end of the follow-up period, the mean DBP was estimated to be 76.0 (95% CI, 74.9–77.2) mm Hg in the highest and 74.7 (95% CI, 73.6–75.9) mm Hg in the lowest tertile of arsenic; 75.4 (95% CI, 74.2–76.5) mm Hg in the highest and 74.9 (95% CI, 73.7–76.1) mm Hg in the lowest tertile of mercury; and 76.1 (95% CI, 74.9–77.3) mm Hg in the highest and 74.0 (95% CI, 72.9–75.2) mm Hg in the lowest tertile of lead.

For cadmium, we conducted stratified analyses by smoking status (Table S5). Significantly greater annualized increases in SBP were observed in upper tertiles of cadmium only among never smokers (*P* for interaction=0.03). In never smokers, estimated annualized increase in SBP was 0.89 (95% CI, 0.80–0.97) mm Hg/y in the highest and 0.74 (95% CI, 0.64–0.83) mm Hg/y in the lowest tertile. No association between cadmium and DBP was observed.

In the model simultaneously incorporating 4 metals, higher rates of increases in both SBP and DBP were observed when a participant had higher concentrations of all four metals (Table 3 and Table S6). After adjustment for potential confounders, the estimated annualized increase in SBP was 0.91 (95% CI, 0.81–1.01) mm Hg/y in the highest and 0.67 (95% CI, 0.57–0.76) mm Hg/y in the lowest tertiles of all four metals. The estimated annualized increase in DBP was 0.19 (95% CI, 0.13–0.26) mm Hg/y in the highest and 0.07 (95% CI, 0.01–0.13) mm Hg/y in the lowest tertiles of all 4 metals. The associations for each metal from these multi-metal models are shown in Table S7.

In the sensitivity analysis, associations between urinary arsenic and blood pressure were evaluated in a subpopulation of 657 participants with seafood intake less than 1.5 times/wk. In this subpopulation, higher rates of increase in SBP were observed in the participants with higher arsenic concentrations; however, the interaction terms between arsenic and time were no longer statistically significant (Table S8), possibly due to a reduced statistical power in accordance with the smaller sample size in this analysis. In the sensitivity analysis assessing associations between urinary N-telopeptide–adjusted lead and blood pressure, similar associations were observed as in the primary analysis (Table S9). Similar associations were also observed when raw values of SBP and DBP were used after adjustment for use of antihypertensive medications in regression models (Table S10).

DISCUSSION

This study examined associations between heavy metal exposures and longitudinal change in blood pressure in midlife women as they aged through the menopausal transition. In this multisite, multiethnic cohort study of women at midlife, urinary concentrations of arsenic, mercury, and lead were associated with a faster rate of increase in both SBP and DBP. Urinary cadmium was associated with a greater rate of increase in SBP among never smokers only. Higher concentrations of all heavy metals were also associated with greater annualized increases in both SBP and DBP.

Even a small increase in blood pressure associated with heavy metal exposures may have substantial public health consequences, given the widespread exposure to metals and the predominance of high blood

Table 3. Estimated Annualized Changes in Systolic and Diastolic Blood Pressures (mm Hg) by Tertiles of Urinary Metal Concentrations in the Model Incorporating All Metals

Tertiles of all metal concentrations	Annualized change (95% CI) in blood pressure, mm Hg*			
	Tertile 1‡	Tertile 2§	Tertile 3‖	*P* for interaction†
Systolic blood pressure	0.67 (0.57–0.76)	0.84 (0.73–0.95)	0.91 (0.81–1.01)	0.06
Diastolic blood pressure	0.07 (0.01–0.13)	0.13 (0.05–0.20)	0.19 (0.13–0.26)	0.0003

*Models were adjusted for age at baseline, race/ethnicity, study site, specific gravity (log-transformed), education, smoking status, alcohol drinking, physical activity, body mass index at baseline, menopausal status, seafood and rice intake at baseline, and interaction term between race/ethnicity and follow-up time.

†*P* for interaction was calculated using likelihood ratio test between the model incorporating interaction terms between tertiles of metals and follow-up time and the model without interaction terms.

‡Annualized changes in blood pressure when arsenic, cadmium, mercury, and lead concentrations were at their tertile 1.

§Annualized changes in blood pressure when arsenic, cadmium, mercury, and lead concentrations were at their tertile 2.

‖Annualized changes in blood pressure when arsenic, cadmium, mercury, and lead concentrations were at their tertile 3.

pressure–related health outcomes in the United States For example, across the 17 years of follow-up, the mean SBP in the highest tertile of arsenic climbed by 15.8 mm Hg, whereas SBP increased by 12.6 mm Hg in the lowest tertile. These elevations in blood pressure are associated with higher risks of cardiovascular disease, stroke, and mortality. Population-based studies suggest that a 1 mm Hg increase in SBP is associated with a 1% increase in age-adjusted stroke mortality[26] and a 2% to 4% increase in cardiovascular mortality.[27] Thus, the impact of metal exposure on blood pressure differences translates to significant differences in long-term cardiovascular end points. Our findings suggest that heavy metals may be an underappreciated contributing factor to accelerated deterioration of cardiovascular health, especially during the potentially sensitive period of midlife.

Arsenic is a ubiquitous industrial and naturally occurring environmental toxicant. Inorganic arsenic is a toxicant and its primary sources are drinking water and certain foods including rice.[14] After absorption from the gastrointestinal tract, inorganic arsenic is rapidly excreted together with its metabolites primarily through the urine. A systematic review including 11 cross-sectional studies, mostly conducted in areas with high exposure to arsenic in drinking water such as Bangladesh and Taiwan, showed a pooled odds ratio of 1.27 (95% CI, 1.09–1.47) for high blood pressure when comparing the highest versus lowest category of inorganic arsenic in drinking water.[9] In contrast, arsenic exposure at the low-to-moderate levels typical of the US general population was not associated with blood pressure or prevalence of hypertension.[28] Our study, leveraging a prospective cohort design, found a positive association between arsenic and longitudinal changes in SBP, suggesting arsenic exposure at low-to-moderate levels in the United States may also incur adverse effects.[14] Experimental studies suggest that arsenic may elevate blood pressure via pathways related to inflammation, oxidative stress, and endothelial dysfunction.[9] Arsenic has also been shown to disrupt renal function, leading to an increased risk of high blood pressure.[29]

Mercury is a ubiquitous and persistent toxicant that has different forms.[30] General populations can be exposed to methylmercury (organic form) primarily through seafood and be exposed to inorganic mercury through occlusal surfaces of teeth that are filled with mercury-containing amalgams[31] and skin lightening products with inorganic mercury compounds.[32] In humans, urinary mercury mainly reflects inorganic mercury.[30] It has also been positively associated with seafood intake in SWAN.[14] Epidemiological studies in population settings and occupational cohorts have produced mixed results. A recent meta-analysis based on 29 studies reported a borderline positive association between mercury and hypertension (pooled odds ratio, 1.35 [95% CI, 0.99–1.83], comparing the highest and lowest categories of mercury concentrations measured in hair, blood, or urine) for populations with relatively high exposures.[10] In contrast, no significant association was observed for populations with relatively low exposures (pooled odds ratio, 1.12 [95% CI, 0.82–1.52]).[10] We demonstrated an association of mercury, particularly its inorganic form, with accelerated increases in SBP and DBP. In animal models, acute or chronic administration of both inorganic mercury and methylmercury have been shown to induce hypertension.[10] Possible mechanisms underlying mercury's effect include oxidative stress, inflammation, changes in vascular smooth muscle, endothelial and renal dysfunction, dyslipidemia, and immune and mitochondrial dysfunction.[33] In our study, an inverse association was observed between urinary mercury and SBP at baseline, even after further adjustment for seafood intake. To the best of our knowledge, no biological evidence supports mercury itself being beneficial for blood pressure control. The observed inverse association at baseline may indicate that mercury concentration is a surrogate measure of dietary seafood intake in our population.[14]

Lead toxicity is acknowledged as a prevalent and persistent public health problem. In adults, >95% of the total lead body burden is found in bone.[34] Bone lead is, therefore, considered a biomarker of cumulative lead exposure.[35–37] Bone lead has been consistently associated with high blood pressure.[7] Bone lead undergoes

constant interchange with lead in the circulation and soft tissue. Urinary lead adjusted for urine dilution rather than whole blood lead has been found to closely reflect lead mobilized from the bone.[25] In our study, urinary lead was associated with a faster rate of increase in both SBP and DBP. Consistent results were found when urinary N-telopeptide–adjusted lead concentrations were used in the sensitivity analysis. These findings support the hypothesis that long-term lead accumulation may increase blood pressure, particularly in midlife for women, attributed in part to a greater mobilization of lead from bone into the circulation during the menopausal transition. Our finding is also consistent with the association between lead and blood pressure in postmenopausal women from the US general population.[38] Impaired renin-angiotensin system function, oxidative stress, inflammation, and neurotoxic effects interfering with autonomic nervous system function may serve as potential mechanisms underlying the association between lead and blood pressure.[7]

A positive association between urinary cadmium and annual rate of change in SBP was observed among women who never smoked, which accords with previous findings. A stronger association between blood cadmium and blood pressure among never smokers compared to former/current smokers has been observed in US adults using data from National Health and Nutrition Examination Survey 1999 to 2004.[39] The positive association between urinary cadmium and blood pressure has also been found among never smokers but not former/current smokers in a recent study of American Indian adults.[22] Importantly, as smoking is a primary source of cadmium, we did observe higher urinary concentrations of cadmium in smokers in SWAN.[14] Given this, our finding suggests that the association between cadmium and blood pressure is unrelated to other toxicants in cigarette smoke. Alternatively, it is possible that other sources of cadmium exposure exist in our cohort. Coexposure to other toxicants which are correlated with cadmium in those sources may also contribute to the elevation in SBP. More investigations into the potential sources of cadmium exposure and the association between cadmium and blood pressure in populations with diverging context of exposure levels are needed in the future.

The primary strength of the current study is that it used a large cohort of community-based midlife women from four racial/ethnic groups and followed them for up to 17 years. To our knowledge, this is the first investigation of associations of heavy metal exposures with trajectories of blood pressure in midlife women. Standard annualized measures also provided reliable estimates of changes in blood pressure and ensure temporality between exposure and outcome.

Our study also has several limitations. First, we measured metal concentrations in urine and urinary concentrations may not consistently reflect metals in all forms and from all exposure sources. Second, urinary metal concentrations were measured at a single time point at the SWAN-MPS baseline. Existing evidence demonstrates the long-term constancy in arsenic exposure.[40] Cadmium is not rapidly excreted and has half-lives of years to decades, and urinary cadmium has suggested a biomarker for long-term exposure. Urinary lead adjusted for urine dilution has been found to closely reflect lead mobilized from the bone,[25] where bone lead is a biomarker of long-term exposure and has been suggested as an endogenous and primary source of lead in midlife and late-life.[41] Third, only total arsenic was measured in urine samples and information on arsenic metabolism was not available. Recent studies suggested that the pattern of arsenic metabolisms including monomethylated and dimethylated compounds was associated with cardiovascular disease and diabetes risks.[42] Additional measurements of arsenic metabolism would improve our understanding of arsenic exposure and its associated health risks. Finally, we cannot eliminate residual confounding due to the observational nature of the study, although we have controlled for many known confounders.

PERSPECTIVES

In this prospective cohort study, we observed that higher urinary concentrations of arsenic, mercury, and lead accelerated the rate of elevation of blood pressure in midlife women, during the menopausal transition, a life stage when women are at greater risk of cardio-metabolic diseases. Urinary cadmium was associated with accelerated elevation of SBP among never smokers. High exposure to all heavy metals was also associated with greater elevation of blood pressure. Our findings have potentially important public health implications. They suggest that heavy metal exposure may exacerbate blood pressure profiles. Continued efforts to reduce heavy metal exposures are needed, especially in midlife women.

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Affiliations

Department of Epidemiology (X.W., C.A.K.-.G., W.H.H., S.D.H., S.K.P.), Department of Biostatistics (B.M.), Department of Environmental Health Sciences (S.K.P.), School of Public Health, and Department of Internal Medicine (W.H.H.), University of Michigan, Ann Arbor.

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REFERENCES

1. Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, Colantonio LD. Trends in blood pressure control among US adults with hpertension, 1999-2000 to 2017-2018. *JAMA*. 2020;324:1190–1200. doi: 10.1001/jama.2020.14545
2. Wan EYF, Yu EYT, Chin WY, Fong DYT, Choi EPH, Lam CLK. Association of blood pressure and risk of cardiovascular and chronic kidney disease in hong kong hypertensive patients. *Hypertension*. 2019;74:331–340. doi: 10.1161/HYPERTENSIONAHA.119.13123
3. Taylor BC, Wilt TJ, Welch HG. Impact of diastolic and systolic blood pressure on mortality: implications for the definition of "normal". *J Gen Intern Med*. 2011;26:685–690. doi: 10.1007/s11606-011-1660-6
4. Kahn LG, Trasande L. Environmental toxicant exposure and hypertensive disorders of pregnancy: recent findings. *Curr Hypertens Rep*. 2018;20:87. doi: 10.1007/s11906-018-0888-5
5. Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. *Toxicology*. 2011;283:65–87. doi: 10.1016/j.tox.2011.03.001
6. Alissa EM, Ferns GA. Heavy metal poisoning and cardiovascular disease. *J Toxicol*. 2011;2011:870125. doi: 10.1155/2011/870125
7. Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. Lead exposure and cardiovascular disease–a systematic review. *Environ Health Perspect*. 2007;115:472–482. doi: 10.1289/ehp.9785
8. Wang X, Mukherjee B, Park SK. Does information on blood heavy metals improve cardiovascular mortality prediction? *J Am Heart Assoc*. 2019;8:e013571. doi: 10.1161/JAHA.119.013571
9. Abhyankar LN, Jones MR, Guallar E, Navas-Acien A. Arsenic exposure and hypertension: a systematic review. *Environ Health Perspect*. 2012;120:494–500. doi: 10.1289/ehp.1103988
10. Hu XF, Singh K, Chan HM. Mercury exposure, blood pressure, and hypertension: a systematic review and dose-response meta-analysis. *Environ Health Perspect*. 2018;126:076002. doi: 10.1289/EHP2863
11. Gallagher CM, Meliker JR. Blood and urine cadmium, blood pressure, and hypertension: a systematic review and meta-analysis. *Environ Health Perspect*. 2010;118:1676–1684. doi: 10.1289/ehp.1002077
12. Staessen JA, Celis H, Fagard R. The epidemiology of the association between hypertension and menopause. *J Hum Hypertens*. 1998;12:587–592. doi: 10.1038/sj.jhh.1000670
13. Sánchez-Rodríguez MA, Zacarías-Flores M, Arronte-Rosales A, Correa-Muñoz E, Mendoza-Núñez VM. Menopause as risk factor for oxidative stress. *Menopause*. 2012;19:361–367. doi: 10.1097/gme.0b013e318229977d
14. Wang X, Mukherjee B, Batterman S, Harlow SD, Park SK. Urinary metals and metal mixtures in midlife women: the Study of Women's Health Across the Nation (SWAN). *Int J Hyg Environ Health*. 2019;222:778–789. doi: 10.1016/j.ijheh.2019.05.002
15. Ding N, Harlow SD, Batterman S, Mukherjee B, Park SK. Longitudinal trends in perfluoroalkyl and polyfluoroalkyl substances among multiethnic midlife women from 1999 to 2011: the Study of Women's Health Across the Nation. *Environ Int*. 2020;135:105381. doi: 10.1016/j.envint.2019.105381
16. Wang X, Karvonen-Gutierrez CA, Herman WH, Mukherjee B, Harlow SD, Park SK. Urinary metals and incident diabetes in midlife women: Study of Women's Health Across the Nation (SWAN). *BMJ Open Diabetes Res Care*. 2020;8:e001233. doi: 10.1136/bmjdrc-2020-001233
17. Sternfeld B, Cauley J, Harlow S, Liu G, Lee M. Assessment of physical activity with a single global question in a large, multiethnic sample of midlife women. *Am J Epidemiol*. 2000;152:678–687. doi: 10.1093/aje/152.7.678
18. Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. *Stat Med*. 2005;24:2911–2935. doi: 10.1002/sim.2165
19. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B*. 1995;57:289–300.
20. Lloyd-Jones DM, Sutton-Tyrrell K, Patel AS, Matthews KA, Pasternak RC, Everson-Rose SA, Scuteri A, Chae CU. Ethnic variation in hypertension among premenopausal and perimenopausal women: Study of Women's Health Across the Nation. *Hypertension*. 2005;46:689–695. doi: 10.1161/01.HYP.0000182659.03194.db
21. Wang X, Mukherjee B, Park SK. Associations of cumulative exposure to heavy metal mixtures with obesity and its comorbidities among U.S. adults in NHANES 2003-2014. *Environ Int*. 2018;121(pt 1):683–694. doi: 10.1016/j.envint.2018.09.035
22. Franceschini N, Fry RC, Balakrishnan P, Navas-Acien A, Oliver-Williams C, Howard AG, Cole SA, Haack K, Lange EM, Howard BV, et al. Cadmium body burden and increased blood pressure in middle-aged American Indians: the Strong Heart Study. *J Hum Hypertens*. 2017;31:225–230. doi: 10.1038/jhh.2016.67
23. Navas-Acien A, Francesconi KA, Silbergeld EK, Guallar E. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. *Environ Res*. 2011;111:110–118. doi: 10.1016/j.envres.2010.10.009
24. Hernandez-Avila M, Villalpando CG, Palazuelos E, Hu H, Villalpando ME, Martinez DR. Determinants of blood lead levels across the menopausal transition. *Arch Environ Health*. 2000;55:355–360. doi: 10.1080/00039890009604028
25. Wang X, Kim D, Tucker KL, Weisskopf MG, Sparrow D, Hu H, Park SK. Effect of dietary sodium and potassium intake on the mobilization of bone lead among middle-aged and older men: the Veterans Affairs Normative Aging Study. *Nutrients*. 2019;11:E2750. doi: 10.3390/nu11112750
26. Palmer AJ, Bulpitt CJ, Fletcher AE, Beevers DG, Coles EC, Ledingham JG, O'Riordan PW, Petrie JC, Rajagopalan BE, Webster J. Relation between blood pressure and stroke mortality. *Hypertension*. 1992;20:601–605. doi: 10.1161/01.hyp.20.5.601
27. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, Menotti A, Nissinen A, Kromhout D. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. *N Engl J Med*. 2000;342:1–8. doi: 10.1056/NEJM200001063420101
28. Jones MR, Tellez-Plaza M, Sharrett AR, Guallar E, Navas-Acien A. Urine arsenic and hypertension in US adults: the 2003-2008 National Health and Nutrition Examination Survey. *Epidemiology*. 2011;22:153–161. doi: 10.1097/EDE.0b013e318207fdf2
29. Chen JW, Chen HY, Li WF, Liou SH, Chen CJ, Wu JH, Wang SL. The association between total urinary arsenic concentration and renal dysfunction in a community-based population from central Taiwan. *Chemosphere*. 2011;84:17–24. doi: 10.1016/j.chemosphere.2011.02.091
30. Atlanta: Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services. *Toxicological profile for Mercury*. 1999. https://www.atsdr.cdc.gov/toxprofiles/tp46.pdf
31. Mutter J. Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission. *J Occup Med Toxicol*. 2011;6:2. doi: 10.1186/1745-6673-6-2
32. Park JD, Zheng W. Human exposure and health effects of inorganic and elemental mercury. *J Prev Med Public Health*. 2012;45:344–352. doi: 10.3961/jpmph.2012.45.6.344

33. Houston MC. Role of mercury toxicity in hypertension, cardiovascular disease, and stroke. *J Clin Hypertens (Greenwich).* 2011;13:621–627. doi: 10.1111/j.1751-7176.2011.00489.x
34. Barry PS, Mossman DB. Lead concentrations in human tissues. *Br J Ind Med.* 1970;27:339–351. doi: 10.1136/oem.27.4.339
35. Ding N, Wang X, Tucker KL, Weisskopf MG, Sparrow D, Hu H, Park SK. Dietary patterns, bone lead and incident coronary heart disease among middle-aged to elderly men. *Environ Res.* 2019;168:222–229. doi: 10.1016/j.envres.2018.09.035
36. Ding N, Wang X, Weisskopf MG, Sparrow D, Schwartz J, Hu H, Park SK. Lead-Related Genetic Loci, cumulative lead exposure and incident coronary heart disease: the normative aging study. *PLoS One.* 2016;11:1–18.
37. Wang X, Ding N, Tucker KL, Weisskopf MG, Sparrow D, Hu H, Park SK. A western diet pattern is associated with higher concentrations of blood and bone lead among middle-aged and elderly men. *J Nutr.* 2017;147:1374–1383. doi: 10.3945/jn.117.249060
38. Nash D, Magder L, Lustberg M, Sherwin RW, Rubin RJ, Kaufmann RB, Silbergeld EK. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. *JAMA.* 2003;289:1523–1532. doi: 10.1001/jama.289.12.1523
39. Tellez-Plaza M, Navas-Acien A, Crainiceanu CM, Guallar E. Cadmium exposure and hypertension in the 1999-2004 National Health and Nutrition Examination Survey (NHANES). *Environ Health Perspect.* 2008;116:51–56. doi: 10.1289/ehp.10764
40. Navas-Acien A, Umans JG, Howard BV, Goessler W, Francesconi KA, Crainiceanu CM, Silbergeld EK, Guallar E. Urine arsenic concentrations and species excretion patterns in American Indian communities over a 10-year period: the Strong Heart Study. *Environ Health Perspect.* 2009;117:1428–1433. doi: 10.1289/ehp.0800509
41. Hu H, Rabinowitz M, Smith D. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. *Environ Health Perspect.* 1998;106:1–8. doi: 10.1289/ehp.981061
42. Kuo CC, Moon KA, Wang SL, Silbergeld E, Navas-Acien A. The association of arsenic metabolism with cancer, cardiovascular disease, and diabetes: a systematic review of the epidemiological evidence. *Environ Health Perspect.* 2017;125:087001. doi: 10.1289/EHP577